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Virgil Percec *Editor*

Hierarchical Macromolecular Structures: 60 Years after the Staudinger Nobel Prize I

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Virgil Percec
Editor

Hierarchical Macromolecular Structures: 60 Years after the Staudinger Nobel Prize I

With contributions by

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Springer

Editor
Virgil Percec
Department of Chemistry
University of Pennsylvania
Philadelphia
Pennsylvania
USA

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Foreword: Memories of Hermann Staudinger by one of his grandchildren

I am delighted to contribute to this special issue of *Advances in Polymer Science* a few memories of my grandfather Hermann Staudinger, whom I knew for almost 20 years until his death in 1965.

With his first wife, Dorothea Staudinger-Förster, he had four children: Eva, born 1907 in Strasbourg; my mother Hilde, born 1910 in Karlsruhe; Hansjürgen, born 1914 in Zürich; and Klara, born 1916 in Zürich. His daughters and his son married and had ten children that I still regularly see.

Because my father, Theodore Rüegg, died soon after my birth in 1946, and since I was his only child, my mother arranged that I would often see her father and her brother Hansjürgen, who became my godfather. I thus had the unique opportunity of often seeing and talking to both of them and of being partly educated by them.

These get-togethers started right after the end of World War II and took place either in Zürich, where we lived, in Basel, or in nearby Freiburg (Germany). During that time, my mother often travelled north loaded with precious food such as butter, bread, sugar, meat, and coffee beans, the essential ingredient for preparing the preferred morning drink of my grandfather. He would also visit us in Zurich several times a year. As a result of the hard times he had endured during the Nazi regime, he had aged considerably and lost weight (Fig. 1).

In the early 1950s, Hermann Staudinger visited his three daughters and their children in the Zürich area at least twice a year, which would often be the occasion for a family reunion. On his 70th birthday, most family members travelled to Freiburg, as can be seen in Fig. 2. The get-togethers with him, his second wife Magda, and her parents Irmgard and Oskar Woit took place in their house in Freiburg. These visits impressed and influenced me greatly. My mother and I were picked up at the Freiburg train station by a chauffeur-driven Borgward car, which brought us to the impressive house at Lugostrasse 14, where the Staudingers welcomed us (Fig. 3).

My grandfather often took me on walks through their large garden surrounding the house to show me the unique collection of plants and flowers. I have been told that he knew all of the more than 250 plants growing there, as well as their Latin names. He checked them daily and took care of them with the help of a gardener. He

Fig. 1 Hermann Staudinger with grandson Urs in Zurich in 1948

originally wanted to become a botanist, but his high school teacher advised him to first study chemistry, the basis of plant and animal life, which we now call the "life sciences." I remember that at Easter time, when the daffodils and tulips surrounding a small pond in the upper part of the garden were in bloom and smelling wonderfully, we strolled around the garden and I listened to my grandfather's stories. These were inspired by Nature, most of them dealing with wild animals of the jungles and savannas: lions, giraffes, elephants, etc. They talked to each other and to the people around them, like in the stories of Doctor Doolittle. A follow-up came

Fig. 2 Family reunion in Freiburg on the 70th birthday of Hermann Staudinger on 23rd March 1951. From left to right: Hilde Rüegg-Staudinger, Dora Lezzi (at the back), Luzia Kaufmann (in front), Hermann Staudinger, Urs Rüegg (between his knees), Peter Kaufmann (at the back), Eva Lezzi-Staudinger, Hansjürgen Staudinger (at the back), Klara Kaufmann-Staudinger, Gabriele Staudinger-Schwarz, statue of Franz Staudinger (father of Hermann). Not in the picture: Magda Staudinger; Max, Jürg and Markus Lezzi; Monika, Reinhard and Peter Staudinger; Gustav and Ulrich Kaufmann (Courtesy of Markus Lezzi)

in the mornings, when I was invited to join my grandfather and Magda: He then told me stories by Wilhelm Hauff, for example the one about "Dwarf Nose," in which a community is described whose only purpose in life is to work, buy and sell, and earn money. Later on, my grandfather's arms and legs became parts of animals, some of them as dangerous as crocodile jaws; there was the frightening roar of lions that made me run away. The breakfasts that followed compensated for all this suffering. It would start with him reciting one of the many poems by Goethe, Schiller, Rilke, and others that he knew by heart. The themes were again mostly linked to Nature,

Fig. 3 Magda and Hermann Staudinger in front of their house in 1951

for example the Easter poem in Goethe's "Faust." The long-awaited fresh bread, sausages, eggs, and cereals turned these mornings into a veritable feast.

We often went on long walks towards Günterstal, a village at the foothills of the Southern part of the Black Forest. A special treat was to eat a slice of the similarly named cake on the hilltop of Schauinsland, which could be reached with a cable car and which would take us high above the dark fir trees to admire the view. In addition to the cake, I enjoyed the walks through the hills in the company of this expert botanist and storyteller. My cousins Luzia and Peter (cf. Fig. 2) occasionally joined us, and hide-and-seek was added to the touristic program.

Two other attractions were just a few hundred meters south of the Freiburg home, one for my grandfather and one for me. He was an enthusiastic supporter of the "Schrebergärten", land lots where families living in cities and not having a garden could plant vegetables, fruits, and flowers. I assume that he considered it important for the spirit to be outdoors, in touch with the elements and watching the plants grow. When a plan was drafted to construct houses on the grounds of these Schrebergärten, he chaired a committee defending their existence; they negotiated with local politicians and other groups involved in the project and, finally, their initiative was crowned with success.

My personal highlight was of a more technical nature: it was possible to observe the passing trains of the "Höllentalbahn" in a large trench. I enjoyed watching the steam engines pulling a few cars behind them coming out of a tunnel and making their way from Freiburg to Titisee and Neustadt in the Black Forest. At the age of about 10, I was put on one of these trains and travelled alone through the "Hell Valley" to the top station. As the personnel had been informed that I was a fan of trains, and since they knew of my grandfather, they invited me to the driver's platform in the locomotive. I could look into the coal fire, feel the heat and the steam, and assist with the maneuvers for switching the engine before going downhill again. This initiation probably led to my intense fascination with trains.

When not behaving well or when important decisions about my future had to be made, my mother used to consult her brother and my grandfather for advice. Towards the end of my high school education, I wanted to become a photographer. However, my grandfather had a long discussion with me about the values of science and higher education. He told me about his life, how much he enjoyed making discoveries, putting them into question and confirming or rejecting them by experiment; he also liked the discussions with his colleagues in the laboratory and the debates with those at other institutions. He was well informed about academic curricula and suggested that I choose one offering a broad perspective of natural science, for example the Swiss Federal Institute of Technology (ETH) in Zurich, where he had worked – as director of the Institute of Chemistry – some 50 years earlier. After several weeks of discussions with friends and relatives, I followed his advice and have never regretted it.

Much is known about Hermann Staudinger's second wife, Magda, but little has been written about his first wife, Dorothea, with whom he bore his four children. Dorothea was very impressed by Herman's father, Franz, who was a high school teacher and an expert on the philosopher Kant, and who had a social mind. Dorothea became involved in community-oriented activities in Zurich and was one of the founders of what is now known as the Coop Supermarkets, which were, at that time, a non-profit organization catering mostly to underprivileged people. She joined the movement of the priest and professor at Zurich University, Leonhard Ragaz, who combined socialism and christianism, was fighting for the underprivileged and minorities. In the early 1920^{s}, Dorothea and Hermann more and more grew away from each other as they followed their own interests: He was excited about research and science and she was more concerned about matters of the society. As a result, they split up and were separated in 1925. Like most people who knew Dorothea,

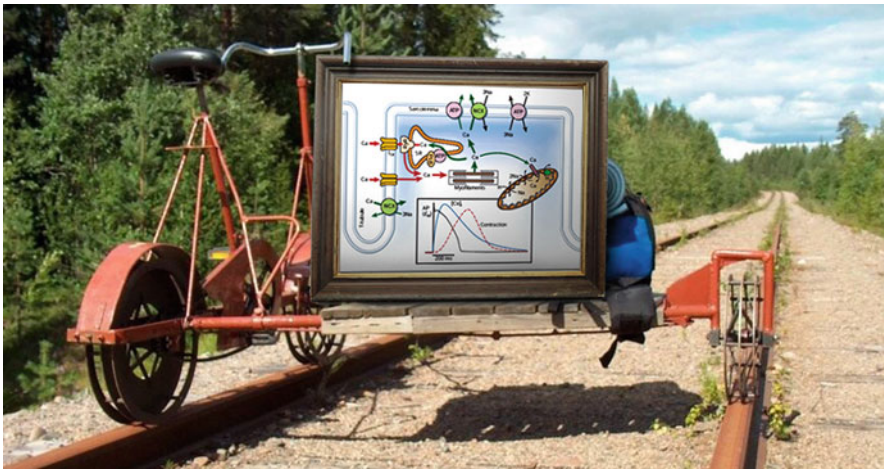

Fig. 4 "Of channels, bicycles and other – mostly public – transporters." Symposium for the author's retirement in July 2012 (Courtesy of one of the author's sons, Martin Ruegg)

I highly respected the thinking and the social ways of my grandmother and I am glad to be able to say a few words about her at this time.

After 20 years as a professor, I retired a year ago. I continue to supervise the research done in my laboratory and continue to teach at the Universities of Geneva and Basel. Also, I keep travelling on trains and bicycles daily – that was the theme of my retirement symposium (Fig. 4).

It is only now, reflecting on the past, that I realize how much I owe my grandfather, his son Hansjürgen, and my mother in coaching me to find my own path in life, both from a professional as well as a personal point of view.

Geneva, Switzerland U.T. Ruegg

Preface

Life and modern society cannot be imagined in the absence of natural and synthetic macromolecules. This volume of *Advances in Polymer Science* is dedicated to the 60th anniversary of the Nobel Prize received in 1953 by Professor Hermann Staudinger (23 March 1881–8 September 1965) "for his discoveries in the field of macromolecular chemistry."

Natural and synthetic macromolecules were known long before Staudinger. However, the status of macromolecular compounds is best reflected by the friendly advice received by Staudinger from Heinrich Otto Wieland, Nobel Prize laureate in 1927. "Dear colleague, abandon your idea of large molecules, organic molecules with molecular weights exceeding 5,000 do not exist. Purify your products such as rubber, they will crystallize and turn out to be low molecular weight compounds." Staudinger also wrote in his memoirs: "Those colleagues who were aware of my early publications in the field of low molecular weight chemistry asked me why I decided to quit these beautiful fields of research and why I devoted myself to such disgusting and ill-defined compounds such as rubber and synthetic polymers which at that time in view of their properties were referred to as grease chemistry ('Schmierenchemie')." The contributions of Hermann Staudinger to the field of macromolecular chemistry, for which he was awarded the Nobel Prize in 1953, are best illustrated by a discussion between the Emperor of Japan and Staudinger, that took place at the Imperial Palace of Japan on 17th of April 1957. His Majesty Emperor Hirohito of Japan asked, "Professor Staudinger, is this a concept that came into your mind to explain various phenomenological behaviors of a group of compounds or did you really prove their existence by rigorous scientific means?" The highly impressed Professor Staudinger answered, "It is this experimental demonstration of the existence of macromolecules which form the essential part of my work in the field of macromolecular science." Therefore, it was Staudinger who demonstrated the covalent rather than colloidal structure of macromolecules.

During the early days of the twentieth century, organic chemists were convinced that natural and synthetic macromolecules were colloidal aggregates of low molecular weight compounds. Staudinger obtained his Ph.D. at the age of 22, with Daniel Vorländer at the University of Halle in 1903. Subsequently, he held faculty

appointments at the University of Strasbourg (1903–1907) where in 1905 at the age of 24 he discovered ketenes. In 1907, he discovered the cycloaddition of ketenes with imines, still the most general and useful method for the synthesis of β-lactams. In the same year, he obtained his Habilitation in the laboratory of Johannes Thiele and moved to the University of Karlsruhe as a junior faculty where, in parallel with his work in the field of organic chemistry, he became interested in polymers. In 1912, at the age of 31, he moved to become full professor at ETH in Zürich and in the same year published his famous book on ketenes. In 1919, he discovered the reaction of azides with phosphines to produce phosphazenes and, subsequently, in the presence of water to yield primary amines. This reaction is known as the "Staudinger reaction" or "Staudinger reduction." In the year 2000, the Staudinger reaction was expanded and elaborated by Carolyn R. Bertozzi into the "Staudinger ligation," which has been labeled by some authors as "a gift to chemical biology." The three Staudinger reactions mentioned here are fundamental in organic chemistry and numerous publications discussing and debating their mechanisms, as well as reviews on them, are being published as I am writing this Preface. No references to them are listed here because most of them are cited in the publications of this special issue. A search of SciFinder will help those interested in finding recent publications on his work and on the very active current research on the Staudinger reactions.

In a publication from 1920, Staudinger coined the name "Makromoleküle" and in 1922 he generated the correct definition of "macromolecules," stating: "For such colloid particles, in which the molecule is identical with the primary particle, and in which the individual atoms of this colloid molecule are linked together by covalent bonds, we propose for better definition the name macromolecule."

In 1926, he moved to the University of Freiburg to replace his "friendly adviser" Heinrich Otto Wieland, who was to be awarded the Nobel Prize in 1927. In Freiburg, Staudinger focused all his research on macromolecules and stayed until he retired from the University in 1951 and as Director of his Institute in 1956. Staudinger received the first Nobel Prize for the field of macromolecular chemistry in 1953, the same year that Watson and Crick published their *Nature* paper on the double helix of the natural macromolecule DNA. In 1940, Staudinger started the Institute of Macromolecular Chemistry at the University of Freiburg, the first in this field in Europe, which received the name "Hermann Staudinger Haus" in 1981. On 19 April 1999, the American Chemical Society together with the German Chemical Society honored the Staudinger Laboratory in Freiburg as an "International Historic Landmark of Chemistry." Wallace H. Carothers, of the Experimental Station of Du Pont, and Hermann F. Mark, to name just two of many, were also influential in establishing the concept of polymers and macromolecules. However, it was the credibility and the reputation of Hermann Staudinger in the field of traditional organic chemistry who helped to set the future of "macromolecular chemistry" as the newest discipline of organic chemistry. If Hermann Staudinger had not started the field of macromolecular chemistry, he most probably would have received a

Nobel Prize for his work in organic chemistry earlier than he received it for macromolecular chemistry, just like his former student from Karlsruhe and Zürich, Leopold Ruzicka, who received it in 1939.

The photo shows on the left from back to front, Virgil Percec (a former postdoctoral student of Hans-Joachim Cantow in the Hermann Staudinger Haus), Helmut Ringsdorf (the last Ph.D. student of Staudinger), Hans-Joachim Cantow (a follower of Staudinger at the Hermann Staudinger Haus), and Hans-Rudolf Dicke (a former Ph.D. student of Walter Heitz). On the right are Martin Möller (a former Ph.D. and Habilitation student of Cantow) and Hubert Bader (a former Ph.D. student of Helmut Ringsdorf). The photo was taken during the IUPAC Symposium on Macromolecules in Amherst, MA, USA (12–16 July 1982). Four of these scientists have contributed to this special issue.

This special issue contains 38 scientific, personal and historic contributions from the fields of organic chemistry, supramolecular chemistry, macromolecular chemistry, bioorganic chemistry, computation science, biotechnology, and nanotechnology. This broad diversity of interests reflects Hermann Staudinger's diversity of scientific interests. From these many outstanding contributors I would like to mention Professor Urs T. Ruegg, one of Staudinger's grandchildren; Professor Helmut Ringsdorf, the last Ph.D. student of Hermann Staudinger; and Professor Jean-Marie Lehn (Nobel Prize in 1987), the inventor of the fields of "supramolecular chemistry" and "supramolecular polymers," the most recent new disciplines of organic chemistry. Many of these contributions provide not only great science but also fascinating stories about the life of Hermann Staudinger, the scientist who paved the way for the birth of macromolecular chemistry and the development of most significant breakthrough technologies of the twentieth century.

16 September 2013 Virgil Percec
Philadelphia, PA, USA

Contents

A Moment of Reflection: Sixty Years After the Nobel Prize for Hermann Staudinger 1
Helmut Ringsdorf

Hermann Staudinger and Polymer Research in Freiburg 21
Hans-Joachim Cantow and Rolf Mülhaupt

Hermann Staudinger: Aspects of Fame and Memory, Motivation and Impact 39
Gerhard Wegner

Staudinger's Time in Karlsruhe and His Later Relations with Karlsruhe 53
Manfred Wilhelm

Why Was the Macromolecular Hypothesis Such a Big Deal? 61
Ulrich W. Suter

Courageous Questioning of Established Thinking: The Life and Work of Hermann Staudinger 81
Markus Weber and Guido Deussing

Staudinger's Footprints in Japan During His 30-Day Visit in 1957 139
Akihiro Abe

The Years After the Retirement of Hermann Staudinger: Research on Solution Properties in the Physicochemical Group of Walther Burchard 151
Walther Burchard

Dynamers: From Supramolecular Polymers to Adaptive Dynamic Polymers 155
Jean-Marie Lehn

From Synthetic Macromolecules to Biological-Like Complex Systems 173
Virgil Percec

The Wonder of Life in Its Chemical Aspect 199
David A. Tirrell

Crosslinking with Hermann Staudinger 211
Fred Wudl

Another Important 60th Anniversary 217
Nadrian C. Seeman

Coordination-Driven Supramolecular Macromolecules via the Directional Bonding Approach 229
Timothy R. Cook and Peter J. Stang

Bridging Polymer Science and Medicine Through Supramolecular Nanoassemblies 249
Horacio Cabral and Kazunori Kataoka

Stereochemical Studies at the Herman F. Mark Polymer Research Institute 263
Mark M. Green

Mechanically Interlaced and Interlocked Donor–Acceptor Foldamers 271
Carson J. Bruns and J. Fraser Stoddart

Probing Macromolecular and Supramolecular Structure, Dynamics, and Function by Magnetic Resonance 295
Hans Wolfgang Spiess

Twenty-First Century Polymer Science After Staudinger: The Emergence of Dendrimers/Dendritic Polymers as a Fourth Major Architecture and Window to a New Nano-periodic System 321
Donald A. Tomalia

Helical Polymers for Efficient Enantiomer Separation 391
Yoshio Okamoto

Index 415

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A Moment of Reflection: Sixty Years After the Nobel Prize for Hermann Staudinger

Helmut Ringsdorf

Abstract The timing of the award of the Nobel Prize for Hermann Staudinger in 1953 was indeed late, but it could not have been chosen better to honour the already blossoming sciences surrounding synthetic as well as biological macromolecules. A director could not have set the scene more perfectly for a historical event: Staudinger received the Nobel Prize in Chemistry at the same time as Hans Krebs and Fritz A. Lipman were able to accept the awards for Medicine.

Attempts to echo and reflect science cannot mean to look only at precise results of research, cannot mean to establish the factual truth alone. We have to try to look behind the curtain of science, look at the acting scientists and the life they had to live and play in. And we have to try to describe what happened since and even tackle predicting the future – at least a little bit.

Keywords H. Staudinger · Responsibility in science · Intelligence and curiosity · Science and sociopolitics

Contents

1 Hermann Staudinger: A Life Devoted to Science, Squeezed in Between Two World Wars and Stepping Across Scientific, Social and Political Barriers 2
2 A Few Personal Remarks About Early Times with Hermann Staudinger, Magda Staudinger and Hermann F. Mark 3
2.1 On My Way to Freiburg: How to Start to Work With a Nobel Prize Winner: Cherchez la Femme! 3
2.2 Mornings at the Desk of Hermann Staudinger (1956–1958) 4
2.3 A "Historical Meeting" in Freiburg in the Late 1970s and Other Memories: Anecdotes from Leo Gros (Fresenius University of Applied Sciences, Idstein) That Contribute to the Teaching of Polymer Science 7

H. Ringsdorf (✉)
Institute of Organic Chemistry, University Mainz, Duesbergweg 10-14, 55099 Mainz, Germany
e-mail: ringsdor@uni-mainz.de

2.4 Hermann Staudinger and Hermann F. Mark: A Wonderful Example of a Short, Intensive Scientific Competition, but a Lifelong Human Relationship 9
3 An "Old" Essay Written to Recall the 50th Anniversary of Hermann Staudinger's Nobel Prize in 1953 10
3.1 Title and Summary of the 2004 Essay in *Angewandte Chemie* 10
3.2 What Was It All About? An Attempt to "Whet the Appetite" to Read or Even Re-read Parts of an Old Essay 10
3.3 When and Why did Hermann Staudinger Step into Polymer Science? A Matter of Opinion? Sure, Especially After 100 Years! 11
3.4 The Nobel Prize Ceremony in 1953: A Historical Moment for Science 12
3.5 Hermann Staudinger Between Two World Wars and Two Women 14
3.6 Did Hermann Staudinger Ever Cross the Bridge of His Dreams, the Bridge to Biology? 15
4 Facts and Dreams 15
4.1 What is the Best Way to Predict the Future? 16
4.2 Linear Thinking, Paradigm Shifts and Serendipity: Science Is Not a One-Way Street 16
4.3 The Joy of Discovery: On the Way! Just a Few Articles and Reviews in the Field of Polymer Therapeutics 17
5 Conclusion 18
References 18

1 Hermann Staudinger: A Life Devoted to Science, Squeezed in Between Two World Wars and Stepping Across Scientific, Social and Political Barriers

In life and science, it is from time to time interesting and important to stop and take stock, to look back, to look around and ahead. In science, this is done pretty often; reviews are abundant. But describing only facts and results is "relatively easy" and thus often done. In this respect, it is also important not to concentrate only on scientific results and achievements, but to try to look behind the curtains of science. One also has to view and respect the acting personalities behind the published scene and consider the times they had to live and work in. This leads directly to the question of what intelligence, creativity and responsibility have in common.

The 60th anniversary of the Nobel Prize for Hermann Staudinger is a perfect occasion for this. He was a remarkable scientist and a strong – sometime even stubborn – personality. His creativity allowed him to step across scientific borders, to induce paradigm shifts, and his stubbornness helped him to survive all "micellar" attacks against his "macromolecules". Even though it was 100 years ago, he had a remarkable international career. He grew up in the "German Kaiserreich", lived in the Swiss democracy, and had to handle the Nazis and their Third Reich. And last but not least, on his way through life and science, he was squeezed between two world wars (Fig. 1).

Fig. 1 Hermann Staudinger (1881–1965)

2 A Few Personal Remarks About Early Times with Hermann Staudinger, Magda Staudinger and Hermann F. Mark

2.1 On My Way to Freiburg: How to Start to Work With a Nobel Prize Winner: Cherchez la Femme!

It was spring 1954 and I was sitting in a train travelling down the Rhine to Freiburg, on my way to meet Professor Staudinger. I arrived early and had a little bit of time and the only person I knew was Else, a former schoolmate of mine. She was working at the Weinbau-Institut (School for Viniculture) in Freiburg. "For heaven's sake, Helmut", said Else, "don't you know that Staudinger got a Nobel Prize, and for months has been surrounded by 'press and people'. You will never have a chance to meet him!"

Sure, I knew that. But in those days – the World War was not yet so far away – Nobel Prizes did not mean so much for a young student. Having worked several times in the rubber industry between terms, I had become interested in polymer science. The experts in industry, e.g. Dr. Graulich at Bayer Leverkusen, suggested that for a polymer-oriented Dipl. Chem. and Ph.D. thesis, I should go to the "old man's" Institut für Makromolekulare Chemie in Freiburg. The old man was Hermann Staudinger. Here I was! To "help me", Else came up with a peculiar proposal: "If you cannot get close to him, just tell the secretary that you and your parents are friends of Prof. Vogt." He was the boss of Else and director of the Weinbau-Institut, member of the Freiburger Rotary Club, and thus a colleague of Hermann Staudinger. I felt uncomfortable!

A few minutes later – the Institut für Makromolekulare Chemie was close by – I talked to Frau Hasel, Staudinger's secretary, a warm-hearted, delicate lady. She did not give me any hope, but went into his office and came back after quite some time: "Sorry, sorry, Prof. Staudinger thanks for your interest in his macromolecules and apologizes for your long trip". Here one has to know that after one of his last Master students had failed his exams, he had decided not to take students without their Dipl. Chem. certificates. My brain was frozen, my heart reacted and I just followed Else's peculiar advice: "But, Mrs. Hasel, excuse me, my family and I are friends of Prof. Vogt!" A smile appeared on her face! She went back and came out seconds later: "I am glad for you; you have a meeting with Professor Staudinger tomorrow at 10:00 a.m. in his house."

I stayed at the youth hostel in Freiburg overnight and went to Lugostraße early: My heart was beating! After a few – for me exciting – minutes and talking with H. Staudinger about my industrial macromolecular experience, about philosophy and the end of the World War, I was accepted! On my way out *it* happened! With a friendly smile on his face, Hermann Staudinger asked: "By the way, how is your relation with my old friend Prof. Vogt?" What could I do? My only chance was to be completely honest and I thus told Professor Staudinger my "Else-story". Seriously listening, his face looked like a theatre scene: colour changes, scene variations from irritation to anger and fury – and back to laughter: "You are a lucky, successful boy and I am looking forward to having you in my lab. My "Rotary Club colleague", the Weinbaudirektor, is a person I even dislike. But I have an old friend, Prof. Vogt, a neurosurgeon. For him I would do everything. You see how lucky you are? See you soon and have a nice trip back!" Thus, I became the very last student of Hermann Staudinger.

2.2 Mornings at the Desk of Hermann Staudinger (1956–1958)

After his retirement (spring 1956) Hermann Staudinger asked two of his last Dipl. Chem. students to continue working with him: Gunter Welzel became involved in Staudinger's journal *Die Makromolekulare Chemie*, and I became engaged in his *Arbeitserinnerungen* [1, 2], and his last talks (in Japan and the USA; by the way, the slides of his last four talks are still in my office here in Mainz). In addition, both of us were working for our Ph.D.s in the research group of Professor Elfriede Husemann (successor of Staudinger). In those days, Hermann Staudinger was completely free of any official duties, which was probably a very new and unexpected experience for him. Our duty was to work with him for two mornings a week in the library of his house in Freiburg (Lugostraße). What a time for two young Ph.D. students! Working with him was only one part of the game; listening to his stories from yesterday, and the day before yesterday was an unbelievable experience and a delight for us in those days.

Fig. 2 Magda Staudinger and her husband (1956)

But! There was a but: Dr. Magda Staudinger, his second wife! She was a highly cultivated and a highly educated personality; maybe a little bit on the formal side, on the cooler side of life. She was the daughter of the ambassador of Litauen (Lithuania) in Germany. Already multilingual as a child, she studied biology, got her Ph.D., and after her marriage she became an emotional and patriotic fighter for her husband's "German macromolecules". Magda Staudinger knew pretty well that her husband enjoyed the mornings with the two young Ph.D. students and she was glad about this. But, she also was aware of the fact that during these hours he also delighted in talking about "his old days". This was a little bit too much for her! In her opinion, a Ph.D. student had to work with her husband, and there was no time to listen to old and very often pretty personal stories of a Nobel Prize winner (Fig. 2).

Here is what one could call a pretty honest protocol of one of my morning working sessions with Hermann Staudinger in those days (1956):

09:00 h	A friendly but short welcome was followed by around 30–40 min discussion about my little changes on the chapter of the *Arbeitserinnerungen* discussed a day before (formulae, references, new results etc.).
10:00 h	By this time, Staudinger had already started to talk about his old days, different places, colleagues, and very personal impressions of these periods. A wonderful session of science history for a young Ph.D. student! From time to time he stopped talking, listened, continued talking – and then it would happen: Magda Staudinger opened the other door of their big private library and there was silence between him and me from this very moment on! She walked across the room and directed a short serious look at us, a look full of opinions! He tried to look as relaxed and comfortable as possible; I tried to be neutral. She went to the bookshelf, picked out a book – probably any book – looked at her husband again, and left the room.

(continued)

Fig. 3 Meeting with Magda Staudinger in Freiburg after a ski-hut seminar (1992) of guests and coworkers of the Mainz research group

10:05 h With the "click" of the door, Hermann Staudinger started talking again, often directly finishing the sentence he had to interrupt when she came in. I think I do not have to describe the "reverse process" of Magda Staudinger's soft attempt to "educate" her husband: click, silence, looks, book back, click, and continuation of our cooperation.

These short, quiet periods of my working time with Hermann Staudinger had a special flavour. They happened sometimes two to three times a morning. Somehow, we both came to like these minutes of quietness, minutes of tension! He never made any remarks about them. But, we slowly learned to enjoy these emotional calm minutes of silence with a smile on our faces. What a time for me!

To avoid any misunderstanding: My relation with Magda Staudinger became better and better over the years. It was a friendly, open-minded, respectful interaction, but always with a certain distance. After Hermann Staudinger's death (1965), we visited her often in the spring time during the "Freiburg Meeting" with coworkers and guests from our Mainzer group (Fig. 3).

During the following years, Magda Staudinger stayed several times in our house in Gonsenheim. In those days she was on her way to the United Nations in New York, working for Unesco: For several years she was the German Representative for the Unesco Biosphere Programme. A perfect place for a multilingual, highly educated Ph.D. in biology; a perfect function for a personality like Magda Staudinger. She was very diplomatic, had research experience in biology and polymer science, and had a lot of international contacts.

This was a successful self-determined time for Magda Staudinger. Her years at Unesco were – in my opinion – a second important, substantial period of Magda Staudinger's life. She was successful, highly respected and unconstrained by her old patriotic fights for her husband's "German macromolecules".

2.3 *A "Historical Meeting" in Freiburg in the Late 1970s and Other Memories: Anecdotes from Leo Gros (Fresenius University of Applied Sciences, Idstein) That Contribute to the Teaching of Polymer Science*

As a Ph.D. student in Helmut Ringsdorf's research group in Mainz, I enjoyed the yearly seminars in a ski hut near the Schauinsland Mountain, not far from Freiburg. These seminars preceded the Freiburger Kolloquium and were meant to prepare the research group for this highlight in German polymer research communication. Each of us had to prepare short presentations on the topic of one of the scheduled presentations or posters, which were then discussed. Walks in the winter landscape (the Kolloquium takes place end of February) and evenings with wine tastings and music made by members of the group were attractive parts of the event. Moreover, Helmut Ringsdorf invited guests who spoke to and discussed with us. One of them was Hans Sachsse (the inventor of a process to produce acetylene, named after him), a chemist-philosopher who enriched our discussions with his interdisciplinary comments.

I keep especially fond memories of Herman Mark's appearance in such a seminar, probably at the end of the 1970s. Given all the tensions that had existed between Herman Mark and Hermann Staudinger, it was quite an achievement to arrange a meeting of Herman Mark and Magda Staudinger one morning in the ski hut: What a happening, what an adventure! Mark mastered it by remaining the gentleman he had always been. They both reported on "their" old days of polymer science, Herman Mark in his light, always positive mentality, Magda Staudinger a little bit more emotional, intensively defending her husband's – unattacked – macromolecules. Only from time to time did our discussion leader, Hans Sachsse have to step in, in his philosophical smiling way. What a moment, a historical, and personally for us young students even a historic one. But the most emotional moment – close, very close to happening – was when Herman Mark laughing and with open arms approached Magda Staudinger at the end in an attempt to embrace her. It did not happen! In the very last moment Magda Staudinger shrank back. . .. and all this in a cheerful, relaxed atmosphere.

In those days, I had the honour to pick Herman Mark up at Freiburg main station with my "VW-Beetle" and drive him to his hotel, the ski hut and back. During these car rides and the long evenings, I learnt lots about his involvement in the development of polymer science. An anecdote he told me was, if I remember correctly, related to his presentation at the Gesellschaft Deutscher Naturforscher in Düsseldorf 1926. This was the "hot period" of Hermann Staudinger's discussions with the "micelle and aggregation mafia". Mark was in these days, with his X-ray investigations of cellulose, basically already on Staudinger's side. In his talk he had not excluded the existence of what we now call macromolecules from the standpoint of crystallography. A renowned organic chemist told him: "You are brilliant, young man, as a crystallographer. Imagine you were a botanist knowing all plants in Europe. After an excursion to Africa you come back and still being excited about

your trip you mention that you saw an elephant 20 m high and 50 m long. Who would believe you? Why don't you stick to your trade?" This "argument" is topped by the one of another renowned chemist who attended a lecture of Hermann Staudinger in Munich 1935. He sat right behind the student Wilhelm Fresenius (who later became the rector of my university) who heard him saying: "What is this guy after with his sausage molecules?" Coming back to Herman Mark: There are a few more joint moments to remember and they all shed light on his remarkable and unusually open-minded personality.

I am sure that it was not only me to whom he told the story how he, as a man with a Jewish family background, managed to bring part of his money to Canada when he had to leave Europe. Yet, I tell students to back up my opinion that it is always enriching to study chemistry. Teaching chemistry is about matter, structure–property relationships and also about the economic value of scientific achievements. "In 1938, he began preparing to leave Austria by clandestinely buying platinum wire, which he bent into coat hangers while his wife knitted covers so that the hangers could be taken out of the country. Mark's son Hans estimates that the value of the platinum was roughly $50,000, a lot of money in the 1930s" (http://www.acs.org/content/dam/acsorg/education/whatischemistry/landmarks/polymerresearchinstitute/polmyer-research-institute-at-nyu-poly-historical-resource.pdf. Accessed 26 August 2013).

Another emotional moment with Hermann Mark: In 1979 he attended the IUPAC symposium in Mainz. After the meeting, I accompanied him to Mainz train station. While waiting for the train, he had a tea, some toast and a baked camembert cheese with lingonberry marmalade. We chatted about the symposium and his next trips. Hermann Mark was not in good mood, he looked sorrowful. The next day, I learnt from Helmut Ringsdorf that Mark had been sitting alone and looking sadly in the conference hall, sipping tea, when Ringsdorf approached him and asked: "Geheimrat, why are you sitting here so sad and lost?" He answered: "Helmut, my son is about to die of cancer, back home – and I am here. What could I do? I am here only to survive. Sitting at his bed, being unable to talk to him, I felt my life running out. Please, sit down and let's have a cup of tea together." Coming home, Herman Mark could still be with his son for several days.

In 1981 – I had just finished my Ph.D. – I had the chance to visit the famous "Brooklyn Poly" in connection with a meeting in Atlanta. Hermann Mark and Herbert Morawetz were sitting in their offices, crammed full with books, molecular models, journals and laboratory equipment – a working place. We shared a tea and some burnt toast. Herman Mark's equanimity and his constant friendly open-mindedness towards everybody, including youngsters like me, impressed and touched me. I can never teach my students the Mark–Houwink equation without mentioning who he was, what he had to live through and how he mastered this. A good source of Hermann Mark's own view of polymer history is one of his papers "Aus den frühen Tagen der makromolekularen Chemie" [3].

As a teacher of polymer chemistry at Hochschule Fresenius since 1987, I always included a lecture devoted to the history of polymer chemistry [4]. I tried to present the conflicting theories of macromolecules and micelles and the arguments of their

protagonists. Staudinger's conclusive experiment, the hydrogenation of polystyrene [5], is a key element in teaching polymers to beginners. I teach in an institution with a long record and a legacy of analytical chemistry (http://www.gdch.de/gdch/historische-staetten-der-chemie.html. Accessed 26 August 2013). Carl Remigius Fresenius and Hermann Staudinger shared the conviction that correct characterization of materials is the basis for all research in chemistry (see Sect. 3.3).

With stories and anecdotes about scientists in their historical periods, a teacher can add personal flavour to the lessons in his field of science. In this respect, Hermann Staudinger and Hermann F. Mark are wonderful examples: Not only their essential factual contributions, but also their enthusiasm, zeal, tenacity, conflicts and devotion in their times shaped our modern understanding of macromolecules.

2.4 Hermann Staudinger and Hermann F. Mark: A Wonderful Example of a Short, Intensive Scientific Competition, but a Lifelong Human Relationship

After my time in Freiburg (1955–1959), I stayed for nearly 3 years (1960–1962) as research associate at Brooklyn Poly in New York. This was a wonderful time for me to come to know both Staudinger and Mark, not only as scientists.

Sure, there was polymer technology and polymer science in the USA before Hermann F. Mark. One just has to look at W. H. Carothers, the great American pioneer in polymer science and technology, active at the Experimental Station in Dupont, Wilmington in the early 1930s. After Mark was kicked out of Austria by the Nazis in the 1930s, he started at the end of the 1940s at Brooklyn Poly (New York) to pull the American polymer community together. It was nobody less than Paul Flory who stated this during a seminar in Brooklyn in about 1979 – I had the good fortune to be part of it. After having been introduced warm heartedly and with Austrian charm by Mark, Flory repeated smilingly " . . . sure, we got another award for our research in California but the man who unified polymer science in our country was Hermann Mark. I think we can respect him as the "Father of polymer science in America". Not only for me was this a distinguished remark from somebody who normally had the tendency to be a little bit more on the aggressive side.

Hermann Mark's lifelong relationship with Hermann Staudinger was always open and positive. His sympathy and esteem for him cannot be better expressed than in his "Foreword" to the translation of Staudinger's *Arbeitserinnerungen* (entitled *From organic chemistry to macromolecules. a scientific autobiography based on my original papers* [2]) During my time at Brooklyn Poly (1960–1962) I often heard him talking about the old days, the 1920s and his contact with Staudinger in both conflict-rich and "peaceful" times. Remembering all this, it is a pleasure to cite from Mark's "Foreword" [6]:

> . . .. In the clarified atmosphere of hindsight it becomes evident that Staudinger's impact on his time was caused by a triple role which he kept on playing with never failing enthusiasm for more than forty years; as explorer, teacher, and preacher. Guided by true scientific

curiosity for the unknown, Staudinger selected as the work of his life in the early 1920s a field which, at that time, was hardly considered to be a worthy goal for an organic chemist of his reputation – the study of the natural organic substances of high molecular weight. Until then, Staudinger had cultivated typical problems of classical organic chemistry with its well-defined substances which could be characterized by such methods as melting and boiling point, freezing point depression, and boiling point elevation. A stimulating monograph on "The Chemistry of the Ketenes" – published 1912 and written during his time at the University Strasbourg – was the fruit of these efforts, a book which seemed to foreshadow Staudinger's career as that of a synthetic organic chemist worthy of such great predecessors as Bayer, Fischer, or Gattermann and of such distinguished contemporaries as Schlenk and Wilstatter . . ..

. . .. However, he chose the more romantic, though less comfortable, life of an invader of unknown areas, where every step would have to be a fight for new concepts, new methods and new interpretations. . . ..Through work Staudinger ranks first in having introduced the new branch of macromolecular chemistry with the largest number of facts and figures both by observation and by measurement. . . ..

. . .. There exist numerous, unforgettable occasions in the 1920s and 1930s when history of chemistry was made in the eloquent clashes between Staudinger and the representatives of the "aggregation theory of the small units." Holding firm to his main ideas and introducing modifications wherever the facts demanded them, Staudinger emerged from these battles as the grand old man of macromolecular chemistry, the Nobel Prize winner. . . ..

3 An "Old" Essay Written to Recall the 50th Anniversary of Hermann Staudinger's Nobel Prize in 1953

3.1 Title and Summary of the 2004 Essay in Angewandte Chemie

Hermann Staudinger and the Future of Polymer Research: Jubilees – Beloved Occasions for Cultural Piety [7]

Chemistry was his life, but Hermann Staudinger's dream belonged to biology and to the unity of chemistry and biology. That is the central theme of this essay, which, on the occasion of the 50th anniversary of the award of the Nobel Prize to Hermann Staudinger, discusses the significance of Staudinger's discoveries for the biosciences, not only retrospectively, but deliberately also prospectively. General questions of science ethics and the interplay of research, politics and responsibility are also considered.

3.2 What Was It All About? An Attempt to "Whet the Appetite" to Read or Even Re-read Parts of an Old Essay

The essay in *Angewandte Chemie* 2004 [7] ends with a citation from Roald Hofmann: "Most of us are also University teachers and responsible! We have to do better than the usual traditional presentation of technical successes. We have to talk about the scientist, the historical figure and person. And we must get involved, where our competence is required" [7, p. 1070; 8]. This citation underlines that this

essay about Hermann Staudinger was not written at all to stress and summarize his research areas and scientific successes. The paper was written to look behind the curtain of science, to look at the acting personalities, functioning in very different historical periods. For many of us being able to do research and teach in more peaceful times, we have sometimes to be reminded of the tense backdrop against which everyone carried out research and taught in the 1920s and 1930s and not forget two world wars: science as an alliance of scientific objectivity and direct involvement in socio-political responsibilities. These were the critical time periods that scientists like Staudinger and Haber had to work and to live in.

But all this happened about 100 years ago! Sure, but aren't we writing a special issue reporting about Staudinger's scientific results and their consequences for modern science? Isn't there as much to learn from the way these "historical personalities" handled science and life in conflicting scientific and socio-political situations? If I had been asked to re-write the *Angewandte Chemie* 2004 essay, I probably would only have changed a few words and I may have added a subtitle such as "Hermann Staudinger between two world wars and between two women" (see Sect. 3.5).

3.3 When and Why did Hermann Staudinger Step into Polymer Science? A Matter of Opinion? Sure, Especially After 100 Years!

To predict the future is mostly like reading tea leaves. And to do this even for past events may in addition be snow from yesterday. Nevertheless, it is from time to time fun to look back and read and think about "old stories" – especially if one can cite "the master" as witness. There is a pretty logical road from Hermann Staudinger's fascination for synthetically oriented research to his beloved macromolecules: analytical chemistry as the basic concept to know what you have in your hands.

We all know that the "hot phase" of his fight for macromolecules started with three papers in 1920, 1922 and 1924: "Über Polymerisation" [9], "Über die Hydrierung des Kautschuks" [10] (with the first definition of macromolecules as primary valence chain systems), and "Über die Konstitution des Kautschuks" [11]. This was many years after his interest in terpenoid hydrocarbons had pulled him into the synthesis of isoprene. The pyrolysis of these systems yielded isoprene [12]. Because isoprene was obtainable by this procedure on an industrial scale, a patent was applied for in 1910 [13] and taken over by BASF (Ludwigshafen). They reported in 1914 on the industrial polymerization of isoprene into rubber [14]. In praise of the purity of his isoprene, Staudinger wrote in the paper with Klever [12]. ". . .. it contains only small amounts of trimethyl-ethylene as was determined through its conversion into rubber". Polymerization as proof of purity! How this was determined he failed to mention in his article. The first Ph.D. thesis in Staudinger's group about polymerization [15] is mentioned in 1913 (Karlsruhe) although still together with the auto-oxidation of olefins – one of his main topics in

Karlsruhe and at the beginning in Zürich. Nevertheless, it was in these days that Hermann Staudinger started to complain that "Kautschuk" from BASF, as well as his own "polyisoprene", were not identical with natural rubber.

In Zürich, Staudinger taught analytical chemistry and compound characterization as intensively as organic chemistry. As a consequence of this, he published in 1923 the first edition of his long-lasting series of books *Anleitung zur organischen qualitativen Analyse* [16]. The book was translated into Japanese, French, English and Italian. Hermann Staudinger had really "cultivated" the scientific necessity to talk about well-defined compounds only. And where could he "find" badly characterized synthetic compounds? There was nothing less analyzed and less understood than these already technological important polymeric and/or micellar materials. Sure, he certainly did not just look around to find "Schmieren-compounds". But due to his technologically important isoprene synthesis, he was pulled into this game – and could not escape anymore!

Staudinger "described this" in his autobiography *From organic chemistry to macromolecules* [2, p. 98]. He cites one of his talks (1950) where he tried to convince his audience that the unity of "believe and proof" is most important in science:

> In 1950, when I gave a lecture to cellulose chemists, many participants who had published works on the micellar structure of cellulose before assured me that they now believed my theory. I said that it was not a matter of belief and asked them what arguments had convinced them. The answers were often unsatisfactory. Because of this, I started my lecture in the following way:
>
> If a student is asked about the formula of indigo during an examination and replies that he believes that A. von Baeyer's formula is the right one, this would not be enough to pass the examination. He surely would be asked how the formula was proved. Similarly, it is necessary to know exactly the proofs for the macromolecular structure of cellulose and many other natural products, as well as those of synthetic products, if one intends to work with them on the basis of this macromolecular concept.

Even during the visit of Hermann and Magda Staudinger to Japan in April 1957 the characterization and analytical proof of macromolecules played a role when His Majesty the Emperor of Japan asked: "Professor Staudinger, are macromolecules merely ideas to help explain many phenomena, or is there strict evidence for their existence, and if so, by which methods?" The question and Staudinger's answer are cited in his *Arbeitserinnerungen* [2, p. 104]: "It is just this experimental demonstration of the existence of macromolecules which forms the essential part of my work in the field of macromolecular science".

3.4 The Nobel Prize Ceremony in 1953: A Historical Moment for Science

When at the beginning of the 1930s Staudinger's political problems in Germany started, Hans Krebs was one of his colleagues in the Faculty of Medicine. In those days, he was already internationally accepted in an area that later become known as biochemistry (urea cycle, protein–enzyme interaction). The lives and research paths of the biologically interested polymer scientist Hermann Staudinger and the

medical doctor Hans Krebs could have crossed long before their joint honour in1953 in Stockholm – perhaps they even did. The young biomedical genius, Hans Krebs, worked from 1931 on as ward physician in the University Clinic Freiburg. That did not last long. Then came the "turning point", which Lothar Jaenicke described so bitterly yet truthfully [17]:

> In 1932 H. A. Krebs – Freiburg – received the *Venia docendi* and a considerable number of estimable offers for his advancement. Eight weeks later he was ordered to stay away: The Nazis had come to power and with them Germanity had broken out virulently. The highly praised lecturer became a Jew and persona non grata overnight. His old, mildly resistant teacher von Möllendorf was replaced as Rector Magnificus by the mystical opportunist Heidegger as Führerrektor, who existentially provided the philosophical arguments for what came to pass: The students drifted brainlessly but dangerously.

Hans Krebs left Germany in June 1933, went to Cambridge (Great Britain) and continued to work on his "Krebs cycle", the citric acid cycle. In 1937 he became Professor for Physiology at the University of Sheffield and later in Oxford.

As far as the 1953 selection of the Nobel Prize winners for science is concerned, one could look at this event as a perfect stage management of the Nobel Committee. The Nobel Prize for Medicine and Physiology went to Hans Krebs for the "Citric acid cycle and enzymatic reactions", to Fritz Lipmann for "Coenzyme A", and the Nobel Prize for Chemistry to Hermann Staudinger [7, p. 1064]. In addition, Watson and Crick had just rang in molecular biology definitely with their *Nature* article on their DNA model [18].

Polymer science and biomedicine had developed in parallel! What a span of genius and development from the achievements of Hermann Staudinger and his dreams on the biology of life up to this great moment of science in 1953. I do not believe that Hermann Staudinger was aware of Watson and Crick's initial work on the double-helix structure of DNA published in the 1953 April issue of *Nature* [18]. In any case, he ended his Nobel Lecture with precisely what he could have read in that *Nature* publication and what he had dreamed of all his life with farsightedness and hope: "In the light of this new knowledge of macromolecular chemistry the wonder of life reveals itself from its chemical side in the unending diversity and masterful molecular architectonics of living materials" [19 and 7, p. 1067].

It is thus a delight to be able to see such an event in the history of science portrayed in figures paralleled in two journals: *Angewandte Chemie* [7, therein Fig. 3, p. 1067; https://www.gdch.de/gdch/historische-staetten-der-chemie.html] and *Chemie in Unserer Zeit*, 2008 [20, therein Fig. 5, p. 350]. The photos show the Nobel Prize winners in one case comparing their watches before the ceremony [7] and then afterwards with the documents in their hands [20].

It is a pity that the brilliant essay of Klaus Roth about Hans Krebs [20] is only available in German: "Dann machte ich mich alleine auf den Weg, um den Elf-Uhr-Zug zu erreichen" ("Then I started off alone, to reach the 11 o'clock train"). This review describes in many details the situation of Krebs, Staudinger and especially Heidegger at the University of Freiburg in 1933, right from the beginning on.

3.5 Hermann Staudinger Between Two World Wars and Two Women

Hermann Staudinger's attitude towards Germany was visibly different during the First and Second World Wars. During her time in Basel, I had the good fortune to talk several times to his daughter, Mrs. Ruegg, about the "two lives" of her father.

Before and during the First World War, Hermann Staudinger taught chemistry at the ETH-Zürich. In those days, he was married to Mina Mathilde (neé Förster) and they had four children. Mina Staudinger was a socio-politically oriented personality. She stood rigorously on her husband's side in his active conflicts with the German Generality, his letters against the war, and his struggle with Fritz Haber: "Science directed and disturbed by two world wars" [7, pp. 1067 and 1069].

In 1926 Hermann Staudinger – divorced in the meantime – went to the University of Freiburg. This was in the very short period of the first German Democracy. Nevertheless, it was in no way a "non-political" transition. But, what happened when at the very beginning of the "Third Reich" (1933) the Nazi dictatorship immediately Aryanized the universities and then "generously" supported each branch of science that accepted its racism and war plans? And what happened when in these days the famous German philosopher Martin Heidegger (existential philosophy), a mystical Nazi opportunist and "Führungsrektor" at the University of Freiburg, planned to kick Hermann Staudinger out of office? Did the importance of rubber technology and polymer technology for the war plans of Hitler and his generals, or the diplomatic contacts of his second wife Magda Staudinger (neé Woit), save him? She was a highly cultivated personality, daughter of the Ambassador of Lithuania in Germany, Ph.D. in Biology and pretty patriotic [7, therein ref. 65, pp. 1066 and 1075].

Hermann Staudinger was no friend of the Nazi regime, but he was not an opponent either. His attitude in the Third Reich was for the sake of his research and to retain his research group. Thus, to be able to travel to conferences abroad, he made offers to the university management to represent German science abroad, to defend his "German macromolecules". If Hermann Staudinger had held to his pacifistic stance during the First World War to only the slightest extent [7, p. 1070], he would have lost office and could not have continued to work in the polymer field. He might even have been forced to leave the country like Hans Krebs [17, 20].

What do we nowadays really know about the inhumanity of such political pressures? Can we imagine the intensity of such strict political control and the lack of personal freedom? A profound tragedy and entanglement of science and humanity in the conflicting field of society and politics.

3.6 Did Hermann Staudinger Ever Cross the Bridge of His Dreams, the Bridge to Biology?

"In the 1930s polymer science exploded in many laboratories around the world, the age of plastics had arrived. Hermann Staudinger looked upon it with joy and pride. However, he personally could not give up the fight for his macromolecules, supported rigorously with Baltic patriotism by his second wife Magda (neé Woit). . .." [7, p. 1066]. The already flourishing protein chemistry in the biomedical field and the detailed knowledge of one of his former students, Rudolf Signer, would have been an immensely important bridge to the biosciences and to molecular biology: A bridge that Hermann Staudinger never had the good fortune to cross. "Thus his vision and desire for the union of his chemistry and his biology remained for him a dream. Towards the end he was so trapped in the Don Quixotic battle for his synthetic macromolecules that he could no longer recognize the extent to which the biosciences and the blossoming field of molecular biology had long taken on board his macromolecules and used his analytical methods almost routinely as a working basis. This is an example of the 'human' nature of science, an example whereby it is difficult to know what one should admire more: the creativity of the scientist or the constancy of his adherence to his original idea" [7, p. 1066].

At the end – and just out of curiosity – there is a pretty interesting question for science and science history: What do you know about the really essential role of Rudolf Signer (Bern) – once a student of Staudinger – for the Nobel Prize of Watson and Crick? It was nobody less than Maurice Wilkins who talked about this in his Nobel lecture of December 1962 [7, therein ref. 20a].

4 Facts and Dreams

At the end of these "Reflections" about Hermann Staudinger – chemistry was his life and the biology was his dream – I have to apologize for my "yesterday remarks" about synthetic polymers in the biomedical field as published in the "old" *Angewandte Chemie* 2004 paper: Chapter 5.1. "From synthetic macromolecules to biological structures" and Chapter 5.2. "Polymers as pharmacologically active compounds. the pharmaceuticals of the future?" [7, p. 1068]. I know that in the meantime the word "nanomedicine" has become popularized and many new approaches in the drug delivery field are on the way. As early as 2003 with her article "The dawning era of polymer therapeutics" Ruth Duncan opened the curtain [21 and 7, p. 1069 and 7, therein ref. 48]. In the meantime, her essay (with over 1,800 citations) has "highlighted research at the interface of polymer chemistry and biomedical science that continues to lead to advances in the application of nanotechnology in medicine" [22].

Nevertheless the gap between synthetic polymers and biomedicine, and especially the attempt to develop modern drugs, is not yet closed. In contrast to this, the road to polymer technology and to the development of essential materials seems to be much easier. One of the reasons might be that in our universities we still teach chemistry

and medicine out of nearly "separate boxes", with not enough overlap and certainly not with the same superimposed intensity as for chemistry and physics. Is the different teaching culture the only reason?

4.1 What is the Best Way to Predict the Future?

Richard Feynman (1918–1988), Nobel Prize in Physics (1965), banjo player and "expert" in opening safes during his time in Los Alamos during the war, was one of the great, creative scientists of the last century. Like Hermann Staudinger, he liked to step across scientific borders and like him, he also had to work in difficult times. When asked, "what is the best way to predict the future, he smiled: "The best way to predict the future is to invent it". Logic and linear thinking is helpful but in addition we need luck – and we have to catch it if it walks by.

4.2 Linear Thinking, Paradigm Shifts and Serendipity: Science Is Not a One-Way Street

It seems to be indeed easier to develop synthetic polymers linearly into essential materials than to guide them into pharmacy and pharmacology. The discovery of a new, active drug is already a difficult task, and to "design a drug" is the next step in sophistication. In 1984, Georges Jolles, (Rhône-Poulenc Santé, Paris) published a book based on the proceedings of the conference "Drug design: facts or fantasy" [23]. In the "Introduction" he states:

> The discovery of a new drug is indeed an extremely difficult task. Maybe it was imprudent of us to adopt this shining expression 'Drug Design' from people who are really designers, who design aeroplanes, cars, equipment: They know exactly what they are aiming for; they are aware of most of the parameters involved in their project; they can calculate. The crucial difference in drug research is that we do not dominate all parameters as far as we have even identified them and, therefore, work under a serious handicap.

The expertise in materials science cannot be directly transferred into biomedical materials, not even to talk about in vivo active drugs. The extremely high number and the physiological complexity of cell types and tissue classes hardly allow a logical, linear development: All we know is that we know exactly what we don't know. This is certainly the case for most serious diseases, e.g. AIDs, Alzheimer, multiresistant microbes and cancer. It is thus not amazing that from about 20 new drugs per year, on the average only one or two lead to a real advancement for patients. Too often and too long the pharmaceutical industry has mainly looked for drugs that could be developed fast (in 2 to 3 years) and could be planned linearly: a perfect platform for the popular "me-too compounds", which are just variations of successful drugs (see "Editorial: A decade in drug discovery" [22]).

In this respect, it is important and really enjoyable to see that industry is again showing growing interest in long-term research and in nanomedicine, with the aim

of progressing pre-clinical drug candidates to market (http://www.starpharma.com/news/157).

In research and teaching we have to realize that progress in science does not only happen via linear planned research or through the continuous collection of facts. In addition we need "revolutionary" processes, which induce the replacement of existing models of explanation (paradigms) by new concepts: A paradigm shift! It was Thomas S. Kuhn who first discussed this in his book *The structure of scientific revolutions* [24]. When talking about the importance of unexpected results, the notion "serendipity" is often used, especially in the medical field. This is based on an old oriental fairy tale of the three princes – maybe young scientists – of Serendip (Sri Lanka): On their journeys, with luck and courage they always discover new, unexpected things.

4.3 *The Joy of Discovery: On the Way! Just a Few Articles and Reviews in the Field of Polymer Therapeutics*

To mark the tenth anniversary of *Nature Reviews Drug Discovery*, the journal brought together analyses data and trends in the field [22]; some of them are cited here:

- Patent watch: Key patent-related events of the past 10 years [25]
- How were new medicines discovered? [26]
- Membrane transporters in drug development [27]
- Knocking down barriers in siRNA delivery [28]
- Angiogenesis: an organizing principle for drug discovery [29]
- Recent advances with liposomes as pharmaceutical carrier [30]

In the following list are some more papers from different "research desks":

- Polymeric micelles [31, 32]
- Enhanced permeability and retention effect [33, 34]
- Endocytosis and intracellular trafficking [35, 36]
- Polymer therapeutics: the end of the beginning [37]
- Nanomedicine(s) under the microscope, history and status (containing about 500 key references) [38]
- Preclinical safety and regularity implication for design and development of polymer therapeutics [39]
- The physics of cancer [40]
- Liposomal antitumor vaccines [41]
- Polymer-based antitumour vaccines [42]
- Natural Product and Material Chemistries – separated forever? [43]

5 Conclusion

By the way, one should not too often ask elderly scientists to write "Reflections".

A picture that was supposed to illustrate this statement in a humorous way could unfortunately not be printed: not because it was too sexy, but only because I could not resolve the intricate question of the printing rights.

Do we scientists really always know where our good ideas are coming from, or what our source of inspiration is?

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Hermann Staudinger and Polymer Research in Freiburg

Hans-Joachim Cantow and Rolf Mülhaupt

Abstract Between 1926 and 1956, Hermann Staudinger carried out his groundbreaking research on macromolecular chemistry at the University of Freiburg. He recognized that biopolymers and synthetic polymers are formed according to the same blueprint. Fighting vigorously against his numerous opponents, he established his concept of macromolecules. Since the pioneering days, his bioinspired molecular design of multifunctional polymeric materials has stimulated remarkable progress in materials science, biosciences, and engineering, accompanied by an extraordinary growth in polymer production. In 1940, Staudinger founded the Institute of Macromolecular Chemistry as the first European center for interdisciplinary polymer research. In 1999, his laboratory was honored as an International Historic Chemical Landmark dedicated to the foundation of polymer sciences. Today, macromolecular (bio)systems engineering, inspired by Staudinger's visions, plays a prominent role in sustainable development.

Keywords Bioinspired materials · Hermann Staudinger · History · International Historic Chemical Landmark · Macromolecule · Polymer · Polymer sciences

Contents

1 Staudinger's Laboratory as International Historic Chemical Landmark 22
2 Staudinger: Pioneer of Bioinspired Chemical Research 24
3 Staudinger's Viscosity Law 25
4 Imaging of Single Macromolecules 26
5 Hermann Staudinger and the Third Reich 27

H.-J. Cantow and R. Mülhaupt (✉)
Institute of Macromolecular Chemistry, Freiburg Materials Research Center, FMF, and Freiburg Center of Interactive Materials and Bioinspired Technologies, FIT, of the University Freiburg, Stefan-Meier-Strasse 31, 79104 Freiburg, Germany
e-mail: rolfmuelhaupt@web.de

6 Staudinger and His Institute of Macromolecular Chemistry 28
7 Staudinger's Visions Toward (Bio)System Integration 31
8 The Days After Hermann Staudinger in Freiburg 32
References 36

1 Staudinger's Laboratory as International Historic Chemical Landmark

On April 19, 1999 in Freiburg, the American Chemical Society and the German Gesellschaft Deutscher Chemiker jointly honored Hermann Staudinger's laboratory at the Albert-Ludwigs University of Freiburg as an International Historic Chemical Landmark dedicated to the foundation of polymer sciences by the Nobel laureate Hermann Staudinger (1881–1965). The goal of the landmark program of the American Chemical Society is to enhance the public's recognition and appreciation of the seminal achievements in the history of chemical sciences and chemical engineering with deep impact on society and modern life. Today, the landmark plaque (see Fig. 1), donated by the American Chemical Society, is on display at the entrance of the building "Hermann Staudinger Haus" in Stefan-Meier-Strasse 31, hosting the Institute for Macromolecular Chemistry. The institute was founded by Hermann Staudinger in 1940 as the first European polymer research center. The English translation reads:

> International Historic Chemical Landmark, Foundation of Polymer Sciences, Albert-Ludwigs-University Freiburg, State of Baden-Württemberg, 1926–1956. This building is named after Hermann Staudinger, who, between 1926 and 1956, carried out his path-breaking research on macromolecular chemistry in Freiburg. His theories on the polymer structure of fibers and plastics and his later research on biological macromolecules formed the basis for countless modern developments in the fields of materials science and bio-sciences and supported the rapid growth of the plastics industry. For his work in the field of polymers, Staudinger was awarded the Nobel Prize for chemistry in 1953 [1].

Once again, this late honor acknowledged Staudinger's remarkable courage during the 1920s, when he decided to leave the highly prestigious and safe harbor of classical organic chemistry, pushing his revolutionary but still unproven concept of macromolecules against the established doctrines of colloid chemistry and against the harsh opposition of his colleagues. Although in 1920 no experimental proof was at hand, he had postulated the existence of "high polymers," which he renamed in 1922 as "makromolekel" and "macromolecules." As first indirect experimental evidence for covalent bond formation in the polyisoprene backbone, Hermann Staudinger and Jakob Fritschi at ETH Zürich applied catalytic hydrogenation of polyisoprene. After complete hydrogenation, a highly viscous solution was retained, thus failing to produce distillable small molecules as expected for supramolecular assemblies of cyclic isoprene dimers [2]. Among his strong opponents, crystallographers favored colloidal assemblies as they were firmly convinced that large crystalline molecules could not exist because such large crystalline

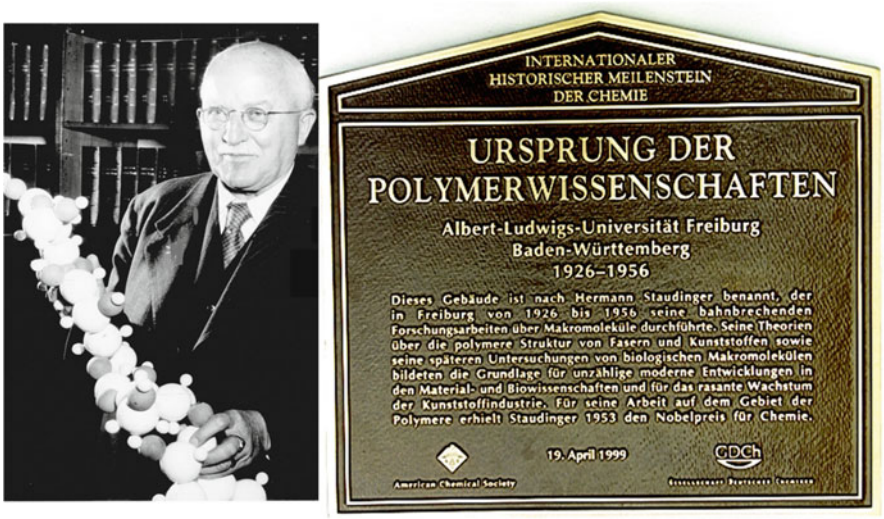

Fig. 1 *Left*: Hermann Staudinger showing his favorite rigid rod cellulose molecule (source: University Library of the University of Freiburg). *Right*: The International Historic Chemical Landmark plaque of the American Chemical Society displayed at the entrance of the Institute of Macromolecular Chemistry in Freiburg (source: Archives of the Institute of Macromolecular Chemistry)

polymers would never fit into the extremely narrow confinement of the small crystallographic unit cell.

In 1926, Hermann Staudinger followed Heinrich Wieland and became the director of the Chemical Laboratory at the Albert-Ludwigs University in Freiburg. His relocation from Zurich to Freiburg marks a distinct transition in his science and also in his private life [3–6]. When he moved to Freiburg, Hermann Staudinger rigorously abandoned his prosperous and highly successful field of small molecule organic chemistry. Fighting tough battles with his numerous opponents, he boldly took the risk of embarking on an, at that time, uncertain journey into the stormy and dangerous seas of the emerging polymer sciences. After his divorce from his wife Dora in 1925 and his move to Freiburg, he left behind in Switzerland three daughters and one son. In 1928, he married Magda Woit, a highly cultured woman born in Latvia, who soon became his fierce and most feared ally in his never-ending struggle for macromolecules. Holding a PhD in biology and as experienced botanist, Magda Staudinger shared and encouraged his visions concerning the prominent role of polymers in biology.

When Hermann Staudinger left the Swiss democracy in 1926, he exposed himself to the political and economic turbulences of postwar Germany, that was soon followed by the Nazi tyranny of the Third Reich, which finally led to the suffering and devastating destructions during World War II. In spite of the manifold political, economic, and wartime obstacles, Staudinger made significant progress in macromolecular chemistry. Several books and reviews have addressed Staudinger's

role in polymer sciences [3–11]. Today, polymeric materials prepared according to Staudinger's molecular design principle, are indispensible in daily life. At the beginning of the twenty-first century, we are living in the "Plastics Age." As highly cost-, eco-, resource-and energy-efficient materials polymers are pacemakers for the progress in modern sustainable technologies, bringing great benefits to society. Polymers secure health, mobility, communication, shelter, clothing, protection, resources, and reliable supplies of food and energy. Above all, the versatile polymeric materials with tailored property profiles render high-technology products affordable for those living in industrial and developing countries. They contribute to substantial savings in energy and resources and help meet the demands of the rapidly growing world population.

2 Staudinger: Pioneer of Bioinspired Chemical Research

When Hermann Staudinger moved to Freiburg, he shifted his entire research focus and thrust toward macromolecular chemistry, preparing and characterizing a wide variety of macromolecules. These included biopolymers such as cellulose, natural rubber, and chemically modified biopolymers as well as a wide variety of new synthetic polymers ranging from polystyrene and polyoxymethylene to polysilicic acid. Inspired by his close affiliation to botany, learning from nature was an integral part of his research for decades. In fact, originally Staudinger had planned to study botany. However, his father, the school teacher Franz Staudinger, advised him to study chemistry first "in order to be able to understand botanical problems better." As an organic chemist, he carefully studied nature, successfully isolated natural ingredients, identified their structure, and developed chemical syntheses for preparing them in the laboratory. This led him to the development and temporary wartime commercial use of synthetic surrogates for the flavors of pepper and roasted coffee, which were not available in Germany during World War I. Together with Leopold Ružička and Staudinger's former PhD student Tadaeus Reichstein, he identified pyrethroids as natural biodegradable insecticides produced by the chrysanthemum flower. Due to their very low mammalian toxicity, pyrethroids are in high demand today as common household insecticides. It was extremely fortunate for the polymer community that Staudinger's synthetic efforts failed to produce the appropriate stereochemistry of three-membered ring in the pyrethroid structure, thus enabling him to move to new horizons and pioneer macromolecular chemistry.

It was Hermann Staudinger who recognized that biopolymers and synthetic polymers are assembled according the same blueprint, linking together a huge number of small monomer molecules by covalent bond formation. This approach toward bioinspired research and molecular bionics was revolutionary, because at that time the formation and properties of natural and synthetic polymers were thought to be vastly different. In Staudinger's view, synthetic polymers represent excellent model systems for achieving a better understanding of biopolymers and

the much more complex biosystems. In 1927, jointly with Gustav Mie, the Freiburg physicist and expert in scattering and X-ray diffraction, he published his research on "the polymeric formaldehyde, a model for cellulose" [12]. This highly successful interplay of polymer chemistry and physics in Freiburg clearly demonstrated that purely synthetic polymers can form fibers that resemble natural fibers. At that time, fiber formation was thought be an exclusive domain of biopolymers and living organisms such as spiders. Without any doubt, this paradigm shift in scientific conception has stimulated the development of synthetic fibers, as started by Wallace Carothers, who during the 1930s pioneered synthetic polyamide and polyester fibers at Du Pont. Staudinger's bioinspired molecular polymer design opened a new dimension for the development of advanced polymeric materials in chemistry and biotechnology, going well beyond the scope of the purely "trial-and-error" development typical of the very early days of polymer technology. Moreover, the insight that he gained into the crystallization behavior and crystal structure of polyoxymethylene clearly proved that only a very small section of the polymer chain is allocated in the crystallographic unit cell of a crystalline polymer. At the end of the 1920s, crystallographers gave up their opposition and vividly engaged themselves in polymer research.

In Freiburg, Giulio Natta from the Polytecnico di Milano, Italy, learned how to use the tool of crystallography, This new experience was essential to his research when he identified the molecular architecture of isotactic polypropylene. In his Nobel speech, in 1963, Giulio Natta stated [13]: "After I had the luck to meet Professor Staudinger in Freiburg in 1932, I was attracted by the study of linear high polymers and tried to determine their lattice structures. To this end I also employed the electron-diffraction methods which I had learned from Dr. Seemann in Freiburg and which appeared particularly suitable for the examination of thin-oriented films. I applied both X-ray and electron-diffraction methods also to the study of the structure of the heterogeneous catalysts used for certain important organic industrial syntheses." Staudinger is the father of macromolecular chemistry, but he also is the pioneer of bioinspired chemistry and molecular bionics [14].

3 Staudinger's Viscosity Law

In the pioneering days, an important shortcoming hampered the progress in polymer sciences, which was the lack of methods for molecular weight determination. Staudinger's solution viscosity measurements were prone to be sensitive to the molecular weight of polymers, solvent interaction, and to formation of colloidal aggregates. Significant progress was made in 1926 when Svedberg and Fåhraeus developed the ultracentrifugation technique for protein characterization. They measured the equilibrium sedimentation of hemoglobin [15]. This research afforded clear experimental proof for the existence of high molecular weight proteins.

In 1929, Staudinger tried to bring an ultracentrifuge to Freiburg. However, his proposal was rejected by the Notgemeinschaft der Deutschen Wissenschaft, the

precursor of the Deutsche Forschungsgemeinschaft (DFG). Therefore, he intensified his efforts, aiming at finding a correlation between molecular weight and the viscosity of non-spherical colloid particles. He tried to adapt Einstein's viscosity law, established for spherical particles, to polymer chains. This led him to a relationship that became known as the Staudinger law, correlating the polymer molecular weight with the specific viscosity of dilute solutions, and extrapolating it to infinite dilution ("Staudinger index" or intrinsic viscosity) [16]. Using a calibration with polymer samples of known molecular weight, it became possible to estimate the molecular weight. This concept was refined by Kuhn, Mark, Houwink and others, who substantially improved this correlation. Today, this correlation is known as the Mark–Houwink and also as the Kuhn–Mark–Houwink–Sakurada equation. This valuable and robust viscosimetry technique is still in use today in academia and industry. It is well known as very reliable and facile method for molecular weight determination. Unlike ultracentrifugation and gel permeation chromatography, no costly investment is needed. Moreover, using this method it was possible to distinguish between spherical and rod-like conformations of macromolecules in solution. It should be noted that Staudinger clearly favored a rod-like fully stretched polymer conformation, resembling a Mikado stick (see Fig. 1). In his view, highly ordered polymers rather than spaghetti-like random-coil polymers account for the specific functions of polymers in nature. For many years and also for other reasons, he heavily opposed Werner Kuhn and Hermann F. Mark, who pushed forward the concept of random-coil polystyrene. A detailed description of the dispute between Staudinger, Mark, and Meyer concerning the size and shape of macromolecules is given by Priesner [4]. During his "habilitation" in Staudinger's laboratory, in the 1930s, Günter Victor Schulz introduced osmometry as an accurate measurement for molecular weights.

4 Imaging of Single Macromolecules

In Freiburg the Staudinger group successfully made early attempts at characterizing the morphology of polymers using ultraviolet phase contrast microscopy and also transmission electron microscopy (TEM), which was invented in 1931 by Max Knoll and Ernst Ruska. It was Magda Staudinger who started research on microscopic imaging of polymers in Freiburg during the late 1930s. In 1940, Elfriede Husemann in collaboration with Helmut Ruska, working at the laboratory of electro-optics of Siemens & Halske AG, successfully employed TEM to visualize a single spherical glycogen macromolecule with molecular weight of around 1.5 million, as determined by osmosis, and an average diameter of 10 μm [17].

They achieved substantial improvement of contrast when they examined the *p*-iodobenzoyl derivative of glycogen with a much higher molecular weight of six million. From the molecular weight, using the Einstein viscosity law, they calculated an average diameter of the *p*-iodobenzoyl glycogen macromolecule to be 30 μm, which is in remarkably good accordance with the diameter measured by

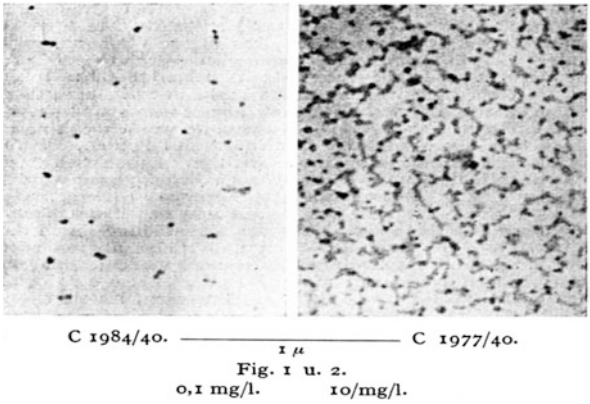

Fig. 2 Visualization of a single *p*-iodobenzoyl-modified glycogen molecule of six million molecular weight and its supramolecular assembly at elevated concentration (Husemann and Ruska [18], with permission of Springer)

TEM (see Fig. 2) [18]. Although single glycogen molecules were detected only at low concentration, supramolecular assemblies of glycogen macromolecules were observed upon increasing the glycogen concentration. This exciting ground-breaking research came to an abrupt end when Staudinger's laboratory was destroyed by bombing in 1944. In 1964, Bittiger together with Husemann published fascinating microscopic images of cellulose tricarbanilate single molecule single crystals [19].

5 Hermann Staudinger and the Third Reich

As probably the only German chemist during World War I, Staudinger publically opposed the use of poisonous gas as a chemical weapon of mass destruction and even proposed to the German High Command to stop the war because of the imbalance of power when the overwhelming US military and economic power joined the allied war effort. Many Germans questioned Staudinger's loyalty and accused him of anti-German sentiments. Hence, members of the selection committee of the University of Freiburg visited him in Switzerland, thoroughly checking on his patriotism and national spirit before accepting him as candidate. Details on Staudinger's experience with German politics and his difficult time in the Third Reich are reviewed by Priesner [5]. It should be noted that both Staudinger's father and brother and his first wife had very close left-wing political affiliations. Staudinger's younger brother Hans, who was an economist and Social Democrat member of the German Reichstag 1932–1933, opposed the Nazis and was arrested. He managed to escape from Germany in 1933 and became a professor of economics at the New School for Social Research in New York City. Hence, it is not surprising that Staudinger was not considered a trustworthy follower of the Nazi movement.

Shortly after the Nazis seized power in 1934, the Dean of Freiburg University and famous philosopher Martin Heidegger, new member of the Nazi party and at that time deeply impressed by the Nazis, denounced Hermann Staudinger. He proposed the immediate dismissal of Hermann Staudinger by claiming without any proof that Staudinger would be an opponent and was only pretending in public to support the Nazi movement [15]. Staudinger was summoned by the secret police (Gestapo) and questioned for many hours. They forced him to sign his own dismissal request without dating it, threatening him that they would immediately seize him as soon as he opposed the regime. The Nazis imposed on him a ban on foreign travel, which massively disabled his scientific activities. Staudinger understood this clear message. In public he demonstrated his obedience and his Nazi-conforming attitude. However, his application for Nazi party membership was rejected. Although Staudinger tried hard to acquire the reputation of an anti-Semite, expressing his concerns about the presence of too many non-Aryans in academia, in his institute he helped his half-Jewish assistants like Gerhard Bier to survive. He pointed out to the Nazi government their important contributions to the German war effort, thus enabling them to carry on their work in his institute. Among others, Hermann Staudinger's coworker Elfriede Husemann also suffered under the Nazi rule. Her career was delayed on purpose because the Nazis saw the primary role of women in motherhood but not in academic careers [20]. On November 27, 1944 the Allied bombing destroyed a large part of the city of Freiburg, including Staudinger's laboratory and the entire chemical laboratory. Although his institute was rebuilt, the difficult situation and shortages typical of the German postwar period severely impaired Staudinger's research.

6 Staudinger and His Institute of Macromolecular Chemistry

For many years, Staudinger's macromolecular chemistry was an unloved and alien daughter of organic chemistry. Since most industrial polymers have fairly broad molecular weight distributions and frequently ill-defined composition, comprising complex multicomponent and multiphase systems, most hard-core organic chemists considered polymer chemistry to be *Schmierenchemie* (goo chemistry). Soon, Hermann Staudinger realized that a new platform was in urgent need to foster interdisciplinary research on polymer sciences, train students, and communicate research results. In 1940, Staudinger founded the Institute of Macromolecular Chemistry in Freiburg as the first European research center devoted exclusively to research on polymer sciences. At the beginning, his institute was embedded in the organic chemistry department, but became an independent research institution of the state of Baden in 1945. Then, in 1956, it was integrated as an independent institute into the University of Freiburg. Figure 3 shows an artist's contemporary view of a Staudinger laboratory in the 1950s.

Fig. 3 Staudinger's chemistry laboratory in the 1950s (lithography by the artist Helmut Philipp, property of R. Mülhaupt)

Many of Staudinger's students took the lead in industrial polymer research, among them prominent directors like Adolf Steinhofer at BASF AG, Hans Batzer at Ciba-Geigy AG, Gerhard Bier at Hoechst AG, and Ernst Trommsdorff at Röhm & Haas AG. When the University of Mainz was founded after World War II, the two chairs of physical and of organic chemistry were taken by G.V. Schulz, who did his habilitation in Freiburg, and by Werner Kern who was a former Ph.D. student of Hermann Staudinger. Later, two other former Staudinger students joined the Mainz faculty, namely Helmut Ringsdorf and R.C. Schulz. In an early version of a public–private partnership, Staudinger rallied prominent representatives and research directors of polymer industries in an association (Förderverein für Makromolekulare Chemie e.V.), supporting and advising the activities of Staudinger's institute in Freiburg.

In order to communicate polymer research results, Staudinger founded the first polymer journal, *Journal für Makromolekulare Chemie* (*Journal of Macromolecular Chemistry*), in 1943 as a new branch of the *Journal für praktische Chemie* (*Journal for Practical Chemistry*), for which he had served as the editor-in-chief since 1939 with the Barth publishers in Leipzig, Germany. In the postwar time, at the beginning of the cold war, Freiburg in the French zone, was cut off from access to East Germany, which was occupied by the Russian army. Therefore, Staudinger's journal was published under the new name of *Die Makromolekulare Chemie* (*Macromolecular Chemistry*) by the publishers Wepf & Co. in Basel, Switzerland. Today this journal is renamed *Macromolecular Chemistry and Physics* and, together with a family of sister journals, is published by Wiley. In several textbooks published by Staudinger, among them the "bible" of polymer chemistry entitled *Makromolekulare Chemie und Biologie* (*Macromolecular Chemistry and Biology*) [21], are taught the basic principles of polymer sciences, serving for decades as an entry to the fascinating world of macromolecular chemistry.

Fig. 4 Hermann Staudinger and his successor Elfriede Husemann (source: Archives of the Institute for Macromolecular Chemistry, Freiburg)

In 1950, Staudinger opened his internal macromolecular colloquium to the public, converting it into a national polymer conference. Since then his "Makromolekulares Kolloquium" has turned into one of the largest European polymer conferences, held annually in the last week of February and attracting around 800 participants. In 1951, he retired from the University of Freiburg, was followed by Arthur Lüttringhaus in organic chemistry, but remained the managing director of his independent Institute for Macromolecular Chemistry until 1956. All his attempts to bring a Max Planck Institute for polymer research to Freiburg had failed. Hence, he was somewhat frustrated when he retired. Known for his very strong personality and his extremely low level of tolerance regarding opinions deviating from his own, Staudinger's rule in the institute and the chemical laboratory resembled that of an ancient warlord.

In the aftermath of Staudinger's Nobel Prize of 1953, his successor Elfriede Husemann (affectionately called "Husefrau") was awarded the new chair for macromolecular chemistry, which was installed in 1956 when the institute was finally reintegrated into the University of Freiburg. In contrast to Staudinger, Husemann was open-minded, accepting and responding to different views from different people and different scientific disciplines. In 1962, under her leadership, the institute moved to a new building located in the nearby Stefan-Meier-Strasse 31. Figure 4 shows Elfriede Husemann, who was a passionate motorcyclist, driving together with Hermann Staudinger in front of the the new building of macromolecular chemistry, which was undergoing construction during the early 1960s. On September 8, 1965, Hermann Staudinger passed away and is buried in the central cemetery of Freiburg (see Fig. 5).

Fig. 5 The grave of Hermann and Magda Staudinger in Freiburg

7 Staudinger's Visions Toward (Bio)System Integration

In his Nobel lecture on December 11, 1953 [6] Hermann Staudinger stated [22]: "With a few bricks it is impossible to erect a great variety of buildings; nevertheless, provided that 10,000 or 100,000 bricks are available it is quite possible to construct the most diverse buildings, . . . The existence of macromolecules and the steadily deepening knowledge of their properties have revealed the nature of the building units which the living cell requires to create matter". .. Today his vision is inspiring many researchers in chemistry, materials science, and biotechnology to tailor multifunctional polymeric materials with complex functions and architectures. Hermann Staudinger concluded his Nobel speech with the statement [22]: "In this way macromolecular chemistry appears today to fit between low molecular organic chemistry and cytology. It is the connecting link between them, growing systematically out of low molecular chemistry but, with the incomparably larger

wealth of its chemical scope, forming living matter. ... In the light of this new knowledge of macromolecular chemistry, the wonder of Life in its chemical aspect is revealed in the astounding abundance and masterly macromolecular architecture of living matter". Going well beyond the scope of tailoring single macromolecules, Hermann Staudinger has foreseen the unique opportunities of the emerging macromolecular systems engineering, which is not at all restricted to biosystems. Advanced synthetic, biological, and biohybrid polymer systems can be tailored to exhibit features typical for living organisms such as sensing, recognition, learning, stimuli-response, adaptation, energy autonomy, self-assembly, self-healing, and even self-replication. Although polymer sciences and engineering has more than just one father, Hermann Staudinger has successfully created inspiring visions that will continue to stimulate progress in science and technology for many years to come.

8 The Days After Hermann Staudinger in Freiburg

The history of the Institute of Macromolecular Chemistry and polymer research in Freiburg reflect the growth and paradigm shift in polymer science and engineering and the impact of individual researchers. The gallery of the research directors and today's collaboration partners from other faculties is displayed in Fig. 6. Originally, polymer properties were varied by tailoring single macromolecules through varying monomeric units, chain length, and shape of polymer chains. In the second half of the twentieth century, polymer properties were tuned via controlled nanostructure formation in bulk and at surfaces, exploiting assembly of macromolecules at interfaces, controlled nanostructure formation, and functional processing. In the early days of polymer sciences, the search for surrogates of natural materials such as silk, ivory and the strategically important natural rubber had claimed top priority, exploiting predominantly biobased raw materials such as carbohydrates.

Under the leadership of Elfriede Husemann (1956–1974), whose special field of research expertise was carbohydrate chemistry with a focus on starch and glycogen research, Freiburg became an "Eldorado for polysaccharide chemistry" [20, 23]. As an excellent organizer and manager, Elfriede Husemann substantially broadened the horizon of polymer research in the Institute, bringing together the fields of polymer chemistry with biopolymers, physical chemistry, and modern electron microscopy. In 1962, the new building significantly improved the polymer research facilities in Freiburg (Fig. 7). Her student and coworker Beate Pfannemüller became a distinguished female scientist in starch research, well known for her contributions such as the enzymatic synthesis of amylose [20]. Another student and coworker of Elfriede Husemann was Walter Burchard, who in 1956 introduced static light scattering and in 1978 dynamic light scattering. He made significant progress towards a better understanding of the conformation of linear and branched polymers as well as gelation [24].

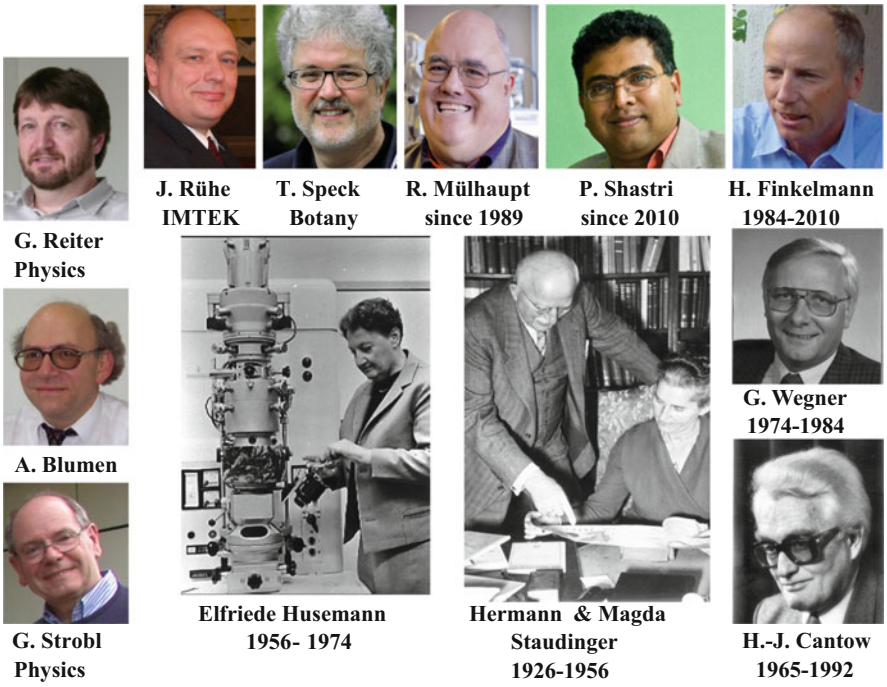

Fig. 6 The research directors of the Institute of Macromolecular Chemistry and their partners in physics, microsystems engineering (IMTEK) and the Freiburg Botanic Garden

Fig. 7 The Institute of Macromolecular Chemistry (*left*), the Freiburg Materials Research Center, FMF (*center*) and the new Freiburg Institute for Interactive Materials and Bioinspired Technologies (FIT), which is currently under construction

In 1965, Hans-Joachim Cantow, at that time a young industrial chemist at Chemische Werke Hüls (now Evonik) who had just completed his habilitation at the University of Mainz, took the new chair of physical chemistry of macromolecules. Since then, the Institute has had two directors. Going beyond the traditional polymer characterization methods, Hans-Joachim Cantow introduced supraconductive nuclear magnetic resonance spectroscopy, pyrolysis–gas chromatography, thermodynamic approaches, rheology, element-specific transmission electron microscopy, environmental scanning microscopy, scanning tunneling microscopy, and atomic force

microscopy, thus enabling new insights into the role of nanostructure formation in multiphase polymers and blends. Surfaces and interfaces were studied not only in macromolecular, but also in inorganic crystalline systems. Besides model polymers, stereocomplexes and amphiphilic block copolymers, thermoreversible elastomers containing cellulose and donor-acceptor groups were synthesized, and their structure–property interplay studied. In cooperation with colleagues in the "regio basiliensis," Cantow started the regio symposia and founded the "Graduiertenkolleg Polymerwissenschaften" (Graduate Training Program in Polymer Sciences). He was assisted by Hans-Adam Schneider and Wolfram Gronski. In 1974, Gerhard Wegner followed Elfriede Husemann, shifting the focus of the Freiburg polymer research from carbohydrate chemistry towards self-assembly of functional macromolecular materials, conducting polymers, hairy rod polymers, formation of ultrathin layers, and topochemical polymerization in single crystals [25]. This marked the beginning of the new age of advanced macromolecular materials and systems.

After Gerhard Wegner had left Freiburg to become the co-founder and director of the Max Planck Institute for Polymer Research in Mainz, Heino Finkelmann joined the Institute in 1984. In his research, Heino Finkelmann successfully combined the anisotropy of liquid crystals with the viscoelasticity of polymers [26]. This led him to the discovery of new generations of liquid crystalline elastomers, tunable lasers, and stimuli-responsive "smart" macromolecular materials.

In view of the increasing demand for advanced polymeric materials and bioengineering in regenerative medicine, Prasad Shastri from Vanderbilt University in Nashville, USA, followed Heino Finkelmann in 2010 as director of the Institute, professor of biofunctional macromolecular chemistry and cell signaling environments, established jointly with the Center for Biological Signalling Studies (BIOSS). In the emerging field of health sciences and nanomedicine, his research focus is placed upon bioactive macromolecular systems and bioengineering.

In 1990, initiated by Hans-Joachim Cantow, the Freiburg Materials Research Center (FMF; Fig. 7) was founded as a resource center of the University of Freiburg, serving as a highly dynamic platform for interdisciplinary and interfaculty research on new materials, technologies, and advanced systems. In the FMF, research groups from chemistry, physics, biology, earth and environmental sciences, medicine, and microsystems engineering work together. The FMF technology laboratories substantially expanded the Freiburg polymer research in the field of functional processing and technology, ranging from extrusion and injection molding to 3D printing and scale-up of specialty polymers. In 1989, Rolf Mülhaupt, who for several years had worked in industry at Du Pont/USA and Ciba-Geigy AG/Switzerland, joined the University as professor for macromolecular chemistry and followed Cantow in 1992 as director of the Institute of Macromolecular Chemistry and as the managing director of the Freiburg Materials Research Center. In his research, Rolf Mülhaupt combined polymer chemistry and polymerization catalysis with polymer processing and polymer technology. Under the roof of the FMF, jointly with the Institute of Macromolecular Chemistry, a team of scientists from different faculties has built the Freiburg chain of knowledge

spanning from synthetic polymer chemistry and polymerization catalysis to polymer physics, nanotechnology, bionics, biobased plastics, and processing. Today an important focus of applied polymer research in FMF is placed upon the development of sustainable materials for applications in lightweight engineering, energy technology, medicine, and microsystems technology.

Inspired by Staudinger's vision concerning macromolecular system engineering and macromolecular biometics, the new Freiburg Center for Interactive Materials and Bioinspired Technologies (FIT) was founded in 2010. A new research building will be completed by 2015 at the campus of the University of Freiburg near Freiburg airport (Fig. 7). The primary research objectives of FIT include the development of adaptive and responsive macromolecular materials and surfaces, biobased and biomimetic materials and their biosystem integration, as well as advanced embedded energy autonomous microsystems, which do not require external power supply because they contain built-in power harvesting and storage.

During Staudinger's era, the Institute of Macromolecular Chemistry was just an isolated tiny island hidden in the organic chemistry department. In the days after Hermann Staudinger, the Institute of Macromolecular Chemistry has been turned into a world-class polymer research center. Today, interdisciplinary polymer science and engineering have top priority at the University of Freiburg, creating a unique interdisciplinary and interfaculty research environment for basic and applied polymer sciences by bridging the disciplines of chemistry, physics, biology, medicine, and microsystems engineering. Since the mid-1980s, several chairs have been established in other faculties. These include the chairs of experimental polymer physics (Gert Strobl, 1985–2006, followed by Günter Reiter in 2008) and theoretical physics (Alexander Blumen since 1991) in the Faculty of Mathematics and Physics, as well as the chairs for chemistry and physics of surfaces and interfaces (Jürgen Rühe since1999) and process technology (Holger Reinecke since 2004) in the Department of Microsystems Engineering (IMTEK) of the Engineering Faculty. Polymer sciences also play a prominent role in bionics research (Thomas Speck, professor of botany, functional morphology, and bionics in the Faculty of Biology, and director of the Botanic Garden of the University of Freiburg since 2006). The aspects of forestry-based biomaterials and bioresources are addressed by Marie-Pierre Laborie, who holds a chair of forest biomaterials in Faculty of Environment and Natural Resources. Inspired by nature, the focus of the interdisciplinary polymer research at The University of Freiburg is placed upon the sustainable development of highly energy- and resource-efficient multifunctional polymeric materials for modern technologies.

The unique polymer research environment in Freiburg has stimulated scientific achievements in top-notch polymer research. Moreover, it has motivated and enabled numerous young scientists to start a successful career in industry and academia, among them German professors like Günter Victor Schulz (Mainz), Werner Kern (Mainz), Rolf C. Schulz (Mainz), Helmut Ringsdorf (Mainz), Gerd Greber (Vienna), Ernst G. Klesper (Aachen), Hartmut Seeliger (Ulm), Hans R. Kricheldorf (Hamburg), Walther Burchard (Freiburg), Manfred Hallensleben (Hannover), Claus Eisenbach (Stuttgart), Reimund Stadler (Bayreuth), Martin Möller (Aachen),

Robert Schuster (Hannover), Alfred Saupe (Halle), Jörg Kressler (Halle), Walter Richtering (Aachen), Kai Saalwächter (Halle), Claudia Schmidt (Paderborn), Bernd Tieke (Bonn), Jörg Tiller (Dortmund), Holger Frey (Mainz), Stefan Mecking (Konstanz), Rainer Haag (Berlin), and Sabine Ludwigs (Stuttgart).

In Staudinger's time, Freiburg was isolated in the outmost southwestern corner of Germany, close to the borders of France and Switzerland, which were impermeable during war times. Today, Freiburg is located in the heart of Europe, without any restrictions by frontiers between the adjacent countries. The upper Rhine valley is the trinational region of the neighboring cities of Basel in Switzerland, Freiburg in Germany, and Strasbourg in France, forming an European high-tech triangle in academia and industry with one the highest densities of top-notch research in chemistry, polymer sciences, and life sciences. There are many very close interactions between Swiss, French, and German polymer research groups, owing to the highly complementary expertise in polymer sciences and the very close proximity of Basel, Strasbourg, and Freiburg, which enables an exchange of students and staff even on a daily base. In 2010, the International Research Training Group "Soft Matter Science – Concepts for the Design of Functional Materials," funded by the Deutsche Forschungsgemeinschaft, was established to promote international graduate training and research on advanced macromolecular materials and systems.

In 2013, the universities of Strasbourg and Freiburg started a joint master degree training program in polymer sciences, paralleled by the new national master degree program in Freiburg, entitled "Sustainable materials – polymer sciences," as well as the master degree in chemistry with specialization in macromolecular chemistry. At the University of Freiburg, the unique training and research environment in polymer sciences is built upon the chain of knowledge in polymer sciences and engineering. Interdisciplinary research combined with multicultural training is the prerequisite for creating innovations and for achieving significant progress in the emerging field of macromolecular (bio-, micro-) systems engineering. This is essential for the sustainable development of advanced functional materials with high energy- and resource-efficiency and of modern technologies to meet the urgent needs of the growing world population.

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Hermann Staudinger: Aspects of Fame and Memory, Motivation and Impact

Gerhard Wegner

Abstract This article searches for the origins of the concepts and scope of macromolecular science in the context of the time before and after World War I. Although Hermann Staudinger's contributions to the fundamentals of polymer science were honored by a Nobel-Prize in 1953, an appropriate scientific community was only slowly coming to life, mainly stimulated by the needs of an explosively growing plastics ("polymer") industry, which could only evolve once the fundamentals had been laid down. The lack of this scientific community explains the surprisingly small impact that Staudinger's work on macromolecules found among his contemporaries in the community of organic chemists, in which he holds a firm place for his work on organic synthesis.

Keywords Hermann Franz Mark · Hermann Staudinger · History of polymer science · I.G. Farben Industries

Contents

1 How a House Got a Name 40
2 The Birth of a Concept: Motivation, Reception, and Impact 44
References 52

G. Wegner (✉)
Max Planck Institute for Polymer Research, Ackermannweg 10, 55128 Mainz, Germany
e-mail: wegner@mpip-mainz.mpg.de

1 How a House Got a Name

In early spring of 1980, the two directors of the Institute for Macromolecular Chemistry of the Albert-Ludwigs University of Freiburg in Germany started to deliberate how to commemorate the 100th birthday of the late Hermann Staudinger (1881–1965), famous proponent of macromolecular chemistry and former Professor of Organic Chemistry and head of the "Chemical Laboratory" of this university from 1926 to 1951. The event was due in the following year and was to be connected with the traditional "Makromolekulares Kolloquium," the yearly gathering of polymer scientists at Freiburg. The fact that Hermann Staudinger had received the Nobel Prize in Chemistry in 1953 for his many contributions to macromolecular chemistry had greatly enhanced his fame and made his scientific legacy even more important.

In 1980, there was no visible memory of his achievements, neither in the University and nor in the city of Freiburg except in the archives and in the mind of his contemporaries. Therefore, the two directors in charge of the Institute created the idea to name the Institute for Hermann Staudinger on occasion of the celebration of his 100th birthday in 1981. Hans-Joachim Cantow (born 1923) was the elder of the two directors and had held a Chair in Physical Chemistry of Macromolecules at the Institute since 1965. The younger one was Gerhard Wegner (born 1940), who had been appointed a professor in Macromolecular Chemistry at the Institute in 1974.

It turned out to be a difficult task to realize the initial idea because of two major obstacles. First, one needed permission from the university authorities for this action and, second, more difficult, one needed consent from the widow of Hermann Staudinger, Dr. Magda Staudinger (1902–1997), who was a fierce and powerful custodian of the scientific legacy of her late husband.

With the backing of the Faculty of Chemistry H.-J. C. and G.W. approached the chief administrator of the University, Dr. Siburg, who flatly refused to give consent to the request. Dr. Siburg, who carried the title "Chancellor of the University" was a dyed-in-the-wool bureaucrat. He had a sincere antipathy to anything for which there was no precedent. And indeed, in Freiburg at that time there was no example where the name of a former scientist and/or university teacher of fame was linked to a scientific institute or institution.

In consequence, Dr. Siburg heavily resisted the idea proposed by H.-J. C. and G.W. In hindsight, he might have had good reason, for the University of Freiburg had a history rich in outstanding scientists, philosophers, and historians, as well as professors in medicine who – besides their role in academia – had a life beyond the walls of academia. The latter gave reason to heated debates in the public and the press. The chancellor probably liked to protect "his" university from such ugly debates. However, in the case of H.S. there was evidence beyond any doubt that H.S. was involved in deplorable activities.

Eventually, H.-J. C. and G.W. had a decisive meeting with the chancellor in May of 1980 in which a compromise was found after long debates. H.-J. C. and G.W. no

longer insisted on naming the Institute for H.S. and the chancellor agreed that the Institute's building could be baptized "Hermann-Staudinger-Haus" (Hermann-Staudinger building). Such naming of buildings is typical in Anglo-Saxon universities and he could not flatly reject this precedent in view of the fact that the University had some standing internationally.

The second obstacle was to be removed by G.W. Dr. Magda Staudinger had watched all of the developments related to macromolecular chemistry at Freiburg with displeasure, ever since the formal retirement of H.S. in 1951, when he had turned 70 years old. Although H.S. had maintained some scientific activity as an honorary director of a state-supported but non-university institute, the Staatliches Forschungsinstitut für Makromolekulare Chemie (State Institute for Macromolecular Chemistry), it was partly located in his private villa at Lugostrasse and partly in a shabby laboratory attached to the old building of the Chemisches Laboratorium (Organic Chemistry Institute) of Freiburg University. It was only in 1956 that Elfriede Husemann (1908–1976), a long-time associate of H.S., was officially promoted to Chair in Macromolecular Chemistry on occasion of the final retirement of H.S.

Dr. Magda Staudinger felt that her husband had been badly treated by the University in consequence of his retirement in 1951. Firstly, they pushed him out of "his" chemical laboratory, which he had directed since his move to Freiburg in 1926 and only thanks to his standing and connections to the State of Badenia, was he given the chance to stay active in experimental science. Secondly, the Faculty of Science chose a successor who had no interest whatsoever in macromolecular chemistry: Arthur Lüttringhaus (1906–1992), an organic chemist of high reputation at that time. Thirdly, the Faculty decided in 1956 to offer the Chair in Macromolecular Chemistry to Elfriede Husemann rather than to Hans Batzer, whom Magda Staudinger wanted to see in this position. Hans Batzer had gained a doctorate in chemistry in 1946 working under Staudinger and had taken care of saving what was left of the Chemisches Laboratorium after Allied bombing had destroyed most of it in 1944. He efficiently managed to rebuild provisional laboratories and lecture halls under the rules of French occupation. He had left Freiburg, infuriated, when he realized that the Faculty disliked continuation of macromolecular chemistry as an academic subject of priority. Instead, he started a successful career in the Swiss chemical industry and soon became a research director at CIBA, Basel. Among other achievements, Hans Batzer was the driving force in making CIBA a leader in the profitable world market for epoxy resins and additives to polymers meant to stabilize them against photochemical degradation and autoxidation. He also was an honorary professor at the Technical University of Stuttgart in Germany.

In summary, Magda Staudinger believed that she had many good reasons to maintain unfriendly relations with the Faculty of Chemistry of Freiburg University. In particular, she disliked Elfriede Husemann, despite – or maybe, because – of the fact that Elfriede Husemann had been a close cooperator and academic associate of her late husband. She had been promoted to the rank of Associate Professor by the University in 1947. Given the difficulties of the time, she had an impressive record in scientific achievements when the Faculty decided to offer her the directorship of

the Staatliches Forschungsinstitut für Makromolekulare Chemie as the successor to H.S. upon his final retirement in 1956.

Elfriede Husemann was not only an outstanding scientist but was also exceptionally skilled in the wheelings and dealings of academic affairs, both locally and on the level of the state administration. She succeeded in reintegrating the Forschungsinstitut into the University as the Institut für Makromolekulare Chemie (Institute for Macromolecular Chemistry) with its own identity; moreover, she gained a second chaired professorship on the physical chemistry of macromolecules for this Institute. This chair was first given to H.-J. C. in 1965. Her most impressive achievement, however, was to gain support and financial means to create a brand-new laboratory building for the Institute, which was eventually finished in 1962. These were all achievements that H.S. and his companion and wife Magda had always dreamt of, but had never achieved.

In fact, H.S. never set a foot in the new building nor did Magda Staudinger within the lifetime of Elfriede Husemann. The first time Magda Staudinger came to visit the building was only in 1978 after many soothing encounters and diplomatic actions by G.W., who had come to Freiburg as the successor of Elfriede Husemann in 1974.

Magda Staudinger had gained a doctorate in biology shortly before she met H.S. for the first time. They married in 1926, the year he moved to Freiburg from Zürich. She would become his most ardent companion and coworker in the development of macromolecular chemistry; moreover, she turned into a fierce and powerful defender of the achievements of H.S. whenever the priority of his ideas and work was challenged or even slightly questioned. Magda Staudinger – a person of the highest intellectual caliber – made quite an impression. She was, and acted like, a true lady. Her clear, melodious, and sometimes soothing voice, which easily filled a large lecture hall without technical assistance, fitted her figure of a Wagnerian opera singer. She must have been a beauty as a girl and was quite handsome even in her later years. Educated in pre-World War I Russia (she came from a well-to-do Baltic *baltendeutsch* family), she spoke several languages fluently, among them Russian, German, English, and French. She also played the violin and the piano with great skill. Her father had once been the ambassador of Latvia to post-World War I Germany, which she would mention whenever there was a fitting occasion.

Magda Staudinger played a distinctive role in her husband's scientific activities both as coworker and ardent supporter of his ideas and visions. After his death in 1963, she became a distinguished and influential member of the Editorial Board of *Makromolekulare Chemie*, the journal that was founded by H.S. in 1946 as the first worldwide journal specializing in macromolecular chemistry.

Magda Staudinger had other interests as well. She was a leading member of an influential circle pushing for more recognition of female scientists in academia. As a patriot in the best of all senses, she became a member of the German delegation to UNESCO and soon rose to a leading figure in the UNESCO subcommittee "Man and his Environment," a duty that she carried out most successfully and with international recognition over many years in the 1970s.

Returning to the story of the Staudinger House: It was the task given to G.W. to gain the consent and approval of Magda Staudinger for the name-giving act. G.W. had met her first in 1973 on occasion of a meeting on macromolecular science in Switzerland organized by Hans Batzer, who introduced him to her in a very kind manner. After this first encounter many others followed, initially on occasions of conferences and meetings and later by private invitations to her mansion in Lugostrasse, Freiburg. She seemed to develop very friendly feelings toward G.W. and considered him openly as the "scientific grandson" of her late husband (and, of course, hers as well).

Based on her affection, G.W. was able to convince her to make a first-in-her-lifetime visit to the Institute building at Stefan-Meier-Strasse, Freiburg in 1978. In 1980, G.W. tried to convince her to agree to confer the name of Hermann Staudinger on the building. Of course, it would have been correct to attach the names of both H.S. and Elfriede Husemann to the building; however, that would have never found the approval of Magda Staudinger.

Eventually, she approved for the good reason that the naming would reinforce her continuing efforts to defend the priority of H.S. in the field of macromolecular science. In the context of gaining her approval, she suggested very strongly that G.W. should embark on writing a textbook on the history of macromolecular chemistry. G.W. suggested that he was too young and inexperienced for such a challenge and instead proposed the name of Herbert Morawetz (born 1915 in Praque, Professor at Polytechnic University, Brooklyn, New York, USA) as potential author. He also agreed that he would try to convince Herbert Morawetz to undertake such a work and would invite him for a longer stay at Freiburg so that Magda Staudinger could have ample time and opportunity to expose her thoughts and experiences.

That proposal helped greatly and Morawetz came indeed to Freiburg in 1983 for a long stay. His book, a true landmark in scientific writing on the origins and contexts of the evolution of polymer science, appeared finally in 1985 [1]. At that time, G.W. had moved to Mainz in Germany as one of the founders of the newly created Max Planck Institute for Polymer Research (together with E.W. Fischer). But this is another story.

The name "Hermann-Staudinger-Haus" for the Institute building in Freiburg, Stefan-Meier-Street 31, was eventually formally presented and announced in March 1981 in the presence of Magda Staudinger. As planned, this event was also linked to the commemoration of the 100th birthday of H.S.

Incidentally, and not unrelated, Magda Staudinger gave a thoughtful and moving speech as an honorary guest on occasion of the formal opening ceremony of the Max Planck Institute for Polymer Research in Mainz on March 10, 1986. She spoke about the longings of H.S. (and herself) for recognition of their priority in macromolecular science and their unsuccessful attempts to convince the Kaiser-Wilhelm Gesellschaft (KWI), the predecessor of the Max Planck Society, to create an institute in Freiburg. However, now and because the Max Planck Society had decided to have such an institute in Mainz, she was pleased to see that the visions of her late husband would further be developed, if not in Freiburg at least in Mainz.

2 The Birth of a Concept: Motivation, Reception, and Impact

The landmark book by Morawetz [1] on the origins and growth of polymer science presented an unbiased, transparent, and historically painstakingly correct picture of the evolution of polymer science as a branch of general science in its own right. The book describes in particular the conceptual difficulties that existed at the time when Staudinger first claimed the existence of large molecules, which he called *Hochpolymere Verbindungen* (high polymer compounds) and later *Makromoleküle* (macromolecules). Staudinger had to fight against the community of colloidal chemists, who maintained the position that "macromolecules" were merely associates (or aggregates) of low molar mass species held together by (unknown) colloidal forces and not by covalent bonds. This dispute has been described many times [1–3] and does not need to be repeated here. It suffices to summarize that it was the lack of theory, combined with a lack of analytical and physical methods and ill-defined scientific concepts, that fueled the dispute. Once these methods and concepts were in place, the dispute was settled around the year 1930. Morawetz gives a full account of the work of the many outstanding scientists who contributed the methodological, analytical, and theoretical studies to establish the field of polymers, among them Hermann Mark and Kurt H. Meyer, Wallace H. Carothers, Paul Flory, G. V. Schulz, and many others. This tableau of an emerging science gives Staudinger a prominent role but puts it into a balanced historical perspective.

Magda Staudinger was obviously not totally pleased by this perspective and she made contact with yet another person whom she had learned was ready to write a history of polymer science: Yasu Furukawa. His work entitled *Inventing polymer science: Staudinger, Carothers and the emergence of macromolecules* came out in 1998 [2].

In the foreword, Yasu Furukawa acknowledges intensive interactions and correspondence with Magda Staudinger. The book is another excellent text based on thorough research into historical texts and archives, including interviews with surviving contemporaries of the two key players, Staudinger and Carothers. It tells the moving story of the ill-fated Wallace H. Carothers [1886–1937] but in the end it comes to the same conclusions already presented in the foregoing book by Morawetz [1]: The emergence of polymer science had not one but many ingenious contributors.

Both books also refer to Staudinger's activities in societal issues both in World War I and II. Those who are interested in these issues should also read the book by Ute Deichmann [4], who gives a well-researched documentation of Staudinger's life as a university professor and key representative of German science between 1933 and 1945 (and beyond).

A question that has been rarely treated in the literature considers the motivation that drove H.S. to leave the safe ground of accepted organic chemistry and turn to the field of high polymers. We do not have direct evidence but an inspection of the general situation in the historical context of the 1914–1918 war and the years

immediately following helps to elucidate the motivation. Although living and working in peaceful Switzerland at ETH Zurich, this country was completely surrounded by warring nations. Moreover, his private and scientific ties to Germany were very strong. As the war started, Germany was almost completely cut off from all external supplies of raw materials, foodstuffs and the like; so was Switzerland, despite its status as a neutral country. In consequence, H.S. started research activities with his students and coworkers to find *Ersatzstoffe* (surrogates) that could replace natural products in times of need. He found an artificial coffee aroma and a replacement for pepper. More importantly, he witnessed the death of tens of thousands of soldiers in the trenches and military camps of the war – not killed by enemy action but by contagious diseases, most of them transmitted by insect bites from bugs, mites, lice, and fleas. The spotted fever (typhus exanthematicus) was the most dangerous and life threatening of the diseases. In the light of this situation he convinced his brilliant coworker Leopold Ruzicka (1887–1976, Nobel Prize 1939) to start research on insecticides. Ruzicka identified the active substance in the so-called Pyrethrum or Dalmatian insect powder obtained from a chrysanthemum species and he showed the way to its synthesis. A series of brilliant papers, published between 1924 and 1926 with H.S. as a co-author, originated from this effort.

A most serious situation affecting the population in Central Europe was the lack of supply of raw materials for textiles. Prior to 1914, 98% of all material for fiber spinning and further production of textiles was imported. The cut-off from resources caused tremendous suffering among the population for lack of proper clothing. Similarly, the lack of supply of natural rubber was a serious drawback for the increasingly important motorization, firstly for the military but for the civilian sector as well. Certainly, the debate on the chemical nature of cellulose, the most important natural fiber, and on the structure–property relationship of natural rubber had been started long before [1]; however, the pressing need due to the lacking supply of the natural products was a strong driving force for scientific attention. There is little doubt that H. S. drew his motivation from this situation. This was certainly enhanced by a widespread general discussion in Germany between 1914 and 1920 on how to organize research activities in order to reduce the dependence on external supplies and thereby increase the competitiveness of the German textile industry. It should be recalled that the production of textiles was a very important sector of industry at the time, only rivaled by the steel industry.

During the war, the (German) textile industry pressed for more research in terms of a centralized institute solely dedicated to fibrous materials and their processing. Eventually, and after much public debate [5], the central government and parliament agreed in 1919 to give the Kaiser-Wilhelm Gesellschaft (KWG) the mandate to found a new institute to be named the Institut für Faserstoffchemie (Institute for Chemistry of Fibrous Materials) in Berlin. The new institute was to be supported both by public and private, industrial funds. An organizing committee was formed with the following members: Fritz Haber (chemist), Carl-Dietrich Harries, Reginald Oliver Herzog, Walter Nernst, and Richard Willstätter. The new institute started

working on June 1st, 1920, initially in preliminary rooms in Haber's institute, and later in its own building in Berlin-Dahlem.

The Institute consisted of three departments: (i) Department of Organic Chemistry, headed by Max Bergmann (1886–1941), who would move to Dresden in 1921 as the new and sole director of another newly created KWI, namely the Institut für Lederforschung (Institute for Leather Research); (ii) Department of Physical Chemistry, headed by Michael Polanyi (1891–1974); and (iii) Department of Technology, headed by A. Geiger (until 1921) and from there on by Hermann Franz Mark (1895–1992). The institute's overall director was Reginald Oliver Herzog (1878–1935).

Herzog as well as Polanyi had spent time at the Technical University of Karlsruhe in its Institute of Physical Chemistry and, therefore, were known to Fritz Haber. Bergmann was considered a "rising star" among organic chemists of the time. He was Emil Fischer's most brilliant student. Fischer (1852–1919; Nobel Prize 1902) had strongly supported the idea for a central research institute in fibrous materials. Mark came to the new institute via his connections to the Fischer school.

It is safe to assume that H.S. was fully informed on the debates in scientific and industrial circles predating and surrounding the foundation of the new institute. The same is true for the other newly created (in 1921) Institute for Leather Research in Dresden, which was meant to concentrate on protein research for the fundamental part and on tannery and its processes for the industry-related part. Max Bergmann would be announced as the director in 1921 [6]. He would soon turn out to be an ardent opponent of the ideas of H.S. and would deny the existence of Macromolecules (proteins in his case) until the late 1930ies.

Staudinger, working at the best-known academic institution for industry-related research – the Swiss Institute of Technology (ETH) in Zurich, certainly felt obliged to contribute his ideas to the research programs of the two newly founded institutes in Germany: a strong motivation indeed! His suggestions on the existence of large, linear macromolecules as the common feature of all fibrous materials as well as rubber, starch etc. was met with disbelief by the major players of the two new institutes and their supporters in academia, for Staudinger's scientific arguments were not very strong, at least initially in the early years 1920–1928. Whole academic circles rejected his ideas in favor of explanations for the behavior of natural fibers, leather, and other protein-based materials given by "colloid science." Colloid science, a field made highly popular by Wolfgang Ostwald (1883–1943) had many supporters, among them Emil Fischer, Karl Freudenberg, Max Bergmann, and C. D. Harries. This is difficult to understand from today's point of view but it must also be said that today's "colloidal science" has little, if anything, to do with the writings and readings of Wolfgang Oswald, the key propagator of the "world of unknown dimensions," and his followers at the time of 1920–1940. In consequence, Staudinger's concept, although innovative, was not yet based on solid evidence and did not find favorable reception in academic science.

An unbiased inspection into the record of citations of Staudinger's publications demonstrates the evidence. Table 1 gives a list of titles and citations of his ten most cited publications.

Table 1 The ten most cited papers of H. Staudinger, according to Thomson-Reuter's Web of Science as of 2013

Citation order	Details
1	On new organic phosphorus bonding III Phosphine methylene derivatives and phosphinimine (Über neue organische Phosphorverbindungen III. Phosphinmethylenderivate und Phosphinimine). HELVETICA CHIMICA ACTA, 2, 635–646, **1919**, **cit. 1059**, Staudinger H., Meyer J.
2	On new organic phosphorus bonding IV Phosphinimine (Über neue organische Phosphorverbindungen IV. Phosphinimine). HELVETICA CHIMICA ACTA, 4, 861–886, **1921**, **cit 363**, Staudinger H., Hauser E.
3	Ketene (zur Kenntnis der Ketene, Diphenylketen) JUSTUS LIEBIGS ANNALEN DER CHEMIE, 356, 1/3, 51–123, **1907**, **cit. 258**, Staudinger H.
4	On new organic phosphorus bonding II Phosphazine (Über neue organische Phosphorverbindungen II. Phosphazine). HELVETICA CHIMICA ACTA, 2, 619–635, **1919**, **cit. 145**, Staudinger H., Meyer J.
5	On highly polymeric compounds, 116(th) Announcement – On the limit swellable poly-styrene (Über hochpolymere Verbindungen 116. Mitteilung: Über das begrenzt quellbare Poly-styrol. BERICHTE DER DEUTSCHEN CHEMISCHEN GESELLSCHAFT, 68, 1618–1634, **1935**, **cit. 135**, Staudinger H., Husemann E.
6	Concerning polymerisation (Über Polymerisation). BERICHTE DER DEUTSCHEN CHEMISCHEN GESELLSCHAFT, 53, 1073–1085, **1920**, **cit. 125**, Staudinger H.
7	Substances for killing insects I. The isolation and constitution of effective parts of dalmatian insect powder (Insektentötende Stoffe I. Über Isolierung und Konstitution des wirksamen Teiles des dalmatinischen Insektenpulvers) HELVETICA CHIMICA ACTA, 7, 177–201, **1924**, **cit. 121**, Staudinger H., Ruzicka L.
8	Relationship between viscosity and molecular weight in poly sterols (Über hochpolymere Verbindungen 33. Mitteilung: Beziehungen zwischen Viskosität und Molekulargewicht bei Polystyloren) BERICHTE DER DEUTSCHEN CHEMISCHEN GESELLSCHAFT, 63, 222–234, **1930**, **cit. 108**, Staudinger H., Fritschi J.
9	On the hydration of rubber and on its constitution (Über Isopren und Kautschuk, 5. Mitteilung: Über die Hydrierung des Kautschuks und über seine Konstitution) HELVETICA CHIMICA ACTA, 5, 785–806 , **1922**, **cit. 108**, Staudinger H., Heuer W.
10	Action of aliphatic diazo compounds on the thioketones (Einwirkung von aliphatischen Diazoverbindungen auf Thioketone) HELVETICA CHIMICA ACTA, 3, 833–840, **1920**, **cit. 103**, Staudinger H., Siegwart I.

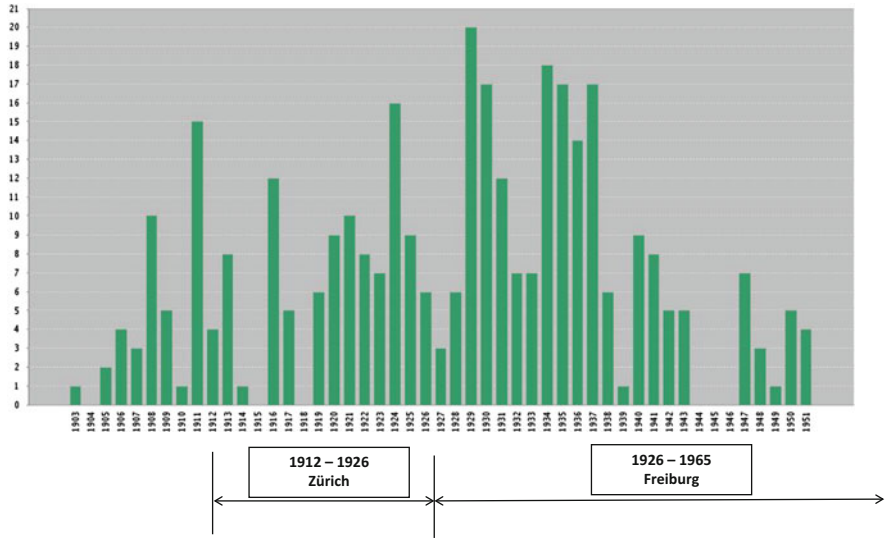

Fig. 1 Publication frequency of Staudinger according to *Thomson Reuters Web of Science* as related to periods of his association with places (Strasbourg, Karlsruhe 1900–1911), Zurich (1912–1915), and Freiburg (1926–1965)

First of all, the relatively low number of total citations is somewhat surprising. Of course, we should realize that the number of active scientists has increased exponentially since the times when H.S. wrote his papers and, therefore, the citation frequency of important papers has increased in terms of their absolute numbers in modern times. However, we can safely compare the impact (in terms of citations received) internally among the papers of H.S. as they are relevant to different subjects or topics. Six out of his ten most cited papers refer to synthetic organic chemistry and have nothing to do with macromolecules. Noteworthy is the impact of his work in organo-phosphorous chemistry; his papers are still cited today as a key reference. Compared to over 1,000 citations that his paper on phosphine methylene derivatives and phosphinimine has obtained, his 1920 paper on polymerization (considered a cornerstone paper by science historians) has merely drawn 125 citations to date. Even some of the papers together with Ruzicka on insecticides are cited more frequently. Another fact that needs mentioning is that monographs played a much more important role in earlier times than they do today. Staudinger laid ground to his fame as a synthetic organic chemist by his book on ketenes, a class of organic compounds that he had first found and explored. As such, it does not appear in the citation index on which much of today's academic evaluation is based. It may be deplorable, but it is a fact.

The frequency distribution of his publications, based on the records of *Thomson-Reuters Web of Science*, reflects the changing motivation behind Staudinger's activity (Fig. 1). Staudinger was called to ETH Zurich in 1912. He needed to install himself there and build a research group. In consequence, we see a first minimum in

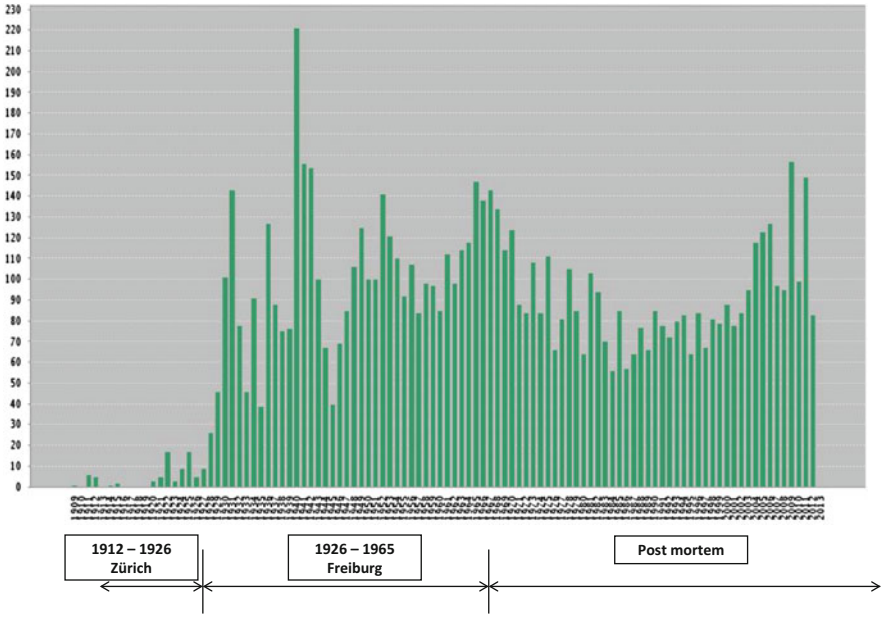

Fig. 2 Impact (citations received) of Staudinger according to *Thomson Reuters Web of Science*, indicating the periods of Staudinger's life

1914–1915 when all of his previous work had been published. A second maximum around 1924–1925 concerns the work of his research group at the ETH. In 1925–1926 Staudinger moved to Freiburg University and from there on his papers were more or less all related to polymers and the behavior of this "class of organic compounds" as Staudinger referred to them. The time of the Second World War and destruction of his laboratory by war action explains the last minimum 1944–1947. Very few and insignificant papers from his hand appeared from then on until his retirement in 1951.

Figure 2 shows the impact of Staudinger's writing in academia. Again, the rather low absolute number per year is quite surprising. A word of caution has already been said and should prevent a hasty jump to conclusions. The data reflect the situation in academic chemistry (and physics) of the time. The majority of chemists working in academia were occupied with quite different topics and research targets; in other words, what Staudinger was proposing as a novel area of organic chemistry had simply no relevance in the eyes and circles of his contemporaries. Moreover, it seemed that "colloidal science" as it was defined in those days was a sufficiently powerful concept to enable meaningful work on natural products, e.g., textiles, leather, and rubber processing.

A list of Nobel prizewinners for the years between 1911 and 1934 is given in Table 2. It sheds light onto the international scene and what were considered the most important contributions to progress in chemistry. Synthetic organic chemistry and natural products chemistry were considered to be at the forefront, followed by

Table 2 Winners of the Nobel Prize for Chemistry 1911–1934

Year	Nobel prizewinner	Year	Nobel prizewinner
1911	Marie Curie	1923	Fritz Pregl
1912	Victor Grignard/Paul Sabatier	1924	Not given
1913	Alfred Werner	1925	Richard Adolf Zsigmondy
1914	Theodore William Richards	1926	Theodor Svedberg
1915	Richard Martin Willstätter	1927	Heinrich Otto Wieland
1916	Not given	1928	Adolf Otto Reinhold Windaus
1917	Not given	1929	Hans K.A.S. von Euler-Chelpin/ Arthur Harden
1918	Fritz Haber	1930	Hans Fischer
1919	Not given	1931	Friedrich Bergius/Carl Bosch
1920	Walther Hermann Nernst	1932	Irving Langmuir
1921	Frederick Soddy	1933	Not given
1922	Francis William Aston	1934	Harold Clayton Urey

Table 3 Winners of the Adolf von Baeyer Medal of the German Chemical Society 1911–1934

Year	Winner of Adolf-von-Beyer memorial prize
1911	Paul Friedlaender, Darmstadt
1914	Richard Willstätter, München
1919	Wilhelm Connstein, Berlin
	Karl Lüdecke, Berlin
1921	Max von Laue, Berlin
1924	Oscar Dressel, Bonn
	Bernhard Heymann, Leverkusen
	Richard Kothe, Leverkusen
1925	Otto Heinrich Warburg, Berlin
1927	Adolf Windaus, Göttingen
1929	Adolf Grün, Grenzach
1931	Otto Diels, Kiel
1934	Richard Kuhn, Heidelberg

work on new methods and process design or on general chemical physics. There was simply no interest in what is called “materials chemistry” today.

A similar picture is given by the list of winners of the Adolf-von-Baeyer Prize of the German Chemical Society from 1911 to 1934 (Table 3). This gold medal is the highest award to be given by the German Chemical Society to chemists who have made outstanding contributions to chemistry in general. Natural products and synthetic organic chemistry have, again, the highest interest in the selection of the winners. In fact, the only winner of this medal from the community of polymer-related chemists was Paul Schlack in 1958 for his work on poly(amide)s.

A similar picture is seen in the list of winners of the Emil Fischer Medal of the German Chemical Society, another highly regarded prize. It is considered to be the highest award for work in organic chemistry. The list of winners between 1912 and 1935 is given in Table 4.

Table 4 Winners of Emil Fischer Medal 1912–1935

Year	Winner of Emil Fischer Medal
1912	Fritz Hofmann, Breslau
1919	Otto Hahn, Berlin
1922	Carl Neuberg, Berlin
1927	Franz Fischer, Mülheim/Ruhr
	Alwin Mittasch, Mannheim
1928	Fritz Schönhöfer, Wuppertal-Elberfeld
	Werner Schulemann, Wuppertal-Elberfeld
	August Wingler, Leverkusen
1930	Kurt H. Meyer, Ludwigshafen
	Hermann Staudinger, Freiburg
1931	Felix Ehrlich, Breslau
1933	Fritz Kögl, Utrecht/Niederlande
1934	Hans Mauβ, Wuppertal-Elberfeld
	Fritz Mietsch, Wuppertal-Elberfeld
1935	Adolf Butenandt, Danzig

Here, Hermann Staudinger holds a place in the year 1930; however, not alone but jointly with Kurt H. Meyer (1882–1952). Meyer was Director of Research at BASF (Ludwigshafen), at the time part of the powerful IG-Farben Consortium. Meyer, a chemist very well known in those years for his academic work in physical organic chemistry (keto-enol tautomerism) had been hired by BASF in 1921 in order to reorganize and enlarge the research division of BASF. Once in Ludwigshafen, Meyer quickly realized the potential of research in fibrous materials and thereby polymers [7]. In 1926, he hired Hermann F. Mark away from his position at the aforementioned KWI für Faserstoff-Forschung in Berlin and gave him all the resources to build a research group of 50 people at Ludwigshafen. Meyer and Mark, both well aware of the work of H. S., were congenial partners and soon started to publish together. Staudinger considered this to be "unfair" competition and started to claim plagiarism of his ideas. In other words, he considered Meyer his arch-enemy, which is difficult to understand from today's point of view and even more difficult considering that Mark was an early and scientifically strong supporter of Staudinger's concept of macromolecules. One needs to mention that many patents concerning polymerization, processing of polymers, and their application resulted from the work at BASF [7], which counteracted Staudinger's activities, who himself was a quite industrious writer of patent applications.

Moreover, H. S. had strong ties as well as strong financial support from another constituent of IG-Farbenindustrie, namely Farbwerke Hoechst. In fact, he had been hired in 1927 as an "external coworker" with considerable financial remuneration for his consulting services [4]. In consequence, H. S. did not have very good feelings on receiving the Emil-Fischer Medal jointly with Meyer. The competition between the two never ceased and was, in the mind of H. S., even aggravated by the fact that Meyer and Mark succeeded in editing the first monographs on "high polymer natural products" in 1930 [8, 9], 2 years before H. S. was able to bring out his first book on "high molecular organic compounds" in 1932 [10]. Another book by Meyer and Mark appeared in 1937 [12].

However, this part of the story illustrates that the concepts developed by H. S. had the strongest impact on research and development in industry and led to revolutionary activities in the production of polymer-based materials. Among others, Wallace H. Carothers was a careful reader of Staudinger's publications [1, 2]. The two scientists actually met once in 1937 [2] and seemed to have understood each other very well. Another record describing the tremendous impact and response of the concepts of H. S. on industrial developments is to be found in the book by Ernst Trommsdorff [11] on the achievements of Otto Röhm, the founder of Röhm and Haas Company. This company did significant work in the industrial development of acrylate chemistry and materials based on this chemistry, all as a consequence of applying the ideas of H. S.

In summary, although H. S. always felt himself to be a true innovator in organic chemistry, this innovation found little applause by his contemporaries working as organic chemists in academia. It needed the wisdom and thought of the Nobel Prize committee to point to the enormous importance of Staudinger's work in the development of modern chemistry, in particular to the chemical industry as a supplier of modern materials. It was the success in industry that then spurred the development of a scientific community of polymer scientists (and engineers) as a branch of modern science in its own right.

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Staudinger's Time in Karlsruhe and His Later Relations with Karlsruhe

Manfred Wilhelm

Keywords Staudinger · Karlsruhe

Contents

1 Staudinger and Karlsruhe up to 1920 53
2 Staudinger and Karlsruhe, 1920 to 1945 56
3 Staudinger's Letters to Karlsruhe after 1945 58
References 59

1 Staudinger and Karlsruhe up to 1920

As a first remark, it should be noted that large portions of the archives of Karlsruhe University were lost during World War II (WWII) so that official documents about, e.g., the hiring process and the departure of Staudinger do not exist any longer (K. Nippert, July 2013, personal communication).

Hermann Staudinger finished his high school degree in 1899 at the age of 18 in Worms, the same city in which he was born in 1881. Worms is about 90 km from Karlsruhe. As the University of Karlsruhe has existed since 1825 and as his father had a Ph.D. degree, the family was certainly aware of the University of Karlsruhe. In 1903, Staudinger finished his Ph.D. in chemistry (at the University of Halle) after only 4 years of study, which included (!) the work for his Ph.D. thesis. Shortly before leaving for Karlsruhe, Staudinger married his first wife Dorothea Förster in 1906 and

M. Wilhelm (✉)
KIT, Karlsruher Institut für Technologie, Institut für Technische Chemie und Polymerchemie, Engesserstrasse 18, 76131 Karlsruhe, Germany
e-mail: manfred.wilhelm@kit.edu

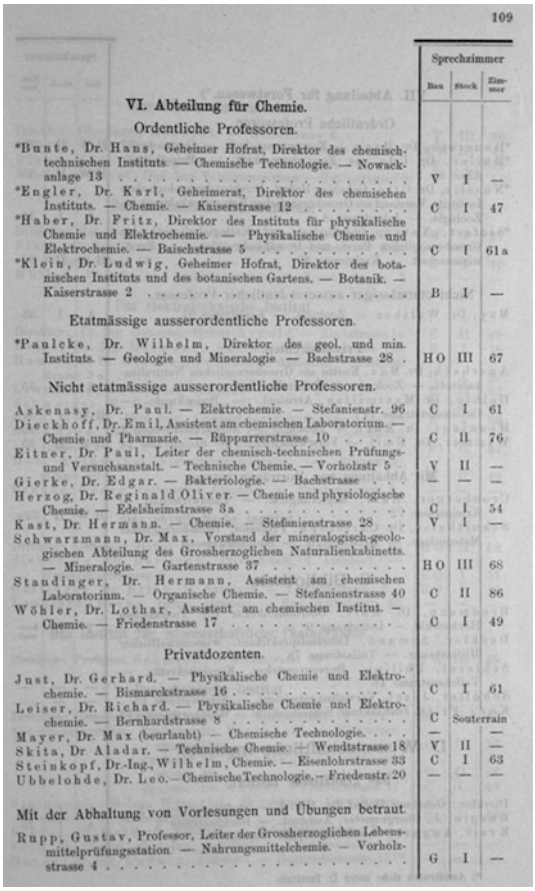
soon had a family with four children. In 1907, at the age of 26, Staudinger obtained his "habilitation" in Strasbourg with Johannes Thiele for his work on ketenes, and in 1907 became a professor at Karlsruhe University as the successor to Roland Scholl. Staudinger was deeply impressed in Karlsruhe by Carl Engler's personality (Engler played an important role in the hiring of Staudinger), and their close friendship lasted until Engler's death in 1925. Engler served as a role model in terms of organization and industrial contacts for Staudinger, as well as for Fritz Haber.

In Karsruhe, Staudinger's work was mainly related to ketenes, diazo compounds, oxalyl chloride, the preparation of isoprene and butadiene, and the polymerization of different compounds [1, 2]. In 1907 Carl Engler was 65 years old and very well known. Engler was on the Board of Directors for BASF, where he influenced the development of ammonia production via the Haber process [3]. Engler's main research interest was mineral oils, but he was also connected to polymers. The terms "polymers" and "polymeric" had already been coined by J.J. Berzelius in 1833 [4] and were used by Engler. Engler and Kronstein had published a first work on the polymerization of styrene as early as 1902 [5].

In his lecture notes for a presentation to "Der Schweizerischen Gesellschaft für chemische Industrie" on 7th October 1917 [6], Staudinger remarked on Engler's statements that auto-oxidation can speed up polymerization and this was the reason why Staudinger wanted to study this effect. This study was conducted between 1911–1913 as part of the Ph.D. thesis of Ludwig Carl Lautenschläger (see below).

To give a feeling for the faculty members at the time we refer to Fig. 1, where the chemistry faculty of Karlsruhe in 1910/1911 is listed, including their private addresses. Prior to the introduction of the internet, it was very common for German universities to mention the private addresses of the professors and university employees.

Please be aware that this page lists all members of the chemistry faculty of Karlsruhe in 1910. On pages 72 and 73 of this university calendar (not shown), a joint colloquium for the students of Engler and Staudinger, taking place every semester, is listed. Besides Fritz Haber and Staudinger (see Fig. 1), Staudinger's Ph.D. student at the time, Leopold Ruzicka, also eventually received a Nobel prize. After finishing his Ph.D. with Staudinger, Ruzicka continued to work with him as an assistant. It was again Carl Engler who introduced Staudinger to questions related to technical chemistry. For example, Engler developed a rheometer and Leo Ubbelohde (also listed in Fig. 1) from the same faculty developed a very simple and efficient viscosimeter to study low-viscosity mineral oils. Even today, an "Ubbelohde" is in use in many polymer laboratory courses. Therefore, there is a good chance that Staudinger developed his interest in the viscosity of liquids during his time in Karlsruhe. The measurement of the viscosity of polymer solutions became a very important scientific tool for him in his later time in Freiburg, especially as the "Notgemeinschaft der deutschen Wissenschaft" (Hardship Association of German Science) refused to give him an ultracentrifuge in 1929. Professor Paul Askenasy (Fig. 1) was the direct successor of Carl Engler in technical chemistry and had previously taught electrochemistry and battery technology in Karlsruhe between



109

	Sprechzimmer Bau	Stock	Zimmer
VI. Abteilung für Chemie.			
Ordentliche Professoren.			
*Bunte, Dr. Hans, Geheimer Hofrat, Direktor des chemisch-technischen Instituts. — Chemische Technologie. — Nowackanlage 13	V	I	—
*Engler, Dr. Karl, Geheimerat, Direktor des chemischen Instituts. — Chemie. — Kaiserstrasse 12	C	I	47
*Haber, Dr. Fritz, Direktor des Instituts für physikalische Chemie und Elektrochemie. — Physikalische Chemie und Elektrochemie. — Baischstrasse 5	C	I	61a
*Klein, Dr. Ludwig, Geheimer Hofrat, Direktor des botanischen Instituts und des botanischen Gartens. — Botanik. — Kaiserstrasse 2	B	I	—
Etatmässige ausserordentliche Professoren.			
*Paulcke, Dr. Wilhelm, Direktor des geol. und min. Instituts. — Geologie und Mineralogie. — Bachstrasse 28	H O	III	67
Nicht etatmässige ausserordentliche Professoren.			
Askenasy, Dr. Paul. — Elektrochemie. — Stefanienstr. 96	C	I	61
Dieckhoff, Dr. Emil, Assistent am chemischen Laboratorium. — Chemie und Pharmazie. — Rüppurrerstrasse 10	C	II	76
Eitner, Dr. Paul, Leiter der chemisch-technischen Prüfungs- und Versuchsanstalt. — Technische Chemie. — Vorholzstr 5	V	II	—
Gierke, Dr. Edgar. — Bakteriologie. — Bachstrasse	—	—	—
Herzog, Dr. Reginald Oliver. — Chemie und physiologische Chemie. — Edelsheimstrasse 3a	C	I	54
Kast, Dr. Hermann. — Chemie. — Stefanienstrasse 28	V	I	—
Schwarzmann, Dr. Max, Vorstand der mineralogisch-geologischen Abteilung des Grossherzoglichen Naturalienkabinetts. — Mineralogie. — Gartenstrasse 37	H O	III	68
Staudinger, Dr. Hermann, Assistent am chemischen Laboratorium. — Organische Chemie. — Stefanienstrasse 40	C	II	86
Wöhler, Dr. Lothar, Assistent am chemischen Institut. — Chemie. — Friedenstrasse 17	C	I	49
Privatdozenten.			
Just, Dr. Gerhard. — Physikalische Chemie und Elektrochemie. — Bismarckstrasse 16	C	I	61
Leiser, Dr. Richard. — Physikalische Chemie und Elektrochemie. — Bernhardstrasse 8	C	Souterrain	
Mayer, Dr. Max (beurlaubt) — Chemische Technologie.	—	—	—
Skita, Dr Aladar. — Technische Chemie. — Wendtstrasse 18	V	II	—
Steinkopf, Dr.-Ing., Wilhelm, Chemie. — Eisenlohrstrasse 33	C	I	63
Ubbelohde, Dr. Leo. — Chemische Technologie. — Friedenstr. 20	—	—	—
Mit der Abhaltung von Vorlesungen und Übungen betraut.			
Rupp, Gustav, Professor, Leiter der Grossherzoglichen Lebensmittelprüfungsstation. — Nahrungsmittelchemie. — Vorholzstrasse 4	G	I	—

Fig. 1 Karlsruhe University calendar 1910/1911, page 109, listing members of the chemistry faculty [29]

1910–1911. This topic is once again, after 100 years, a very active research area. Askenasy was Jewish and was forced to leave the faculty in 1933. He was followed in 1933 by Friedrich August Henglein [7].

Other interesting facts from this Karlsruhe period should be noted: Staudinger studied insecticides between 1910–1916 with Leopold Ruzicka, and Paul Immerwahr financially supported this study [8]. After 1916, Staudinger developed synthetic pepper substitutes in Zurich together with Paul Immerwahr. Paul Immerwahr was the brother of Clara Immerwahr, who was Fritz Haber's wife [9]. In 1915, Clara Immerwahr committed suicide in Berlin after a large poison gas attack on France by Germany in WWI because Haber was integrally involved in the technical development of poison gas warfare. This led to a major conflict in the friendship between Staudinger and Haber. It should further be noted that Kurt Hans Meyer, with whom Staudinger later had a substantial scientific dispute, was indirectly connected to Karlsruhe because Meyer worked under Haber from 1917 on poison gas warfare in Berlin.

During his time in Karlsruhe until 1914, Staudinger published in total about 40 papers of which approximately 30 were related to ketenes. Most of these publications were authored by Staudinger alone, or co-authored with typically only one or two co-authors. In total, 16 different co-authors can be found among these papers. Since a Ph.D. took about 2 years to complete at that time, we can estimate that his group might have consisted of around five to eight Ph.D. students.

As already mentioned, one of these students was Ludwig Carl Lautenschläger, who conducted work for his Ph.D. from 1911 to 1913 in Karlsruhe. This work was supervised by Engler, but was in very close collaboration with Staudinger and was on the topic of "Auto-oxydation und Polymerisation ungesättigter Kohlenwasserstoffe" (Auto-oxidation and polymerization of unsaturated hydrocarbons). In this Ph.D. thesis on p.24 and p.26, the influence of the oxygen content on the polymerization kinetics of different monomers was investigated, e.g., isoprene and styrene (up to 90% conversion in 4 h). In these early days, the polymerization product of styrene was called metastyrene because it came after styrene (in Greek, "*meta*" means "after"). Lautenschläger even tried to polymerize α-methylstyrene, but with very little success. Years later, it was found that the ceiling temperature of poly(α-methylstyrene) is extremely low. Two people were acknowledged at the end of this thesis: C. Engler and H. Staudinger. The relationship with Lautenschläger became important again in 1933 (see the next section).

One of the monomers used to make synthetic rubber was also introduced in Karlsruhe and started a whole series of 53 publications [6]: "Über die Darstellung von Isopren aus Terpenkohlenstoffen" (On the synthesis of isoprenes from terpenoide hydrocarbons) [10]. In this work, 1,4-polyisoprene is simply an eight-member ring built of two monomers.

In 1912, Staudinger received a call to go to ETH-Zurich in Switzerland as successor of Richard Willstädter, and Haber sent him a humorous "condolence" letter remarking that the times of simply working would soon be over. On 12 July 1912, the students of Staudinger presented him with a "good-bye" brochure, which was named after the political satire magazine *Simplicissimus*, to lighten his leaving [11]. In Fig. 2, page 9 of this brochure is reprinted and shows the dance of butadiene molecules to finally form synthetic rubber.

2 Staudinger and Karlsruhe, 1920 to 1945

In 1931, Lautenschläger and Staudinger finally published together parts of Lautenschläger's Ph.D. thesis [12]. This was 18 years after the oral examination! Nevertheless, the reconnection with his former Ph.D. student from Karlsruhe became important for Staudinger for a totally different reason. In August 1933, Staudinger asked Lautenschläger to write a letter of reference for him personally and for his work [13]. Times had changed and from April 1933 until April 1934 the philosopher Martin Heidegger was the first rector of the University of Freiburg after Hitler came into power. Heidegger put Staudinger under substantial pressure to

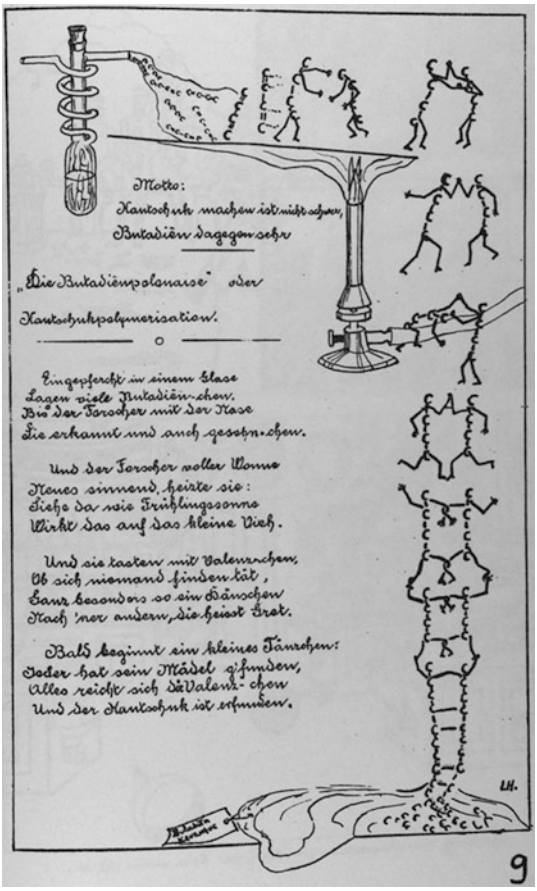


Fig. 2 The subject of page 9 of the special *Simplicissimus* brochure is a humorous poem concerning the polymerization of butadiene to obtain synthetic rubber (*Kautschuk* in German). This brochure is dated 12 July 1912 and was created for Staudinger on the occasion of his departure from Karlsruhe to take up an appointment at Zurich-ETH

leave [14] because, in his opinion, Staudinger did not seem to be nationalistic enough. This was especially because of several publications at the end of WWI and afterwards described the translation, in which Staudinger described translation of the energy generated from technical sources into the useful energy a horse produces within 1 year (*Pferdekraftjahre*, equivalent to 2,100 kWh/year) or later into "technical slaves" because a person is approximately one seventh of a horse's working equivalent, i.e., 300 kWh/year. The analysis showed that in 1919 the USA had many more "technical slaves" available [15]. Staudinger eventually had to sign a sheet that would be used as an application for dismissal in case he did not behave well. Lautenschläger, Staudinger's former Ph.D. student, was by then the first director of pharmaceutical research at IG-Farben in Hoechst and, from 1931, he was also on the IG-Farben Board of Directors. Later, in 1942, he became "Wehrwirtschaftsführer" (head of an important factory for warfare materials) [16], therefore the support of Lautenschläger was important for Staudinger. Additionally, Staudinger became a supporting member of the SS and NSDAP [13, 17],

most probably to show that he was not directly opposing the ruling system. The SS might have also demanded protection money from him [18]. There are two articles that reflect the high personal pressure that Staudinger was under at the time and are very much worth reading. The first publication discusses his conflict with Meyer that found climax in "Über hochpolymere Verbindungen, 140, Zur Entwicklung der makromolekularen Chemie. Zugleich Antwort auf die Entgegnung von K.H. Meyer und A. van der Wyk" [19]. The second article is related to the importance of rubber to the independence of a nation: "Über Isopren und Kautschuk, Der Aufbau der makromolekularen Stoffe Kautschuk und Isopren" [20]. In Freiburg, Staudinger was not only in a scientific conflict with Meyer (being a former assistant of Haber), but also with Werner Kuhn. Werner Kuhn was meanwhile Professor for Physical Chemistry in Karlsruhe from 1930 to 1936. During his time in Karlsruhe, Kuhn worked on the molecular conformation of polymers in solution and was the subject of the following rhyme by Staudinger's students: "die Kuhnschen Knäul sind uns hier ein Gräuel" (the statistical Kuhn segments are a horror to us). Staudinger didn't really believe that macromolecules are flexible [21]. It is not clear if Staudinger and Kuhn met either in Karlsruhe or Freiburg to discuss their opposing views about polymer conformations and the degrees of freedom that a polymer can have in solution. However, it would have been a train ride of only 1 h between Freiburg and Karlsruhe. Only at the end of his career did Staudinger accept the idea of flexible macromolecules, e.g., in "Über die röntgenographische und viskosimetrische Kettenlänge von Fadenmolekülen" [22]. He writes on page 306: "Daraus ergibt sich der Schluss, dass auch bei den Polyvinylverbindungen, wie bei Polyvinylchloriden, Polyvinylacetaten etc. die Abweichung vom einfachen Viskositätsgesetz mit einer Fadenform der Moleküle vereinbar sind, und nicht dafür Verzweigungen verantwortlich gemacht werden müssen"; translation: ". . .therefore we come to the conclusion that also for vinyl polymers, e.g., PVC, PVAc, etc. the discrepancy from the simple viscosity law can be related to the random, strand shape of a molecule and branching might not be needed as a further argument."

In 1945, directly after WWII, his former student from Karlsruhe, Leopold Ruzicka, helped Staudinger with a letter that allowed him to work again in the French zone, where Freiburg was located [14].

3 Staudinger's Letters to Karlsruhe after 1945

During wartime, and especially afterwards, Staudinger had an intense relationship with Karlsruhe and mostly with Prof. F.A. Henglein. Henglein was a technical chemist and from the beginning was on the editorial board of Staudinger's *Journal für Makromolekulare Chemie*, later renamed *Die Makromolekulare Chemie*. He was the successor of Prof. P. Askenasy (see also Fig. 1).

The letters between Karlsruhe and Freiburg are very personal and reflect the problems at the time, but also issues that come up in any faculty. Most of the letters were sent from their homes to the private address of the other and were signed

accordingly "*..mit herzlichen Grüßen von Haus zu Haus*" (..with warm greetings from house to house). It seems that they also visited each other frequently and stayed overnight in each other's homes [23]. Once Henglein could not visit Staudinger because he could not get a visa, Karlsruhe being in the American sector and Freiburg in the French sector [23]. Staudinger was asked to help the daughter of a former colleague so that she could study medicine in Freiburg [23] and also to accept a Ph.D. student in Freiburg [24]. In one case, names were asked for a potential professor in organic chemistry in Karlsruhe [25]. Staudinger himself told Henglein that due to electricity shortage, publications would be delayed [26]. In another case, Henglein asked Staudinger for an organic chemist with a Ph.D. degree as an assistant [27].

In 1950, Henglein wrote a letter to his own faculty on the occasion of the 125th anniversary celebration of the University of Karlsruhe suggesting that Staudinger receive an honorary Ph.D. He stated that Staudinger had always keep close relationships with Karlsruhe and basically came every year to present his work within the "Chemische Gesellschaft" of Karlsruhe [28].

The time in Karlsruhe was very productive for Staudinger. He got to know Carl Engler and his way of organizing a group. Staudinger appreciated Engler's orientation towards industrially relevant questions. In addition to Engler, perhaps the most important people he met in Karlsruhe from 1907 to 1912 (for very different reasons in his life) were Haber, Lautenschläger, Paul Immerwahr, Ubbelohde, and Ruzicka. Scientifically, Staudinger became familiar with polymers, viscosity, and industry while in Karlsruhe. All these are aspects that became very important during his later career.

And what happened in Karlsruhe with respect to polymers after Staudunger left? The work was continued and new professorships were established. Recent professors with a focus on polymer science have been, so far: B. Vollmert (1965–1986, synthesis), H. Nimz (1968–1983, lignin), M. Ballauff (1990–2003, colloids), G. Wenz (1993–2002, polyrotaxanes), S. Höger (2002–2006, synthesis), M. Wilhelm (2006–, rheology), C. Barner-Kowollik (2008–, synthesis), and M. Meier (2010–, biopolymers).

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Why Was the Macromolecular Hypothesis Such a Big Deal?

Ulrich W. Suter

Abstract Natural macromolecular materials have been in use since before *Homo sapiens* evolved. Macromolecular manmade materials, products of ancient chemical technology, have a shorter history, but still date back to before the advent of man. We trace these materials from their earliest form through antiquity and the industrial revolution to today's complex "plastics." We then consider the evolution of chemistry and the molecular concept and explore the confusion in the nineteenth century concerning the possible existence of large molecules. Despite experimental results, beginning in 1825, that pointed to molecular weights in the tens of thousands, the predominant scientific view was that no such molecules could exist. This stubbornly upheld position was overturned by the efforts of an initially small number of scientists, led by Herrmann Staudinger, who changed the understanding of the nature of macromolecules within roughly a decade, from about 1920 on.

Keywords History of chemistry · History of materials · Macromolecules · Plastics · Polymers

Contents

1 How Macromolecular Substances Came Into Use 62
2 Chemistry and the Molecular Concept 66
3 The Big Deal 69
References 78

U.W. Suter (✉)
Department of Materials, ETH Zurich, Zurich, Switzerland
e-mail: uwsuter@ethz.ch

The central theme of our education is often based on the conviction that practice follows scientific understanding. But it is more common that practice and its surprising and exceptional results stimulate the scientific quest and only then allows, in turn, scientifically inspired progress in practice. This is most evident in the way in which macromolecular substances and our interactions with them have changed human life. Chemistry is one of the great steps in our conceptual development (and we should not forget physics), but the experience was first and the chemical understanding of matter, and particularly of macromolecular matter, only evolved after many millennia of beneficial experimentation with and use of macromolecular substances. Here we would like to substantiate this fact once more.

First, however, a cautionary note: the ideas presented here are not original nor based on the author's work. What you read in the following is entirely derivative and rests exclusively on the publications of others. The author attempts to cite the work of the major contributors and the reviews from which he also learned, but admits that he has left out many great contributions and conceptual creations. The reviewers that most influenced him are Paul J. Flory [1], Herbert Morawetz [2, 3], and Dietrich Braun [4].

1 How Macromolecular Substances Came Into Use

Natural macromolecular materials have been in use since before *Homo sapiens* evolved. At first, these were natural substances, available for use without any intervention. Our ancestors and mankind from its beginnings have protected themselves with skins and weavings, used fibers and sticks, and employed bitumen for gluing and sealing. Macromolecular manmade materials have a shorter history, but still date back to before the advent of *Homo sapiens*, i.e., to species existing before us (see [5] and its excellent bibliography!). The substance possibly used earliest is birch bark pitch, an adhesive (and arguably medical chewing substance [6]) made by controlled heating of white birch bark under exclusion of air [7], that was invented by *Homo erectus* or Neanderthal man, certainly at least 80,000 years [8, 9] and possibly more than 180,000 years ago [10, 11], and was ubiquitously produced globally. It is a "product of ancient chemical technology" [12]. *Homo sapiens* made a wide range of adhesives by artisanal production more than 70,000 years ago in South Africa [13, 14].

Other natural products were also converted into useful materials [15]. Development and use was worldwide and left its traces in all high cultures, from which artifacts are still available. Adhesive bonding apparently was everywhere the first use. There are reports of discoveries in the early Middle Eastern societies such as Assyria, Mesopotamia, Babylon, etc. (see [16] and sources cited therein), as well as Rome [17], and ancient Egypt [18] that demonstrate many parallels but also show interesting differences. With time, the use of macromolecular substances evolved from adhesives to shapes; at first as inlay material (e.g., for weapons and jewelry in the Bronze Age [19]), then as material from which entire shapes could be

fabricated. The report of an early rubber (vulcanized caoutchouc) dates it at around 1600 BC; it was used by the Olmecs in today's Mexico to produce a range of products [20]. A particularly well-documented example is the manufacture of a plastic out of casein, which is obtained from low-fat cheeses [21]. The formula was chronicled by the Benedictine clergyman and alchemist Wolfgang Seydel (also Seidel) from Bavaria in 1530. The recipe explains how to first purify casein and then transform it with lye into a transparent and colorless artificial resin – "a transparent material, similar to sheep's horn." The product could be formed according to one's desire, dyed, and polished. The style of the recipe is so prosaic that it seems evident that there must have been many such formulae at the time; it is likely that the practice of manufacturing plastics has simply not been of interest to historians.

After the onset of the industrial revolution, around 1800, the growing economies led to the emergence of physics and chemistry as fields of study. Numerous new macromolecular materials appeared. The early nineteenth century was the time of passionate inventors and diligent entrepreneurs. In 1833, Friedrich Lüdersdorff wrote about the manufacture of a nanocomposite material made of colloidal gold and gum Arabic [22]. In 1838 H. Victor Regnault accidentally obtained a white powder from gaseous vinyl chloride after exposure to sunlight in his laboratory, today known as polyvinyl chloride, PVC [23]. In 1839, Eduard Simon extracted styrene from storax, a natural product already known to the Romans [24], and noticed that the "influence of air, light and heat" converted styrene into a solid resin [25]. He thought he had styrene oxide, but John Blyth and August Wilhelm von Hofmann discovered in 1845 that the solid matter obtained through heating styrene had the same elemental composition as styrene and therefore called it "metastyrene" – today's polystyrene [26]. In the middle of the nineteenth century, new plastics were invented at an increasing rate and many industrial uses were found for them. First among them was the "European" rubber (for the Mesoamerican rubber see [20]), invented by Charles N. Goodyear through vulcanization of caoutchouc by sulfur in 1839 and patented in the USA in 1844 [27]. Goodyear was probably followed in invention, but overtaken in patenting, by Thomas Hancock in England [28]. The plastics industry as we know it today originated from the production of rubber. An idea of the impact of rubber on society can be glimpsed from the architectural literature of the 1860s. For Gottfried Semper [29], eminent architect, stylist, and art historian, it was evident that clothing, housing, transportation, etc. would soon be dominated by objects made from rubber. The outside walls of houses would be rubber-coated and hence made waterproof, similarly waterproof wall paper, furniture, book coverings, and umbrellas would be made from rubber, and many, many other things. Semper ended his article with the enthusiastic exclamation: "A stylist faced with a material of this kind will be at a loss for words!"[1] [30]

Macromolecular materials have contributed greatly to the elevated living standard of the population at large, rendering articles inexpensive that before had

[1] "Bei einer solchen Materie steht einem Stilisten der Verstand still!" [29]

been affordable only by the wealthy. They enabled efficient manufacture of better quality products and also possessed a previously unknown portfolio of properties.

The next great step after rubber came with derivatives of cellulose, esterified into nitrocellulose even before 1850. The completely nitrated form, cellulose trinitrate, was used as gun cotton, an explosive, while the equally flammable cellulose dinitrate was called collodion cotton and utilized as a varnish and in medicine. Several inventors tried to make the material less hazardous by adding other substances. In 1856, Alexander Parkes was the first to succeed in producing a practical thermoplastic material from cellulose dinitrate, oil, and camphor ("Parkesine") [31], but he was not able to market it successfully. The breakthrough came in 1868 when John W. Hyatt, in an effort to win 10,000 US dollars in prize money,[2] managed to mix cellulose dinitrate and camphor [32]. The material was registered under the trademark Celluloid and was produced and sold starting in 1870. Its success was due in large part to the thermoplastic character of the material, as well as the good dyeability. Combs, dentures, eyeglass frames, bowls, jars, fountain pens, knife handles, etc. were the result. Celluloid also played a key role in the development of photography and cinematography: as a stiff, tough, and completely transparent film, it made photography easier and cheaper. From 1884 on, celluloid made motion-pictures possible – "to capture on celluloid" became synonymous with putting on film (although less flammable plastics have displaced celluloid, and digital motion pictures do not need any transparent carrier material). Other great plastics have other origins: Galalith, for instance, is a material obtained from milk and formaldehyde, accidentally discovered by Adolf Spitteler and Wilhelm Krische in 1897 and patented in 1899 [33–35].

The synthetic textiles industry also evolved on the basis of cellulose, a very pure and cheap raw material. Cellulose is infusible, insoluble in nearly all liquids, and difficult to process. Efforts were directed at making it soluble. In 1855, George Audémars patented the manufacture of fine fibers from cellulose nitrate [36]. In 1888, Joseph Swan drew fibers from cellulose nitrate in acetic acid to make filaments in electric lamps; he also recognized the textile potential and was the first to create cloth from it [37]. A great advancement was made by Hilaire Bernigaud, Comte de Chardonnet de Grange, who spun cellulose nitrate out of a mixture of alcohol and ether in 1884 and who presented the fabric at the World Fair in 1889 in Paris [37]. This fabric was soon known as "Chardonnet silk" and led to the first synthetic textile factory being built in Besançon. Chardonnet rendered the fabric less flammable through denitration in a hydrosulfide bath. Just one year after the Paris exhibition, Louis Henri Despaisses discovered that cellulose can be dissolved via copper oxide and ammonia and precipitated again in diluted sulfuric acid; he used Chardonnet's spinning technique for the "regenerated cellulose" [37]. The next step in the evolution of synthetic fibers was the accomplishment of

[2] The prize was advertised by the Phelan Collender Billiard Factory in New York, which had been looking for a substitute material for ivory in billiard balls; the award would be valued at a million dollars today on the basis of an average worker's wages.

Charles F. Cross, Edward J. Bevan, and Clayton Beadle with the so-called "viscose process": using alkali and carbon disulfide, cellulose is reversibly converted into the xanthogenate (or xanthate) and thus rendered soluble (the gelatinous solution was called "viscoid"), spun, and then transformed back into cellulose in an acid bath, and now called "rayon" [38]. But it wasn't until 1900, with the invention of modern spinning equipment by Charles F. Topham, that it became possible to create cellulose fibers commercially [39]. Jacques E. Brandenberger succeeded in producing crystal clear films out of rayon in 1908 in Paris with a new type of machine; he called the product cellophane – the first flexible, transparent, and waterproof packaging material – and patented the process in 1918 [40].

For four decades chemists and inventors had tried to create a practical plastic from formaldehyde and phenol (both very inexpensive waste products from the thriving chemical industry), when in 1907 Leo H. Baekeland managed to produce, using an alkaline formulation and ground wood as filler, a synthetic resin [41]. He wanted to find an insulating material that could replace shellac, manufactured from the secretions of the Indian *Kerria lacca* (lac insect), which was becoming scarcer and therefore more expensive. Bakelite satisfied all these requirements and more. It served for many years as an ideal electric insulating material and is still manufactured today. The first large-scale Bakelite lots were produced in 1909. Bakelite proved to be very versatile, known as the material of a thousand uses. When the patent on the Bakelite production process expired, other manufacturers appeared on the market and the production of phenol resins surged.

When Victor Regnault had discovered in 1838 that gaseous vinyl chloride turned into a white powder under the influence of sunlight, he did not appreciate that this solid material would later gain extraordinary significance. After 1900, interest in this and other vinylic substances grew; Friedrich August Heinrich Klatte patented a polymerization process for the industrial use of such monomers [42] and polyvinylchloride became especially interesting from an economic viewpoint because chlorine was available in large quantities as a byproduct of the chloroalkali electrolysis in the rapidly advancing chemical industry. Large scale production was on the horizon.

By 1910, it was evident that the materials of interest here were on the way to becoming the multifunctional materials of modern society. The first journal dedicated to the ill-defined but important class of substances appeared 1911 in Munich and was edited by Ernst R. Escales who had coined the term "Kunststoffe" (roughly equivalent in meaning to "plastics," "synthetics," or "synthetic materials") the year before. The journal's title page was as follows[3]:

[3] KUNSTSTOFFE/Zeitschrift für Erzeugung und Verwendung veredelter oder chemisch hergestellter Stoffe/mit besonderer Berücksichtigung von Kunstseide und anderen Kunstfasern, von vulkanisiertem, devulkanisiertem (wiedergewonnenem) und künstlichem Kautschuk, Guttapercha usw. sowie Ersatzstoffen, von Zellhorn (Zelluloid) und ähnlichen Zellstofferzeugnissen, von künstlichem Leder und Ledertuchen (Linoleum), von Kunstharzen, Kasein-Erzeugnissen usw.

Plastics. Journal for the manufacture and application of processed or chemically fabricated materials with special consideration of artificial silk and other man-made fibers, of vulcanized, devulcanized (reclaimed) and synthetic caoutchouc, gutta-percha etc. as well as substitute materials, of celluloid and similar cellulose products, of man-made leather and leather fabrics (linoleum), of resins, casein products etc.

Note that all the examples given in the subtitles are macromolecular substances, but the use of the term "plastics" ("Kunststoffe") did not imply any claims on the chemical constitution of the material or its constituents. The word "polymer" had already been coined in 1832 by Jöns Jakob Berzelius [43], but his definition differs significantly from modern usage. Berzelius described organic compounds that share identical elemental composition but differ in overall molecular weight, the larger of the compounds being described as "polymers" of the smallest (e.g., glucose, $C_6H_{12}O_6$, was a "polymer" of formaldehyde, CH_2O). The concept that very large molecules play a significant role in the properties of these materials would not have been accepted at the time, neither by Berzelius nor by Escales. Then, chemistry had only the vaguest idea of the molecular nature of the new class of substances.

2 Chemistry and the Molecular Concept

The modern concept of "molecule" originated, one says, from a publication of Robert Boyle in 1661 (he called them "chemical anatomies" or "parcels of matter") [44] and was then further developed by others. By the end of the eighteenth century, the molecular idea was already soundly established (e.g., "Every material having a different form in its molecules and different distance between them . . ."[4] [45]) and large molecules such as albumin and gelatin had already been isolated and characterized [46] (although molecular weight could only be determined by measurement of the vapor density).

Not long afterwards work appeared that pointed in the direction of large molecular weights. In 1825, Johann Friedrich Engelhard [47] determined by elemental analysis that hemoglobins from different species all had roughly the same iron content (0.4% w/w), which led him to conclude that hemoglobins had to have molecular weights of integer multiples of 16,000 (today we know that the hemoglobin "monomer" has a molecular weight of about 17,000). The work was cited and discussed by many sources. In 1839, Gerardus Johannes Mulder published a remarkable paper [48] in which he determined the minimum molecular weight of three proteins (fibrin, egg albumin, and serum albumin) by precise determination of the elemental composition and arrived at values of the order of integer multiples of about 15,000 for all three. We now know that these proteins are complexes with

[4] "Chaque corps ayant une forme différente dans ces molécules et un écartement différent entre elles, ..."

many components of molecular weight significantly higher than 30,000. The early work was roughly correct, even though it was based on little else but elemental analysis and gravimetry of derivatives. Since all molecules known then with generally accepted molecular weights were volatile and, hence, small, the reports such as those by Engelhard and Mulder did not sound credible.

When Berzelius coined the term "polymer," he did not intend for it to mean what we today call a polymer [43] (although it may include the results of addition polymerization). Pierre Eugene Marcellin Berthelot narrowed the definition to only describe the results of addition polymerization[5] [49]; he had himself isolated the first three oligomers of 1-pentene but he did not posit the existence of truly long chains. Probably the first to suggest that much larger molecules could exist (and could be found in the non-distillable fractions of the condensation mixtures) was Agostinho Vicente Lourenço, who prepared several oligomers of ethylene glycol and ethylene succinate and conceived copolymerization [50, 51]. He was followed in his belief in large chain molecules by a number of other chemists, e.g., Heinrich Hlasiwetz and Josef Habermann, [52] who considered proteins to comprise condensed molecular fragments. After 1880, several other researchers obtained molecular weights for natural substances in excess of 10,000, such as caoutchouc and solubilized derivatives of carbohydrates. Alfred Werner postulated in 1896 [53] that Magnus' green salt, $Pt(NH_3)_4$ $PtCl_4$ [54, 55], contained platinum chains. But their combined opinion was not sufficient to sway the position of the scientific community.

Instead, the theory of a colloid state of matter gained ground – this was supposed to be a fourth state like the solid, liquid, and gaseous states. At first there was the discovery of Thomas Graham in 1861 that albumin and other natural substances had extremely small rates of diffusion in solution and also only very slowly permeated semipermeable membranes; this led him to conclude that these materials must exist in an aggregated state, as "colloids" [56]. This interpretation became stronger with time. The connections between the molecules in the aggregate were thought to be labile due to "partial valences" and the apparent molecular weights were, therefore, dependent on concentration, temperature, and composition of the solutions. The structure of the aggregated molecules was most often assumed to be cyclic, thereby avoiding the problems that the apparently non-existing molecular termini posed. The determination of molecular weight in solution only began to be available in the 1880s (the ground-breaking contributions of François-Marie Raoult and Jacobus Henricus van't Hoff on vapor pressure and cryoscopy have been described many times [1, 2]) and the colloid theory seemed to provide very plausible explanations for the strange behavior of what we know today to be macromolecular substances. After the creation of ideal solution theory, colloid science neatly made it possible to explain the unorthodox results of physical-chemical measurements on macromolecular solutions, since the unexpected behavior could be described as the

[5] "La polymérie est l'isomérie des corps formés par la réunion de plusieurs molécules identiques en une seule."

results of association phenomena. The apex of this doctrine was in the early twentieth century and first among the protagonists were Carl Wilhelm Wolfgang Ostwald [57] and Wolfgang Josef Pauli [58] (father of the Physics Nobel Laureate). The quintessence of colloid theory was: "to polymerize" means "to aggregate."

Finally, the anti-large-molecules camp was assisted by crystallographers who analyzed crystalline macromolecular substances (e.g., fibers of cellulose and stretched caoutchouc). There was broad agreement that a molecule could not be larger than its unit cell. Even though Michael Polanyi pointed out, in a public discussion in 1921, the possibility that molecules larger than their unit cells could exist [59],[6] the argument was not taken up again for some time, neither by him nor by others.

Early in the twentieth century, chemists held, almost exclusively, the belief that molecules were always small and could not be stable above a critical molecular weight that appears, from today's vantage point, amazingly modest. They also held the view that a pure substance consisted of a single molecular component. Proponents of this view estimated the limit of molecular weight to be in the few thousand [60]. By 1920, most chemists were firmly sworn to the canon that large-chain molecules could not exist. The 1902 Nobel Laureate in Chemistry, Hermann Emil Fischer, said in 1913 that very large molecular weights were not possible and pointed to the highest known molecular weight of 4,021for an artificial sugar compound [61, 62]. Paul Karrer, who was awarded the Nobel Prize in Chemistry in 1937, wrote in 1921 [63]: "It is surprising that the idea, dozens or hundreds of glucose molecules should be connected in long chains in starch, has survived unimpaired for decades. If this were the case one would certainly have found well-characterized higher intermediates, given the constant buildup and degradation of starch in plants, with enzymatic, acidic cleavage. It is also quite improbable that a plant, in converting sugar into the storage material starch, which soon again might have to be reconverted, would carry out such complicated work as is the

[6] On 7 March 1921, Polanyi gave a speech at the Kaiser-Wilhelm-Institut for Physical Chemistry and Electrochemistry and remarked (our translation):"Either cellulose consists of chains of the form

$$\ldots\ldots - O - \overset{\rightarrow}{C_6H_{10}O_4} - O - \overset{\rightarrow}{C_6H_{10}O_4} - O - \overset{\rightarrow}{C_6H_{10}O_4} - \quad \ldots\ldots$$

or of rings of the form

$$\begin{array}{l} \overset{\rightarrow}{C_6H_{10}O_4} - O \\ | \qquad\qquad | \\ O - O_4H_{10}C_6 \\ \qquad\quad \leftarrow \end{array}$$

"

The arrows were supposed to indicate the unequal position of the aldehyde groups of the glucose moieties with respect to the glycosidic oxygen.

buildup of a polyglucoside with many glucose residues."[7] Apostates were not taken seriously and were often ridiculed. An often quoted letter of the Chemistry Nobel prizewinner of 1927, Heinrich Wieland, to Herrmann Staudinger reads: "Dear colleague, abandon this idea of large molecules; organic molecules with molecular weight above 5,000 do not exist! Purify your products and they will crystallize and reveal themselves as low-molecular-weight compounds"[8] [64]. Another colleague is reported to have written: "Dear colleague, you used to do such beautiful work in the classical organic field; return to this and don't waste your time with gunk chemistry"[9] [64].

3 The Big Deal

There were several scientists who had obtained results that were clearly in disagreement with colloid theory, but their contributions were ignored [1, 3, 65, 66]. A person was needed of high achievement in classical chemistry, convinced of the macromolecular hypothesis (developed and expressed in the several decades before), of unbendable conviction that he was correct, and with the strong, even irascible character of a warrior. Herrmann Staudinger was this hero.

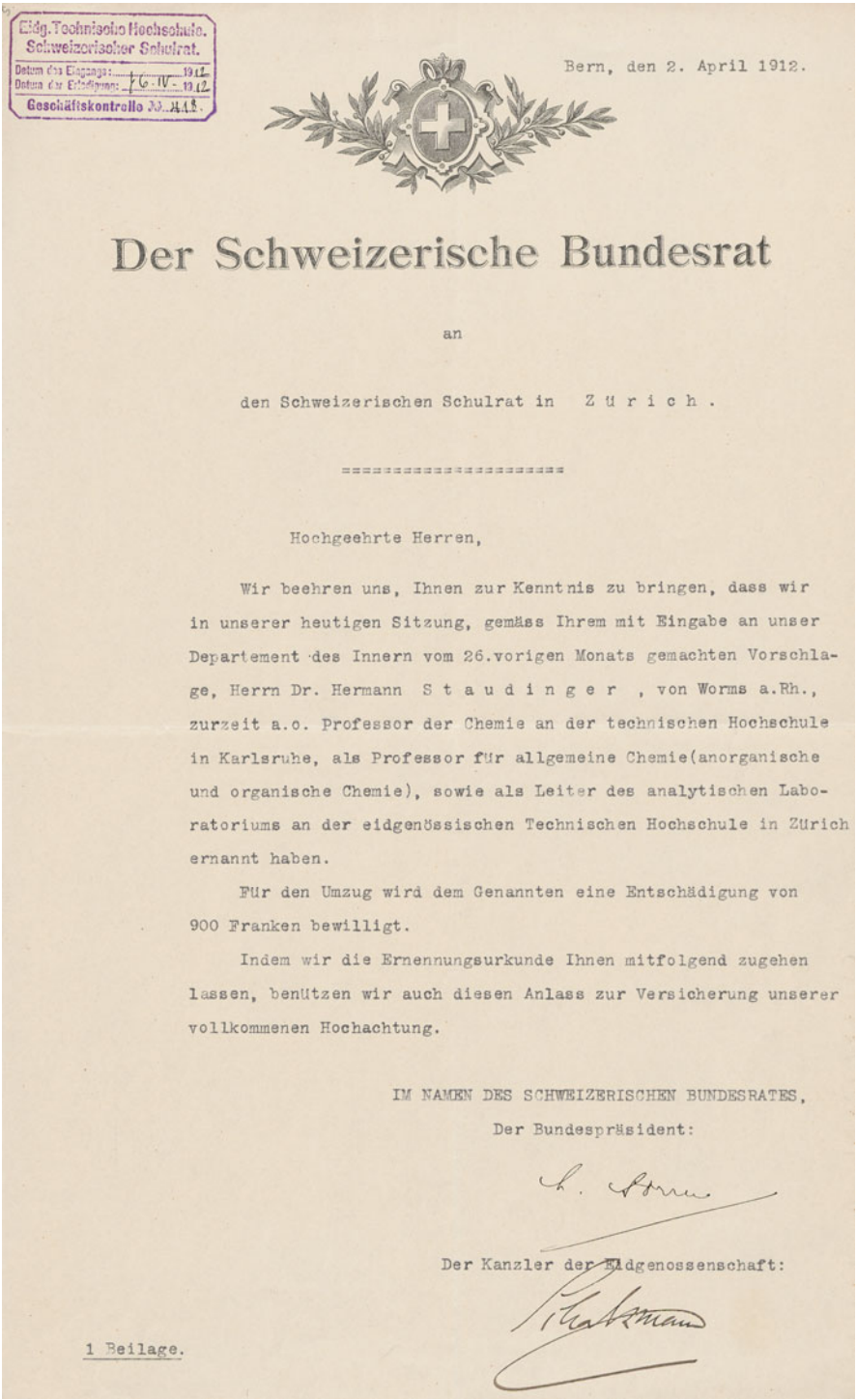
When Herrmann Staudinger, then "Extraordinary Professor" at the Institute of Technology at Karlsruhe, Germany, was appointed to the faculty of the Swiss Federal Institute of Technology in Zurich (eidgenössische Technische Hochschule in Zürich, ETH) on 2 April 1912, the regents of that institute of technology probably did not anticipate what impact this act would have on chemistry, on science in general, and on the civil atmosphere in the academic circles in Zurich (Fig. 1).

Staudinger was convinced of the fallacy of the general notion that polymeric substances had to be association compounds held together by partial valences. At the outset of his quest he was mainly interested in caoutchouc, polystyrene ("metastyrene"), and polyoxymethylene (paraformaldehyde). He first stated his

[7] "Man muss sich füglich wundern, dass die Anschauung, es seien Dutzende oder Hunderte von Glucosemolekeln beim Aufbau der Stärke glucosidisch zu langen Reihen miteinander verbunden, jahrzehntelang sich fast unerschüttert halten konnte. Denn bei dem steten Auf- und Abbau der Stärke in den Pflanzen, bei den enzymatischen und Säure-Spaltungen, hätte man in solchem Fall doch ab und zu wohlcharakterisierte höhere Zwischenprodukte antreffen müssen. Auch ist es recht unwahrscheinlich, dass die Pflanze beim Überführen des Zuckers in den Reservestoff Stärke, der vielleicht sehr bald wieder zurückverwandelt werden muss, so komplizierte Arbeit leisten wird, wie sie der Aufhau eines Polyglucosides mit sehr zahlreichen Glucoseresten wäre."

[8] "Lieber Herr Kollege, lassen Sie doch die Vorstellung mit den großen Molekülen; organische Moleküle mit einem Molekulargewicht über 5,000 gibt es nicht! Reinigen Sie Ihre Produkte, dann werden diese kristallisieren und sich als niedermolekulare Stoffe erweisen."

[9] "Herr Kollege, Sie haben früher so schöne Arbeiten auf dem klassisch-organischen Gebiet gemacht, nehmen Sie diese wieder auf und vergeuden Sie Ihre Zeit nicht mit der Schmierenchemie."



Eidg. Technische Hochschule.
Schweizerischer Schulrat.
Datum des Eingangs: 16. IV. 1912
Datum der Erledigung:
Geschäftskontrolle

Bern, den 2. April 1912.

Der Schweizerische Bundesrat

an

den Schweizerischen Schulrat in Z ü r i c h .

==========

Hochgeehrte Herren,

Wir beehren uns, Ihnen zur Kenntnis zu bringen, dass wir in unserer heutigen Sitzung, gemäss Ihrem mit Eingabe an unser Departement des Innern vom 26.vorigen Monats gemachten Vorschlage, Herrn Dr. Hermann S t a u d i n g e r , von Worms a.Rh., zurzeit a.o. Professor der Chemie an der technischen Hochschule in Karlsruhe, als Professor für allgemeine Chemie(anorganische und organische Chemie), sowie als Leiter des analytischen Laboratoriums an der eidgenössischen Technischen Hochschule in Zürich ernannt haben.

Für den Umzug wird dem Genannten eine Entschädigung von 900 Franken bewilligt.

Indem wir die Ernennungsurkunde Ihnen mitfolgend zugehen lassen, benützen wir auch diesen Anlass zur Versicherung unserer vollkommenen Hochachtung.

IM NAMEN DES SCHWEIZERISCHEN BUNDESRATES,
Der Bundespräsident:

Der Kanzler der Eidgenossenschaft:

1 Beilage.

Fig. 1 Letter of nomination of the Swiss Government for Dr. Herrmann Staudinger, dated 2 April 1912. Source: ETH Library Zurich, SR3: 1912, No. 418

conviction that polymers are "high-molecular" substances consisting of covalently bonded chain molecules in a lecture in 1919 [67]. In his teaching, he already had solidly established the modern concept of polymerization and polymers; lecture notes of his chemistry students show this convincingly. We show here four pages from the notes of Adolf Krebser, who took Staudinger's Organic Chemistry course in the summer semester of 1919. On the second page, addition polymerization is introduced and the structure of polyoxymethylene on the third page is self-evident. The fourth page shows an example of a condensation polymerization (Figs. 2, 3, 4, and 5).

The nomenclature had not been changed yet: the lecture notes of Max Brunner (student in the winter semester 1921/22) give a definition of the term polymer that is almost identical with that of Berzelius (Fig. 6).

In 1920, there followed a landmark paper [68] entitled "On polymerization" in which Staudinger explains his views on polymerization and attempts to separate polymerization from similar processes, such as dimerizations where the dimer is not able to react analogously to the monomer. He also introduced the, now common, chain formulae for polyoxymethylene, polystyrene, and polyisoprene (caoutchouc) – but not without crediting Pickles [66] for inventing the notation with the example of polyisoprene – and the polymeric anhydrides of malonic acid and adipic acid. These were still largely conjectures, but Hermann Staudinger and Jakob Fritschi [69] provided the first convincing experimental proof with the observation that caoutchouc and its saturated derivative ("hydrogenated rubber") exhibit the same "colloidal" behavior, even though caoutchouc has a large number of electron-rich double bonds (before believed to be the cause of the colloidal behavior) and the hydrogenated alkane is entirely devoid of them. In addition, they also emphasized the fact that polymolecularity of such high molecular weight substances was unavoidable.

After 14 years at ETH, Herrmann Staudinger left Zurich in 1926 and assumed a position at the University of Freiburg (Germany), where he continued and amplified his work on macromolecules (Fig. 7).

Staudinger relentlessly championed the molecular, or primary valence, viewpoint in the years that followed [1, 70]. His research group systematically created a number of new polymer classes and he was slowly joined in his views by a larger and larger fraction of scientists. Some exceptional synthetic chemists supported his concepts (e.g., Wallace Hume Carothers [71]) and physical chemists and physicists joined ranks with him (e.g., Kurt Heinrich Meyer [72], Herman Francis Mark [73], Werner Kuhn [74], and Rudolf Signer [75]) although their relationships with Staudinger were more often strained than not. Staudinger was a man of strong character and not always willing to compromise.

In the mid-1930s the battle had largely been won. Only a few pockets of science continued to harbor colloidal concepts for chain molecules (e.g., biology), but these areas had also adopted "Staudinger's" viewpoint by 1940.

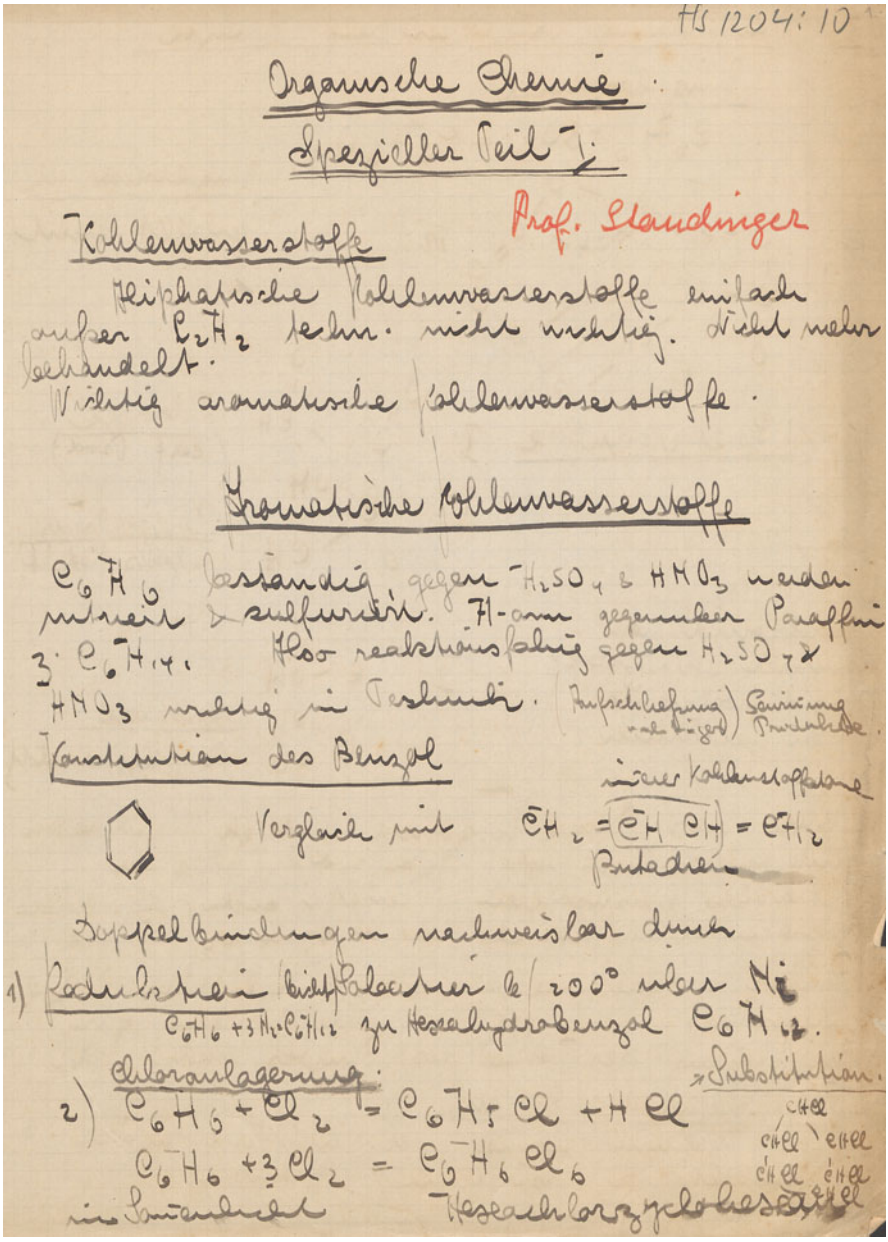


Fig. 2 From the lecture notes of Adolf Krebser in Herrmann Staudinger's class on organic chemistry in the summer of 1919. Source: ETH Library Zurich, Hs 1204, 1919, p 1

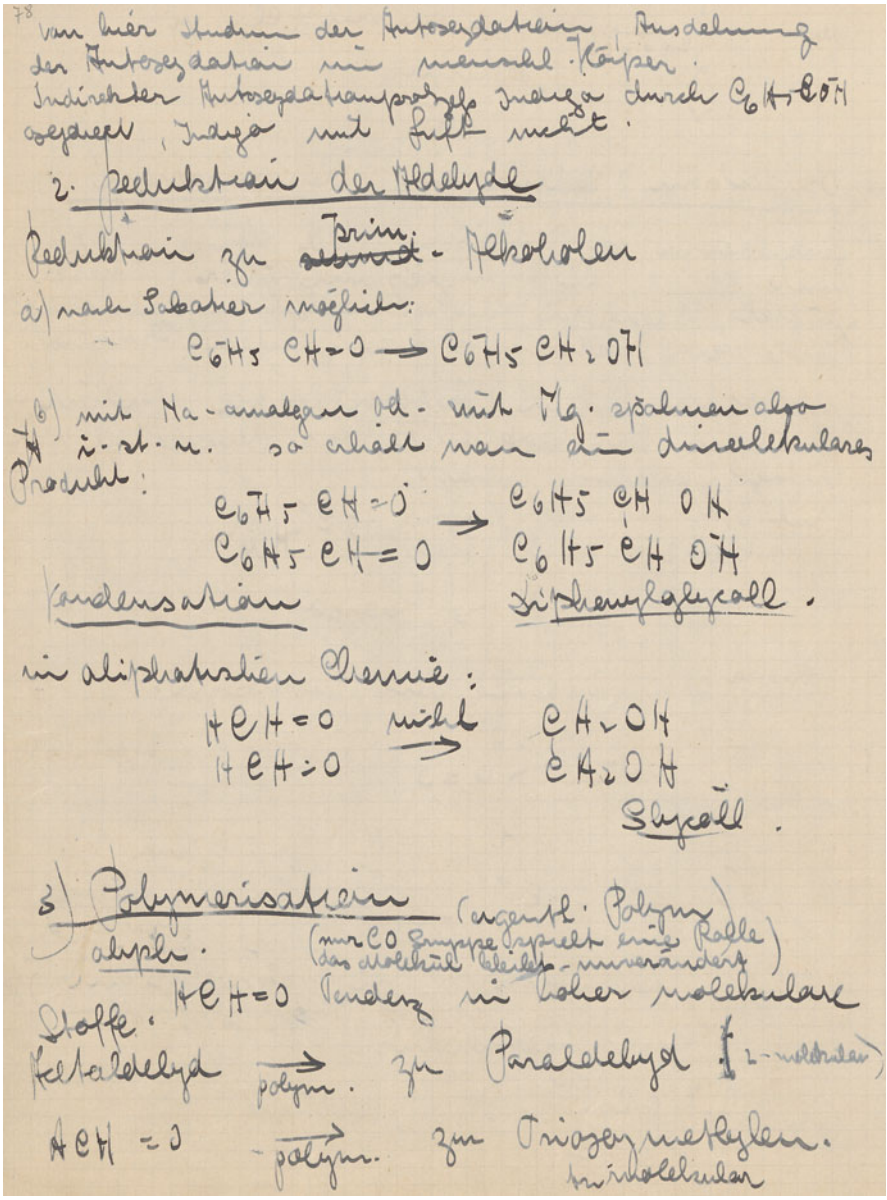


Fig. 3 From the lecture notes of Adolf Krebser in Herrmann Staudinger's class on organic chemistry in the summer of 1919. Source: ETH Library Zurich, Hs 1204, 1919, p 78

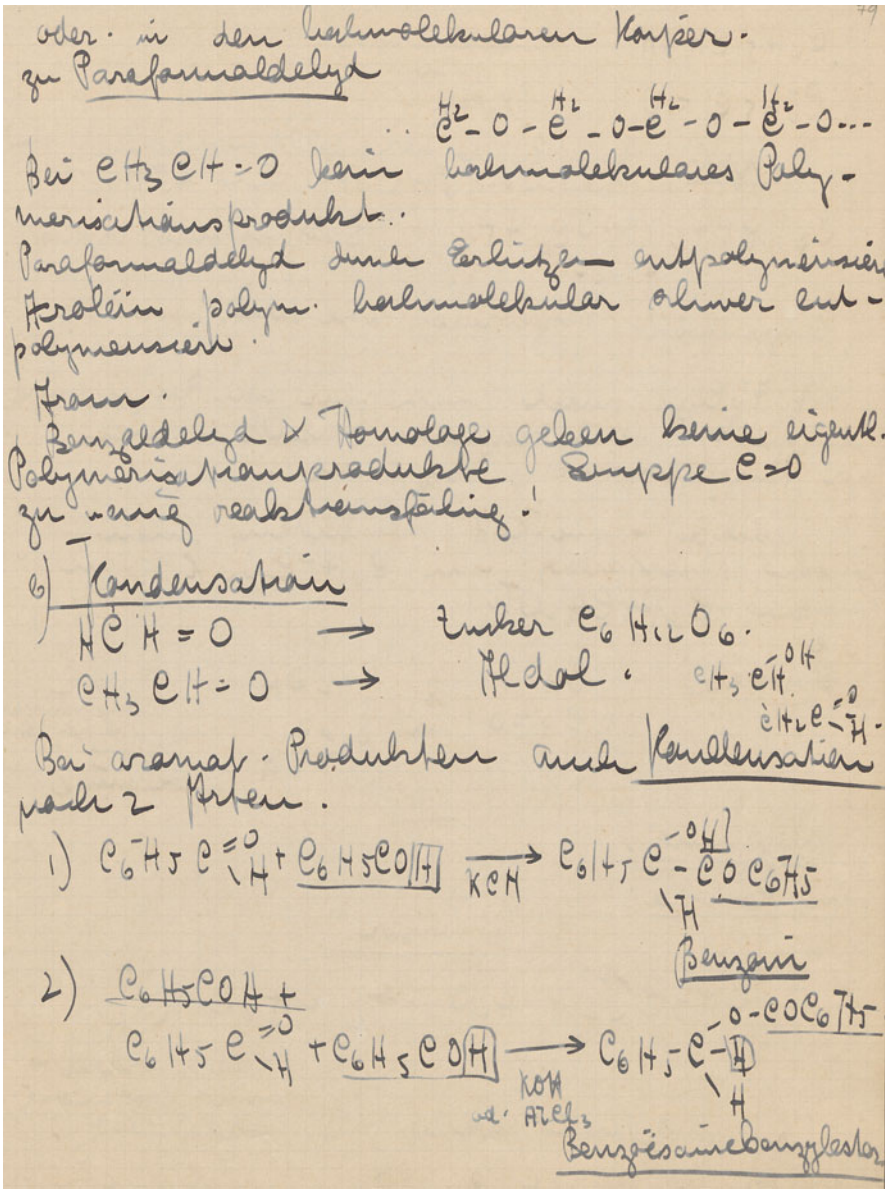


Fig. 4 From the lecture notes of Adolf Krebser in Herrmann Staudinger's class on organic chemistry in the summer of 1919. Source: ETH Library Zurich, Hs 1204, 1919, p 79

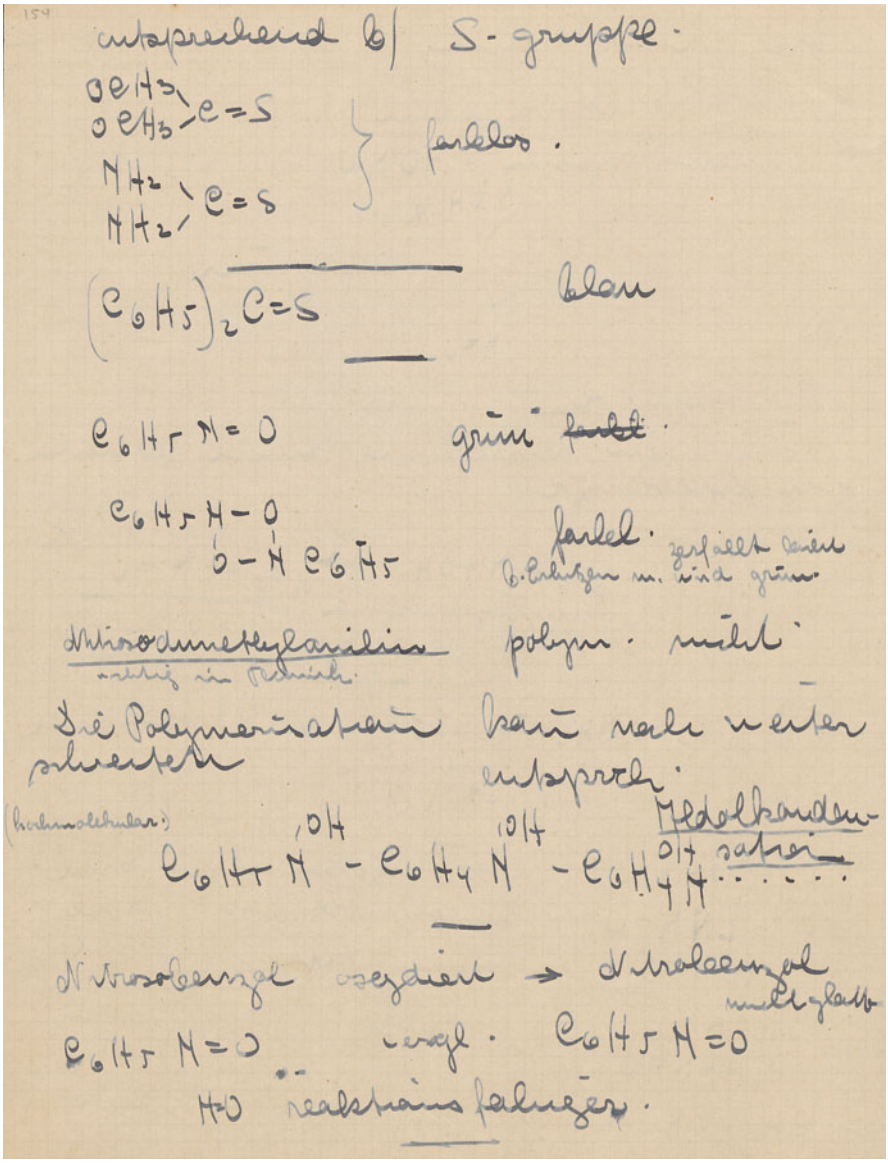


Fig. 5 From the lecture notes of Adolf Krebser in Herrmann Staudinger's class on organic chemistry in the summer of 1919. Source: ETH Library Zurich, Hs 1204, 1919, p 154

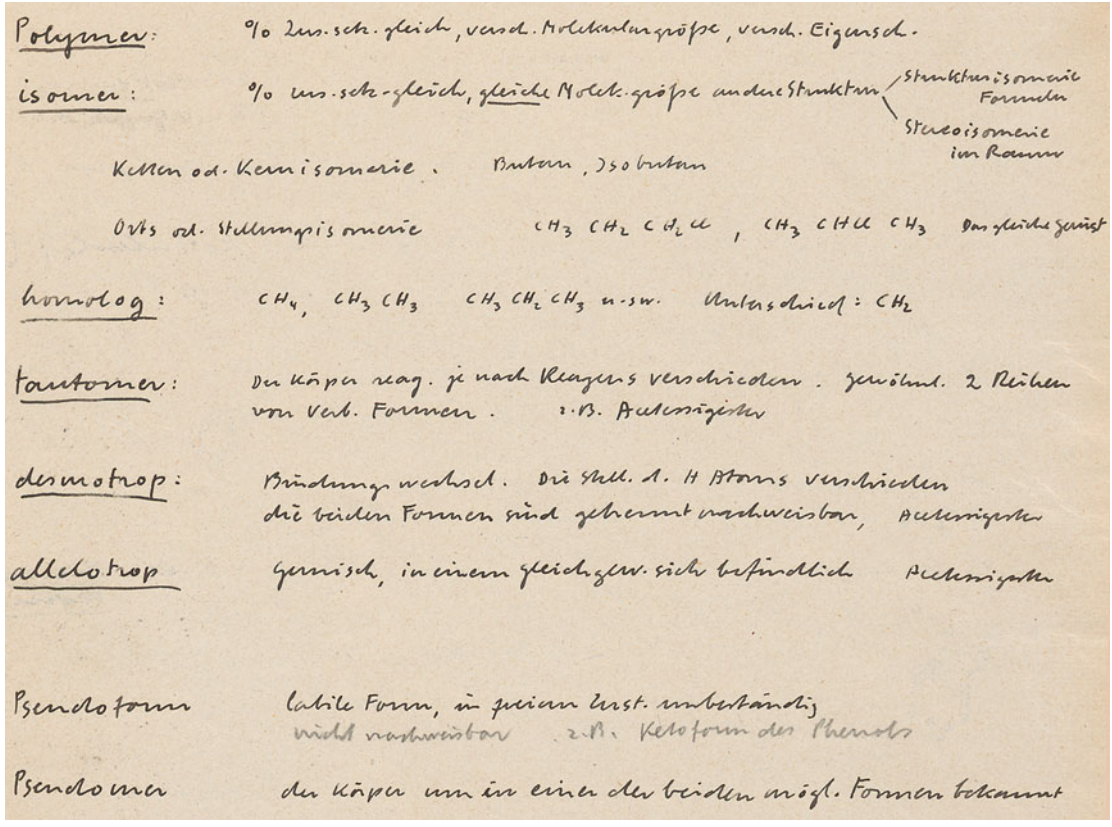
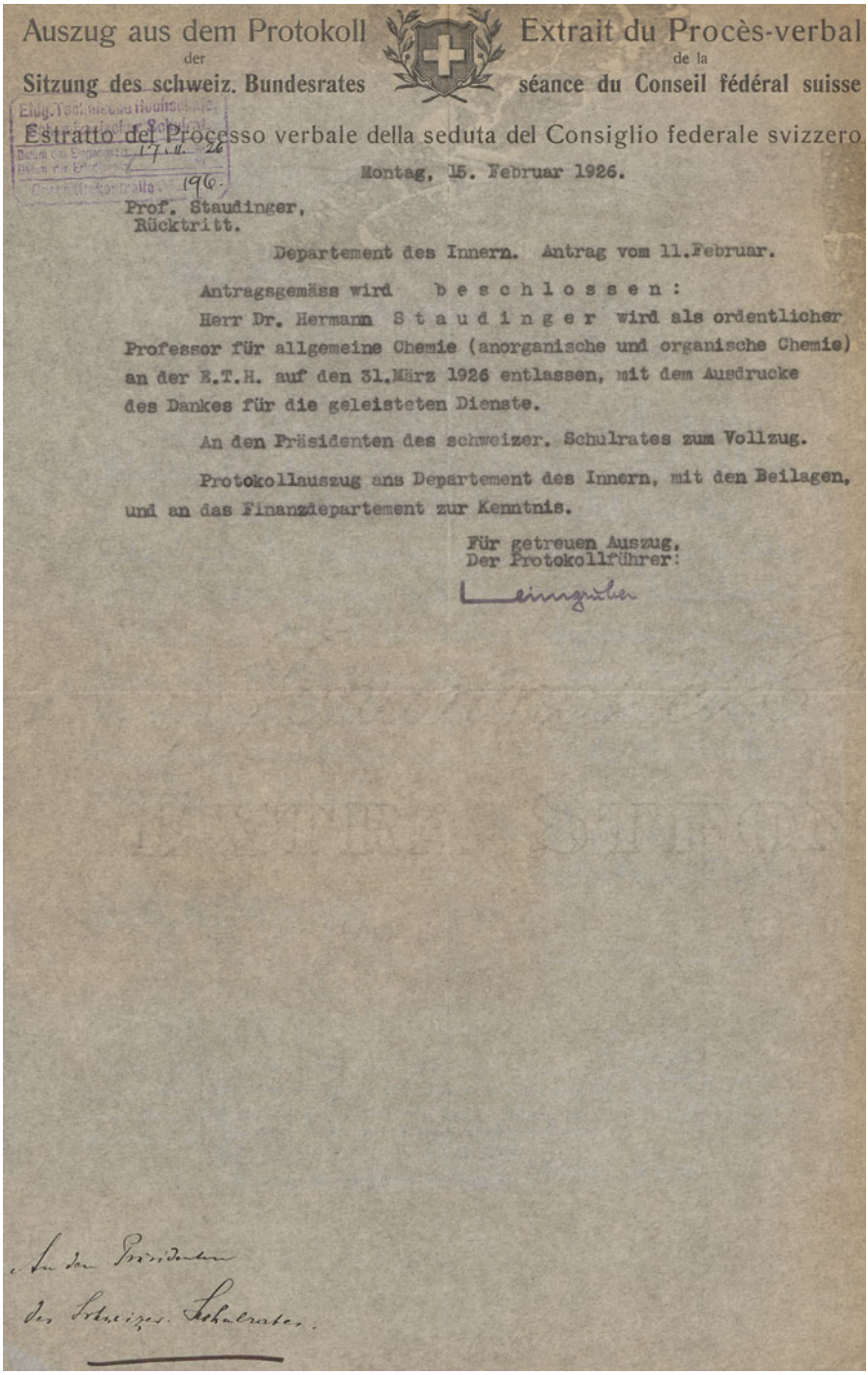


Fig. 6 From the lecture notes of Max Brunner in Herrmann Staudinger's class on organic chemistry in the winter of 1921/1922. Source: ETH Library Zurich, Hs 348 1921/1922, p 6



Auszug aus dem Protokoll
der
Sitzung des schweiz. Bundesrates

Extrait du Procès-verbal
de la
séance du Conseil fédéral suisse

Estratto del Processo verbale della seduta del Consiglio federale svizzero

Montag, 15. Februar 1926.

Prof. Staudinger,
Rücktritt.

Departement des Innern. Antrag vom 11.Februar.

Antragsgemäss wird b e s c h l o s s e n :

Herr Dr. Hermann S t a u d i n g e r wird als ordentlicher Professor für allgemeine Chemie (anorganische und organische Chemie) an der E.T.H. auf den 31.März 1926 entlassen, mit dem Ausdrucke des Dankes für die geleisteten Dienste.

An den Präsidenten des schweizer. Schulrates zum Vollzug.

Protokollauszug ans Departement des Innern, mit den Beilagen, und an das Finanzdepartement zur Kenntnis.

Für getreuen Auszug,
Der Protokollführer:

Fig. 7 Excerpt from the minutes of the session on 22 February 1926 of the Swiss Government: Dr. Herrmann Staudinger is relieved of his duties as professor at ETH per 31 March 1926. His services are appreciated. Source: ETH Library Zurich, SR3:1926, No. 196

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Courageous Questioning of Established Thinking: The Life and Work of Hermann Staudinger

Markus Weber and Guido Deussing

Abstract Hermann Staudinger (23.3.1881–8.9.1965) gave plastics chemistry its theoretical foundations. Although his outstanding career as a scientist – doctorate at 22, professorship at 26 – culminated in the Nobel Prize in Chemistry, Staudinger has remained largely unknown (as a public figure too) and nowadays only specialists are familiar with his life and work. In 1920, Hermann Staudinger published his "Macromolecular manifesto", which gave plastics chemistry its foundations but was rejected resoundingly by the organic chemistry establishment. The opposition that Staudinger faced as a result threatened to isolate him, but he defended his theory stubbornly and continued his attempts to prove experimentally the existence of the "giant molecules" he had postulated in theory.

Hermann Staudinger started a new phase of his life in the 1930s: his theory about the macromolecular structure of polymers, which was hotly contested in the initial stages, finally received the recognition it deserved. While the opposition he faced from the scientific community decreased, new storm clouds developed in 1933, when the Nazis assumed power. Staudinger's life's work culminated in the Nobel Prize in Chemistry, which he received from the Swedish King on 10 December 1953. This was late recognition for a 72-year-old retired professor, who no longer represented the avant-garde of his subject but whose achievements are still being acknowledged. This article aims to rectify this. It portrays Staudinger as a productive and unorthodox thinker, who refused to accept conventional arguments in both his scientific and political activities – until his ideas finally became mainstream convictions.

Keywords Hermann Staudinger · Macromolecular manifesto · Macromolecules · Nobel Prize in Chemistry 1953 · Plastics chemistry · Polymer research

M. Weber (✉)
Thumbstrasse 30B, 51103 Cologne, Germany
e-mail: mediweb@arcor.de

G. Deussing
Uhlandstrasse 16, 41464 Neuss, Germany

Contents

1 The Life and Work of Hermann Staudinger: 1881–1919 83
1.1 Plenty Left for Biographers to Investigate 83
1.2 How Everything Began 84
1.3 To Switzerland for the Next Step in His Career 84
1.4 Prophecies of Doom During the War 85
1.5 No Response to the Call for Peace 86
1.6 Dispute with Fritz Haber About Chemical Warfare 87
1.7 Not an Uncompromising Pacifist 87
1.8 Good Technology, Bad Technology 88
2 The Life and Work of Hermann Staudinger: 1920–1932 89
2.1 Fascinating Class of Substances with Exceptional Properties 90
2.2 The Four Basic Elements of Organic Chemistry 90
2.3 Mysterious Polymerisation 91
2.4 About Monomers and Car Tyres 92
2.5 Carbon Double Bonds of Critical Importance 93
2.6 Staudinger's First Encounter with Polymers 94
2.7 About Primary Valences and Secondary Valences 95
2.8 Basic Research Triggers Industrial Boom 96
2.9 Rejection in Düsseldorf 97
2.10 Reservations About "Gunk Chemistry" 98
2.11 Support Unwelcome 99
2.12 Micelle or Molecular Colloid? 100
2.13 How Staudinger Proved the Existence of Macromolecules 101
2.14 Staudinger's Dispute with Meyer and Mark 102
2.15 Differences and Deficits 104
2.16 Feud Between Colleagues Instead of Coalition 104
2.17 "Academic Claustrophobia" 105
2.18 The Macromolecule Has Several Fathers 106
3 The Life and Work of Hermann Staudinger: 1933–1945 108
3.1 Accusation of "Anti-German Sentiment" 108
3.2 Heidegger Demands Dismissal 110
3.3 "Betrayal Theory" Revealed to Be a Myth 112
3.4 "Supporter of the National Uprising" 113
3.5 Sensational Turn of Events 114
3.6 Anti-Semitic Pretence 116
3.7 No Chance of a Party Membership Book 118
3.8 Two Different Political Faces 121
3.9 Promotion of Defence Chemistry 121
3.10 Funding from Industry 123
3.11 Veil of Silence 124
4 The Life and Work of Hermann Staudinger: 1945–1965 124
Appendix 1 133
Appendix 2 134
Appendix 3 134
Appendix 4 134
Appendix 5 135
References 136

1 The Life and Work of Hermann Staudinger: 1881–1919

"Pioneer of polymer research", "founder of plastics chemistry", "father of macromolecules": all chemistry textbooks abandon their normal matter-of-fact style when they start talking about Hermann Staudinger. Tribute is still being paid to him for his achievements, even though he died 47 years ago. Just about every chemist is still familiar with the name "Staudinger", which plays a prominent role in the history of the field rather than being a mere footnote. Flashback to Stockholm on 10 December 1953, when Staudinger was presented the Nobel Prize in Chemistry by King Gustav Adolf of Sweden at the age of 72, after he had retired from his professorship. This was the absolute highlight of Staudinger's life and work, which had been devoted to basic research, the theoretical foundations for his field, combined with untiring experimental work that took him from Worms, where he was born, to the chemical laboratory at Freiburg University, where he spent much of his life as director for 25 years. More than 500 different publications under his name are a reflection of the meticulous nature of Staudinger's scientific work. Six universities (Mainz, Torino, Salamanca, Karlsruhe, Zurich and Strasbourg) awarded him honorary doctorates, and he was also an honorary member of countless scientific associations.

1.1 Plenty Left for Biographers to Investigate

Staudinger has remained largely unknown outside the academic community, however. A fate that he shares with other pioneers in the plastics chemistry field – even those who were originally famous for their inventions but were soon forgotten in spite of the success of their creations: who still associates nylon with Wallace Hume Carothers (1896–1937), PVC with Fritz Klatte (1880–1934) or Plexiglas/Perspex with Otto Röhm (1876–1939)? The winner of the 1953 Nobel Prize in Chemistry was never really a celebrity, although he did not try to avoid the limelight, as we will see later on. To this day, no biographer has written a detailed, historically accurate description of his life to go alongside Staudinger's *Arbeitserinnerungen*, which appeared in 1961 [1], neither has his life been put in its historical context nor has light been shed on his character and personality on the basis of this. This is particularly surprising, because Staudinger's scientific and political activities happened during the most turbulent decades of recent history, influenced by sudden paradigm shifts and regime changes and – above all – shaken by two World Wars. German Empire, Weimar Republic, Nazi dictatorship, post-war Germany: upheavals in government and society affect the scientific community too – including chemists, who are said to have little interest in politics. Positions had to be adopted, particularly by holders of prominent functions: accepting or rejecting the status quo, opportunistic and flexible or confrontational. Unlike others in his field, Staudinger did not retreat into an ivory tower in his role as a basic research scientist; instead of this, he expressed his opinions on issues that had nothing to do with his scientific

field when he considered this necessary and it did not seem to him to be acceptable to remain silent.

1.2 How Everything Began

Chemistry was still far from Staudinger's mind when he started to think about a career in 1899 on finishing school, where the emphasis had been on classical languages and literature. He was particularly interested in botany, but he decided to get conventional vocational training first before entering the academic world so that he had more than one iron in the fire, since – as the saying goes – a trade in hand finds gold in every land. Staudinger completed an apprenticeship with a carpenter in his home town of Worms. This was a profession he was never to pursue afterwards, because it turned out that he was destined to become a scientist and researcher. Very soon after he had registered to study botany at the University of Halle/Saale, he took the advice given to him by his father, the grammar school teacher and philosopher Franz Staudinger (1849–1921), and started to study chemistry, "in order to be able to understand botanical problems better" [1, p. 1]. After the family moved to Darmstadt, he registered to study at the Technical University there, leaving not only Halle but also botany behind him: the young Staudinger switched completely to chemistry. After two terms in Darmstadt, he took his initial exams and then returned to Halle to study for a doctorate, which he obtained when he was only 22 years old (title of the dissertation was "Accumulation of malonic ester on unsaturated compounds"; his doctoral advisor was Daniel Vorländer, 1867–1941). Once he had completed his doctorate, Staudinger spent another term in Halle as a private scientific assistant, before he moved to Strasbourg University in the autumn of 1903, where he became a teaching assistant of Johannes Thiele (1865–1918) and finally qualified to teach at a university in the spring of 1907 – with a thesis about highly reactive, dimerising ketenes. Staudinger became a professor the same year: Karlsruhe Technical University appointed him to be an Associate Professor for organic chemistry. In this position, he decided to concentrate specifically on polymer research, focussing in particular on isoprene and butadiene, in order to make progress in the development of synthetic rubber, which – however – ended up taking another 20 years and was completed by a different chemist.

1.3 To Switzerland for the Next Step in His Career

Staudinger stayed in Baden-Württemberg for 5 years and then accepted an appointment in Switzerland: the Swiss Federal Institute of Technology (ETH) in Zurich offered him a chair in the summer of 1912. As successor to Richard Willstätter (1872–1942), who moved to the new Kaiser-Wilhelm-Institut für Chemie in Berlin, Staudinger was given a full professorship at the age of 31 and continued his

research into cellulose and rubber in this position. Staudinger spent 14 years in Zurich from 1912 to 1926, turning down offers from Graz and Hamburg Universities. "For a good reason", as the journalist Siegfried Heimlich points out, because "he was able to observe the unspeakable acts of his German fatherland in the First World War from a neutral location in Switzerland without being involved actively himself" [2, p. 82]. However, the years Staudinger spent in Switzerland were not a period in which he kept his head down or looked the other way as though it was none of his business. Staudinger did not maintain silence in a backwater as political and military battles were fought elsewhere. On the contrary: physical distance encouraged independent thinking; Staudinger developed into a man who positioned himself in the frontline against the political and scientific mainstream. Unimpressed by the nationalistic euphoria in his German fatherland, he predicted the military defeat and advocated negotiations to find a peaceful solution as early as 1917. And, not long after the war, he shook up the academic community in his capacity as a scientist, breaking with the past in 1920 by formulating his macromolecule concept in organic chemistry.

1.4 Prophecies of Doom During the War

But let's take things one at a time: in 1917, the third year of the two-front war in which the central powers (Germany, Austria–Hungary, the Ottoman Empire and Bulgaria) were fighting against an alliance of more than 30 different countries (particularly Russia, France, England and the United States), Staudinger published an essay with the title "Technik und Krieg" in the magazine *Friedens-Warte* that appeared in Zurich [3] (this essay was reprinted in [4], pp. 20–40). In it, he stated that "superhuman" technical forces would determine the outcome of the war. The more coal and iron a country had at its disposal to fuel its armaments production, the greater the prospects of victory: "Technology did not play this role in earlier wars [...]. It is, however, already apparent from some of the wars that were fought in the last century that the winner was always technically superior, i.e. that the country with more coal and iron triumphed in the end. For example, the production of coal and iron in Germany was far larger than in France at the time of the Franco-Prussian War" (1870–1871, editor's note) [4, p. 29]. Germany's chances had been good this time as well (cf. [4], p. 48), until America's decision to enter the war in April 1917 changed the balance of power so much in favour of the alliance that "Germany's chances of winning had become minimal" [4, p. 34]: "Separate peace with Russia, which many people in Germany are hoping for, is likely to have little impact in this respect, because the technical superiority of the alliance would only be reduced to a minor extent as a result. It would therefore be very important for the central powers not to try and win the war by military means" [4, p. 34]. In other words, efforts needed to be made to arrange a truce and find a peaceful solution as quickly as possible.

1.5 No Response to the Call for Peace

Staudinger did not make just this one attempt. At the end of 1917, he wrote to the leadership of the German Army directly and demanded a stop to the fighting, because "the opponents of Germany are much superior now" as a result of America's decision to enter the war. New military victories would be bad for Germany in two different respects: "On the one hand, they will intensify the resistance put up by the Americans, while they will, on the other hand, distract the German people from what they should really be doing, i.e. trying to find a peaceful solution on the only possible basis, via negotiation." [5, p. 975]. The 20-page letter to the High Command of the German Armed Forces, which has just been quoted here, is entitled "Zur Beurteilung Amerikas" [6]; the manuscript has survived as part of Staudinger's estate and is kept at the Deutsches Museum in Munich.

Sachsse [5, p. 976] comments as follows: "In view of the German mentality at the time, Staudinger's action was outrageous. Public opinion rejected negotiations of any kind. German university professors had insisted on several occasions that it was necessary to persevere come what may." As expected, the German Emperor and Chancellor did not therefore respond to the offer of peace made by the US President Woodrow Wilson (1856–1924) in January 1918 – the famous "14 points". The outcome of the war was supposed to be decided via a victory or defeat on the battlefield, so the leaders continued to ignore the fact that the country's ability to fight was diminishing, blinded as they were by isolated military successes. In retrospect, Staudinger concluded that July 1918 was the "turning point". In his paper "Der erste Weltkrieg unter technischen Gesichtspunkten" [7] (an extended version was printed later in [4], pp. 45–55), he wrote: "The most recent efforts did not have any major impact even on France, but [. . .] the Americans started to provide particularly intensive support, so that the superiority of the alliance was now clear to see." [4, p. 53]. He accused the political community of failing to heed his warning, the German defeat was "unavoidable" because of the "American opposition": "Germany's fate was decided in the spring of 1917 rather than in the autumn of 1918." [4, p. 53]. Because – in retrospect – the technical balance of power and the growing superiority of the alliance made "the course and end of the war inevitable", so that "even the most talentest of military commanders was unable to avoid the consequences" [4, p. 46].

Staudinger did not just call for a truce; his appeal for peace was more radical than this. In view of the destructive capacity of modern weapons technology, war was completely out of the question for him as a political instrument, because there were only losers now, with both murder and suicide being involved: "In future, a war could [. . .] lead to unimaginable destruction; since this is the case, it appears to be vital for humankind as a whole to find really permanent peace – a problem [. . .] it is particularly important to solve today if entire peoples and cultures are not be in danger of annihilation. Peace that only amounts to a kind of truce would be the worst thing that could happen to Europe." [4, p. 38; cf. p. 48]. Staudinger was

making an indirect case for demilitarisation here, while the allies were negotiating the Treaty of Versailles and nationalistic groups in Germany were already flirting with another armed conflict in order to avenge the defeat in 1918.

1.6 Dispute with Fritz Haber About Chemical Warfare

Staudinger attributed the "destructive capacity of modern warfare" to "the tremendous impact of the latest technology in military conflicts" [4, p. 38]. In this context, he criticised not only explosives ([4], p. 40: "terrible effect") in an essay written for the international Red Cross magazine that appeared in Geneva [8], but also and in particular chemical weapons, which was therefore an attack on Fritz Haber (1868–1934), who won the Nobel Prize in Chemistry in 1918. Haber headed the Kaiser-Wilhelm-Institut für physikalische Chemie und Elektrochemie in Berlin, which is now named after him. During the First World War, he was involved in the first mass use of poison gas at Ypern in Belgium and his institute received financial backing from the German army. He defended the chemical weapons, which – in his opinion – were "no more cruel than exploding pieces of metal", particularly since they did not cause any mutilation (lecture about "Chemistry in the war"; quoted by Klee [9], p. 214). Staudinger's article for the Red Cross enraged Haber, who wrote his colleague a strongly worded letter, accusing him of dramatising the suffering caused by chemical warfare, thus encouraging defamation by their country's opponents and harming the German Empire (see [5], p. 976). Haber felt that the concept of maintaining peace via technical means was wrong, representing a form of idealism that was completely out of touch with reality; what was crucial instead was attitude, a willingness to maintain peace. Staudinger's response was polite but without any concessions: he readily admitted that "attitude" is essential for agreement on peaceful coexistence between different peoples – he himself had already drawn attention elsewhere to "intellectual forces" [4, p. 38] – but an "aspect" that was no less "necessary" was "the material basis" [5, p. 976]. From this angle, it was Haber himself rather than Staudinger who was an idealist, if not a political romantic. Staudinger's analysis of the destructive capacity of modern weapons technology, which was based on mathematical calculations, revealed to a greater extent the mind of a matter-of-fact scientist. Staudinger also rejected the accusation that he was taking sides with Germany's war enemies, since all countries were the object of his criticism. It was, instead, Haber who was demonstrating bias – by making such outdated statements as "For humankind in peace, for the fatherland in war" (quoted by Klee [9], p. 214).

1.7 Not an Uncompromising Pacifist

This argument that war is senseless in the age of technology reflects not the spontaneous passion of an apostle but the well-considered conclusion of a

pragmatist – Staudinger was not an uncompromising pacifist. “Our ancestors had no choice but to drive out their neighbours and obtain more land and thus more space to expand into”, he wrote in 1917 in the essay “Technik und Krieg” [4, p. 35; cf. p. 101] that has already been mentioned. There was even talk of the “right” of earlier generations “to wage a bloody war about the place in the sun” [4, p. 35]. “In the technical age, on the other hand, these old ideas about the necessity of wars – which have brought such profound misery to Europe – must be abandoned” [4, p. 101]. Staudinger rejected the fatalistic attitude “that there have always been wars and that wars are unlikely to stop in future either in view of the nature of humankind” [4, p. 101], because anyone who followed this argument was accepting the possibility of “peoples being destroyed” [4, p. 101] in tomorrow’s world. “Hoping for a war-free future” was encouraged for him specifically by the contemporary “prophecies” claiming “that we [. . .] are facing a time of particularly bitter fighting” [4, p. 38]. This was no paradox – Staudinger was hoping that the destructive capacity of high-tech armies would have a deterrent effect. This was based on the confidence that humankind would be sensible enough to avoid the abyss of self-destruction. The Second World War eliminated much of the basis for such optimism, but at the same time confirmed that Staudinger’s warnings were as important and relevant as ever. As early as 1919, he suspected that his calls for a framework for stable, lasting peace would probably bear little fruit. “It is tragic [. . .] to see that Germany, for which a policy of reconciliation between different peoples would have been so important in view of its location and natural resources, relied most firmly on military aggression, whereas America – the only country that could have allowed itself to adopt such a policy thanks to its riches – has been trying for decades now to promote peaceful coexistence – to no avail, unfortunately” [4, p. 54].

1.8 Good Technology, Bad Technology

If Staudinger is right in saying that war is escalating because of modern technology, then is such technology not evil in itself, so that war should in turn be declared on it too? No, because then it would not be possible to enjoy the benefits of peaceful use of the technology. Staudinger countered technophobic arguments of this kind by outlining a vision of “controlled” technology, that offered excellent “potential for life and development” now and in future [4, p. 101]: “Thanks to technology, more people can live on a limited amount of land nowadays and they can enjoy an easier life than a smaller number of people on the same amount of land in the ‘good old days’” [4, p. 110; cf. p. 103]. It was not technology as such that was evil, but the abuse of it; although technology added incredible destructive potential to wars, they could not be vindicated for this very reason: “There is no justification for wars any more [. . .]” [4, p. 101].

According to Sachsse [5, p. 976], Staudinger was disappointed by the response to his political publications: “Even though they were extremely relevant, they were

not well-known and attracted little attention". This was in contrast to the trailblazing publications in the polymer chemistry field, which caused a stir and led to fierce controversy from 1920 onwards. More is said about this in the next section.

2 The Life and Work of Hermann Staudinger: 1920–1932

The 1920s are generally idealised as the "golden age". Contrary to the cliché, they were in fact a decade with both ups and downs – for Hermann Staudinger too. The chemist, who had been working in Zurich since 1912, started the decade spectacularly. In 1920, he published his "Macromolecular Manifesto", which gave plastics chemistry its foundations but was rejected resoundingly by the organic chemistry establishment. The opposition that Staudinger faced as a result threatened to isolate him, but he defended his theory stubbornly and continued his attempts to prove experimentally the existence of the "giant molecules" he had postulated in theory. This was a project with an uncertain outcome at first and Staudinger suffered setbacks in his private life too: his father died in 1921 and in 1926 he was divorced from his wife Dora, née Förster (1886–1964), who bore him four children in the 20 years of their marriage. 1926 marked the start of a new stage in his career as well – and one that was to prove successful: Staudinger left Zurich and returned to Germany and a position at Freiburg University. He enjoyed recognition and fame here in the Breisgau region – and finally retired from his academic career there too. It was also a happy time for Staudinger again in his private life. He married the biologist Magda Woit (1902–1997) in 1928, who was also his companion in his scientific endeavours up to his death in 1965.

In Germany at the beginning of the 1920s, the war was over and the monarchy was a thing of the past. Hitherto-unknown Republican freedom quickly helped people to forget the authoritarian state. "Anything goes" was the message spread by intellectuals; cities became the stage for experimenting with "liberté" and "libertinage". A great deal was changing in plastics chemistry too. New empirical findings demanded a theoretical basis, but rigid, outdated thinking could not simply be abandoned as long as the explanatory concepts needed were still nebulous. A paradigm shift was in the air, but the "experimental stage" had not yet been passed:

> The term 'plastic' very gradually started to establish itself via a magazine of the same name that was started in 1911 by the (German, editor's note) chemist Richard Escales (1863–1924). Nothing at all was, however, known about how these plastics were in actual fact structured and by what principles they could be synthesised in a laboratory until late in the 1920s. The progress that was nevertheless evident [...] was not based on systematic research but was instead attributable to an explosive cocktail mixed together from such ingredients as experience, speculation, acquired know-how and plenty of sheer luck. [2, p. 79]

Basic research was vital in this uncertain situation. Hermann Staudinger did pioneering work in this field at ETH in Zurich. He was interested in "determining the composition" ([10], p. 15 and [1], p. 77) of polymers, i.e. of the fascinating class

of substances that included such natural substances as rubber in addition to the innovative new synthetic ones – "proper" plastics – like celluloid (1869), Galalith (1897) or Bakelite (1908). Biopolymers include proteins, enzymes, polysaccharides (e.g. cellulose, glycogen and pectin) as well as nucleic acids, the basic components of our genetic structure as research in subsequent decades was to show.

2.1 Fascinating Class of Substances with Exceptional Properties

The polymers produced by mankind ("synthetic") and the polymers that are already available without mankind doing anything ("natural") have exceptional properties and behaviour in common that no other class of substances can boast:

- In contrast to, for example, a saline solution, which cannot be distinguished visually from clear water, polymers form colloidal (i.e. glue-like) solutions, which move between liquid and solid states at relatively low concentrations and are sometimes viscous and sometimes jelly-like (cf. [11], p. 45).
- Other properties that should be emphasised are a marked ability to swell and form fibres, high elasticity, tremendous strength and "above all the unique combination of very high stability with multiple reactivity" ([1], p. 302; cf. p. 95 and [10], p. 14).

It was not, however, clear at the time what gave polymers all these physical characteristics; why a polymer, as it were, has no alternative but to display such properties. Staudinger was convinced that chemists had to find the answers to these questions: "The great variety of the individual phenomena is based [. . .] on the fact that the atoms are joined together in very different ways" [10, p. 5]. In order to "obtain an understanding" of the properties of the polymers, it was therefore necessary "to determine the structure of their molecules; the nature of the bonds and the arrangement of the atoms in the molecule therefore need to be specified" [10, p. 9]. Understanding the specific chemical reaction that led to the creation of polymers also promised to shed light on this matter. The aim was to have this process, which was known as polymerisation, take place in a controlled fashion and to discover suitable auxiliary materials that initiated, maintained and ended the process – not least of all in order to be able to develop versatile new plastics and manufacture them on an industrial scale.

2.2 The Four Basic Elements of Organic Chemistry

Staudinger's primary interest was therefore to decipher the "structural principle" of the polymers [10, p. 11; cf. p. 5]. Anyone who set out to determine their

composition could not restrict himself "merely to analysing the substance" [10, p. 9]. The composition of the polymers was "basically very simple, because just a few types of atom are involved in their structure; mainly carbon, hydrogen, oxygen and nitrogen, the four basic elements of organic chemistry." ([10], p. 6 and cf. [1], p. 311) What was in the final analysis involved was "the chemistry of a single element – carbon. The outstanding feature of its atom is, incidentally, that it has an exceptional ability to bond with others of its own kind as well as with the few above-mentioned other types of atom [...]. This distinctive feature of carbon leads to an enormous number of compounds." ([10], p. 6; cf. [1], p. 85) The crucial statement Staudinger adds is: "Knowing about the composition of an organic compound does not, however, in itself involve any understanding of its formation and properties" [10, p. 6].

In order to dig deeper here, Staudinger put his concept of macromolecules ("giant molecules") to scientific discussion and publicised it on an ongoing basis. Staudinger made a start on this in the essay "About polymerisation" that appeared in the "Reports from the German Chemical Society" on 12 June 1920 [12], in which he postulated a "structure of long chain molecules" for polymers – mention being made, among others, of polystyrenes, polyvinyl chlorides and rubber [1, p. 77]. In this context, Staudinger coined the term "high polymers", which was to be replaced by the term "macromolekel" [13] and, finally, "macromolecule" [14] in subsequent years. In Staudinger's first essay about the chemistry of high polymers, which Priesner ([15], p. 351) calls the "macromolecular manifesto", the central definition is: "Polymerisation processes [...] are all the processes in which two or more molecules combine to form a product with the same composition but a higher molecular weight" ([12]; quoted in [15], pp. 35–36). A chemical molecule could "reach practically any size" [1, p. 7] and therefore grow into a giant molecule in this way: "Identical or similar small groups of atoms join together in constant repetition to form a pattern, as a result of which macromolecules of enormous size are, finally, produced." [16, p. 16]

2.3 Mysterious Polymerisation

Simply defining terminology does not, however, by any means settle adequately what exactly happens in polymerisation and what enables this process to take place. This is therefore explained in further detail step by step below, based on statements made by Staudinger. An appropriate place to start is the phenomenon level, because it can be described and because it presents the mysteries that electrify both naive observers and passionate chemists. Looking back on the early days of macromolecular chemistry, Staudinger writes in 1961 [1, p. 169]: "It had already been known for a long time that some unsaturated compounds turn into products with the same composition but completely different physical properties when left standing for a long time, when exposed to light or when heated." Styrene, for example, "[...] gradually becomes a highly viscous substance [...], finally forming glassy

polystyrene" [1, p. 170]. Such processes, which could be described as spontaneous polymerisation, correspond to polymerisation that is triggered actively with human involvement, e.g. by heating or the exertion of pressure.

What is known as the vulcanisation of rubber is an excellent example of this: in 1839, the American chemist Charles Nelson Goodyear (1800–1860) succeeded in transforming the rubber that occurs naturally into the polymer product that we now call rubber by adding sulfur and applying heat. The undesirable tendency of the rubber to become sticky when heated and crumbly when cooled was overcome as a result.

Strictly speaking, vulcanisation is a type of polymerisation that is comparable to what is called addition polymerisation. The definition of this is that two different raw materials, rather than one and the same raw material, combine in chains to form macromolecules, as is the case – for example – with polyurethanes (see [1], p. 316). If there are by-products, water in particular, as is the case with Galalith (from casein and formaldehyde) or nylon (from hexamethylene diamine and adipic acid), this is called condensation polymerisation instead (cf. [1], pp. 175, 315–316 and [10], p. 15) (see Appendix 1).

2.4 About Monomers and Car Tyres

Vulcanisation is not a completely accurate example, because rubber itself is already a polymer when it combines with sulfur. The British chemist Charles Greville Williams (1929–1910) was the first to propose this hypothesis. Rubber therefore has to be considered the product of natural polymerisation that is attributable to basic components called monomers that have joined together repetitively and continuously, i.e. have combined to form a polymer. The conclusion from this is that it ought to be possible to create synthetic rubber by polymerising the isolated rubber monomer – the hydrocarbon isoprene. Experiments to do this started at Farbenfabriken Bayer in 1906 under the direction of Carl Duisburg and Staudinger had already tackled this research assignment during his time in Karlsruhe (1907–1912) (see [1], p. 5; [17], p. 67; [18], p. 229). "(At this time, editor's note) there was great demand for synthetic rubber due to the rapid growth of the car industry and the rising prices for plantation rubber on the world market associated with this – particularly in the German empire, which depended on raw material supplies from the English and French colonies. This economic situation of his country was another particularly strong incentive [...] for Staudinger to focus on polymerisation reactions like those occurring with isoprene very early on" [18, p. 230].

In order to make it easier to understand what follows, let us recap here: the term "monomer" is used for basic molecules that form macromolecules via standard polymerisation, addition polymerisation or condensation polymerisation. "So macromolecules represent chains of one and the same basic molecule. The number of the latter in the macromolecule is called its degree of polymerisation" [10, p. 11]. Staudinger also characterised polymerisation as a "peculiar chain reaction" ([1],

p. 315; cf. p. 179: "chain polymerisation") and drew a comparison with a box of matches that has been set on fire: "just one match has to be ignited to set all the matches on fire" [4, p. 95].

2.5 Carbon Double Bonds of Critical Importance

It is not, however, the case that all monomers are capable of forming macromolecules. (Chemically unsaturated) hydrocarbons are what primarily have the ability to create a polymer chain. In them, the carbon atoms have multiple bonds and the number of hydrogen atoms is reduced accordingly:

- Single carbon bond, e.g. ethane: each of the two carbon atoms has bonds to the other carbon atom as well as to three hydrogen atoms. As long as no atom is removed, no bonds are available to join a polymer chain (saturated state).
- Double carbon bond, e.g. ethylene: there are two bonds between the carbon atoms. One is easy to break (unsaturated state), so that the molecule can join a polymer chain. Rubber, for example, has numerous ethylene bonds (see [13], p. 785, quoted in [16], p. 55; cf. [18], p. 240, footnote 42).
- Triple carbon bond, e.g. acetylene: the triple bond of acetylene is so easy to break that the molecule falls apart explosively; for this reason, it is only suitable as the component of a polymer chain to a very limited extent.

Unsaturated raw materials with at least one carbon double bond are therefore the primary candidates for the production of macromolecules. This bond can be opened ("activated") under the influence of heat, high pressure or auxiliary agents known as "initiators" (see Appendix 2); it then tries to find other molecules that are capable of forming a bond. This initial step is known as the "start reaction". The chain formation process (polymerisation) that then follows leads to polymers/plastics with very different properties, depending on when the process is terminated. The termination reaction can be initiated in a controlled fashion, e.g. by adding water, atmospheric oxygen (cf. [1], p. 176) or solvents. In this context, a hydrogen atom changes its position and a saturated giant molecule is created. Polymerisability and polymerisation speed do not therefore depend solely on the structure of the molecules; they are also influenced to a large extent by agents that are added to initiate (start reaction), maintain (growth reaction) or end (termination reaction) polymerisation. Staudinger [1], p. 171) says that substituents "can both increase [...] and decrease polymerisability (cf. [10], p. 7) thanks to their impact on the carbon double bond. Oxygen, for example, turns "soluble rubber with unlimited swelling properties [...] into rubber that is insoluble and only swells to a limited extent [...]. The soluble rubber remains unchanged in nitrogen atmospheres, on the other hand" ([10], p. 26 and cf. [1], p. 330 about polystyrene). What is particularly spectacular in this context is that even "minute amounts of substances can lead to exceptionally large changes in the physical properties (of macromolecular substances, editor's note)" [1, p. 329]. "In certain circumstances, it is sufficient for the reactive

substance to react with a single specific group of the macromolecule that only accounts for a small fraction of its mass; the behaviour of the entire macromolecule can be changed as a result" [10, p. 27]. Chemists have unexpected creative powers as a result – as if they were modern alchemists.

2.6 *Staudinger's First Encounter with Polymers*

It is worth remembering that Staudinger's interest in the structure of high-polymer compounds was aroused in direct connection with his research in the low molecular field. After he synthesised a new class of substances – ketenes – when he was qualifying to teach at a university in Strasbourg (see [18], p. 229 for details), he carried out autoxidation experiments on them during his time in Karlsruhe, which "in addition to a number of interesting and analysable products occasionally led to undefinable, resin-like substances as well that are practically impossible to dissolve and have an unclear composition and structure. This was his first, unedifying encounter with polymer substances" [18, p. 229]. "In connection with his initial work on isoprene, Staudinger found out that the synthetic rubber he produced was not completely identical to natural rubber – an observation that was bound to arouse curiosity and chemical interest. He therefore began to produce and make closer examinations of other unsaturated hydrocarbons like polyoxymethylene. This means that the connection to high-polymer chemistry was established as early as 1911. When he moved to Zurich (a year later, editor's note), he was forced to shelve this work to a large extent for the time being due to greater demands made on his time by teaching commitments, administrative assignments of all kinds and other research projects" [18, p. 230]. He worked systematically on making a gradual shift in the focus of his research, however: "I myself have concentrated on macromolecular chemistry since 1920 [. . .], starting at the Swiss Federal Institute of Technology in Zurich" [1, p. 312]. What Staudinger is referring to here is the essay "About polymerisation" that he published in 1920 [12] and that has already been mentioned before, in which he summarises and thinks through his experiences with polyoxymethylenes, polystyrenes, synthetic rubber etc. and then proposes the thesis that high polymers consist of long chain molecules: "This molecular structure in particular is often of crucial importance for the properties of macromolecular substances – both natural macromolecular substances and plastics" [1, p. 95]. An apt example: "The lower links in the polystyrenes with molecular weights between 2,000 and 10,000 [. . .] are powdery and dissolve without swelling, whereas the highest-molecular representatives with a molecular weight of 100,000 and more [. . .] are tough glass materials that acquire elastic properties when heated to more than 120°C" [1, p. 95].

2.7 About Primary Valences and Secondary Valences

Heimlich [2, p. 79] summarises the situation in rather direct fashion: Staudinger "was brutal in his destruction of the legend of small molecules and replaced it by his convictions about giant molecules." Heimlich [2, p. 83] says: "While molecules with what is called a molecular weight of 300 were classified as huge [...] in classic organic chemistry, Staudinger downgraded them to dwarfs in relation to the macromolecules he proposed that had molecular weights of 10,000 or more." Looked at from our current perspective, this was a scientific revolution and a paradigm shift, with which Staudinger laid the foundations for plastics chemistry. Most of his contemporaries failed to realise the significance, however: "The response to Staudinger's article was minimal [...]. At this time, Staudinger was still unable to provide any proof of the existence of long-chain molecules" [19, p. 251]. Doubts about the accuracy of Staudinger's theory dominated; there was opposition primarily to his theories about the bonding forces that existed in high polymers. The predominant view in organic chemistry at the time was that the basic molecules in polymers did not lose their independence, i.e. they were only bonded to form a unit by low electromagnetic attraction. In other words, the existence of high polymers was no reason to give up the concept of low molecules and to postulate macromolecules, which many chemists claimed were nothing more than a figment of the imagination.

Detailed information about this controversy and the people involved will be provided later on. Before this is done, here is an outline of Staudinger's antithesis and the necessary preconditions. The basic rule is: electromagnetic attraction takes place between all the atoms of a piece of material, but the degree of attraction varies. The strongest interaction between the atoms is within the individual molecules. These inter-atomic and/or intra-molecular forces are called primary or covalences (primary bonds). In contrast to them, weaker bonding forces known as secondary or partial valences (secondary bonds) are responsible for inter-molecular cohesion (cf. [15], p. 17). For his macromolecular model, Staudinger now excluded the "assumption of secondary valences" from the outset as being "not necessary" [20, p. 13]. This was a logical conclusion, because the claim was that a macromolecule was an independent entity of a size that had not been considered possible before and was not just a loose collection of familiar small molecular units. With respect to the existing bonding relationships in the macromolecule, Staudinger therefore worked on the assumption of primary valences in the same way as with any other molecule. Secondary valences would only be a subject requiring examination when the discussion moved on to inter-(macro)molecular attraction.

At the latest from 1920 onwards, Staudinger was certain "that standard valence formulae explain the wide range of different polymerisation products sufficiently" ([19], p. 251 and cf. [15], p. 35). In other words: the "thousand to one million atoms" that macromolecules consist of are "bonded via primary valences" ([1], p. 93; cf. p. 77). Since this was the case, the chemist had a stable building

material that made him the architect of buildings of a variety that exceeded everything ever known in the past – an analogy that Staudinger liked to use:

> Not only molecules but also [. . .] macromolecules can be compared to buildings that are made essentially from just a few kinds of building materials – carbon, hydrogen, oxygen and nitrogen atoms. If there are only a few dozen or hundred of them, all that can be made with them are small molecules and, therefore, relatively primitive buildings. However, when 10,000 or 100,000 are available, buildings of endless variety can be produced: residential buildings, factory halls, skyscrapers, palaces etc. Structures can also be produced then that are unimaginable when only a small amount of building material is available. The same is true of macromolecules. It is obvious that new properties are of course observed here too that are not possible with small molecules of low molecular substances. The number of possible macromolecular compounds is infinitely large. The size of the macromolecules also means that they can be designed in no end of different ways, again in the same way as is the case with buildings ([1], pp. 94–95; cf. [1], pp. 330–331, [2], p. 84 and [21], p. 26)

2.8 Basic Research Triggers Industrial Boom

Staudinger himself was certain right from the start that his macromolecule concept was significant not only at the theoretical level and did not just help progress to be made in the laboratory. It was a milestone in basic research that pointed the way to new approaches in the industrial production of polymers. Staudinger expected the "in-depth understanding of the inescapable connections between the structure of the [. . .] plastics, i.e. the size and shape of their macromolecules, and their physical properties to lead to new ways to improve the properties of these substances [. . .]. It will be possible to manufacture products that are adapted to their respective use more effectively than the products supplied by nature by deliberately changing the structure." This quotation is taken from the introduction to the first German plastics manual entitled "Fortschritte der Chemie, Physik und Technik der makromolekularen Stoffe" of which he was one of the publishers ([22]; quoted in [17], p. 169, footnote 224). "Synthetic rubber is, for example, [. . .] tougher than natural rubber [. . .] and it is more suitable for car tyres." [10, p. 15]

Staudinger's self-confident predictions proved to be correct; the macromolecular concept stimulated material research and really did lead to an industrial boom soon afterwards:

- "Thanks to the co-operation with Hermann Staudinger, the second half of the 1920s and the 1930s were trailblazing years for industrial research [. . .], since Staudinger's macromolecular model represented a very viable theoretical resource. It was possible to tackle specific development problems and create new experimental conditions with it" [17, p. 60].
- "During the period between 1929, when the research team at I. G. Farbenindustrie produced the first (marketable, editor's note) polystyrene, and 1932, the group developed synthetic polymers at a speed of about one new product per day. It goes without saying that not all of them were viable, but some

were of tremendous economic significance. The latter included the first polyacrylic compounds, some of which were used later on to manufacture excellent materials such as Orlon and Acrilan and strong, transparent plastics such as Plexiglas. These products alone were enough to form the basis for an extensive and large plastics industry" ([23], p. 104; cf. [10], p. 15).

- "Global production of high-molecular materials (plastics, synthetic resins, chemical fibres etc.) amounted to 100,000 tonnes in 1933, 1 million tonnes in 1950 and more than 2 million tonnes in 1953" (source: www.benzolring.de).

From purely empirical optimisation of materials to molecular material design – this, in a nutshell, is the most tangible progress that has been made thanks to Staudinger's macromolecular concept and that is highlighted when tribute is paid to Staudinger's historical achievements. His "concept [...] that was revolutionary at the time paved the way for the molecular design of functional and decorative polymer materials, the property profiles of which are customised for specific applications via the molecular architectures" [24, p. 1072].

2.9 Rejection in Düsseldorf

All of this was of course still a long way off at the beginning of the 1920s, when the macromolecule concept was still in its infancy. Irrefutable experimental proof of the existence of macromolecular substances had not yet been obtained; some 20 dissertations (cf. [17], p. 65) were compiled at Staudinger's Institute of Organic Chemistry at the Swiss Federal Institute of Technology in Zurich between 1920 and 1926 for this purpose, the results of which Staudinger presented to the Society of German Natural Science Researchers and Doctors when it met in Düsseldorf on 23 September 1926 [25]. Instead of the triumphal reception he hoped for, Staudinger found himself almost completely isolated: "Everyone [...] rejected Staudinger's theory as being thoroughly untenable. Only Richard Willstätter (1872–1942, editor's note), the winner of the Nobel Prize (in 1915, editor's note) declared to his astonished colleagues at the end of the meeting that he was now of the opinion that Staudinger had provided experimental proof of the existence of long chain molecules" ([18], p. 232 and cf. [11], p. 48). The physical chemist Hermann Mark (1895–1992), who was another of the speakers in Düsseldorf, put it more cautiously: "Willstätter [...], the Chairman, indicated in reticent form during his final remarks that he supported the macromolecular concept" ([26], p. 482; quoted in [16], p. 82).

Staudinger faced further resistance from colleagues the same year when he left the Swiss Federal Institute of Technology in Zurich after 14 years of successful work to take up a position at Albert-Ludwigs-Universität Freiburg as successor to Heinrich Wieland (1887–1957), who in turn followed Richard Willstätter at Munich Technical University. Staudinger was to stay committed to Freiburg until he retired in the spring of 1951 at the age of 70, remaining the highly respected

director of the chemical laboratory at the university for a quarter of a century, even though the conditions were anything but favourable at the start. Nationalistic circles had branded Staudinger a "traitor to his country" because of the dedicated appeals he had made in 1917 to decide the outcome of the First World War by negotiation rather than by fighting as Germany was certain to suffer a military defeat due to "material inferiority" (see Sect. 1: "1881–1919"). Due to this, "serious misgivings and even open protest were expressed by the (Freiburg, editor's note) professors" against Staudinger before his appointment [18, p. 228] – but for political reasons and not because of his provocative macromolecule hypothesis. The Freiburg "dean Friedrich Oltmanns (1860–1945, editor's note) travelled to Zurich specifically to meet Staudinger and take him to task personally and it took the latter a great deal of effort to make it clear to Oltmanns and the other Freiburg colleagues that he was not by any means the detractor of Germany which he was to a large extent considered to be. Staudinger became a professor at Freiburg University in 1926 and was even dean of the natural sciences faculty for a time, although not all of his colleagues succeeded in overcoming their animosity against him" [18, pp. 228–229].

2.10 Reservations About "Gunk Chemistry"

Both Staudinger's personal and professional reputations remained tarnished at first: "The rejection of the concept of macromolecules by most organic chemists turned into disdain at the end of the 1920s" [19, p. 253]. The opponents included the already mentioned Heinrich Wieland, former holder of the Freiburg chair, a specialist for organic nitrogen compounds and winner of the 1927 Nobel Prize in Chemistry. It is reported that Wieland gave Staudinger the following piece of advice at the end of the 1920s: "My dear colleague, abandon the idea of giant molecules, organic molecules with a molecular weight of more than 5,000 do not exist. Purify your products, like rubber, and then they will crystallise and prove to be low-molecular substances" (quoted in [19], p. 253; cf. [1], p. 79 and [11], pp. 47–48).

This criticism of Staudinger was based on two associated presuppositions that were themselves questionable:

- *Premise A*: Substances or substance blends in a non-crystalline state, such as rubber and other resins, were not chemically pure. Such "gunk" was not something that deserved investigation from the outset, chemists were only supposed to focus on pure, crystalline compounds – following possible extraction from the sticky resins. Looked at from this point of view ("chemistry of pure substances"), not only the alleged giant molecules but also their supposed alternative, i.e. clusters (aggregates) of small molecules, disappeared into thin air because both of them could only be found if the "gunk" in question was inadequately purified, so that they were, strictly speaking, only pseudomaterials (cf. [20], p. 12).

- *Premise B*: The smallest atomic components of a crystal that could be determined with the help of X-rays were called basic elements or elementary cells, These three-dimensional structures in the low molecular organic range were all larger than the molecules of the substance in question. With respect to high-polymer materials, X-ray structural analysis showed that crystalline cellulose, for example, only had an elementary cell consisting of a few glucose units. In view of past experience in the low molecular range, it was concluded that cellulose was not a macromolecule candidate – after all, the cellulose molecule had to be even smaller than the elementary cell, which was small anyway (cf. [18], p. 232 and [15], p. 30). It was of course unscientific to generalise this finding, i.e. to apply it to all supposedly macromolecular substances and solutions of them without carrying out appropriate experiments, but this did not inhibit the mainstream traditionalists in the low molecular field much at all.

Other natural scientists apart from chemists were also dogmatic in their criticism of Staudinger's giant molecules, such as the Swiss mineralogist Paul Niggli (1888–1953): "When Staudinger gave a lengthy lecture at a scientific conference in 1925 in which he presented his latest evidence demonstrating the existence of macromolecules, Niggli exploded right in the middle of it. He stood up and shouted across the room. 'Such things do not exist!'" ([11], p. 232; cf. [1], p. 86). Later on, Niggli was to admit his error openly and laugh about his premature conclusion, in contrast to "colleagues, who chose to keep quiet about their misinterpretation and took over Staudinger's macromolecular concept that they had fought so fiercely at first – as if it was a matter of course" ([18], p. 240, footnote 44).

2.11 Support Unwelcome

The low-molecular dogma started to be questioned more and more and the anti-Staudinger front was far less unified than it appeared on the surface to be. The physical chemist Kurt Hans Meyer (1883–1952), for example, criticised the widespread inaccurate evaluation and/or interpretation of X-ray spectroscopic results. The head of the IG Farbenindustrie plant in Ludwigshafen (see [15], p. 77 for extensive information about Meyer's life) made it unmistakably clear that the size of the elementary cell did not dictate maximum molecular size: "It is [...] completely wrong to look for the limitations on organic molecules, i.e. on the atomic complex held together by primary valences, in the basic element" ([27]; quoted in [16], p. 88). Hermann Mark also conceded that "an organic molecule could under certain circumstances be larger than the crystallographic basic element" ([26], p. 482; quoted in [16], p. 82). In his summary of the – for Staudinger frustrating – conference in Düsseldorf, annoyance is expressed too: "The situation for the representatives of X-ray structural analysis was somewhat disappointing. Before the conference, it seemed as if the small basic elements were a crucial

objection to macromolecules; now, after settling their role, they were compatible with both small components and long chains." [16]

Amazingly enough, Staudinger was anything but enthusiastic about receiving "support from representatives of physical chemistry and X-ray structural analysis" [19, p. 253]. He did in fact maintain a long-running feud with Meyer and Mark. We will be looking into his reasons for this later on.

In 1927, Staudinger succeeded in providing proof that "individual ( ) molecules can encompass a large number of elementary cells" [18, p. 232]. His X-rays of polyoxymethylene showed "an elementary cell with only four methylene oxide groups [. . .], whereas it was, on the other hand, an undisputed fact that this substance definitely had to consist of far more such basic units" [18]. In spite of this, the evidence in favour of the macromolecule concept was still too tenuous to change the minds of opponents and notorious sceptics. Staudinger had to come up with proof that focussed on the core of his theory and made it watertight, i.e. that there were primary valence bonds between all the links in the postulated chain molecule with respect to electromagnetic attraction. Because only they were able to weld atoms and molecules together to form a stable unit irrespective of size (cf. [10], p. 6 and [1], p. 317) and substantiate the difference between an individual molecule and a molecular complex, i.e. between a genuine macromolecule in the form of an integrated whole and a pseudo-macromolecule (in the sense of a combination of several molecules forming a compound that is only held together by weaker secondary valence bonds). But how was the difference between macromolecules and clusters of low molecular particles, also known as micelles (see Appendix 3), to be demonstrated specifically in a thoroughly convincing way?

2.12 Micelle or Molecular Colloid?

Staudinger [1], p. 108) said: "The procedure adopted in explaining composition issues in macromolecular chemistry is exactly the same as in low-molecular chemistry, i.e. the substance is dissolved and the size and composition of its dissolved particles are investigated" (cf. [10], p. 15). The premise was: "In view of the size of the molecules, macromolecular substances can [. . .] only dissolve colloidally" [1, p. 119]. If dissolved substances do in fact take on this glue-like consistency, less is, however, achieved than hoped, because it cannot be concluded that the dissolved substance is macromolecular in structure on the basis of the formation of a colloid alone; this can be a characteristic of micelles too (cf. [16], p. 10). In other words, it would only be definite that the substance consisted of macromolecules if it could be proved that "the colloidal nature [. . .] was due to the special composition of the substance" [1, p. 111]. Staudinger coined the term "molecular colloid" to describe this finding: "In micelle colloids, the colloid particles are loose collections of small molecules, whereas the colloid particles in molecular colloids are the macromolecules themselves" [1, p. 320].

Micelle colloids form, for example, in aqueous solutions of soaps and dyes (see [10], pp. 8–9; [1], pp. 80–81; [19], p. 250). However, soaps dissolve "normally" [1, p. 81], i.e. without micelle formation, in alcohol (cf. [10], pp. 8–9). This is also true of the high-polymer material rubber if menthol is used as the solvent [1, p. 81]. The crucial role played by the solvent (cf. [15], p. 208) therefore makes it difficult to determine correctly whether a low or highmolecular substance is involved. Depending on the nature, concentration and temperature of the solvent, it is evidently the case that primary valence bonds can break too, while secondary valence bonds remain stable. Even if a colloid proves to be resistant to many different solvents, there is still some uncertainty about whether the dissolved substance can be identified definitely as macromolecular. The process is not therefore conclusive enough. Staudinger himself also felt that resistance was merely "a valuable indication but not definite proof that the colloid particles are macromolecular in structure" [1, p. 119]. "Determination of the size [...] does not reveal the inner structure of the particles. This question is answered via chemical experiments that are carried out here at the same time, like when investigating the structure of particles of low-molecular organic compounds [...], in order to demonstrate that the atoms in a particle of a certain size are bonded by primary valences, i.e. that this particle represents a chemical molecule" [10, pp. 15–16].

2.13 How Staudinger Proved the Existence of Macromolecules

But how could the necessary proof be provided? This is exactly what the Japanese Emperor also wanted to know from Staudinger when he granted an audience to the man who was later to win the Nobel Prize: "Professor, are macromolecules merely concepts that enable many different phenomena to be explained or is there strictly scientific proof of their existence too and, if so, what methods are used to supply the proof?" [1, p. 115]. The answer was: experimental proof of the existence of macromolecules has been provided when a substance "is transformed into derivatives without changing (or reducing) its degree of polymerisation" [1]. "Transformation of this kind [...] into derivatives with the same degree of polymerisation is known as polymer-analogue conversion" [10, p. 17].

This reasoning is based on the assumption "that a secondary valence bond [...] does not survive chemical conversion unchanged. [...] The secondary valences must disappear at least in the transition state of the reaction" [15, p. 342]. If the colloids prove to be resistant even so, i.e. their degree of polymerisation does "not" change even "in such profound chemical conversion processes as esterification or saponification", it is definite that "all the basic molecules [...] are bonded to each other via primary valences" [10, p. 17] and not by secondary valences, which "are definitely destroyed [...] by such chemical intervention" [26, p. 482]. In a nutshell, in this case, macromolecules and not micelles must be involved. "Such proof [...]

has been provided for cellulose, starch, glycogen, rubber and various plastics, including polyvinyl acetates" [19, p. 411].

Staudinger produced the first experimental results as early as 1922 together with his doctoral student Jakob Fritschi with the hydrogenation of rubber, i.e. the saturation of its carbon atoms with hydrogen. The hydrorubber created proved to be "just as tough as the original substance and produced only colloid solutions as well" [11, p. 47]), "which prompted the research scientists to work on the assumption that macromolecules were involved rather than micelles or relatively low-polymerised molecules" [17, p. 67]. The original publication states: "Rubber is [...] a very high-molecular hydrocarbon with numerous ethylene bonds [...]. The ethylene bonds can be saturated partially or completely by adding halogen, hydrogen halide or sulfur chloride in vulcanisation, without the colloidal properties changing, i.e. without the 'macromolecule' disintegrating" ([13]; quoted by [18], p. 240, footnote 42). "These conclusions about the macromolecular structure of rubber and hydrorubber were confirmed by experiments conducted on polystyrene between 1923 and 1926" [1, p. 84].

"Polymer-analogue conversion is a method that is based exclusively on the application of organic chemical principles, is intrinsically logical and is very convincing" [15, p. 342]. It is an excellent example of "how scientific progress [...] can be achieved using a modified concept with the help of established methods" [19, p. 249]. The dispute about Staudinger's macromolecules was not over, however. Although their existence had been confirmed in principle and the plastics industry took advantage of Staudinger's model, there were still a number of controversial details and unsettled issues "relating in particular to explanation of the physical properties of the high polymers" [15, p. 208].

2.14 Staudinger's Dispute with Meyer and Mark

The physical chemists Hermann Mark and Kurt Hans Meyer, who have already been mentioned briefly, were particularly critical observers of Staudinger's research. Both of them worked at the central laboratory of I.G. Farben in Ludwigshafen. Mark was appointed Professor of Physical Chemistry at Vienna University in 1932 and established a polymer chemistry teaching and research programme there. Meyer, who used to be on the staff of Fritz Haber and Richard Willstätter, left I.G. the same year and took up an appointment as professor at Geneva University. Both of these research scientists had "already acknowledged the existence of macromolecules in 1928 – following initial rejection of them – but had modified Staudinger's concept in this context" [19, p. 404]. Mark and Meyer agreed with the assumption of "primary valence chains", but considered that "micellar forces", i.e. secondary valences, acted between them (cf. [15], p. 337). This was a concept that Staudinger called the new or "second micellar theory" ([1], p. 90) and thus rejected as outdated. A close look reveals that Mark and Meyer were in fact firmly in the Staudinger camp, except that they tried by fluctuating

outwardly between macromolecules and micelles to make more distinctions in the theory of high-polymer materials and, if necessary, to correct Staudinger. Meyer and Mark insisted in particular that the significance of secondary valences should not be underestimated:

- Meyer [28] writes: "Staudinger assumes that association to form molecular groups or micelles has only been determined with soaps, that hold a special position because of their salt character. We would like to draw attention to the fact that they can be detected in all higher-molecular compounds [. . .]" (quoted by [15], p. 96).
- Meyer [29] writes: "In contrast to Staudinger, [. . .] we observe the structure of the [. . .] high polymers in solution, when Staudinger says [. . .] that they have no micellar character. We, however, are convinced that cluster or micelle formation plays a key role in the high-polymer materials in solution too" (quoted in [15], p. 108).
- Priesner et al. [15], p. 337) comment: "Whereas to Staudinger there was a clear distinction between primary and secondary valences and no attempt was made to obtain information about the nature of the individual types of bond, the physical chemistry approach demanded stronger distinction. [. . .] The strength of both primary and secondary valences was not observed to be constant; instead of this, it varied according to the structure of the molecules. As far as size was concerned, a strong secondary valence could therefore very definitely correspond to a weak primary valence."

On the basis of what we know now, Mark and Meyer were in actual fact "not completely wrong" [11, p. 48], because it is true that macromolecules can "definitely in suitable conditions form micelles in their solutions too ([11], p. 48; cf. [18], p. 233). "More or less highly aggregated groups of molecules are also solvated in colloidal solutions alongside individual molecules, depending on the solvent concentration. Micelles are just as real as individual macromolecules" [15, p. 115], although the term is nowadays reserved exclusively for "aggregates of small molecules" [15, p. 82]. Minssen and Walgenbach [20, p. 99] go even further: "The concept of chemical primary valence with its defined bonding relationships does not explain all the characteristics of a substance." Denaturation of enzymes could, for example, be described best by saying that the primary valence bonds were maintained, whereas the secondary valence bonds were broken. Minssen and Walgenbach [20, pp. 60–61] go on: "In the case of what are known as biological macromolecules, e.g. nucleic acids and 'proteins', particularly enzyme proteins, the sensitivity to heat [. . .] cannot be explained any more via a molecular structure involving primary valences. [. . .] Staudinger is wrong when he says that the reason for the instability when exposed to heat is because the molecules 'disintegrate' due to the elimination of primary valences (1926). The introduction of secondary valences accordingly allows [. . .] the description of more complicated structures and behavioural patterns than is the case when the theory is reduced to standard valences." Staudinger's concept needed "to be abandoned as too limiting. To this extent, his opponents are celebrating a belated triumph."

2.15 Differences and Deficits

Another point of contention was Staudinger's insistence on the stick model in macromolecular theory that he propagated vehemently into the 1940s; he thought that the chain polymers were "always rigid, stretched structures. He liked to use long Mikado sticks to illustrate his ideas" ([15], p. 208; cf. [19], p. 254 and [18], p. 233). Meyer, on the other hand, already emphasised in 1928 "the elasticity of rubber with the tendency of the isoprene chains to form curves and to get tangled up, an interpretation that was new and correct at the time, as we now know" [19, p. 254].

What was known as Staudinger's viscosity formula, which assumed a correlation that was determined by the laws of nature between the degree of polymerisation and/or the molecular weight of macromolecular substances on the one hand and the viscosity level of their solutions on the other hand, was a source of further dissent. Staudinger's widow remembers: "This formula occurred to Hermann Staudinger on a beautiful autumn day in 1929 while we were on one of our rambles in the Black Forest and we then used it in the laboratory on numerous occasions to determine molecular sizes – while leading to just as many attacks from the scientific community!" [30, p. 42]. Hermann Mark considered the proportionality assumed by Staudinger to be too vague and started viscosity experiments of his own in the 1920s. His "goal [. . .] was to find a relationship that was based on precise mathematical principles" [15, p. 111; cf. p. 348]. "There was an additional complication for Staudinger in the form of the causal link between his (narrow, editor's note) idea of the 'form' of the macromolecules and the accuracy of his viscosity law" [15, p. 190].

Staudinger's critics proved to be mistaken about the core issue – molecule size: "Whereas Mark and Meyer were right in assuming that there were strong intermolecular forces, they continued to underestimate the length of the primary valence chain (of the macromolecule) for many years" ([19], p. 254; cf. [15], pp. 82, 208). It should be pointed out that neither of them claimed to be able to determine molecular sizes on the basis of their domain (X-ray structural analysis) (cf. [15], p. 347) and that they said they had no particular ambitions in this area either: "In all our work, [. . .] we have considered it much less important to determine that chains exist and have given much higher priority to finding out exactly the location and shape of the chains, the bonds between the links in the chain, the micellar forces etc." ([29]; quoted in [15], p. 108).

2.16 Feud Between Colleagues Instead of Coalition

The opposing positions here were not irreconcilable in principle, and definitely had more in common than separated them. And, although "in a sense both sides were right" [18, p. 233], the controversy refused to end, becoming increasingly fierce and

polemic as the years went by. Priesner [15, p. 211] concludes that Staudinger and Meyer/Mark had "no reason" at all "to compete with each other, because the former was at home in the preparative organic chemistry field, while the latter focussed on physical chemistry". Both sides were committed to different angles and issues, which complemented each other rather than ruling each other out. In spite of "two different starting points", the results were "very similar conclusions" [15, p. 58]. Priesner therefore wondered what might have prompted the rivals to fight each other ruthlessly, instead of forming a coalition to combat established low-molecular thinking – the real opponent: "The opportunity of benefitting mutually from the skills of the other via close co-operation and of helping the macromolecular theory to make a breakthrough against the resistance of the strong group of the proponents of the low-molecular 'aggregation theory' [. . .] was squandered" [15, p. 58; cf. p. 349].

Priesner found out the reason for the feud specifically once he analysed the correspondence between Staudinger and Mark/Meyer, which forms part of the Staudinger estate that is kept at the Deutsches Museum in Munich: "What this controversy involved was not [. . .] a theoretical dispute [. . .], but the question of to whom priority was due with respect to a position that was maintained by both parties in a similar way" [15, p. 349; cf. p. 351]. There never was a quarrel between Staudinger and Mark/Meyer in the sense of a dispute of fundamental significance about scientific theory, because Staudinger's attacks to all intents and purposes ignored Mark's and Meyer's "actual Achilles' heel", the relatively small size of the primary valence chains [15, p. 93]. Psychology and not logic was therefore required to understand what fuelled the controversy [cf. 15, p. 350].

2.17 "Academic Claustrophobia"

Because Staudinger considered himself to be the "intellectual father of macromolecular chemistry" [15, p. 250] and had the necessary self-confidence to claim that he alone was "responsible for determining the composition of high polymers" [15, p. 184], he understood "any assessment of his work that was not unreservedly positive to be an attack" [15, p. 240]. For this reason, it could be said that he suffered from over-sensitivity [15, p. 240] or even a "kind of academic claustrophobia" [15, p. 330]. And that is not all: in his determination to smother any perceived attempt to dispute his claim to priority at the earliest possible stage, Staudinger opted to go on the offensive before he needed to defend himself at all: "Staudinger initiated the controversy at the start and as it went on, there are no examples of Mark or Meyer attacking Staudinger themselves either" [15, p. 351].

It was Mark in particular who tried repeatedly to calm things down. He explicitly took sides with Staudinger, because "we essentially think the same, i.e. that the high-molecular substances consist of long chains that are held together by primary valences, and are only unclear about the most appropriate term for this" (letter to Staudinger of 11 December 1928; quoted in [15], p. 99). On another occasion, Mark pointed out: "I think that we [. . .] should proceed together and should not emphasise

differences between our personal views that are in my opinion minor; if we did, the high-polymer community could easily make the mistake that is only too familiar from politics; that a major issue was not given close enough attention and was not presented clearly enough because of minor differences between opinions that were not far apart." (letter to Staudinger of 2 November 1928; quoted in [15], p. 94; see Appendix 4 for the complete letter)

Staudinger, however, dug his heels in even more and contradicted himself into the bargain. Priesner [15], p. 350 reveals the paradox "that Staudinger claimed he was being copied by Mark and Meyer, while stating at the same time that their theory was wrong. The only way for anyone to get into such a situation was if he thought that any activities by other people in the high-polymer chemistry field were [. . .] a violation of scientific rights he claimed for himself, if the person in question also advocated the existence of large molecules." Staudinger's contemporary, Wallace Hume Carothers (1896–1937), the inventor of nylon, drew conclusions about him that were just as embarrassing. In a discussion held in 1932, Carothers started by paying tribute to Staudinger's tremendous importance as a scientist, before outlining his personal weaknesses: "Opinions abandoned by former opponents are presented and refuted again; apart from this, the contributions made by other research scientists are not acknowledged to a sufficient extent" ([31]; quoted in [19], p. 255). As late as 1936, Meyer still criticised "Staudinger's practice of repeatedly misquoting other research scientists and accusing them of holding the opposite of their true views" (quoted in [15], p. 197).

2.18 The Macromolecule Has Several Fathers

In view of this, the final question that the scientific historian still has to answer is the extent to which Staudinger's uncompromisingly formulated claim to priority is justified, not only with respect to Meyer and Mark (synchronic angle) but also with respect to possible predecessors from earlier days (diachronic angle). In other words: was the macromolecular concept the major discovery of a pioneer or did Staudinger benefit from the work of others before him and more or less tacitly uncover something that had already been discovered but then forgotten? The answer is complex:

- Priesner [15, pp. 350–351] writes: Staudinger's first announcement about high-polymer compounds [12] "indisputably contained all the fundamental principles of macromolecular chemistry, but these principles were not exclusively original creations by Staudinger", because "a large proportion of them had already been thought and expressed before him. It goes without saying that Staudinger was more than a compiler, but he was that as well" (cf. [15], p. 336).
- Meyer [29] says: "It is not correct that 'the publications by K.H. Meyer essentially reproduce opinions that Staudinger has been expressing in numerous publications and lectures for years'". Together with Mark, he, Meyer, built

"not on Staudinger but on general teaching in the past, which is outlined very soundly in Emil Fischer's work about polypeptides and proteins in particular" (quoted in [15], p. 107; cf. pp. 95–96).

- Deichmann [19, pp. 249–250] uses rubber as an example to talk about different opinions, traditions and fashions that determined the concept of macromolecules and alternated up to 1930: "In 1860, the British chemist Charles G. Williams (1829–1892, editor's note) expressed the suspicion that rubber could consist of numerous individual components, while the work done by other research scientists supported the theory that a large molecule was involved. The idea that the naturally occurring substances rubber, cellulose, starch and protein had a high-polymer structure was a widespread view at the end of the nineteenth century. Thinking then started to go in the other direction, represented most significantly by Carl Harries (1866–1923, editor's note), who was one of the most well-known rubber chemists of his time in Germany and was convinced that rubber had a low-molecular structure." Priesner [15, p. 9] qualifies: "However, Harries too initially expressed the opinion that 'rubber' was 'a hydrocarbon of very large, unknown molecular size'" (see also [11], p. 45).

Staudinger's achievements cannot be overstated in spite of all this: even if the macromolecule has several "fathers", it is justifiably identified primarily with Staudinger. What is certain is that Staudinger is "the first chemist who confirmed the existence of macromolecules experimentally" [19, p. 254]. Krüll [18, p. 233] stresses: "It remains a fact that they (i.e. macromolecules, editor's note) have dimensions unsuspected in the past that are the reason for their specific properties and behavioural patterns which differ completely from molecules of 'normal' size. Credit is due to Staudinger for being the first to have claimed and proved this. Indirectly, however, we owe the basic theoretical concept behind macromolecular chemistry – and thus modern plastics chemistry – to Staudinger's numerous scientific opponents in particular too. Because their constant doubts and counterarguments are what forced Staudinger to keep on looking for new ways and means to prove his theories." Priesner, to whom Staudinger is "indisputably one of the most important polymer chemists ever", delivers a balanced verdict from a historical distance: "All in all, the macromolecular concept is not the work of a single person. Like almost always in scientific history (and not just there), it becomes clear when a closer look is taken that the development of human insight is to a large extent the result of the achievements of many different people, co-operation between whom is the source of but also precondition for scientific development and human society" [15, pp. 359–360].

Staudinger's position in Germany was already being considered in a similar way at the beginning of the 1930s: more and more chemists sheepishly joined the macromolecular camp, while the number of sceptics and adversaries shrank. Although this was gratifying for Staudinger, a new challenge was already lying in store for him in 1933, when the Nazis came into power: would the scientist, who faced political hostility, be allowed to continue his research unhampered or would he be unable to enjoy the results of his work?

3 The Life and Work of Hermann Staudinger: 1933–1945

Hermann Staudinger started a new phase of his life in the 1930s: his theory about the macromolecular structure of polymers – which was hotly contested in the initial stages – finally received the recognition it deserved; the outsider who was considered to be suspicious became a celebrated iconoclast with a worldwide reputation. More and more of the organic chemists among his colleagues embraced Staudinger's "giant molecules" concept. The same was true of Kurt Hans Meyer and Hermann Mark, who Staudinger said were his main opponents in the priority dispute, because their primary valence chains competed with his macromolecules (see Sect. 2: "1920–1932"). The "new micellar theory" propagated by Meyer and Mark was soon to be history; the two physical chemists gradually abandoned it as they made progress in their work (see [1], p. 93 and [15], pp. 214, 380).

While the opposition he faced from the scientific community decreased, new storm clouds developed in 1933, when the Nazis assumed power. What did the totalitarian state have in store for Staudinger as head of the chemical institute at Freiburg University? And how did he position himself politically with respect to the fascist rulers, who operated in line with their well-known motto: "If you're not for us, then you are against us"?

3.1 Accusation of "Anti-German Sentiment"

Krüll [11, p. 48] claims that Staudinger profited from the Nazi regime and its racial ideology, although the latter did not encourage this: "After 1933, Staudinger suddenly benefited from the fact that Mark and Meyer were Jews. In the context of 'German natural science', Staudinger was of course a priori in the right here, at least within the area controlled by the Nazi Party". This assessment requires correction to the extent that Staudinger was neither dependent on support from any anti-Semites nor did he receive any such official support with respect to the scientific priority dispute. The Nazis did not by any means come to Staudinger's defence against anyone; on the contrary, they attacked him themselves, accusing him of "anti-German sentiment" and making him a public enemy.

One of the first to investigate Hermann Staudinger politically was the philosopher Martin Heidegger (1889–1976), a new member of the Nazi party and the first Nazi vice-chancellor of Freiburg University (period of office: 23 April 1933 to 23 April 1934). Heidegger did not just denounce colleagues in his faculty, particularly those of Jewish origin such as the philosopher Richard Hönigswald (1975–1947), who lost his chair at Munich University because of a negative report compiled by Heidegger ("particularly dangerous brilliance", "vacuous dialectics") [32]. Heidegger also denounced scientists from all other faculties and "races" who were identified as political opponents, particularly Communists and Social Democrats, but also people who were not members of any party but did not express Nazi/

soldierly views. This was a description that – in Heidegger's opinion – fitted Staudinger; the research done by the vice-chancellor produced so much incriminating evidence of this that he initiated impeachment proceedings against Freiburg's star chemist:

- In July 1933, vice-chancellor Heidegger contacted the physicist Alfons Bühl (1900–1988) who had qualified to be a professor in Freiburg but was now teaching at the Swiss Federal Institute of Technology in Zurich, where Staudinger used to work. Bühl was supposed to get to the bottom of "various rumours" [33, p. 209], particularly the rumour that Staudinger had "acted as an advisor to enemies abroad" during the First World War, with respect to "the production of chemicals of importance to the war effort, particularly [...] dyes and pigments" [33, p. 203]. This had at any rate been investigated by the German Embassy in Bern at the time. Bühl was unable to find out anything specific and was referred by a member of the staff of the Consulate General in Zurich to the Baden district authorities in Karlsruhe, where "material about Mr Staudinger from the year 1919 was available" [33, p. 209]. In this context, Heidegger's biographer, Hugo Ott, stresses that the Staudinger affair was definitely attributable to the action taken by Heidegger; the driving force was not, as has often been claimed, the Ministry of Culture in Karlsruhe, which was only involved later on. Deichmann [19, p. 398] writes: "Staudinger never found out that it was Heidegger who denounced him in 1933; his wife, Magda Staudinger, heard about it in 1982 via an article by Hugo Ott in the *Badische Zeitung* newspaper." (cf. [33], p. 207)
- On 29 September 1933, the head of the university department at the Baden Ministry of Culture, Eugen Fehrle (1880–1957), was in Freiburg and was "informed" by Heidegger about "incriminating political material about Hermann Staudinger [...]" [33, p. 202]. Just one day later, Fehrle submitted a report to the Freiburg police – 30 September was the deadline for the initiation of proceedings for political reasons on the basis of the Act passed on 7 April 1933 to restore the civil service, which enabled the Nazis to arbitrarily remove civil servants who had made themselves unpopular from their offices. The investigations against Staudinger were then taken over by the secret police in Karlsruhe under the pseudonym "Sternheim Project" (cf. [34], p. 177). It says in the files that Heidegger "was unable [...] to provide the secret police with any useful information" [33, p. 202]; instead of this, he merely passed on rumours. In the subsequent months, the secret police therefore collected "three extensive bundles of files" [33, p. 202] from documents at the Karlsruhe district authorities (Staudinger worked at Karlsruhe Technical University until 1912), from the German Consulate General in Zurich and from the German Embassy in Bern. Farías [34], pp. 177–178) writes: "The material obtained by the secret police [...] was sufficient for a case to be initiated against Staudinger in Karlsruhe."

3.2 *Heidegger Demands Dismissal*

- On 6 February 1934, Heidegger was "asked" by the Baden Ministry of Culture "to submit comments urgently, enclosing the files", because "Paragraph 4 of the Act (to restore the civil service, editor's note) must be applied, if necessary, by 31 March 1934" [33, p. 204]. The Freiburg vice-chancellor replied on 10 February, i.e. only 4 days later, and argued in favour of a dismissal of Staudinger from his position as a civil servant. Among other things, Heidegger's letter says:

> All the reports by the German Consulate General in Zurich from the War [. . .] talk about the disclosure by St. of German chemical manufacturing processes to foreign (enemies). [. . .] Staudinger has [. . .] 'never denied that he was in complete opposition to the national movement in Germany and has declared on numerous occasions that he will never defend his fatherland with weapons or by service in other forms'. [. . .] No less incriminating evidence is the fact that Staudinger wrote a petition for the pacifist Dr. med. (Georg Friedrich, editor's note) Nicolai (1874–1964, editor's note), who had refused to take the oath of allegiance, in Zurich in 1917. [. . .] These facts alone require application of Paragraph 4 of the Act to restore the civil service. Since they have become and remained known to large numbers of people in Germany since the discussions about the appointment of Staudinger to the position in Freiburg in 1925/26, action also needs to be taken in order to protect the reputation of Freiburg University [. . .]. Dismissal is likely to be the better option rather than retirement. Heil Hitler! Heidegger. (Quoted in [33], p. 205) (see for photo of Nicolai)

The Baden Minister of Culture, Otto Wacker (1899–1940), supported Heidegger's demand on 22 February 1934 (see [34], p. 178, [33], p. 206 and [19], p. 397) and proposed: "The Ministry of State is asked to suggest to the Reich Governor that Professor Dr Hermann Staudinger [. . .] is dismissed from the Baden civil service" (quoted from [33], p. 206). Staudinger was "no longer a suitable teacher for German academic youth; I consider that the conditions for removal from Freiburg University in accordance with §4 of the Act (to restore the civil service, editor's note) are satisfied" [33].

The fact that Staudinger was an annoyance to staunch Nazis was attributable to more than mere rumours:

- The political background of Staudinger's family was strongly left-wing. His father Franz (1849–1921) had a doctorate in philosophy, sought to combine the theories of Kant and Marx, published in the "Sozialistische Monatshefte", was involved in the co-operative movement and maintained personal friendships with such prominent Social Democrats as Eduard Bernstein (1850–1932). Staudinger's first wife, Dora (1886–1964), née Förster, was also actively involved in the co-operative movement as well as "in the religious-pacifist and religious-socialist circles led by the (Swiss, editor's note) clergyman (Leonhard, editor's note) Ragaz (1868–1945, editor's note), who then lost his position in the ministry" [33, p. 204]. Staudinger's brother Hans (1889–1980), Secretary of State in the Prussian Ministry of Trade, was a member of the Social Democratic Party and was married to the Jew Else

Maier (1889–1966). He was immediately dismissed from the civil service and arrested in 1933. In 1934, he was able to emigrate to the USA, where he became economics professor at the New School for Social Research in New York (cf. [19], pp. 396–397). As is generally known, the Communist and Social Democratic Parties were branded as subversive right from the start and their members were persecuted systematically. On the basis of what was known as the Reichstag fire regulation of 28 February 1933, the 81 parliamentary seats held by the Communist Party were revoked on 8 March and the assets of the party were confiscated on 26 May. With reference to the Social Democratic Party, the Reich Minister of the Interior, Wilhelm Frick (1877–1946), called on the state governments to ban the party's activities on 22 June:

> The Social Democrats cannot [...] be allowed to carry out propaganda activities of any kind. [...] The assets [...] that have not already been confiscated in connection with the dissolution of the free unions will be seized. It goes without saying that it is not possible for civil servants and employees who receive salaries, wages or pensions from public funds to continue being members of the Social Democratic Party in view of its treacherous character. (Quoted from http://library.fes.de/fulltext/bibliothek/chronik/band2/e235f1109.html)

The Reich Ministry of Justice announced in this context: "Officials who used to be members of these parties must be required to submit a written statement that they no longer maintain a relationship of any kind to the two parties (Social Democratic and Communist Parties, editor's note), their support and substitute organisations and their representatives abroad. Their attention must be brought to the fact that dismissal is the punishment for the provision of false information" (quoted from [16], p. 171).

- The accusation Staudinger faced that he failed to demonstrate "sympathy for the national cause" was based primarily on his attempts to obtain dual citizenship during his years in Zurich, i.e. after he acquired a Swiss passport in addition to his German one. In his letter of 10 February 1934, in which he demanded Staudinger's dismissal, Heidegger criticised: "In January 1917, i.e. when the fatherland was at its time of greatest need, St. applied for Swiss citizenship without their being any professional or other necessity for this. Implementation of this plan was prevented by the German Consulate General. [...] On 9.1.1919, i.e. directly after Germany collapsed, St. submitted his request for permission to become a citizen of Switzerland again [...]. Naturalisation occurred on 23.1.20, without German approval being obtained" (quoted from [33], p. 205). This went hand in hand with the accusation of "pacifist sentiment" [33, p. 204]: although he was rejected as unfit for military service at the age of 23, Staudinger was examined again by military doctors during the First World War at the age of 34 and this time he was merely exempted from military service temporarily. Staudinger probably applied for a Swiss passport in order to avoid being called up, as was to be expected (cf. [33], p. 203). This interpretation is, however, contradicted by the fact it took almost two years for Staudinger to do this; his commitment to Switzerland can therefore be interpreted instead as the adoption

of a neutral position with respect to the participants in the war, whom he called on in 1917 to cease all fighting and to initiate peace negotiations.

3.3 "Betrayal Theory" Revealed to Be a Myth

- After the USA joined in the war, Staudinger felt that Germany was bound to be defeated on the battlefield, because it was inferior to the Americans both economically and where armaments were concerned (see Sect. 1: "1881–1919" for details). Staudinger was therefore vilified as a "pacifist and annihilator of German military power" [35, p. 604] by nationalistic circles after 1918 and, in particular, after 1933, this being quoted as key evidence for what came to be known as the "betrayal theory". According to this theory, a revolt on the "home front" undermined the German Army, which was "undefeated in the field" and was to blame for the defeat. Staudinger [4, p. 42] countered this by saying that the political leaders failed by believing illusions about a German victory rather than taking up the offer of peace made by US President Wilson (cf. [4], p. 42). The misjudgement of the military situation had extended the war unnecessarily – although there was no longer any chance of winning it – and had made Germany's defeat particularly bitter (cf. [4], pp. 41, 44, 53). The betrayal theory was developed to distract from this political mistake: it "made the German people forget the military defeat suffered in the First World War, which [. . .] military leaders admitted in awareness of their responsibility", as can be read in Staudinger's writings [4], p. 44. His chief witness in this context is General Erich Ludendorff (1865–1937), who confessed in his *War memoirs* that appeared in 1919: "8 August (1918; the start of the battle near Amiens, editor's note) established the demise of our combat powers [. . .]. This meant [. . .] that the campaign took on the character of an irresponsible gamble that I always considered to be ruinous. The fate of the German people was too important to me to risk it in a game of chance. The war needed to be ended" (quoted from [4], pp. 42–43). A view that Field Marshal Paul von Hindenburg (1847–1934) also voiced unmistakably: "Under these circumstances, it is essential to discontinue the fighting, in order to avoid useless sacrifices by the German people and their allies. Every further day costs thousands of courageous soldiers their lives" (quoted from [4], p. 44). With this quote, Staudinger revealed that the alleged betrayal theory was a myth – and also that the man who was later to become President of the Reich was a liar, since he was soon to betray his own convictions. Because Hindenburg said in his appeal to the German people at Christmas 1918: "This powerful instrument of war (i.e. the German people in arms, editor's note) did not collapse under attack by enemy armies. It withstood a world of enemies to the final hour, until the order was issued to end the fighting and return home. [. . .] German warriors are leaving all the battlefields undefeated" (quoted from [4], p. 45).

Since the "betrayal theory that developed in the years after the First World War [...] was later taken up again by the Nazi Party in particular" [4, p. 44], there were irreconcilable differences between Staudinger and the Nazi authorities in this respect too. So it is no surprise that "accusations of anti-German behaviour during the First World War" were made against Staudinger in the course of the interrogations that were held during the impeachment procedure [19, p. 397].

3.4 "Supporter of the National Uprising"

Staudinger had nothing to win by defending his position. So he decided to say during his hearing at the Baden Ministry of Culture on 17 February 1934 that he "abandoned his earlier political views a long time ago" (see [33], p. 207). "The accusation that he harboured 'anti-national sentiments' could not be made against him any longer since he started working in Freiburg; on the contrary, he had 'welcomed the start of the national revolution enthusiastically'" [19, p. 397]. A tactical manoeuvre that the Nazis were reluctant to believe. Heidegger, for example, was very sarcastic about the fact that "Staudinger now claims to be a 110% supporter of the national uprising" (quoted from [33], p. 205). Deichmann ([19], p. 397) confirms this: "He was unable to refute the allegations of anti-German behaviour during the First World War by adopting this defence strategy" (cf. [33], p. 206). Staudinger therefore responded again by rejecting descriptions of himself as "anti-German" and a "pacifist":

- Staudinger was forced to contend with the accusation that he had abandoned Germany and "had been abroad for too long" [16, p. 193] until the end of the 1930s. He tried to refute it by pointing out how he maintained close contacts to German industry during his time at the chemical institute at the Swiss Federal Institute of Technology in Zurich:

> 'Throughout this period from 1912 to 1926, I maintained relationships to German industry and carried out a number of major projects with the same [...].' Staudinger lists: 1. Pest control, 2. Pepper synthesis, 3. Trials to synthesise an artificial coffee aroma. All of these projects were connected with the production of substitutes during the First World War. [...] 'I would also like to note that the desire to return to Germany was the only reason for me to accept the appointment offered (in Freiburg, editor's note) in 1926, in order to continue my work about macromolecular chemistry, which I considered and still consider important, there. The Swiss educational authorities had made me attractive offers to persuade me to stay. I doubled the size of the laboratory in Zurich during my time in office there, whereas the Freiburg laboratory offered far less appealing working conditions in every respect at the time – a situation that has only changed fundamentally now.'" (Letter from Staudinger dated 7 November 1938, quoted from [16, p. 193])

- Staudinger tried to prove the Nazis wrong in accusing him of being a pacifist by disassociating himself from fundamentalist positions: "He was not a pacifist in the strictly religious sense of the Quakers or conscientious objectors; he was, instead, a pacifist 'because of my convictions about the importance of technology in armed combat'" [33, p. 207]. To defend himself against the attempts made to discredit him, Staudinger now followed the arguments he put forward back then, which he insisted were strictly scientific and thus non-political, by an article written for the *Völkische Zeitung* newspaper in Düsseldorf, which appeared on 25 February 1934 with the title "Die Bedeutung der Chemie für das deutsche Volk" ("The importance of chemistry to the German people") [36]. He had reprints of this newspaper article sent to the Baden Minister of Culture, Otto Wacker, and the Nazi Mayor of Freiburg, Franz Kerber (1901–1945) (see [33], p. 207; [19], p. 398). This article includes the following statements by Staudinger:

> The German people only have two options open to them, in order to survive. On the one hand, as many products as possible must be obtained from the land available by taking particularly good care of it. Attempts also need to be made, on the other hand, to reduce imports. [. . .] If German technology can be expanded [. . .] in the next few years, major steps will have been taken to give Germany an independent position in the world. (Quoted from [16], p. 182)

No capitulation to the Nazis, but instead – as Ott [33, p. 207] says – "a 'goodwill move'" by which Staudinger accepted the policy of independence adopted by the Nazi government and tried to recommend himself as a contributor on the basis of his scientific know-how. As a result, "he could now have 'an extremely wide range of possible activities' in the Nazi state" [33, p. 207].

3.5 Sensational Turn of Events

All in all, Staudinger's attempts to defend himself against the attacks by the Nazis do not appear to be a particularly convincing way to avoid dismissal from the civil service. What was, at least, dropped was "the charge of the betrayal of manufacturing secrets" to foreign enemies ([33], p. 205; cf. [19], p. 397). Staudinger himself was not, however, in a position to save his neck completely. What helped him, in the final analysis, was his professional reputation. Heidegger himself advised on 5 March 1934 – reluctantly – that "consideration is given to the position that the person in question holds in his scientific field abroad", although not without mentioning "that there cannot of course be any change in the facts of the matter. What is only involved here is the avoidance if at all possible of a new foreign policy problem" (quoted from [33], p. 208). A retreat, although he continued to insist that sanctions needed to be imposed on Staudinger, albeit in a milder form: Heidegger suggested that Staudinger should not, after all, be dismissed without pay but be

allowed to retire instead (cf. [34], p. 178; [33], p. 209). This "act of mercy" [33, p. 209] would of course have meant the end of Staudinger's career in Germany too. The last word had not been spoken, however, and the scandal was avoided: "Various interventions – the Nazi mayor of Freiburg, Dr Kerber, expressed support for Staudinger, for example, as did – presumably – the chemical industry – with the result that the (Baden, editor's note) Ministry of Culture withdrew the application (made on 22 February 1934, editor's note)" ([19], p. 397; cf. [33], p. 207).

A sensational turn of events, but not without the Nazi authorities humiliating Staudinger again to save face: he himself "was required to submit the official application for dismissal from the Baden civil service, which was then filed for six months. Since the accusations were based on a situation that took place a long time in the past, 'an official decision' about the application for dismissal would only be 'made if concerns arose again.' This was not the case [...] and Staudinger was, as agreed, allowed to withdraw his application in October 1934. The case was closed, although it was a close shave for Staudinger" ([33], p. 208; cf. [34], p. 178; [19], p. 398).

He continued to be resented just as much, because – as Heidegger put it – "there cannot of course be any change [...] in the facts of the matter". Staudinger realised how thin the ice was on which he was standing. The fascinating question is how he responded to this and what strategy he chose to make himself as untouchable as possible. He stayed put at any rate, rejecting the offer of an appointment at Berlin Technical University, which then chose Franz Bachér (1894–1987) to take over the vacant chair – "an active Nazi and insignificant chemist" [19, p. 183]. In view of the extent to which he was disliked by the Nazis, the capital of the Reich must have seemed to Staudinger to be a veritable lion's den, so he felt it was better for him to stay in Freiburg in spite of the crisis he had just faced. The situation there did not ease, however; if anything, it was made even more difficult for him to work: "From June 1933 to October 1936, Staudinger made five trips abroad to various European countries. With reference to his political past, he was, however, asked by the Reich Ministry of Education to turn down invitations to Zurich (in 1937), Riga (in 1937) and Rome (to the International Congress for Chemists in 1938)" [19, p. 399]. A letter from the Reich Minister of Science and Education, Bernhard Rust (1883–1945), to the vice-chancellor of Freiburg University, Otto Mangold (1891–1962), dated 2 November 1938 includes the following statements about this:

> I reserve the right to take the decision about applications submitted by Professor Dr H. Staudinger, Director of the Chemical Laboratory at the University of Freiburg i.B., in future relating to the approval of scientific trips abroad. I request that Professor Staudinger is informed in an appropriate way of the fact that it does not appear to me to be desirable for Professor Staudinger to carry out scientific activities abroad until further notice in view of his political past. (Quoted from [16], p. 192)

Due to the pressure exerted on him, Staudinger was afraid that he would be marginalised at the international level, so that other scientists would be able to claim responsibility for work that he had done: "In American literature, the situation is already described frequently as if Carothers created high-molecular chemistry", he complained on 23 November 1934 in a letter to Georg Kränzlein

(1881–1943; quoted from [19], p. 404), "one of the directors of I.G. Farben, who [. . .] was in charge of the Alizarin Department at the Hoechst factory" [19, p. 399]. Following the collapse of the "Third Reich", Staudinger was to accuse the Nazis – in a memorandum submitted in July 1945 – of weakening Germany's position as a scientific location and of causing the country to fall behind in the international competitive environment:

> Party considerations [. . .] prevented a major new area of German research (i.e. macromolecular chemistry, editor's note) from being represented adequately abroad; this is a particularly unfortunate fact, because this area has been given particularly strong support in England and America due to its technical and scientific importance. [37, p. 11]

3.6 Anti-Semitic Pretence

In order to be able to carry out scientific research undisturbed, Staudinger tried to make sure that he did not give the authorities any new targets for political attacks or that such attacks were ineffective. He developed a strategy of ingratiating himself with the Nazis, taking a variety of different actions in this context. In view of the rejection of his macromolecule concept in the early stages, he claimed – for example – that he was a "victim of Jews" [19, p. 404], criticised their alleged dominance in the scientific world and was even willing to use anti-Semitic clichés and slogans.

In a letter written on 9 June 1941 to the Cologne businessman Wolfgang Klever (1881–1970), a personal friend and former student, Staudinger spun a yarn about "a completely self-contained clique [. . .], which formed earlier on before 1933 and still sticks together today. It is very difficult to prevail against these Jews abroad and here in Germany" (quoted from [15], p. 329). What Staudinger failed to mention here was, on the one hand, the fact that it was a Jewish winner of the Nobel Prize in Chemistry, Richard Willstätter (1872–1942), who was the first to subscribe to his macromolecule theory. On the other hand, he dug up the hatchet, which had really been buried for years, and attacked his former opponents Kurt Hans Meyer and Hermann Mark (see Sect. 2: "1920–1932"), because they were the target of the criticism he expressed. Jaenicke [35, p. 604] talks in this context about "bogey-men". There can be question of the two chemists ever conspiring to oppose Staudinger and there was certainly no threat to him from them since they emigrated: from 1932 onwards, Meyer taught at Geneva University, after his appointment to Berlin Technical University, which was certainly thwarted by Staudinger himself (see [15], pp. 306–307, and [19], p. 255). After permission for him to teach at Vienna University was withdrawn and he was imprisoned for a time, Mark escaped from the Nazis by moving to the USA in 1938, where he started working at the Polytechnic Institute of New York in Brooklyn in 1940 (cf. [15], p. 327, and [19], p. 183). Staudinger did not stop presenting himself as a victim even so. In June 1938, for example, he wrote "in a distortion of the truth" [19, p. 406] the following

letter to the Reich Ministry of Education, after this Ministry had prohibited him from attending the International Congress for Chemists in Rome:

> My position in the German chemical community is being influenced very unfavourably by a scientific battle that I [...] have had to fight against what are primarily Jewish circles. The field of high-molecular substances (rubber, cellulose, plastics) that is involved here is of both scientific and technical significance. My results were rejected at the 1926 conference for natural science researchers in Düsseldorf, since numerous Jewish scientists had completely different views at the time. From 1928 onwards, they then – above all K. H. Meyer – tried to take over major results of my work without mentioning me, something that is standard practice in the scientific world otherwise. Since I was unable to accept this, an argument began that continued for years and was very disadvantageous for me personally, since K. H. Meyer as a member of the Management Board of I.G. Farben-Industrie and director of the plant in Ludwigshafen held a very influential position in the German chemical community. The success that Jewish circles have in the scientific world is based on the same method that they apply in other areas too: emphasising their own achievements and expressing biting criticism of others. [...] They make their very negative influence felt at domestic and foreign congresses, particularly – for example – at the International Congress for Chemists in Madrid in 1934. These circles, that I opposed in Madrid, will be particularly delighted by my failure to attend the congress in Rome. My only regret is that the battle I have been fighting for decades to overcome the Jewish influence in this important chemical field has as a result to all intents and purposes been fought in vain. (Quoted from [19], pp. 406–407)

This was a shot that backfired: the Reich Ministry of Education confronted I.G. Farben with the contents of the letter and asked Georg Kränzlein (who has already been mentioned) from the Hoechst plant to comment. Kränzlein was "disgusted by the criticism that Staudinger expressed about I.G. too via the accusations about Meyer" and "rejected Staudinger's claim of having become a victim of Jewish intrigues as untenable" [19, p. 407]. But what prompted Staudinger to make further offensive anti-Semitic comments ("self-contained Jewish clique") about Meyer and Mark 3 years later, as has already been mentioned? The occasion was the appearance of the textbook *High-Polymer Chemistry* written by the two of them, "which, in spite of the fact that both were Jews by Nazi definition, was published in Leipzig in 1940 and was reviewed positively" in the magazine *Die Naturwissenschaften* [19, pp. 408–409]. It says in this "with reference to Staudinger: 'Read the section about viscosity. Although a direct and simple relationship between molecule size and chain length is rejected with convincing arguments, the writer specifically emphasises the viability of viscosity measurement for evaluating the solutions of high-molecular substances. This chapter will be particularly instructive to those who go as far as to virtually confuse chain lengths or the degree of polymerisation and indicators derived from viscosity'" [19, p. 409].

Priesner ([15], p. 331) concluded that all this was "an unmistakable indication that Staudinger continued to see his fellow-chemists as enemies" and added: "It is frightening that the small amount of intellectual freedom which still existed in Germany in 1941 was vilified as an intrigue on the part of a group of conspirators" [15, p. 330]. Jaenicke ([35], p. 604) criticises Staudinger's "attacks ( ) on the Jewish surrounding of German macromolecules by anti-German polymer chains" and "the typical [...] unoriginal adoption of other people's ideas and culture for commercial

purposes" as "embarrassing, [. . .], obsequious and opportunistic" and concludes: "Genius does not protect against stupidity" [35, p. 604]. Staudinger did not make himself many friends among the Nazis with his anti-Semitic pretence either. I.G. Director Georg Kränzlein, who subsequently became the regional head of the Nazi technical authorities in Hesse-Nassau and SS-Hauptsturmführer (captain)" [19, p. 406], reprimanded him:

> In my opinion, you make the mistake of arguing with Jews the whole time. [. . .] There is no need for you to start polemic discussions with Jews, because by doing so you give them too much honour. Avoid and ignore these people, because otherwise you let them have the last word over and over again, which regularly harms you. We disassociate ourselves systematically from the Jews, as the Nuremberg Laws prove. By doing this, we send them back to where they came from. Why don't you disassociate yourself in the scientific world? Here too, they need to return to the intellectual ghetto they came from, back to their Talmud, which they are incapable of escaping from. [. . .] Instead of this, you incite the Jews to band together against you more and more and this will harm you in the long run. [. . .] Now it is your duty not to mention the Jews again at all, definitely not allowing yourself to continue a polemic debate with them.
> (Letter of 3 June 1936 from Kränzlein to Staudinger, quoted from [15], p. 317; cf. p. 318 and [19], p. 405)

Staudinger nevertheless continued to do everything in his power to be considered an anti-Semite: "As early as 1936, he had worried that too many 'non-Arians' could study at his institute; and in May 1942, he again expressed misgivings to the vice-chancellor in writing – now that there were no more Jews at German universities – about too many 'half-breeds' among the chemistry students" ([38], p. 11, footnote 32).

3.7 No Chance of a Party Membership Book

The aim of "his application for membership of the Nazi party" [39, p. 230] was to eliminate any doubts about his loyalty to party principles, but this application was rejected, officially "because of former membership of a Masonic Lodge" [39, p. 230]. Membership was a family tradition – Staudinger's father was "Grand Master of the Grand Lodge 'zur Eintracht'" [18, p. 225]. Incidentally, Staudinger was only registered as a passive member of the SS because the latter "blackmailed him [. . .], forcing him to pay protection money from time to time" [35, p. 604].

Even though Staudinger – as has been indicated – did everything in his power to make the impression of being a staunch follower of the Nazis, Krüll ([11], p. 48) confirms that he was "no Nazi". Rightly so, because Staudinger generally showed no interest at all in Nazi ideology in his position as head of the institute and could not have been more politically incorrect in his actions, protecting students and assistants who were disapproved of by the Nazis:

- Staudinger came to the defence of Ernst Trommsdorff (1905–1996), "one of my best assistants and staff members" (quoted from [16], p. 176), who Staudinger

had supervised when he obtained his doctorate in 1932 and who was now in danger of being dismissed from the civil service because of his "Jewish origins". On 1 August 1933, shortly before he himself became a target, Staudinger wrote a letter to vice-chancellor Martin Heidegger:

> Since they work together, there is a strong feeling of solidarity in my laboratory between the laboratory staff, the lecturers, the assistants and the students. Dr Trommsdorff is a fully integrated member of this team. Last year, for example, he and seven other assistants helped me to write a book about rubber and cellulose. This community spirit will be destroyed if a member of the team is required to leave in these circumstances. (Quoted from [16], p. 175)

In another line of argument, Staudinger deliberately tried to portray Trommsdorff as someone who sympathised with the Nazi movement, with the aim of taking the wind out of the sails of those who wanted to harm him:

> In all his opinions, Dr Trommsdorff has a very positive attitude towards the state as it is today. One of his brothers is a member of the Hitler Youth organisation. The position Dr Trommsdorff holds among his comrades is made most clear by the fact that he has acted as group leader in military sports exercises. I have discussed this matter with Dr (Ernst Otto, editor's note) Leupold (born in 1903, editor's note) too, who is the representative of the assistants in the laboratory for which I am responsible; he agrees with my view that the assistants and students do not feel that Dr Trommsdorff should be covered by the [...] Act (to restore the civil service, editor's note). This statement was important to me, since Dr Leupold has been a member of the SS for a long time now and has studied Nazi issues intensively. (Quoted from [16], p. 174)

It may well have been quite a clever move "to make progress with his own cause" [16, p. 191] for Staudinger to "assume or use moral concepts followed by the ruling class" [16, p. 183]. Anyone who believes that "one does not change at all in the process" [16, p. 191] is subject to an error of judgement; however, like it or not, one's own personality is distorted as a result.

Staudinger did not succeed in preventing Trommsdorff from being dismissed; the latter was unable to pursue a normal scientific career in the Nazi state. "I would have liked him to have qualified as a professor here, but this is not unfortunately possible at the moment", Staudinger regretted in a letter of recommendation to the British chemist Sir Robert Mond (1867–1938), with which he tried to help his assistant to make a career for himself in England (quoted from [16], p. 176). Instead of this, Trommsdorff joined Röhm und Haas AG, Esslingen and Philadelphia, where he became Research Manager in 1939.

- "Not only Staudinger was accused of spending too much time abroad; one of his staff was among those who faced the same charge. Political pressure had increased in the meantime. No-one needed to be an 'enemy of the state' any more [...] in order to suffer professional problems. It was sufficient for someone not to stand up for Nazi ideology actively enough, 'to fail to show commitment to the Nazi state'", as can be read in [16, pp. 193–194]. In June 1941, Dr Rolf Mohr (born in 1910), one of Staudinger's staff, who he wanted to make his scientific assistant, was the victim. The application to this effect was initially approved by the Dean of the natural science/mathematical faculty, but the Nazi

leader of Freiburg's lecturers (Eduard, editor's note) Steinke (1899–1963, editor's note) raised "concerns for political reasons" [16, p. 195]:

> It is a well-known fact that Mohr obtained all of his education and training outside Germany (in Switzerland; editor's note). During the many years of his activities here (since 1933, editor's note), he has demonstrated no commitment to the Nazi state [. . .]. He only recently joined a Nazi unit and has been in the armed forces since the spring of this year. Since the lecturers' leadership is of the opinion that Mohr is not a suitable candidate for an academic career in view of his overall attitude and views, I do not consider it justified to appoint him to the position of scientific assistant; instead of this, I would be grateful if he were allowed to continue holding such a position on a provisional basis for the time being.
> (Official party letter written by Steinke to the vice-chancellor's office at Albert Ludwigs University in Freiburg on 10 June 1941; quoted from [16, p. 196])

Vice-chancellor Wilhelm Süss (1895–1958) agreed with Steinke's assessment:

> Dr Rolf Mohr cannot be appointed to be a scientific assistant yet. Dr Mohr has been evaluated unfavourably in political appraisals in the past. Since he only recently joined a Nazi unit, a lengthy probationary period will be necessary before any change is made in the current assessment of his political views. I would be grateful if Dr Mohr was to continue holding a position as assistant on a provisional basis. (Letter written by the vice-chancellor to Staudinger on 30 June 1941; quoted from [16, p. 196])

In response to this, Staudinger threatened the vice-chancellor on 5 July "to inform Dr Mohr about the contents of your letter, since he has turned down attractive technical positions in the hope of being able to qualify for a professorship here" (quoted from [16], p. 197). Staudinger was not allowed to inform Mohr about the arguments against his appointment as an assistant in writing; he "is instructed to make contact with the lecturers' leader before taking further action" [16, p. 198]. It has been lost in the mists of time exactly how the Mohr issue was resolved in the Third Reich. What is definite is that Mohr did not qualify for a professorship in Freiburg until 1946 with a thesis "About the stabilisation of cellulose nitrates".

- In June 1942, Staudinger's "half-Jewish" student Gerhard Bier (1917–2003), whose mother was a Jew, was prohibited from completing his chemistry degree, after he had already been forced to discontinue studying medicine elsewhere in 1939. However, the Freiburg "vice-chancellor Süss and Professor Staudinger make it possible for him to stay another few months to graduate" [19, p. 86]. Bier remembers:

> There were a number of other 'half-Jews' who studied chemistry apart from me. After the final exams, Staudinger said to me: 'If you want, I can find out whether you can work here.' He phoned the military research authorities responsible and received approval to deploy me as a scientific professional for work in the macromolecular research institute that was of importance to the war effort. I was paid as an untrained scientific assistant, i.e. received 100 RM per month. (Quoted from [19], p. 86)

Bier managed to graduate in 1942 (cf. [19], p. 412), but then things got too dangerous for him in Germany in 1944, so that he fled to Switzerland [19, p. 86], where he completed a doctorate at Bern University in 1946.

3.8 Two Different Political Faces

In view of all this, Staudinger's behaviour in politically difficult contexts must be considered contradictory. Although he was a conformist at times, he was a troublemaker at others; all in all, he remained unpredictable, managing not only to express politically correct views with impressive vehemence but also to step out of line subversively. This meant that he acted neither as a model Nazi nor as a figure with whom anti-fascists could identify. In the end, the Nazi regime abandoned the strong reservations against him and came to terms with the man who was originally reviled as a "traitor to his country".

The turning point came in 1940: a separate research department for macromolecular chemistry was established at Staudinger's institute and was affiliated to the chemical laboratory at the university. This was after the institute had already been expanded twice in 1933 and 1937, "in order to create additional capacities for the [...] growth in macromolecular chemistry" [2, p. 84]. Staudinger was to head this department, which was the first in Europe to be devoted exclusively to the new area of research into polymer sciences, until he retired in 1951. After this, he remained in charge for another 5 years on an honorary basis. The ban on foreign travel was lifted in 1940 too, when Staudinger's "name was cleared completely at the political level" [19, p. 399]. Reich Minister of Education Rust received the following letter from the head of the scientific authorities at his ministry, represented by Otto Wacker, on 26 January 1940:

> The district controller in Freiburg has informed me that he has decided to deploy Professor Staudinger politically to a certain extent too in view of his impeccable conduct in recent years. He will as a result be speaking to a selection of political leaders for the first time in the next few days. The district controller therefore considers that the Staudinger case is now closed completely. At the same time that I am informing you about this fact, I think that I am in a position to express the opinion that no fundamental objections should be raised any more in future to scientific activities by Professor Staudinger abroad. (Quoted from [19], p. 399)

Between 1942 and 1944, Staudinger was used for cultural propaganda purposes "in foreign countries occupied or annexed by Germany" and completed a total of eight lecture tours during this time, which took him to such places as Prague, Mulhouse and Strasbourg: "Staudinger had won the trust of the Nazi rulers." ([19], p. 399; cf. [39], p. 230).

3.9 Promotion of Defence Chemistry

It can be assumed that the sudden change in the Nazis' position was attributable less to a fundamental re-evaluation of Staudinger as a person and more to an increase in their appreciation of what he had to offer professionally as the "natural science figurehead of Freiburg University" [38, p. 11]. This was due to the fact that the

organic and polymer chemistry he represented was considered to be of importance to the war effort in 1940, something that Staudinger's pupil Gerhard Bier had already benefited from, as has been indicated. Staudinger seized the opportunity and never tired of emphasising that he could – and wanted to – be of use to Germany in the war. In the spirit of the Nazi policy of self-sufficiency, he tried to convince the authorities of his ability "to supplement the chemical arsenal by adding plastics and substitute materials" ([35], p. 604; cf. [19], p. 397 and [17], p. 115). He was also willing to make his laboratory available for the promotion of what was known as defence chemistry. As early as 5 September 1939, 4 days after the attack on Poland, he wrote to the Freiburg vice-chancellor Mangold:

> A number of projects of importance to the war effort have been carried out at the chemical institute here for years now, e.g. in connection with the gas protection department at the Ministry of War and with Draeger-Werke in Lübeck. At the suggestion of the latter, work has been done about mustard gas protection (the original name for the chemical weapon yellow cross was "Lost" [. . .]) and I am involved in developing a reaction for the detection of traces of Lost. Studying cellulose and nitrocellulose have prompted visits to explosives factories, so that I have become acquainted with problems faced by the explosives industry. (Quoted from [39], 222)

On 19 October 1939, Staudinger drew attention to the importance of his work to the war effort and the country in a letter to Rudolf Mentzel (1900–1987), President of the German Research Association (DFG) and a member of the Nazi party since 1925: "He stressed that the findings about the structure of cellulose, e.g. the identification of imperfections in the molecule, are of significance with respect to the production of gun cotton and nitrate powders and emphasised the general importance of his work in relation to the constitution of Buna and chlorinated rubber, which is used as a rust-proofing agent. He quoted projects about an agent providing protection against weapons and a new gas mask as examples of work done by his institute that was of special importance to the war effort. The production of synthetic pepper, which came onto the market in Germany in the First World War, had been started again too. (Peter Adolf, editor's note) Thiessen (1899–1990, director of the Kaiser Wilhelm institute for physical chemistry and electrochemistry and a member of the Nazi party since 1925; editor's note) acknowledged that Staudinger's work was important to the war effort and the country, with the argument that although Staudinger's research was not of direct importance to the war effort, it was of considerable significance to the raw material situation, because it could at any time lead to practical consequences for the cellulose manufacturing industry, the plastics field etc." [19, pp. 411–412]

"Staudinger also carried out a research project for the Reich Ministry of Aviation and the commander-in-chief of the air force that focussed on 'Investigations into nitrocellulose'" [19, p. 412], which – according to Gerhard Bier, his pupil at the time – was the area of operation of greatest relevance to the war effort:

> Nitrocellulose was an industrial product, the raw material for celluloid [. . .] and for civil and military explosives as well as for civil and military ammunition fuels. Problems of storage stability arose in the large-scale production of nitrocellulose during the war. For unknown reasons, nitrocellulose or a mixture containing nitrocellulose degenerated

> occasionally, which led – for example – to premature explosions. By carrying out systematic tests, Staudinger's staff found out that traces of sulphuric acid in the nitrocellulose were the reason for why the nitrocellulose was not stable in storage. The precondition for high storage stability was to wash out the nitrocellulose thoroughly, in the context of which the sulphuric acid ester groups needed to be hydrolysed too. The sulphuric acid was a necessary component of the nitration mixture. I am not aware of the details of this work. [...] Other work done during the war related to the plastics sector and the synthesis factor sector, e.g. polyamides.
> (Letter written by Gerhard Bier to Ute Deichmann on 2 September 1996, quoted from [19], 412)

3.10 Funding from Industry

There is no doubt about it: between 1939 and 1945, the most important institute at Freiburg University as far as the war effort was concerned – alongside the physics institute – was the chemical institute (for details see [39], p. 223, and [38], p. 11, footnote 32) and it received appropriate funding. This funding came from many different sources, with "industry providing far more money for (Staudinger's, editor's note) research than the Emergency Association/German Research Association" [19, p. 401]:

- "As an external member of staff, Staudinger received RM 10,000 per year from I. G. Farben from 1927 to 1937 for studying rubber and high-molecular natural and artificial substances/plastics. [...] In 1943, Staudinger became an external member of the staff of I. G. again, this company supporting him to the tune of 10,000 RM in both 1943 and 1944." [19, pp. 400–401; cf. p. 241]. Westermann [17, p. 68] points out in this context: "This means that he had additional research funds at his disposal that amounted to far more than half of his annual income as professor. Between 1930 and 1932, Staudinger earned RM 1,166.66 per month, increasing to RM 1,350.66 with all allowances."
- "Staudinger's research into cellulose and other fibres started to receive funding from the Emergency Association/German Research Association in 1936. He received regular support of between RM 3,000 and RM 12,000 per year until 1943" [19, p. 401]. The funds provided by the German Research Association and the Reich Research Council are said [19, p. 232] to total RM 66,160 in the period 1934–1945.
- "Staudinger's work [...] was also funded by the Reich economic development authorities as of 1941; the amounts provided are not known" [19, p. 412].

This list is in curious contrast to Staudinger's own statements after the war: "The research activities of the undersigned were made more difficult by the fact that he was viewed unfavourably by the party [...]. Due to the position adopted by the party, other major authorities, such as the Reich Research Council, the Reich economic development authorities, etc., were influenced either to refuse funding for the work at the institute here or only to approve minor financial support" [37, p. 11].

Apart from this, Schnabel ([39], p. 230) criticises the fact that Staudinger makes no mention at all of the research he did that was of importance to the war effort, something which he had played as his trump card during the time of the Nazi regime, in the "Report about the influence of National Socialism on the teaching activities of the chemical institute" [37], which has just been quoted above. In his review of the "Third Reich", Staudinger criticised party-political nepotism in the making of appointments to scientific and university administration positions and the lack of funding for young academics:

> In my practical experience, it was frequently the case during the Nazi period that qualified assistants contemptuously rejected suggestions that they pursued an academic career and opted instead to accept technical positions – not just for financial reasons but also and primarily due to the uncertainty of an academic career because of intervention by the Nazis; during this time, the institute director was unable to guarantee even the most capable of chemists a successful academic career, as the official controller responsible for the students and lecturers as well as the head of the training camps had much greater influence than the performance of the applicant. A successful academic career was as a result dependent more on party activities than on scientific achievements. [37, p. 7]

3.11 Veil of Silence

After 1945, it was not unusual for chemists to cast a veil of silence over their involvement in the crimes of the Nazi regime. Deichmann ([19], p. 414) brought up this painful subject: "In contrast to prominent German physicists, who professed after the war that they had not been in favour of the production of the atomic bomb for moral reasons, neither Staudinger nor other chemists claimed that they were unable to synthesise an artificial fibre, an explosive, a poison gas or an antidote because they had not wanted to for moral reasons. They were honest about this. However, Staudinger (and all his fellow chemists) failed to comment on the enormous crimes that were committed with the involvement of chemists. [. . .] The killing of mentally disturbed Germans by carbon monoxide and of European Jews by Zyklon B (is, editor's note) not mentioned."

4 The Life and Work of Hermann Staudinger: 1945–1965

Staudinger's life's work culminated in the Nobel Prize in Chemistry, which he received from the Swedish king on 10 December 1953, 60 years ago now. This was late recognition for a 72-year-old retired professor, who no longer represented the avant-garde of his subject but whose achievements are still being acknowledged today. In 1999, 34 years after Staudinger's death, the American Chemical Society paid tribute to his life's work by unveiling a plaque in his honour at the Institute of Macromolecular Chemistry at Freiburg University ("Hermann-Staudinger-Haus"; see Appendix 5). This final section covers the post-war period until Staudinger's

death in 1965 and focusses on the Nobel Prize. The colourful reports published by daily newspapers are included here for the first time.

Freiburg, Lugostrasse 14, on 5 November 1953, shortly after 8 a.m.: the man of the house and his wife were still in bed this Thursday morning, so the cleaning lady took it on herself to accept the telegram from Stockholm. What it said in a brief but clear message was:

> The Royal Academy of Sciences has awarded you the Nobel Prize in Chemistry. Letter will follow – Westgren, secretary (cf. [40], p. 24, and [41]).

The telegram was addressed to Prof. Dr. phil. Dr.-Ing. E. h. Dr. rer. nat. E. h. Hermann Staudinger. It was not at all unusual for the Nobel committee to opt for a chemist from Germany that year, because this honour had already been given to 19 other representatives of this subject who were German nationals before Staudinger, although only two of them had been chosen since the Hitler dictatorship and the end of the war (Otto Diels, 1876–1954, and Kurt Alder, 1902–1958) (cf. [42]). What is more unusual is that Staudinger had dual nationality, so that he can be counted as both a German and a Swiss winner of the Nobel Prize. What is most unusual, however, is the fact that Staudinger received the prize as a 72-year-old retired professor for what he had proposed as a 39-year-old and had proved soon afterwards – the existence of "giant molecules" (macromolecules). With this groundbreaking concept, Staudinger revolutionised polymer and plastics chemistry in the 1920s and 1930s, against stubborn resistance (see Sect. 2: "1920–1932"). The *Wochenend* newspaper that appeared in Nuremberg wrote:

> The professor has demonstrated in his research that the most important natural products consist of particles (molecules) of unusual size and that they are composed of numerous (often millions) of atoms. The model for the technology to imitate and even reproduce these natural products was available as a result. [41]

An achievement that definitely deserved the Nobel Prize: "The outstanding university professor Dr Hermann Staudinger was already honoured indirectly quite a long time ago, when two of his former pupils received the Nobel Prize, i.e. Professor Dr (Leopold, editor's note) Ruzicka (1887–1976, chemistry, editor's note) in 1939 and Professor Dr (Tadeus, editor's note) Reichstein (1897–1996, medicine, editor's note) in 1950", the Düsseldorf publication *Der Fortschritt* remembers [42]. Staudinger shared the fate of many scholars, especially natural scientists, all the same: "He was famous in the scientific community, but was practically unknown to a broader public", as the *Radio Revue* from West Berlin stated when the Nobel Prize was presented to Staudinger. It is a telling fact that the *Westdeutsche Allgemeine Zeitung* newspaper (*WAZ*) gave him the wrong first name in its article of 6 November 1953: instead of Hermann, Franz was celebrated as being the winner of the Nobel Prize. That was the name of Staudinger's father, who had died as long ago as 1921. Journalists concluded in 1953 that Staudinger was largely unknown and asked the following questions:

> How many of the pretty young girls and women who draw particular attention to their attractive legs by wearing nylon or perlon stockings, how many of the car drivers whose vehicles are fitted with tyres made of synthetic rubber and how many of the people who sell

> the countless everyday articles made of plastics of all different kinds ever think even once of the outstanding research scientist to whose scientific work the technical production of all these materials – which are essential features of modern-day life now – is in the final analysis attributable? [42]

The fact that Staudinger had never been in the limelight much until then was due in no small part to his attempts to avoid being in the public eye. The *Radio Revue* concluded that he was not a man who drew attention to himself. The *WAZ* emphasised that Staudinger's pupils left "one after another to earn top salaries in industry, while the old man himself stayed modestly where he was in his institute making sure his findings were absolutely watertight". So it is no surprise that Staudinger was unwilling to believe the rumours which went around for days beforehand that he would be receiving the Nobel Prize in Chemistry that year. The news finally came out on 4 November 1953 and spread throughout the world press. Staudinger himself had still not received official confirmation from the Nobel Prize committee so, as he revealed later: "I was rather uncomfortable with the coverage, since all the press releases appeared to me to be somewhat premature." This was quite apart from the fact that he was not looking forward to all the interest in his person that he anticipated and preferred to be evasive for the time being:

> 'I thought of my colleague from Freiburg, who received this honour in 1935 – (the biologist, editor's note) Dr (Hans, editor's note) Spemann (1869–1941, editor's note). He had a terrible night at the time. I therefore disconnected my phone in the evening and slept well' The seventy-two-year-old told this story as if it were a successful practical joke [. . .]. The professor was asleep and did not notice any of the fuss that was being made at the Freiburg telephone exchange, where the switchboard operators were put under pressure by phone calls from Rome, Paris, New York and many German towns and cities requesting connection at long last to number 2874, the one that belonged to the new Nobel Prize winner. [41]

When he woke up on 5 November, he was therefore very pleased to read the telegram from Stockholm that has already been mentioned above, as it eliminated any doubts. "When asked to comment on the award that had been made to him, the new German winner of the 1953 Nobel Prize in Chemistry said: 'It is the final recognition of my work and it is wonderful that I am still here to enjoy it!'" [42]. He considered the Nobel Prize to be the "culmination of a battle about the controversial field of macromolecular chemistry, for the scientific recognition of which he had been forced to fight for many long years" (quoted from *Hamburger Echo*, 6 November 1953). "The Strasbourg Professor (Charles, editor's note) Sadron (1902–1993, editor's note), who ran an institute of macromolecular chemistry himself, had explained to him the previous year that he, Staudinger, would probably not have obtained so many groundbreaking insights into macromolecular chemistry if he had not been attacked so fiercely from all sides. This conflict with his opponents is what drove him to do all his hard work and made him a truly great research scientist", the *Schwarzwälder Bote*, to whom the new Nobel Prize winner had given an interview, wrote on 8 November 1953.

Staudinger was embellishing his past a little to the press here. Because although he faced resistance from his scientific colleagues initially, industry quickly "took

over his theories [...], once it became clear that application of them made it possible to manufacture plastics systematically" [43, p. 7]. Staudinger himself pointed out that "industry accepted his views much more quickly than the scientific community" (*Hamburger Echo*, 6 November 1953). He enjoyed playing the role of the "fighter" even so, continuing to play it when the hatchet had long been buried, i.e. when he was already preaching to the converted where his macromolecule theory was concerned (see Sect. 3: "1933–1945"). It almost appears that he was afraid he might lose the victory he had won again if he no longer needed to defend it against anyone. Staudinger seemed to be driven by emotional forces of some kind that required him to prove himself again and again and to seek approval – something that is also confirmed by his never-ending stream of publications. This was even though no-one disputed his success; on the contrary, three general universities (Mainz, Salamanca and Torino) and three technical universities (Karlsruhe, Strasbourg and Zurich) awarded Staudinger honorary doctorates. He also received the Emil Fischer Commemorative Medal from the Association of German Chemists (VDCh), the Leblanc Commemorative Medal from the French Chemistry Association (SFC), the Cannizzaro Prize from the Italian Accademia dei Lincei, the Golden Commemorative Badge from the Association of Finnish Chemists and, in 1952, the Grand Order of Merit of the Federal Republic of Germany. It is quite possible even so that Staudinger only obtained the final certainty he needed to be unimpressed by adversaries and opponents when he received the Nobel Prize as the highest possible form of acknowledgement. Not least of all, the Nobel Prize brought him a great deal of money: Staudinger received a cheque for 175,292.94 Swedish krona, which was worth about DEM 140,000 (cf. [41]). The *Wochenend* newspaper [41] congratulated him as follows: "While [...] the whole of Germany can share the glory, the scholar alone decides what the money is used for".

The impact of the honour bestowed on Staudinger was felt in particular by Freiburg, the city in Baden-Württemberg where he had been university professor from 1926 to 1951. The news that Staudinger had received the Nobel Prize in Chemistry spread there like wildfire on 5 November 1953; Freiburg professors and about 400 students held a torchlight procession to Staudinger's house the same evening to honour the prize winner. "The whole of Lugostrasse was bathed in vivid, warm torchlight – and the beautiful old song 'Gaudeamus igitur' was sung in triumph after the speeches" [40, p. 24]. The *Schwarzwälder Bote* (8 November 1953) summarised the speeches:

> The current professor of chemistry at Freiburg University, Professor Dr (Arthur, editor's note) Lüttringhaus (1906–1992, editor's note), paid tribute [...] to his predecessor's life's work. Professor Staudinger had helped the German scientific community to develop an excellent reputation by carrying out his trailblazing research [...]. The chemical community in Germany had been expecting Professor Staudinger to be given the highest award for his work some time for years now. The rector of Freiburg University, Professor (Walter-Herwig, editor's note) Schuchhardt (1900–1976, editor's note) thanked Professor Staudinger primarily for remaining loyal to Freiburg University for 25 years. The name of Freiburg University had become famous throughout the world as a result of his work.

Staudinger received congratulations from Bonn during this time too: on behalf of the German government, the German Minister of the Interior, Dr Gerhard Schröder (CDU), congratulated him on 5 November and the German Chancellor Dr Konrad Adenauer (CDU) followed on 10 November.

Staudinger had to wait until 10 December for the official presentation of the Nobel Prize by the Royal Swedish Academy of Sciences. The trip to Stockholm was to be unforgettable. His wife Magda writes:

> Although it was the darkest time of the year, Stockholm was brightly lit on the day of the ceremony. The Nobel Prizes were presented by [...] King Gustav VI. Adolf [...] in a thoroughly festive ceremony. Hermann Staudinger received the 1953 Nobel Prize in Chemistry from him. It was a memorable picture: both men were the same height and roughly the same age. This picture was published throughout the chemical press all over the world, with the caption: "High Polymers bring High Honours". [40, p. 24]

To understand the satisfaction that Staudinger must have felt in Stockholm, it is only necessary to remember what difficult decades were behind him: gruelling scientific disputes in the 1920s (see Sect. 2: "1920–1932") were followed by tortuous political manoeuvring during the Nazi period (see Sect. 3: "1933–1945"). In 1940, Staudinger succeeded in adding a research department for macromolecular chemistry to the university chemical laboratory. "The first European research centre that focussed exclusively on research into macromolecules in nature and industry as well as on the new area of polymer science research" is the description given in a current profile issued by Freiburg University (http://www.uni-freiburg.de/universitaet/portrait/ehrungen-und-preise/Nobelpreis/broschuere-nobelpreisträger-uni-freiburg.pdf). Work was hampered by the war to an increasing extent; however, it continued until the chemical institute (including the library, collections and equipment) was, finally, destroyed almost entirely in a bomb attack on Freiburg on 27 November 1944. "Thanks to the immediate action taken by assistants and students, the few remaining parts were saved and were installed again in some cases after the end of the war. It was therefore possible to start teaching and research again to a modest extent as of 1947." ([40], p. 22)

Staudinger was already 66 years old in 1947 and the best of his scientific career was long behind him. He was, however, indefatigable in contributing to the laborious reconstruction process, devoting himself in particular to the research department for macromolecular chemistry that he had established, into which he put all his energy – demonstrating both persistence and obstinacy: "Staudinger did not establish an interdisciplinary teaching and research programme; no-one except he held lectures about macromolecular chemistry in Freiburg" [19, p. 150]. Staudinger finally retired in the spring of 1951 at the age of almost 70, but he did not sit back and take things easy afterwards. On the instruction of the Baden State President, Leo Wohleb (1888–1955, editor's note), the research department for macromolecular chemistry had just been converted into a government research institute and Staudinger was quick to accept the invitation to head it for the next 5 years. This was to be in an honorary capacity, of course, while the financial support provided to the institute also left a great deal to be desired: "In spite of its impressive name, this research facility was rather modest", concluded Magda

Staudinger ([40], p. 22). This was particularly the case for the premises, which were located in Staudinger's own home to start with: "A white, somewhat weather-beaten, wooden sign saying 'Institute of Macromolecular Chemistry' was to be found on the garden gate at Lugostrasse 14" [41]. When Staudinger was awarded the Nobel Prize in this situation, the *Handelsblatt* from Düsseldorf issued the following appeal on 6 November 1953:

> Although Staudinger's research institute is a state facility, its budget is so inadequate that large personal sacrifices have been necessary to enable it to continue operating. The 'Fonds der chemischen Industrie' made DEM 10,000 available a few days ago, but perhaps the state of Baden-Württemberg will now at long last decide to make a generous extension to the institute. There can be no doubt that this would be the honour that Staudinger would appreciate most as a result of the Nobel Prize!

Staudinger's own plan to develop the government research institute of macromolecular chemistry into a federal institute "in line with its importance for the modern chemical industry and to broaden its financial basis" [42] came to nothing due to a lack of support. When Staudinger resigned from the position of head of the institute as agreed in 1956, the Baden-Württemberg Ministry of Education established an extraordinary professorship for macromolecular chemistry – the University Institute of Macromolecular Chemistry was set up and then, in 1962, moved to a new building that is known today as "Hermann-Staudinger-Haus" (cf. [40], p. 22).

On 23 March 1956, Staudinger's 75th birthday, Albert Ludwigs University in Freiburg held an official ceremony, at which Staudinger was honoured in appropriate fashion as he retired from his position as honorary head of the institute. The university rector, Bernhard Welte (1908–1983), a professor of philosophy of religion, spoke at the ceremony:

> Thirty years ago now, you created an opening in the dark wall of nature, which science is constantly trying to illuminate and penetrate. [...] Today, the opening is so large that an entire world has gone through it – and is still going through it. The entire world of industry, of fibres and plastics, spread throughout all the countries of the earth, without which our lives today would no longer be conceivable, and the entire world of all those who use these fibres and plastics of many different kinds. [...] A huge new field of science, business and life has developed behind the opening that you made [...] with your scientific work! (Quoted in [1], p. 305)

Asked about his plans for the future just after he won the Nobel Prize, Staudinger had already revealed his intention to start studying botany again – the subject that he gave up in favour of chemistry when he was a young man (see Sect. 1: "1881–1919"): "He studied chemistry because this was the basic science that preceded botany. 'Now [...] the time has come to start studying botany.' The Nobel Prize winner [...] plans to be become a student. That's the way it is – you never stop learning." [41]. Magda Staudinger ([40], p. 10) says: "When he was quite old, he used to say that he did not know enough chemistry yet to start studying botany. In response to this, the dean of his faculty in Freiburg said at a small ceremony in connection with the presentation of the Nobel Prize in 1953 that the faculty now – after this event – expected the would-be botany student to take his

exams in this subject at long last!" There is a realistic background to what sounds just like an anecdote: Staudinger's return to botany illuminated the origins of his macromolecule theory, while it also opened up a new area of research – molecular biology – to him at the same time. This interface makes it clear just how stimulating Staudinger must have found his encounter with the botanist Dr. phil. Mag. rer. nat. Magda Woit, who became his wife when he married for the second time in 1928, at the scientific level too. Staudinger got to know the daughter of the Latvian ambassador, who came from Riga, on Helgoland in August 1927. Magda Staudinger ([40], pp. 17–18) remembers this as follows:

> I studied [. . .] in Berlin, because my father was the first ambassador of the state of Latvia in Berlin in the 20s after the country became independent. I obtained my doctorate there in 1925 with the plant physiologist Gottfried Haberlandt (1854–1945, editor's note); I then returned to Riga, took the state examination at Riga University and became an assistant to Nicolai Malta in the botanical laboratory. I was particularly interested in marine algae and I was delighted when I was given a job as a guest at the biological institute on Helgoland in the summer of 1927. I was interested in the cell membrane of the algae and I tackled my experiments with the equipment and know-how about colloidal substances that were available at the time. The Freiburg botanist Friedrich Oltmanns (1860–1945, editor's note), who was an algae specialist, came to Helgoland in August too. I had got to know him by taking two algae courses with him while I was still a student. One day, he was standing on the jetty in Helgoland with another gentleman and spoke to me as I walked by. He introduced the other gentleman to me: 'My colleague from the chemistry department, Hermann Staudinger' and, turning to Staudinger, he mentioned that I was working on cell membranes of algae at the biological institute. Hermann Staudinger was interested to hear this and asked if he could take a look at my experiments: he had just published a paper about a model for cellulose, the main component of plant cell membrane. That in turn interested me and we arranged that he would visit the laboratory. He came on 24 August, took a look at my experiments and had me explain them. Suddenly, he then said to my amazement: 'It is all completely different', sat down on a laboratory stool and started to talk: 'There are macromolecules and they will be tremendously important to biology in future, because living cells can only be constructed with such large molecules. Thanks to their size, they have different shapes; the different structures that the living cell needs are possible as a result. Thanks to their size, they can – in turn – accommodate very different reactive groups.' He talked about these things for quite a while and explained phenomena that were in some cases only demonstrated at the experimental level many years later. On the basis of his cellulose model and stimulated in his thinking by my experiments, the role played by macromolecules in biological processes occurred to him there and then at this time on 24 August 1927. It was like a vision to him. Molecular biology now exists today and is very successful. The name does not come from us; it was used first by the English chemist (William Thomas, editor's note) Astbury (1898–1961, editor's note) around 1945. The first conversation about these ideas took place back then on Helgoland, however. In my opinion, this is therefore when molecular biology first began.

In view of this, Jaenicke ([35], p. 604), was accurate in describing Magda Staudinger as "the Moira who helped to spin the macromolecular threads". The couple did not carry out systematic "experimental trials on living cell substances" until after 1945, however, due – among other things – "to the destruction of the institute during the war" [40, p. 18]. The direction was clear, however, the vision stayed alive and there was also tremendous general interest outside the scientific community, as the reports in the daily press in the context of the presentation of the

Nobel Prize to Staudinger show: "Macromolecular chemistry is [...] likely to be of the greatest importance to biology and medicine. It is definite that life processes are associated inseparably with macromolecules. Chemically speaking, life consists of the formation, conversion, dissolution and also reproduction of macromolecules that follow the laws of life" – this is how the *Lindauer Zeitung* put it ([44]; cf. [10], pp. 24, 25, 29 as well as [1], pp. 302, 306–307, 333–334). "All our modern plastics are [...] large molecules. But all living substances are macromolecular too. Staudinger's theory will therefore be celebrating its greatest triumphs in the biological field", wrote *Die Welt* [45]. Expectations that have been met: "Current thinking in the molecular biology field is inconceivable without the macromolecular concept. Genetic science, which is developing rapidly today, is also based on the macromolecular principles proposed by Hermann Staudinger" ([43], p. 7; cf. [46], pp. 135–136).

Staudinger already had an excellent international reputation too, even before he won the Nobel Prize, and he was also in demand as a speaker outside Germany. In November 1950, for example, he was invited to Rome to speak at the Centro Romano di Studi. The Staudingers took this opportunity to attend a private audience with Pope Pius XII at St. Peter's Basilica [40, p. 23].

However, it was no longer possible to ignore the fact that Staudinger, who once led the avant-garde in the organic chemistry field, now held mainstream positions that were no longer in tune with the times in all cases. Staudinger was in danger of being overtaken by scientific progress or even of being left behind. Where new findings conflicted with his own views, he classified them as improper attacks, ignored them or fought a losing battle against them. He did not accept the physical-chemical proof of the flexibility of linear macromolecules, for example, and stubbornly maintained his concept of macromolecules as rigid, rod-like structures. He was just as unwilling to accept modifications to his law about the relationship between molecule size and viscosity:

> On the basis of the assumption that linear macromolecules can also exist as clusters, Hermann Mark (1895–1992, editor's note) co-operated with the Dutch physical chemist Roelof Houwink (1899–1987, editor's note) in Vienna to continue empirical development of Staudinger's viscosity equation (Mark–Houwink equation). [...] The corrections/additions to Staudinger's viscosity law made by Mark and Houwink proved to be correct, but they were still being rejected by Staudinger in the 1950s. ([19], p. 410)

Staudinger lagged behind polymer science in the USA in particular. Here, at the Polytechnic Institute of New York in Brooklyn, was where Hermann Mark worked, the man with whom Staudinger had held a fierce dispute from 1926 onwards (see Sect. 2: "1920–1932"). Mark fled to the USA in 1938 to get away from the Nazis, after he lost his licence to teach at Vienna University because he was a Jew and was put in prison for a while. Helmut Ringsdorf (born in 1929, editor's note), one of Staudinger's undergraduate and doctoral students, worked at Mark's institute in Brooklyn from the end of the 1950s onwards as a post-doctoral student. Staudinger did not do well in a comparison of the "two worlds".

According to Ringsdorf:

> "The Freiburg Institute was no longer the world leader in the polymer field in the 50s. Although the work done there was sound, it was generally classical. As the head of the institute, Hermann Staudinger definitely continued to focus too much on the virulent and tough battles he had fought in the 1920s. Hermann Mark, on the other hand, had activated macromolecular chemistry on a broad basis in the USA after the war. He brought physicists, chemists and technologists together and developed a modern version of polymer science as a result. This gave the institute in Brooklyn the prominent international position it held at the time. This development took somewhat longer at Staudinger's institute [. . .]. I only learned in Brooklyn what new developments were going on in polymer chemistry." (Quoted in [19], p. 150)

The two worlds then collided in 1957: Staudinger accepted an invitation to Brooklyn that Mark issued to him to give a lecture there. He was received "as the polymer pioneer, as the person 'who led the polymer crusade'" [19, p. 186]. Staudinger did not make a good impression, however. Ringsdorf remembers:

> I arranged the slides for Staudinger's lectures back then and so I knew what he was going to talk about. Compared with what was being done in Brooklyn at the time, it has to be said that these lectures almost represented the dark ages of polymer science. I can make this statement particularly emphatically, because I still have the original slides [. . .] of the last four lectures. The young people in Brooklyn in particular certainly admired and revered Hermann Staudinger at this time as the grand old man of macromolecular chemistry. They were probably forgiving about what he said, particularly in view of the fact that he spoke in German. (Quoted in [19], pp. 186–187; cf. [40], p. 25)

1957 was also the year when Staudinger gave guest lectures in Japan. This was the country where his early writings about high-molecular organic compounds were still revered as if they were the Bible (see [40], p. 20). During this stay, Staudinger met the Tenno, the Japanese Emperor [40, pp. 20, 26]. In 1958, Staudinger headed the German delegation at the international "Science House" at the World Fair in Brussels. He continued to receive honours as well: Staudinger was awarded the Grand Order of Merit of the Federal Republic of Germany twice more, in 1957 with Star and in 1965 with Star and Sash. "He had good fortune that only a few scientists share: being able to experience and enjoy all the success of his work", Krüll ([11], p. 49) writes about Staudinger's retirement. His health deteriorated, however; Staudinger had heart problems [47, p. 93]. "His intellect remained keen, however, and he continued to be interested in world affairs and the progress made in macromolecular science right until the end. Hermann Staudinger was still able to experience the beginning of space travel in the form of the first satellites. He was told that this development was only possible because there are macromolecular materials that stand the conditions encountered in space. Hermann Staudinger spent the summer of 1965 in his garden, thoroughly enjoying his flowers. He then passed away on 8 September 1965" [40, p. 27]. He was laid to rest in the central cemetery in Freiburg. The obituaries about the 84-year-old included the following statements:

- "An unusually bright star in the chemistry sky has now died – one that in recent decades cast radiant light on many areas of chemistry that had been dark beforehand" [48, p. XLI].

- "He was a research scientist, a teacher and an apostle. [...] His inquiring mind drove him to follow unexplored paths, which may well involve hard and uncomfortable work but which were, on the other hand, necessary in order to open up virgin territory for research, teaching and applied science" [47, p. 93].

The final words come, appropriately enough, from his widow:

> A year later, three Japanese stood before me: they wanted to be shown Hermann Staudinger's grave, because they said they had been asked to hold a memorial ceremony in accordance with their particular rite. They put a large bouquet of white flowers on the grave – white is their mourning colour. They then lit incense sticks they had brought with them and started to recite the words of their rite, bowing down almost to the ground again and again in front of the grave with the fragrant burning incense sticks in both hands. I have to admit that I was very moved. A completely different, distant country, a completely different, unfamiliar religion honoured a man here who had added to the world's pool of knowledge. This world has become a small one thanks to our technology; we are all neighbours. And that means we have an increasingly urgent commitment to humane behaviour as creatures who share mother earth. Because that is the only way we will survive. Hermann Staudinger was a strong advocate of this in various ways throughout his life. And I think that this can be considered to be his legacy. [40, pp. 27–28]

Appendix 1

Addition is the name given in chemistry to a process in which a new substance is formed from two other substances without any by-products. In *addition polymerisation*, molecular components or monomers with different structures are linked to create high polymers with the migration of hydrogen atoms. This type of polymerisation is generally carried out by subjecting the monomers to heat and pressure. Two significant groups of plastics are manufactured by this process nowadays: polyurethanes and epoxy resins. *Condensation polymerisation* can take place when the reactants each have two functional groups that can combine with each other by producing water. Staudinger ([1], p. 108) writes: "Condensation polymerisation is characterised by a chemical reaction between two compounds with groups that are of the same or different kinds but are reactive, in which [...] there are low-molecular by-products such as water, alcohols, ammonia, hydrochloric acid or similar substances. [...] It is an absolute technical necessity for the by-products of the reaction to be removed in the condensation process [...] for the reaction to go smoothly and successfully. The list of technically important plastic groups that are manufactured by the condensation polymerisation process includes the following: (1) the group of phenol formaldehyde resins (i.e. typical duroplasts such as Bakelite); (2) polyamides (nylon and perlon) and linear polyesters (particularly polycarbonates as thermoplastics); and (3) crosslinked polyesters as lacquer and casting resins. [...] (In addition to this list, editor's note) silicones".

Appendix 2

Initiators are substances that need to be present to produce certain high polymers. They help to bring about polymerisation and can appear in the end product – in contrast to *catalysts* (reaction accelerators). Although the latter are involved in the chemical reaction temporarily, they are unchanged by it.

Appendix 3

The Swiss botanist Carl Wilhelm von Nägeli (1817–1891) coined the term "micelle" (from the Latin word *micella*, meaning "crumb") in the nineteenth century. His studies about starch, cellulose and various types of protein led him to assume that "organised bodies", i.e. substances extracted from biological systems, consisted of aggregates that were in turn made up of molecules. Nägeli named these aggregates, the size of which was between molecules and visible crystals, micelles. Staudinger [10, pp. 8–9] writes: "[. . .] numerous small molecules are held together by weak inter-molecular forces in a micelle; an increase in temperature or a change in solvent can already cause them to disintegrate as a result."

Appendix 4

Letter of 2 November 1928 from Hermann Mark to Hermann Staudinger (excerpt; quoted in [15], pp. 93–94):

I was sorry to read in your letter that you feel your priority has been violated by the statements made by Professor Meyer. I am convinced that nothing was further from Professor Meyer's mind than this and I myself have also tried especially hard to emphasise the importance of your fine work appropriately, not only in our work but also and in particular in my lecture in Hamburg.

I do, however, consider it sensible to introduce the word 'primary valence chain', because it refers to structures that are not completely identical to what has been called a molecule up to now. I always associate the word 'molecule' with the concept of a large number of completely identical structures, whereas the term primary valence chain is specifically supposed to include the fact that the same substance contains structures that are very similar to each other, cannot be separated from each other by chemical methods but differ from one another a little in their size, so that while it is not possible to indicate a precise molecular weight, an average primary valence chain length can be quoted. If this fact is specifically added to your macromolecule, then the two terms are, as far as I can see, identical and it is a question of convenience whether one says 'primary valence chains' or 'macromolecules of fluctuating size'.

For this reason, I would not want to stress this difference too much; I think that it is much more expedient and much more appropriate to the situation if we agree that we essentially think the same, i.e. that the chemical primary valences play a crucial role in the structure of high-polymer substances. I consider it less important that we give different names to the intermediate factors. The main issue in the near future will, after all, be whether the positions held by you and us as well as Freudenberg, Willstätter and others prevail or whether the people will be proved right who think that it is necessary to assume new kinds of association forces not yet detected in chemistry up to now in order to explain everything that we have experienced. I think that we should proceed together in commenting on this issue and should not emphasise certain differences between our personal views that are in my opinion minor; if we did, the high-polymer community could easily make the mistake that is only too familiar from politics; that a major issue was not given close enough attention and was not presented clearly enough because of minor differences between opinions that were not far apart.

I will try and find a way to come to Freiburg again as soon as possible, because I would like very much to talk to you in detail about this issue.

Until then I remain

yours sincerely,

H. Mark

Appendix 5

Nomen est Omen

Hermann Staudinger's memory is kept alive not least of all by the various uses to which his name has been put. Although they enhance scientific vocabulary in particular, one comes across them in day-to-day life as well, because schools and roads are among the things that have been named after Staudinger. Here is a short list:

- **Staudinger reaction**
- **Staudinger synthesis**
- **Staudinger index:** The relationship between the viscosity and the molecular mass of dissolved polymers
- **Hermann Staudinger Prize:** Endowed by BASF AG at the Society of German Chemists (GDCh) and awarded for the first time in 1971
- **Roads:** Roads named after Hermann Staudinger (with and without his first name) can be found in Baden-Württemberg (Emmendingen, Freiburg, Karlsruhe, Münsingen, Waldshut-Tiengen), Bavaria (Aschheim, Helmbrechts,

Munich, Rehau, Trostberg, Viechtach), Hamburg, Hesse (Bürstadt, Darmstadt, Rodgau, Viernheim), Lower Saxony (Braunschweig, Lage/Lippe), North Rhine-Westphalia (Gütersloh, Velen) and Schleswig-Holstein (Norderstedt).

- **Schools:** Staudinger Primary School and Carmelite/Staudinger-Realschule plus (former Staudinger-Hauptschule) in Worms, the city where Hermann Staudinger was born on 23 March 1881; Hermann-Staudinger-Realschule in Konz/Rhineland-Palatinate; Staudinger Comprehensive School in Freiburg im Breisgau; Hermann Staudinger Grammar School in Erlenbach/Bavaria; and Hermann Staudinger Graduate School at Albert Ludwigs University in Freiburg im Breisgau
- **Staudinger cactus:** Echinopsis × Trichocereus Multihybrid Hermann Staudinger with large flowers, hybrid BS.1491/2006 (breeder: Ingo Bartels, Burgdorf)
- **Hermann-Staudinger-Haus:** The building is in Freiburg im Breisgau: it was established in 1962 and houses the Freiburg University Institute of Macromolecular Chemistry. The American Chemical Society and the Society of German Chemists unveiled a plaque in honour of Hermann Staudinger here on 19 April 1999. This plaque says:

> Historic International Milestone in Chemistry – Origin of Polymer Sciences. Albert Ludwigs University, Freiburg, Baden-Württemberg, 1926–1956: This building has been named after Hermann Staudinger, who carried out his pioneering research on macromolecules in Freiburg from 1926 to 1956. His theories about the polymer structure of fibres and plastics as well as his later studies of biological macromolecules formed the basis for countless modern developments in the materials and biosciences and supported the rapid growth of the plastics industry. Staudinger received the Nobel Prize in Chemistry in 1953 for his work in the polymer field.

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Staudinger's Footprints in Japan During His 30-Day Visit in 1957

Akihiro Abe

Abstract Professor and Frau Dr. Staudinger made an epoch-making visit to Japan in the cherry blossom time in 1957, 4 years after his Nobel Prize. Japan was gradually recovering from the damage of World War II. In accordance with the strong demand from industry, research activities on polymeric substances became popular in major national universities. Through various contacts, including two major lectures in Tokyo and Osaka, they left an impressive lesson on "what science is all about" for young researchers in this new field.

Keywords Appreciating the essence of Japanese culture · Lectures on macromolecular concept · Short reunion · Staudinger effect · Visiting Emperor Hirohito

Contents

1 Introduction 140
2 Official Duties 140
2.1 Lectures and the Impact 140
2.2 Who Carried Out the Mission to Promote Public Awareness of the Macromolecular Concept in Japan? 142
3 Off-Duty Days 143
4 Short Reunion 143
5 Epilgogue 144
6 Polymer Activities in Japan in Those Times 146
6.1 Early Polymer Activities in Japan 146
6.2 Rise of the Polymer Industries 147
6.3 Polymer Activities Around the 1920–1930s 147

A. Abe (✉)
Tokyo Institute of Technology, 6-27-12 Hiyoshi-Honcho, Kohoku-ku, Yokohama 223-0062, Japan
e-mail: aabe34@xc4.so-net.ne.jp

6.4 Remarks on the Irreplaceable Role of Sakurada 147
6.5 Polymers in the War Times 148
6.6 A Fresh Start After World War II 149
References 149

1 Introduction

The timing was superb. Their visit brought a sort of "Staudinger effect" on the polymer activities just taking off in Japan (see Sect. 6). According to the remaining documents, the following account is why and how it happened.

Professor and Frau Dr. Staudinger visited Japan in the cherry blossom time in 1957, 4 years after his Nobel Prize. Keikichi Arai, the Secretary General (one of the founding directors) of the Society of Polymer Science, Japan (SPSJ) left a detailed report on this historic event. According to his note, Professor Staudinger had the idea to come to Japan on the occasion of his 77th anniversary. In the Asian custom, this is a happy occasion to be celebrated by family and friends. His desire was forwarded to the SPSJ through Eiji Ochiai (his former research associate), who at that time was the president of the Pharmaceutical Society of Japan. A tentative schedule was proposed by the SPSJ committee that included a minimum amount of official duties: two main lectures, one in Tokyo and the other in Osaka, and a couple of visits to textile companies. The rest of the days were mostly open to enjoy more relaxing events of the flowery season. The plan was favorably supported by the textile and plastic industries, which were just recovering from the huge damage suffered during World War II.

2 Official Duties

2.1 Lectures and the Impact

Professor Dr. and Frau Dr. Staudinger arrived at Haneda Airport on April 1st, 1957. The lecture in Tokyo was held on April 5th (Fig. 1). The large auditorium of Tokyo University could not accommodate all the attendants, leaving more than 1,000 people out on the campus under cherry flowers. In the lecture entitled "Die macromolekulare Chemie, ein neues Gebiet der organischen Chemie," Staudinger emphasized that the origin of macromolecules must be sought in organic chemistry. The physical and chemical properties of polymers were, however, determined not only by the internal structure of molecules, but more significantly by their spatial configuration, such as size and shape. Although most of the participants were already very familiar with his views on "macromolecules" as well as with the

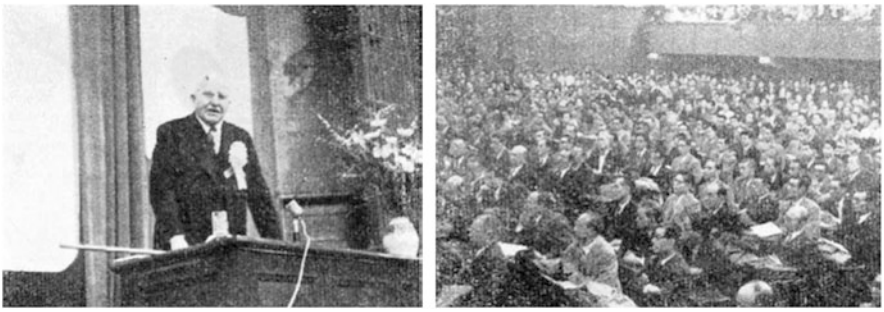

Fig. 1 The long-hoped-for lecture at Tokyo University and the audience

Fig. 2 Enthusiastic welcome in Osaka

outstanding contribution of Wallace Hume Carothers on the synthesis of macromolecules through various papers, this was the first opportunity to attend the live performance of the person himself. The scientists, such as Teiji Tsuruta, who were there vividly remember the atmosphere, stating that the lecture was really powerful and persuasive. Staudinger's talk apparently gave some emotional encouragement to younger researchers.

The second lecture "Uber dei Konstitution der Cellulose" was delivered in Osaka on April 12th: the auditorium of 600 seats was entirely filled with people. The presentation to the enthusiastic audience in Osaka covered topics from the chemical structure to the solid-state properties of cellulose fibers, with a plenty of evidence. The lecture was followed by a cheerful beer party, attended by more than 100 people, including his former associates Eiji Ochiai, Ryuzaburo Nodzu, and others (Fig. 2).

In a separate program, Frau Dr. Magda Staudinger, who was also a well-known biologist, was asked to give a speech at the International House of Japan in Tokyo on April 6 (Fig. 3). She talked about the activities of women in German universities.

Fig. 3 Ladies' program in Tokyo

According to the note of Ms. Fumiko Yamazaki, the president of the lady's association of Japanese universities, ladies from various countries were invited to attend and three languages were used in the lecture. They also enjoyed the party with the Staudingers in the garden blooming azalea.

The most commemorative highlight event took place in the middle of the month: on the 17th, Hermann and Magda Staudinger were invited to deliver a lecture on macromolecular chemistry in the presence of Emperor Hirohito at the Imperial Palace. The Emperor was known to be a biologist. He naively raised a question on the main theme of the lecture on macromolecules. "Is this a concept that came into your mind to explain various phenomenological behaviors of a group of compounds, or did you really prove their existence by rigorous scientific means?" Professor Staudinger was astonishingly impressed by this pertinent interrogation. The conversation went on and on for almost 1 h beyond the time (20 min) allotted to this ceremonial meeting.

2.2 Who Carried Out the Mission to Promote Public Awareness of the Macromolecular Concept in Japan?

After all, Staudinger's visit was a big event for the polymer community, intended to attract public attention to this newly emerging field of science and technology. Documents from those days indicate that SPSJ, which was established in 1951, continued to grow by gaining about 400 members each year until the trend stopped because of the oil crisis in the early 1970s (Sect. 6).

In connection with the strong growth of polymer science and technology in Japan, readers might be curious about what had happened to those who witnessed the hot debate on the macromolecular concept, as the associates of relevant parties in Germany. Four students studied in Staudinger's laboratory in the 1920s. Ryuzaburo Nodzu, who was known for his contribution to Staudinger's viscosity formula, became a professor of organic chemistry at Kyoto University, but he

Fig. 4 With Kabuki actor, Ennosuke Ichikawa

mostly stayed in his field without many accomplishments in polymer science. Michizo Asano and Eiji Ochiai later became professors of pharmacology at Tokyo University. Taizo Yamashita worked for a pharmaceutical company. None pursued a career in the macromolecular field. In his book [1], Yasu Furukawa stated, "ironically, it was a group of students coming from the opponent school who played a major role in the promotion of polymer science in Japan." Tsukumo Tomonari (Kurarey Co.), Ichiro Sakurada (Kyoto University), Motoi Wadano (Daicel Co.), and Hiroshi Sobue (Tokyo University), all from Hess's group, played leading roles in the polymer community. Ichiro Sakurada and Kisou Kanamaru (Tokyo Institute of Technology) learned colloid chemistry with Wolfgang Ostwald. The reasons behind this have been variously speculated in the relevant articles [1, 2].

3 Off-Duty Days

On this trip to Japan, unlike ordinary scientific visits, the Staudingers had plenty of time to enjoy cultural activities such as watching kabuki, visiting museums, and sight-seeing tours to various spots including Izu, Ise, Kyoto, Nara, and Hiroshima. All these trips seemed to be accompanied by a lively group of friends and former research associates. Some of the photos of the events are reproduced below (Figs. 4, 5, 6, and 7). Apart from scientific discussions, Staudinger played the role of a good-natured old man with dignified appearance.

4 Short Reunion

On the way back to Freiburg, the Staudingers took a flight to Zurich (Kloten) on the 30th of April. When landed, they were interviewed by a journalist. A photo and their short comments appeared in a Swiss magazine *Su unt Er* on May 16th 1957 (Fig. 8): "Prof. Staudinger weilte auf Einladung von acht wissenschaftlichen

Fig. 5 Feeding deer in the Nara Park

Fig. 6 Warm hospitality in Kyoto

Gesellschaften in Japan; er zeigte sich von der industriellen Entwicklung Japans, besonders seiner Textilindustrie, stark beeindruckt und gab vor allem seiner Überzeugung Ausdruck, daß Japan große eigene Leistungen und nicht nur eine Kopierung des Westens vollbringe."

5 Epilgogue

Soon after this visit, Professor Staudinger was elected to honorary membership in SPSJ. The IUPAC Macromolecular Symposium was held in Tokyo and Kyoto in 1966. On behalf of her husband, who had died a year earlier, Frau Dr. Magda Staudinger delivered the address to the audience at the opening ceremony of the meeting.

Fig. 7 At the Ohara Museum of Art in Kurashiki, with Tomonari (*left*) and Sakurada (*right*)

Kurzes Wiedersehen

ZÜRICH: Auf der Rückreise von Japan nach seinem Wohnort Freiburg i. Br. hielt sich Prof. Dr. Hermann Staudinger, Chemie-Nobelpreisträger und fünffacher Ehrendoktor, einige Tage in Zürich auf. Er ist mit der größten Schweizer Stadt durch enge Bande verbunden, wirkte er doch einst während 14 Jahren als Chemiedozent an der ETH, während welcher Zeit ihm auch das Bürgerrecht von Zürich verliehen wurde. Und seine drei Töchter sind alle in Zürich glücklich verheiratet. Prof. Staudinger weilte auf Einladung von acht wissenschaftlichen Gesellschaften in Japan; er zeigte sich von der industriellen Entwicklung Japans, besonders seiner Textilindustrie, stark beeindruckt und gab vor allem seiner Ueberzeugung Ausdruck, daß Japan große eigene Leistungen und nicht nur eine Kopierung des Westens vollbringe. Unser Bild zeigt Prof. Staudinger mit seiner Gattin bei der Ankunft in Kloten; Frau Staudinger ist übrigens selbst eine anerkannte Biologin.

Fig. 8 Article about Staudinger's visit to Japan, in *Su unt Er*, 16th May 1957

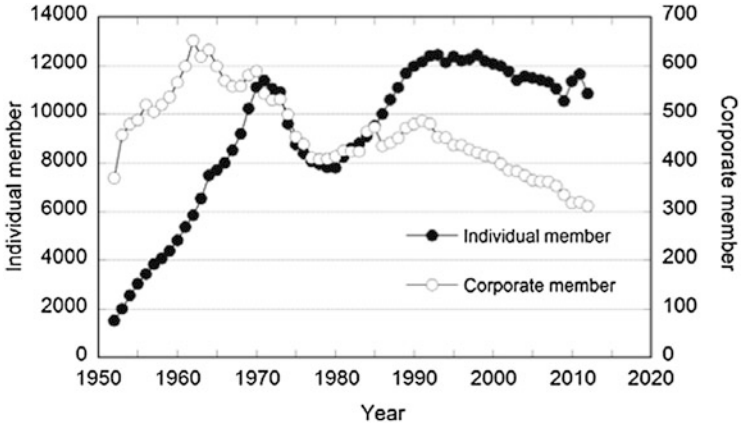

Fig. 9 Variation in SPSJ membership over the years

6 Polymer Activities in Japan in Those Times

To facilitate understanding of the atmosphere greeting the Staudingers in 1957, it may be helpful to provide a brief overview on the growth of polymer activities in this country up to the mid-1950s. Looking back on the history, these years were the inflection point where a rapid expansion was just taking off. Japanese people, as well as the society, were making sure of directions to leave the turmoil of World War II. The membership of the polymer society, SPSJ, had increased from 1,887 at the beginning (1952) to 5,380 in 1960 (Fig. 9). More than half of the individual members were from plastics or textile industries. After the maximum (11,932) was reached in 1971, growth was abruptly terminated due to the oil crisis [3].

6.1 Early Polymer Activities in Japan

Like any other country, long before the scientific recognition (concept) of macromolecular substances, polymer-related industries had been developed and functioned in society on the basis of empirical techniques. According to the chronological table in *Japanese history in polymer science and technology* edited by Tsuruta et al. [4], fiber (silkworm culture) and paper manufacturing businesses, along with iron production, were quite popular in the Genroku era (1688–1703). In 1853, the Japanese conservatives were forced to give up their old-fashioned closed-door policy by the visit of Commodore Perry's "Black Ships" (USA) to the Uraga Bay. Soon after the removal of restrictions, the export of silk became one of the major businesses of Japan (1859), and in 1909, Japan became the largest producer of silk in the world. According to the literature, the percentage production of the top four countries over the period 1908–1912 were Japan 37%, China 31%, Italy 17%, and France 2% out of the total amount 2.4×10^4 tons/year.

6.2 Rise of the Polymer Industries

The first paper mill was built by Eiichi Shibusawa in Tokyo in 1872. Some tons of natural rubber were imported from India and the USA in 1880–1890 and, concurrently, a rubber manufacturing company was built (1886). Celluloid products were first imported from Germany in 1877, and their domestic production started around 1890. The most interesting example is the Japanese urushi lacquer made from the poison oak tree. Because of its bright and clear color, the lacquer has been widely used from commodity to art works in Japan. In 1883, Hikorokuro Yoshida published a research article on the urushi lacquer, describing an enzyme (later named laccase) that initiated the polycondensation of urushiol [5]. After 1903, scientific study on the urushi lacquer was continued by Rikou Majima [6].

6.3 Polymer Activities Around the 1920–1930s

Since the beginning of the twentieth century, extensive efforts have been made to develop cellulose fiber (cotton and rayon) industries. In academia, two major research groups were established by Gen-itsu Kita (Kyoto University) and Katsumoto Atsuki (Tokyo University) in this field. As a result of the tense cooperation between industry and academia, Japan climbed to become the top producer of semisynthetic fibers (rayon) in the world in 1937. In the same year, Japanese production of celluloid goods was also said to be the top runner. In the 1930s, all other polymer industries including rubber and plastics were experiencing a rising trend. In 1938, the announcement of the invention of Nylon from Du Pont came as a tremendous shock to the Japanese textile industries. Urgent need for the scientific study and development of synthetic polymers was emphasized.

6.4 Remarks on the Irreplaceable Role of Sakurada

It might be interesting here to mention the important role of the late Professor Ichiro Sakurada for the wide spread of the Staudinger concept [7]. He first studied cellulose chemistry under the guidance of Gen-itsu Kita at Kyoto Imperial University. He spent some years (1928–1931) in Germany to learn chemistry under Wolfgang Ostwald in Leipzig and Kurt Hess in Berlin (two well-known opponents of Staudinger), and returned to Kita's group in 1931. After a certain period of serious consideration, Sakurada, once a member of the "colloid" school as a student of Hess, made a "Copernican" revolution in 1935 to accept most of Staudinger's views [1, 2, 8]. He then demonstrated a strong sense of responsibility and commitment to his mission on the sound growth of polymer science and technology [1, 2, 8]. Sakurada is often regarded as the father of polymer science in Japan.

6.5 Polymers in the War Times

During times of war (1937–1945), international interactions were seriously interrupted. Advancement of basic science and technology was, however, encouraged by the government and supported by society as well. Major scientific contributions, mostly disclosed after World War II, are as follows:

- 1937: San-ichiro Mizushima et al. proposed the rotational isomeric state model for internal bond rotation [9].
- 1939: Ichiro Sakurada, Sungi Lee et al. announced the invention of polyvinyl alcohol (PVA) fiber [8, 10]. A test pilot plant for the commercial production of "Vinylon" was built in 1946.
- 1940: Sakurada derived an equation for polymer viscosity (the original article has been reproduced in English: cf. ref [11]) independently from the Mark–Houwink formula:

$$\left(\eta_{sp}/c\right)_{c\to 0} = KP^n \tag{1}$$

where P stands for the degree of polymerization. The relation is often called Mark–Houwink–Sakurada equation.

- 1941: Establishment of the Japanese Research Association for Synthetic Fibers to promote collaboration between government, industry, and academia. The association was later renamed the Federation of Polymer Chemistry.
- 1942: Syoten Oka derived a formula [12] for the end-to-end distance of polymer chains having independent rotational potential:

$$< r^2 > /nl^2 = [(1+\cos\theta)/(1-\cos\theta)][(1+\cos\phi)/(1-\cos\phi)] \tag{2}$$

with θ and ϕ respectively representing the bond angle and bond rotation angle.

- 1943–1947: Ryogo Kubo published a series of papers on the statistical theory of rubberlike substances, and wrote a book [13].
- 1944: The Federation of Polymer Chemistry published the first issue of the journal (in Japanese) named *Kobunshi-Kagaku* (High Polymer Chemistry).
- 1944: Balloon bombs, the first intercontinental weapon, were made out of Japanese paper (long fibers from local trees) coated (pasted) with Konnyaku mannan (jelly made from devil's-tongue starch). The balloon (diameter ~10 m, weight ~200 kg) was inflated with a given amount of hydrogen so that they rose to a height where they could be carried by the jet stream to the west coast of America. Toshio Hata left a note stating that a group of polymer chemists from Tokyo Institute of Technology was involved in various aspects of this project, mainly as technical advisers. Several hundred balloons (out of ~9,000) reached the west coast of the USA (Oregon). The number of casualties caused by this "high tech" weapon was, however, said to be minor [14].

6.6 A Fresh Start After World War II

Massive numbers of young soldiers came back from the battlefield to universities to pursue their career in peace. At this time, in accordance with the strong demand from industry, research activities on polymeric substances became popular in major national universities. According to the statistics of the Japan Plastics Industry Federation, the domestic production of plastics increased rapidly from 5×10^3 tons in 1946 to 551×10^3 tons in 1960. The figure rose to 15×10^6 tons by 2000. Important results from scientific activities were now encouraged to be published in English.

- 1951: SPSJ was established [3] and Katsumoto Atsuki was nominated as the first president of the society. The journal, *Kobunshi-Kagaku* (*High polymer chemistry*) was transferred from the Federation of Polymer Chemistry to SPSJ.
- 1953: A polymer symposium was held in conjunction with the international conference on theoretical physics in Tokyo and Kyoto: the invited lectures were delivered by Paul J. Flory, John G. Kirkwood, Akira Ishihara, and Ei Teramoto [15].
- 1957: Professor Dr. and Frau Dr. Staudinger visited Japan to give lectures in Tokyo and Osaka and received a warm welcome from big audiences [16].

Acknowledgments I thank Professor Hermann Ringsdorf for telling me about various episodes from his days with Professor Staudinger. This information greatly helped me to understand the background of the excitement that welled up at Staudinger's visit to Japan. Section 6 was included following his valuable guidance. The author is greatly indebted to Professors T. Tsuruta, Y. Furukawa, M. Yamamoto, H. Furuya, and Dr. J. Sakamoto for their critical reading and suggestions during the preparation of this article.

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The Years After the Retirement of Hermann Staudinger: Research on Solution Properties in the Physicochemical Group of Walther Burchard

Walther Burchard

Contents

1 The First Years 151
2 Light Scattering, a New Technique for Polymers 152
3 Branched Polymers 152
4 Chain Stiffness and Excluded Volume Effects 152
5 Hyperbranching 153
6 Ongoing Work 153
References 153

1 The First Years

In 1954, Professor Elfriede Husemann became the successor of Professor Staudinger and took the chair for Macromolecular Chemistry in Freiburg. To prove that her enzymatically synthesized amylose is a covalently linked macromolecule she needed a reliable method for molar mass determination and expanded the mainly chemical research towards physicochemical investigations.

W. Burchard (✉)
Institute of Macromolecular Chemistry, University of Freiburg, Stefan-Meier-Strasse 31, 79104 Freiburg, Germany
e-mail: walther.burchard@makro.uni-freiburg.de

2 Light Scattering, a New Technique for Polymers

In 1956, Walther Burchard, a Diploma Physicist, entered the institute and built up the new light scattering (LS) technique. After 7 months, reliable LS measurements could be performed. The required molar mass determination of the enzymatically synthesized amylose was possible after full derivatization of the OH-groups with phenyl isocyanate that led to good solubility in organic solvents. Since amylose and cellulose differ chemically solely by the type of the glycosidic bond, the derivatized cellulose was also included in this study. The structural influence of the different glycosidic links could clearly be demonstrated [1].

3 Branched Polymers

Amylose is present in starch to about 20%, the rest is the highly branched amylopectin. At that time the molar mass and macromolecular size was unknown. The complexity of branched structures was frightening to most chemists and the study of amylopectin was avoided. In 1967, Professor Manfred Gordon (Essex University at Colchester, UK), gave a lecture on the powerful possibilities of branching theory to calculate the molar mass averages M_w and M_n, and some important properties on the elastic modulus of networks formed after gelation in a randomly crosslinking system. The unperturbed radius of gyration was also calculated. In Colchester in 1969, the branching theory was extended to static and dynamic light scattering by Kanji Kajiwara, Walther Burchard, and Manfred Gordon [2]. Two years later, the theory of AB_2 polycondensates (now better known as "hyperbranched" (hb)-polymers) was developed [3] and proved to be helpful for interpreting such polymers. At that time the paper did not attract much interest.

4 Chain Stiffness and Excluded Volume Effects

Chain stiffness and the effects of excluded volume became the dominating issue in the years between 1980 and the start of the new millennium. Percolation simulations indicated strong effects on the unperturbed polymer conformations due to excluded volume interactions [4]. With specially synthesized model substances (prepared by the Burchard group), the transition from mean-field to highly perturbed conformation was explored [5–17]. Studies in 1996 [8] on randomly branched, and in 2004 on hyperbranched polymers [8, 18–20], showed that the fractal conception could be quantitatively adjusted to the scattering behavior of linear and branched structures over the whole q-domain and offered valuable insight into the structure in space [16].

5 Hyperbranching

With the work by Holger Frey and Rolf Mühlhaupt on the synthesis of hyperbranched polyglycerols, a renascence of interest in hyperbranched samples emerged. The comparatively easy preparation and the many possibilities for modifying the hyperbranched samples caused a virtual explosion of activity worldwide. Chemical analysis of the modified hyperbranched samples often only allowed an intuitive interpretation. A more detailed answer was found by the combination of chemical synthesis in combination with static and dynamic light scattering and the corresponding branching theory [18].

6 Ongoing Work

Despite the retirement of WB, his work is continued in cooperation with groups in Germany and other countries in Europe. The study of polysaccharides has a long tradition at the Freiburg Institute and was continued by studies in close and fruitful cooperation with the Professores Mariella Dentini and Tommasina Coviello at the University di Roma "La Sapienca" in Italy [21–23]. The enzymatically synthesized structure of biopolymers still remains largely ignored by synthetic chemists. Yet this type of research has a high impact on applications in oil drilling and nutrition technology.

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Dynamers: From Supramolecular Polymers to Adaptive Dynamic Polymers

Jean-Marie Lehn

Abstract Dynamers may be defined as constitutional dynamic polymers of either supramolecular or molecular nature, i.e., polymeric entities whose monomeric components are linked through reversible connections, which can be either non-covalent interactions or reversible covalent bonds. They may for example implement hydrogen bonding, resulting in supramolecular hydrogen-bonded polymers. Alternatively, covalent dynamic polymers may be derived from the formation of imine-type bonds. Dynamers thus present the capacity to modify their constitution by exchange and reshuffling of their components. These constitutional dynamic features confer on dynamers the ability to modulate their properties in response to external chemical or physical triggers such as heat, light, medium, chemical additives, etc. They thus give access to higher levels of behavior such as self- healing and adaptation. The exchange of monomeric components defines constitutional dynamic networks of interconverting polymeric entities of different constitutions, presenting agonistic and antagonistic relationships between their constituents, and responding to chemical or physical stimulations by upregulating or downregulating specific linked entities. Such arrays represent adaptive constitutional networks that may be implemented for the development of tunable adaptive materials and technologies, towards the advent of a systems polymer/materials science in line with the emergence of systems chemistry.

Keywords Adaptation · Constitutional dynamic chemistry · Constitutional networks · Dynamic materials · Hydrogen bonding · Imine formation · Supramolecular chemistry

J.-M. Lehn (✉)
ISIS, Université de Strabourg, 8, allée Gaspard Monge, 67000 Strasbourg, France
e-mail: lehn@unistra.fr

Contents

1 Introduction 156
2 Dynamers: Constitutional Dynamic Polymers 157
3 Dynamers: Constitutional Dynamic Polymers 159
3.1 Supramolecular Non-covalent Dynamers 159
3.2 Molecular Covalent Dynamers 159
3.3 Dynamers with Multiple Dynamic Processes 163
4 Dynamers: Adaptive Features 163
5 Adaptive Polymer Networks Towards a Systems Materials/Polymer Science 166
6 Conclusion 169
References 170

1 Introduction

I have never met the hero of the present (his)story, Hermann Staudinger, whose 1953 Nobel Prize is being celebrated here, although he was practicing his art near to Strasbourg, in Freiburg-im-Breisgau, and sowing the gold nuggets of macromolecular chemistry along the Rhine, *Rheingold* [1]! (and Main...). I was led to polymer chemistry through supramolecular chemistry, *La Forza del Destino* [2]! And, I wish at the start to thank very warmly all those chemists and physicists who have helped along the way and contributed to the journey.

There is, nevertheless, a close connection between my Alma Mater, the University of Strasbourg and Hermann Staudinger: indeed, here he discovered ketenes [3][1] in the course of his "Habilitation" under Johannes Thiele, at a time when this geographic region was part of an empire extending to the west of the river. Times of the past, and may they remain so forever, as we are now all Europeans!

I approached polymer chemistry via the recognition that there could be such a thing as supramolecular polymer chemistry [4–6]. After a slow start and some braking of the motion here and there, it has become a full part of the world of polymer science, expounded for instance in a recent *summa opere* (for an up-to-date, in-depth review of the field of polymer science, see the 10-volume set [7]). The field embraces chemistry, physics, and biology as both a science and a technology, as testified by the many original publications, reviews, and books, which are far too numerous to be extensively cited (for a selection of reviews, see [8–19]; for supramolecular materials, see also [20, 21]; for coordination and metallosupramolecular polymers, see [22–28]).

One may remark that supramolecular polymers are to some extent just that type of entity that Staudinger had to fight to establish the notion of very large molecules, macromolecules, built entirely on covalent bonds, for by definition [4–6, 22–32]

[1] This discovery was recognized in 2009 by a Citation for Chemical Breakthrough Award and the inauguration of a commemorative plaque by the Division of History of Chemistry of the American Chemical Society on March 7th 2011 at the Chemistry Institute in Strasbourg, coinciding with the launch of the International Year of Chemistry 2011 in Strasbourg.

they consist of chains resulting from the polyassociation of covalent monomers linked through non-covalent interactions. But, now peace reigns and coexistence is thriving for the mutual fertilization of the molecular and supramolecular chemistry of polymeric entities, with active cross-talk between the two areas [22–32].

The topics covered in the present text will be limited to some aspects of the more recent developments that have emerged from supramolecular chemistry and have been carried over to polymer chemistry. They concern the implementation of a basic feature of supramolecular chemistry, its dynamic character. Indeed, novel perspectives are opened if one considers that supramolecular chemistry is intrinsically a dynamic chemistry in view of the lability of the interactions connecting the molecular components of a supramolecular entity and its resulting ability to incorporate, decorporate, and exchange its molecular components. It is thus a dynamic non-covalent chemistry (DNCC). This dynamic character may be imported into molecular chemistry by introducing into molecular entities covalent bonds that may form and break reversibly, so as to allow for a continuous change in the covalent constitution by reorganization and exchange of building blocks, . The resulting dynamic covalent chemistry (DCC) has developed extensively in recent years [33–41]. DNCC and DCC have been brought together under the unifying concept of constitutional dynamic chemistry (CDC) [41–43] covering both the molecular and supramolecular areas. CDC introduces into the chemistry a paradigm shift with respect to constitutionally static chemistry and opens new perspectives. It leads to the generation of chemical diversity within constitutional dynamic libraries of compounds of either molecular (DCL, dynamic covalent) or supramolecular (DNCL, dynamic non-covalent) nature. It enables adaptation through constitutional variation at both levels and thus opens towards an adaptive chemistry whose entities are able to respond to physical stimuli or chemical effectors.

2 Dynamers: Constitutional Dynamic Polymers

Application of the considerations above to polymer chemistry leads to the definition of constitutionally dynamic polymers, dynamers, of both molecular and supramolecular types (Fig. 1) [29–32]. They behave as dynamic combinatorial entities, based on dynamic libraries whose constituents have a combinatorial diversity determined by the number of different monomers. The components incorporated by polyassociation or by polycondensation into the supramolecular or molecular polymer chains depend on the nature of the connections (recognition patterns or functional groups) and core groups, as well as on the interactions with the environment, so that dynamers possess the capacity of adaptation by association/growth/dissociation sequences.

Extending these notions to materials science in general, one may define constitutional dynamic materials as materials whose components are linked through reversible covalent or non-covalent connections and undergo spontaneous and continuous change in constitution by assembly/disassembly processes in a given

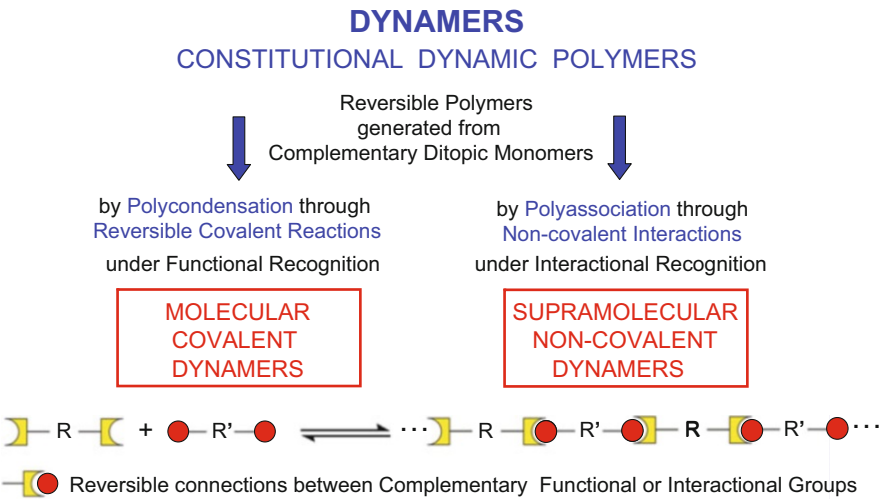

Fig. 1 Dynamers: dynamic (reversible) polymers of molecular (covalent) and supramolecular (non-covalent) nature

set of conditions. Because of their intrinsic ability to exchange their components, these materials may in principle select them in response to external stimuli or environmental factors and therefore behave as adaptive materials of either molecular or supramolecular nature. The dynamic and combinatorial features of dynamic materials, in particular of dynamers, give access to higher levels of behavior such as healing, adaptability, and response to external stimulants (heat, light, chemical additives, etc.).

Supramolecular chemistry has opened new perspectives in materials science towards the design and engineering of supramolecular materials. In particular, a supramolecular polymer chemistry has developed that concerns polymers of supramolecular nature (i.e., dynamic non-covalent polymers) generated by self-assembly through polyassociation of monomers interconnecting through groups presenting complementary patterns of interactional recognition.

Dynamic covalent polymers involve the implementation of DCC in polymer chemistry. They result from the polycondensation of monomers bearing suitable reactive groups via reversible chemical reactions under functional recognition.

Dynamers in general may undergo (reversible) modifications of their properties (mechanical, optical, etc.) via incorporation, decorporation, or exchange of their monomeric components.

The above considerations will be briefly illustrated by a few examples of supramolecular polymers and dynamic covalent polymers, taken from studies performed in our group, acknowledging at the start the many creative contributions from numerous other laboratories. For more details, the reader is referred to the relevant sections of earlier general presentations [29–32, 41–43] and to the original papers.

3 Dynamers: Constitutional Dynamic Polymers

3.1 Supramolecular Non-covalent Dynamers

As pointed out above, numerous studies have been devoted to the chemistry of supramolecular polymers, based on various types of more or less directive non-covalent interactions of various strengths. These interactions can range from the organic type [8–21, 44–52], such as hydrogen bonding, to the inorganic type involving metal ion binding in metallosupramolecular coordination polymers [22–28, 53–55].

The progressive generation of entities of increasing complexity by hierarchical build-up at the supramolecular level is a process of major significance for the emergence of complex matter and is subject to active investigation. As an illustration, one may consider the very first case of a main-chain supramolecular polymer [4–6]. Their formation and behavior may be dissected into a three-stage conditional process, starting from complementary molecular components that form supramolecular main chains through hydrogen bonding. These chains, in turn, assemble into cylindrical triple-helical columns that finally yield helical fibrils by side-chain entanglement (Fig. 2). This type of one-dimensional (1D) supramolecular polymer has been visualized by scanning tunneling microscopy (STM), thus confirming the supramolecular chain-type structure proposed earlier [56].

A two-dimensional (2D) supramolecular polymer array can be generated for instance from ditopic monomers containing two terminal guanine residues, which form potassium cation-stabilized supramolecular macrocyclic guanine quartets (Fig. 3) [57, 58]. A hydrogel is obtained that is reversibly switchable between gel and sol states through binding and release of the metal cations by a pH-modulated cryptand ligand. On the other hand, covalent polymers incorporating tris-urea motifs, derived from carbohydrazide and isocyanate components, establish a 2D pattern in which one direction (that of the covalent chain) is molecular and the orthogonal direction (that of the hydrogen bonding between the urea subunits) is supramolecular [59].

A different approach to the generation of supramolecular polymers resides in first generating supramolecular monomers and subsequently connecting them through covalent bonds. Such a process has been realized in oxidative polymerization by formation of C–C links between ditopic supramolecular building blocks, which yields supramolecular microcapsules on deposition on a surface (the three steps are shown in Fig. 4) [60].

3.2 Molecular Covalent Dynamers

Dynamic covalent polymers have been generated by using various reversible chemical reactions for linking monomers ([61–75] for an early implementation of

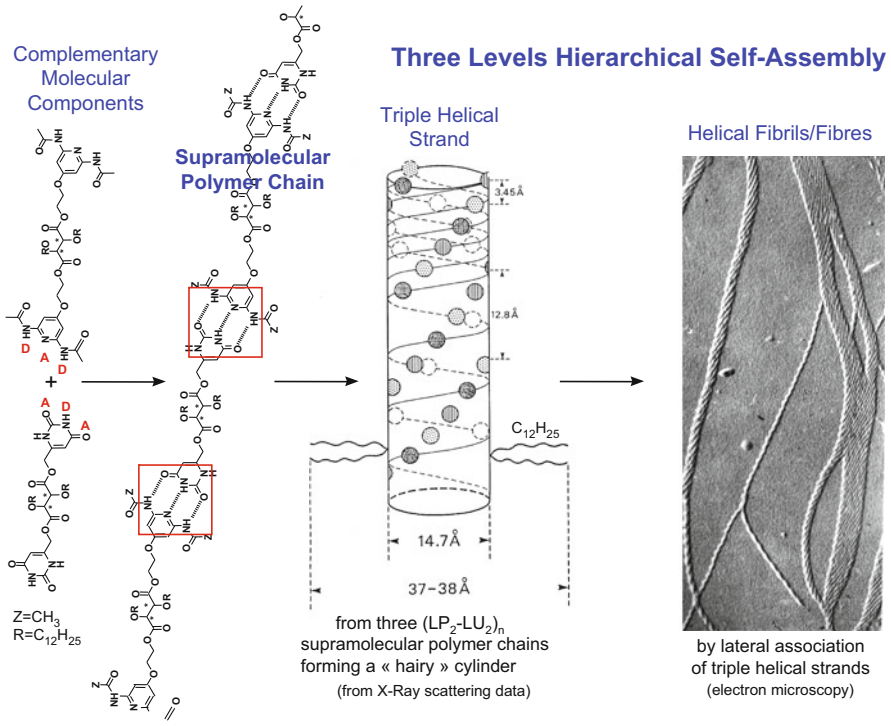

Fig. 2 Generation of supramolecular fibrils in a three-step hierarchical process involving: (1) formation of a supramolecular chain by polyassociation of ditopic molecular monomers through complementary hydrogen-bonding patterns; (2) assembly of three supramolecular chains into a triple helical strand; and (3) formation of fibrils from triple helical strands by lateral association through entangling of side-chains

imines for the reversible crosslinking of polymers, see [61]). Of particular interest because they present a wide field of implementation that covers organic chemistry, biochemistry, and materials science are the different types of amine-carbonyl condensations that produce carbon–nitrogen double bonds C=N. The acylhydrazone group presents special features because it combines, in a small molecular subunit, the hydrogen bonding features of the amide function (present in polyamides and in peptides) with the reversibility conferred by the imine group (see also scheme 3 in [30]). It has been exploited in a range of covalent dynamers formed through polyacylhydrazone connections.

Like dynamic polymers in general, those of covalent type present specific properties that non-reversible polymers do not possess. They have been illustrated for instance in degradable "green" polymers based on imine connections [72], in polymer blending [73], in the modification of mechanical [74] and optical [75] properties. Metallosupramolecular polymers are also able to undergo dynamic modification of their mechanical and optical properties, as shown in Fig. 5 [53–55].

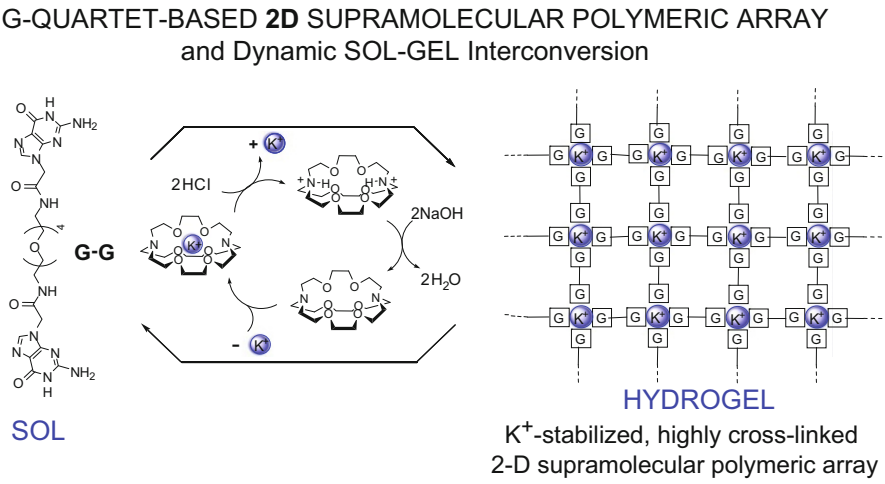

Fig. 3 Polyassociation of bis-guanine monomers (*G–G*) into a two-dimensional supramolecular polymeric array based on the formation of G-quartets, stabilized by potassium cations, and interconversion of the resulting hydrogel with the corresponding sol state through reversible cation binding and release by the [2.2.2] cryptand, modulated by acid–base alternation. The 2D array on the *right* is represented in an idealized fashion ignoring any defect

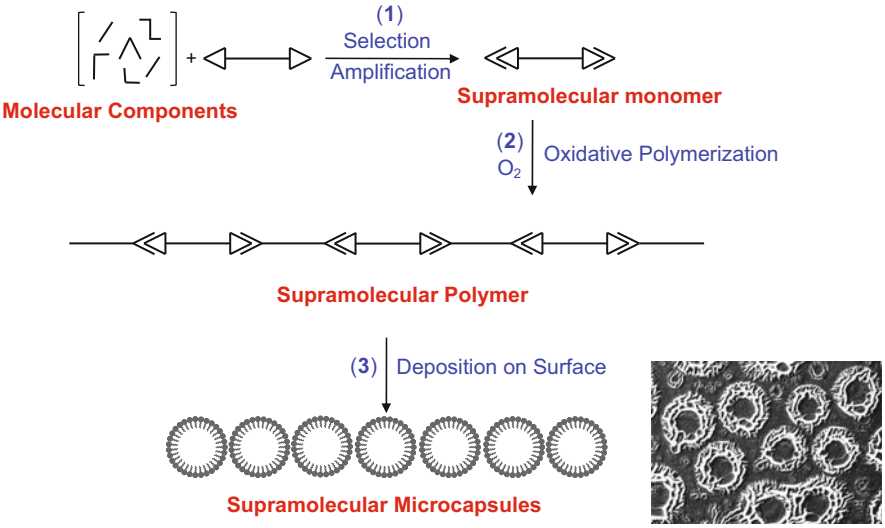

Fig. 4 Formation of a supramolecular polymer by covalent connection between pre-formed supramolecular monomers, involving the following steps: (*1*) formation of a ditopic supramolecular monomer by amplification of the complementary partner from an equilibrating set of constituents; (*2*) generation of the supramolecular polymeric chain by establishment of covalent C–C bonds between the monomers through oxidative coupling; and (*3*) generation of supramolecular microcapsules of about 5–10 μm diameter on surface deposition, with characterization by SEM imaging (see [60] for more details)

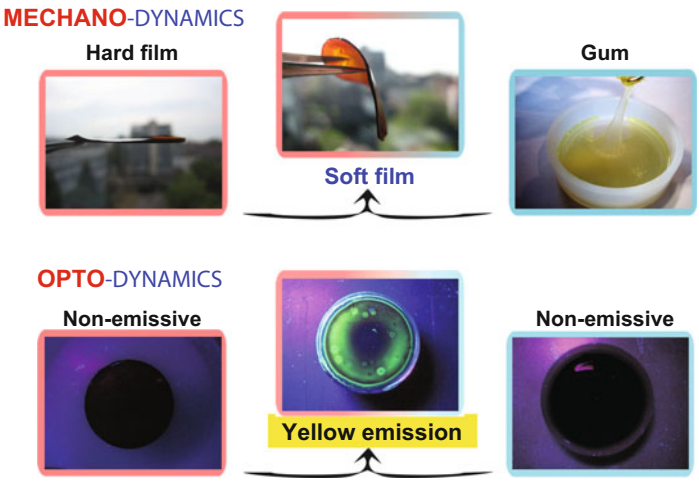

Fig. 5 Dynamic modification of the mechanical and optical properties of two metallodynamers by recombination of their components via ligand exchange coordination dynamics. *Top*: Mechanical change involving blending of a hard film and a gum into a soft film. *Bottom*: Optical change produced by blending of the two non-emissive dynamers into a material presenting a yellowish emission (see [54] for more details)

Of great interest is the ability of dynamers, and of constitutional materials in general, to undergo supramolecular or molecular self-healing through reoganization and/or reestablisment of non-covalent interactions or of covalent bonds, thus offering opportunities to develop mendable polymer materials [76–80] of supramolecular [59, 81–85] or molecular [67, 86, 87] type, based for instance on the implementation of reversible Diels–Alder reactions [67, 76, 86, 87].

Biodynamers are dynamic analogs of biopolymers and may be derived by connecting biological-type (biologous) building blocks through reversible linkages. Hybrid entities are obtained when biological and nonbiological partners are combined within the same dynamer. Thus, dynamic analogs of nucleic acids, DyNAs, are generated as cationic dynamers bearing nucleobase residues, whose polymerization is driven by the binding of polyanionic substrates [88] (see also figure 9 in [42]).

Hybrid dynamic proteoids, containing alternating imine and acylhydrazone linkages, have been obtained by polycondensation of amphiphilic dialdehydes with amino acid hydrazides. The polymerization displays nucleation–elongation behavior driven by hydrophobic effects, resulting in the formation of globular particles reminiscent of folded proteins (Fig. 6) [89].

Glycodynamers of main-chain type (Fig. 6) [90] or resulting from the polycondensation of monomers bearing lateral glycosidic residues [91, 92] (see also figure 8 in [42]) have been obtained. In the latter case, the formation of a compact bottlebrush type of structure results in a fluorescent dynamer entity. The dynamic nature of this glycodynamer is demonstrated by the progressive constitutional conversion of a compound presenting a blue emission into one emitting green light by component exchange on addition of the adequate partner (Fig. 7) [91, 92].

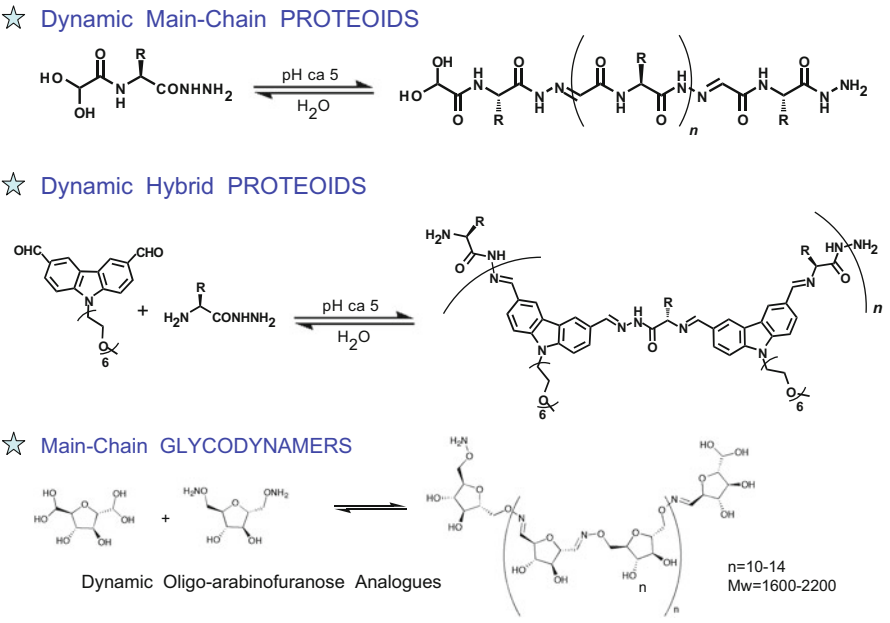

Fig. 6 Biodynamers. Dynamic proteoids generated by polycondensation of either hetero-ditopic amino acid derivatives (*top*) or of an aromatic hydrazide with an amphiphilic dialdehyde (*middle*). Formation of main-chain glycodynamers: dynamic oligo-arabino-furanose analogs (*bottom*)

3.3 Dynamers with Multiple Dynamic Processes

A marked widening of the field is offered by dynamic polymers that incorporate several, preferentially orthogonal, dynamic processes. For instance, there could be two different covalent processes (e.g., based on disulfide and hydrazone groups) [93], two different non-covalent processes (hydrogen bonds and metal ion coordination) [94–97], a covalent together with a non-covalent process (e.g., imine groups and hydrogen bonding or metal ion coordination) [53–55, 98], or three types of dynamics (disulfide, imine, and coordination) [99]. Such features are presented by double dynamic supramolecular polymers whose main chain is built on H-bonding and imine groups [98] as well as by the neutral metallodynamers incorporating metal coordination centers and imine groups [53–55].

4 Dynamers: Adaptive Features

The most far-reaching general feature of CDC is that it gives access to the next step in complex matter behavior, that is to systems capable of adaptation through constitutional variation by dynamic selection of components, which is on the road

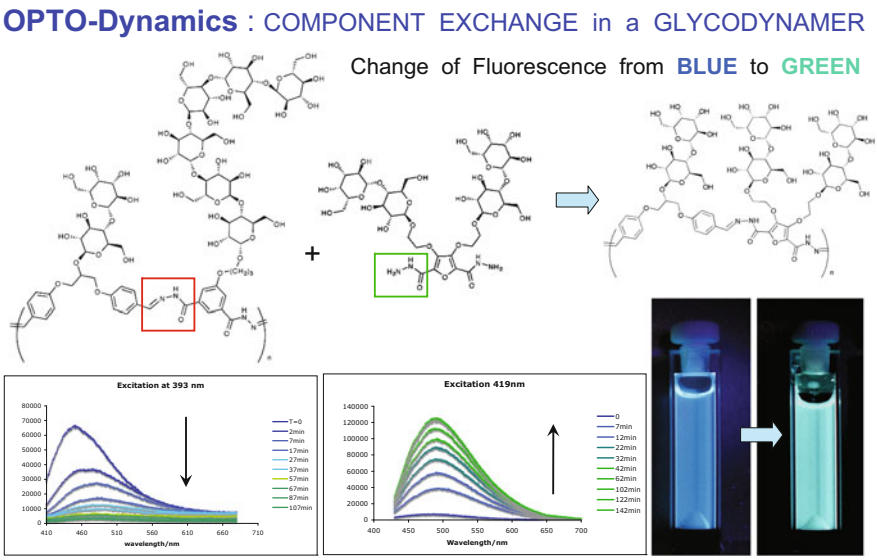

Fig. 7 Dynamic optical effects in glycodynamers. *Top*: Progressive conversion of a main-chain acylhydrazone-based dynamer, fitted with glycosidic side chains, presenting a blue fluorescence (*left*), into another dynamer displaying green fluorescence by exchange of its bis-hydrazide component for an added bis-hydrazide monomer (*center*), resulting in a novel glycodynamer incorporating the new component (*right*). The reacting functions are marked by *boxes*. *Bottom*: Evolution of the emission spectra as a function of time under different excitation wavelengths, and actual optical change observed in fluorescence cells (*right*)

towards adaptive chemistry [41, 43]. Thus, supramolecular as well as molecular dynamers may undergo adaptation in response to physical stimuli such as temperature [100, 101], light, pressure, phase change (for crystallization-driven constitutional change of metallodynamers in response to neat/solution conditions, see [102]), or electric field (for the response of a dynamic library of liquid crystalline compounds to an electric field, see [103]) as well as to chemical effectors such as protons [100] and metal cations [104–107]. In general terms, a library of dynamers built on a sufficiently diverse set (a sort of "complete" set!) of monomeric components should in principle be able to respond to various stimuli or effectors and undergo component rearrangement by recombination of interactions or bonds. This would enable the generation of a dynamer whose constitution would be best adapted to respond to a particular stimulus on the basis of the set of components available. In addition, a given dynamer thus formed may express or induce a specific functional property (Fig. 8).

Thus, the cooperative, bottom-up polycondensation of amphiphilic monomeric components driven by hydrophobic effects generates rigid-rod nanostructures [108] and yields thermoresponsive dynamers presenting thermally induced, reversible chain elongation with a change in physicochemical behavior from a soluble polymer at low temperature to aggregation into large bundles or fibers at higher temperatures

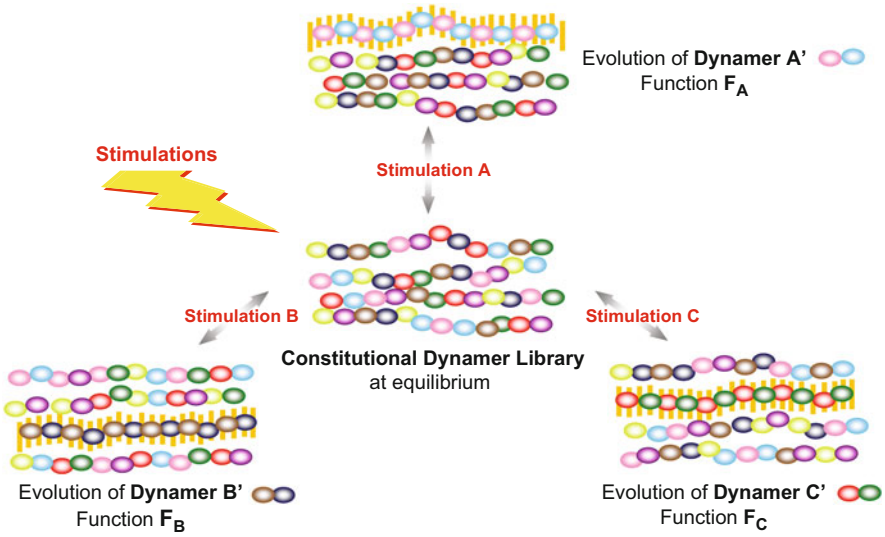

Fig. 8 Towards adaptive functional materials. Constitutional adaptation of a library of dynamic polymers in response to different stimulations *A*, *B*, and *C* that drive a component rearrangement leading to evolution of the system towards the generation or amplification of the best-suited, "fittest," dynamer *A′*, *B′* and *C′*, respectively (*highlighted*). As a consequence, specific functional properties F_A, F_B, and F_C may be induced. The stimulations may be physical factors (temperature, pressure, light, electric or magnetic field, etc.) or chemical effectors (protons, metal ions, substrate molecules, medium, etc.)

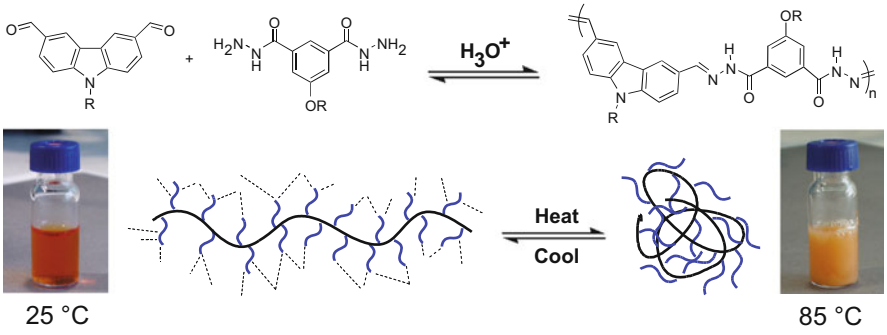

Fig. 9 Thermoresponsive dynamers. *Top*: Generation of an amphiphilic poly(acylhydrazone). *Bottom*: Inverse thermal response to heat stimulation, with thermally induced, reversible size modification through large and reversible polymer growth in response to an increase in temperature

(Fig. 9) [109]. The process is also sensitive to acidity, so that the system displays double control of the dynamer state by two orthogonal agents: a physical stimulus, heat, and a chemical effector, protons. It thus represents a prototype for dynamic

materials displaying multiple control adaptive behavior. Significantly, the process presents strong component selection driven by medium/hydrophobic effects. The process generates the dynamer that incorporates the monomer possessing the largest hydrophobic area into the compact rod-like nanostructure so as to minimize contacts between hydrophobic residues and water [110] (see also figure 13 in [42]).

The constitutional plasticity of constitutional dynamic materials endows them with tunability and responsiveness to stimuli, as for instance in the transport features of dynamic polymer membranes [111], in the stimuli-responsiveness of supramolecular polymeric materials [112], and in the design of adaptable functional materials and devices [113–115].

5 Adaptive Polymer Networks Towards a Systems Materials/Polymer Science

The behavior of adaptive chemical systems can be conceptualized in terms of adaptive networks. Such a representation also applies to adaptive materials, and in particular to dynamic polymers. I shall recall here some points made earlier [41, 43, 116] and present some additional aspects that will be expanded in more detail on another occasion.

The sets of dynamically interconverting constituents generated by CDC that are connected structurally (molecular and supramolecular arrays) and eventually also through reaction (sets of connected reactions) define constitutional dynamic networks (CDNs). These CDNs may couple to either reversible or irreversible thermodynamic processes and present a specific stability or robustness with respect to external perturbations. The constituents present agonistic and antagonistic relationships depending on whether the increased expression of a given constituent decreases or increases one or more of the others. Thus, feedback between the linked species leads to simultaneous upregulation/amplification or downregulation of the different constituents depending on the type of connection.

CDNs may be represented by weighted graphs, in which vertices, edges, and diagonals represent the connections between the members of a set, their agonistic or antagonistic relationships, as well as their relative weights. The simplest case is that of four constituents, AB, AB′, A′B, and A′B′, located at the corners of a square and generated from four components A, A′, B, and B′ by reversible connection of A, A′ with B, B′. If, for example, subjecting such a system to the action of a physical stimulus or to the interaction with a chemical effector, E, drives the upregulation of AB, it will simultaneously amplify its agonist A′B′ and downregulate its antagonists AB′ and A′B, with which it shares a component (see also figure 14 in [116]). Thus, CDNs are adaptive, responding to the action of various factors by a change in the weight or fraction of the different linked constituents, and may be termed adaptive constitutional networks (ACNs).

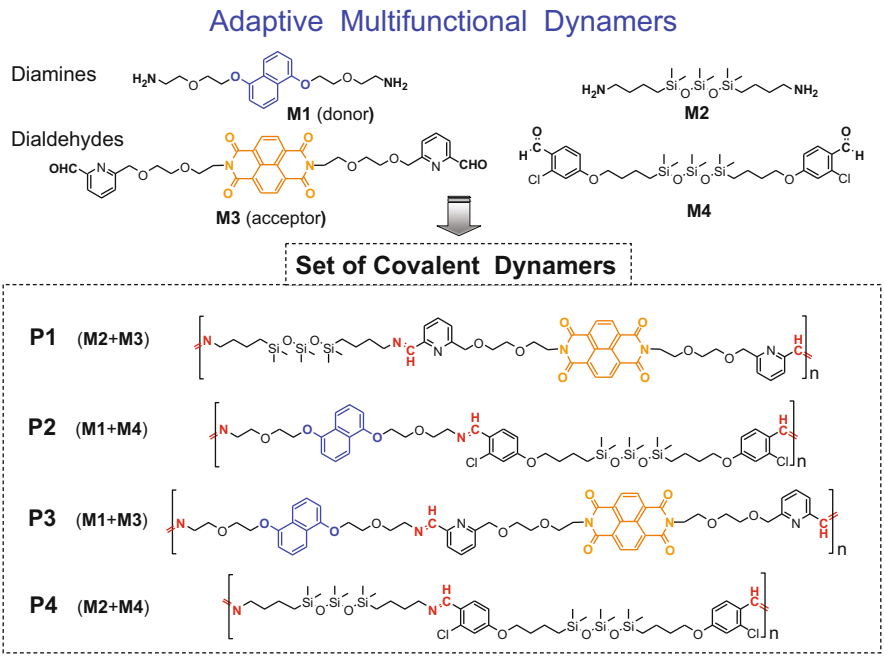

Fig. 10 Generation of a set of four multifunctional dynamers **P1**, **P2**, **P3**, and **P4** via reversible imine formation between two diamine monomers **M1** and **M2**, and two aldehydes **M3** and **M4**, containing non-covalent supramolecular interaction subunits: a donor (**M1**), an acceptor (**M3**), a potential cation binding fragment (**M1** and **M3**) and a "neutral" linker (the dimethylsiloxane units in **M2** and **M4**)

It has been pointed out that an intriguing feature of such ACNs is that agonistically related constituents amplify each other [43]. As a consequence, enhancement of the "fittest," in response to a given effector, also induces promotion or survival of the "unfittest" (with respect to an effector or a set of conditions)! It may well happen that the unfittest for a given effector E may present specific desirable properties, so that the effector E may be used to indirectly drive amplification of the unfittest and thus the generation of these properties.

These considerations also apply to a set of dynamic polymers undergoing redistribution of the monomeric components when subjected to the action of various factors (Fig. 8). They will be illustrated here by the case of multifunctional dynamers responding to the interaction with metal cations [107]. Thus, the four monomers **M1**, **M2**, **M3**, and **M4**, containing respectively a donor (**M1**), an acceptor (**M3**), a potential cation-binding fragment (**M1** and **M2**), and a "neutral" linker (the dimethylsiloxane units in **M2** and **M4**), generate the set of four dynamers **P1**, **P2**, **P3**, and **P4** through reversible imine formation between the diamines **M1**, **M2** and the dialdehydes **M3**, **M4** (Fig. 10).

The dynamer **P3** assembles the donor, acceptor, and cation binder subunits into the same chain. Starting with the initial composition of the set of covalent

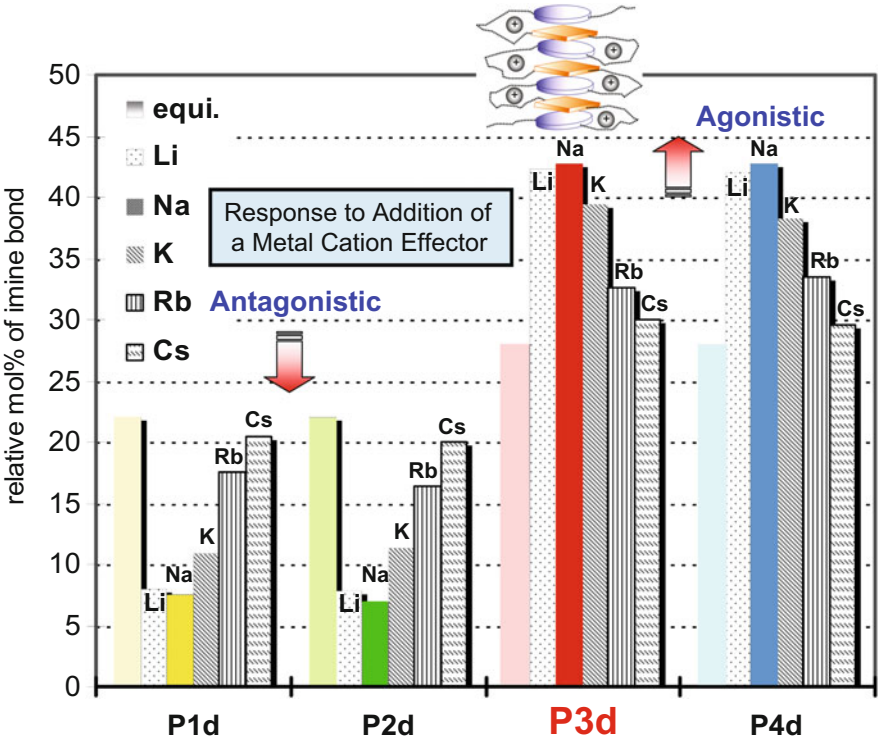

Fig. 11 Adaptation of the set of multifunctional dynamers **P1**, **P2**, **P3**, and **P4** (see Fig. 10) by variation in constitutional distribution in response to the addition of alkali metal cations Li^+, Na^+, K^+, Rb^+, and Cs^+. The initial relative amounts of the four dynamers are shown in *pale colors* (on the *left* of each set). Large variations in relative amounts are observed on addition of alkali metal cations. A marked increase in the fraction of the trifunctional dynamer **P3**, containing the donor, acceptor, and cation binding fragments, occurs as a result of its ability to bind alkali cations in a helically folded form (shown in the *top middle*). The fraction of its agonist **P4** is increased similarly, whereas the fractions of antagonists **P1** and **P2** are strongly decreased. The changes occurring in the case of Na^+ are shown in *darker colors*. *P1d*, *P2d*, *P3d*, and *P4d* indicate the repeat units of the four corresponding dynamers

dynamers, the addition of alkali metal cations results in a redistribution of the monomeric components between the members of the set, leading to a marked modification of the fractions of the four constituents. The effect is largest for lithium, sodium, and potassium ions, which bind best to the receptor site formed on helical wrapping of the **P3** dynamer chain, favored also by interaction between the donor and acceptor subunits brought into proximity (Fig. 11). In addition, the latter feature induces a color change. Considering more specifically the sodium cation effector, the four dynamers can be arranged in a square network, in which the couples **P1**, **P2** and **P3**, **P4** are agonists (connected via the diagonals) and are respectively both repressed and amplified (Fig. 12). Thus, this system displays adaptation by dynamer redistribution, with component selection as well as agonist

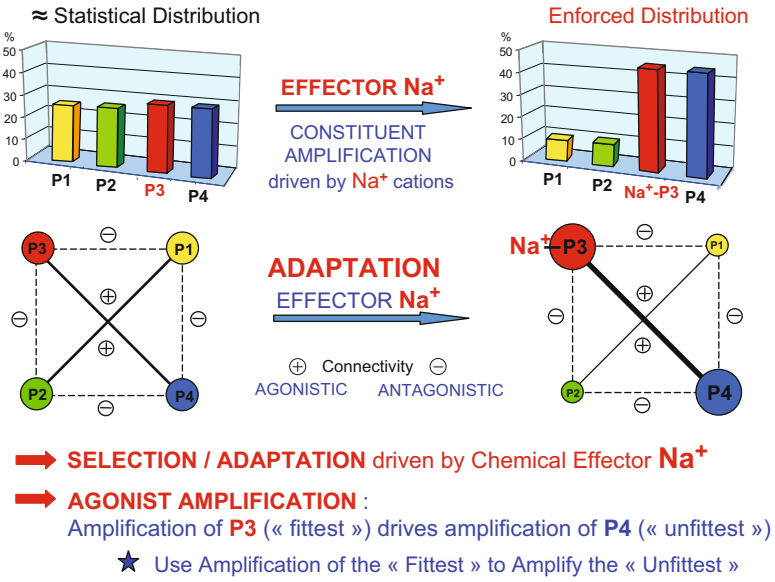

Fig. 12 Adaptive networks of constitutional dynamic polymers. Two-dimensional network representation of the effector-driven adaptation of the set of dynamers **P1**, **P2**, **P3**, and **P4** in response to a chemical effector, the sodium cation Na^+ (see Fig. 11). The initial, close to statistical distribution of the four dynamers is strongly modified by addition of the cations, leading to an enforced distribution that displays a strong upregulation of **P3**, which binds Na^+, and the simultaneous increase of its agonist **P4**, whereas the antagonists **P2** and **P3** are strongly downregulated

amplification. The upregulation of **P3**, favored by both cation binding and donor–acceptor interactions, also simultaneously increases **P4**, which presents neither of these two properties. However, **P4** might confer to the system some other desirable property(ies), such as softness. A great variety of sets of dynamers may be imagined and implemented for the generation of various tunable properties.

6 Conclusion

It is clear that, since the pioneering work of Hermann Staudinger, the science and technology of polymer chemistry has grown immensely, enriched by the work of innumerable research and engineering laboratories, and it will continue to do so. The present contribution tries to paint one aspect of the full picture and to point to some lines of development. The incorporation of constitutional dynamics opens new perspectives. The analysis above may be extended to any set and network of dynamers, with more constituents, for which application of a given action will lead to a complex constitutional variation, resulting in a novel set of

features (optical, mechanical, chemical, etc.) whose occurrence may in principle be fine-tuned via a stimulus or effector. One may thus foresee an implementation of CDNs generated by CDC for the development of tunable adaptive materials and, more broadly, the advent of systems polymer/materials science in line with the emergence of systems chemistry.

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From Synthetic Macromolecules to Biological-Like Complex Systems

Virgil Percec

Abstract "His Majesty the Hirohito Emperor of Japan asks: Professor Staudinger, is this a concept that came into your mind to explain various phenomenological behaviors of a group of compounds or did you really prove their existence by rigorous scientific means? The highly impressed Professor Staudinger answers: It is this experimental demonstration of the existence of macromolecules which forms the essential part of my work in the field of Macromolecular Science." From the discussion between the Emperor of Japan and Professor Staudinger on 17th of April 1957 at the Imperial Palace of Japan

Keywords Biological mimics · Macromolecules · Self-assembly · Supramolecular Chemistry

Contents

1 Hermann Staudinger Haus 174
2 What Did Hermann Staudinger Do Conceptually New for Organic Chemistry? 177
3 From the Discovery of Self-Assembling Dendrons, Dendrimers, and Dendronized Polymers to a Materials Genome Approach to Biological-Like Complex Systems 179
4 Mediating Chemical Reactivity and Backbone Conformation with Spherical and Globular Visualizable Macromolecules Generated from Quasi-Equivalent Self-Assembling Dendrons 184
5 Transforming a Helix–Coil into a Helix–Helix Transition and Eliminating Intramolecular Electrocyclization 186
6 Dendritic Dipeptides as Aquaporin Transmembrane Protein Mimics 188
7 Self-Assembly of Amphiphilic Janus Dendrimers into Monodisperse and Stable Dendrimersomes 190
8 Glycodendrimersomes as Mimics of Biological Membranes 192
References 193

V. Percec (✉)
Roy and Diana Vagelos Laboratories, Department of Chemistry, University of Pennsylvania, Philadelphia, PA 19103-6323, USA
e-mail: percec@sas.upenn.edu

1 Hermann Staudinger Haus

In 1981 between March 4 and 7, I attended the "Makromolekulares Kolloquium" organized by the Institut für Makromolekulare Chemie in Freiburg. For many years this traditional meeting was held in "Im Grossen Hörsaal Biologie I," near the Institute. This lecture room could accommodate about 500 people and it was always full. The 1981 meeting was dedicated to the 100th Anniversary of Hermann Staudinger and during this event the name "Hermann Staudinger Haus" was added to the name of the Institute. Hermann Francis Mark and Magda Staudinger attended this Anniversary. I had met Hermann F. Mark during the days when I was an undergraduate student in Iasi, Romania. However, this was the first and last time I met Magda Staudinger. I recall that the last student of Hermann Staudinger, Helmut Ringsdorf, mediated with Magda Staudinger to have Hermann F. Mark attend this Anniversary. The first symposium ever organized in Hermann Staudinger Haus was, most probably, a very small bilateral Seminar on Macromolecular Chemistry between Iasi and Freiburg, that took place immediately after the 1981 Makromolekulares Kolloquium. I also attended this seminar and presented two lectures. The Universities of Iasi and Freiburg had a collaboration that continues today, and Hans-Joachim Cantow, one of the followers of Staudinger, quite often used to visit the University in Iasi, where I met him during my Ph.D. studies. He facilitated this joint Iasi–Freiburg seminar. These were very special days in my professional carrier since almost every important scientist in the field of macromolecular chemistry from Germany, France, Austria, and Switzerland, with a few selected guests from the USA and other countries, would attend and continue to attend this colloquium. Very condensed invited lectures were followed by extensive discussions, short talks, and posters, all taking place in the very charming city of Freiburg, located near the ski resorts of the Black Forest and the Swiss Alps, making this meeting a "must attend" scientific event. This was one of my first trips to a Western country after many years of not being allowed to travel even to an Eastern country.

This situation changed in 1978 when my mentor Cristofor I. Simionescu could not attend the IUPAC Symposium on Macromolecules that took place in Tashkent, USSR (October 17–21, 1978). Because his Invited Lecture was part of my Ph.D. thesis and was prepared by me, he made the necessary arrangements to send me to present this lecture. This was my first trip to any country after 7 years of being prohibited to travel. This was about 1 year after the defense of my Ph.D. thesis and I was scared when I looked at the audience. All the scientific big names that I knew only from textbooks and publications were sitting in the first rows waiting to see what was going on with this underage "Invited Speaker." I survived the discussions that followed my lecture. At the end of the lecture, Helmut Ringsdorf stood up from the first row and came over to me to introduce himself. I knew the name, but I would not have even dared to talk to him. He said that he enjoyed my lecture very much, in which I was talking about the synthesis of the *cis*- (some of the first helical

conformations accomplished in synthetic polymers) and *trans*-stereoisomers of polyphenylacetylene and other polyarylacetylenes and their structural analysis by NMR. This will be discussed later in this publication. Most of the work presented was on the synthesis of the *cis*- and *trans*-stereoisomers of poly(pentadeuterophenylacetylene) because there was a single proton in the NMR spectrum of the repeat unit of the polymer and its structure could be analyzed in great detail. Briefly, the *cis*-isomers do not undergo *cis–trans* isomerization but instead an intramolecular electrocyclization. Ringsdorf continued by saying that he would like to invite me to the IUPAC Symposium on Macromolecules that would be organized in Mainz. My answer was brief: "I would be very happy to attend, but unfortunately I am not allowed to travel." At this point, Ringsdorf interrupted our discussion. He said, "since you are an Invited Speaker like me, you must have a car and a driver as I have and an accompanying person as a translator. Ask the driver to follow my car. We will go outside the city into the nearby forest. Ask the accompanying persons to let us spend some time alone walking in the woods, and we will continue to talk about your story." This discussion led to a lasting friendship, scientific inspiration, and long-lasting appreciation for the Staudinger scientific family. Cantow was a very curious, dedicated, and friendly scientist but I did not know that so many from the Staudinger scientific community were not only dedicated to science but also concerned with the lives of other scientists. This discussion also facilitated travelling to scientific meetings, including the 1981 Makromolekulares Kolloquium in Freiburg. However, after returning home from Freiburg I did not get permission to travel again.

I will not disclose here how I ended up a few months later at the IUPAC on Macromolecules in Strasbourg (July 6–9, 1981). I gave my presentation and afterwards I met Ringsdorf, who gave me some good news. He said, "we have just finished the Editorial Board meeting of *Polymer Bulletin* (which was the fastest publishing journal in the field at that time and, due to its highly regarded editors, Hans-Joachim Cantow, Joseph P. Kennedy and Takeo Saegusa, had a very high reputation) and you were elected to its Editorial Board." I had to confess to him that I had just decided not to return to my native country. Ringsdorf said, "this could delay our decision because we may not want to let your country believe that you were elected because you defected." He returned to the Editorial Board meeting and, indeed, this was the final decision: elected, but to be printed on the Editorial Board 1 year later. In my mind I said: "Welcome to the Western civilization!" Cantow was the next to learn of my decision to defect. He was quick in his answer: "You would be welcomed in Freiburg if you would like to join us." A few days later I was in Freiburg at the Hermann Staudinger Haus. I got a bench in the laboratory and started to do experimental work the same day. Cantow gave me all the freedom. Even today, I believe that at that time Hermann Staudinger Haus was the best place on this planet to do research in macromolecular chemistry. Hans R. Kricheldorf, Claus D. Eisenbach, Manfred Schmidt and many others were doing their "Habilitation" and soon became professors all over Germany. Martin Moller and Reimund Stadler were doing their Ph.D.s in Cantow's group. There were more seminars by visitors from all over the world than you had time to attend. Walter H. Stockmayer

had a permanent office in the Haus. Gerhard Wegner and Hans-Joachim Cantow were doing research at the top of the field and, at the same time, they were some of the best science administrators I have ever met. Everybody had lunch and dinner at the cafeteria across the street and there was nothing unusual to see people working in the laboratories at 1 or 2 am. Initially, I thought that all were immigrants like me but soon I learned that they were not. This was the working style in the Haus at that time. Hermann Staudinger Haus was excelling in "as good as possible structural analysis and characterization of the organic molecules and macromolecules," just as Staudinger did in his own work, to convince the world about macromolecular compounds being what they are. Both Cantow and Wegner explained everything I needed to know about being a scientist on any continent and in any country in this world since both had been postdoctoral students in the USA and felt at home in any country where the word "polymer" was known. Cantow and his wife took a vacation for a while and let me stay in their home. They said, here is the house, one car, the refrigerator with everything needed to eat, the swimming pool, and the wine cellar. Use everything you need. I used only one of their bicycles. Before the end of August, Joseph P. Kennedy learned about my decision and renewed an invitation to join his laboratory, which previously I had to refuse due to travel restrictions. When I considered going to the USA, Cantow asked, "why not stay in Germany?" I said, "I have a wife and a young daughter; what do I do here, and how do I bring them here?" His answer was that he believed that I would be a professor in Germany quite soon. I knew that I was an immigrant and I flew to USA several days before my passport was going to expire. One of the first people that I met after joining Kennedy's laboratory was Hermann F. Mark, who was attending an Anniversary of the Institute of Polymer Science from the University of Akron. While I was shaking his hand I reminded him that I had met him when he visited Iasi many years ago. He looked at me and said, "of course I remember you!" How could he when there were so many undergraduates like me in the same laboratory with me during his visit many years ago to Iasi? But he was a charming person. When I mentioned that I had decided to stay in the USA, he immediately continued, "Virgil, welcome to this country! Now you are one of Ours!" This statement by Hermann F. Mark set the beginning of my life in the USA and made me never regret that I never definitively returned to Europe on the many occasions that I was offered the opportunity. About 1 month later, I heard that Ringsdorf was giving a plenary lecture at the local ACS meeting in Rochester, New York. I borrowed a car and drove for the first time in my life on a highway during a strong rain with a driving license from a country I was sure that no policeman in the USA had ever heard of. I saw Ringsdorf at the end of his lecture. He was talking to a very young man whom he said to me that I must know. I shook the hand of the young man and he told me his name: David Tirrell. Ringsdorf took the rest of the day off from the meeting and advised me on science and life in the USA. The comments of Wegner and Ringsdorf on living in the USA were as good and reliable as their science. After 5 months in Kennedy's laboratory I joined Case Western Reserve University as a

faculty member and continued to go back to Hermann Staudinger Haus at least once a year, several times as visiting professor and many times accompanied by some of my graduate students. One day after we returned to the USA, one of my graduate students, Brian Auman now at the Experimental Station of DuPont, asked me to let him spend one extra year in Freiburg, as I promised all of them. When he returned to the USA after the extra year in Freiburg, with the young secretary of Cantow as his wife, I thought that this was the end of my visits to Hermann Staudinger Haus. But, my visits to the Haus in Freiburg continue even today. In 2012, I gave the opening lecture at the Makromolekulare Kolloquium in Freiburg. I checked the new lecture room the evening before. More than 1,000 people could be accommodated in this lecture room. On the morning of my lecture there was not a single empty sit, even for me, and many people were standing up. Cantow, Ringsdorf, and the current directors were in the first row. In 2013, I lectured during the 90th Anniversary of Cantow in the same full lecture room. I wished Hermann and Magda Staudinger could have seen the more than 1,000 people in the audience of their Kolloquium. Their Haus has educated many generations of scientists, shaped their lives, and continues to do so on a much larger scale than when they knew it.With one exception, I never could turn down a request from the scientists of the Staudinger scientific family. About 10 years after I came to the USA, Hermann F. Mark called my office and asked me to become an Editor of the *Journal of Polymer Science: Part A: Polymer Chemistry*, which he founded in 1946. I answered as politely as I could that I felt I was too young to invest my time in editorial work. He did not object. Quite a number of years later, David Tirrell called and asked me again to be Editor. I debated with him the same way as with Hermann F. Mark but ultimately he convinced me. His argument was: "You will learn more about the life of scientists than in any other way!" When Tobias Wassermann from Springer invited me to be the Editor of this special issue of *Advances in Polymer Science* dedicated to the 60th Anniversary of the Nobel Prize of Hermann Staudinger, my first reaction was to turn it down because it takes a lot of time to convince the "right people" to write a brief review or story. However, I remembered David Tirrell's advice and everything Hermann Staudinger Haus had done for many of us. David was one of the first to accept my invitation to write for this issue.

2 What Did Hermann Staudinger Do Conceptually New for Organic Chemistry?

Hermann Staudinger was a highly regarded organic chemist who contributed substantially to the field of traditional organic chemistry. From the discovery of ketenes [1] to the elaboration of the "Staudinger reaction" or "Staudinger reduction" of azides with phosphines [2], his high organic chemistry credibility was

essential to the development of macromolecular chemistry [3, 4] (for a brief review of the scientific activities of Staudinger see [5]) as the newest branch of organic chemistry. Elaborations of the Staudinger reaction into the Staudinger ligation [6] and other methodologies continue even today. Very few new fields of organic chemistry have developed since then, the most notable being supramolecular chemistry [7], but none of them has produced the scientific and technological impact to become a separate independent department as macromolecular chemistry has done. The following event marks in the simplest way the impact of Staudinger on organic chemistry. On 17th of April 1957, Hermann Staudinger gave a 20 min lecture on macromolecular chemistry at the Imperial Palace invited by the Emperor Hirohito of Japan, who was educated as a biologist. At the end of the lecture, The Emperor asked the following question about macromolecules: "Is this a concept that came into your mind to explain various phenomenological behaviors of a group of compounds, or did you really prove their existence by rigorous scientific means?" Staudinger was highly impressed by this question and answered: "It is this experimental demonstration of the existence of macromolecules which forms the essential part of my work in the field of macromolecular science." This discussion expanded the lecture time from 20 min to 1 h. For more details about this visit to Japan see publications in this issue by Helmut Ringsdorf [9] and by Akihiro Abe [8]. The Nobel Lecture of Hermann Staudinger [4] impresses mostly through the use of organic chemistry methods like polymer analogous transformations to demonstrate the covalent rather than colloidal nature of the macromolecules. He elegantly states: "The only difference between macromolecules and the small molecules of low molecular substances is one of structural size. . . . Possibly the most important distinction between low molecular and macromolecular compounds is that the latter can exhibit properties which cannot be predicted even by a thorough study of the low molecular substances." He realizes also the role of diversity in architectural design by stating: "With a few bricks it is impossible to erect a great variety of buildings; nevertheless, provided that 10,000 or 100,000 bricks are available it is quite possible to construct the most diverse buildings, vis, houses, halls, etc., the special construction of which cannot simply be predicted from the buildings comprising few bricks." He gives credit to Magda Staudinger, a biologist, as being " the originator in particular of new considerations in respect of the relations between macromolecular chemistry and biology." He recognized that synthetic macromolecules "are inseparable mixtures of polymer homologous series . . . while some natural polymers are monodisperse." Staudinger's Nobel Prize and his Nobel Lecture [4] were in parallel with the discovery of the double helix of DNA, published in *Nature* by Watson and Crick [10] and, therefore, the concluding remark to his Nobel Lecture is timely even today: "In the light of this new knowledge of macromolecular chemistry, the wonder of life in its chemical aspect is revealed in the astounding abundance and masterly macromolecular architecture of living matter." It took a little time until his last student, Ringsdorf, was able to bridge the gap between macromolecular chemistry, biology, and medicine, which is a subject of great fundamental and technological interest in the fields of organic, macromolecular, biological, and supramolecular sciences today.

3 From the Discovery of Self-Assembling Dendrons, Dendrimers, and Dendronized Polymers to a Materials Genome Approach to Biological-Like Complex Systems

In 1982, a year after the naming of Hermann Staudinger Haus, while continuing to develop methodologies for polymer and organic chemistry, our research in Case Western Reserve University departed from the work done in Iasi, in Hermann Staudinger Haus, and in Kennedy's laboratory. The most influential on our way of thinking were Aaron Klug [11, 12], with his work on the elucidation of the assembly of rod-like and icosahedral viruses; Helmut Ringsdorf [13], with his work on liquid crystals and mimics of biological membranes; and Jean-Marie Lehn [7, 14–17], with his work on supramolecular chemistry and supramolecular polymers. I was particularly influenced by a lecture of Klug on his work, which immediately received the Nobel Prize [11], in which he stated: "The study of the structure of a virus or an assembly of molecules in a cell helps us to understand how they function in complex biological systems." This sentence is usually interpreted to mean "structure determines function" and the methodology represents the definition of structural biology and of molecular biology. Structural and molecular biology elucidate the functioning of complex biological assemblies by determining their structure under conditions as close as possible to those encountered in vivo. The role of chemistry is to predict the structure that provides a function. Therefore, we decided to develop a building block that would mimic the structural events exhibited by biological macromolecules such as proteins, but be simpler to synthesize in a large diversity of monodisperse structures and, further, to elaborate the principles that are required to predict the primary structure of a macromolecule that determines a particular function (Fig. 1). Being able to mimic at least at the most primitive level, the self-assembly of rod-like and icosahedral viruses with synthetic monodisperse macromolecules, as Klug elucidated by his work, would be a good starting point. For a number of years we had no good ideas on how to approach this problem. The Story of the discovery of self-assembling dendrons and dendrimers and self-organizable dendronized polymers is reported in more detail elsewhere and therefore it will be mentioned only briefly here.

One day during the mid-1980s, Alfred Saupe came to my office with two publications. The first one was on the first lyotropic biaxial nematic liquid crystal [18]. The second publication was a brief communication reporting the first thermotropic biaxial nematic liquid crystal [19]. The thermotropic biaxial nematic liquid crystal was only monotropic. Saupe mentioned that Helmut Ringsdorf advised him to contact me in order to help him transform the monotropic phase into an enantiotropic one. I looked at the structure of the molecule published by Malthête [19] and I explained to Saupe that this would be a simple experiment: functionalization of the molecule (consisting of a combination of disc-like and rod-like segments) at the end of the rod-like part with a polymerizable group that after polymerization should transform the monotropic phase into an enantiotropic phase (Fig. 2).

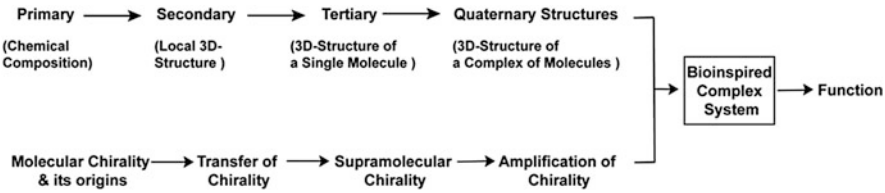

Fig. 1 Designing functions via "first principles" represents a "materials genome approach to functions"

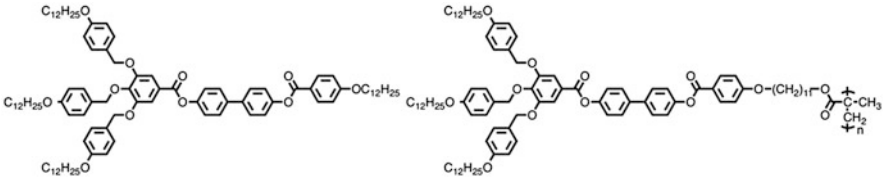

Fig. 2 Malthête "biaxial nematic" [19] and Jim Heck's corresponding polymer [23–25]

This was a well-established event in the field of side-chain liquid crystal polymers, as pioneered by Ringsdorf [20] (for a brief account of the first 100 years of research in liquid crystals, Staudinger's connection to them, and the meeting with Ringsdorf in Tashkent in 1978 see [21]), and had been explained theoretically by our laboratory in collaboration with Andrew Keller [22]. I immediately called the junior graduate student Jim Heck to my office and gave him this short project. I expected it to be a routine experiment. The first discovery by Heck was that the extremely pure molecule duplicating Malthête's structure did not display a biaxial nematic phase. This was later published but we did not want to co-author this paper. I asked Heck to synthesize libraries of related molecules and their corresponding polymers. All of them failed to produce the expected result [23]. A more detailed report of this story was published (for a more detailed account of these experiments see [24]; for a comprehensive review on dendron-mediated self-assembly, disassembly, and self-organization of complex systems containing also the structures synthesized by Heck see [25]). One day, Heck said that he did not want to continue on this project and showed me Fig. 3, displaying the supramolecular structures he expected to result from this research failure (a more detailed version of Fig. 3 is figure 14 in [25]). They all looked like the structures of Tobacco Mosaic Virus (TMV) elaborated by Klug. Although Heck was disappointed by these results, I started to smile and dream of the building blocks that would mimic the self-assembly of TMV. At that time, Keller was a visiting professor in our department and I showed him these structures. His comment was: "Fire this student. Since when can organic chemists predict the crystal structure of organic molecules?" I did not fire Jim Heck and, subsequently, Goran Ungar from Keller's laboratory demonstrated that indeed the structures predicted by Heck (Fig. 3) were correct.

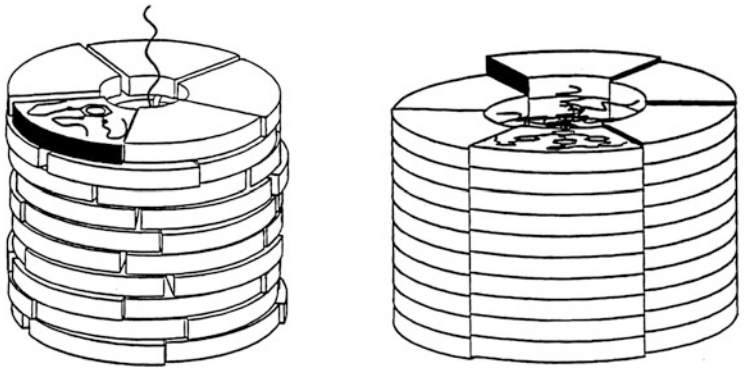

Fig. 3 Jim Heck's models. A helical polymer backbone induced by the supramolecular column assembled from tapered dendrons jacketing the backbone (*left*) and a tubular helical polymer without a polymer backbone (*right*)

The low molar components were the first examples of first generation self-assembling dendrons, and their polymerized structures were the first examples of self-organizable dendronized polymers [23–42]. However, once time-consuming crystallographic studies were involved, the publication of this work was delayed by many years [26–42]. A series of invited reviews of this early and later work were published [24, 25] (for early and more recent reviews on this topic see [43–58]). In addition, these initial "research failures" were not published in prestigious journals. By using the disc-like fragment of the repeat unit from Fig. 2, Heck wanted to prepare even higher generation dendrimers. I was not enthusiastic because dendrimers were already known, even if these molecules were made by the reverse process of that elaborated by Tomalia [59]. Nevertheless, higher generations of these AB_3-based self-assembling dendrons and dendrimers were ultimately synthesized by Jim Heck, resynthesized by Gary Johansson, and after many years of X-ray, electron diffraction combined with molecular models, simulation and electron density map studies they demonstrated globular [60] or icosahedral, rather than rod-like, structures that were self-organizable into new periodic and quasi-periodic lattices [60–68] including the first organic quasi-crystals [65]. In order to elucidate the correlation between the primary structure of the self-assembling dendrimer and its supramolecular structure, a "generational" approach to libraries of self-assembling dendrons based on constitutional isomeric AB_2 and AB_3 self-assembling dendrons was elaborated [69–71]. As expected, constitutional isomeric libraries provided different supramolecular structures and, therefore, different functions [71]. The amphiphilic benzyl ether dendrons were considered by us to be the simplest self-assembling synthetic "mimics" of peptides, in which the peptide bond derived from α-amino acids was replaced with the more flexible benzyl ether and the linear topology was replaced with a branched one in order to increase the probability of the discovery process. Were these supramolecular structures micellar or did they display internal order like biological assemblies?

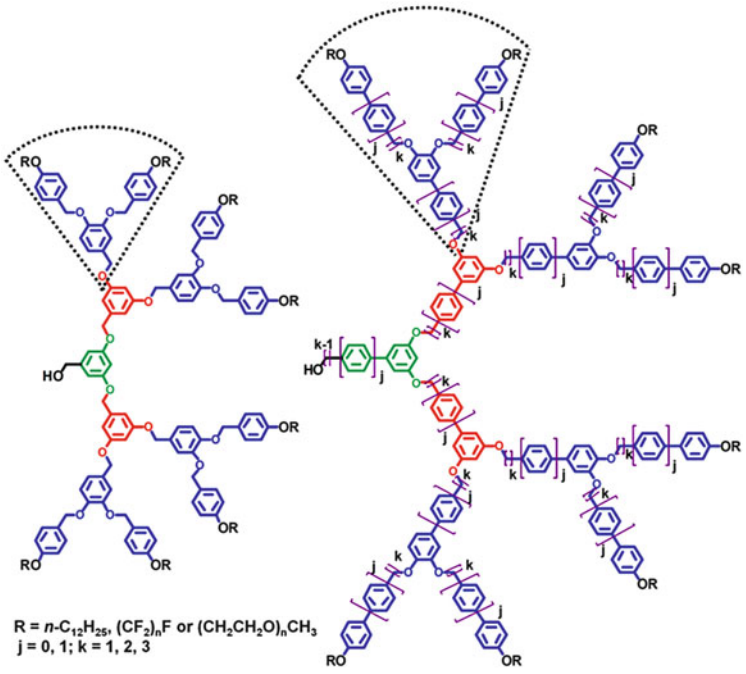

Fig. 4 Self-assembling amphiphilic dendrons based on benzyl ether, biphenylmethyl ether, biphenylpropyl ether, and biphenylpropyl ether

The answer came from transplanting the biological methodologies of structural analysis, including X-ray diffraction methods employing helical diffraction theory [72] on aligned fibers [34–36], isomorphous replacement [73], electron diffraction and electron density maps [60, 63–65] combined with circular dichroism [74–77] experiments. They demonstrated that both rod-like [72, 76, 77] and globular [74, 75] assemblies are helical and, therefore, are chiral. The next critical question was whether the primary structure of the dendron or the structure of the repeat unit determines the supramolecular organization. Subsequently, we investigated additional constitutional isomeric libraries of AB_2, AB_3, AB_4, and AB_5 amphiphilic dendrons in which the benzyl ether was replaced by a biphenylmethyl ether [78], a phenylpropyl ether [79], or a biphenylpropyl ether [80] and even more complex dendrons [81, 82] as mimics of β- , γ- , and δ-amino acids.

Figure 4 summarizes these structures for the case of 3,5-disubstituted AB_2 repeat units (its 3,4-disubstituted constitutional isomer, 3,4,5-trisubstituted AB_3, and higher order AB_4 and AB_5 are not shown). These new libraries demonstrated that the primary structure rather than a small variation in the repeat unit is responsible for the tertiary structure; therefore, an 85% predictability [80] for the primary structure that provides a specific tertiary structure was demonstrated. Once the

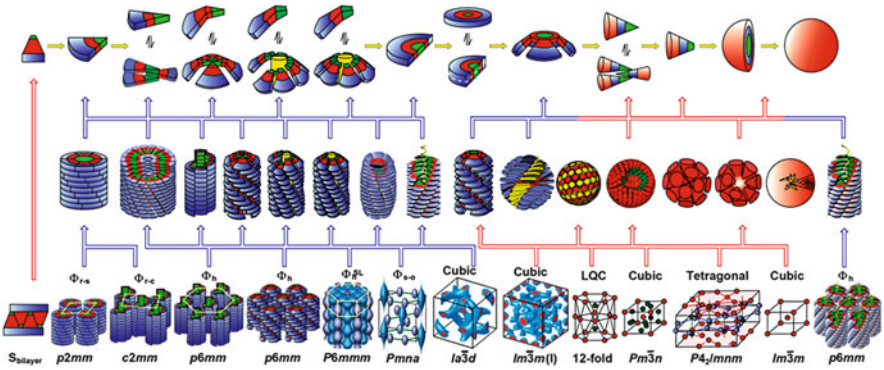

Fig. 5 Accelerated synthesis of libraries of quasi-equivalent self-assembling dendrons via the retrostructural analysis of their periodic and quasi-periodic assemblies. Reprinted with permission from [80]. Copyright 2009 American Chemical Society

"generational" approach to libraries did not provide additional discoveries, a novel "deconstruction" approach [83] to libraries was elaborated. Figure 5 summarizes the accelerated synthesis of libraries of quasi-equivalent self-assembling dendrons and dendrimers via the retrostructural analysis of their periodic and quasi-periodic assemblies.

A brief inspection of Fig. 5 reveals that these supramolecular structures could be similar to those self-assembled from block copolymers. Two major differences exist between self-assembling dendrons and block copolymers. First, all structures in Fig. 4 are generated from the same chemical composition but different primary structure, including constitutional isomeric primary structures, and second, they exhibit intramolecular order. Block copolymers provide micellar morphologies with different structures determined by different ratios between their dissimilar segments.

A combination of supramolecular and polymer chemistries, as outlined in Fig. 5, can be used to transit from supramolecular assemblies to macromolecular self-organizable assemblies. The results in Fig. 5 are obtained with the simplest dendrons and dendronized polymers in which the dendron is attached to the polymerizable group from their apex. More complex dendrons like twins [84–86], Janus [87, 88], and complex dendronized polymers [84–86, 88] (Fig. 6) were investigated but will not be discussed here. Figure 6 illustrates representative examples of supramolecular and macromolecular dendronized polymers with more complex structures than available in Fig. 5 [88]. Once libraries of primary structures that provide a specific structure are available (Fig. 5), methodologies to predict the primary structure that will provide a function become accessible. Several examples will be illustrated in the following sections.

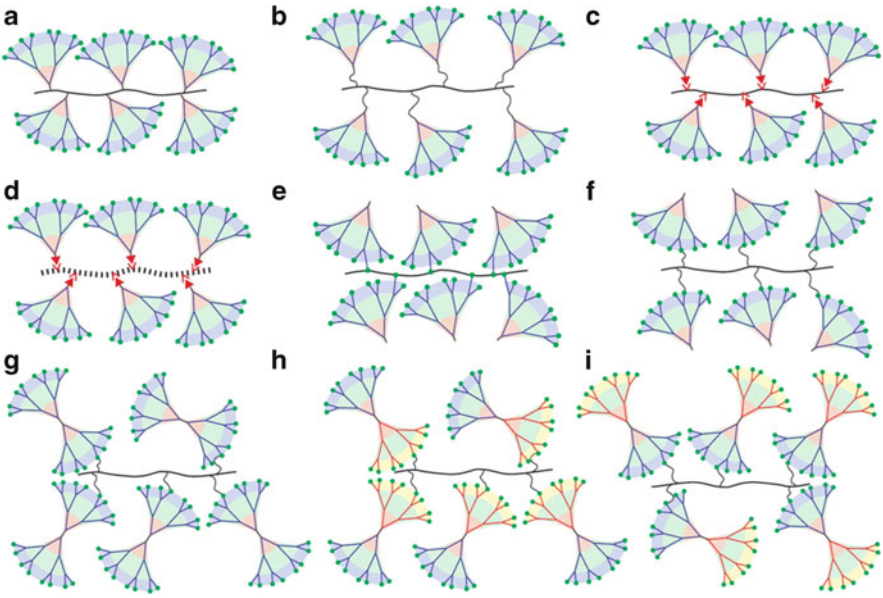

Fig. 6 (**a–i**) Topologies of supramolecular and covalent macromolecules dendronized with self-assembling dendrons, twin dendrons, and Janus dendrimers. Reprinted with permission from [88]. Copyright 2012 American Chemical Society

4 Mediating Chemical Reactivity and Backbone Conformation with Spherical and Globular Visualizable Macromolecules Generated from Quasi-Equivalent Self-Assembling Dendrons

Figure 7 outlines the concept to be discussed here. It is expected that the attachment to a polymer backbone of a tapered dendron that self-assembles into a supramolecular helical column will incorporate the polymer backbone in the center of the column, and that the conformation of the polymer will become helical regardless of the stereochemistry of its backbone.

The number of dendrons forming the cross-section of the column will determine the helical pitch of the backbone. We can envision mediating the backbone conformations from helical to fully extended by using this process. Alternatively, a conical dendron conformation will induce a random-coil backbone conformation at low degrees of polymerization, whereas a non-dendronized polymer usually adopts an extended conformation. We expect that quasi-equivalent dendrons will change their shape from conical to tapered via temperature and degree of polymerization and, subsequently, the shape of the polymer will change from globular to rod-like and its conformation from random-coil to extended. Will this process affect

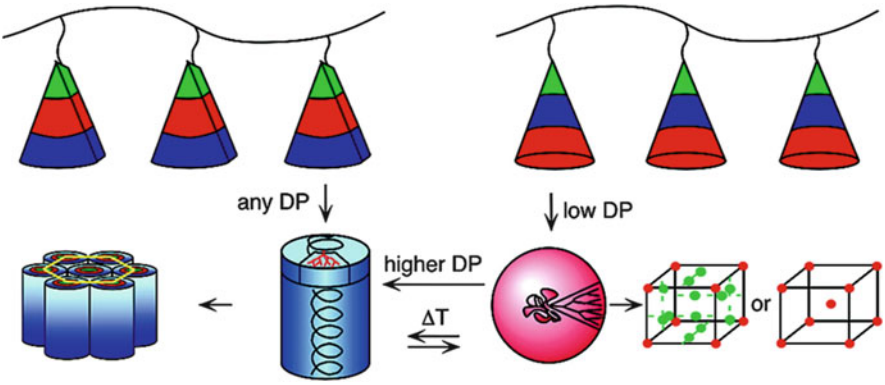

Fig. 7 Interconversion of supramolecular assemblies and self-organizations obtained from macromolecules dendronized with quasi-equivalent self-assembling dendrons. *DP* degree of polymerization. Reprinted with permission from [54]. Copyright 2008 American Chemical Society

the chemical reactivity of the growing active species, the rate of polymerization, and the polydisperity of the resulting polymer?

Figure 8 summarizes a series of experimental results generated during conventional radical polymerization in dilute solution and in the self-assembled state [62, 89]. Due to steric constraints, in dilute solution the rate constants and rates of bimolecular termination and chain transfer are reduced or even eliminated while the rate constant and rate of propagation decrease with the increase in chain length and become equal to zero when the polymer adopts a globular shape [62, 89]. As a result, globular polymers with an extremely narrow molecular weight distribution and predetermined molecular weight, just like in living polymerization processes, are obtained by conventional radical polymerization. When the polymerization takes place in self-assembled state, the polymerizable groups are part of a self-assembled nanoreactor. This provides an extremely fast polymerization that yields cylindrical macromolecules with molar mass up to 4,000,000 in several minutes [90, 91].

During this process, the quasi-equivalent dendron mediates the transition from globular to rod-like polymer [62]. Because the diameters of these dendronized polymers are larger than 4 or 5 nm, both globular and rod-like polymers can be characterized by X-ray diffraction and visualized by scanning force microscopy on various surfaces (Fig. 9). Detailed analysis of single synthetic polymer chains and of libraries of polymers, including their chain length and polydispersity, became available from these experiments [62, 90–92]. Libraries of self-organizable dendronized polymers with varying chain stiffness were designed, and annealing of single chains on surfaces enabled visualization for the first time of the transition from single macromolecules to their 2D and 3D ordered assemblies [62, 90–92]. Visualization of single natural macromolecules was accomplished first in the Staudinger laboratory [93].

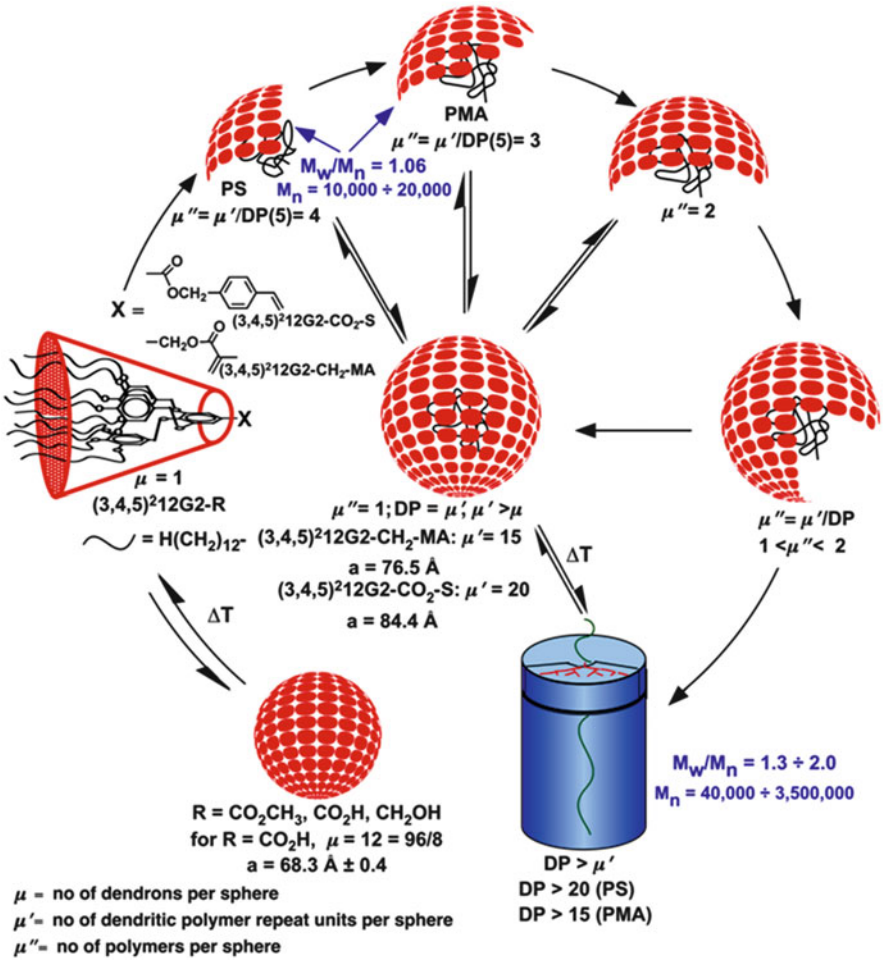

Fig. 8 Dependence of the shape of the macromolecule dendronized with quasi-equivalent dendrons on the degree of polymerization (*DP*). Reprinted with permission from [62]. Copyright 1998 Macmillan Publishers Ltd. (Nature)

5 Transforming a Helix–Coil into a Helix–Helix Transition and Eliminating Intramolecular Electrocyclization

As demonstrated in the lecture given during the IUPAC of Macromolecules in Tashkent in 1978 [94], in its contributing publications, and in more recent publications [94–103], the *cis*-transoidal and *cis*-cisoidal polyphenylacetylenes exhibit helical conformations that undergo an intramolecular electrocyclization during their transition to the coil conformation. A limited extent of *cis–trans* isomerization takes place during this process (Fig. 10).

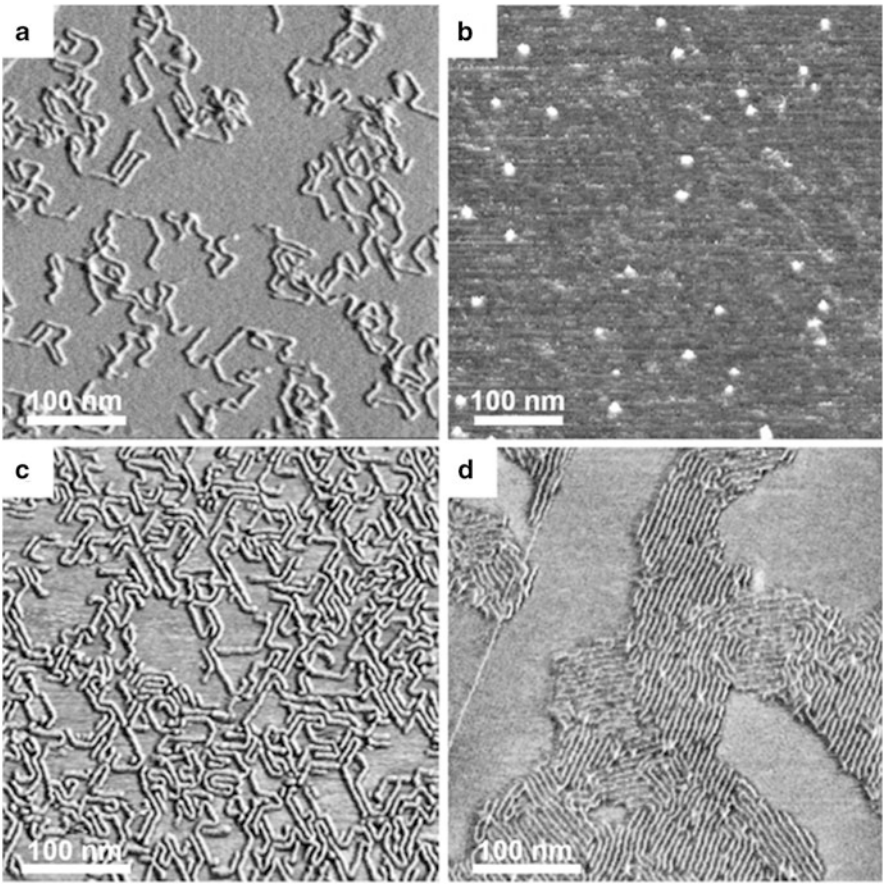

Fig. 9 Scanning force microscopy images of individual cylindrical dendronized polymers (**a**), globular dendronized polymers (**b**), and of libraries of cylindrical dendronized polymers before (**c**) and after annealing (**d**), visualizing the formation of 2D ordered arrays. Reprinted with permission from [90] and [65]. Copyright 1998 and 2000 American Chemical Society

Encapsulation of any of these *cis*-conformers into libraries of columnar supramolecular dendrimers eliminates the intramolecular electrocyclization and replaces the helix–coil transition with an unprecedented helix–helix transition and a reversible transition from *cis*-transoidal to *cis*-cisoidal. When the repeat unit of the dendronized polymer also contains a stereocenter, this reversible process can be monitored by circular dichroism (CD) and visualized by different methods [104–111]. This concept was used to elaborate molecular machines that were interfaced for the first time with the real world to lift heavy objects [111].

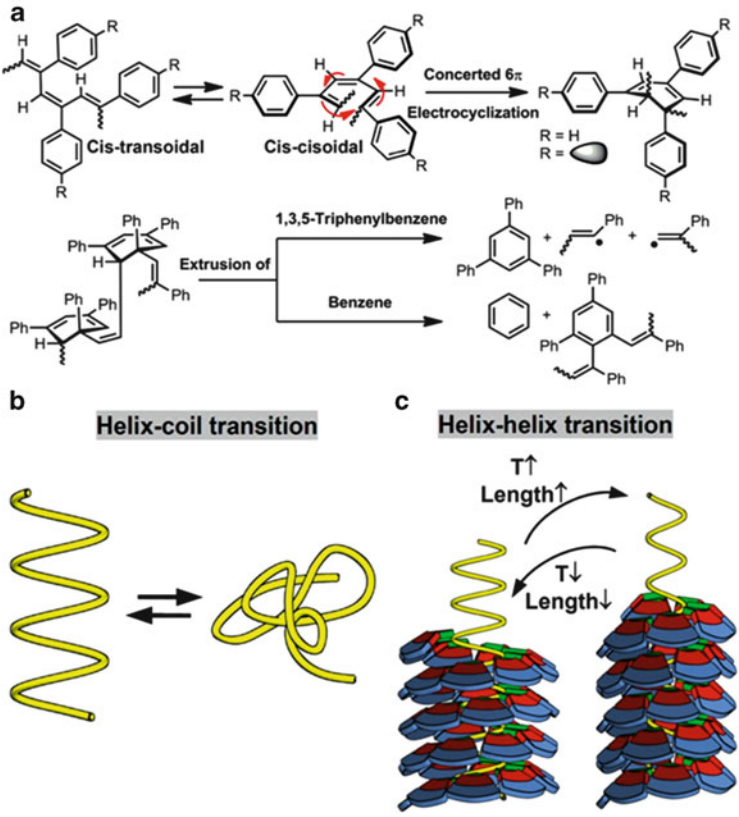

Fig. 10 The irreversible intramolecular electrocyclization of *cis*-transoidal polyphenylacetylene (**a**) taking place during the helix–coil transition of the polymer (**b**), its elimination by encapsulation of the polymer in a cylindrical supramolecular polymer and the transformation of the helix–coil into a helix–helix transition (**c**)

6 Dendritic Dipeptides as Aquaporin Transmembrane Protein Mimics

Aquaporin (AQP) is an hour-glass transmembrane channel that mediates the transport of water through biological membranes [112]. AQP transports water with 100% selectivity at a rate of 3×10^9 molecules of water per second per channel. No protons, protonated water, or other ionic species pass through AQP. A primitive mimic of AQP was accomplished by attaching homochiral Tyr-Ala dipeptide containing a diversity of protecting groups at the dendron apex [113].

Figure 11 outlines the structure of the homochiral enantiomers of the dendritic dipeptide, the CD and UV spectra as a function of temperature recorded in cyclohexane (a solvent that mimics the hydrophobic wall of the biological membrane and mediates self-assembly), and the structures of the supramolecular assemblies

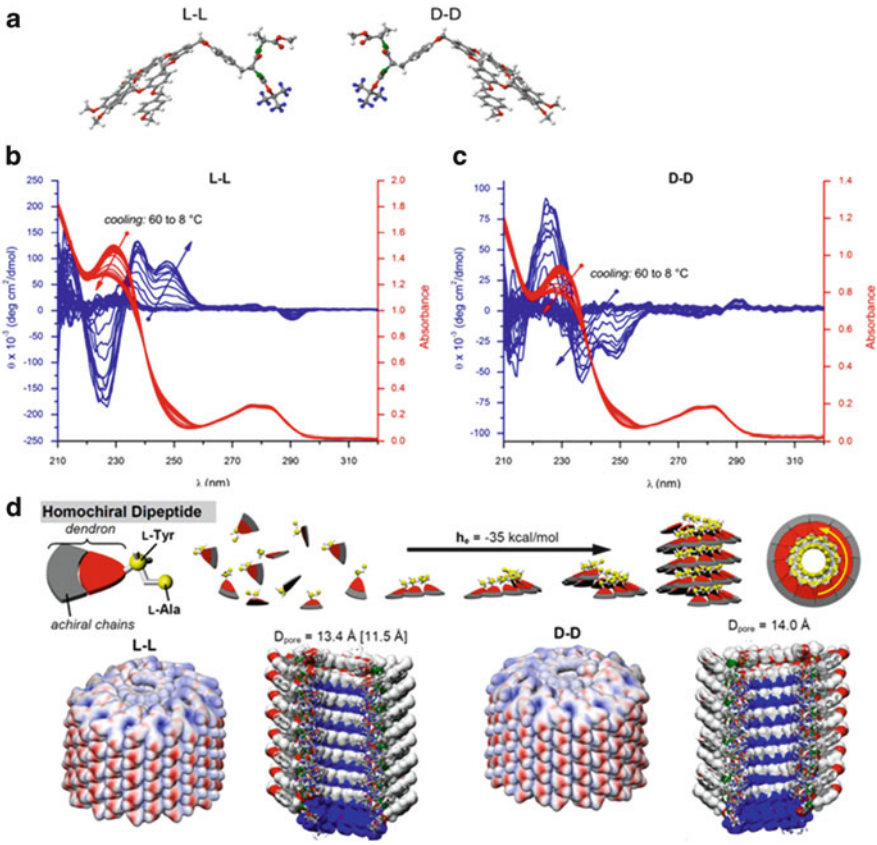

Fig. 11 Structures of the homochiral dendritic dipeptides (**a**), their CD (*blue*) and UV (*red*) spectra recorded during self-assembly in cyclohexane (**b, c**), the nucleation and growth mechanism of cooperative supramolecular helical polymerization and the structures of the supramolecular assemblies (**d**). Modified with permission from [114]. Copyright 2011 American Chemical Society

[114]. The structure of this AQP mimic is persistent in solution and in bulk and, therefore, combinations of methods for solid state and solution were used to elucidate the cooperative helical polymerization mechanism of self-assembly of this dendritic dipeptide [114]. This concept applies to a diversity of nonpolar dipeptides, protective groups, and dendrons containing various numbers of carbons in their alkyl groups [113, 115–121]. This AQP mimic transports water through biological membranes but does not separate protons [121]. However, ion pairs are not allowed to pass through this hydrophobic channel. The cooperative mechanism of self-assembly of these dendritic dipeptides involves nucleation and growth, as demonstrated in the case of TMV [114]. Subsequently, all stereochemical permutations of Tyr-Ala, including the racemic one, were synthesized and their mechanism of self-assembly in solution and in bulk were investigated in order to answer the very fundamental question: "Why are biological systems homochiral?" The

answer seems to be related to the supramolecular structure of the assembly that is based on strong nonbonding interactions, including H-bonding. As a consequence, the homochiral derived assembly resembles an isotactic polymer, the heterochiral a syndiotactic polymer, and the racemic an atactic polymer. As a consequence, the homochiral assemblies are crystalline, the heterochiral assemblies are semicrystalline, and the racemic assemblies are amorphous and in solution are micellar rather than highly ordered structures [55, 58, 113, 114]. These series of results are discussed in more detail in other publications and provide an answer to the question of why biological systems are homochiral: "Most probably because homochirality provides order for free!" Self-assembling dendrons forming porous structures without the aid of dipeptides were also discovered [122]. The replacement of the tapered self-assembling dendron (from the dendritic dipeptide) with a conical dendron changes the mechanism of self-assembly such that the structure changes from a porous protein mimic to a hollow globular container that is also chiral [123].

7 Self-Assembly of Amphiphilic Janus Dendrimers into Monodisperse and Stable Dendrimersomes

Biological membranes are self-assembled from phospholipids containing cholesterol, transmembrane proteins, glycolipids, and glycoproteins. During the 1980s I listen repeatedly to the lectures of Ringsdorf, who was demonstrating that biological phospholipids alone do not form stable synthetic liposomes [13]. He employed a large arsenal of methodologies for the stabilization of vesicles and liposomes [13]. Stable vesicles and liposomes are of great interest as containers for the delivery of drugs, nucleic acids, and proteins, and as models of contemporary and primitive biological membranes [124, 125]. Most successful and commercially available for the delivery of cancer drugs are the stealth liposomes elaborated by Teresa Allen (Fig. 12) [126]. They are obtained by the co-assembly of phospholipids with poly(ethyleneoxide)-conjugated lipids and are stabilized with 50% cholesterol. As prepared, they are polydiserse and require extensive fractionation. Polymersomes (Fig. 12), discovered by my Penn colleague Dan Hammer [127], are vesicles assembled from amphiphilic block copolymers.

Polymersomes are stable in time but polydisperse and require fractionation. In addition, they are generated from block copolymers that are not always biologically compatible and nontoxic. One day, Dan Hammer challenged our library approach as a potential tool to solve the problem of vesicles. We synthesized 11 libraries of the simplest possible amphiphilic Janus dendrimers and, to our surprise, most of them self-assembled, by simple injection in water of their ethanol or THF solutions, into stable and monodisperse vesicles that were named dendrimersomes [128].

Figure 13 shows an example of an amphiphilic Janus dendrimer library containing 13 molecules (Fig. 13a), the cryo-TEM of the self-assembled monodisperse dendrimersomes (Fig. 13b), and the confocal microscopy photo of a giant

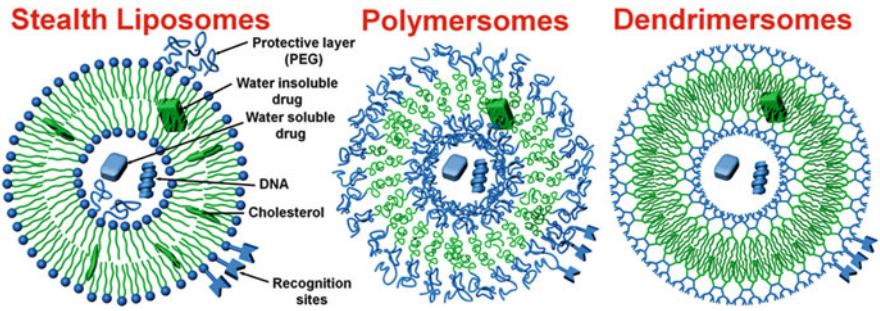

Fig. 12 Stealth liposomes, polymersomes, and dendrimersomes. Reproduced with permission from [129]. Copyright 2011 American Chemical Society

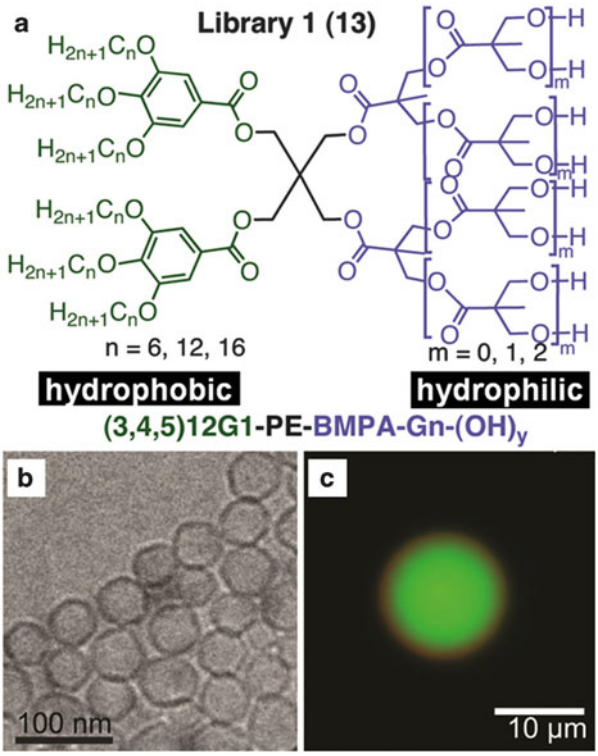

Fig. 13 An example of library of amphiphilic Janus dendrimer (**a**), the cryo-TEM of the corresponding monodisperse dendrimersomes (**b**), and confocal microscopy image of a giant dendrimersome containing hydrophobic (*red, outer ring*) and hydrophilic (*green, inner core*) dyes (**c**). Reproduced with permission from [128]. Copyright 2010 American Association for the Advancement of Science

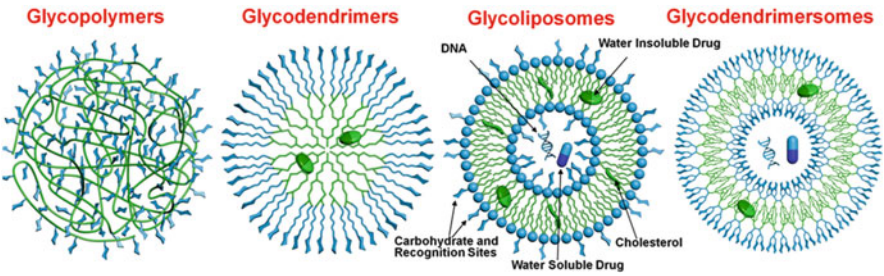

Fig. 14 Glycopolymers, glycodendrimers, glycolyposomes, and glycodendrimersomes

dendrimersome containing hydrophobic and hydrophilic dyes (Fig. 13c) [128]. These glycodendrimersomes are nontoxic to cells and can be used for the delivery of cancer drugs [128]. Their size can be predetermined by the concentration of the solution injected. Last by not least, because the structure of their bilayer in the bulk state is similar to that of the bilayer in the dendrimersome, their mechanical properties and dimensions can be predicted with an extraordinary accuracy from X-ray diffraction experiments [129].

8 Glycodendrimersomes as Mimics of Biological Membranes

The glycolipids and glycoproteins from the surface of biological membrane form the glycan ligands responsible for the interaction of cellular membranes with sugar-binding proteins known as lectins and galectins, as well as with other receptors.

Figure 14 illustrates the current mimics of membrane glycan: glycopolymers [130–133], glycodendrimers [134, 135], and glycoliposomes [136, 144]. Glycopolymers and glycodendrimers have sugars in each of their repeat units and are efficient for the binding of lectins. However, they do not mimic cellular membranes because they do not have an empty cavity. Glycoliposomes are generated by the co-assembly of phospholipids with phospholipids conjugated with carbohydrates, or by other complex modification and co-assembly methods. Recently, we applied the concept of amphiphilic Janus dendrimers to the synthesis of amphiphilic Janus glycodendrimers. A series of seven libraries containing 51 amphiphilic Janus glycodendrimers [137] were investigated to discover the molecular principles required to predict the primary structures of Janus glycodendrimersomes that self-assemble into monodisperse and stable (in buffer) soft glycodendrimersomes containing mannose, galactose, and lactose on their periphery. Agglutination experiments with plant, bacterial, and human lectins demonstrated that they are excellent mimics of the glycan of biological membranes and have great potential as cancer vaccines and for other medical applications [137].

The same library approach was used in our laboratory to understand the principles required for the design of molecular electronics [138–143] and other functions, including complex catalytic systems. The few examples illustrated here demonstrate that Staudinger's dream of bridging macromolecular, organic, supramolecular chemistry, biology, and medicine is currently one of the most active topics of research in the field of macromolecular chemistry, of whose existence he convinced the organic chemistry community.

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The Wonder of Life in Its Chemical Aspect

David A. Tirrell

Abstract Hermann Staudinger was deeply interested in both macromolecular chemistry and biology. This chapter reviews briefly the shared origins of studies of natural and synthetic polymers, the subsequent divergence of the two fields, and their more recent convergence, made possible by the development of recombinant DNA methodology. The use of recombinant DNA technology to prepare well-defined macromolecular materials is discussed, along with the use of non-canonical amino acids as probes of protein synthesis in complex cellular systems.

Keywords Molecular biology · Non-canonical amino acids · Nucleic acids · Proteins · Recombinant DNA

Contents

1 Introduction 200
2 Control of Supramolecular Architecture and Macromolecular Materials Properties 201
2.1 Chain-Folded Lamellar Crystals from Periodic Polypeptides 201
2.2 Smectic Liquid Crystals from Monodisperse Rod-Like Polymers 203
2.3 Programming the Viscoelastic Behavior of Macromolecular Solutions and Gels .. 205
2.4 Artificial Extracellular Matrix Proteins 206
3 Non-canonical Amino Acids as Probes of Biological Processes 206
3.1 The BONCAT Method 207
3.2 Cell-Selective BONCAT 208
4 Convergence of Macromolecular Chemistry and Biology 209
References 209

D.A. Tirrell (✉)
Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, CA 91125, USA
e-mail: tirrell@caltech.edu

1 Introduction

> ". . .macromolecular chemistry appears today to fit between low molecular organic chemistry and cytology. It is the connecting link between them, growing systematically out of low molecular chemistry but, with the incomparably larger wealth of its chemical scope, forming living matter. . .. In the light of this new knowledge of macromolecular chemistry, the wonder of life in its chemical aspect is revealed in the astounding abundance and masterly macromolecular architecture of living matter."
>
> Hermann Staudinger, Nobel Lecture, 1953 [1]

Macromolecular chemistry and biology were closely linked at the start. In the introduction to his scientific autobiography [2], Hermann Staudinger tells us, "I did not intend to study chemistry. I preferred botany, because from an early age I had been interested in floristics. . ." The controversy that surrounded Professor Staudinger's macromolecular hypothesis in the early days is well known to readers of this volume. Natural polymers figure prominently in this story, beginning with the demonstration that the hydrogenation of natural rubber does not destroy its macromolecular character [3]. In his 1970 article, "The macromolecular concept and the origins of molecular biology," historian Robert Olby argues that key evidence in favor of the covalent structure of macromolecules was provided in the 1920s by independent measurements of the molecular weight of hemoglobin. Ultracentrifugation produced a "clear band" and an estimated molecular weight of 68,000, while osmotic methods yielded a value of 66,500 [4]. The implication of monodispersity in the ultracentrifugation result, coupled with the consistency in molecular weights determined by two different methods, argued against aggregation through non-covalent forces as the origin of the macromolecular behavior of hemoglobin. Olby goes on to cite Staudinger's "biologists' viewpoint" as central to his early investigations of macromolecular chemistry.

As the commercial value of synthetic polymers grew through the mid-twentieth century, studies of natural and synthetic polymers diverged. The remarkable physical properties of synthetic polymers, along with their ease of processing and relatively low cost, led to extraordinary growth in industrial polymer production. At the same time, structural and biophysical studies of DNA [5] and proteins [6] began to reveal the molecular origins of genetic information, enzyme catalysis, and immune recognition. Polymer chemistry and physics became closely aligned with materials science and engineering, while the study of proteins and nucleic acids formed the core of the new discipline of molecular biology. Moreover, the two fields were distinguished by the relative value each placed on the complementary roles of synthesis and analysis. Few biologists shared the view of Jacques Loeb, who "considered the main problem of biology to be the production of the new, not the analysis of the existent" [7]; in contrast, the polymer chemistry community was driven, both by curiosity and by the prospect of practical impact and financial return, to explore a broad range of synthetic routes to new macromolecular materials. Just 10 years after Staudinger received his Nobel Prize, Karl Ziegler and Giulio Natta were honored similarly for their development of new synthetic methods that enabled the production of polyolefins with unprecedented control of structure and properties.

The emergence of biology as an engineering discipline took a major step forward with the advent of recombinant DNA technology in the 1970s. Although the first recombinant DNA experiments were motivated by fundamental questions about the organization of genetic information [8], the prospect of using the technology to make valuable proteins was appreciated very quickly [9]. Forty years later, the global market for the products of biotechnology rivals that for polymeric materials.

By the mid-1980s, recombinant DNA technology had advanced to the point where it could be used reliably even by investigators working in fields other than molecular biology. For those of us in polymer chemistry, the availability of recombinant methods created some especially important opportunities, in that it afforded the possibility of making new macromolecules with essentially complete control of the molecular architecture. Although it was not entirely clear how general the method would prove to be, it seemed likely that artificial genes could be used to direct the synthesis of a wide variety of protein-like macromolecules of defined length, sequence, and stereochemistry. The prospect of making such well-defined macromolecules raised important new questions about the connections between macromolecular structure and function, and opened the door to new ways of thinking about macromolecular design. The boundaries between natural and synthetic polymers began to blur.

We started to think about these issues in 1986, with the objective of using artificial genes to program both molecular and supramolecular architecture in macromolecular systems. Our first targets, conceived and pursued with our colleagues Maurille Fournier and Thomas Mason at the University of Massachusetts, were predetermined crystal structures and liquid crystal phases. We were soon drawn to the design of supramolecular gels and to analogs of extracellular matrix proteins for use in surgery and regenerative medicine, and to the challenge of making artificial proteins from amino acid building blocks that do not appear in natural proteins. What we did not anticipate was that our interest in such "non-canonical" amino acids would lead us to new ways of exploring fundamental biological questions. The following sections describe these and related developments at the intersection of macromolecular chemistry and biology.

2 Control of Supramolecular Architecture and Macromolecular Materials Properties

2.1 Chain-Folded Lamellar Crystals from Periodic Polypeptides

The widespread occurrence of chain-folded lamellar crystals in synthetic polymers of regular structure has been known since the 1950s [10]. We wondered whether it might be possible use artificial genetic information to program the formation of such crystals through the design of periodic polypeptides, with control of chain

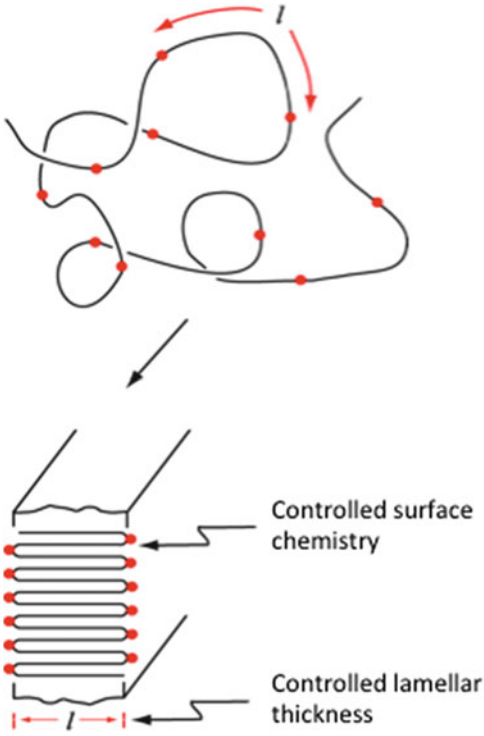


Fig. 1 Formation of lamellar crystals from designed periodic polypeptides. AlaGly repeats are shown as the *solid line* and the periodic Glu residues are represented as *circles*

conformation, unit cell structure, lamellar thickness, and lamellar surface structure. With this goal in mind, we designed a family of polypeptides (**1**) made up of repeating alanylglycine (AlaGly) dyads separating regularly spaced glutamic acid (Glu) residues [11]. The basis of the design was simple: AlaGly-rich polypeptides (including silkworm silk) were known to adopt β-sheet structures [12], which we imagined would serve well as the crystal "stems" in the lamellar aggregate. The Glu residues seemed likely to be excluded from the interior of such aggregates because of their large size relative to Ala and Gly, and because their polar side chains would be strongly solvated during crystal growth from polar solvents. We also noted that Glu is the weakest β-sheet former among the 20 canonical amino acids, according to the Chou–Fasman rules for secondary structure prediction [13].

The anticipated lamellar structure is shown in schematic form in Fig. 1. Exclusion of the Glu residues from interior sites confines them to the surfaces of the lamella, while the number of AlaGly dyads in the periodic repeating unit determines the lamellar thickness. We expected that the chain conformation in the crystal stems, and the unit cell structure, would be dictated by the strong β-sheet preference and the packing requirements of the AlaGly dyads. Reversal of the chain direction at the lamellar surfaces leads to an antiparallel arrangement of the β-sheets.

Crystallization of the variant containing three AlaGly dyads in the repeating unit from 70% formic acid yielded stacks of lamellar crystals. The antiparallel β-sheet

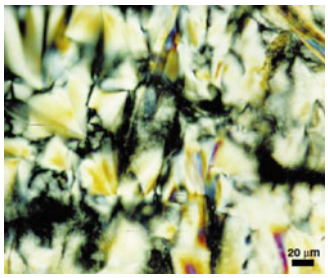


Fig. 2 Fan-like texture of monodisperse PBLG in $CHCl_3$:TFA mixture. Reproduced from [14] with permission of the publisher

structure was established by X-ray diffraction and by vibrational and solid-state NMR spectroscopy. Small-angle X-ray scattering indicated a characteristic spacing of 3.6 nm perpendicular to the crystal mat. Although we obtained no direct evidence of surface confinement of the Glu residues, the long spacing is consistent with the calculated fold-to-fold distance of 2.8 nm and the additional volume required by Glu residues at the folds. When we increased the separation between the Glu residues, the long period spacing increased and the intersheet spacing decreased, as expected. We believe that these experiments represent a significant advance in the level of control that can be achieved in the engineering of crystal structure in synthetic macromolecules.

2.2 Smectic Liquid Crystals from Monodisperse Rod-Like Polymers

Rod-like polymers often form nematic liquid crystal phases in which the chains assume orientational, but not positional, molecular order. We wondered whether it might be possible to engineer smectic phases in such systems by narrowing the chain-length distribution through genetic control. We chose as a model system poly (γ-benzyl-α,L-glutamate) (PBLG), a helical rod-like polymer that forms nematic, cholesteric, and columnar phases in its conventional polydisperse form [14–17]. We expressed two variants of poly(α,L-glutamic acid) in bacterial cells and esterified the side chains of each polymer to produce monodisperse PBLGs with degrees of polymerization (DP) of 76 and 94.

Figure 2 shows a polarizing optical micrograph of a 35% solution of the DP 76 variant in a 97:3 mixture of chloroform and trifluoroacetic acid. The solution exhibits the fan-like texture characteristic of smectic order [18]. When films of monodisperse PBLGs were probed by small-angle X-ray scattering, well-defined maxima were observed at spacings of 11.4 and 14.0 nm, in excellent agreement with the calculated chain lengths of the helices of DP 76 and 94, respectively (Fig. 3). In striking contrast, the conventional polydisperse sample showed no evidence of a maximum in the scattering pattern.

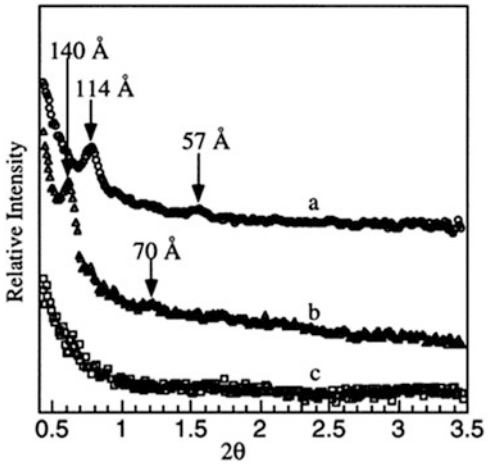
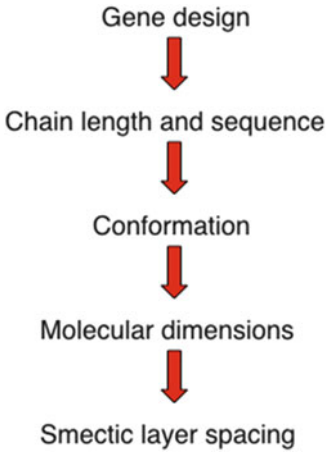


Fig. 3 Small-angle X-ray scattering patterns obtained from films of PBLG: (*a*) monodisperse sample, DP 76; (*b*) monodisperse sample, DP 94; and (*c*) polydisperse sample



Scheme 1 The process of programmed molecular assembly as applied to the design of smectic mesophases in PBLG solutions and films

The successful engineering of smectic phases in solutions and films of monodisperse PBLGs is representative of the more general process by which molecular assembly can be programmed through the use of artificial genetic information. The process as applied to PBLG is shown in Scheme 1. The artificial gene directly controls the length and sequence of the molecule of interest. The sequence of the polymer determines its conformation; the fact that PBLG is helical in chloroform: TFA mixtures fixes the molecular dimensions in the nanometer range. The uniformity

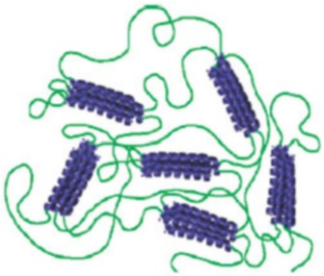


Fig. 4 Multidomain leucine zipper proteins designed to form reversible hydrogels. *Helices* represent leucine zipper peptides; *Lines* represent central polyelectrolyte domains. Reproduced from [22] with permission of the publisher

of those dimensions allows the formation of a smectic phase of predetermined layer spacing. Thus, genetic information can be used to program not only the molecular architecture, but also the supramolecular organization of the system.

2.3 Programming the Viscoelastic Behavior of Macromolecular Solutions and Gels

We next turned our attention to the prospect of programming the dynamic behavior of macromolecular systems [19]. Here, the initial target was a reversible hydrogel formed through assembly of multidomain artificial proteins (Fig. 4) in which helical "leucine zipper" endblocks flank an unstructured, water-soluble polyelectrolyte domain. The rationale for this design arises from two seemingly contradictory requirements for macromolecular gelation: interchain interactions must be strong enough to form junctions in the molecular network, but the chains will precipitate if they exclude water completely. We imagined that multidomain leucine zipper proteins might solve this problem by confining strong interchain interactions to the zipper domains, while the polyelectrolyte domain would remain highly hydrated. The expected result was a swollen, viscoelastic molecular network with leucine zipper aggregates at the junction points and polyelectrolyte domains linking the network junctions (Fig. 4).

Hydration of polymers of this kind at concentrations above about 4% w/v yielded viscoelastic hydrogels that could be reversibly converted to viscous solutions through changes in pH or temperature. Because the zipper domains in our initial designs were highly acidic, raising the pH of the solution caused an increase in the rate of strand exchange in the network [20] and conversion to a viscous liquid. Heating the sample above the denaturation temperature of the zipper domains was accompanied by similar changes in behavior. More recent experiments have shown the importance of controlling network topology through careful selection of zipper sequences [21] and the capacity of such physical gels to undergo

striking shear-thinning that enables easy injection through conventional syringes [22]. The "injectability" of such gels is potentially useful in cellular transplantation therapy, a subject that we address briefly in the following section.

2.4 Artificial Extracellular Matrix Proteins

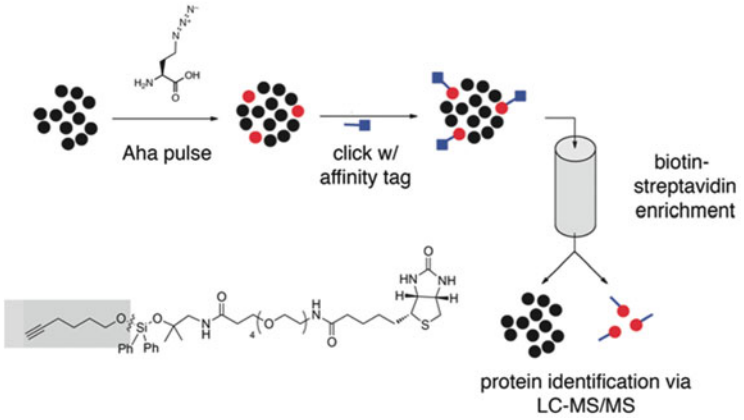
It seems likely that the first practical applications of artificial proteins will be in surgery or medicine. Polymer chemists have had great success in creating materials for reconstructive surgery, drug delivery, and other medical procedures [23], and engineered proteins provide an especially convenient platform for the creation of new macromolecules with well defined and useful biological properties. Given recent advances in stem cell biology, the design of protein matrices for cell transplantation appears to be an exciting and important challenge.

We began working on this problem in the late 1990s by constructing "artificial extracellular matrix" (aECM) proteins that combine domains drawn from the natural ECM proteins elastin and fibronectin. Our designs drew heavily on earlier work by Dan Urry, who showed that many of the most important physical properties of elastin are retained by simple repeating polypeptides rich in valine, glycine, and proline [24], and by Erkki Ruoslahti and Jeffrey Hubbell, who demonstrated that short sequences of fibronectin could be used to induce cells to bind to artificial substrates by engaging cell-adhesion receptors of the integrin family [25, 26].

Over the past 15 years, we have made many variants of aECM proteins, including photocrosslinkable versions that contain the photosensitive non-canonical amino acid *p*-azidophenylalanine [27]. Our most recent experiments in this area are being done in collaboration with Teresa Ku and Arthur Riggs at City of Hope, and are directed toward the development of matrices for maturation and transplantation of human pancreatic β-cells for treatment of Type 1 diabetes [28].

3 Non-canonical Amino Acids as Probes of Biological Processes

We realized early in our studies of artificial proteins that some of the things we wanted to do would require expansion of the set of 20 "canonical" amino acids that cells normally use to make proteins. We were confident that some expansion would be possible because translationally active amino acid analogs had been reported as early as 1951 [29]. As it turns out, the chemistry of cellular protein synthesis is considerably more permissive than we imagined, and our laboratory and many others have now developed dozens of new amino acids that can be used to engineer and probe protein behavior [30–32].



Scheme 2 The BONCAT method. The structure at *lower left* is a typical affinity tag for use with the non-canonical amino acid azidohomoalanine (Aha)

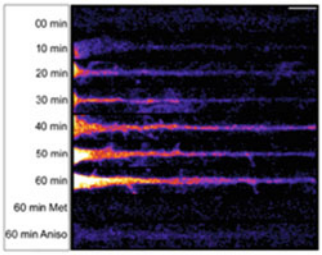


Fig. 5 Dye-labeling of newly synthesized proteins in neurons tagged with azidohomoalanine. Reproduced from [37] with permission of the publisher

3.1 The BONCAT Method

Our studies of non-canonical amino acids were motivated initially by an interest in making proteins with novel properties. Our interest broadened when our colleague Daniela Dieterich suggested that pulsed metabolic labeling of cellular proteins with non-canonical amino acids might provide a method for time-resolved analysis of protein synthesis in neurons. With Daniela and Erin Schuman, we developed this idea into the BONCAT (bio-orthogonal non-canonical amino acid tagging) method shown in Scheme 2 [33].

In the BONCAT method, the cellular system of interest (cultured cells, tissue slices, or live animals) is pulse-labeled with a non-canonical amino acid that carries a reactive side chain. In our initial experiments, we used azidohomoalanine (Aha) as the label because Aha-labeled proteins can be selectively tagged with dyes or affinity reagents through copper-catalyzed or strain-promoted azide-alkyne cycloaddition reactions [34–36]. Tagged proteins can then be separated from other

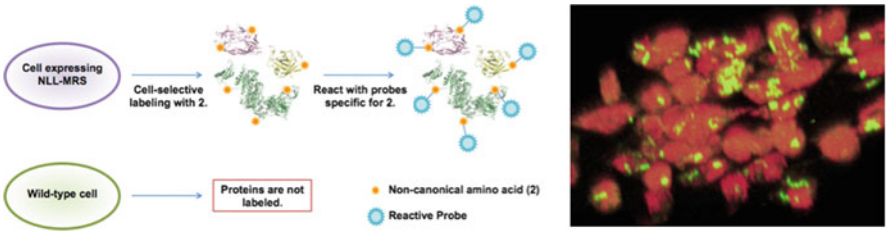


Fig. 6 *Left*: Cell-selective BONCAT method. Cells that carry the mutant MetRS (NLL-MRS) can be labeled with the methionine surrogate azidonorleucine (Anl, **2**). Other cells are inert to Anl. *Right*: Bacterial cells carrying the NLL synthetase are labeled with a fluorescent alkyne dye (*green*) in the presence of mammalian macrophages (*red*). Macrophage proteins are not labeled

cellular proteins by affinity chromatography, and identified by high-throughput mass spectrometry. Because other cellular proteins are essentially inert to the tagging chemistry, proteins made during the Aha pulse are highly enriched and easily identified. Tagging with dyes allows one to determine the cellular locations of the proteins made during the Aha pulse (Fig. 5) [37].

3.2 Cell-Selective BONCAT

In studies of complex biological systems, it is often important to determine what is going on in one particular type of cell, rather than averaging information obtained from many different cell types. Labeling with Aha does not discriminate among cells because Aha is activated for protein synthesis by the wild-type methionyl-tRNA synthetase (MetRS) present in all cells. To enable cell-selective labeling, we developed the longer-chain methionine analog azidonorleucine (Anl), which is not a good substrate for the wild-type MetRS and requires a mutant synthetase for activation. Cell-selective labeling can then be achieved by ensuring that the mutant MetRS is expressed only in the cells of interest.

Figure 6 shows a schematic representation of the cell-selective BONCAT method, and a sample in which bacterial cells have been labeled selectively in the presence of mammalian macrophages [38]. We are currently using such methods to examine host–pathogen interactions, bacterial biofilms, and cell-selective processes in live animals. We have also shown that labeling can be rendered sensitive to cell "state" as specified by the activation of one [39] or two [40] promoters, and that multiple cell types can be labeled with different dyes [41]. These methods allow investigators in microbiology, cell biology, neurobiology, and developmental biology to probe protein synthesis in complex biological systems with unprecedented specificity.

4 Convergence of Macromolecular Chemistry and Biology

Professor Staudinger's studies of macromolecular chemistry spanned natural and synthetic polymers; he drew heavily on both fields as he developed his ideas about macromolecular structure and behavior. He retained an interest in biological problems until late in life, stimulated in part by his wife, Magda, who was trained in plant physiology [1, 4]. In reading Professor Staudinger's Nobel Lecture [1], one can't help but be struck by his fascination with "the wonder of life in its chemical aspect," and with the role that macromolecular chemistry would play in helping us understand how living systems work. I believe Professor Staudinger would be pleased by the extent to which macromolecular chemistry and biology have now converged.

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Crosslinking with Hermann Staudinger

Fred Wudl

Abstract The key to the concept of re-mendable covalently bonded polymers developed in our group is a polymerization/crosslinking reaction discovered by Staudinger and later applied, partially, by Stille. This account gives the historical perspective on our results based on the Staudinger cyclopentadiene polymerization and crossing paths with Staudinger in personal life.

Keywords Cyclopentadiene · Polyesters · Reversible polymerization

Contents

1 Introduction 211
2 Prolog 212
3 Herman Staudinger and Re-Mending Crosslinked Polymers 213
4 Epilog, Hermann Staudinger's Niece 215
References 216

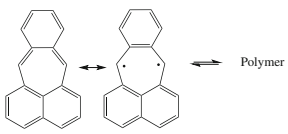
1 Introduction

I have crossed paths with Hermann Staudinger twice in my career. Once, understandably, as our research group developed self-mending polymers and a literature search revealed the 1926 paper by Staudinger and Bruson (see below). The second encounter was entirely serendipitous and will be explained later. The account is divided into three sections: "Prolog," "Hermann Staudinger and re-mending crosslinked polymers," and "Epilog, Hermann Staudinger's niece".

F. Wudl (✉)
Department of Materials, University of California, Santa Barbara, CA 93106, USA
e-mail: wudl@chem.ucsb.edu

2 Prolog

On October 1996, the research proposal "'Duranes': ultrahard high-strength organic polymeric materials" was submitted to the National Science Foundation (NSF). The summary page stated "We propose to develop a new approach to extended network, very high strength organic polymeric materials. Some of these materials will have ultrahard high-strength . . . ." and ". . . preparation of new extended network polymers based on reversible Diels Alder polymerizations. . ." The basic idea was that by multiple equilibrating reversible steps, the crosslinked polymeric solid would reach its lowest thermodynamic energy state with, possibly, concomitant maximum strength. Whitesisdes [1], among others, approached the preparation of very strong and very hard organic solids by exploring high degrees of sp^2 hybridized carbon crosslinking. We reasoned that, because the high density of crosslinks in the polymerization process leads to early gelation, the resulting material would be inherently low molecular weight and highly disordered. We further rationalized that fully reversible crosslinking and polymerization, first in the melt or solution and ultimately in the solid state, should lead to higher crosslinking density as well as higher degree of polymerization and hence strength. Although this would be almost impossible with sp^2 hybridized carbon networks, it should be possible with a combination of singly and doubly bonded carbon atoms. Early attempts to implement the concept with pleiadene (**l**) [2] and anthracene (**2**) [3] derivatives were not satisfactory. In the process of this exploration, we discovered that a previous study of pleiadene dimerization, where the authors [4–6] concluded that it was a concerted process, was incorrect. Dimerization proceeds through a diradical. Since these two approaches did not yield the desired result of accessible reversible polymerization, we examined a multi-furan (**4**) with a multi-maleimide (**5**) [7]. This system was successful in a different but equally interesting way, namely resulting in a re-mending solid that, unlike its predecessors [8], was capable of multiple cracking and re-mending.



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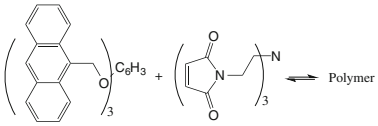

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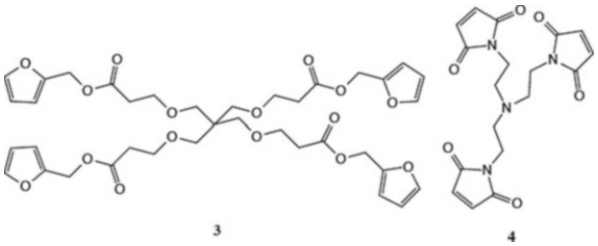


3 4

$$2(\mathbf{3}) \quad + \quad 3(\mathbf{4}) \rightleftharpoons \textbf{Polymer}$$

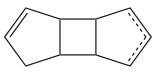
Because the reversibility of the Diels–Alder reaction at accessible temperatures was key to the concept of re-mending a polymeric solid, we considered other diene dienophile combinations but were dissatisfied with all we found in the literature for various reasons, but in the process realized that cyclopentadiene is a molecule that is a diene and a dienophile, a property that was a definite advantage over systems **2** and **3** + **4**. This led to our first encounter with Hermann Staudinger.

3 Herman Staudinger and Re-Mending Crosslinked Polymers

Cyclopentadiene (Cp) is thermodynamically unstable, converting itself to the Diels–Alder dimer. As is well known, cracking of the latter at 180°C is the standard method for the laboratory-scale production of Cp. By preparing α,ω-alkylidene bis (Cp), Stille and Plummer (S&P) employed the reversible dimerization of Cp as a possible polymerization reaction [9]. These scientists found, not surprisingly, that their monomers **3** were rather unstable at room temperature, so they purified them by low temperature chromatography. They also observed that their polymers became insoluble after a period of time at room temperature and even though they stored the monomers and polymers under anaerobic conditions, the polymers still became insoluble. These polymer scientists concluded "bulk polymerization. . . . even in the presence of free radical inhibitors gave insoluble thermosetting polymers, undoubtedly through a vinyl-type addition polymerization" [8] but did not explain how this "vinyl-type" polymerization was initiated. Stille and Plummer were aware of Staudinger and Bruson's (Sr&B) research on oligomerization and polymerization of Cp [10] but were not satisfied with Sr&B's conclusion that they had prepared $(Cp)_n$ and stated:

> Although a portion of the higher molecular weight polymer is a result of vinyl addition polymerization, the oligomers are formed through successive additions of cyclopentadiene through a Diels–Alder reaction

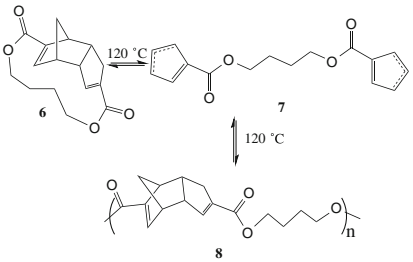
The statement that the higher molecular weight polymers of Sr&B were due to vinyl addition polymerization was made without providing a reference nor their own experimental results to support this assertion. Interestingly, Staudinger had a wrong structure for the dimer **5** in 1926, a logical structural assignment for the time, that was later corrected by Alder and Stein [11–13] in the period 1931–1934. The latter also characterized Staudinger's trimer and tetramer. Li Lao repeated Sr&B's work in 2001 [14] and showed by MALDI-MS that the higher polymer was at least $(Cp)_{18}$. Electron ionization mass spectroscopy (EI-MS) showed that the fragmentation was a clean successive loss of 66 atomic mass units (amu), corresponding to successive Cp loss. The polymer is completely intractable because it is insoluble in all common solvents (purified by multiple Soxhlet extractions) and infusible, with a TGA-determined decomposition at 321°C. Li Lao had no evidence of vinyl addition in the NMR spectra of the oligomers and of the hot trichlorobenzene-soluble fraction of the polymer. More recently, we were able to process the polymer through sintering [15].

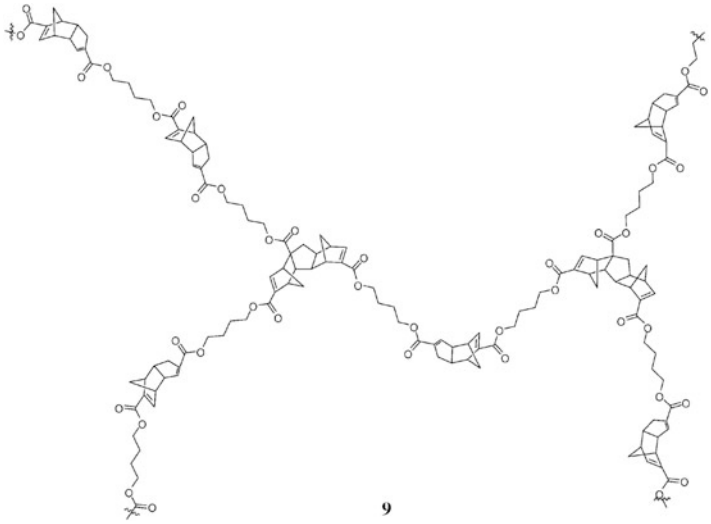


5

Even though the system **3** + **4** was excellent for proving the re-mending concept based on reversible polymerization and crosslinking, there were two salient problems: First, the tris(imide) **4** was insoluble in **3**, requiring a solvent that needed to be removed before polymerization was initiated. Second, the stoichiometry was very difficult to control. This led us to cast about and find a way to use a single component system where all that was required was to heat the starting material to obtain a crosslinked monolith. We were inspired by S&P for a monomer and Sr&B for the crosslinking. However, we did not want to have to go through the difficulties that were described by the former in isolating the bis(Cp) alkyls. Eventually, we designed the pre-monomer **6**. The latter, when cracked open produced the S&P-type monomer **7** that polymerized to **8**. The latter, in the presence of unreacted **7**, underwent Sr&B crosslinking to the final solid that could be hypothesized to have the idealized structure **9** [16] based on the Sr&B oligomers and polymer.[1]

[1] The design and synthesis of **6** was proposed to the NSF in 1999 as a renewal proposal of the 1996 proposal mentioned in the "Prolog". The proposal was reviewed negatively and future attempts to obtain funds from the NSF for this research had an equal fate, putting an end to the program in our group.





We believe that S&P did not need to interpret the thermosetting of their bis(Cp)s to a vinyl-type addition but to Cp Diels–Alder crosslinking. The approach to re-mending plastics through precursor monomers of type **6** proved to be quite versatile in that one could prepare a wide variety of plastics ranging from brittle solids to stretchable rubbers by simply varying the number of carbons and heteroatoms in the tether, as well as the crosslinking temperature [17].

In summary, a relatively obscure work of Staudinger that has laid dormant and partially applied by Stille could have important implications in modern, functional polymers.

4 Epilog, Hermann Staudinger's Niece

The indirect contact with Herman Staudinger was through Mrs. Ruth Schaffner. Mrs. Schaffner was an art dealer in Los Angeles, Santa Barbara and Nairobi, Kenya. Schaffner was her married name. She was born in Germany and emigrated via Paris

to New York as a young woman. Her husband was Joseph Schaffner of the famous Hart Schaffner & Marx clothing fame. I met Ruth when I purchased property from her in Santa Barbara. When she learned about my profession, she stated that her uncle was also an organic chemist, in fact, she said he was a Nobel laureate, had I heard of Hermann Staudinger? Actually she was the daughter of another famous Staudinger, Hans Staudinger (http://en.wikipedia.org/wiki/Hans_Staudinger), an economist and sociologist. Because of his political beliefs and being married to a Jewish woman, he had to escape Germany, ultimately landing in the USA and becoming the Dean of the New School of Social Research in New York City.

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Another Important 60th Anniversary

Nadrian C. Seeman

Abstract The combination of synthetic stably branched DNA and sticky ended cohesion has led to the development of structural DNA nanotechnology over the past three decades. Sticky ends on synthetic molecules can be programmed to interact to self-assemble into a variety of geometrical species. Thus, simple branched molecules lead directly to the construction of polyhedra whose edges consist of double helical DNA, and whose vertices correspond to the branch points. Stiff branched motifs must be used to generate self-assembled two-dimensional and three-dimensional periodic lattices of DNA (crystals). DNA has also been used to make a number of nanomechanical devices, including molecules that change their shape, and molecules that can walk or somersault along a DNA sidewalk. Complex mechanical arrangements have been constructed, such as a nanoscale assembly line.

Keywords Branched DNA · Sticky Ends. Information-Directed Self Assembly · Structural DNA Nanotechnology

This volume celebrates the 60th anniversary of the award of the Nobel Prize to Hermann Staudinger in 1953 for his work in establishing the field of polymer chemistry. However, this is also the 60th anniversary of another landmark in polymer science, the proposal by Watson and Crick [1] of the iconic double helical structure for the DNA molecule, arguably the most influential polymer structure known. We are all aware that DNA is the molecule that nature uses as genetic material. The information content of DNA is linearly encrypted in the sequence of

N.C. Seeman
Department of Chemistry, New York University, New York, NY 10003, USA
e-mail: ned.seeman@nyu.edu

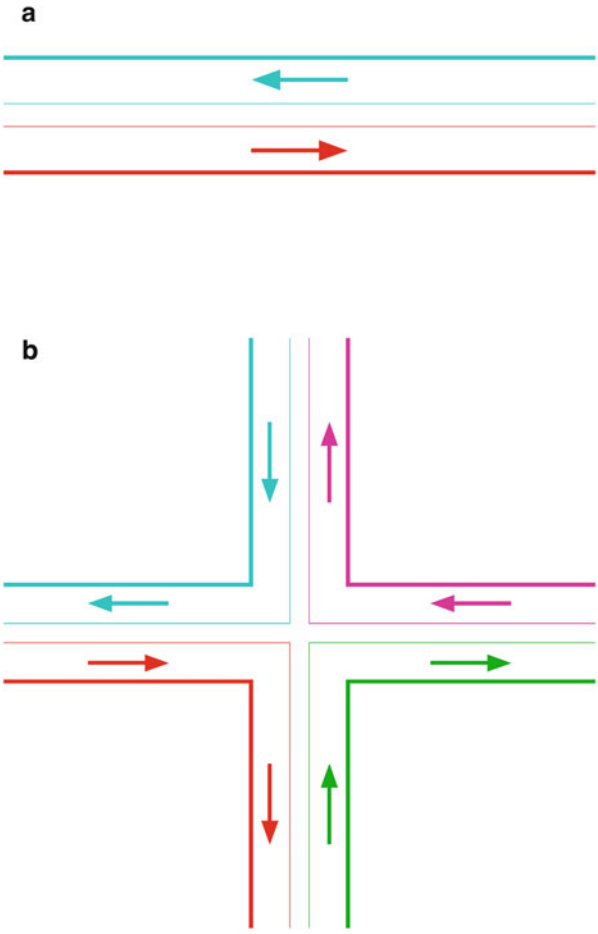

Fig. 1 DNA as a highway. (**a**) An unwound double helix of DNA. The two lanes represent the two antiparallel strands of the DNA double helix. The direction of traffic flow is indicated. (**b**) A four-arm branched junction as an intersection in a highway. The directions of traffic flow indicate the ways that the strands in a four-arm branched junction would go

the side chains (called bases) in each residue (called a nucleotide). Its double helical structure facilitates high fidelity recognition between the nucleotides of complementary molecules. The Watson–Crick pairing of the four DNA bases in pairs, adenine (A) with thymine (T) and of guanine (G) with cytosine (C), is clearly the favored type of interaction between polynucleotides. This form of molecular recognition lies at the heart of our understanding of molecular biology, particularly molecular genetics. Nevertheless, biology is no longer the only branch of science where DNA is finding a significant role: It is now possible to exploit DNA complementarity to control the structure of matter.

The two strands of the double helix are antiparallel, so it is natural to think about them as being analogous to the lanes of a road, as illustrated in Fig. 1a. The drawing shows two different directions of traffic flow, and a thin divider between the lanes. The divider is analogous to the helix axis, and it is clearly linear. Regardless of whether the road is straight (as drawn) or curved, the divider remains linear, in that

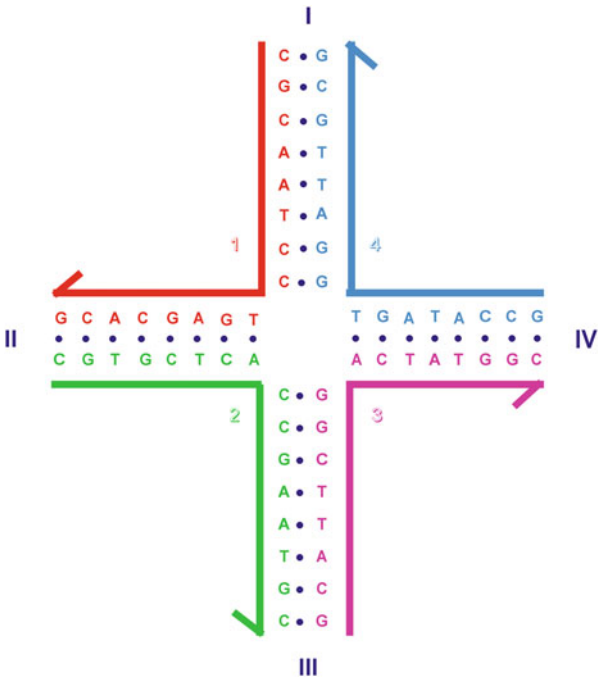

Fig. 2 The sequence of a four-arm branched junction. The pairing shown is consistent with the formation of this junction. The sequence has been selected so that the target junction shown is the most likely structure to form. Seeman [2] describes how to design a sequence like this one

it is unbranched. Thinking about DNA as a road makes it easy to imagine an intersection in the road, as illustrated in Fig. 1b. In this case, all of the traffic is shown to turn right when it reaches the intersection. What we are showing is DNA branched at the level of secondary structure. Synthetic strands of DNA can be designed to produce branches like this simply by selecting their sequences to form the base pairs that support this type of structure [2]. An example is shown in Fig. 2.

Genetic engineers have used the notion of sticky-ended cohesion since the early 1970s to stitch DNA molecules together [3]. This approach has allowed them to clone genes and to make linear DNA arrangements (including circular molecules) for a variety of purposes, ranging from study of genes, the high level production of gene products (proteins), and for synthetic biology. The idea behind sticky ended cohesion is shown in Fig. 3. At the top, Fig. 3a shows two (unwound) double helices, each of which contains a pair of strands; one of the two strands is four nucleotides longer than the other. This length difference leads to an overhang on each duplex. The central portion of Fig. 3a shows that the two overhangs can cohere, if they are complementary. This is very powerful because it is an affinity interaction that can be programmed with great diversity in synthetic molecules. The bottom of Fig. 3a shows that it is possible to ligate the two molecules to be covalently linked if one wishes to do so. Figure 3b shows a portion of a crystal structure that is held together by sticky ends. The key point illustrated here is that sticky-ended cohesion leads to a predictable local product structure, which is B-DNA, the conventional structure of DNA with which we are all familiar [4]. Thus, not only is sticky-ended cohesion a

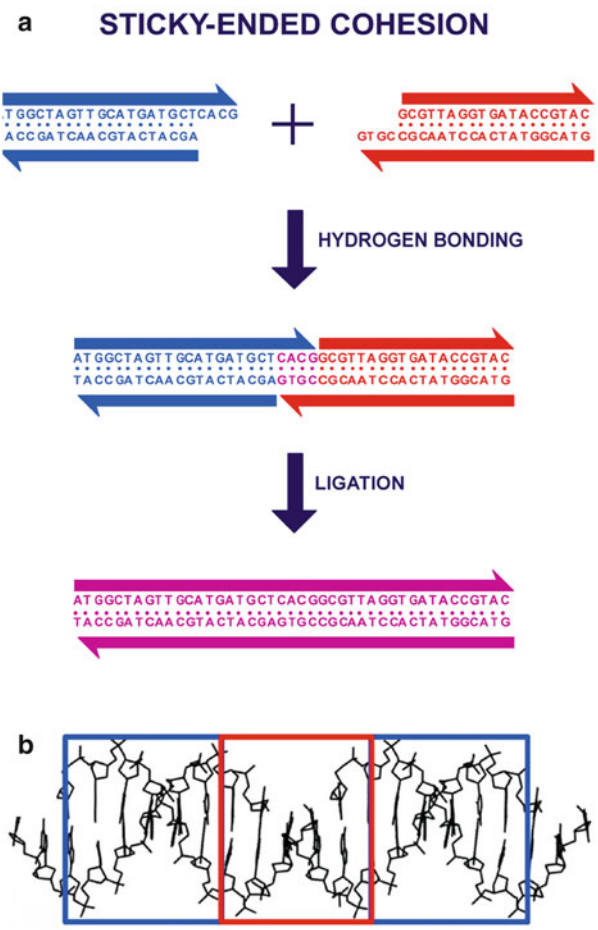

Fig. 3 Sticky-ended cohesion. (**a**) Cohesion between two molecular overhangs. Two duplex molecules are shown (*top*). Each has a single-stranded molecular overhang that is complementary to the overhang on the other molecule. When mixed, the two molecules can cohere in solution (*center*). The four strands can be ligated to form two strands from the original four (*bottom*). (**b**) Structural features of stick-ended cohesion. A crystal structure [4] is shown that contains DNA decamers whose cohesion in the direction of the helix axis (*horizontal*) is directed by dinucleotide sticky ends. This interaction is seen readily in the *center box*, where the continuity of the chains is interrupted by gaps caused by the absence of phosphate linkages. The two *outer boxes* contain B-form duplex DNA. It is a half-turn away from the DNA in the *center box*, so it is upside-down from it, but otherwise the structure is the same. Thus, sticky ends cohere to form B-DNA, and one can use this information in a predictive fashion to estimate the local structures of DNA constructs held together by sticky ends

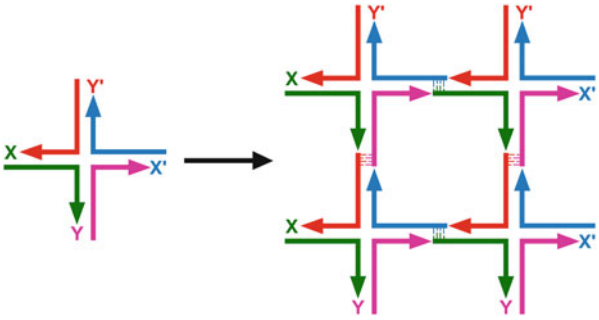

Fig. 4 Self-assembly of branched DNA molecules to form larger arrangements. *Left*: Four-arm branched junction made from four differently colored strands. Its double helical domains are tailed in 5′ sticky ends labeled (counter-clockwise from the left) *X*, *Y*, *X*′, and *Y*′; the sticky ends are indicated by small extensions from the main strand (our convention is to represent 3′ ends by *arrowheads*). The primed sticky ends complement the unprimed ones. *Right*: Four of these junctions can self-assemble through this complementarity to yield a quadrilateral. The sticky ends have come together in a complementary fashion. Note that this assembly does not use up all the available sticky ends, so that those that are left over could be used to generate a lattice in 2D, and, indeed, in 3D

programmable nanoscale affinity interaction, the geometrical relationship of the two participants is known a priori.

Figure 4 illustrates how branched DNA is combined with sticky-ended cohesion in structural DNA nanotechnology [2]. A branched junction is shown on the left of the drawing; its helices terminate in sticky ends X and Y, along with their complements, X' and Y'. The right side of Fig. 4 shows how four of these junctions are assembled into a quadrilateral by the sticky ends. It is evident that there are many sticky ends on the outside of the quadrilateral, so the assembly is not limited to just this individual object, but can be extended into an infinite 2D lattice. If the motif is rigid (the one shown in the illustration is not, but many are known), the use of sticky ends to bring branched DNA molecules together can lead to the programmability of the structure of matter, not only in the two dimensions shown, but in 3D.

Many complex and rigid motifs have been built. The simplest branched motifs consist of N strands of DNA that form branched junctions with N arms, as shown in Fig. 5 [5]. The front end of each strand pairs with the back end of the strand next to it, thereby forming a double helical arm. These simple motifs are known not to be rigid, but they can be used to construct simple polyhedral catenanes, such as the cube [6] and the truncated octahedron [7] shown in Fig. 6. Rigid motifs usually require double helices to be joined more than once. Examples are the two-domain and three-domain molecules shown in Fig. 7. The notion of reciprocal exchange, which enables two strands to be fused, creating a crossover point is shown in Fig. 7a [8]. Figure 7b shows a variety of sample motifs that have been used in the area of structural DNA nanotechnology. The rigid DX motif contains two helical domains joined twice; in the DX + J motif another helix has been added to the DX motif (its

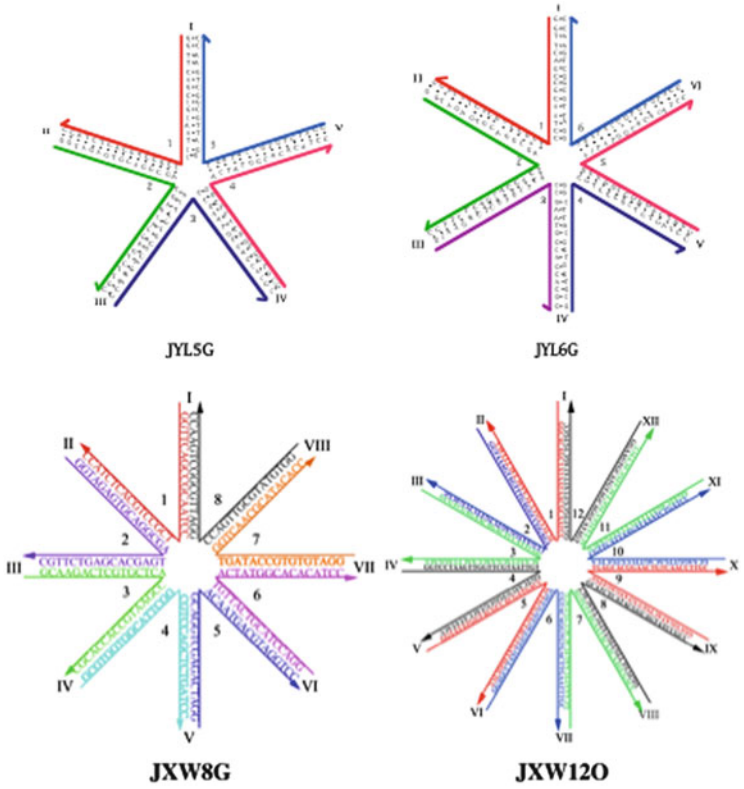

Fig. 5 Multi-arm junctions. Five-arm and six-arm junctions are shown at the *top*, whereas eight-arm and twelve-arm junctions are shown at the *bottom*. The color codes for the five-arm, six-arm and eight-arm junctions are arbitrary, but that of the twelve-arm junction is designed to show that the junction flanking sequences are the same every four arms. Regardless of this aspect of sequence symmetry, the junctions do not appear to undergo branch migration

helix axis is usually perpendicular to the plane of the DX's helix axes). The TX motif contains three double helical domains. The DX and the TX motifs contain crossover points formed by reciprocal exchange between strands of opposite polarity. Two other motifs are shown, the PX motif and a topological variant of it, the JX_2 motif; these motifs are formed by reciprocal exchange between strands of the same polarity. Note that the PX motif and the JX_2 have identical tops, but that their bottoms are rotated by a half turn. As a practical matter, crossovers are placed in motifs by sequence selection [2], i.e., choosing sequences that continue Watson–Crick complementarity only if the backbone switches its pairing partners, inducing crossovers.

The rigidity of the DX motif [9] enabled it to be used as the basis for the first 2D array designed from DNA. Objects that do not entail repeating motifs can be rigid or flexible, depending on the ultimate uses to which they will be put. However, if one is building a repeating (periodic) array, it is necessary to incorporate sufficient

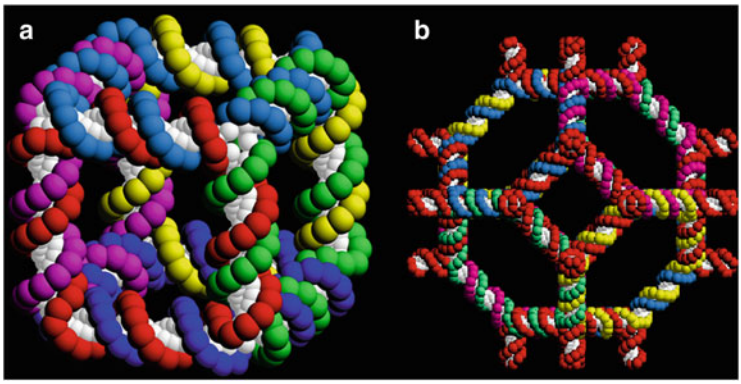

Fig. 6 Ligated products from flexible DNA components. (**a**) Stick cube and (**b**) stick truncated octahedron. The images show that each edge of the two figures contains two turns of double helical DNA. There are two turns of DNA between the vertices of each polyhedron, making them, respectively, a hexacatenane and a 14-catenane

rigidity to ensure that the growing array does not bend back on itself, thereby poisoning the growth of the lattice. Figure 8 shows three lattices [10, 11] built from motifs shown in Fig. 7. Figure 8a shows a two-tile array that alternates DX motifs with DX + J motifs. The extra domain in the DX + J motif leads to a stripe in the pattern. The size of the motifs is 16 nm in the horizontal direction, so the stripes should be separated by 32 nm, which can be seen in the atomic force micrograph on the right. A related array is shown in Fig. 8b, where three DX motifs and a single DX + J motif are seen to form an array with ~64 nm stripes. Figure 8c illustrates a motif made from two TX motifs connected from the top of one to the bottom of the other (A and B), creating gaps in the lattice. The gaps are filled by a rotated TX molecule (C') and by a duplex (D). The AFM image can be seen on the right.

The success in self-assembling the variety of 2D arrays shown in Fig. 8 suggests that it ought to be possible to organize DNA motifs into 3D crystals. The criteria for evaluating crystals are stricter than those for evaluating 2D arrays: Atomic force micrographs usually yield resolutions of about 7–10 nm, but crystals of DNA must diffract X-rays to at least 4–5 Å to be readily interpretable. The motif that has been used to produce 3D crystals is the tensegrity triangle [12], first developed by Chengde Mao. Sticky ends can be added to these molecules to produce self-assembled designed rhombohedral crystals of the requisite resolution [13]. Figure 9a illustrates the environment of a single tensegrity triangle in a crystal. The three helices are colored differently, and it is evident that the axes of the three helices point in three independent directions in space. Figure 9b shows that the centers of the triangles can be placed on the vertices of a rhombohedron. The cavity within the rhombohedron has a volume of about 100 nm^3.

A large variety of nanomechanical devices have been produced from DNA. The most interesting ones are those that avail themselves of the programmability of DNA because they can be individually addressed, thereby enabling their states to be

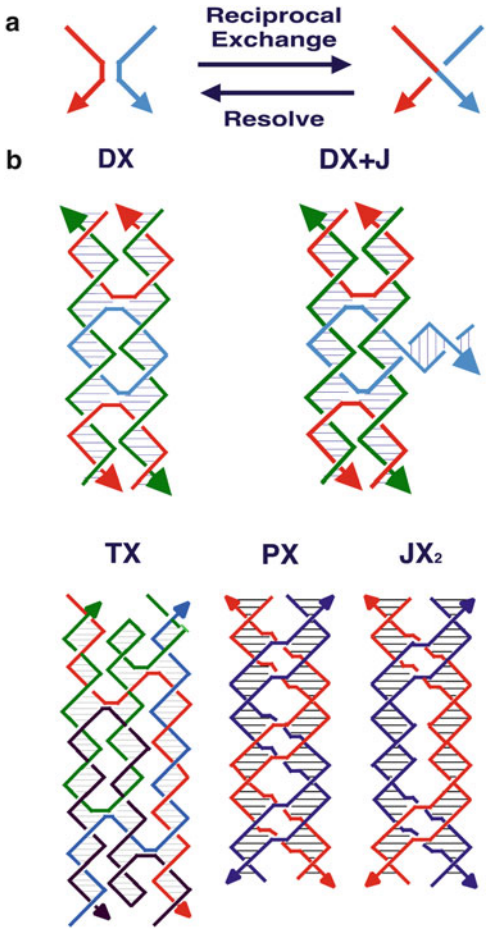

Fig. 7 Motif generation by reciprocal exchange. (**a**) The fundamental operation. The basic operation of reciprocal exchange is shown: A *red* strand and a *blue* strand become a *red–blue* and a *blue–red* strand following the operation. (**b**) Motifs that can result from reciprocal exchange of DNA molecules. The DX motif results from two reciprocal exchanges between double helical motifs. The DX + J motif contains another DNA domain. Usually this domain is oriented perpendicular to the plane of the two helix axes in the DX part of the motif. When this orientation is achieved, the extra domain can behave as a topographic marker for 2D arrays containing the DX + J motif. In the TX motif , a third domain has been added to a DX motif; again the exchanges take place between strands of opposite polarity. The PX molecule is formed by exchanges between strands of identical polarity at every possible position. The JX_2 molecule is one of the topoisomers of the PX motif and lacks two of these exchanges, leading to its bottom being flipped a half-turn, relative to its top

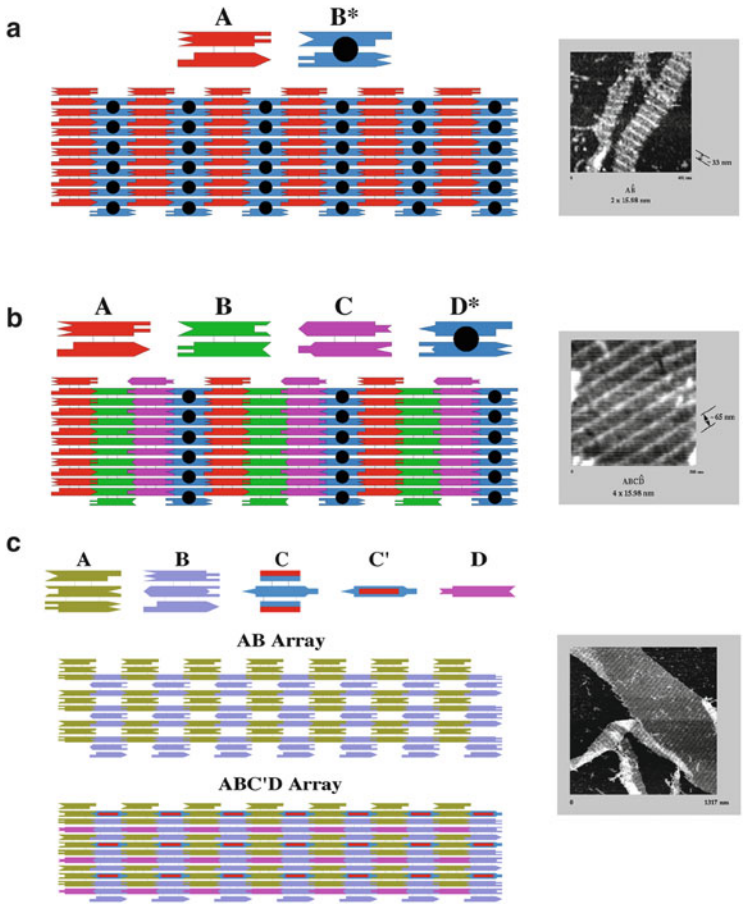

Fig. 8 2D DNA arrays. (**a**) Two DX molecules tile the plane. Conventional DX molecule, *A*, and a DX + J molecule, *B**, are seen to tile the plane. The extra domain (*black circles*) on B* leads to *stripes* in the array. The molecules are 4 × 16 nm, so the stripes are ~32 nm apart, as seen in the AFM image on the *right*. (**b**) Four DX molecules (*A*–*D**) tile the plane. This arrangement is similar to (**a**), but there is only one DX + J molecule, *D**, so the stripes are separated by ~64 nm, as seen on the *right*. (**c**) TX array. Two TX tiles, *A* and *B*, are connected by complementarity between their first and third double helical domains, resulting in spaces between the tiles. *D* is a linear duplex that fits in the *yellow rows*, and *C* is a TX re-phased by three nucleotide pairs, and the rephased version is labeled *C*′; it fits into the *gray rows* and extends a double helical domain beyond the AB plane in both directions, as shown on the *right*

changed independently. The PX–JX_2 device is an example of such a two-state sequence-dependent device: It switches its shape by a rotation through a half-turn from the PX conformation to the JX_2 conformation; the portions of the PX and JX_2 motifs that contain toeholds [14] are flanked by nicks that enable them to be exchanged to produce a robust device [15]. Figure 10 illustrates the first nanoscale

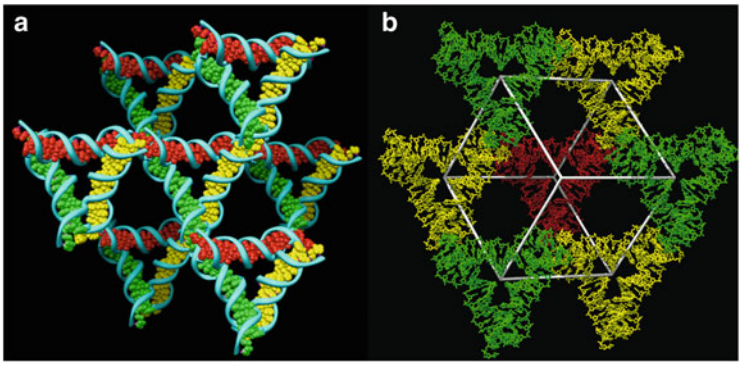

Fig. 9 The 3D lattice formed by tensegrity triangles. (**a**) The surroundings of an individual triangle. This simplified image distinguishes the three independent directions by the colors (*red*, *green*, and *yellow*) of their base pairs. Thus, the *central triangle* is shown flanked by three other pairs of triangles in the three differently colored directions. (**b**) The rhombohedral cavity formed by the tensegrity triangles. This view shows seven of the eight tensegrity triangles that comprise the corners of the rhombohedron. The outline of the cavity is shown in *white*. The *red triangle* at the back connects through one edge each to the three *yellow triangles* whose centers lie in a plane somewhat closer to the viewer. The *yellow triangles* are connected through two edges each to two different *green triangles* that are in a plane even nearer the viewer. A final *red triangle* that would cap the structure has been omitted for clarity. That triangle would be directly above the *red triangle*, and would be even closer to the viewer than the *green triangles*

assembly line [16]. It consists of three independent PX–JX_2 devices that have been incorporated into a large programmed 2D DNA surface, known as DNA origami [17]. DNA origami consists of a long scaffold strand, typically M13 single-stranded DNA (about 7,500 nucleotides) and about 200 "staple strands" that fold it into its shape; each can be addressed individually. Thus, specific PX–JX_2 devices are located in each of the three positions near the top of the origami construct, and each carries a specific cargo. The three cargoes (left to right in Fig. 10) are a 5 nm gold nanoparticle, a pair of coupled 5 nm gold nanoparticles, and a 10 nm gold nanoparticle. The bottom of the construct contains a row of sites where a somersaulting tensegrity triangle walker can pass by the three cargo stations. If the PX–JX_2 device is in the JX_2 conformation, nothing will happen when the walker passes the cargo station. If the walker is in the PX conformation, the cargo will be transferred to the walker. Thus, depending on the programming of the assembly line, eight different products (2^3) can be produced. Figure 10 shows the assembly of the product consisting of adding all cargoes to the walker. The right-hand column shows AFM images of the assembly line that correspond to the schematics in the middle column.

I have tried to give a flavor of structural DNA nanotechnology by illustrations of work from my own laboratory. A decade ago this would have been a very complete coverage of this field. However, the field has grown enormously since then, and much more has been done. There are numerous laboratories worldwide that have participated in this enterprise, and each contains many workers, not just a principal

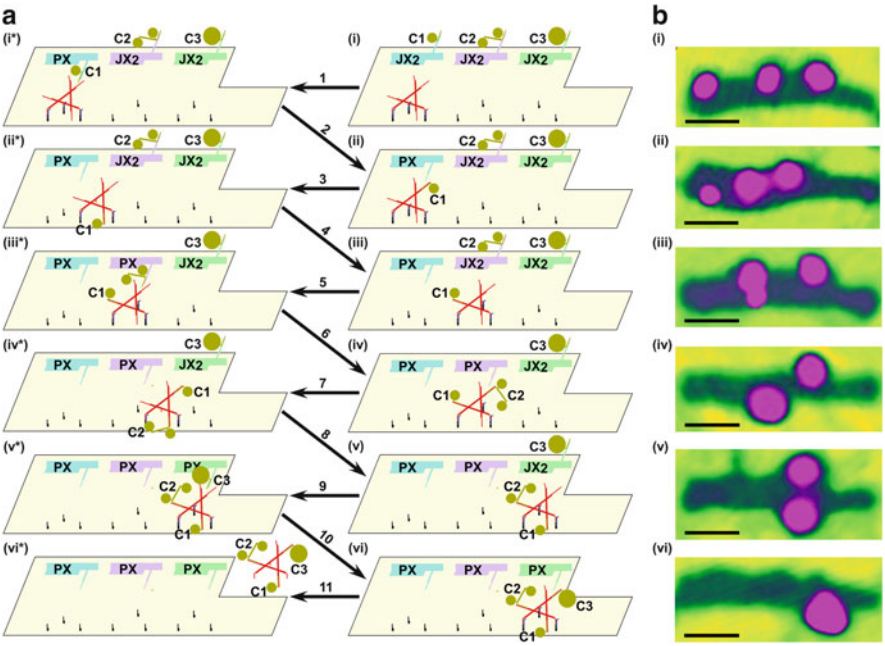

Fig. 10 Steps in the assembly of a triple addition product by a nanoscale assembly line. Schematics are shown in (**a**) and atomic force micrographs of the *right-hand column* of (**a**) are shown in (**b**). AFM was performed by tapping in air; this mode of AFM results in only the nanoparticles and the origami being visible, and the individual nanoparticle components are not resolved from each other. Panel (**ai**) illustrates the origami array with cassettes and walker in the starting position. The cassettes are set to the default JX_2 (OFF) state, with their arms pointing away from the walker pathway. Different cargoes on the arms (*C1*, 5 nm Au nanoparticle on cassette 1; *C2*, a linked 5 nm Au pair of nanoparticles on cassette 2; and *C3*, a 10 nm Au nanoparticle on cassette 3) are visible both schematically (**a**) and in the AFM (**b**). *Step 1* shows cassette 1 switched from the JX_2 state to the PX (ON) state, bringing cargo 1 (*C1*) close to the walker hand (**ai***). *Step 2* illustrates the addition of cargo 1 from the cassette 1 to the walker by DNA branch migration; the movement of cargo 1 is evident in the AFM (**bii**). *Step 3* shows the walker with cargo 1 walking the first step along the pathway. *Step 4* illustrates the walker with cargo 1 walking the 2nd step, positioning itself near cassette 2, which is visible both schematically and in the AFM (**biii**). *Step 5* shows cassette 2 is switched from the JX_2 state to the PX state, bringing cargo 2 (*C2*) close to the walker. *Step 6* illustrates the addition of cargo 2 from cassette 2 to the walker by branch migration; the addition of cargo 2 is evident in the AFM (**biv**). *Step 7* shows the walker with cargo 1 and cargo 2 walking the 3rd step along the pathway. *Step 8* illustrates the walker with both cargo 1 and cargo 2 walking the 4th step to be close to cassette 3; the walking is clearly visible in the AFM (**bv**). *Step 9* shows cassette 3 switched from the JX_2 state to the PX state, bringing cargo 3 (*C3*) close to the walker. *Step 10* illustrates the addition of cargo 3 from cassette 3 to the walker by branch migration; the addition of cargo 3 is visible in the AFM (**bvi**). *Step 11* shows the walker with all three cargo components released from the origami. Scale bars: 50 nm

investigator. Thus, there are many investigators who are using the information in DNA to form nanoscale materials and structures for a variety of purposes. The growth of this field in the last decade is arguably the most important thing that has

happened to it. I look forward to the advances of the coming decade, and I am optimistic about the work that will be produced in the seventh decade since both Staudinger's recognition and the Watson–Crick proposal.

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Coordination-Driven Supramolecular Macromolecules via the Directional Bonding Approach

Timothy R. Cook and Peter J. Stang

Abstract Coordination-driven self-assembly is a process that generates supramolecular architectures from molecular precursors by exploiting the favorable properties of metal–ligand bonding. The discrete supramolecular coordination complexes (SCCs) thus obtained have enjoyed multiple decades of development, focused initially on the design and reactivity of rigid building blocks with specific directionalities and angularities, thereby populating a molecular library of complementary donor and acceptor subunits. More recently, efforts have broadened to encompass pre- and post-self-assembly modifications, which have lead to new routes for obtaining functionalized metallacages and metallacycles, multicomponent assemblies incorporating multiple types of ligands in a single scaffold, and supramolecular transformations that quantitatively alter the structure of a given SCC, furnishing an entirely new architecture.

Keywords Coordination-driven self-assembly · Directional bonding · Metallacage · Metallacycle · Supramolecular coordination complex

Contents

1 Introduction 230
2 Molecular Squares: Establishing a Molecular Library 233
3 Triangles, Hexagons, and Other 2D Metallacycles 234
4 Supramolecular Polyhedra 236
4.1 Platonic and Archimedean Solids 236
4.2 Prismatic Metallacages 238

T.R. Cook (✉) and P.J. Stang
Department of Chemistry, University of Utah, Salt Lake City, UT, USA
e-mail: timcook@chem.utah.edu

5 Multicomponent Self-Assembly 240
5.1 Platinum-Pyridyl-Carboxylate Multicomponent Assembly 241
5.2 Prismatic Metallacages 241
5.3 Supramolecule-to-Supramolecule Transformation 243
5.4 Post-Self-Assembly Functionalization 245
6 Summary, Conclusion, and Outlook 245
References 246

Abbreviations

4,4′-bipy	4,4′-Bipyridine
bzqn	7,8-Benzoquinoline
Cp	Cyclopentadienyl
DArF	*N*,*N*-Diarylformamidinate
dppp	Diphenylphosphinopropane
en	1,2-Diaminoethane
OTf	Triflate anion
SCC	Supramolecular coordination complex
thpy	2-(2-Thienyl)pyridine
UH	Uracil monoanion

1 Introduction

The motto "united we stand, divided we fall" has broad implications, resulting in its widespread use in songs, public speeches, political movements, and popular culture. Although attributed to Aesop (ca. sixth century BC) [1], nature has ultimately championed this concept on the molecular level with many examples of complex architectures that owe their syntheses and stabilities to the spontaneous formation of weak, non-directional interactions. When these hydrogen bonds, van der Waals interactions, etc. work in concert to adjoin multiple molecular building blocks, fascinating examples of complexity, symmetry, and function result, oftentimes unparalleled and irreproducible in the laboratory. Singularly, these bonds are easily ruptured, with hydrogen bonds providing a mere 4–5 kcal mol^{-1} of stabilization per instance. Van der Waals interactions, encompassing Keesom, Debye, and London dispersion forces, are even weaker still. Yet, when the 500,000 to 2.5 million hydrogen bonds of an exemplary macromolecule such as human genomic DNA are considered in aggregate, the resulting species is greatly stabilized by these interactions that are pauce in strength but not in number. Likewise, the myriad van der Waals interactions between a surface and the spatulae projecting from the footpads of gecko lizards provides the sole attractive force by which these creatures adhere to a number of materials – a fascinating example of the collective robustness of seemingly trivial molecular interactions [2].

Whereas natural systems are advantaged by millions of years of evolution, providing biosynthetic routes to carefully control and organize weak interactions that are otherwise difficult to direct, scientists can exploit materials and conditions

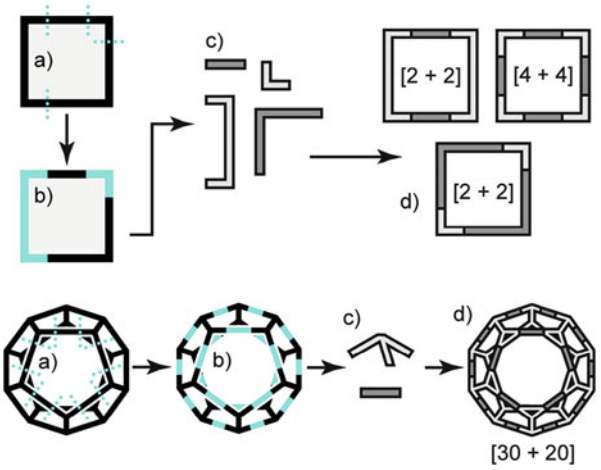

Fig. 1 The directional bonding method fragments a target polygon or polyhedron (*a*) at logical breaking points (*b*) to define the angularity and directionality of individual precursors (*c*) which can be combined in specific ratios to generate a supramolecular analogue (*d*)

without the bounds of natural serendipity. As such, molecules that would otherwise never combine by random chance can be brought together using solvents and conditions that would be unheard of outside of the chemist's domain, with exacting control over the various parameters that affect a reaction. With this level of control also comes the realization that the favorable properties of the weak interactions found in natural macromolecules are preserved in metal–ligand interactions, which also provide a means to control directionality.

Specific transition metals afford predictable and controllable coordination geometries that facilitate manipulation of the arrangement and number of substitutionally labile sites at a given metal center, thus imparting spatial control over Lewis-acidic "acceptor" building blocks. Likewise, the orientation and directionality of multiple Lewis-basic sites can be tuned using rigid organic moieties such as phenyl, ethenyl, and ethynyl groups, providing a route for the rational design of "donor" precursors. These complementary donor and acceptor molecules interact through the spontaneous formation of metal–ligand bonds. Careful considerations regarding the directionalities of the building blocks and the stoichiometries of mixing allow the self-assembly reactions of single, discrete metallacycles or metallacages known as supramolecular coordination complexes (SCCs).

Theoretically, a given polygon, polyhedron, prism, etc. may be deconstructed to its constituent edges, vertices, and faces. Reproducing such a shape on the molecular level through self-assembly demands that the angles, sizes, and shapes of these constituents be reproduced as encoded information in the donor and acceptor building blocks, as defined above. If the necessary directionalities are preserved and the complementary precursors are mixed in proper ratios, as determined from the relative number of edges, vertices, and faces found in the target architecture, the spontaneous formation of multiple metal–ligand bonds will provide the driving force for the formation of discrete SCCs (Fig. 1)

In practice, the random bimolecular interactions of donors and acceptors need not orient the precursors found in a resulting intermediate oligomer to afford the directionality demanded of the target polygon or polyhedron. However, the use of

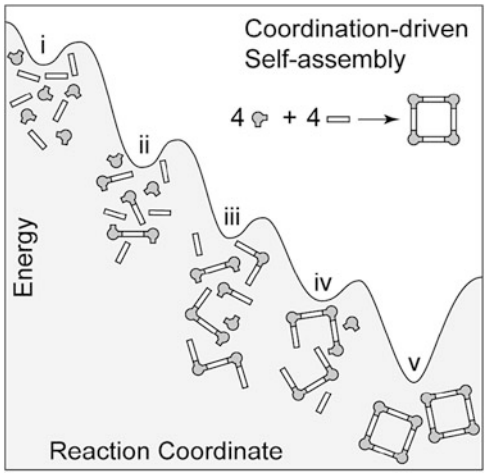

Fig. 2 An ensemble of molecular precursors is randomly distributed upon mixing (*i*). The spontaneous formation of metal–ligand bonds generates small intermediates (*ii*), which grow in scope to include multiple building blocks (*iii*) that may not be correctly oriented. Random dissociation and further coordination generates increasingly stable intermediates (*iv*) that ultimately funnel to discrete, complete SCCs as a thermodynamic minimum (*v*)

reversible metal–ligand coordination provides a mechanism for "self-healing" in these system, a process by which the ongoing formation and dissociation of oligomeric intermediates eventually corrects these defective orientations. As such, coordination-driven self-assembly is most effective under thermodynamic control, where any and all kinetic intermediates ultimately funnel to a single, thermodynamic product. Since the angularity, stoichiometry, and size of the precursors were selected with the demands of a given target shape in mind, the target SCC geometry is enthalpically favored. Furthermore, the discrete nature of an SCC provides an entropic impetus over undesirable polymeric products, which would minimize the total number of molecules formed (Fig. 2). A second caveat that must be considered in the design of SCCs arises from molecular distortions that can occur even when using the most rigid of functional groups. Rotations about bonds, deviations from idealized coordination geometries, and other deviances can alter the theoretical angularities of building blocks. This is particularly apparent when considering the solid state structure of certain SCCs. Recently, a de novo-based computational method was introduced by Young and Hay that addresses these distortions [3]. Although the authors present their computational approach in contrast to the directional bonding method, in reality it is a useful enhancement rather than a new approach entirely. As it better identifies the encoded angularities of the precursors found in distorted SCCs, it serves to illustrate the power and versatility of directional bonding: a method that can be applied for simple systems with a basic understanding of geometry yet also lends itself to contemporary computational sophistication in order to explore more complex scaffolds in the context of molecular distortions.

Herein, recent advances in coordination-driven self-assembly are discussed in the context of the historical foundation of the directional bonding approach and its use to furnish supramolecular coordination complexes [4–8]. In the interest of brevity, this

narrative focuses on edge- and face-directed self-assembly, however, the application and extension of direction bonding to novel design strategies and new functions must not be overlooked [7, 9–16]. The paradigm of two-component assembly, wherein single types of donor and acceptors are combined, is broken with the realization that heteroligated metal sites provide a new means to control interactions between subunits. This technique can be used to effect supramolecule-to-supramolecule transformations and provide scaffolds for functionalized SCCs via pre- and post-self-assembly modifications.

2 Molecular Squares: Establishing a Molecular Library

Among the simplest of the SCCs are square metallacycles. Following the technique of directional bonding as introduced above, a square is easily reduced to four vertices and four edges, wherein the angle at each vertex is 90°. Despite this simplicity, even metallacyclic squares afford some level of versatility regarding the choice of subunits. A [4+4] assembly represents each edge and vertice as an individual subunit, demanding a ditopic 90° tecton interaction with a complementary ditopic linear subunit. An early first example of directional bonding, predating further development of this strategy by almost a decade, is the tetranuclear square $\{(CO)_4M\}_4(P(OCH_2)_3P)_4$ (M = W, Cr) prepared by Verkade and coworkers [17]. The combination of four equivalents of a metal acceptor with an equal amount of a linear donor was later demonstrated with square planar Group 10 metal ions and N-heterocyclic donors, two broad categories of building blocks that would later enjoy use in many new self-assembly reactions. Pd-based squares, of which the $[(en)Pd(4,4'\text{-bipy})]_4(NO_3)_8$ variant of Fujita and coworkers is a primary example [18], were quickly joined in the literature by Pt analogues, such as $[(en)Pt(UH\text{-}N1, N3)]_4(NO_3)_4$ (en = 1,2-diaminoethane, UH = uracil monoanion) [19]. Upon replacing the amine capping group with phosphine-based ligands, Stang and coworkers systematically developed a suite of molecular squares, beginning with $[(dppp)_2M(4,4'\text{-bipy})]_4(OTf)_8$ (dppp = diphenylphosphinopropane, M = Pd, Pt) [20]. This intial [4+4] square established a general synthetic route for the combination of *cis*-capped Pt and Pd phopshine acceptors with linear, neutral donors to furnish cationic tetranuclear SCCs [21].

These squares provided the first evidence that such self-assembly reactions were general for a variety of building blocks; the specific donors and acceptors used could be changed without affecting the result of a [4+4] square (Fig. 3). The fledgling directional bonding method was further developed by the recognition that squares could also be generated in a [2+2] fashion, provided that two of the requisite 90° angles could be encoded into the donor precursor. This was achieved first by inbedding an organometallic Pt-aryl corner into a nitrile donor [22, 23] and later by generating a diypridyl iodonium ligand capable of interacting with the previously employed *cis*-capped Pt and Pd acceptors [24, 25]. The use of titanocene to install a 90° angle for [2+2] squares [26] later inspired a relatively rare

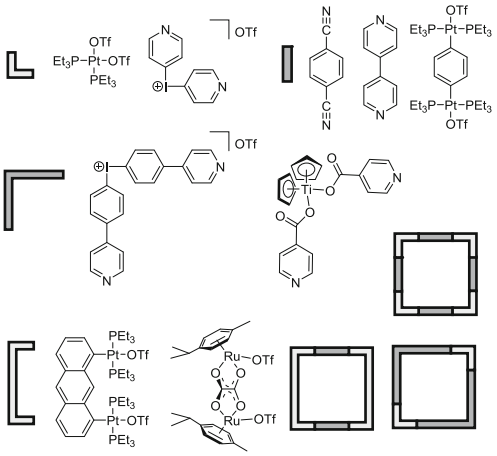

Fig. 3 Molecular examples of the various building blocks used in the construction of square metallacycles

self-assembly of a single, self-complementary building block containing both donor and acceptor sites, $[(Cp)_2Ti(C_6H_5\text{-}4\text{-}py)]_4(OTf)_4$ [27].

The modular nature of coordination-driven self-assembly of SCCs allowed the rapid evolution of pioneering structural studies to deliver materials of increasing complexity. For instance, shortly after establishing routes to molecular squares, techniques to introduce chirality were explored, either through pendant chiral auxiliary groups as capping ligands [28], the use of ditopic diaza ligands of specific symmetry [29], or incorporating chiral coordination environments about the metal nodes [30]. Likewise, the use of mononuclear metal nodes based on capped square or octahedral coordination geometries is not a rigorous requirement but rather one of convenience. When the requisite 90° angle can be encoded by different means, for instance by using two *cis* sites of a dinuclear paddlewheel motif, octanuclear squares may be obtained, such as those based on the $Mo_2(DArF)_3^+$ anion (DArF = *N*,*N*′-diarylformamidinate) fragment bridged by ditopic dicarboxylate anions [31].

3 Triangles, Hexagons, and Other 2D Metallacycles

Although the fewer number of sides of a triangle compared with a square suggests a simpler design, the addition of triangular SCCs to the library of known structures occurred some years after the pioneering work on squares. An early example of a [3+3] triangle, comprising three ditopic 60° tectons and three linear building blocks, is found in the self-assembly of 4,7-phenanthroline with palladated 1,2,4,5-tetrakis(*n*-butylthiomethyl)benzene or 1,2,4,5-tetrakis(phenylthiomethyl) benzene, which acts as a linear acceptor [32]. A complementary assembly in which a linear donor is combined with a 60° acceptor has been achieved upon mixing 4,4′-bipy with 2,9-diplatinatedphenanthrene acceptor (Fig. 4) [33]. The existence of square/triangle equilibria for certain combinations of linear and 90°

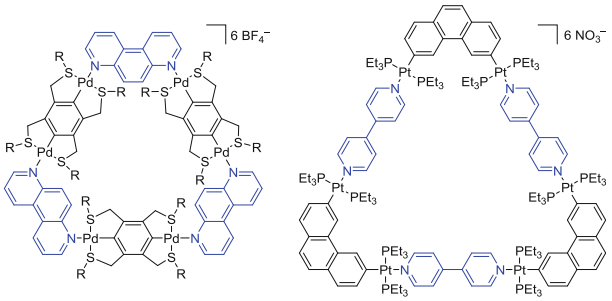

Fig. 4 Two triangular SCCs illustrating [3+3] assembly and the modularity of directional bonding wherein the 60° donor (*left*, *blue*) and linear acceptor (*left*, *black*) can trade roles to give a complementary structure comprising a linear donor (*right*, *blue*) and 60° acceptor (*right*, *black*)

precursors has also provided evidence for [3+3] triangles, wherein distortions in the building blocks relax the encoded angularities [31, 34–36]. In some cases, despite the use of *cis*-capped square planar metal environments, triangles may still be obtained provided that the ligand can accommodate the necessary distortions [37], as when mixing (en)$PtCl_2$ with 2,2′-bipyrazine in the presence of $AgNO_3$ [38], or by linking the luminescent Pt(thpy)(Hthpy)Cl or [$n$$Bu_4N$][Pt(bzqn)$Cl_2$ precursors with sodium benzimidazolate, thereby cyclizing a 90° acceptor with a 150° donor [39]. Alternatively, the use of "piano-stool" metal centers fused with 3-hydroxy-2-pyridone, which can chelate using its oxygen atoms and complete a bridge via N-coordination to a second metal node, will also furnish trigonal SCCs [40].

Given the 120° angularity associated with sp^2 hybridized centers and with *meta* substitution of a benzene ring, encoding the necessary directionality for hexagonal SCCs was easily achieved by using the increasingly established tenets of the directional bonding approach. As such, the first molecular hexagons came in the form of [6+6] assemblies of linear ditopic building blocks with 120° tectons, wherein the angularity of the donor and acceptor could be swapped to delivery complementary metallacycles [41]. As with the triangular systems discussed above, wherein distortions permitted formation even when square planar geometries were present, so too may hexagons from six Pt(II) centers be bridged simply by cyanide ligands [42]. When a hexagon is deconstructed to a [3+3] assembly, wherein both donor and acceptor subunits require 120° angularity, deviation from these directionalities can result in rhomboid/hexagon equilibria [43]. When the angles of the donors and acceptors are more rigidly enforced, the formation of rhomboids is obviated and hexagonal SCCs are the sole self-assembly products [44]. The requisite 120° angularity can also be encoded with less common functionalities such as thiabicyclo[3.3.1]nonane, which can orient two pendant pyridyl groups to combine with a linear diplatinum acceptor to furnish a [6+6] hexagon [45].

Fivefold symmetric molecular pentagons are rarer than hexagons, despite an early example appearing a few years after the growing work on squares. Five tris-bipy ligands organized five equivalents of $FeCl_2$ into a pentagonal metallacycle wherein

each Fe center adopted an octahedral geometry [46]. More recently, when metal-carbonyl-cluster-coordinated dipyridyl donors were combined with a linear Pt-based acceptor, the reaction products could be tuned between a pentagon/hexagon mixture and pure pentagons, depending on the bulkiness of the building blocks used [47].

4 Supramolecular Polyhedra

The 2D SCCs described above serve to illustrate the versatility of the directional bonding method in the preparation of supramolecular metallacycles. However, this design strategy is in not limited to planar assemblies. Whereas the edge-directed deconstruction of polygons demands the use of ditopic ligands of various angles, introducing a third, fourth, or more donor or acceptor sites on a given building block unlocks the rational design of 3D architectures. Although theoretically more complex than their metallacyclic counterparts, in practice, the formation of metallacages follows the same basic design principles first established for the formation of molecular squares and extended to higher order polygons.

Whereas the building blocks of metallacycles occupy the edges of their target polygons, dubbed "edge-directed assembly", the formation of polyhedra via the coordination-driven self-assembly permits "face-directed" strategies in which precursors can be used to occupy entire faces of a target metallacage. This can be illustrated by considering the cube; edge-directed assembly demands eight tectons to represent the vertices in the form of tritopic species with 90° angularities between binding sites. These vertices can then be joined by 12 linear ditopic donors to act as the edges of the cube [48]. In contrast, the six faces of a cube can be represented by tetratopic panels with 90° angles between each adjacent binding site [49]. These panels will become the faces of a cube upon assembly with twelve 90° ditopic building blocks, which lie at the center of each edge (Fig. 5).

4.1 Platonic and Archimedean Solids

The Platonic solids were popularized thousands of years ago when Plato hypothesized that they were the building blocks of the classical elements. The criteria of possessing congruent regular polygonal faces that meet at symmetrical vertices limits the number of Platonic solids to five: tetrahedron, cube, octahedron, dodecahedron, and icosahedron (Fig. 6). These requisites are relaxed slightly in the classification of Archimedean solids, which possess two types of regular polygonal faces but still demand identical vertices. Of the 15 polygons of this type, the truncated tetrahedron, cuboctahedron, and rhombicuboctahedron are the most relevant in the context of coordination-driven self-assembly, although other geometries have been realized.

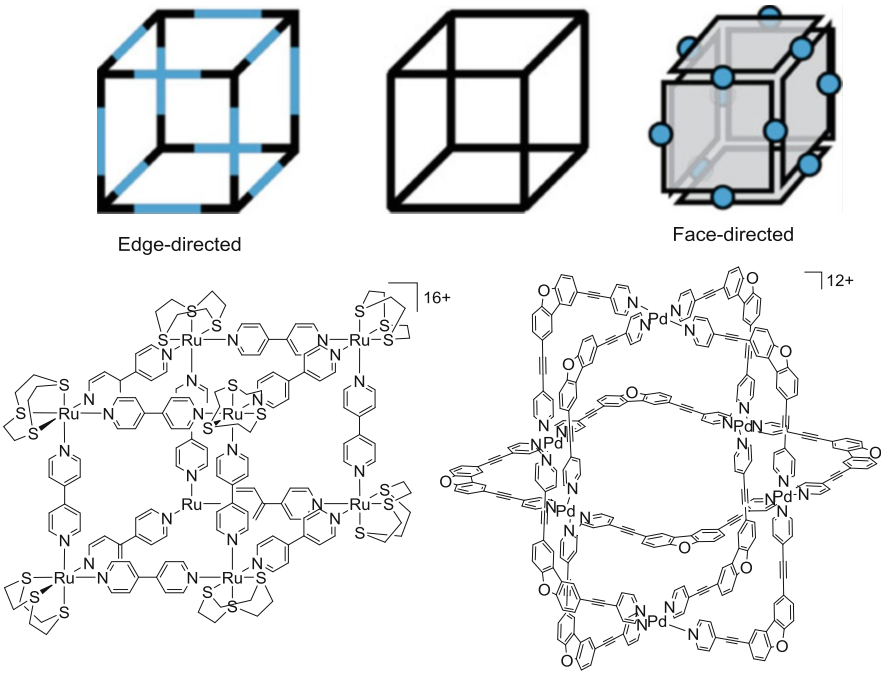

Fig. 5 Polyhedra can be formed by edge-directed (*left*, *top*) or face-direct (*right*, *top*) self-assembly. Twelve linear donors bridge eight tritopic 90° acceptors in an edge-directed cube (*left*, *bottom*). Alternatively, six tetratopic acceptors are joined by twelve 90° ditopic donors for a face-directed cube (*right*, *bottom*)

Fig. 6 The Platonic solids thought to be the building blocks of the classical elements: tetrahedron (fire), cube (earth), octahedron (air), icosahedron (water), and dodecahedron (universe)

After establishing a number of novel 2D metallacycles through directional-bonding methods, Stang and coworkers applied their expertise to the smallest of these highly symmetric cages, the truncated tetrahedron. Upon mixing four planar tritopic building blocks with 120° angularity with six ditopic 90° tectons, the planar panels orient themselves as the faces of a truncated tetrahedron. This face-directed assembly was demonstrated with a number of different molecular precursors, further proving that the nature of the donor and acceptor can be freely swapped to give complementary cages without significant synthetic redesign of the self-assembly process [50, 51]. Although tritopic panels are suitable for face-directed truncated tetrahedron assembly, a hexatopic panel may also be used provided the

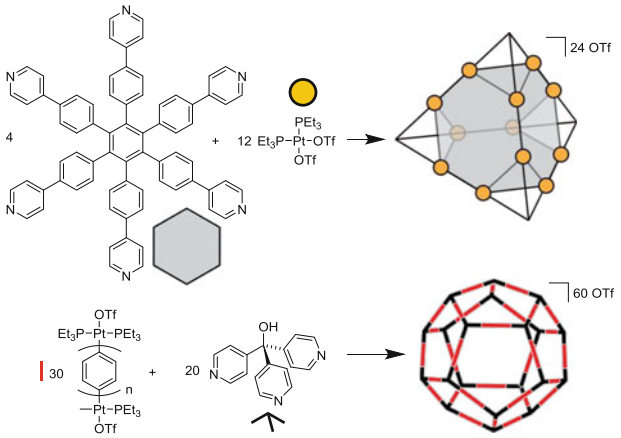

Fig. 7 Both face- and edge-directed assembly can be used to form polyhedra: hexatopic panels self-assemble with 90° acceptors to generate face-directed truncated tetrahedra (*top*). Even larger edge-directed dodecahedra form upon mixing linear acceptors with tritopic donors (*bottom*)

donor-to-acceptor ratio is modified. Combining four hexatopic panels with twelve 90° acceptors also generates truncated tetrahedra [52].

The large cuboctahedron also contains trigonal faces, which link together with idealized 108° angles. As seen with 2D metallacycles, the theoretical angularity of building blocks is not rigorously maintained due to the distortions of the metal coordination environment and the bends and twists accommodated by organic moieties. As such, combining planar, tritopic 120° building blocks with ditopic 109.5° tectons in a twelve to eight ratio affords molecular cuboctahedra [53].

More impressive is the [20+30] self-assembly of nanoscale dodecahedra, which were obtained through edge-directed designs. When tritopic ~108° donors were mixed with linear ditopic acceptors in the proper ratio, dodecahedra with molecular weights over 60,000 g/mol were obtained as the singular reaction products (Fig. 7) [54].

4.2 Prismatic Metallacages

Edge- and face-directed self-assembly are used extensively to form regular and semi-regular polyhedra such as the Platonic and Archimedean solids introduced in the previous section. A combination of these two approaches generates a third type of polyhedra, the prisms. Prisms are 3D solids comprising two congruent faces joined such that any parallel cross-section made anywhere along the length produces a polygon identical to the congruent faces. A given prism is named simply on the basis of the polygon found at its faces.

The wide availability of planar, polytopic ligands makes finding suitable "face" components a facile task. These panel-like tectons need then be linked by building blocks that will occupy the remaining edges of a given prism. For two-component assembly, the archetypal design strategy is to use so-called "molecular clip" precursors comprising two metal centers, each with a single substitutionally labile site held parallel to one another. This provides a 0° directionality of the coordination vectors, with a displacement that will determine the ultimate length of the prism.

An example of such a design uses tripyridyl 120° ligands, thus enforcing a trigonal prismatic structure. These tritopic ligands may be fused with diplatinum molecular clips supported by anthracene backbones [55]. The resulting [3+2] assembly establishes a general [*n*+2] self-assembly process, where *n* is the number of sides of the polygon found at the ends of the prism (i.e., $n = 3$, trigonal prism; $n = 4$, tetragonal prism, etc.). The dimensions of a prism can be tuned in all directions either by changing the size of the molecular clip, thus adjusting the length of a prism, or by extending or contracting the extent to which the binding sites of the polygonal panel building block point into space, thereby enhancing or attenuating the width of the structure [56, 57]. Complementary prisms can also be made by generating 0° clip-like donors, such as functionalizing an anthracene backbone with two pyridyl groups instead of the organoplatinum moieties of the prisms described above [58]. Due to the slight (~11°) splay associated with the coordination vectors of the pyridyl groups, these clips are well suited to interact with trimetallic acceptors with angularity between 108° and 112°. As such, the resulting prisms are slightly puckered relative to their idealized geometric analogues, which are rigidly planar at the faces.

When a tetratopic panel is used in place of the pioneering tritopic examples, the self-assembly process requires but a simple change to the stoichiometry of clip required. Once adjusted, the quantitative formation of tetragonal prisms via [4+2] assembly can take place [59].

Of course, this process is by no means limited to platinum-based prisms. Arene-ruthenium molecular clips are more than suitable for self-assembly reactions and are often compatible with the same polypyridyl ligands used with Pt-based molecular clips. As such, the combination of oxalate-bridged and other chelate-bridged diruthenium clips with tritopic donors furnishes analogous trigonal prismatic SCCs [60]. Likewise, alkoxide-bridged rhenium centers can serve as molecular clips to deliver hexanuclear trigonal prisms under solvothermal conditions [61]. The generation of alkoxide-bridged clips during self-assembly has also been used to form tetragonal prisms [62]. For Re-based prisms, some systems offer two routes to formation: either the molecular clip precursor can be generated in an independent step and then used for self-assembly [63], or it can be formed in a single-pot reaction, whereby 11 unique components come together to form a given trigonal prism [64]

A second prismatic structure achievable by coordination-driven self-assembly are the so-called "open boxes." Rather than positioning a polytopic ligand at the ends of the prism, this design uses square-like panels to complete the sides of the construct, forming, for instance, trigonal prisms [65] or hexagonal prisms [66].

5 Multicomponent Self-Assembly

The SCCs discussed above all use two components, a donor and an acceptor, in the formation of identical metal–ligand bonds. The use of only two types of components greatly simplifies the self-assembly process. However, given the favorable energetics associated with forming regular, unstrained metallacycles, the combination of carefully selected precursors exceeding only two components can still result in well-defined products. For instance, the concept of self-organization and size-selective self-assembly has been explored by Stang and coworkers, defining conditions by which desired structural outcomes can be favored over statistical product mixtures [6].

It is also possible to develop self-assembly reactions whereby the combination of more than two types of precursors does not select for singular, two-component assemblies, but rather favors the sole formation of one type of discrete SCC containing all three building blocks. Such reactions have been referred to as "multicomponent assembly." Although somewhat of a misnomer given that even simple two-component assemblies technically involve multiple components, this moniker is intended to reflect those mixtures with three or more different building blocks.

In order for such multicomponent assemblies to occur with efficiency, there must be a thermodynamic preference for heteroligated coordination environments about the metal centers being used [67]. In some sense, the Re-based prismatic SCCs that form molecular clips during the self-assembly process can be thought of as multicomponent assemblies owning to the preference of the Re centers to acquire one bridging ligand, often a chelator, along with a polypyridyl donor. This process has been most systematically explored with platinum-based acceptors and pyridyl and carboxylate donors.

A second method is to use spatial control, wherein homoleptic coordination is hindered by the size and shape of the ligands used. In such cases, it is possible to form discrete SCCs with multiple ligands at each metal node, as elegantly demonstrated by Schmittel and coworkers using phenanthroline-based donors [68–70]. If substituted pyridyl ligands are combined with unfunctionalized analogues in mixture with acceptors containing *cis*-oriented substitutionally labile sites, heteroligation will occur due to the steric constraints associated with coordinating two of the bulkier pyridyl ligands to the same metal node, as demonstrated by Fujita and coworkers [71, 72].

It should be noted that, in some cases, exploiting the kinetics of a system can also afford control over multicomponent assembly. For instance, Lusby, Barran, and coworkers demonstrated the formation of selected isomeric SCCs by varying the sequence of addition of building blocks in a Pt-based system with metal–ligand bonds inert enough to avoid rapid funneling to a single thermodynamic product [73]

5.1 Platinum-Pyridyl-Carboxylate Multicomponent Assembly

Although the use of multiple pyridyl-based ligands demands a creative use of steric bulk, size selectivity, or other method to prevent a statistical mixture of coordination combinations, it is possible to select two different donors that differ enough such that there is an inherent selectivity for heteroligation. This strategy has been explored experimentally with the discovery that combinations of pyridyl and carboxylate donors favor mixed Pt-O, N coordination motifs when placed in solution with platinum acceptors [74–77].

Simple [4+2+2] assemblies are the multicomponent analogue of [4+4] square reactions. Whereas the use of two different lengths of linear pyridyl ligands would give a mixture of products, the linear carboxylate and pyridyl ligands funnel exclusively to heteroligated coordination environments to deliver rectangles as the sole reaction product [78]. This strategy was described qualitatively as based on "charge separation" by which the anionic carboxylate ligands and neutral pyridyl ligands are paired up so as to reduce the amount of electrostatic repulsion between like ligands with the same charge. That said, the preference for heteroligation is probably due to a number of effects, with varying contributions depending on the specific system being considered. These factors include a potential alleviation of ring strain, orbital-related phenomena such as *cis* influences (akin to the better known *trans* influence in which multiple bonds to the same sigma-type $d_x^2 - y^2$ orbital reduce subsequent bond enthalpy), and electrostatic effects. Although the magnitude of these contributions and the exploration of other factors remains an ongoing effort at the forefront of multicomponent assembly, in practice a number of different SCCs have already taken advantage of this heteroligation motif. Similar factors may also play a role in mixed pyridyl/imidazole systems, in which some preference for heteroligation has also been observed [79].

Because multicomponent assembly provides a way to include multiple ligands in a single SCC scaffold, it becomes possible to access increasingly more complex structures by using functionalized ligands. For instance, a four-component assembly, in which ten molecular building blocks from four unique species fuse into a single discrete species, is possible. In this example, the dipyridyl donor used is built upon a bis(pyridinium)ethane core, which can act as a guest for crown ethers, forming [3]catenane species [80].

5.2 Prismatic Metallacages

One structure type that can take advantage of multicomponent assembly is that of the prismatic SCCs [81]. Rather than using a molecular clip to bridge polygonal faces, the requisite 90° angles can be encoded using traditional ditopic

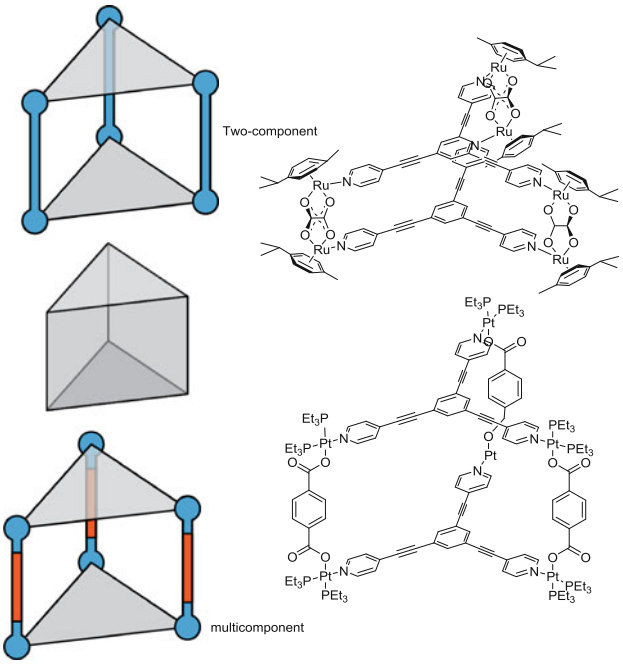

Fig. 8 Trigonal prisms can be formed either by traditional two-component assembly (*top*) by using molecular clips, or by multicomponent strategies involving heteroligated metal centers (*bottom*)

90° acceptors that are themselves linked by a separate linear donor. This approach has been demonstrated using both platinum [78] and palladium prisms [82]. In such instances, the [*n*+2] self-assembly is modified to an [2*n*+*n*+2] assembly. For each Lewis-basic site of the *n*-sided panel ligand, there will be a metal acceptor. Since there are two such *n*-sided polygons per prism, found at each end, 2*n* metal acceptors are required. For each pair of metal acceptors, a single linear donor will act as the lengthwise edge of the prism (Fig. 8).

In most cases, the polygon ends are occupied by pyridyl-based ligands, such as the tripyridyl 120° donor previously employed for trigonal prisms. However, this design strategy is readily applied to tetragonal prisms, for instance when a tetrapyridyl porphyrin or other rigid, planar tetrapyridyl donor is used, thereby requiring eight equivalents of a 90° acceptor and four linear carboxylates [78]. When hexapyridyl donors are instead used, the stoichiometry must be adjusted further to twelve metal acceptors and six linear carboxylates [83]. These are trivial changes in practice, which require no adjustments to reaction time or conditions provided the precursors used do not differ greatly in terms of solubility.

5.3 Supramolecule-to-Supramolecule Transformation

Another extension of multicomponent assembly is supramolecule-to-supramolecule transformation. Such transformations can be triggered by external means, such as light, solvent, or chemical signals [84–89]. For Pt-based SCCs, this process exploits the same preference for heteroligation as is used in multicomponent assembly. In short, when a homoligated Pt-pyridyl SCC is mixed with a Pt-carboxylate SCC, both initial structures become kinetic intermediates in the context of forming a new, heteroligated structure. As such, upon their combination in solution, the reversibility of Pt-ligand coordination sunders both original species and the system ultimately arrives at a new multicomponent assembly [78]. This is most simply illustrated by mixing three [4+4] Pt-pyridyl squares with four [3+3] Pt-carboxylate triangles. Since this delivers the Pt acceptor in a 4:2:2 ratio with the linear pyridyl and linear carboxylate donors, the stoichiometry is set to afford a [4+2+2] rectangle quantitatively (Fig. 9).

This transformation process works equally well to deliver multicomponent prismatic SCCs. Both initial SCCs must contain 90° acceptors and a single type of donor. Since the final prisms typically contain a polypyridyl donor at each end, the first initial SCC must be composed of exclusively these two building blocks. It is possible to form discrete SCCs using both tritopic and tetratopic planar donors with 90° acceptors. When a tripyridyl donor is mixed with a 90° acceptor in a 6:4 ratio, a truncated tetrahedron is obtained. This establishes the formation of a trigonal prism as the result of the supramolecule-to-supramolecule transformation in the form of a [6+3+2] self-assembly. This means that for every truncated tetrahedron, the potential for two trigonal prisms exists relative to the number of pyridyl donors. However, there is a shortage of platinum acceptor, which must be corrected by the addition of a Pt-carboxylate triangle. Serendipitously, the combination of a [6+4] truncated tetrahedron and two [3+3] triangles gives a total of two pyridyl donors, 12 platinum acceptors, and six carboxylate donors, which is the exact ratio needed to form two trigonal prisms.

Likewise, the self-assembly between certain tetragonal donors and 90° acceptors results in the formation of an open box trigonal prism, where three donors form the square faces along the width of the prism, joined at each vertex by a sum total of six platinum acceptors. This trigonal prism can be transformed into its multicomponent counterpart upon the addition of the same carboxylate triangle. Since only three pyridyl donors are found in each open box prism, each pair of prisms affords enough donors for three transformed SCCs. This demands four equivalents of triangle in order to achieve the necessary [8+4+2] prism stoichiometry.

A second type of transformation does not involve the mixture of two discrete homoligated SCCs to form a third heteroligated multicomponent structure, but rather takes a single homoligated SCC and transforms it upon the addition of an exogenous small molecule. One strategy to achieve this, developed by Stang and coworkers, is to adjust the angularity of a precursor after it has already been used to

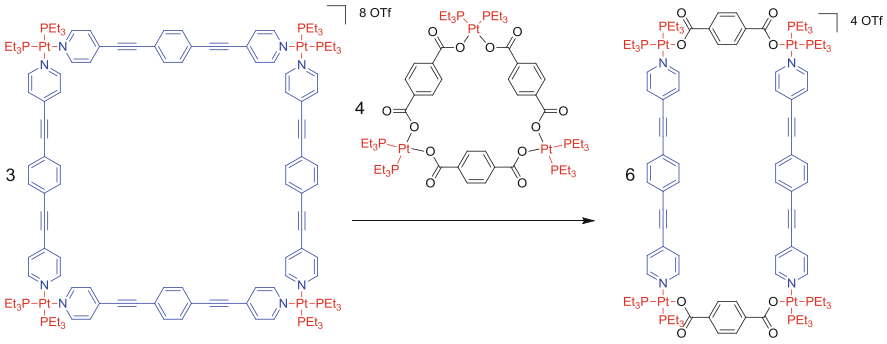

Fig. 9 When mixed, a Pt-pyridyl square and a Pt-carboxylate triangle will transform into a multicomponent rectangle containing mixed Pt-N,O heteroligation

form an SCC [87]. Since ethynyl groups are found as linear spacers in the organic backbones of many donor precursors, chemistry altering the angularity of this inherently 180° moiety will completely change the structure of the SCC. This was specifically demonstrated using $Co_2(CO)_6$ and SCCs containing linear donors with ethynyl groups. Upon treatment with the metal carbonyl, the triple bonds participate in the formation of M_2C_2 cores, which reorient the ligands to contain 120° rather than 180° angularities. Thus, a [6+6] hexagon no longer finds itself containing six linear ligands, but rather six 120° donors, effecting a transformation to [3+3] hexagons. Likewise, in a square/triangle equilibria comprising linear donors and 90° acceptors, the linear donors will become bent, thus favoring rhomboidal SCCs [87].

The addition of exogenous species need not enforce a change in directionality. The driving force for heteroligation can also be used to bring out post-self-assembly structural modifications. For instance, beginning with a homoligated [6+4] truncated tetrahedron containing a tritopic pyridyl donor and 90° acceptor, equivalents of carboxylate donors can be added, which will become incorporated into the initial SCC [52]. If a tritopic carboxylate donor is used, a single pyridyl panel of the truncated tetrahedron will be substituted in order to give more favorable Pt-N,O coordination. Likewise, ditopic carboxylate donors can instead be used, which spring open the truncated tetrahedron, ejecting a single pyridyl panel to afford partial prisms. Given enough equivalents of linear carboxylate donor, such assemblies can be transformed entirely to host/guest-capable trigonal prisms. One possibility that such transformations realize is the incorporation of functionalized precursors, thereby decorating an initially unfunctionalized SCC with a chemically active moiety. This was demonstrated using a ferrocene-functionalized carboxylate donor, which ultimately produced a new SCC with two redox-active groups attached [52].

5.4 *Post-Self-Assembly Functionalization*

Although functionalization can be introduced using the transformations described above, more traditional methods can also be used, wherein an intact SCC participates in an established organic transformation by virtue of selecting precursors with reactive functional groups. Using these precursors in a multicomponent assembly provides a way to functionalize structures that would be difficult to achieve by other means. Carboxylate donors built on phenyl backbones can often include a second functionality attached. These ditopic donors would be limited to 2D metallacycles for homoligated SCCs; however, the development of multicomponent assembly permits their use to form functionalized prisms. In this way, Stang and coworkers developed a suite of tetragonal prisms with a range of pendant functionalities, including amines, ferrocenes, alkoxides, etc [90]. Although the caveat exists that these functionalities must not interfere with the metal–ligand coordination that is at the heart of the self-assembly process, in practice even moderately Lewis-basic moieties may be used.

When amine- or maleimide-functionalized carboxylate donors are used, the resulting SCCs are well suited to interact with isocyanates and maleic anhydride (in the case of the amine variant) or undergo Diels–Alder reactions (for the maleimide variant), providing a means to attach functionalities directly to the edges of a prismatic SCC. When redox-active groups containing ferrocene are used, the resulting functionalized prism is amenable to electrochemical characterization to confirm that a quantitative coupling takes place without affecting the core of the SCC [91].

This technique does not require multicomponent assembly, and can be demonstrated on simpler platforms as a proof-of-concept. One example is post-self-assembly click chemistry [92]. By designing a parent cyclooctyne-functionalized metallacycle, Stang and coworkers demonstrated self-assembly functionalization with a variety of azide-bearing small molecules, from simple benzylazide to a significantly more complex biotin azide substrate. In all cases, [3+2] Huisgen cycloadditions took place under mild conditions (Fig. 10) [93].

6 Summary, Conclusion, and Outlook

The development of the directional bonding approach to coordination-driven self-assembly has given rise to a vast molecular library of building blocks and supramolecular coordination complexes. From the design principles first established using simple self-assembly reactions to obtain square metallacycles, increasing complex polygons and polyhedra have been constructed, demanding creative new approaches to encode angularity and deconstruct target geometries, but without requiring significant synthetic redesign. Whereas natural systems deftly manipulate ensemble of weak non-directional interactions, chemists can mimic this approach using metal–ligand bonding, which simplifies the process by allowing a higher degree of control.

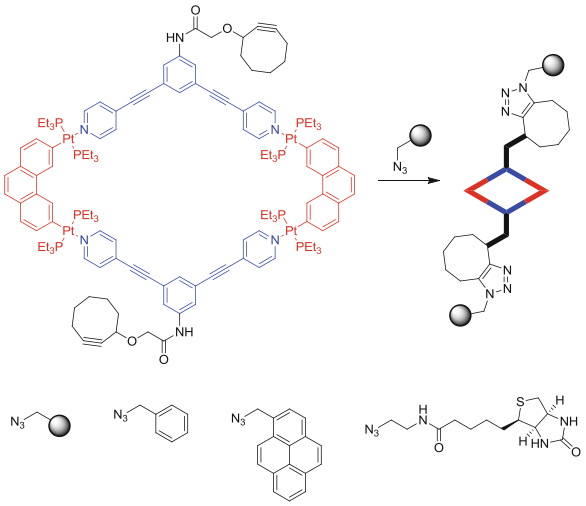

Fig. 10 Huisgen cycloaddition (*top*) is one method of post-self-assembly modification, providing a means to decorate an SCC with a variety of pendant groups (*bottom*)

The unique chemistry of transition metals has more recently provided inroads to developing multicomponent assembly that exploits various means to favor heteroligated coordination environments, thereby allowing the use of multiple ligands in a given self-assembly mixture without resulting in a statistical mixture of products. As these methods are developed, they unlock new strategies for supramolecular transformations, whereby discrete SCCs are themselves subjected to structural modifications. Likewise, multicomponent assemblies have provided scaffolds on which to study post-self-assembly functionalizations using traditional covalent transformations to decorate a given SCC through coupling chemistry.

Whereas supramolecular coordination complexes are themselves formed by stepwise increases in complexity, each simple metal–ligand bond representing but one small part of what is ultimately a complicated metallacycle or cage comprising a number of small components, so too does the field of coordination-driven self-assembly march forward with novel design strategies and methods of growing sophistication. Each new pursuit builds upon the fundamental scientific principles that are the heart of directional bonding, reflecting the importance of understanding even the simplest interactions of molecular precursors and demonstrating the fascinating macromolecules that become accessible when doing so.

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Bridging Polymer Science and Medicine Through Supramolecular Nanoassemblies

Horacio Cabral and Kazunori Kataoka

Abstract Boundaries between synthetic polymers and biology are disappearing as an increasing number of manmade macromolecular constructs take a central role in biological processes. The research in this area has been continuously growing since the structure of polymers was proposed by Hermann Staudinger, with landmark findings in the 1970s, 1980s, and 1990s. Polymeric systems in the biological interface have evolved from linear bioactive polymers into self-assembled nanostructures with compartmentalized architectures that perform versatile complex processes within specific cellular locations. Due to their supramolecular nature, it is possible to integrate the structural and functional information of these nanoassemblies just by engineering the starting macromolecules. These assemblies have demonstrated high clinical potential for efficient site-specific sensing, transport, and modulation of bioactive molecules by taking advantage of their controlled interaction with physiological environments.

Keywords Block copolymers · Polymer-drug conjugates · Polymeric micelles · Polymeric vesicles

H. Cabral
Department of Bioengineering, Graduate School of Engineering, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8656, Japan

K. Kataoka (✉)
Department of Bioengineering, Graduate School of Engineering, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8656, Japan

Center for Disease Biology and Integrative Medicine, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

Department of Materials Engineering, Graduate School of Engineering, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8656, Japan
e-mail: kataoka@bmw.t.u-tokyo.ac.jp

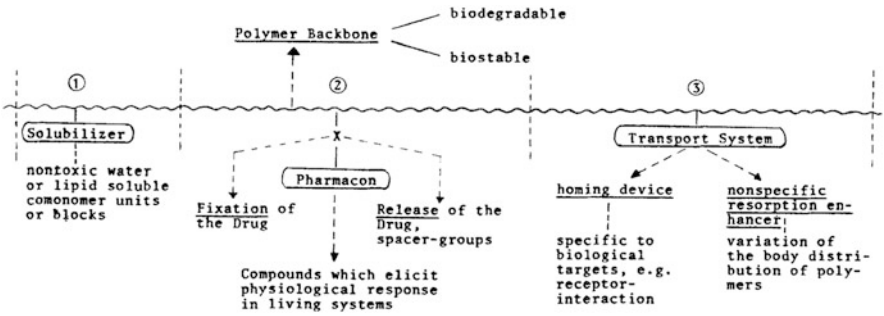

Fig. 1 Rationale for a model drug carrier system according to Ringsdorf [11]. Reprinted with permission from Reference [11]

From Hermann Staudinger's 1920s pioneering article, "Über Polymerisation" ("On polymerization") [1], and his definition of macromolecules, covering both synthetic and natural polymers, to the present, macromolecules have taken a central role in the growth and well-being of our society, with applications ranging from aeronautics to art to medicine. Since his early work, Staudinger stressed the importance of macromolecules in biology, which he highlighted in the final paragraphs of his Nobel lecture in December 1953 [2] and throughout his career, by attempting to bridge polymer science and the biosciences.

From the beginnings of polymer science, synthetic macromolecules were associated with biomedicine as structural and functional materials, such as bone cements [3], heart valves [4], sutures [5], implantable depots for controlling the release rate of pharmaceuticals [6], or plasma expanders [7]. These applications demonstrated the wieldy interface of synthetic polymers and biological tissues, and the potential for developing biocompatible and biodegradable pharmacologically active macromolecular agents. By tailoring the composition and structural parameters of such pharmacologically active polymers (for example, by copolymerizing hydrophilic, hydrophobic, and bioactive monomers), the precise modulation of their biological activity can be achieved. Early approaches for polymeric drugs such as poly(ethylene sulfonate) [8] and poly(divinyl ether-*co*-maleic anhydride) (DIVEMA) [9] had been configured for showing potent biological activity, but their toxicity impeded their clinical use as therapeutics [9, 10]. It was Helmut Ringsdorf, former student and research assistant of Staudinger at the University of Freiburg, who defined, in 1975, a rationale for targeted polymeric drugs composed of a solubilizer, a pharmacon (for drug conjugation and controlled release) and a transport system (for homing and nonspecific resorption) (Fig. 1) [11]. This polymeric drug model merges important concepts from polymer science, medicine, and biology, including the biocompatibility and biodegradability of the main chain for avoiding immune responses, the lysosomotropic delivery of macromolecular drugs proposed by Christian de Duve [12] for enhancing the specificity and efficacy of chemotherapy, and the haptophore–toxophore model of Paul Ehlrich's "magic bullets" [13], by using the appropriate homing system for specific targeting through

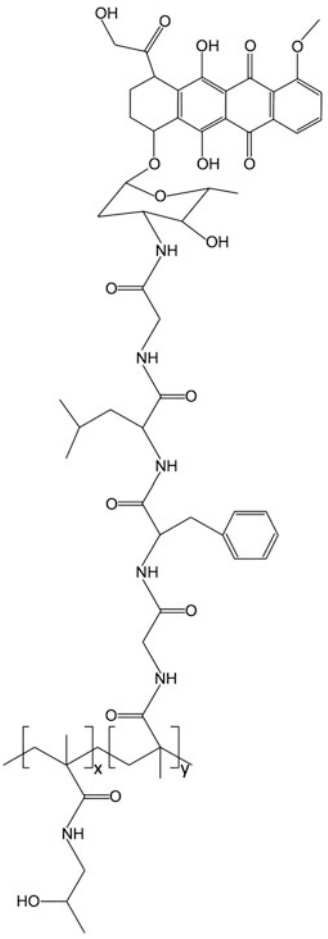

Fig. 2 Structure of *N*-(2-hydroxypropyl) methacrylamide copolymer incorporating doxorubicin (PK-1), the first polymer–drug conjugate to reach clinical trials. The molecular weight of the polymer–drug conjugate is 28 kDa and the drug content is 8.5% (w/w) [16]

receptors expressed at diseased sites and a selective cleavable spacer for triggered drug release. Moreover, the model includes the controlled distribution of the carriers in the body, as macromolecules larger than the molecular weight of the threshold for glomerular filtration (42–50 kDa) have reduced clearance through kidneys, while the nonspecific resorption enhancer (Fig. 1) avoids unspecific interaction with components of the reticuloendothelial system.

During the late 1970s and early 1980s, Jindřich Kopeček and Ruth Duncan reported several polymer–drug conjugates based on Kopeček's poly(hydroxypropyl methacrylamide) (PHPMA) copolymers [14]. PHPMA present several points in common with the Ringsdorf model because it is hydrophilic, nonimmunogenic, nontoxic, its side groups can be modified for incorporating transport systems and pharmacon, and it has prolonged circulation in the bloodstream. PHPMA incorporating the potent anticancer drug doxorubicin, via a tetrapeptide linkage (i.e., Gly-Phe-Leu-Gly) for selective lysosomal release after cleavage by cathepsin B

(Fig. 2) [15], was the first polymeric drug conjugate to reach clinical trials [16]. It demonstrated enhanced antitumor efficacy and proved that polymer–drug conjugation decreased dose-limiting toxicities, setting a novel standpoint in pharmaceutical science. Another successful polymeric drug that resembles Ringsdorf's model was developed by Hiroshi Maeda and his group by combining poly(styrene-*co*-maleic acid/anhydride) and neocarzinostatin (SMANCS) [17–19]. Even though the molecular weight of SMANCS is only 16 kDA, its blood half-life is extended by reversibly binding to serum albumin [18], which increases its size to over the glomerular excretion of kidneys. During early preclinical studies, Maeda, together with Yasuhiro Matsumura, observed that SMANCS and several other macromolecules selectively accumulated in solid tumors, which they attributed to the tumors' hypervasculature, i.e., the enhanced permeability of tumor vasculature to macromolecules and the retention of those macromolecules due to impaired lymphatic drainage [19]. They called these phenomena the enhanced permeability and retention (EPR) effect (Fig. 3) [18], and it has become one of the foundations of tumor-targeted polymeric drugs.

Another milestone in the development of polymer–drug conjugates also occurred in the 1970s and 1980s, when Frank F. Davis and Abraham Abuchowski modified proteins with poly(ethylene glycol) (PEG) with the aim of extending their half-life in blood and controlling immunogenicity [20–22]. The unique physicochemical properties of PEG, including its neutral charge, nontoxicity, high flexibility, and degree of hydration, demonstrated to be essential for improving several aspects of the modified proteins in vivo, including solubility, reduced interaction with plasma proteins and phagocyte uptake, prolonged blood circulation, reduced immunogenicity, increased stability, and protection from proteolytic degradation [20–22]. The first clinically approved PEG–protein conjugates were PEG–enzymes, followed by PEG–interferons and PEG–granulocyte colony-stimulating factor, which demonstrated that PEG modification decreased dosage frequency without compromising efficacy, and also reduced toxicity [20]. In addition, PEG was also used for modifying the surface of liposomes for drug delivery, prolonging their circulation in blood and reducing unspecific distribution [23, 24]. Thus, PEG conjugation is widespread as a safe and efficient method for protecting bioactive molecules and surfaces, and the term "PEGylation" has become a common word for describing this strategy.

When PEG, or other hydrophilic polymer, is conjugated to hydrophobic macromolecules, the resulting block copolymers can self-assemble in aqueous environment into various nanoscaled structures, having a hydrophobic center surrounded by a PEG shell. Macromolecular self-assembly occurs spontaneously in nature through intermolecular forces, and is essential for the performance of structural proteins, bioactivity of proteins, and complex biological processes [25]. Moreover, various natural carriers, such as viruses or casein micelles, are self-assembled structures of polypeptides, and their supramolecular structures precisely modulate their interaction with the biological environment for controlled delivery of their cargo. The mechanisms of self-assembly, the structural conformation, and the functions of natural supramolecular structures are programmed at the molecular

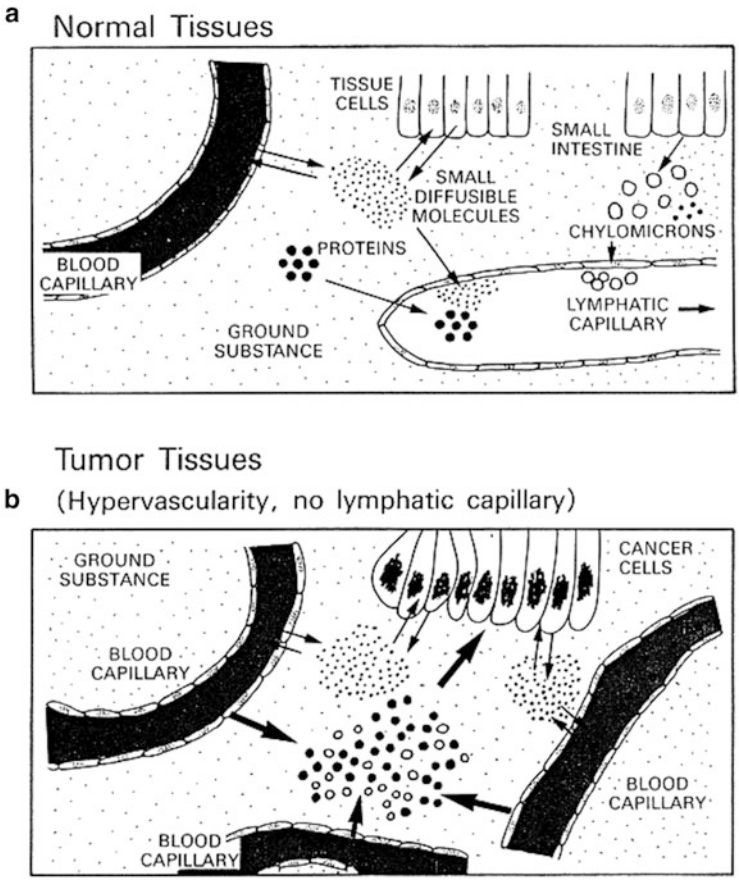

Fig. 3 Structures of (**a**) normal and (**b**) tumor tissue, and the in/out transport from capillaries of various substances. Although large macromolecules cannot penetrate normal tissue, and small molecules and proteins are cleared by lymphatics, blood vessels in tumors present large fenestrations that cause macromolecules to permeate extensively into the tumor tissue. Moreover, slow venous return and poor lymphatic clearance retain macromolecules in the tumor. These phenomena are called the enhanced permeability and retention (EPR) effect [18]. Reprinted with permission from Reference [18]

level of the proteins. Likewise, engineering the blocks of copolymers can facilitate the development of supramolecular nanoassemblies with increasing structural and functional complexity.

The first polymeric self-assemblies for biological application were micelles formed by amphiphilic diblock copolymers through the hydrophobicity of their core-forming blocks. Accordingly, in the late 1980s, Ringsdorf and coworkers reported that PEG-*b*-poly(L-lysine) copolymer associated into micelles after conjugation of the hydrophobic anticancer drug cyclophosphamide with the poly(L-lysine) block [26]. Alexander Kabanov's group prepared polymeric micelles based

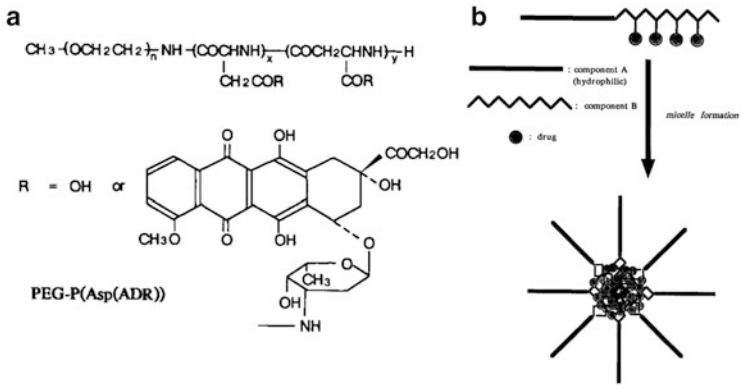

Fig. 4 (**a**) Structural formula of doxorubicin-conjugated PEG-*b*-poly(aspartate) copolymers. (**b**) The concept of micelle-forming polymeric drugs, as reported in [29]. The optimized formulation of these micelles was the first clinically tested polymeric micelles (NK911)

on poly(ethylene oxide)-*b*-poly(propylene oxide)-*b*-poly(ethylene oxide) triblock copolymers (Pluronics), which physically incorporated haloperidol by hydrophobic interaction with the poly(propylene oxide) backbone [27]. Our group developed micelles from PEG-*b*-poly(aspartate) copolymers, covalently attaching doxorubicin on the side-chain moieties of the poly(aspartate) block (Fig. 4) [28]. The latter can also promote the physical incorporation of active free doxorubicin in the core to show longevity in blood circulation as well as appreciable antitumor efficacy in animal models [29]. The optimized formulation of the latter was the first micellar therapeutic to reach clinical trials, under the development name NK911 (Nippon Kayaku, Co., Japan) [30]. As of today, several micellar formulations incorporating hydrophobic anticancer drugs such as paclitaxel (Genexol-PM, Samyang Co., Korea; NK105, Nippon Kayaku Co./NanoCarrier Co., Japan), SN-38 (NK012, Nippon Kayaku Co.), doxorubicin (NK911, Nippon Kayaku Co.), cisplatin (NC-6004, NanoCarrier Co.), (1,2-diaminocyclohexane)platinum(II) (NC-4016, NanoCarrier Co.), and epirubicin (NC-6003, NanoCarrier Co.) are under clinical evaluation and demonstrate high efficacy and lower side effects than the free drugs [30–33]. The advantage of polymeric micelles as drug carriers is based on their intrinsic features for operating in the biological interface [34, 35] (Fig. 5):

Their dense and soft PEG shell, which protects the bioactive payload in the core, hinders the interaction with plasma proteins and cells, prolongs the circulation in the bloodstream, avoids recognition by macrophages, and contributes to the permeation through tissues [36]

Their relatively small diameter, which can be tuned from 10 to 100 nm and resembles that of natural viruses, facilitates overcoming physiological barriers such as interstitial flow and lymphatic transport to lymph nodes after intradermal injection [37], facilitates selective extravasation and deep penetration even in

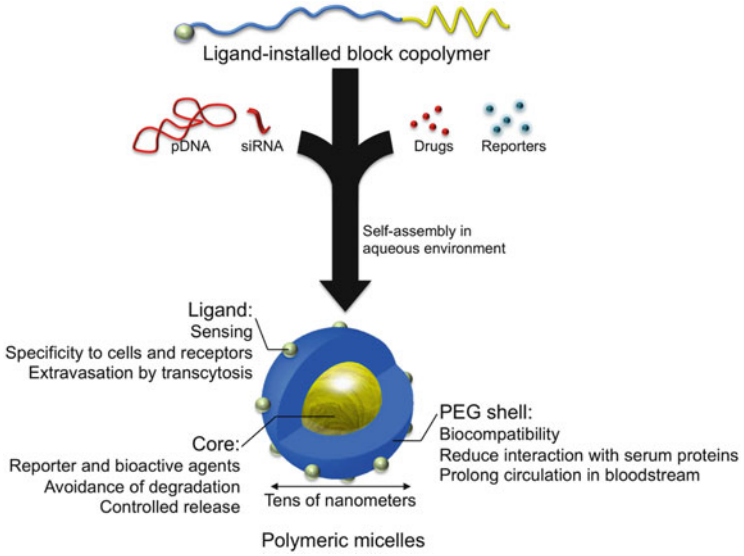

Fig. 5 Polymeric micelles offer a versatile self-assembled platform for incorporating reporters or bioactive molecules within the nanostructure through various intermolecular forces. The relatively small size, PEG shell, and controlled interaction of the cargo with the core-forming block of polymeric micelles are remarkable advantages for operating at the biological interface

tumors with low permeability after systemic administration [38], and reduces their accumulation in the organs of the reticuloendothelial system

The controllable release of cargo, which can be achieved by tailoring the bond between the payload and the micelles or by using stimuli-responsive block copolymers, permits triggered therapeutic activity [39, 40]

Their ability to dissociate into the former block copolymers, which can be excreted by glomerular filtration in the kidney, avoids any long-term side effects

Besides hydrophobic interactions, block copolymers present high versatility for engineering the intermolecular forces that can be used to segregate the compartmentalized nanoarchitecture of nanoassemblies [34, 35, 41, 42]. Accordingly, our group have demonstrated the possibility to self-assemble core–shell polymeric micelles via electrostatic interaction by using a pair of oppositely charged block copolymers, i.e., PEG-*b*-poly(aspartic acid) and PEG-*b*-poly(L-lysine) [43, 44]. Through a similar approach, we have constructed micelles incorporating negatively charged antisense oligonucleotides [45], plasmid DNA [46], proteins [47], and siRNA [48] in their core. We have named these assemblies polyion complex (PIC) micelles. Whereas the therapeutic efficacy of proteins and genes is hampered by their instability in physiological conditions and low cellular internalization, and the in vivo application of polymeric gene vectors based on polycations is limited because of aggregation and toxicity, PIC micelles have demonstrated high efficacy and low toxicity in vivo, suggesting great potential for development of

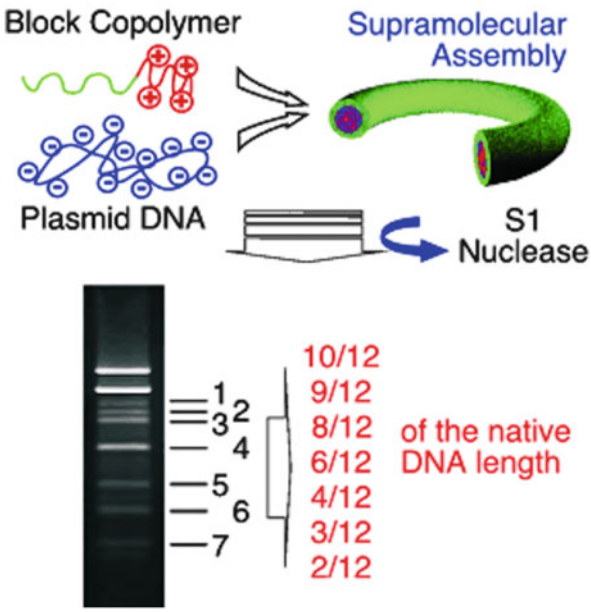

Fig. 6 Polymeric micelles can assist in mechanistic studies of molecular interactions of highly ordered states and folding of proteins. For example, cleavage of supercoiled plasmid DNA by S1 nuclease after complexation with PEG-*b*-poly(L-lysine) resulted in highly ordered fragments, suggesting that DNA folding during condensation may proceed under constraints of DNA topology [55]

safe and efficient artificial gene carriers [35]. Moreover, the complexation of metal ions to the core-forming backbone has been used for constructing various polymeric micelles [49–51]. Platinum anticancer drugs incorporated into polymeric micelles by this method showed extended circulation in the bloodstream and enhanced accumulation and efficacy against solid tumors [50, 51]. The creation of multiple hydrogen bonds between the core-forming blocks, as occurs in base pairs in DNA and RNA in biological systems, can also spontaneously form micelles in aqueous solution [52]. Moreover, the polyanion of PEG-*b*-polyanion copolymers has been used for controlling the growth of calcium phosphate crystals in the core of micelles, while the PEG shell avoids aggregation of the particles [53].

Because of the diversity of intermolecular forces for self-assembly and the dense PEG palisade, which can eliminate the aggregation of otherwise agglomerating supramolecular systems, these supramolecular assemblies also represent a useful platform for studying the mechanistic details of the molecular interactions that stabilize highly ordered states and folding of proteins, which is a central goal of theoretical biophysics. Accordingly, by cleaving the looped DNA strand within rod-like micelles of PEG-*b*-poly(L-lysine) with S1 nuclease, we have recently observed highly ordered fragmentation of plasmid DNA (Fig. 6) [54]. Moreover, plasmid DNA folding into rod structures occurs at fixed lengths of $1/2(n + 1)$ of the original plasmid DNA length [55]. These results suggest that DNA folding during condensation may proceed under the topological constraints of DNA [54, 55]. Block copolymers assemblies have also been used for studying the highly ordered structures of β-amyloid peptide fibrils [56], which are the main component of the neuritic plaques of Alzheimer's disease [57]. The structural determination of β-amyloid

fibrils is difficult due to the poor solubility of the peptides and the noncrystalline nature of fibrils [58]. Thus, PEG-*b*-β-amyloid peptide block copolymers self-assembled into fibrils by assuming parallel β-strand conformation, providing structural information not only on the fibrillogenesis mechanisms, which are important for the disease progression, but also on protein folding and self-assembly [56, 58].

Further supramolecular architectures of block copolymers also display unique features for bridging polymer science and biology. Adi Eisenberg and colleagues reported polymeric vesicles (i.e., polymersomes), which encapsulate bulk solution phase in their hollow reservoir, constructed by controlling the length of the hydrophilic block and the hydrophobic block in poly(acrylic acid)-*b*-poly(styrene) copolymers [41, 59]. Polymersomes offer the possibility of incorporating hydrophilic biomolecules in their hollow interior, which can be isolated from the external environment, as well as hydrophobic molecules in the bilayer membrane. Similarly to polymeric micelles, polymersomes can be formed from various intermolecular forces, such as hydrophobic interactions with amphiphilic block copolymers [41, 59], electrostatic interactions from oppositely charged block copolymers [60], and metal complexation [61]. Depending on the self-assembling type, the permeability of the polymeric membrane of the polymersomes can be suitably tuned for regulating in–out diffusion of molecules and the molecular weight cut-off of the membrane. Accordingly, polymersomes have been used for controlling the interaction and maintaining the activity of hydrophilic proteins in biological environments via their protection in the hollow core of polymersomes and the exchange of small molecules through their membrane. Such is the case for polymersomes as carriers of hemoglobin [62] or myoglobin [63] as well as enzyme-loaded polymersomes [64] for creating nanoreactors. Worm-like micelles, reported by Dennis Discher and colleagues [65], also present an elegant example on how the shape of supramolecular constructs affect their interaction with the biological environment. Thus, although the blood circulation of polymersomes was approximately 24 h, worm-like micelles remained in the bloodstream for more than 1 week due to their high flexibility, which reduces macrophage uptake [65]. This high versatility of block copolymer nanoassemblies for combining structural features with bioactive functions has prompted their application in other areas of biotechnology, such as tissue engineering and regenerative medicine [66, 67], offering a handy toolbox for developing therapeutic approaches with clinical translation.

Although the PEG surface of nanoassemblies minimizes their contact with cellular membranes, their surface can be functionalized with ligands capable of recognition of cell-specific surface receptors (such as antibodies, antibody fragments, aptamers, peptides, transferrin, and small molecules), which provides modulated cellular interaction and superior intracellular delivery [68]. Moreover, ligand-installed assemblies have been used for enhancing the tumor targeting because the targeted receptors are displayed in cancer cells or tumor-associated cells more frequently than in healthy tissues [68]. In addition, due to the presence of multiple ligand molecules on the surface of nanoassemblies, the binding affinity of the whole system can be enhanced by multivalent binding, which augments their internalization rate [69]. Ligand-installed nanoassemblies can also be used for

overcoming physiological barriers, such as the blood–brain barrier [70], suggesting the potential for reaching inaccessible tissues in the body after systemic injection of these nanoassemblies.

Macromolecular nanoassemblies have the potential to control the intracellular trafficking and subcellular delivery of their cargo, which can augment the activity of the incorporated drugs [71]. For example, polymeric micelles incorporating (1,2-diaminocyclohexane)platinum(II) selectively delivered the drug to its therapeutic target (i.e., nuclear DNA), which allowed the micelles to overcome cytoplasmic resistance mechanisms [72]. For delivering genes, nanoassemblies should escape from endosomes into the cytoplasm or nucleus. Various mechanisms such as pore formation in the lipid bilayer of endosomes, fusion with the endosomal membrane, and the pH-buffering effect of protonable moieties have been proposed for assisting in the endosomal escape of nanoassemblies [73]. Moreover, several cell-penetrating peptides can be installed on the surface of nanoassemblies for translocation across the plasma membrane into the cytosol of cells, which enhances the delivery of their cargo [74]. In addition, installation of ligands on the surface of nanoassemblies may also direct their subcellular localization after reaching the cytosol [75].

Supramolecular structures allow the complexity and functions to be increased for producing innovative nanodevices in which loaded materials and the carrier are integrated both structurally and functionally for sensing, processing, reporting, and operating inside the cells [76], undertaking precise roles at specific subcellullar compartments. Staudinger's dream of polymers and the biosciences is here and now, and the continuous innovations in materials and polymer sciences, together with life sciences, will keep promoting the development of novel synthetic biopolymers, with unparalleled control of supramolecular architectures and unprecedented biological activities. These new polymeric structures will eventually allow controlled in situ interaction with specific biomolecules, modulating their expression and tailoring their function in molecular and physiological events.

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Stereochemical Studies at the Herman F. Mark Polymer Research Institute

Mark M. Green

Abstract Although stereochemistry plays a key role in the structure and function of biological polymers it was not until the discovery of isotactic polypropylene, now about 60 years ago, that the role of stereochemistry was seen to be of importance in synthetic polymers. Staudinger had predicted that although the nature of the bonding in small molecules and in macromolecules was identical, polymers would have special properties associated with the size of macromolecules. This article outlines how stereochemical studies demonstrate Staudinger's prescience in many ways. The story takes us from the tactic nature of vinyl polymers and their unrecognized and recognized chirality, to helicity, a characteristic shared by biological and certain synthetic polymers. There is an advantage to studying stereochemistry in synthetic polymers: their chiral characteristics can be manipulated in ways not possible in biological polymers, allowing discovery of new phenomena that cross boundaries outside of the polymer realm.

Keywords Chirality · Helix · Macromolecules · Mark · Polymers · Staudinger · Stereochemistry · Tactic polymers

Scientists who joined the Polymer Research Institute at Brooklyn Polytechnic were encouraged by Herman Mark to carry out research in areas they might have been familiar with in their studies of small molecules. Professor Mark knew from his scientific experience that there existed no boundaries between the principles of the science that depended on molecular size. In 1980 therefore when I first met him on joining Polytech he asked about my background and, on discovering that I had an interest in stereochemistry and chirality, he suggested that I look at the stereochemical properties of the vinyl polymers. This led me to read the work of two

M.M. Green (✉)
Department of Chemical and Biological Science, Herman F. Mark Polymer Research Institute, Polytechnic Institute of New York University, 6 Metrotech Center, Brooklyn, NY 11201, USA
e-mail: mgreen@duke.poly.edu

prominent members of the Italian school, Piero Pino and Mario Farina, chemists who had been present at the genesis of the discoveries of stereoregular polymers in Milan under the guidance of Giulio Natta. I discovered from this reading how important was the year 1953, when the Nobel Prize was awarded to Hermann Staudinger, who fought, finally successfully, to convince the world of science that the kinds of long chains arising from styrene, vinyl acetate, vinyl chloride, and ethylene, among others, were what he imagined them to be and what his experimental work demonstrated – long chains linked by the kinds of covalent bonds well accepted in small molecules. Staudinger expressed this view in the beginning of his Nobel lecture [1]: "The only difference between macromolecules and the small molecules of low molecular substances is one of structural size." Nevertheless, he fully realized that new phenomena would arise as a consequence of the considerable size differences, as he expressed a few sentences later in the same lecture: "It is desired to lay down a boundary between macromolecular and low molecular compounds – there are of course transitions linking the two groups – the substances with a molecular weight greater than 10,000, i.e. the molecules of which consist of 1,000 or more atoms, may be classified as macromolecular. Beyond roughly this size, characteristic macromolecular properties occur." As discussed below, stereochemical considerations of macromolecules and especially issues of chirality are excellent examples of Staudinger's prescient views about "characteristic macromolecular properties." The story begins in Milan when polypropylenes of various tacticities were produced.

There is something very interesting about the stereochemistry of atactic polypropylene. From inspection of the structure of a single chain, even stretched out in a planar zig-zag conformation so as to avoid dissymmetry arising from chiral shapes, it is apparent that the irregular configurations of the pendant methyl groups would mean that mirror images do not superimpose, even for a portion of the chain. This is the foundation of chirality and must mean that atactic polypropylene is chiral. However, although it follows that there is a potential for the observation of optical activity, this observation was never made for atactic polypropylene or for other atactic polymers such as polystyrene. Why not?

In small molecules, the absence of optical activity at some wavelength for chiral molecules is almost always ascribed to the fact that the ensemble of molecules contains equal number of both enantiomers – a racemic mixture. However, in a chain longer than a hundred or so units, statistical considerations demonstrate that the presence of mirror image isomers of enantiomeric chains, and therefore for racemic states, is virtually impossible, which leaves the absence of optical activity in atactic vinyl polymers an open question. The answer turned out to be one that never arises in small molecule stereochemistry: an ensemble of polymer chains of an atactic polymer is a mixture of diastereomeric chains, each one chiral but without the enantiomeric chain present in the ensemble. If a single chain could be studied by a method that could reveal chiral optical properties, optical activity should be observed. However, each chain in the ensemble (a very large number of chains) would exhibit a different optical activity, even of differing sign. The optical activity properties of a sample of an atactic polymer would arise as the sum

of random numbers and such a large number of random numbers would yield a sum of zero. The absence of optical activity in such a sample of polymers does not therefore arise from the absence of a chiral structure, nor does it arise from the chiral structures with equal numbers of enantiomers (a racemic mixture), but rather arises from what is never seen in small molecules, a large number of chiral diastereomers each one in an enantiomerically pure state. Remarkable! [2].

Is there something equally remarkable about isotactic polymers? In any isotactic polymer, the segment at the initiating end and that at the terminus of the chain must differ and, therefore, if one considers the entire chain the conclusion is that this is a chiral structure. In his review in *Topics in Stereochemistry* in 1987 [3], Mario Farina noted that the overwhelming number of units along the chain are oblivious to the end groups of the polymer chain. Considering a limited number of these internal units, one sees a plane of symmetry and therefore an achiral structure. Alternatively, one could assign the absence of observed optical activity in isotactic polypropylene to cryptochirality, a term coined by Mislow [4] for molecules in which optical activity is too small to be detected at observable wavelengths. If these factors were not reason enough for the absence of any chiral optical measure, the nature of the polymerization suffices in producing a racemic mixture of chains. The enantiotopic faces of the incoming propylene monomers approach the Ziegler–Natta catalyst with equal probability.

There is, however, another aspect of the chirality of isotactic polymers, which is associated with the helical form of isotactic polypropylene first observed in the X-ray diffraction experiments conducted in Milan by the Natta group. In this manner, Natta discovered the reason for the crystalline properties of this polymer synthesized from the catalyst developed by Karl Ziegler. But, in a sample of isotactic polypropylene, or other isotactic polymers arising from vinyl monomers, both left- and right-handed helical conformations are present so that no chiral optical property is observed. Each crystalline state in a sample of isotactic polypropylene is a racemic mixture of helical forms.

There is more to the story of isotactic polypropylene arising from Piero Pino's interest in answering the following question: Does the helical property of isotactic polypropylene in the crystalline regions of the sample extend into the amorphous regions, as in the melted state? Pino decided to address this question by observing the possibility of chiral optical properties in structural variations of polypropylene.

Pino synthesized variations of isotactic polypropylene in which the methyl group was substituted for by a chiral alkyl group [5]. When these groups, which replaced the pendant methyl groups along the chain, were enantiomerically distinct or enriched, or even placed randomly among the methyl groups along the chain, the optical activity properties of the polymer could be shown to arise from a helical conformation and not simply from the chiral optical properties of the chiral pendant group. Pino was able to further demonstrate that placing such chiral groups among phenyl pendant groups, as in a random copolymer, gave rise to chiral optical properties for the chromophore of the phenyl groups on the chain. These experiments, carried out in Pisa, left no doubt that the helical conformations of the

isotactic polymers were not restricted to the crystalline regions where the helical state could be directly observed by the diffraction data.

From the intense interest in polymers at Brooklyn Polytechnic and needless to say the presence of Herbert Morawetz, Eli Pearce, and Fred Eirich in addition to Herman Mark, one could not avoid an attraction to the field, whose signature characteristic, one early learns, is cooperativity. The results from Pisa [3, 5], in fact, were a perfect example of the cooperativity arising from the helical conformation. However, the helical state of vinyl-derived polymers does not exist in a deep energy well and therefore the helix is easily interrupted by defects in this conformational state. The ease of these interruptions and the inherent flexibility of the bonds along the backbone of the polymer lead to a limited persistence length. The polymer can be described as a random coil on a small length scale.

At DuPont corporation in the 1950s, as it became clear that control of nylon 6,6 production and sale would inevitably be out of the corporation's control, a polymer was synthesized, nylon 1, which was designed to allow DuPont to control another nylon-forming fiber that was of possible commercial importance. Anionic polymerization of alkyl isocyanates yields a polymer $-$(R)NCO$-$ with stiff fiber-forming properties. However, hopes were dashed when the ceiling temperature of the polyisocyanate (nylon 1) was discovered to be near the boiling point of water.

There was, however, a theoretical interest in these polymers because of their very high viscosity at moderate molecular weights, and diffraction data that showed a helical conformation. The viscosity properties demonstrated a resistance of the polymer chain to distort from a single conformation, consistent with an unusually high measured persistence length, and this was further confirmed by the observation for poly(*n*-hexyl isocyanate) of lyotropic liquid crystal formation. Walter Stockmayer and other polymer physicists took an interest in the question of the source of the limit to the persistence length of such a helical polymer. This interest turned out, in a surprising manner, to be connected to work on this polymer at the Polymer Research Institute. Murray Goodman, in the late 1960s, showed optical activity properties for the polyisocyanates when the alkyl pendant groups on each nitrogen atom of the chain were chiral. The experimental results were seen as consistent with polymer dissymmetry, which was interpreted as a "preferred conformation of the polymer backbone" [6].

One possibility for the limit to the persistence length in the polyisocyanates was seen as the presence of helical reversals along the chain backbone. These defects in the conformational regularity could arise as a consequence of the stereochemical necessity that the left- and right-handed helices are enantiomerically related and therefore of equal probability. Helical reversals are especially interesting considering that such states are blocked (with rare exceptions) in biological helical polymers. If one blocked or reduced the number of helical reversals in this synthetic polymer, by favoring one helical sense, would the persistence length increase? However, how is one to accomplish favoring one helical sense without decreasing the torsional motions along the chain backbone, which is another source of the polymer flexibility and therefore also a limit to persistence length? Chiral pendant groups, as used by Pino on the vinyl polymers, and Goodman on the polyisocyanates, are inherently

bulky and would change the conformational torsional motions along the backbone. Conclusions could not therefore be drawn about the role of the helical reversals.

An answer to this quandary arises from the fact that a polymer chain with an extended uninterrupted helical conformation will be highly cooperative, with any per-unit influence favoring one helical sense being amplified by the number of cooperating units. Might it therefore be possible that a minute chiral influence, which would not affect the torsional motions along the backbone in each unit of the chain, could substantially favor one helical sense because of this expected amplification?

Enzymatic reduction of deuterated aldehydes led to poly(*n*-hexyl isocyanate) in which the CH_2 group adjacent to the chain backbone was converted to a chiral carbon atom by virtue of stereospecific deuterium substitution for one of the hydrogen atoms, CHD. In this manner, for a single configuration of the deuterated carbon, (*R*) or (*S*), the left- and right-handed helical states would no longer be enantiomerically related and therefore, in principle, no longer of equal probability. Although the energetic difference between the handed helical conformations depended only on the presence of the deuterium, very large optical activities were experimentally observed, which was especially remarkable considering that, as expected, the monomer D-line optical activities were close to zero. Circular dichroism experiments demonstrated that the chiral optical properties of the polymer arose from the chromophore of the helix. Apparently, the minute per-unit energy favoring one helical sense was amplified, as expected, by the extended helical conformation.

Herman Mark encouraged international collaborations and this tradition at the Polymer Research Institute led to critical collaborations that allowed full exploitation of these findings. Shneior Lifson of the Weizmann Institute was visiting New York to lecture at the Courant Institute of NYU and to visit Herbert Morawetz, whose wife Cathleen Synge Morawetz had headed this institute. On learning of the observation of a large amplification occurring on deuterium substitution of a helical polymer, Lifson noted that he had, some time ago, created a partition function precisely describing, at the time, an unknown conformational situation in which an interaction between a very small energy and a far larger energy controlled the conformational properties of a cooperative system. The small energy, in the deuterated polymer would certainly be the favoring of one helical sense over the other, per unit, arising from the chiral deuterium substitution. The far larger energy would be the excess energy of the helical reversal along the chain backbone.

In order to attempt to fit Lifson's partition function to the optical activity data observed for the deuterated polyisocyanate, it was necessary to have a series of samples of widely varying degrees of polymerization, each with a narrow dispersity, and then to study these polymers as a function of temperature. Yoshi Okamoto, another member of the Polymer Research Institute, suggested a Japanese collaboration, which led to a connection with Osaka University in Japan. The necessary samples were produced by Akio Teramoto's group, who had the gel permeation chromatography equipment and the experience to produce these narrow dispersity polymers by controlled breakdown of a sample with a high degree of polymerization and also to assign precise degrees of polymerization. Study, in

Brooklyn, of the temperature dependence of these samples with variable degrees of polymerization precisely fit Lifson's partition function predictions. The smaller energy, which could be termed a chiral structural deuterium isotope effect, was near to a single small calorie per mole of units, while the larger energy, the cost of a helical reversal, was near to 4,000 cal/mol [7].

The changes observed for the optical activity (a measure of the excess helical sense), as a function of temperature and degree of polymerization, fit the picture of the cooperative phenomenon. The change in the optical activity of the deuterated polyisocyanate as a function of degree of polymerization, below about 1,000 units, was almost linear with increasing chain length and with a very small dependence on temperature. The samples with higher degrees of polymerization, on the other hand, showed no dependence of the optical activity on chain length, but exhibited a very large dependence of the optical activity on temperature.

A helical reversal energy of about 4,000 cal/mol of individual units translates, at ambient temperature, to approximately one reversal for every 1,000 units. Short chains with degrees of polymerization substantially below 1,000 units would therefore be almost entirely free of helical reversals. The amplification of the chiral deuterium isotope effect would therefore increase with degree of polymerization, because there are no interruptions on the conformational state of the chain, until reaching a chain length at which helical reversals became probable. For this reason, the excess helical sense would increase with degree of polymerization as would, therefore, the optical activity as observed experimentally (see above).

For longer chains in which helical reversals were probable, the limit to the amplification of the chiral deuterium isotope effect would no longer depend on the chain length but rather on the number of units between reversals. The amplification would therefore strongly depend on temperature because the probability of a helical reversal along the chain backbone depends exponentially on temperature, following the Boltzmann equation, $e^{-E/RT}$, where E is the excess energy of the helical reversal.

The results on the deuterated polyisocyanate described above begged the question of how small the chiral influence could be. An experiment was designed in which poly(*n*-hexyl isocyanate) with no preference for helical sense was dissolved in a series of chiral enantiomerically pure solvents. In every solution, the CD spectrum at the wavelength of the helical chromophore showed an excess helical sense. Remarkably, fitting these data as a function of temperature and degree of polymerization to Lifson's partition function showed that the energy term per mole of units favoring one helical sense, as a consequence of the chiral solvent, was less than 0.1 cal/mol. Moreover, the excess helical sense, left-handed for some solvents and right-handed for other solvents, could not be made sense of from structural considerations. These data, and the inability to generate a structural interpretation, demonstrated the limits to structural theory. It follows that structural interpretations are not possible (the foundations of physical organic chemistry) for cooperative systems in which properties involve minute, but amplified energies. Energy differences below several hundred calories per mole do not allow assigning structural interpretation for the source of the observations [8].

The cooperative picture drawn above suggested other experiments. Polyisocyanates were synthesized in which a few chiral pendants were dispersed among large numbers of achiral pendants along the chain backbone. Large excesses of one helical sense were observed, as measured by the chiral optical properties, with these observations quantitatively fitting to Ising models (the mathematical formalisms of one dimensional paramagnetic materials). This theoretical connection was developed by Jonathan Selinger of the Navel Research Laboratories. Further experiments involved synthesis of polyisocyanates in which enantiomeric units competitively favoring opposing helical senses were randomly dispersed along the chain backbone. Remarkably, slight excess of one of the competitive chiral units was adequate to produce polymers with large excesses of one helical sense, again described in quantitative detail by Selinger's theoretical work. In an interesting aspect of this work, which finds an analogy in human experience, the theory and the experimental results show that the larger the energy favoring one helical sense by the chiral group in excess in this experiment, the less influence this chiral group has on its preferred helical sense [9–11].

These kinds of experiments were appropriately termed the "sergeants and soldiers effect" and "majority rule," and were found by other research groups to apply to other helical polymers and to varieties of materials subject to cooperative phenomena associated with chirality, and even with two dimensional materials. Literature searches under these metaphors yield hundreds of references spanning a wide variety of fields that involve cooperative effects on chiral measurements.

In summary, therefore, Staudinger's efforts in setting the stage for studies of the properties of polymers are demonstrated across the spectrum of polymer classes in stereochemical phenomena associated with chirality studied at the Herman F. Mark Polymer Research Institute at the Polytechnic Institute of Brooklyn [12–17].

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Mechanically Interlaced and Interlocked Donor–Acceptor Foldamers

Carson J. Bruns and J. Fraser Stoddart

Abstract The emergence of a class of organic oligomers and polymers that lie at the intersection of the fields of mechanically interlocked molecules (MIMs) and synthetic foldamers is described in this review. These macromolecules are based on 4,4′-bipyridinium ($BIPY^{2+}$) and 1,5-dioxynaphthalene (DNP) recognition units incorporated into linear oligo- or polymeric chains (threads) and macrocycles (rings), where the threads fold their way through a series of rings in a serpentine-like fashion. The well-defined geometries of these polyelectrolytes are rendered by the [C–H ⋯ O] hydrogen bonding interactions that transpire between the polyether chains appended to DNP and the acidic protons of $BIPY^{2+}$, as well as the π–π and donor–acceptor (D–A) charge transfer interactions that cause DNP and $BIPY^{2+}$ units to pack into extended mixed stacks. The unique folding motif of these pseudorotaxanes and rotaxanes makes them attractive candidates for novel multiferroic and mechanically tunable materials.

Keywords [C–H ⋯ O]·interactions · Donor–acceptor · Foldamers · Mechanostereochemistry · Polyelectrolytes · Rotaxanes · π–π interactions

Contents

1 Introduction 272
2 D–A Pseudorotaxane Foldamers in the Solid State 273
2.1 Early Signs of Extended D–A Stacking 274
2.2 Infinite-Chain Lattice of D–A Oligo-Pseudorotaxanes 276

C.J. Bruns and J.F. Stoddart (✉)
Department of Chemistry, Northwestern University, 2145 Sheridan Road, Evanston, IL 60208, USA
e-mail: stoddart@northwestern.edu

3 D–A Rotaxane Foldamers in Solution 278
3.1 Folding in D–A Polyrotaxanes 279
3.2 Systematic Investigations of Oligorotaxane Foldamers 281
4 Computational Evaluation of D–A Oligo-Pseudorotaxanes 288
5 Conclusions and Outlook 290
References 291

1 Introduction

The burgeoning of molecular nanotechnology near the turn of the 21st century has brought with it the emergence of new fields in the chemical sciences fueled by the manipulation of atomic-and molecular-scale matter with ever-increasing dexterity and precision. Among them, the fields of mechanically interlocked molecules (MIMs) and synthetic foldamers, both of which assume 'bottom-up' approaches in the construction of functional nano-architectures, have seldom[1–3] crossed paths.

Foldamers are sequence-specific synthetic oligomers that adopt well-defined, compact geometries [4, 5]. They represent an attempt to mimic the exquisite control expressed by natural systems in their three-dimensional arrangement of functional groups, which underwrites the activity of proteins and biopolymers, for example. Chemists interested in foldamers have invested their efforts in the rational design of macromolecules with well-defined structural hierarchies, which involve the assembly of components into stable secondary, tertiary, and quaternary structures. Mastering the synthesis and assembly of foldamers on all these fronts will allow, in principle, molecules to be engineered with precise three-dimensional shapes and properties customized for particular applications. The remarkable capabilities of biomolecules afforded by their complex and diverse structures suggest that this course will likewise have far-reaching implications for catalysis, sensing, information storage, and so on. Foldamers are most commonly constructed from peptidic [6–12] or aromatic [13–17] sequences, and the current state-of-the-art is summarized in a number of reviews [18–21] and monographs [22, 23] that have been published recently.

Mechanically interlocked molecules (MIMs), such as catenanes and rotaxanes, are molecules with at least two components that are not covalently bound, but interlocked in such a manner that they cannot be separated without the breaking of a covalent bond. Since this physical linkage is known as a mechanical bond [24], we refer to the stereochemistry of MIMs as mechanostereochemistry [25]. MIMs have been appreciated for their synthetic challenge and aesthetic value [26] as well as their potential applications. In particular, MIMs have garnered much interest as artificial molecular switches and machines [27–31] because their internal noncovalent bonding interactions can be modulated by external stimuli to control the relative translational and/or circumrotational motions of their interlocked

components. The mechanical structures and switchablitity of MIMs are being exploited in applications that encompass catalysis [32–35], drug delivery [36–38], and molecular electronics [39–41], to name but a few examples. Polymeric MIMs [42–47] are of special interest for new applications because they have the capacity to scale [31, 48] the concerted actuation of bistable MIMs to a macroscopic size regime.

The (supra)molecular recognition motifs that are common to mechanostereochemistry and foldamers include metal–ligand coordination [49–51], ion-pairing [52–56], hydrogen bonding [6–12, 57–59], solvophobic forces [60–62], anion binding [63–66], and the distinctive [67, 68] van der Waals interactions that arise in stacked planar π-conjugated systems. Over two decades of research [69] in our group has been focused on the development of MIMs templated by donor–acceptor [70] (D–A) interactions between π-electron rich and π-electron poor aromatic recognition units. Strategies that utilize π-associated D–A interactions to create foldamers include D–A copolymers with flexible backbones that give "pleated" secondary structures (also known as aedamers) [71–82], as well as the stabilization of serpentine-like aromatic oligomers resulting from the regular intercalation of aromatic tweezer molecules [83–88].

Although many similarities exist between their noncovalent bonding motifs, foldamers and MIMs typically utilize weak inter- and intramolecular interactions in fundamentally different ways. Whereas MIMs leverage noncovalent interactions to interlace cyclic and acyclic components in the templation of mechanical bonds and then control relative intramolecular motions, foldamers use noncovalent bonds to render well-defined macromolecular conformations and three-dimensional geometries. Recent work in our laboratories, however, has shown that these two paradigms are not mutually exclusive. We have developed a family of mechanically interlaced polyelectrolytes that adopt well-defined folded secondary structures, both in the solid state (Sect. 2) and in solution (Sect. 3). The proclivity of these macromolecules to form [C–H ⋯ O] hydrogen bonds and extended π-associated D–A stacks has allowed us to elaborate a genre of pseudorotaxanes and rotaxanes with compact three-dimensional geometries that embody the traits of foldamers. Here, we review our findings related to the construction of D–A rotaxane and pseudorotaxane foldamers.

2 D–A Pseudorotaxane Foldamers in the Solid State

The unique packing motifs of π-associated organic donor and acceptor molecules in the solid state is being investigated [89–96] by the organic electronics community in order to create materials with novel optoelectronic and multiferroic properties. Whereas segregated stacks of crystalline donors and acceptors express remarkably high conductivities [89–91] or photoconductivies [92], for example, mixed-stack crystals of alternating donors and acceptors can exhibit ferroelectric behavior below certain transition temperatures [93–95]. Recently, we demonstrated [96] that

applying the principles of supramolecular chemistry to stabilize mixed D–A stacks with noncovalent bonding interactions greatly enhances their ferroelectric properties, allowing them to maintain their polarization at and even above room temperature. The crystalline mechanically interlaced D–A foldamers we describe herein possess similarly stabilized D–A stacks. The investigation of this new class of compounds is therefore driven, not only by curiosity and fundamental inquiry, but also by the prospect of uncovering new applications based on crystalline organic materials.

2.1 Early Signs of Extended D–A Stacking

Donor–acceptor rotaxanes and catenanes and their interlaced precursors are, more often than not, constructed (Fig. 1a) around 4,4′-bipyridinium ($BIPY^{2+}$) and 1,5-dioxynaphthalene (DNP) recognition units and their macrocyclic counterparts, cyclobis(paraquat-*p*-phenylene) ($CBPQT^{4+}$) and dinaphtho[38]crown-10 (DN38C10). The charge and planarity present in these compounds and complexes lend themselves to facile crystal growth, and dozens of mechanically entwined crystal structures based on these recognition units have accumulated over the years. Evidence for extended D–A π–π stacking in these molecules was apparent from the very beginning. Indeed, we noted the continuous sequence of alternating donors and acceptors (Fig. 1b) back in 1989 when we crystallized [97] $BIPY^{2+}$ and DN38C10 in a 2:1 ratio to obtain the complex $[BIPY^{2+}]_2 \subset$ DN38C10. Likewise, the reverse recognition system $[DNP]_2 \subset CBPQT^{4+}$ crystallizes [98] in a 2:1 stoichiometry, accommodating an extended D–A stack (Fig. 1c). This 2:1 binding motif is only observed in the solid state; the same pairs of components form stable 1:1 inclusion complexes in solution [99, 100]. The [2]catenane based on DN38C10 and $CBPQT^{4+}$, which was initially synthesized [101] in 1991, contains within itself two D–A pairs and also packs with its neighbors into an infinite D–A stack (Fig. 1d).

The most significant noncovalent bonding interactions that stabilize the sorts of D–A systems illustrated in Fig. 1 are [C–H ⋯ O] hydrogen bonding interactions between the acidic α-$BIPY^{2+}$ protons and the polyether oxygen atoms, and π–π and charge transfer interactions between aromatic donors and acceptors in van der Waals contact. When DNP is a guest inside of $CBPQT^{4+}$ (as in Fig. 1c, d), additional [C–H ⋯ O] interactions between the 4/8 DNP protons and the phenylene units of $CBPQT^{4+}$ further stabilize the complex. The [C–H ⋯ O] hydrogen bonds [102, 103] are especially vital to these systems and have been estimated [104] to contribute fourfold more stabilization energy to the $BIPY^{2+} \subset$ CDN38C10 complex than π–π interactions. The [C–H ⋯ O] interactions dominate DNPC ⊂ $CBPQT^{4+}$ complexes likewise, since appending polyether chains to the DNP unit increases the binding constant by almost two orders of magnitude [105].

The natural progression of our research dealing with structures of the kind depicted in Fig. 1 led to the development of oligomeric DNP and $BIPY^{2+}$ threads. Crystallization of tetraethylene glycol-linked DNP trimers encircled by $CBPQT^{4+}$

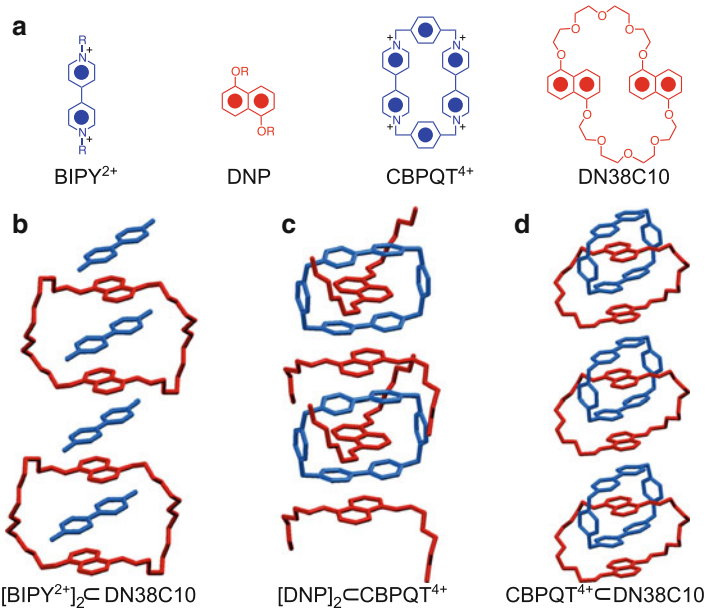


Fig. 1 Some early pointers to extended donor–acceptor stacks. (**a**) Molecular formulas of four building blocks commonly used in the construction of D–A pseudorotaxanes and MIMs. (**b**) The D–A stack formed between $BIPY^{2+}$ and DN38C10. (**c**) The D–A stack formed between a DNP unit with diethylene glycol appendages and $CBPQT^{4+}$. (**d**) The D–A stack formed by face-to-face packing of the [2]catenane comprising $CBPQT^{4+}$ and DN38C10

produced results that inspired the subsequent development of the interlaced foldamers described in Sects. 2.2 and 3. The crystal structures depicted in Fig. 2 demonstrate that the flexible tetraethylene glycol chains employed to connect the adjacent DNP units form multiple [C–H ⋯ O] interactions with the α-$BIPY^{2+}$ protons, while allowing the unencircled DNP units to extend a D–A mixed stack by docking alongside of $CBPQT^{4+}$. Rather than competing with one another, the important [C–H ⋯ O] and π–π interactions participate in a mutually beneficial relationship wherein the natural curvature of the glycol chains works synergistically with the stacking of aromatic recognition units to stabilize the complexes. The solid-state structure of the two-component pseudorotaxane 3NPBn ⊂ $CBPQT^{4+}$ (Fig. 2a) was obtained [106] in 1994, whereas that of the three-component complex 3NPE ⊂ $[CBPQT^{4+}]_2$ (Fig. 2b) came [107] much later while carrying out the solution-state work described in Sect. 3. It is also noteworthy that both 3NPBn ⊂ $CBPQT^{4+}$ and 3NPE ⊂ $[CBPQT^{4+}]_2$ crystallize with secondary structures that utilize all of the available recognition units in a D–A stack; no π-electron donors or acceptors are located in isolation from a counterpart recognition site of the opposite kind. Although each of these complexes maintains an internal D–A stack, they do not pack in register with other complexes so as to extend the stack indefinitely.

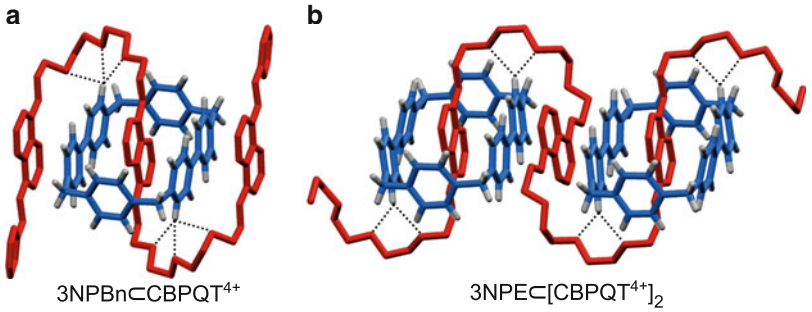


Fig. 2 DNP trimers bridged by tetraethylene glycol linkers fold in a serpentine-like fashion through the cavities of the $CBPQT^{4+}$ ring in both two-component (**a**) and three-component (**b**) complexes to produce a continuous D–A stack stabilized primarily by [C–H ⋯ O] hydrogen bonding (*dashed lines*) and π–π stacking interactions

2.2 *Infinite-Chain Lattice of D–A Oligo-Pseudorotaxanes*

Although high molecular weight (HMW) polymers are exceedingly difficult to obtain as macroscopic single crystals because of diffusion limitations, chain entanglements, and heterogeneous length distributions, it has been demonstrated [108] that their crystal structures can be discerned by single crystal analysis of their small-molecule homologues. When we lengthened the glycol-bridged DNP oligomers from trimers (Fig. 2) to pentamers (Fig. 3), we happened upon the surprising discovery [109] that the solid-state structures were crystallographically indistinguishable from an infinite D–A polyrotaxane with a 2:1 DNP : $CBPQT^{4+}$ ratio. Although the crystals comprise discrete and relatively small molecules, the components pack so efficiently into a continuous D–A stack that structural defects (discontinuities in the infinite-chain lattice that necessarily exist on account of the finite size of the oligomers) are crystallographically invisible. Two different DNP pentamers, 5NPE (Fig. 3a) and 5NP (Fig. 3b), which differ in the presence or absence of a terminal tetraethylene glycol chain, respectively, yield nearly identical final structures when co-crystallized with $CBPQT^{4+}$. The 5NPE ⊂ $[CBPQT^{4+}]_n$ and 5NP ⊂ $[CBPQT^{4+}]_n$ crystals share the same space group and very similar unit cell parameters. Thus, the solid-state structure of a HMW polyDNP ⊂ $[CBPQT^{4+}]_n$ polypseudorotaxane complex can be predicted and understood by single-crystal analysis of its small-molecule homologues, despite the fact that such crystals have not been (and may never be) obtained.

Figure 4 illustrates some of the defect sites that must exist in the "polymeric" superstructures of the 5NPE ⊂ $[CBPQT^{4+}]_n$ and 5NP ⊂ $[CBPQT^{4+}]_n$ crystals. Since 5NPE is not a HMW polymer, a mixture of discrete pseudorotaxanes sum to a lattice with 1/6 DNP site vacancy. Although the vacancy can occur either inside (Fig. 4a) or alongside (Fig. 4b) $CBPQT^{4+}$, the structure refines to site occupancy factors of 0.900 and 0.767 for encircled and unencircled DNP units, respectively, indicating that alongside DNP units are preferentially vacated over encircled ones.

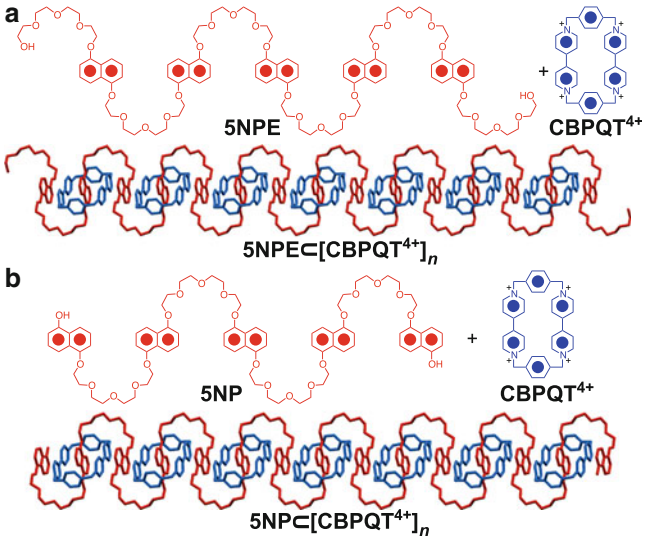


Fig. 3 Structural formulas and X-ray single-crystal superstructures of the apparently infinite polypseudorotaxanes formed between $CBPQT^{4+}$ and 5NPE (**a**) or 5NP (**b**)

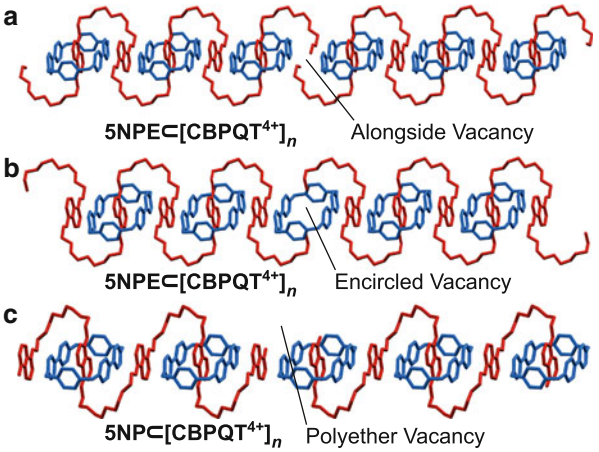


Fig. 4 Representations of the vacancies that occur in pseudorotaxanes formed between pentameric DNP threads and $CBPQT^{4+}$. In 5NPE ⊂ $CBPQT^{4+}$, one in six DNP sites are vacant, with a preference for alongside DNP units (**a**) over encircled DNP units (**b**) as the vacated site. 5NP ⊂ $CBPQT^{4+}$ can maintain a continuous D–A stack by equal co-crystallization of three- and four-component pseudorotaxanes, leaving one in five polyether loops vacant (**c**)

Note that 50% of the DNP sites are occupied by $CBPQT^{4+}$ in the infinite-chain lattice superstructures of these pseudorotaxanes, although an odd number of recognition sites on the oligomeric threads prevents this 2:1 stoichiometry from manifesting itself in any individual complex. Whereas 5NPE ⊂ $[CBPQT^{4+}]_n$

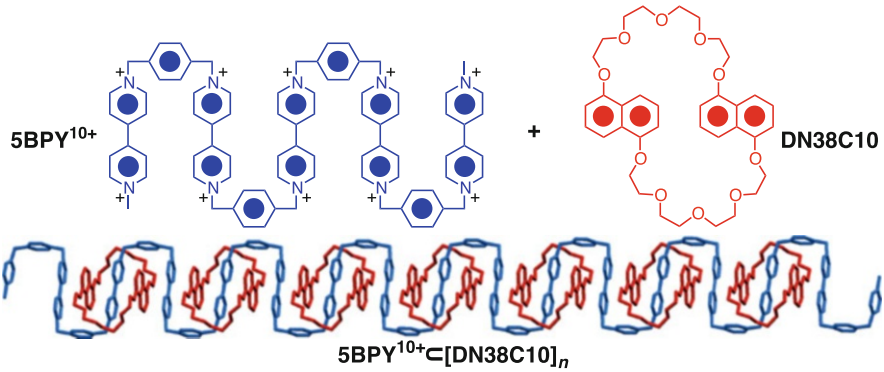


Fig. 5 Structural formula and X-ray single-crystal superstructure of the apparently infinite polypseudorotaxane formed between $5BIPY^{10+}$ and DN38C10

crystallizes primarily as a four-component complex (three rings, one thread) with alongside vacancies, $5NP \subset [CBPQT^{4+}]_n$ can preserve a continuous D–A stack with no DNP vacancies by crystallizing as an equal mixture of three-component (5:2 DNP : $CBPQT^{4+}$ ratio) and four-component (5:3 DNP : $CBPQT^{4+}$ ratio) complexes (Fig. 4c). In this latter case, the tetraethylene glycol chains sum to a 1/5 vacancy in the lattice.

Crystals grown from 7-, 9-, and 11-mers of the DNP threads have identical unit cell dimensions to the pentamers, suggesting that all of the oligomers with five or more DNP units adopt the same superstructure. Because the DNP trimers described in Sect. 2.1 do not co-assemble with $CBPQT^{4+}$ into an infinite D–A stack, it would seem that the critical chain length to obtain a polymeric lattice lies between three and five DNP units.

The phenomena described in Figs. 3 and 4 are not unique to the DNP : $CBPQT^{4+}$ recognition system. Indeed, the co-crystallization of DN38C10 with a *p*-phenylene-bridged $BIPY^{2+}$ pentamer $5BIPY^{10+}$ (Fig. 5) has produced an analogous result: an apparently infinite-chain pseudorotaxane with a continuous D–A stack is enabled by the serpentine-like folding of the thread. The arrangement of oligomers in the "polymeric" $5BIPY^{10+} \subset$ DN38C10 lattice most closely mirrors $5NP \subset CBPQT^{4+}$, since it is best refined to an equal mixture of three- and four-component complexes with 1/5 *p*-phenylene linker site vacancy.

3 D–A Rotaxane Foldamers in Solution

The low-temperature solution-processability and highly tunable mechanical properties of organic polymers is what makes them so ubiquitous in the materials that support our contemporary lifestyles, revolutionizing everything from packaging

and textiles to transportation, construction, and electronics. As a cornerstone of modern society, plastics and related organic compounds are continually evolving, under the umbrella of fundamental research, into materials with ever more diverse and tailorable physical properties. The fact that solution-processable organic materials are continually growing in their scope and reach provides ample motivation to explore the properties of new classes organic polymers with well-defined (super) structures in solution.

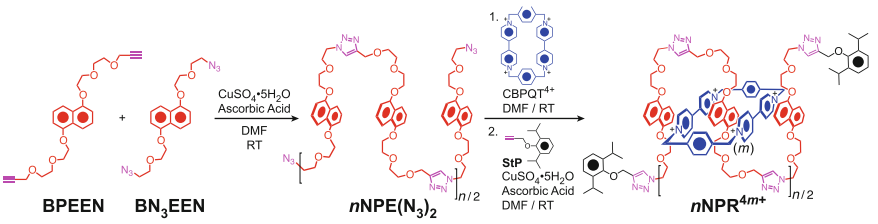
3.1 Folding in D–A Polyrotaxanes

Around the time that the copper-catalyzed azide-alkyne 1,3-dipolar cycloaddition (CuAAC) click reaction was emerging as a powerful tool for the construction [110, 111] of MIMs, we became interested in using this reaction to prepare polyrotaxanes. Our first attempt turned up compelling evidence that the folded solid-state structures described in Sect. 2 also persist to a large extent in solution.

We used CuAAC in the step-growth copolymerization of the azide-terminated DNP monomer BN_3EEN and the propargyl-terminated DNP monomer BPEEN to prepare polymeric DNP threads. Applying different feed ratios ($N_{BPEEN}/N_{BN3EEEN}$) of 0.905, 0.975, and 1.000 gives polyDNP dumbbells 81NPE$(N_3)_2$ (MW 32 kD; polydispersity index, PDI 1.90), 133NPE$(N_3)_2$ (53 kDa, PDI 1.78), and 453NPE $(N_3)_2$ (181 kDa, PDI 1.71) as products in the click reaction (Table 1) with a number average n of approximately 81, 133, and 453 DNP units per chain, respectively. Finishing the reaction with a slight excess of BN_3EEN ensured that the dumbbells were terminated with azide functionalities so that their corresponding pseudorotaxanes could be subsequently stoppered with CuAAC using a bulky propargyl-functionalized stopper. The threading reaction took 24 h to reach equilibrium after the addition of 0.6 equivalents of $CBPQT^{4+}$ with respect to the DNP units. The slow equilibration was expected because threading can occur only at the ends of the polymer, requiring each ring to migrate further toward the interior sites of the polymer before new rings can thread. The final click reaction to stopper the polypseudorotaxanes was initiated when the charge transfer absorption band near $\lambda = 500$ nm (characteristic of DNP $\subset$ $CBPQT^{4+}$ complexes) reached its maximum intensity. The pure polyrotaxane products $81NPR^{4m+}$, $133NPR^{4m+}$, and $453NPR^{4m+}$ were obtained by precipitation into an aqueous EDTA solution to remove copper, filtration through a DNP-functionalized membrane in DMF to eliminate unbound $CBPQT^{4+}$, and precipitation into $CHCl_3$ to remove uncharged monomers and low molecular weight (LMW) oligomers. ^{1}H NMR spectroscopic analysis was used to estimate DNP site coverage to be 90, 74, and 58%, respectively, corresponding to the average values for m (number of threaded $CBPQT^{4+}$ rings) given in Table 1.

The polyDNP threads and corresponding rotaxanated polyelectrolytes were characterized by gel permeation chromatography (GPC) in DMF. All three polyrotaxanes exhibited smaller hydrodynamic radii than their parent threads, as indicated by their increased retention volumes (Table 1, Fig. 6). The apparently

Table 1 Average number of repeat DNP units and $CBPQT^{4+}$ rings, molecular weights, polydispersity indexes, and retention volumes by gel permeation chromatography of polymeric DNP threads and their corresponding D–A polyrotaxanes



Thread	No. of DNP units (n)[a]	MW (kDa)	PDI	Retention volume (mL)[b]	Rotaxane	No. of rings (m)[c]	MW (kDa)[d]	Retention volume (mL)[b]
81NPE $(N_3)_2$	81	32	1.9	24.1	$81NPR^{4m+}$	72	112	25.0
133NPE $(N_3)_2$	133	53	1.78	23.3	$133NPR^{4m+}$	98	161	24.9
453NPE $(N_3)_2$	453	181	1.71	22.3	$453NPR^{4m+}$	262	470	23.3

[a]Average number of DNP units
[b]Retention volume by GPC
[c]Average number of CBPQT4$^+$ rings was calculated based on the reported values for % DNP sites occupied, as estimated by 1H NMR spectroscopy
[d]Molecular weight estimation was based on calculated values for m

more compact size of the polyrotaxanes is particularly remarkable, given the fact that their molecular weights are over twice that of the parent threads. In order to confirm this surprising result, we used atomic force microscopy (AFM) to image individual polymer chains, which were drop-cast from dilute DMF solutions onto highly ordered pyrolitic graphite (HOPG) substrates. Representative AFM images, cross-sectional heights, and fitted histograms of the measured lengths for the largest pair of polymers $453NPEN_3$ and $453NPR^{4m+}$ are shown in Fig. 7. Indeed, the two polymers show distinct differences in their dimensionality. The rotaxane polymer $453NPR^{4m+}$ shows a decrease in length and corresponding increase in height and width compared to the parent thread $453NPE(N_3)_2$. The fitted histograms that plot molecular lengths in Fig. 7 show that the polyrotaxane is almost 10 nm shorter on average than its counterpart thread. The AFM results suggest that the $CBPQT^{4+}$ rings cause the polymer backbone to compress along its long axis, while expanding along the other two axes. This picture of a shorter, fatter macromolecule is fully consistent with the hypothesis of a highly folded conformation analogous to those observed in the solid state (Sect. 2), which maximizes the stabilizing [C–H $\cdots$ O] and D–A π-stacking interactions within these polyelectrolytes.

What began as a highly efficient approach to the synthesis of a new class of mechanically interlocked macromolecules set the stage, not only for the controllable fabrication of intricate nanoscale molecular architectures, but also for the

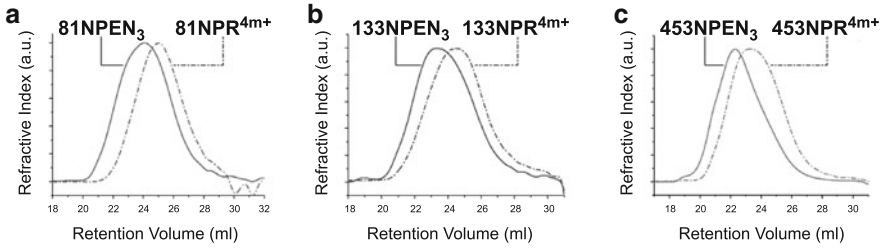


Fig. 6 Gel permeation chromatograms of D–A polyrotaxanes overlaid with their parent polyDNP threads: (**a**) 81NPE$(N_3)_2$ and 81NPR^{4m+}; (**b**) 133NPE$(N_3)_2$ and 133NPR^{4m+}; (**c**) 453NPE$(N_3)_2$ and 453NPR^{4m+}

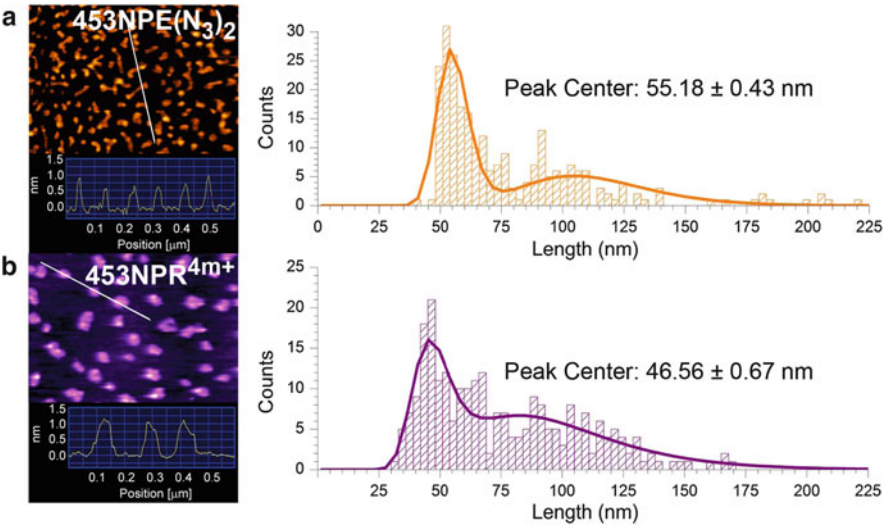
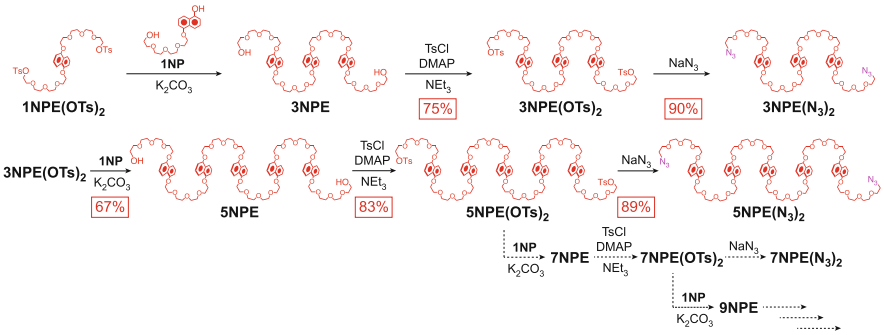


Fig. 7 AFM data for individual polymer chains cast from solution on highly ordered pyrolitic graphite substrates: (**a**) 453NPE$(N_3)_2$; (**b**) 453NPR^{4m+}

elaboration of a novel strategy to instill molecules with well-defined folded secondary structures in solution.

3.2 Systematic Investigations of Oligorotaxane Foldamers

These remarkable results for the folded polyrotaxanes motivated us to undertake a more detailed investigation of analogous monodisperse oligomers in order to shed more light on the dynamics and secondary structures they adopt in solution. We anticipated that a more complete understanding of the solution-state structures and

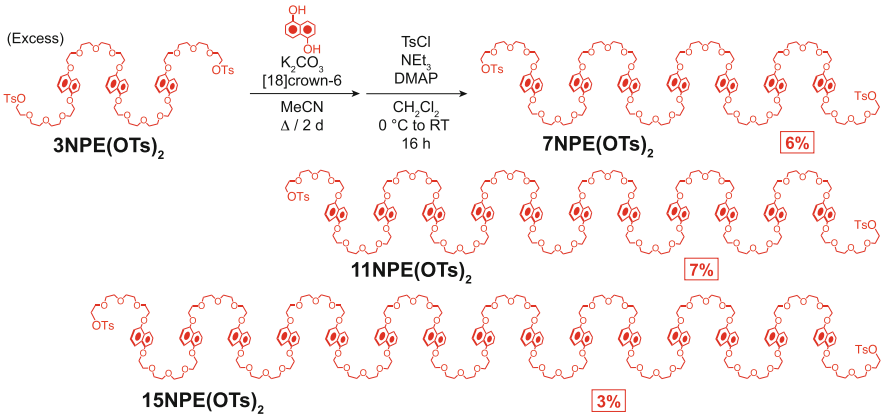


Scheme 1 Stepwise approach to the synthesis of DNP oligomers

dynamics would help identify novel areas of research and applications for this new class of rotaxane–foldamer hybrid. Whereas X-ray crystallography provides ample structural information in the solid state, the structural features and dynamics of molecules in solution can be examined in detail by high-field NMR spectroscopy. Hodge and Owen [112] used ^{1}H NMR spectroscopy to estimate the loading capacity of various hydroquinone-based polymers for threaded CBPQT^{4+} rings in 1997, and expanded on that work in 2000 to suggest [113] that these pseudorotaxanes can adopt folded conformations in solution. It was not until very recently, however, that we mustered the synthetic prowess to be able to access [107, 114] a large family of monodisperse oligomeric threads of increasing chain length and their corresponding D–A oligorotaxanes, which allowed us to perform more detailed spectroscopic analysis and uncover trends that emerged in their collective ^{1}H NMR spectra, providing new insights about their solution-state structures and dynamics.

The synthesis of discrete oligomers with high molecular weights is significantly more challenging than that of either small molecules or polydisperse macromolecules. We initially undertook [107] a stepwise approach to the synthesis of DNP oligomers (Scheme 1), which adds new repeating units incrementally at each terminus of the preceding oligomer in the sequence. Azide-terminated oligomers 3NPE$(N_3)_2$ and 5NPE$(N_3)_2$ were the tetraethylene glycol-bridged small-molecule analogues of the clicked polymers in Sect. 2.1. Although we obtained some promising initial results suggesting that oligorotaxanes prepared from these small oligomers fold as expected in solution, the stepwise synthesis of DNP oligomers proved too resource-intensive for us to continue expanding the library of oligorotaxanes.

Because the S_N2 substitution that is often employed to functionalize DNP with a tosylated counterpart is not very efficient, the use of this reaction in a step-growth polymerization should yield only LMW polymers. Although this situation is typically undesirable, we exploited the low efficiency of the reaction to isolate [114] a series of DNP oligomers of different chain lengths in one pot (Scheme 2). By reacting commercially available 1,5-dihydroxynaphthalene with 3NPE$(OTs)_2$ and tosylating the crude product mixture, a collection of pure, monodisperse



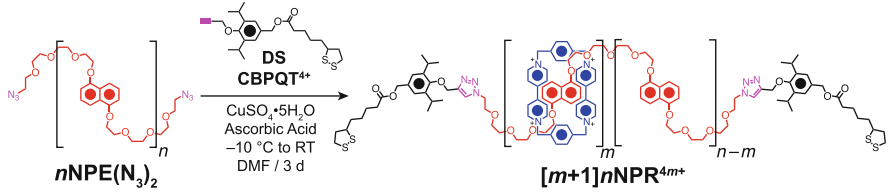
Scheme 2 One-pot synthesis of tosylated DNP oligomers

compounds with up to 15 repeating units were separated by conventional flash column chromatography. Although the yields of the oligomers are low (<10%), the products are still obtained in appreciable (200–700 mg) quantities when the reaction is run on a gram scale with respect to 1,5-dihydroxy-naphthalene, and the one-pot reaction results in dramatic savings in time and resources. By contrast, 13 steps would be required to obtain 15NPE(OTs)$_2$ from the same precursors using the stepwise approach.

The tosylated oligomers isolated from the one-pot reaction were converted to azides with NaN_3 in high (>90%) yields to afford the parent threads *n*NPE(N$_3$)$_2$ (where *n* is the number of DNP units) for the final stoppering reaction. Despite using nearly stoichiometric amounts of CBPQT^{4+} with respect to DNP in the stoppering reaction, the product distribution (Table 2) was heavily biased toward oligorotaxanes in which only approximately half of the DNP units are threaded, suggesting that a folded superstructure, similar to those observed in the solid state (Sect. 2.2, Fig. 3), persists in solution. The isolation of a total of 16 discrete and monodisperse oligorotaxanes from the mixtures that emerged from the stoppering reactions was no less of an achievement in organic synthesis than the one-pot synthesis and purification of the necessary precursors. Since the rotaxanes became increasingly hydrophilic as more tetracationic cyclophanes were added, preparative-scale reversed-phase high-performance liquid chromatography (RP-HPLC) was indispensible in this exercise, efficiently separating products with different numbers of threaded rings.

The development of an efficient protocol for accessing a wide range of DNP - CBPQT^{4+} oligorotaxanes allowed us finally to conduct a rigorous investigation [114] of their folding behavior in solution. All of the isolated oligorotaxanes can be grouped into to one of three families, depending on their internal DNP : CBPQT^{4+} ratios. Because an [X]rotaxane has a total of X interlocked components in its constitution, X can be related to *n*, the number of DNP units per oligomer chain,

Table 2 Distribution of oligorotaxane products isolated after kinetically stoppering pseudorotaxanes formed between DNP oligomers and $CBPQT^{4+}$



No. of DNP units (*n*)	"Confused" [0.5(*n*–1) + 1]rotaxanes			"Happy" [0.5(*n*–1) + 2]rotaxanes			"Frustrated" [0.5(*n*–1) + 3]rotaxanes		
	Compound	No. of rings (*m*)	Yield[a] (%)	Compound	No. of rings (*m*)	Yield[a] (%)	Compound	No. of rings (*m*)	Yield[a] (%)
1	–[b]	–[b]	–[b]	[2]3NPR^{4+}	1	55	–[b]	–[b]	–[b]
3	[2]3NPR^{4+}	1	44	[3]3NPR^{8+}	2	8	[4]3NPR^{12+}	3	–[c]
5	[3]5NPR^{8+}	2	8	[4]5NPR^{12+}	3	25	[5]5NPR^{16+}	4	–[c]
7	[4]7NPR^{12+}	3	7	[5]7NPR^{16+}	4	28	[6]7NPR^{20+}	5	5
11	[6]11NPR^{20+}	4	6	[7]11NPR^{24+}	6	15	[8]11NPR^{28+}	7	4
15	[8]15NPR^{28+}	7	–[c]	[9]15NPR^{32+}	8	10	[10]15NPR^{36+}	9	4

[a]Yields reported are isolated yields
[b]Only one type of rotaxane can be prepared from the DNP monomer because of its singular recognition site
[c]No product was isolated

by a mathematical expression. Like the oligomers in Sect. 2.2, any thread containing an odd number of DNP units cannot accommodate rings on exactly 50% of its recognition sites. For these compounds, rotaxanes with [0.5(n–1) + 1] components have slightly less than 50% of their DNP units occupied by rings and belong to the "Confused" family of oligorotaxanes. Those with [0.5(n–1) + 2] components are "Happy" oligorotaxanes that express slightly more than 50% occupancy, as do the "Frustrated" [0.5(n–1) + 3] oligorotaxanes. These nicknames, which reflect the "moods" of each oligorotaxane family, stem from their observed solution-state behavior as probed by ^{1}H NMR spectroscopy.

Because the oligorotaxanes possess more DNP units than $CBPQT^{4+}$ rings to occupy the DNP units, one can envision a variety of isomers involving the occupation of rings at different sites along the oligomer backbones, a phenomenon known [115] as translational isomerism. Our ^{1}H NMR spectroscopic investigations led us to uncover the following empirical selection rule: *the most stable translational isomers of any oligorotaxane will have no two* $CBPQT^{4+}$ *rings occupying adjacent DNP sites*. This selection rule is consistent with the notion that unencircled adjacent DNP sites can participate in the stabilization of the rotaxanes by extending the D–A stack, and also elegantly explains the trends observed in the ^{1}H NMR spectra of the oligorotaxanes in CD_3CN at 233 K. The moods we designate to each family of oligorotaxanes are rooted in this selection rule. The Confused oligorotaxanes are so-named because they adopt multiple stable translational isomers that are slow to equilibrate on the NMR timescale, leading to highly complicated ^{1}H NMR spectra. The Frustrated oligorotaxanes are likewise complicated by translational isomerism, but the signals are more broad and featureless because they cannot adopt a co-conformation that fully obeys the selection rule. Only the Happy oligorotaxanes express singular rule-compliant translational isomers in solution. These moods are demonstrated by the isomers illustrated in Fig. 8 using the oligorotaxanes derived from the heptameric DNP thread, the smallest oligomer from which compounds in all three families were isolated. Note that, although an uninterrupted D–A stack can be achieved in both the Confused and Happy rotaxanes, the product distribution is typically biased towards the Happy compounds. Although this situation is convenient for NMR interpretation, it most likely results from the use of a relative excess of $CBPQT^{4+}$ in the reaction, rather than from major differences in their stabilization energies.

Structural diagrams of the solution-state co-conformations of every isolated Happy oligorotaxane are presented in Fig. 9. Our detailed ^{1}H NMR spectroscopic analysis of each member in the Happy family confirmed that the highly folded co-conformation with extended D-stacking is indeed a major contributor to the overall solution-state secondary structure of this class of molecules. To summarize our findings, the protons of all the DNP and $BIPY^{2+}$ recognition units resonate at lower and lower frequencies as the lengths of the oligomers are extended. DNP and $BIPY^{2+}$ protons at the center of the molecules always resonate at the lowest frequencies, whereas protons in the most peripheral recognition sites always resonate at the highest frequencies. Comparison of the chemical shifts of the resonances for the α- and β-$BIPY^{2+}$ protons in the homologous series of Happy oligorotaxanes

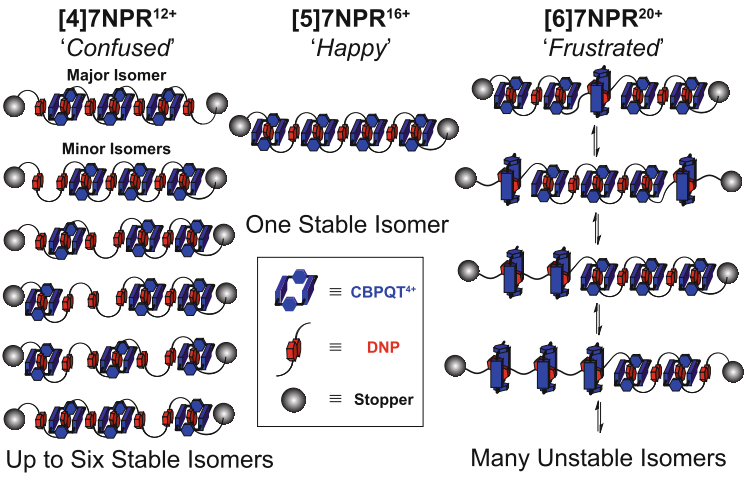


Fig. 8 The three families of oligorotaxanes, exemplified by compounds derived from a heptameric DNP thread. The rotaxanes' moods depend on their adherence to a selection rule forbidding $CBPQT^{4+}$ to occupy adjacent DNP sites. Whereas Confused rotaxanes can adopt multiple stable translational isomers and Frustrated rotaxanes cannot obey the rule at all, Happy rotaxanes express a single rule-compliant isomer

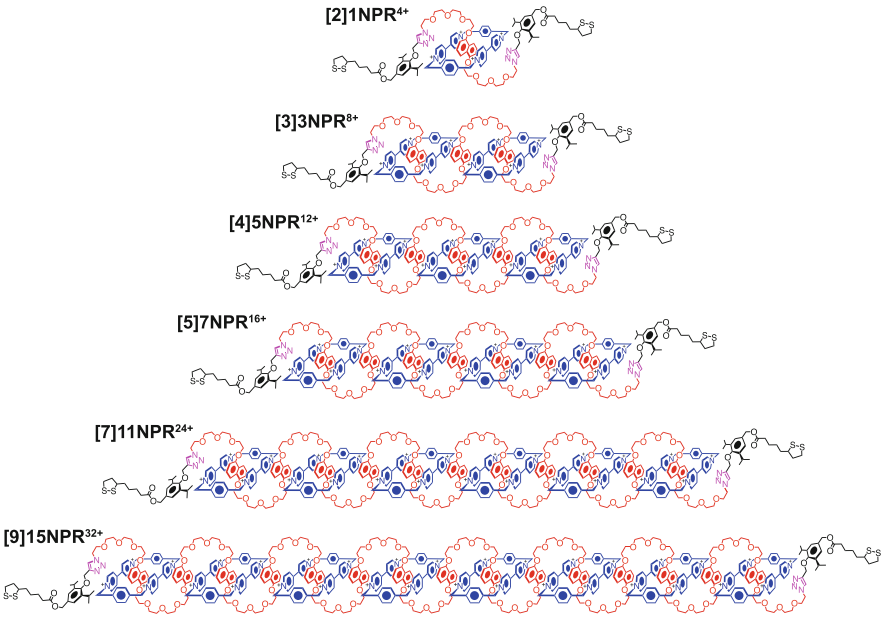


Fig. 9 The proposed most stable secondary structures of the Happy oligorotaxanes

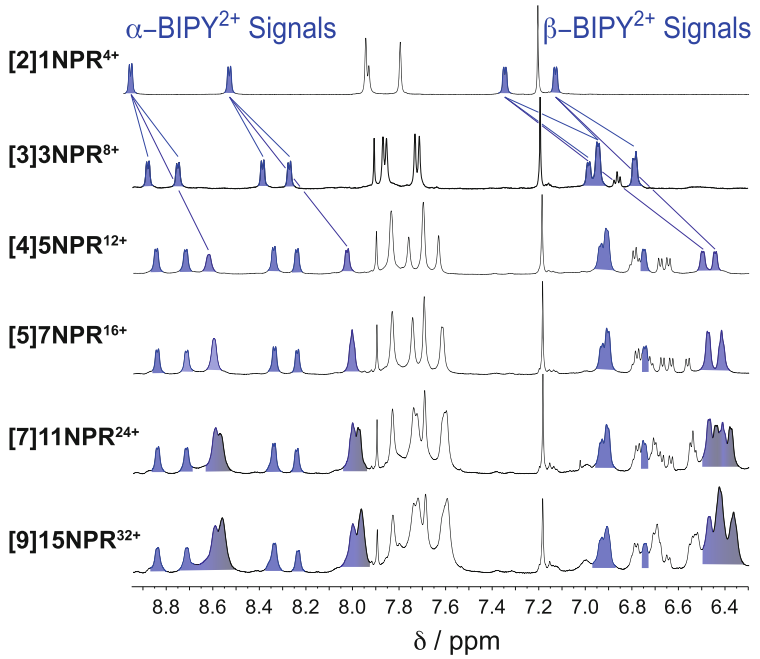


Fig. 10 Stacked plot of the partial ^{1}H NMR spectra (CD_3CN, 600 MHz, 233 K) of the Happy oligorotaxanes, showing the migration of the $BIPY^{2+}$ α- and β-protons to lower frequencies as the oligomers grow longer. Resonances in *darker shades* correspond to protons located closer to the center of the oligomers

(Fig. 10) demonstrates the continual migration of internal α and β-$BIPY^{2+}$ resonances to lower frequencies as the oligomer chains are extended (darker shades in Fig. 10 represent protons located closer to the center of the oligomer). This more efficient shielding of the interior recognition units can be explained by the accumulated aromatic ring-current shifts that can be expected in a folded co-conformation with face-to-face stacking and not in an alternative unfolded one. This cumulative effect of multiple π-stacking interactions on the continual upfield migration of the relevant chemical shifts is commonly observed in systems with discrete stacks of aromatic molecules [116, 117].

In Fig. 11, the chemical shifts of protons that exist in similar chemical environments (the 2/6 and 3/7 protons of encircled DNP units; the 2/6, 3/7, and 4/8 protons of alongside DNP units; and the α- and β-protons of $BIPY^{2+}$ units) are averaged and subtracted from the average chemical shift of the same protons in the parent dumbbells that bear no $CBPQT^{4+}$ rings. These differences (Δδ) in chemical shifts, for which the mechanical interlocking of $CBPQT^{4+}$ rings around the dumbbells are responsible, are plotted against the number of components in the corresponding oligorotaxanes. This plot visualizes the extent to which lengthening the oligomers affects Δδ. The data strongly support the hypothesis of a folded rotaxane with extended D–A stacking as the dominant secondary structure in solution, since the

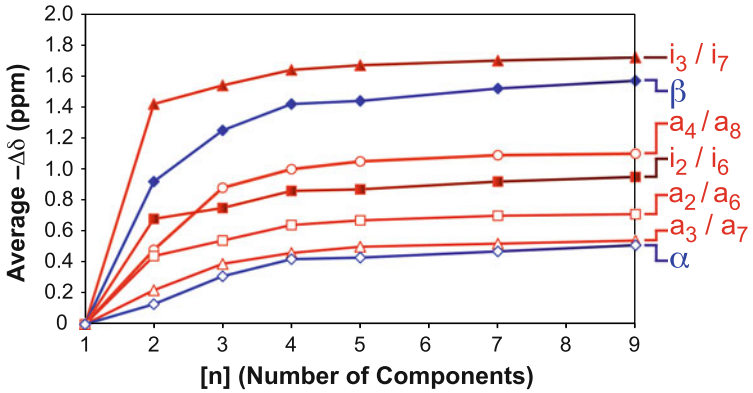


Fig. 11 The changes in chemical shift of DNP and $BIPY^{2+}$ protons of the Happy oligorotaxanes with respect to their parent non-interlocked components, plotted against the number of components in the oligorotaxane. The DNP proton traces are separated into alongside DNP units (a_2/a_6, a_3/a_7, a_4/a_8) and inside DNP units (i_2/i_6, i_3/i_7), corresponding to their positions in the molecules with respect to $CBPQT^{4+}$

alongside DNP protons experience similar changes in chemical shifts as the $BIPY^{2+}$ and encircled DNP resonances, which would not be expected if they were not also participating in π–π stacking interactions.

In addition to these accumulated aromatic ring-current shifts, a number of through-space correlations between alongside DNP protons and the $BIPY^{2+}$ protons of $CBPQT^{4+}$ verify that the folded structure contributes significantly to the average solution-state secondary structure of these oligorotaxanes. A detailed co-conformational analysis [114] revealed that the oligorotaxane foldamers are quite dynamic in solution. The alongside DNP units and DNP ⊂ $CBPQT^{4+}$ subcomplexes execute rapid 180° rotations within the D–A stack on the ^1H NMR timescale in a process we call "superrotation," which leads to signal averaging of otherwise constitutionally heterotopic protons. The complicated dynamics of these compounds calls for more specialized analytical techniques and computational modeling to gain a deeper understanding of the timescales involved and the alternative co-conformations that are accessed as intermediates.

4 Computational Evaluation of D–A Oligo-Pseudorotaxanes

As the evolution of molecular nanotechnology carries us closer to the rational design and synthesis of macromolecules with three-dimensional geometries and properties that rival the intricacy and functionality of Nature's proteins and enzymes, more and more demands will be placed on the predictions of chemical theory. Collaboration between theorists and experimentalists is therefore

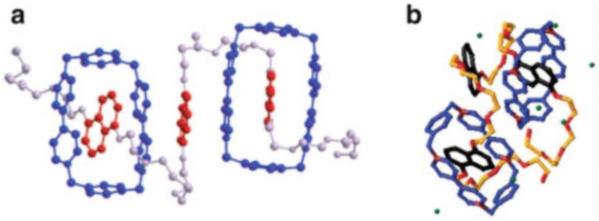


Fig. 12 Different energy-minimized structures calculated for 3NPE ⊂ $[CBPQT^{4+}]_2$ under different conditions. (**a**) Goddard's structure of 3NPE ⊂ $[CBPQT \cdot 4PF_6]_2$ calculated using M06 DFT functionals with continuum solvent corrections for MeCN. (**b**) The model of 3NPE ⊂ $[CBPQT \cdot 4Cl]_2$ in a continuum high-dielectric medium, minimized by Franco et al. using simulated-annealing molecular dynamics with the MM3 force field, is a representative example of the globular structures that repeatedly manifest themselves using this method, even with explicit MeCN solvent and PF_6^- counterions. Images adapted with permission from [107] (copyright 2011 John Wiley & Sons) and [119] (copyright 2011 American Chemical Society).

indispensible for the sake of progress on both sides of the enterprise. Our group has collaborated extensively with the Goddard group on the theory behind π-associated D–A systems. Goddard's group concluded [118] that, among the popular B3LYP, PDB, X3LYP, and M06 density functional theory (DFT) functionals, only the M06 class of DFT methods predicts the stability of complexes like DNP ⊂ $CBPQT^{4+}$. The alternative functionals incorrectly identify a net repulsive interaction between host and guest, which is attributed to their poor descriptions of the attractive medium-range interactions (e.g., London dispersion forces, π–π stacking) that play an integral role in the stabilization of these D–A complexes. These results raise the important point that computational predictions are extremely sensitive to the level of theory that is chosen to explore these π-associated D–A systems because of the importance of their weaker medium-range interactions. Thus, theory and experiment must be extensively cross-checked in a rigorous feedback loop until a robust theoretical framework for these compounds is developed.

The current state of affairs for computational modeling of the D–A oligorotaxane foldamers is marked by contradiction, a fact that is illustrated by the two camps in contention over the predominant solution-state geometry of the 3NPE ⊂ $[CBPQT^{4+}]_2$ pseudorotaxane. The Goddard group optimized [107] the geometry of 3NPE ⊂ $[CBPQT^{4+}]_2$ at the M06 − L/6 − 31G * * level in the gas phase, applying the M06-2X functional and 6 − 311 + + G * * basis set to calculate single-point energies and solvent corrections based on single-point self-consistent Poisson–Boltzmann continuum solvation calculations for MeCN. Using this method, the Goddard group observed an energy-minimized solution-state superstructure (Fig. 12a) that closely matched the X-ray crystal structure (Fig. 2b) of 3NPE ⊂ $[CBPQT^{4+}]_2$.

In the other camp, Franco et al. evaluated [119] the same system using simulated annealing (SA) molecular dynamics (MD) simulations with the MM3 force field, and concluded that the 3NPE ⊂ $[CBPQT^{4+}]_2$ complex adopts a π-stacked folded co-conformation only in the crystal environment. According to their simulations,

a compact globular geometry (Fig. 12b) is preferred both in vacuum and in solution. Unfortunately, most of these calculations were performed with Cl^- counterions in H_2O, whereas our experimental investigations and Goddard's computations were carried out using PF_6^- counterions in MeCN. Thus, a perfect comparison between the computational methods cannot be made. However, one set of SA MD simulations with explicit MeCN solvent and PF_6^- counterions still led to a collapse of the π-stacked structure after ~500 ps, although it was partially recovered (up to 75%) again after ~2,500 ps when using an OPLS-AA force field that applied more diffuse charges to the pyridinium rings of $CBPQT^{4+}$. Franco et al. concluded that the folded secondary structure with extended D–A stacking is stabilized by crystal packing effects rather than the weak forces such as charge transfer, π–π stacking, and the C–H ⋯ O hydrogen bonding interactions that we have claimed [114] persist in solution. We side with the secondary structure (Fig. 12a) proposed by the Goddard group because it agrees with the chemical shift data we observe over and over again by ^{1}H NMR spectroscopy. We acknowledge that the information provided by ^{1}H NMR spectra represents an average of all the dynamic structures that are sampled in solution; indeed, the globular co-conformations (Fig. 12b) described by Franco et al. most likely make fleeting contributions to the dynamic solution-state superstructures. We note, however, that the protons in the unencircled DNP unit of the structure in Fig. 12b should resonate at higher frequencies than an isolated DNP unit, on account of its location orthogonal to the shielding cone of the nearby $BIPY^{2+}$ unit. Since the average chemical shifts of all alongside DNP are observed to resonate uniformly and consistently at lower frequencies than their isolated counterparts (Sect. 3.2), we conclude that the π-stacked superstructure (Fig. 12a) outcompetes the globular superstructure (Fig. 12b), at least at 233 K in MeCN.

The (contradictory) results of modeling these charged D–A mechanically interlaced foldamers presents an enticing challenge to the chemical theory community to build a robust methodology for predicting accurately the behavior of these secondary structures mediated by relatively strong intramolecular noncovalent bonding interactions in polar solvents in the presence of soft counterions.

5 Conclusions and Outlook

We have described a class of oligo- and polyrotaxanes and pseudorotaxanes that adopt well-defined folded secondary structures in the solid state and in solution as a result of stabilizing donor–acceptor charge transfer interactions between the aromatic recognition units, aided and abetted by multiple C–H ⋯ O interactions between polyether chains and bipyridinium protons. In the solid state, oligomers above a certain critical chain length (between three and five repeating units) crystallize into a lattice that is essentially indistinguishable from an infinite polymer, offering a predictive glimpse at hypothetical polymers that are much more difficult to obtain as single crystals. When these types of pseudorotaxanes are

kinetically stoppered in solution, there is compelling evidence to suggest that the same folded superstructure with extended donor–acceptor stacking contributes heavily to the dynamic solution-state structure. This folding motif influences the physical size of the corresponding macromolecules, making them more compact than their parent threads, even as they double their molecular weights as a result of the added rings. By systematically investigating a large family of homologous oligorotaxanes, we have been able to describe in more detail the nature of their translational isomerism and dynamics. Computational input on these polyelectrolytes appears to be highly sensitive to the chosen methodology; conflicting results on the degree of folding call for deeper investigation by chemical theorists.

The generality of this folding phenomenon and potential utility of mixed-stack packing will make donor–acceptor mechanically interlaced foldamers attractive to materials scientists interested in tuning the mechanical and multiferroic properties of charge-transfer materials, either in solution or the solid state. For example, could this accordion-like folding motif be leveraged in the context of molecular springs or elastomers? Could the ferroelectric properties of crystalline donor–acceptor mixed stacks be translated to plastics by appropriately engineering the secondary structures and transition temperatures of these polymers? Indeed, the future holds many exciting possibilities for this emerging class of compounds that lie at the intersection of mechanically interlocked molecules and synthetic foldamers.

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Probing Macromolecular and Supramolecular Structure, Dynamics, and Function by Magnetic Resonance

Hans Wolfgang Spiess

Abstract The use of magnetic resonance spectroscopy, both electron paramagnetic resonance (EPR) and nuclear magnetic resonance (NMR) for elucidating the structure, dynamics, and function of macromolecular and supramolecular systems is described. The role of chain conformation in governing supramolecular organization is emphasized. Examples include polymers with conformational memory, polypeptides, dendronized polymers, as well as functional macromolecular and supramolecular systems for organic-based electronics. Acknowledging Hermann Staudinger's vision similarities between synthetic polymers and biopolymers, e.g., partially disordered proteins, are addressed. Moreover, the need to apply a multitude of techniques in studying the structure and dynamics of such complex systems is emphasized.

Keywords Biopolymers · Dynamics · Electron paramagnetic spectroscopy · NMR spectroscopy · Polymers · Structure

Contents

1 Introduction 296
2 Solid State NMR and Pulsed EPR Techniques for Analyzing Structure and Dynamics . 297
3 Structure and Dynamics of Macromolecular Systems Governed by Their Local Conformations 298
3.1 Conformational Memory in Synthetic Polymers 298
3.2 Self-Assembly and Dynamics of Polypeptides 302
3.3 Protein Dynamics and Flexibility: Order and Disorder in Proteins 304
3.4 Dendronized Polymers 306

H.W. Spiess
Max-Planck-Institute for Polymer Research, P. O. Box 3148, 55021 Mainz, Germany
e-mail: spiess@mpip-mainz.mpg.de

4 Functional Materials 309
4.1 Elastin-Like Polypeptides and Drug Delivery 309
4.2 Columnar Stacks 311
4.3 Pi-Conjugated Macromolecules for Organic Electronics 313
5 Conclusion 316
References 317

1 Introduction

To state that precise knowledge of the structure and dynamics of macromolecules of well-defined architectures is of utmost importance when tailoring them for specific functions nowadays sounds like *ululas Athenas portare*. In his Nobel lecture in 1953 on macromolecular chemistry [1] Hermann Staudinger emphasized the importance of determining the *structure* of macromolecules, but did not mention their *dynamics*. He listed several experimental techniques for determining the structure and the molecular weight of macromolecules that were in use at that time, when the macromolecular nature of both synthetic and biomacromolecules was under debate, but magnetic resonance was not among them. This is easily explained by the fact that magnetic resonance (MR) techniques based on electron spins (i.e., electron paramagnetic resonance, EPR, spectroscopy) and on nuclear spins (i.e., nuclear magnetic resonance, NMR, spectroscopy) were in their infancies, being discovered in 1944 by E. K. Zavoisky [2], and in 1945 by F. Bloch and E.M. Purcell, respectively [3, 4]. Naturally, their potential in macromolecular science was not yet known. As early as the 1960s, however, G. Natta and coworkers took advantage of the new NMR technique to elucidate the stereoregularity of poly(propylene) [5], providing a new way of structural characterization of macromolecular chains [6]. Polymer dynamics is closely linked to the mechanical properties of polymer materials [7]. As molecular dynamics leads to narrowing of NMR lines, the analysis of ^{1}H NMR line shapes of bulk polymers offered a means for a better understanding of these delicate relationships [8]. Indeed, as early as 1959, W. P. Slichter published a seminal paper [9], again in Staudinger's journal, entitled "Nuclear resonance studies of motion in polymers," describing these developments. Much later, ^{2}H NMR on selectively deuterated polymers provided unique possibilities for elucidating both the time scale and geometry of molecular dynamics in polymers [10].

Today, NMR spectroscopy has advanced to become an indispensable tool in polymer research. The introduction of Fourier transform NMR and its extension to two and higher dimensions [11] made it possible to include low-sensitivity, yet highly informative, spectroscopy of rare nuclei such as ^{13}C or ^{15}N. These techniques are now mainly applied to study biomacromolecules [12] in solution, but increasingly also in the solid state [13]. In the latter case, multidimensional NMR techniques were actually developed first for synthetic polymers [14]. Later, advances in solid state

NMR under fast magic angle spinning (MAS) offered an attractive way to elucidate the packing and local dynamics of the building blocks in supramolecular assemblies [15]; for a review of the early examples see [16].

In the early days of magnetic resonance, NMR and EPR spectroscopy were developed in parallel and often by the same people [17, 18]. Later on, the two techniques largely separated, but recent developments in microwave technology have allowed spectroscopists to use pulse methods in EPR as well [19] and it is rewarding to see the two "sister spectroscopies" merge again. In fact, the current revival of EPR (ESR) spectroscopy in macromolecular science [20–22] is largely due to the development of pulsed methods by groups active in both solid state NMR and EPR [23, 24]. Using these techniques, together with site-directed spin labeling [25], the structure of biomacromolecules and supramolecular assemblies can now be probed on the nanometer scale, which nicely augments the subnanometer information provided by NMR. A singular advantage of MR methods is the fact that structure determination does not require single crystals, as needed for X-ray diffraction or neutron scattering [26]. Therefore, MR can be applied to condensed matter in all forms: liquids, crystalline solids, disordered solids, liquid crystals, and even gases.

This chapter collects a few recent studies on the structure and dynamics of macromolecular and supramolecular systems, largely based on the author's group in collaboration with other more synthesis-oriented colleagues. For additional reading we refer to a recent perspective article [27] and recent reviews [28–30]

2 Solid State NMR and Pulsed EPR Techniques for Analyzing Structure and Dynamics

Signals originating from hydrogen-bonded protons are well separated in ^{1}H MAS NMR spectra, typically resonating between 8 and 20 ppm [11, 16]. Therefore, the ^{1}H chemical shift provides semiquantitative information about the strength of the hydrogen bonds. In addition, the ^{1}H chemical shift is also a sensitive probe of so-called ring currents associated with aromatic moieties [16]. They are observed as a low field shift compared to the corresponding liquid state signal and may thereby serve as a direct hint for π–π interactions. Likewise, the low field shift can be simply related to the packing via so-called nucleus independent chemical shift (NICS) maps [31]. This augments the well-known sensitivity of ^{13}C NMR chemical shifts to local conformation [6], known as the "γ-gauche effect". Detailed packing information is obtained from distance measurements between specific proton sites at adjacent building blocks via high resolution double quantum (DQ) solid state NMR under MAS [16, 28]. This is particularly important for supramolecular assemblies involving aromatic groups and functional polymers for organic electronics [32, 33].

Solid state NMR, however, is probably even more powerful for probing the time scale and geometry of rotational motions [14]. For instance, disk-shaped aromatics often stack into columnar structures as part of discotic liquid crystals (DLC)

[34]. In the liquid crystalline phase, the disks rotate around the column axis. A particularly simple way of characterizing such restricted molecular dynamics is provided by the dynamic order parameter S, $0 \leq S \leq 1$. It is defined as the ratio between the motionally averaged and the static anisotropic NMR interaction, e.g., dipole–dipole coupling, anisotropic chemical shift, or quadrupole coupling [14]. For the rotation of disks in a perfectly packed column, $S = 0.5$ for ^{13}C–^{1}H dipole–dipole coupling or ^{2}H quadrupole coupling, centered around the C–H (C–D) bond direction. Imperfections of the packing in the liquid crystalline phase, where disks can be inclined to the column axis, lead to reduction of S below 0.5 and values as low as 0.15 have been found [35]. Thus, S provides both dynamic and structural information. In general, solid state NMR yields site selective information about the amplitude and time scales of molecular motions over broad ranges of length and time; for a recent review see [30].

The information about the structure and dynamics of polymers that EPR can provide is very similar [19, 21]. For synthetic polymers, biopolymers, and supramolecular assemblies, nitroxide spin probes and spin labels are particularly useful [36]. In solution, their EPR spectra are governed by the g-factor and the hyperfine splitting (denoted as a) to the ^{14}N nucleus of the NO group. In solution, the former determines the frequency of the center of the triplet arising from the hyperfine coupling. Both parameters are sensitive to the electronic environment. In the solid state, the anisotropy of the g-tensor leads to broad characteristic EPR line shapes, similar to those in solid state NMR. Likewise, the EPR spectra are averaged by rotational motions, yet on time scales in the nanosecond scale rather than the microsecond scale that is relevant in NMR [14, 19]. This motional averaging has been exploited extensively in macromolecular science, due to the pioneering work of J. Freed [37]. Moreover, similar to NMR, the dipole–dipole couplings between electron and nuclear spins can be exploited to determine intermolecular distances below 1 nm. The much stronger couplings between two electron spins can probe distances up to about 8–10 nm. Both types of measurements are achieved by pulsed electron–nuclear or electron–electron double resonance techniques [23, 24], respectively.

3 Structure and Dynamics of Macromolecular Systems Governed by Their Local Conformations

3.1 Conformational Memory in Synthetic Polymers

In flexible polymers, the chains tend to form random coils and the local conformations allow isotropic rotational motions of the residues by a combination of angular fluctuations and conformational transitions [14, 38]. Stiff macromolecules with flexible side groups, however, lack conformational freedom within the backbone,

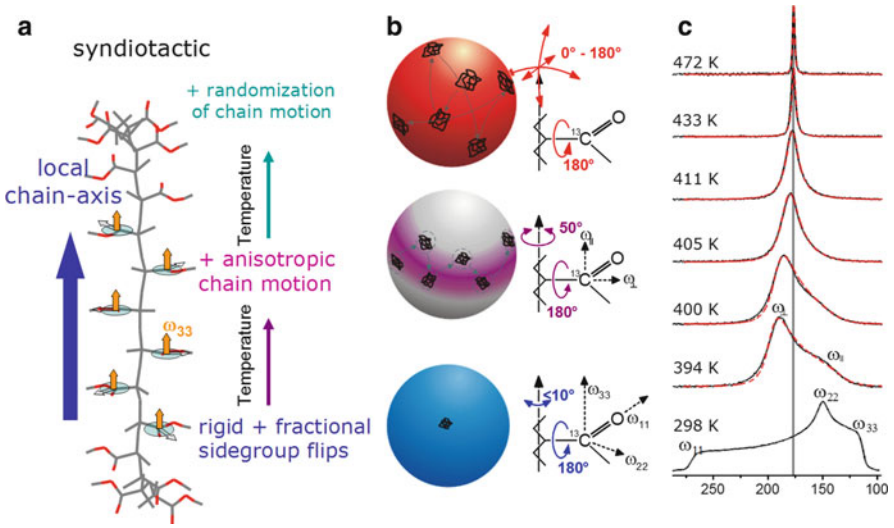

Fig. 1 (**a**) Extended chain conformation of syndiotactic poly(*n*-alkyl methacrylates). (**b**) Anisotropic chain motion during glass process. (**c**) ^{13}C NMR spectra indicating anisotropic motion above T_g, as described in the text

which leads to formation of layered structures even in the melt and highly anisotropic motion [39]. The question then arises whether in more conventional polymers extended conformations involving several repeat units can exhibit conformational memory manifesting itself in collective anisotropic motions. Randomization of conformation leading to locally isotropic reorientation could then occur as a separated process on a longer time scale. Structurally heterogeneous poly(*n*-alkylmethacrylates), which consist of a polar backbone and flexible nonpolar side groups $R_n = C_nH_{2n+1}$, are candidates for polymers with conformational memory, and indeed exhibit unusual relaxation behavior [40]. The backbone of these polymers contains extended syndiotactic sequences, which lead to extended chain conformations (see Fig. 1a).

Molecular dynamics of a macromolecular chain involves both conformational and rotational motions. Along these lines, the backbone dynamics of poly(*n*-alkyl methacrylates) has been elucidated by advanced solid state NMR, which enables conformational and rotational dynamics to be probed separately [41]. The former is encoded in the isotropic ^{13}C chemical shift. The latter is probed via the anisotropic ^{13}C chemical shift [14] of the carboxyl group with unique axis along the local chain direction. Randomization of conformations and isotropization of backbone orientation occur on the same time scale, yet they are both much slower than the slowest relaxation process of the polymer identified previously by other methods [40]. This effect is attributed to extended backbone conformations, which retain conformational memory over many steps of restricted locally axial chain motion (Fig. 1b, c). These findings were rationalized in terms of a locally structured polymer melt, in

which the polar and less flexible polymethacrylate backbones form disordered layers. This structure has been confirmed through temperature-dependent wide-angle X-ray scattering (WAXS) [42]. The anisotropic chain motion occurs within the layers; conformational randomization and rotational isotropization require extended chain units to translate from one structured unit to another. The variation in the molecular weight of PEMA showed that a minimum chain length of five to ten repeat units is required for this effect to occur [43]. In the vicinity of the glass transition temperature (T_g), the time scales of the two processes for PEMA differ by more than an order of magnitude, where the anisotropic motions follows a simple Arrhenius law and the isotropization process follows the Williams–Landel–Ferry (WLF) equation [7].

Recently, such peculiar chain dynamics were studied in nanoparticles onto which PEMA was grafted [44]. Through selective ^{13}C labeling, different parts of the PEMA brush were labeled: at the particle surface (brush A), in the middle (brush B), and at the chain end (brush C). In both brush A and brush B the isotropization is significantly slowed down, in particular at elevated temperatures (see Fig. 2a, b). The increased curvature of the data indicates a significant increase of T_g by about 20 K as well as significant changes in WLF parameters. Remarkably, the part of the chain directly bound to the surface, brush A, consisting of about 40 repeat units, displays virtually identical reduction in isotropization mobility as the part in the middle of the brush, brush B, where the labeled part is separated from the core by about 60 repeat units. This is remarkable because the nanostructures of PEMA mentioned above involve five to ten repeat units only.

This suggests that these structures, which are the reason for the clear separation of the time scales of the local chain motion and the isotropization in PEMA, are significantly affected by the presence of the nanoparticle. One can compare this effect with the significant reduction in the chain reptation in star polymers, where the star point does not move and chain motion can only occur via arm-retraction [45]. In fact, from ^2H NMR on selectively deuterated four-arm star poly(butadiene), Brereton el al. [46] found a similar behavior, namely almost uniform dynamics for the middle part of the arm, yet significantly shorter correlation times for the chain ends. Our work also motivated computer simulation of chain dynamics of grafted chains. It was found that the repeat units at the end relax faster than units further inside along the chain, as previously observed for planar brushes but at variance with theoretical expectations [47].

This example of studying polymer chain dynamics by advanced NMR techniques illustrates what kind of unique information this technique can provide. Many different types of information are accessible and its site selectivity is unmatched by other methods. In addition to the local dynamics, chain motion on mesoscopic length scales in polymer melts have been elucidated by various NMR techniques including DQ NMR in high and low magnetic fields [29, 48]. Last, but not least, the translational motion of poly(ethylene) chains from the crystalline to the noncrystalline regions and vice versa has been quantified in samples of different morphology, unraveling the decisive role of the interface [49].

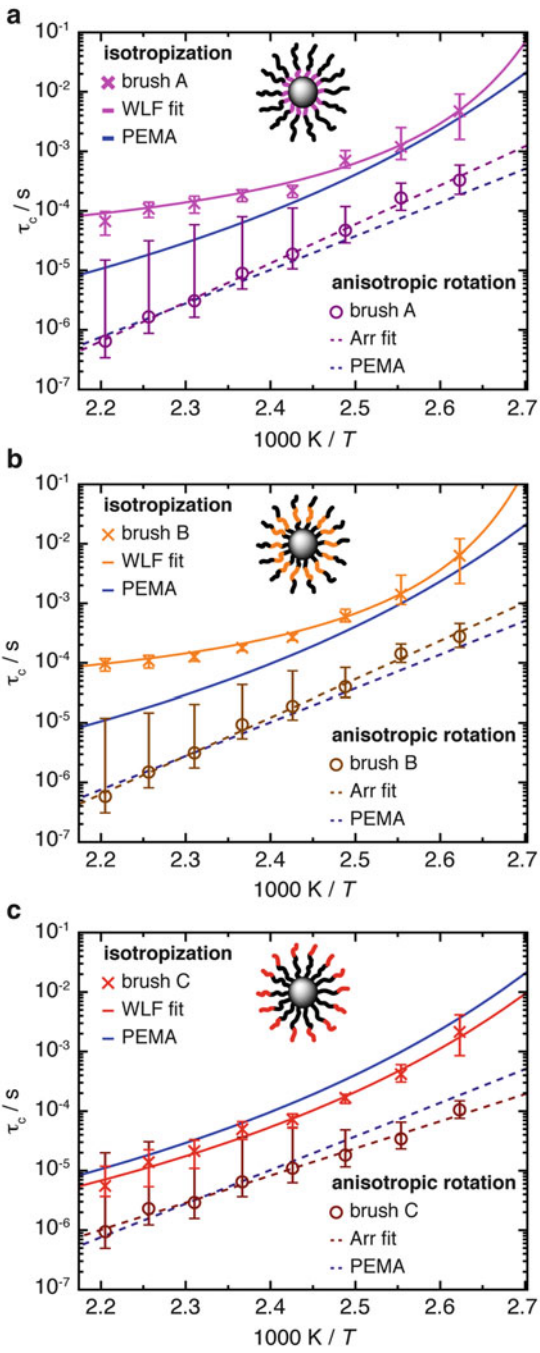

Fig. 2 Arrhenius plots of the two dynamic processes (isotropization and ansiotropic chain motion) for (**a**) brush A labeled at the particle surface, (**b**) brush B labeled in the middle of the brush shell, and (**c**) brush C labeled at the chain ends. For details see [44]

3.2 Self-Assembly and Dynamics of Polypeptides

It is remarkable that Hermann Staudinger had already considered synthetic and biomacromolecules in parallel and noted their similarities as well as their differences [1]. Following this, we note that local chain conformations also play a vital role in the organization of polypeptides, i.e., macromolecules composed of amino acids. Resembling biomacromolecules, they are considered for use in drug delivery and gene therapy and thus have been the subject of intensive studies [50, 51]. In addition, it is known that the superb performance of biological polypeptide-based materials such as hair or spiders' silk is due to a hierarchical superstructure over several length scales, where structure control is exerted at every level of hierarchy [52]. The two most common local conformations of polypeptides, known as secondary structures, are the α-helix, stabilized by intramolecular hydrogen bonds, and the β-sheet, stabilized by intermolecular hydrogen bonds. These secondary structures can be probed directly by solid state NMR [14] and their packing can be obtained from X-ray studies [53]. In addition, the α-helical structure posts a permanent dipole moment along its backbone and can, therefore, be classified as a type-A polymer in Stockmayer's classification [54]. This dipole moment can be measured precisely using dielectric spectroscopy (DS) and can be used as a probe of the persistence length of the secondary structure [55]. Over the years, we have studied various polypeptides by different NMR techniques, X-ray scattering, and dielectric spectroscopy [8] in order to better understand their hierarchical self-assembly (Fig. 3).

As shown in an extended review [56], the concerted application of these techniques has shed light into the origin of the glass transition, the persistence of the α-helical peptide secondary motif, and the effects of topology and packing on the type and persistence of secondary structures. Protein function and application often depend on these issues. Using poly(γ-benzyl-L-glutamate), PBLG, as an example, it was shown that helices are objects of rather low persistence in the bulk as well as in concentrated solutions in helicogenic solvents.

Copolypeptides, on the other hand, with their inherent nanometer length scale of phase separation, provide means of manipulating both the type and persistence of peptide secondary structures. As examples, we refer to the partial annihilation of α-helical structural defects due to chain stretching, to the induced chain folding of β-sheets in block copolypeptides with incommensurate dimensions, and to the destabilization of β-sheets in peptidic blocks having both secondary motifs [57, 58]. These effects should be taken into account when such peptides are going to be employed. in applications such as drug delivery.

Proline residues are of exceptional significance in protein conformation and protein folding because proline is the only amino acid where the nitrogen bears no amide hydrogen, preventing hydrogen bonding. Furthermore, the bulky pyrrolidine ring restricts the available conformations. Therefore, polypeptides with proline residues offer a unique possibility for unraveling the interplay between hydrogen bonding and geometric packing effects. In a recent multi-technique study of diblock copolymers of PBLG and poly(L-proline) (PLP) their hierarchical self-assembly was

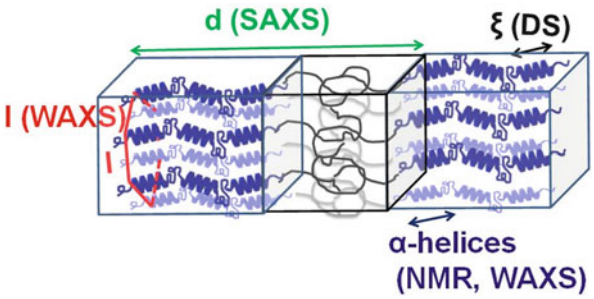

Fig. 3 Assembly of a lamellar-forming polypeptide-coil diblock copolymer, depicting the main techniques employed in our studies. Small-angle X-ray scattering (SAXS) is employed for the domain spacing, *d*. ^{13}C NMR and wide-angle X-ray scattering (WAXS) are employed to identify the type of peptide secondary structure (α-helical in the schematic). WAXS is further employed to specify the lateral self-assembly of α-helices within the polypeptide domain (a hexagonal lattice is indicated in the schematic). Dielectric spectroscopy (DS) and site-specific NMR techniques are employed for the dynamics. Furthermore, the most intense DS process provides the persistence length, l_p, of α-helical segments [56]

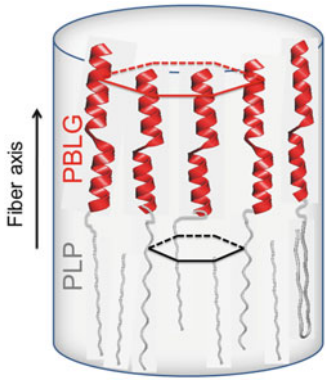

Fig. 4 Copolymer self-assembly, showing PBLG and PLP α-helices (NMR, WAXS) that are packed (WAXS) with significantly differently sized hexagons. The respective unit cells are indicated. The *arrow* indicates the fiber axis. Adopted from [59]

investigated. Both blocks possess helices stabilized either by hydrogen bonds (PBLG) or by steric hindrance (PLP) and are packed in two hexagonal cells of different dimensions. An intriguing *trans–cis* conformational change of PLP upon confinement was observed that mimics the isomerization of isolated proline residues in proteins. These *cis*-PLP conformations reside primarily at the PLP/PBLG interface, alleviate the packing frustration (see Fig. 4), and permit PBLG and PLP helices to pack with the bulk [59].

3.3 *Protein Dynamics and Flexibility: Order and Disorder in Proteins*

Hermann Staudinger concluded his Nobel lecture [1] by saying "macromolecular chemistry makes use of a number of qualitative correlations: those of shape and of the associated configurational scope, up to the level of the "atomos" of living substance, on which the game of Life ensues. In the light of this new knowledge of macromolecular chemistry, the wonder of Life in its chemical aspect is revealed in the astounding abundance and masterly macromolecular architecture of living matter." Thus, he clearly looked at synthetic macromolecules and biopolymers in parallel and looked for synergies in their understanding [60]. Moreover, self-organization and dynamics are common aspects in synthetic and biological systems alike [61, 62].

As far as proteins are concerned, the wealth of structural data available today [63] are from X-ray studies of protein single crystals. However, as stated in an extended review [64], the occurrence of unstructured regions of significant size (>50 residues) is surprisingly common in functional proteins. These disordered regions are characterized by great structural flexibility and plasticity. Obvious similarities between proteins and synthetic polymers are that both classes span a wide range of organization, from completely disordered random coils via molten globules and linked folded domains to mostly folded crystallizable proteins [64] in the case of biopolymers, and amorphous via self-organized structures to semicrystalline polymers in the synthetic case [53]. A reason for the attention being paid to disordered regions of proteins today is that techniques have recently been developed to analyze their structural propensities in solution by multidimensional NMR and pulsed EPR spectroscopy [64–68]. These studies of intrinsically disordered proteins (IDPs) or disordered protein regions indicate that proteins in general have a conformational ensemble of varying breadth.

As a specific example from our group showing that well-ordered proteins also can gain significant flexibility, let us consider the functional structure of human serum albumin (HSA). It is the most abundant protein in human blood plasma and serves as a transporting agent for various endogenous compounds and drug molecules [69]. Its capability to bind and transport multiple fatty acids (FA) has been studied extensively in the past. The research on HSA was severely hampered by the complexity of the protein and benefited tremendously from crystallographic high-resolution structures. Nearly 20 years ago, He and Carter reported the first crystal structure [70]. To date, a plentitude of crystal structures have been deposited in the Protein Data Bank. Even more important for understanding the binding properties of the protein, however, are the structures of complexes of HSA and transported molecules, such as fatty acids. Due to the pioneering work of Curry et al., crystal structures of various HSA–fatty acid complexes have become accessible [71]. In particular, it was found that fatty acids are distributed highly asymmetrically in the protein crystal, despite the fact that HSA itself exhibits a symmetric primary and secondary structure.

In the context of partially disordered proteins, we note that the surface exposed parts of HSA show a high degree of flexibility, which constitutes a key to the protein's

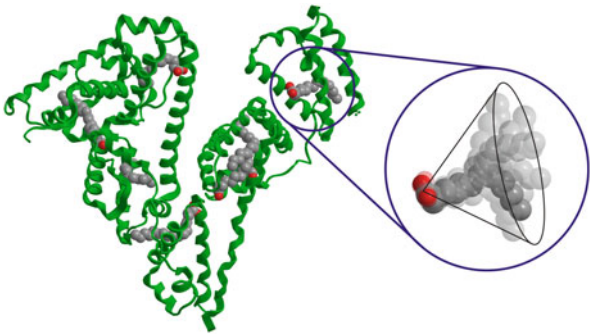

Fig. 5 Flexibility of the fatty acid binding site entry points, which results in a much more homogeneous and symmetric distribution over the protein surface than expected from the crystal structure. Only one binding site is shown for clarity. Adopted from [74]

binding versatility towards various molecules. As early as the 1950s, Karush developed a concept that accounted for conformational adaptability of the binding sites [72] and later a model was proposed that took into account the conformational entropy arising from the flexibility of the fatty acid alkyl chains [73]. As noted in Sect. 2, distances and distance distribution between spin labels on the nanometer scale can now be determined with pulsed electron–electron double resonance, DEER [20, 24]. By using spin-labeled fatty acids, it is possible to unravel the functional structure of HSA with respect to its binding of fatty acids directly from the fatty acids' point of view [74]. In this way, the distribution of the fatty acid binding sites is detected without any contribution from the complex protein itself, which is an enormous simplification. Structural information of the binding sites is obtained by determining the distance distributions between the fatty acids in frozen solution. In order to sample distances between different binding sites, fatty acids with different labeling positions can be applied. In 5-doxylstearic acid (5-DSA), the unpaired electron resides near the anchoring carboxylic acid group, in 16-DSA it is located near the end of the methylene chain. Thus, information can be retrieved separately from the anchor positions in the protein and from the entry points into the fatty acid channel formed by the protein.

The experimental distribution of 5-DSA, probing the anchoring points, nicely fits that of the crystal structure. In contrast, the distance distribution of the entry points (16-DSA) strongly deviates from that of the crystal structure and indicates that the entry points are distributed much more symmetrically and homogeneously over the protein surface than expected from the crystal structure. As depicted in Fig. 5, this leads to a picture of the functional protein structure that contains a more rigid, asymmetric inner part of the protein, while the surface of the protein shows much larger structural flexibility. These findings [74] suggest that the conformational flexibility at the periphery of HSA is a prerequisite for its function as a carrier for so many different compounds. When comparing these EPR-derived results with similar measurements on bovine serum albumin (BSA), one finds that in BSA the structural (peripheral) flexibility is far less than in HSA [75].

3.4 Dendronized Polymers

Inspired by Staudinger's vision [1], mimicking the size and eventually the function of biomacromolecules has been a dream of chemists for decades [76]. This requires not only giant molecular structures to be generated, whose dimensions are on the order of tens and even hundreds of nanometers, but also that these man-made objects should have a useful, predetermined shape. Last, but not least, at both the periphery and the interior they should contain functionalities such as recognition or catalytically active sites. Moreover, their interaction with solvents, in particular water, should be controlled and exploited in their self-organization. It is evident that successful projects in this direction will have considerable impact on both biological and materials sciences.

One approach along these lines is to incorporate building blocks such as amino acids (see Sect. 3.2), generating bioinspired polymers [77]. A full synthetic approach makes use of the enormous variety of dendrons and dendritic groups [78]; for recent reviews see [76, 79]. The structure of dendritic groups can be varied in different ways, e.g., by controlling their size by their generation, by generating amphiphilic character by incorporating hydrophobic and hydrophilic building blocks, or by varying the conformational freedom from completely rigid (polyphenylene) dendrimers [80] to highly flexible as in hyperbranched polymers [81]. Linear polymers jacketed with dendrons attached via their apex provide a conceptually simple class of dendronized polymers. For such polymers with conventional backbone, poly(styrene) or poly (methacrylate), the polymer shape can be controlled through the self-assembly of flexible dendritic side-groups and the degree of polymerization (DP) [82]. For low DP, spheres are observed, whereas for high DP, cylinders are obtained. ^{1}H and ^{13}C solid state NMR on the latter have revealed details of the organization of the dendritic groups within the supramolecular polymer [83]. The dendrons contain aromatic moieties and flexible ethylene oxide linkers (Fig. 6). In the supramolecular assembly, however, they largely lose their flexibility and exhibit dynamic order parameters S as high as 40–80%, displaying a gradient of mobility that decreases from inside out. This significant immobilization nicely demonstrates their role as structure-directing moieties displaying "edge-on" and "face-on" contacts between the ethylene units and the aromatic rings, facilitating the formation of helices (see Fig. 6).

The shape of macromolecular objects can also be changed by external stimuli [84]. For instance, thermoresponsive polymeric materials are of great interest owing to their potential use in fields such as actuation, drug delivery, and surface modification [85]. Ever since the discovery by Wu and coworkers of the coil–globule transition of single poly(*N*-isopropylacrylamide) (PNiPAAm) chains near the lower critical solution temperature (LCST) [86], the collapse mechanism and the formation of stable mesoglobules have been intense topics of research [84, 87]. Despite these efforts, a molecular-scale picture of what happens when thermoresponsive polymers start to dehydrate at a certain temperature, subsequently collapse, and then assemble to mesoglobules, did not exist. This absence severely hampered rational materials design. Dendronized polymers with amphiphilic dendritic groups based on

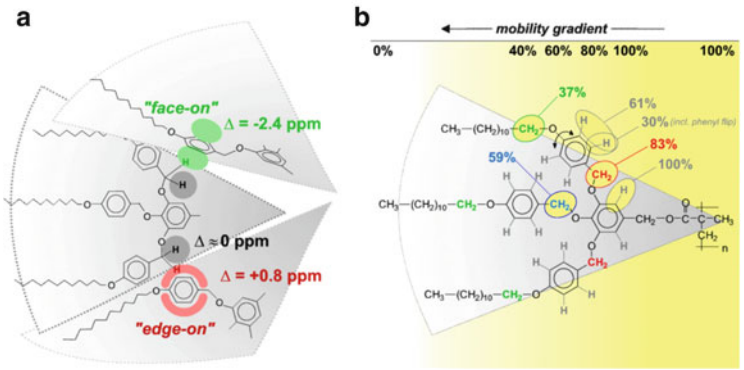

Fig. 6 Structure and dynamics of directing dendrons in cylindrical supramolecular macromolecules. (**a**) Local packing allows the formation of helices. (**b**) Restricted motion, as indicated by high dynamic order parameters, with a mobility gradient inside-out. Adopted from [83]

oligoethyleneglycol (OEG) helped to shed more light on the phase separation because they exhibit fast and fully reversible as well as particularly sharp transitions, as observed in turbidity measurements [88]. These dendronized polymers with terminal ethoxy groups are soluble in water. Their LCSTs lie in a physiologically interesting temperature range between 30 and 36°C and mainly depend on the periphery of the dendrons.

There are indications, however, that such thermal responses proceed by via the formation of structural inhomogeneities of variable lifetimes on the nanometer scale that are still poorly understood. Indeed, this topic has been identified as one of the major challenges of current research in the macromolecular sciences [89]. The structure and lifetime of these local inhomogeneities will obviously influence the aspired function, for instance drug delivery. Magnetic resonance techniques, as intrinsically local methods, are particularly suited to probe structural inhomogeneities of functional macromolecules in general [14, 21] For instance, with multidimensional NMR, the lifetime of dynamic heterogeneities in polymer melts in the vicinity of the glass transition was identified as early as 1991 [90].

A particularly simple way of studying the molecular environment of thermoresponsive dendronized polymers, which undergo a thermal transition, utilizes conventional continuous wave (CW) EPR spectroscopy on nitroxide radicals, as paramagnetic tracer molecules [21]. As noted above, such spin probes are sensitive to the local viscosity, which will give rise to changes in the rotational correlation time and to the local polarity/hydrophilicity [21, 22]. The latter affects the electronic structure of the radical and changes the spectral parameters, specifically the g-factor and the hyperfine coupling constant to ^{14}N. The amphiphilic radical 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) is especially suited to sample both hydrophobic and hydrophilic regions and also mimics a small molecule to be delivered by the dendronized polymer.

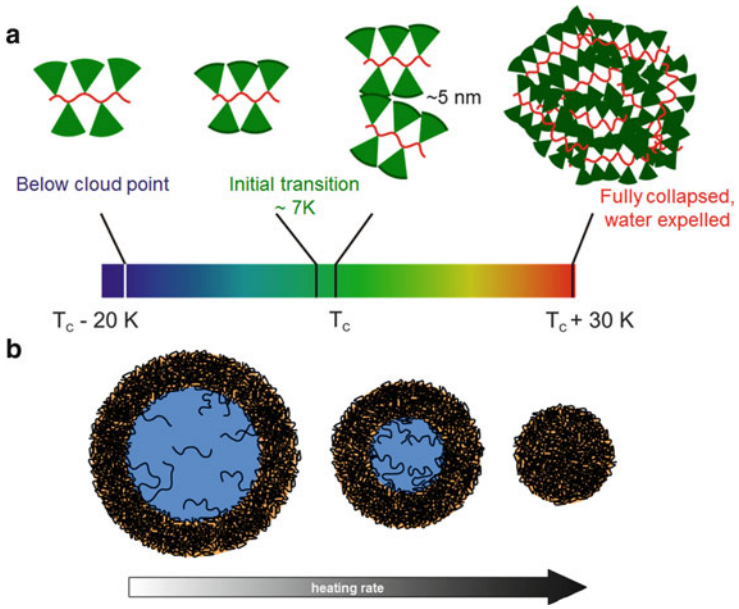

Fig. 7 (**a**) Thermal collapse of dendronized polymers, as deduced from EPR spectroscopy of admixed spin probes [91]. (**b**) Skin barrier effect in mesoglobules of different sizes [91]

The results of such a study [91] are depicted in Fig. 7a. When the temperature is raised above the transition temperature T_C, the aggregation of the complete polymer sample is triggered by dynamic structural inhomogeneities of a few nanometers. In this temperature regime the spin probes exchange between large hydrophilic and small hydrophobic regions. Although macroscopic turbidity measurements suggest a sharp phase transition of the polymer, EPR spectroscopy reveals that the dehydration of the polymer chains proceeds over a temperature interval of at least 30°C. It cannot be described by a single de-swelling process that would be expected for a thermodynamic phase transition. Rather, the dehydration should be viewed as a molecularly controlled nonequilibrium process that takes place in two steps. The local heterogeneities grow in size, and polymer chain fluctuations slow down. Within ~7°C above T_C, the majority of the dehydration is complete and percolation for the fraction and volume of hydrophobic regions is reached. Heating the samples to even higher temperatures leads to additional losses of residual water from the collapsed system. Although the aggregation temperature mainly depends on the periphery of the dendrons, the dehydration process itself is sensitive to the inner core, with the dehydration efficiency being strongly related to the hydrophobicity of the core.

In a subsequent study [92], differences in the EPR spectra in dependence of the heating rate, the chemical nature of the dendritic substructure of the polymer, and the concentration were interpreted to indicate the formation of a dense polymeric layer at the periphery of the mesoglobule (Fig. 7b). This skin barrier [85] is formed in a

narrow temperature range of ~4 K above T_C and prohibits the release of molecules that are incorporated in the polymer aggregate. In large mesoglobules, formed at low heating rates and at high polymer concentrations, a considerable amount of water is entrapped and a microphase separates from the collapsed polymer chains at high temperatures. This results in aggregates possessing an aqueous core and a corona consisting of collapsed polymer chains. Fast heating rates, low polymer concentrations, and hydrophobic subunits in the polymer make the entrapment of water less favorable and lead to a higher degree of vitrification. This has obvious consequences for the design and use of thermoresponsive polymeric systems in the fast growing field of drug delivery.

Following A. D. Schlüter's question of "whether one can create a molecular object, i.e., a molecular system that does not respond to its surrounding, by making a polymer thicker and thicker" [93], shape-persistent dendronized polymers in solution were studied by advanced pulse EPR methods. As expected, DEER spectroscopy yields the size (thickness) of different generations of charged cylindrical dendronized polymers in solution [94]. Moreover, a combination of CW EPR and a modified isotopolog-specific DEER variant provides a better understanding of how amphiphilic molecules can be loaded into and released upon external stimulation from these thick polymers [95].

4 Functional Materials

Macromolecular and supramolecular systems are becoming increasingly important as functional materials in various applications, e.g., ion conductors [96], sensors [97], and organic electronics [98]. In all cases, magnetic resonance provides unprecedented details of structure and dynamics [99–104]. Moreover, applications for synthetic polymers in medicine are emerging [105]. Research at the interface of polymer chemistry and the biomedical sciences has given rise to the first nanosized (5–100 nm) polymer-based pharmaceuticals, the "polymer therapeutics." Polymer therapeutics include rationally designed macromolecular drugs, polymer–drug and polymer–protein conjugates, polymeric micelles containing covalently bound drug, and polyplexes for DNA delivery. Another important route for generating nanoparticles and controlling their interaction with cells is provided by miniemulsion polymerization [106], which can also be used to encapsulate, e.g., magnetic contrast agents for magnetic resonance imaging (MRI) [107].

4.1 Elastin-Like Polypeptides and Drug Delivery

Drug release can, of course, also be realized using building blocks from nature. In this respect, elastin-like polypeptides (ELPs) are particularly interesting [51]. ELPs are genetically encoded polymers composed of repeats of the amino acid VPGXG

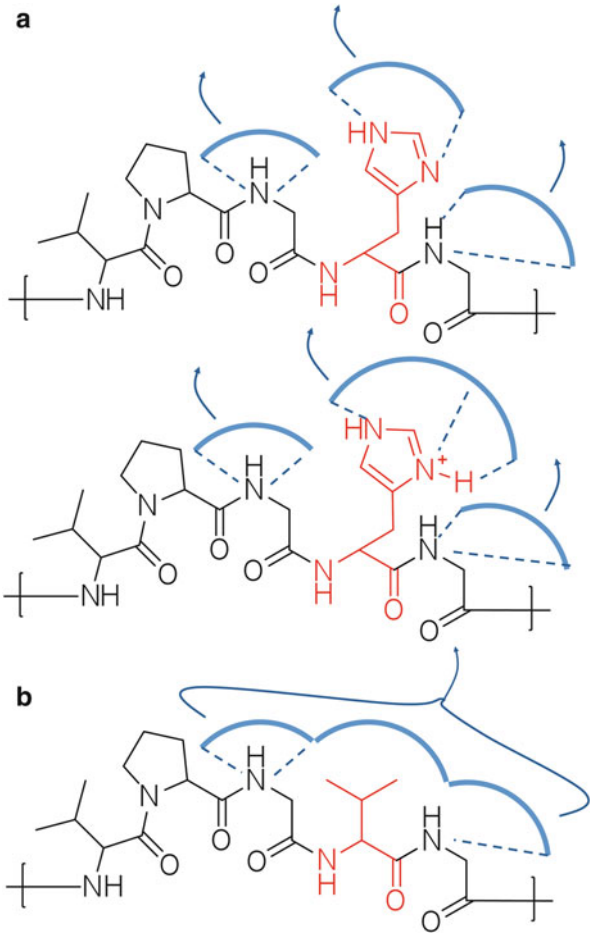

Fig. 8 Putative hydration for ELPs with (**a**) protic guest-residue side chains and (**b**) aprotic guest-residue side chains. (**a**) The hydration layer of the protic guest-residue side chain is individually stabilized by H-bonds and can vanish independently (decoupled) from backbone hydration layers. When the His residues are charged (*bottom*) the individual (decoupled) side chain hydration layers are even more stable than in the charge neutral analog (*top*). The higher stability is schematically depicted as larger hydration shell and larger number of H-bonds. (**b**) The hydration layer of the guest-residue side chain is stabilized via coupling to neighboring backbone hydration layers and, hence, dehydration takes place cooperatively. Adopted from [108]

motif found in tropoelastin (X being the so-called guest residue, which can be any amino acid except proline). Their LCST phase behavior at the molecular level can be fine-tuned by the choice of the guest residue, their chain length, and by the cosolutes [108]. This makes them excellent candidates for studying fundamental aspects of intrinsically disordered polypeptides on the one hand and thermoresponsive polymers, on the other hand.

In a recent study using simple CW EPR spectroscopy [22], new light could be shed on the dehydration mechanism in LCST-polypeptides [109]. It was shown that hydrophilic (backbone) and hydrophobic (side chain) hydration layers of ELPs can exist in a coupled state or a decoupled state (Fig. 8). The decoupled hydration state consists of hydrophobic and hydrophilic hydration layers that respond independently to temperature whereas the coupled hydration state is characterized by a common, cooperative dehydration of both hydration layers. The authors could show that the primary sequence of an ELP can be tuned to exhibit either of the hydration layer coupling modes. Charged side chains lead to decoupling, whereas strongly hydrophobic side chains trigger stronger interaction between hydrophilic and hydrophobic hydration, leading to coupling of both layers. These results indicate that ELPs are the first identified class of polymers that exhibit a first-order inverse phase transition on nanoscopic length scales. These findings are important for the understanding and further use of ELPs in applications such as drug delivery and may also provide insights into the role of hydration layers in governing the structure–function relationship of intrinsically disordered proteins, as discussed above.

4.2 Columnar Stacks

Columnar stacks are the structure-determining feature of discotic liquid crystals (DLCs) [24]. As noted in the "Introduction", the disc-shaped aromatic core units rotate around the column axis, which can conveniently be studied by NMR via ^{1}H–^{13}C dipole–dipole or ^{2}H quadrupole coupling. Moreover, imperfections of the parallel packing within the column lead to a reduction in the dynamic order S to values below 0.5. Such disorder was indeed observed early on for the extended hexabenzocoronene (HBC) units with alkyl chains attached, whereas the smaller triphenylene moieties lead to much narrower DLC phase ranges, but are much better packed [110]. In fact, the high charge-carrier mobility in a highly ordered helical columnar structure derived from a triphenylene derivative [111] generated a remarkable interest in the semiconducting, photoconducting, and other electronic properties of columnar liquid crystal materials. By incorporating a phenylene ring between the HBC core and the alkyl chain, the order within the column of HBC could be greatly improved [112] and, together with perylenediimide (PDI), was used to generate highly efficient self-organized thin films for organic photovoltaics [113].

Indeed, PDI derivatives are attractive in all-organic photovoltaic solar cells and field-effect transistors. These applications rely on the high charge carrier mobilities that made PDI the best n-type semiconductors available to date [113]. PDIs have an elongated shape, and can therefore display considerable dynamics even in the frozen, crystal-like state. This was observed in a triethyleneglycol (TEG)-substituted PDI [114]. From X-ray scattering, we found that the PDI building blocks assemble into columns arranged in a hexagonal unit cell with a lattice parameter of 2.23 nm. The meridional reflections in the wide-angle region are assigned to the π-stacking distance of 0.34 nm between individual molecules in the stacks. Additional weak and diffuse off-meridional reflections show a d-spacing of 0.70 nm, i.e., twice the simple

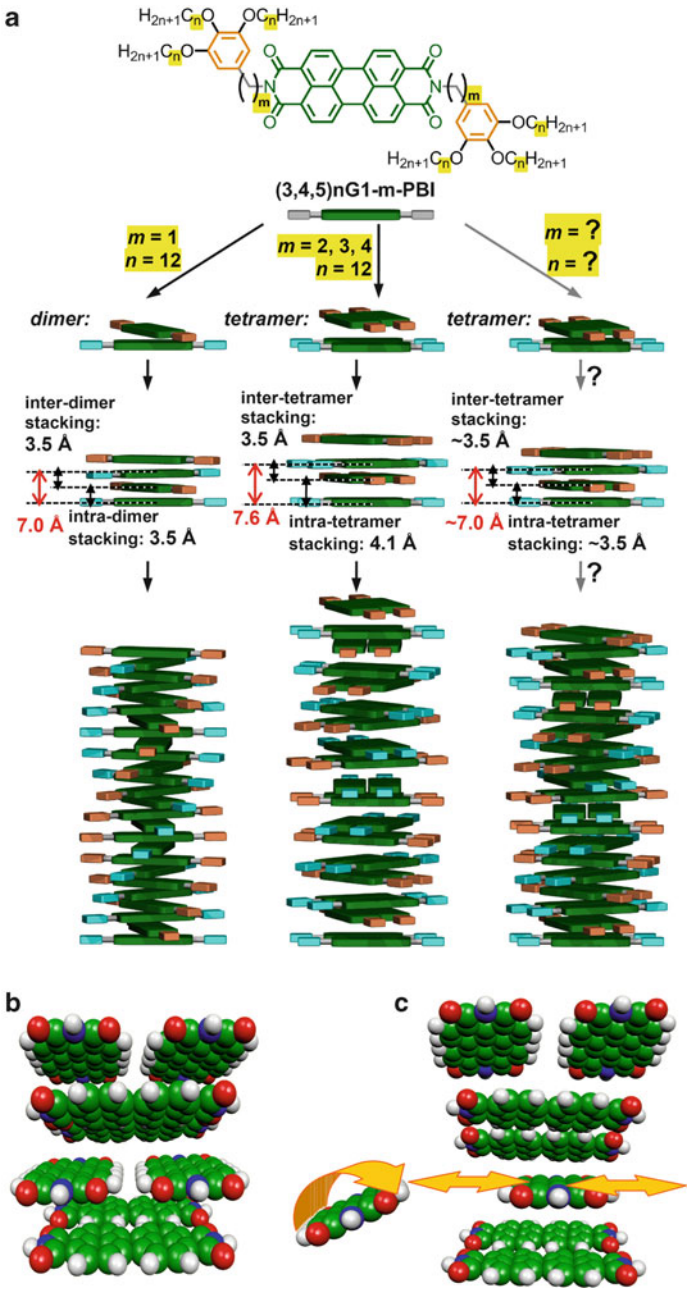

Fig. 9 (**a**) Packing of dendronized PBI with equal intra- and interdimer stacking (*left* and *right*, respectively) of 0.35 nm, but larger intradimer packing of 0.41 nm due to nonequilibrium disorder (*middle*). (**b**) Tetramer motif stacking into columns. (**c**) Molecular reorganization: one PBI leaves the columns, flips over, and enters a column again. Adopted from [117]

π-stacking, indicating correlations of adjacent TEG-PDI molecules perpendicular to each other. The dynamics of these systems was studied by different solid state NMR techniques. These showed that TEG-PDI in its frozen state performs angular fluctuations with amplitudes up to ±40°, reflecting the rather fragile packing of the elongated PDI units perpendicular to each other. In the liquid crystal phase, additional motional averaging in the NMR spectra is observed. The easiest motional process consistent with the observed averaging involves cooperative rotation of the PDI molecules by 90° around the column axis. Thus, whereas the restricted angular fluctuations in the solid phase can be considered as local processes, the increased dynamics in the liquid crystal phase must be highly cooperative in nature. Such cooperative dynamic modes are, of course, particularly important in processing such systems to align the columns on surfaces [115].

Moreover, slow molecular dynamics and very slow phase transformation [116] hamper the formation of the equilibrium phases of DLCs and the different packing in equilibrium and nonequilibrium phases can have pronounced effects on the charge carrier mobilities. This was studied in detail in perylene bis(diimide)s (PBIs) functionalized with dendritic groups [117, 118]. These dendronized PBIs self-assemble into complex helical columns generated from tetramers containing a pair of two molecules arranged side-by-side and another pair in the next stratum of the column, turned upside-down and rotated around the column axis at an intratetramer angle that is different from that of the intertetramer angle (Fig. 9).

In most cases, the intratetramer stacking distance in this column is 0. 41 nm, while the intertetramer distance is 0. 35 nm The architecture of this complex helical column, the structure of its 3D periodic array, and its kinetically controlled self-organization with such a long intratetramer distance are not ideal for the design of supramolecular structures with high charge-carrier mobility. In fact, the mobility of electrons is only moderate. However, in some cases, heating above 100°C in the liquid crystal phase optimizes the packing and results in shorter intratetramer distances and much higher charge mobilities [117, 118]. This is accompanied by substantial narrowing of the ^{1}H NMR lines. Computer simulation showed that this narrowing of the NMR spectra indicates a complex reorganization mechanism, whereby the PBI molecules leave the supramolecular column, flip over, and reenter a column at a later time (Fig. 9b, c).

4.3 Pi-Conjugated Macromolecules for Organic Electronics

Likewise, polymers with extended π-conjugation and low band gaps are of broad scientific interest because of their promising applications as semiconductors in organic electronic devices. Examples include organic photovoltaic (OPV) cells, organic field-effect transistors (OFETs), and organic light-emitting diodes (OLEDs) with optimized properties toward light harvesting, charge-carrier mobility, and light emission, respectively [119–121]. Such polymers with lamellar π-stacks are often semicrystalline [53], i.e., they exhibit phase separation with regions of high and low

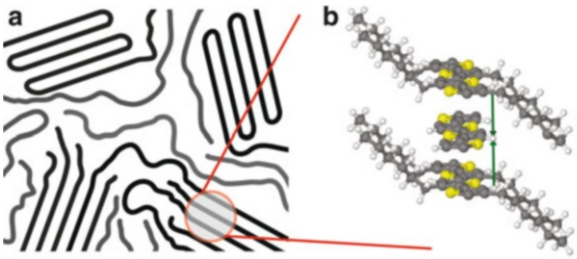

Fig. 10 (**a**) Semicrystalline polymer with regions of high (*black*) and low (*grey*) order. (**b**) View along the stacked P3HT structure, illustrating the alternating packing of P3HT polymer chains. For details see [122]

order. The specific organization of the macromolecules depends on the processing conditions. X-ray diffraction (XRD), which is well established in structure elucidation, requires high order, like that of single crystals, if atomic resolution is sought. From a fiber diagram, often employed in polymer science [53], only information about the relative assembly on a crystallographic lattice, or chain-to-chain and π–π stacking distances, can be derived. Thus, a "multi-technique" approach is required to fully elucidate such structures.

Along these lines, we recently introduced a new systematic strategy for revealing the local packing in such polymer systems [122]. Our strategy makes use of the space group (i.e., one of the first steps in a conventional approach to solve a crystal structure), distance constraints from ^{1}H DQ NMR, and chemical shifts. These experimental results are unified by quantum-chemical calculations, enabling the verification of specific packing models in silico and quantification of π-stacking effects. In order to illustrate the potential of our strategy, we chose poly(3-hexyl-thiophene) (P3HT) as a prominent example. It is one of the most frequently studied semiconducting polymers because of its widespread applications in organic electronic devices, resulting from its facile processability, high charge-carrier mobility (up to 0.1 $Vcm^2\ s^{-1}$), and environmental stability (see Fig. 10) [123].

Our approach can be compared with that employed for determining the solution structures of biomacromolecules by NMR through distance constraints (nuclear Overhauser effect, NOE) and chemical shifts [11, 12]. This, however, requires a large number of NOE constraints, whereas in a crystalline solid, the periodicity described by the space group gives access to the full 3D structure from only a few constraints. Thus, our strategy, which we propose to term "multi-technique crystallography," can be applied in general to provide quantitative insights into the packing of semicrystalline polymers with specific intermolecular packing features, such as hydrogen bonds or stacking of aromatic moieties. In fact, similar approaches, often termed "NMR crystallography" [124] are increasingly applied in unraveling the structures of pharmaceuticals [125–127] or supramolecular systems in general [128, 129].

In order to achieve high charge-carrier mobility, donor and acceptor groups can be mixed, as was done in supramolecular stacks with or without a polymer backbone [130]. Such groups can also be incorporated into a copolymer consisting of an alternating arrangement of cyclopentadithiophene (CDT) as a donor and benzothiadiazole (BTZ) as an acceptor unit, as reported recently [131] (see Fig. 11).

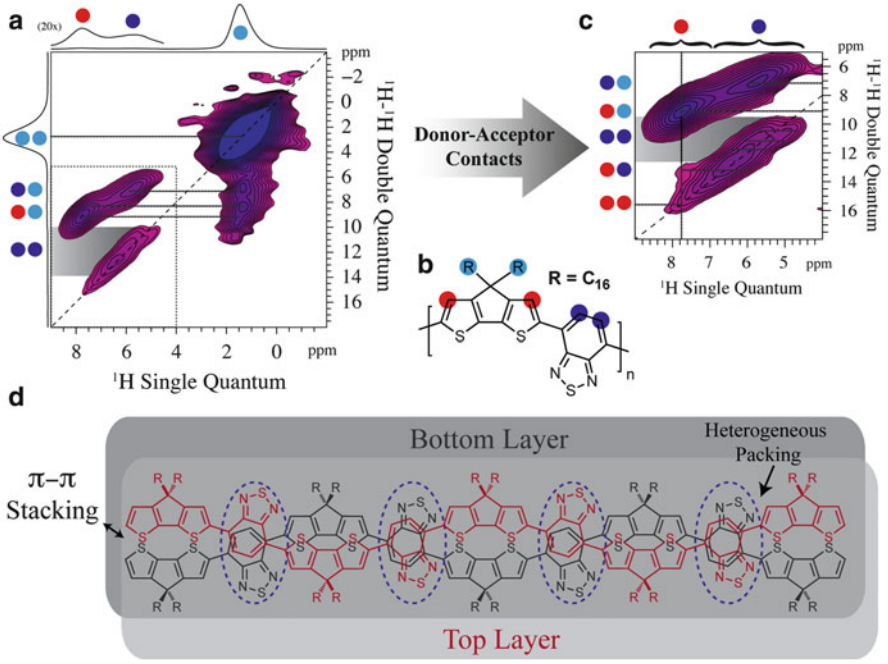

Fig. 11 Local packing and organization of the donor–acceptor groups in a CDT-PTZ copolymer. (**a**) Two-dimensional contour plot of the ^{1}H–^{1}H DQ NMR spectrum. (**b**) Color scheme used for assignments. (**c**) Expansion of the backbone region showing the contacts between donor and acceptor groups. (**d**) Local packing of donor–acceptor groups in two neighboring CDT-BTZ copolymer chains. Adopted from [131]

Field-effect transistor (FET) hole mobilities exceeding 3 V cm^2 s^{-1} have been obtained and these were shown to be strongly sensitive to the molecular weight of the hexadecyl-substituted copolymers. Solid state NMR was used to assess the supramolecular organization of the conjugated chains. The ^{1}H 2D DQ NMR spectra clearly revealed the relevant packing contacts, confirming the expected π–π stacking for the polymer backbone. The packing of the donor and the acceptor groups, however, was found to be more delicate. Donor–acceptor groups are π–π stacked in a lamellar fashion and these groups are ordered in an alternating way, as shown in Fig. 11d. Thereby, the acceptor groups in one layer are located on top of the acceptor groups in adjacent layers; however, they are not always in the exact same position, leading to heterogeneous packing. This model derived from NMR is consistent with the findings of X-ray scattering. It also allows for optimal packing of the side chains, which in the case of long and bulky alkyl chains (C_{16}) should be advantageous in order to avoid steric clash. Conclusively, solid state NMR does not reveal a donor–acceptor overlap within 0.4 nm. Thus, strikingly, donor–acceptor interaction between the neighboring CDT and BTZ groups located at adjacent chains apparently contributes

little, if anything, to the observed improvement in charge-carrier mobility. NMR rather unravels the complexity of this remarkable CDT-BTZ copolymer system.

This result was confirmed by molecular modeling of this system [132], which showed that the longitudinal displacement of the conjugated backbones by 1–2 Å changes the electronic coupling mediating hole hopping by over one order of magnitude. Interestingly, these subtle structural changes have clear fingerprints in X-ray diffraction patterns and ^{1}H NMR chemical shifts, which allow refining the structural parameters down to the molecular scale. From this study, it was concluded that the unprecedented hole carrier mobilities observed in fibers of the CDT-BTZ copolymers arise from a close packing of the polymer chains into a close-to-registry assembly, providing optimal wavefunction overlap, together with the intrinsically higher electronic bandwidth for charge motion along the chains. This arrangement is primarily triggered by van der Waals interactions between the long, linear alkyl chains and not by electrostatic donor–acceptor interactions. This rather unexpected result emphasizes how important the detailed information on the packing provided by a multi-technique approach including solid state NMR is to obtain unbiased structural details, which are needed to optimize the structure for specific applications.

5 Conclusion

Following the pioneering work of Hermann Staudinger [1], advances in the synthesis, characterization, and understanding of macromolecular and supramolecular systems have led to an enormous variety and complexity in the field of polymer science [89]. The traditional separation in terms of structure versus dynamics, crystalline versus amorphous, or experiment versus theory is increasingly being overcome. As far as characterization of such materials is concerned, no experimental or theoretical/simulation approach alone can provide full information. Instead, a combination of techniques is called for and conclusions should be backed by results provided by as many complementary methods as possible [27]. As demonstrated in this contribution, the information provided by NMR and EPR is often indispensable and unique. Combining scattering or MR spectroscopy with computer simulation is well established today in the study of the structure and dynamics of biomacromolecules and provides new insight in the emerging field of partially disordered proteins [64]. The examples described here show the power of such an approach involving the combination of spectroscopy, scattering, and computer simulation in the supramolecular field.

Last, but not least, the development of NMR spectroscopy is far from complete [133]. In particular, in order to meet the ever-increasing demands of miniaturization, the sensitivity of NMR spectroscopy has to be increased substantially and several approaches in response to that challenge are underway [134–137], down to the detection of single spins [138]. Remarkably, in this area the combination of

NMR and EPR called "dynamic nuclear polarization" is very advanced and has already been successfully applied in magnetic resonance imaging [139].

Acknowledgments This tribute to Hermann Staudinger is based on my work at the Max Planck Institute for Polymer Research in Mainz for more than 25 years. It has provided me with a unique scientific environment, in which new ideas and approaches prospered. It gives me great pleasure to thank my colleagues and coworkers for all their contributions. Special thanks are due to Dariush Hinderberger for his suggestions concerning the EPR studies described in this chapter.

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Twenty-First Century Polymer Science After Staudinger: The Emergence of Dendrimers/ Dendritic Polymers as a Fourth Major Architecture and Window to a New Nano-periodic System

Donald A. Tomalia

Abstract Staudinger's (1922) "macromolecular hypothesis" stating that most synthetic and natural polymers could be rationalized as extensive covalently linked linear macromolecules, followed by Crick and Watson's (1953) revelation that life was actually based on poly(nucleotide), helical double-stranded variations of Staudinger's linear architectures, launched two of the most significant technological revolutions of the twentieth century. After Staudinger, a total of four major polymer architectures were recognized and each architecture, namely, (I) linear, (II) crosslinked (bridged), (III) branched, and (IV) dendritic (hyperbranched), is highly valued for its intrinsic and unique macromolecular properties. Upon entering the twenty-first century, members of architectural class IV, dendritic polymers (i.e., dendrimers), have now been accepted by both chemists and physics as quantized nanoscale building blocks due to their atom mimicry features and are referred to as "soft superatoms." Atom mimicry, manifested by both soft and hard superatoms (i.e., organic and inorganic nanoscale clusters), has provided the first steps towards a proposed new nano-periodic paradigm, based on first principles from traditional chemistry and physics, for unifying nanoscience.

Keywords Atom mimicry · Dendrimers · Dendritic effects · Hard/soft nanoelements · Nanocompounds/assemblies · Nano-periodic system · Superatoms

D.A. Tomalia (✉)
NanoSynthons LLC, The National Dendrimer and Nanotechnology Center,
1200 N. Fancher Avenue, Mt. Pleasant, MI 48858, USA
e-mail: donald.tomalia@nanosynthons.com

Contents

1 Introduction 323
1.1 Evolution from Basic Building Blocks to Higher Complexity 323
1.2 The Role of Molecular Architecture in Producing New Properties 325
2 Traditional Polymer Chemistry 328
2.1 Comparison of Traditional Polymer Science with Dendritic Macromolecular Science 330
3 The Dendritic State 332
3.1 History 332
3.2 A Fourth Major New Architectural Polymer Class 334
3.3 Dendritic Polymer Subclasses 336
4 Dendrimer Features of Interest to Nanoscience 341
4.1 Dendrimer Shape Change: A Nanoscale Molecular Morphogenesis 344
4.2 de Gennes Dense Packing: A Nanoscale Steric Phenomenon Not Observed in Traditional Polymers 345
5 Unique Quantized Dendrimer Properties 348
5.1 Critical Nanoscale Design Parameters 348
5.2 Amplification and Functionalization of Dendrimer Surface Groups 349
5.3 Nanoscale Dimensions and Shapes Mimic Those of Proteins 349
6 Dendrimers: Window to a New Nano-periodic System for Defining and Unifying Nanoscience 350
6.1 Elemental Picoscale Periodicity Derived from CADPs 352
6.2 Chemists and Physicists Are Developing a Mutual Consensus on Nanoscale Atom Mimicry and Superatoms 353
6.3 Atom Mimicry: Nanoscale Superatoms and Atom Equivalents 357
6.4 Combining Soft and Hard Nano-element Categories to Create Combinatorial Libraries of Nanocompounds and Nano-assemblies 363
6.5 Nano-periodic Physico-Chemical Property Patterns 368
6.6 First Steps Towards a “Central Dogma” for Synthetic Nanochemistry: Dendrimer-Based Nanochemistry 372
7 Conclusions 379
References 381

Abbreviations

BC	Branch cell
CADP	Critical atomic design parameters
CHDP	Critical hierarchical design parameters
CMDP	Critical molecular design parameters
CMicDP	Critical micron design parameters
CNDP	Critical nanoscale design parmeters
FTIR	Fourier transform infrared
G	Generation
HNE	Hard nano-element
LCB	Long chain branching
MALDI-TOF	Matrix-assisted laser desorption ionization–time of flight
M_n	Number-average molecular weight
M_{w}	Weight-average molecular weight
N_{b}	Branch cell multiplicity

N_c	Core multiplicity
NSF	National Science Foundation
PAMAM	Poly(amidoamine)
ROMP	Ring-opening metathesis polymerization
SCROP	Self-condensing ring-opening polymerization
SCVP	Self-condensing vinyl polymerization
SIS	Sterically induced stoichiometry
SNE	Soft nano-element
TEM	Transmission electron microscopy
TMV	Tobacco mosaic virus
UV	Ultraviolet
VESPR	Valence shell electron pair repulsion

1 Introduction

1.1 Evolution from Basic Building Blocks to Higher Complexity

Understanding the hierarchical principles and parameters involved in the natural evolution of first matter to the present state of complexity has received substantial attention by all the major scientific disciplines. Advancement of the "Big Bang Theory" by physicists has provided a foundation for understanding the early evolution of subpicoscale particles to elemental atoms, presumably based on thermodynamic selection principles. On the other hand, biologists have defined an acceptable hypothesis for the evolution of micro- and macroscale matter to higher complexity, including life and organisms, based on certain environmental selection principles. Between these two extremes, however, resides the unresolved evolutionary domain of the chemist (see Fig. 1). Hierarchical matter in this domain is defined by dimensions between the subnanoscale and the micron level. Recently, J.M. Lehn [1] and others [2] have advanced certain molecular recognition, supramolecular/self-assembly principles as first steps toward qualitatively defining both the natural and synthetic evolution of matter in this size region. Contemporary chemists now view elemental atoms and small, molecular structures (i.e., monomers) as versatile, richly endowed building blocks with important surface chemistry that may be supramolecularly assembled or chemically bonded into an infinite number of combinatorial molecular libraries. These libraries consist of both precise well-defined subnanoscale molecular structures and perhaps less well-defined nanoscale structures that we now refer to as macromolecules or polymers.

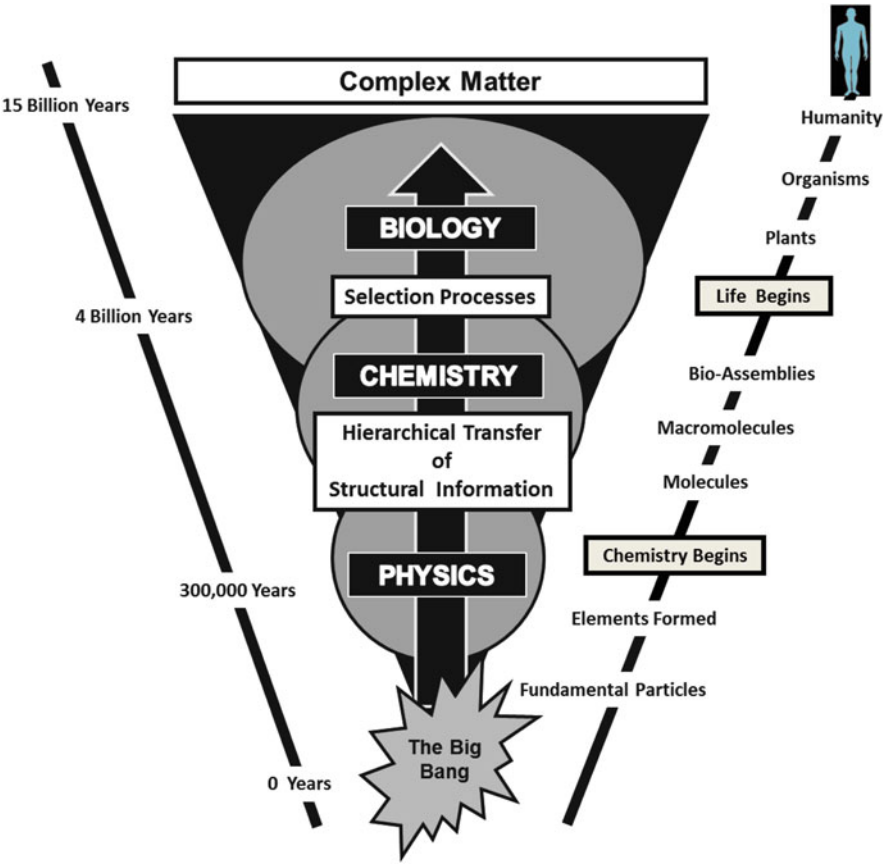


Fig. 1 Evolution of hierarchical building blocks, structural information transfer, and scientific disciplines leading to present material complexity as a function of time lapsed from "the big bang"

1.1.1 Atomic Elements→Small Molecules→Macromolecules→Megamolecules

The seminal "macromolecular hypothesis" proposed in 1922 [3, 4] by H. Staudinger initiated one of the most significant technological revolutions of the twentieth century, namely, the polymer (plastics) revolution [5]. Staudinger was not recognized for this monumental contribution by the Nobel committee until 1953. Coincidentally, in that same year Crick and Watson first reported the characterization and structure of DNA. Perhaps two of the most important chemistry discoveries in the twentieth century were Staudinger's "macromolecular hypothesis" and elucidation of the linear polymer, double helix structure evolved by Nature, namely, DNA [6, 7]. Macromolecular DNA was found to be an elegant covalent biopolymer that was indeed consistent with and could be accounted for by

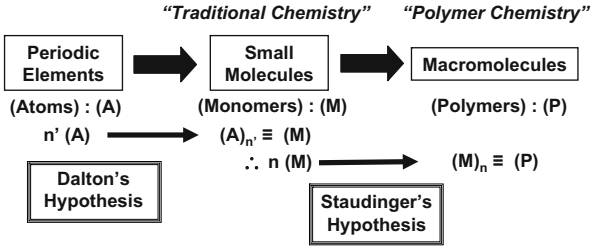


Fig. 2 Historical overview of the major technology revolutions "traditional chemistry" and "polymer chemistry" and their associated pioneers

Staudinger's earlier macromolecular hypothesis. This work by Crick and Watson was later recognized by the Nobel Prize committee in 1962 and initiated an equally important scientific understanding of linear nucleotide biopolymers and their role in storing and transferring critical genetic information as the basis for life. In spite of that, during the first part of the twentieth century, there was an almost fanatical opposition to the notion of Staudinger that atoms or their compounds could be transformed into chemically bonded macromolecular structures. However, in an abstract way, Staudinger's concept may now be viewed as an elaborate continuation of J. Dalton's simple hypothesis (i.e., *New System of Chemical Philosophy*, published in 1808). In essence, the theme of chemically connecting (n') multiples of atomic modules to produce small molecular structures (e.g., monomers) could simply be extended to include the chemical linking of monomers to produce covalent macromolecular structures (Fig. 2).

This earlier atom/molecular hypothesis by Dalton led to synthesis of an endless array of small molecules that are now recognized as our "traditional chemistry". On the other hand, Staudinger's macromolecular hypothesis led to vast libraries of macromolecular structures now referred to as "traditional polymer chemistry." Although the intrinsic features of atoms or monomers as well as their rules for assembly [i.e., (n') and (n)] are most assuredly different, the enormous role that each of these technologies has played in the improvement of the "human condition" and enhancement of the world economy is indisputable. These benefits were largely derived from unique and extraordinary new properties that emerged in each of these areas as the technologies advanced to higher levels of complexity.

1.2 The Role of Molecular Architecture in Producing New Properties

A pervasive pattern apparent in both small-molecule chemistry as well as macromolecular science is the significant role that architecture plays in the determination of new properties. As early as 1825, Swedish chemist Jacob Berzelius clearly demonstrated that small molecular structures possessing identical elemental compositions, but different spatial arrangements, invariably differed in one or more

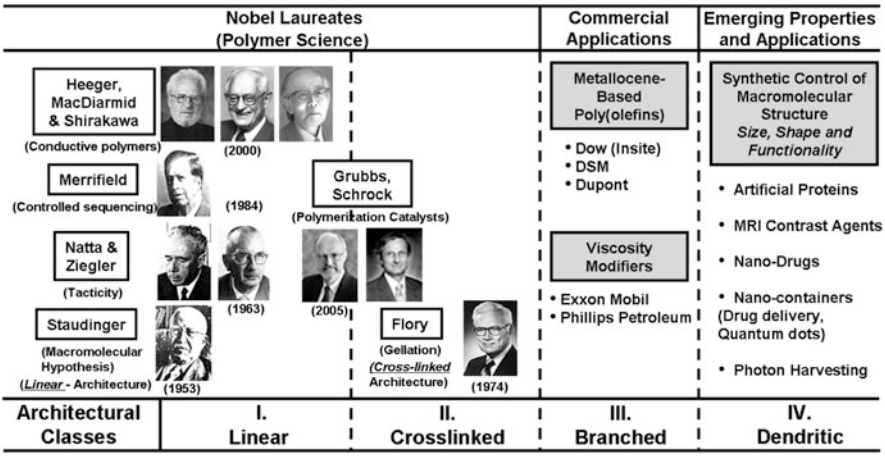


Fig. 3 Nobel recognition, commercial applications, and emerging properties for the four major macromolecular architectures

physico-chemical properties such as melting or boiling point, density, combustion behavior, etc. Referred to as "molecular isomerism," these isomeric states have been widely recognized in traditional inorganic and organic chemistry as geometric/position isomerism, valence isomerism, optical stereoisomerism, tautomerism, etc. In the polymer world, these analogous structural issues are referred to collectively as "macromolecular or architectural isomerism" [8]. Such macromolecular structures derived from identical monomeric building blocks in the same stoichiometric proportions but in different architectural or spatial configurations may be expected to manifest substantially different properties and macroscopic behavior. Thus, it was not surprising that traditional polymer architectures such as crosslinked (bridged) and simple branched polymers (after Staudinger's first linear architectures) clearly manifested uniquely different as well as complementary properties ideally suited for the emergence of a vast array of diverse commercial applications. Early commercial polymer development usually involved the manipulation of three key parameters: (1) architecture (i.e., thermoplastic versus thermoset configurations and gels); (2) elemental composition (i.e., monomer or copolymer); and (3) molecular weight and molecular weight distribution. Ultimately, all macroscopic properties were determined, including process ability and performance. The advent of a fourth new macromolecular architecture (i.e., dendritic) exhibiting totally unprecedented physico-chemical properties compared to the traditional architectural classes (i.e., linear, crosslinked, and simple branched; see Fig. 3) led in the 1990s to a fresh examination of macromolecular architecture categories [9] and their impact on new emerging properties [10, 11].

Four major macromolecular architectural classes are now recognized based on their unequivocal importance in driving new and differentiated properties. These four

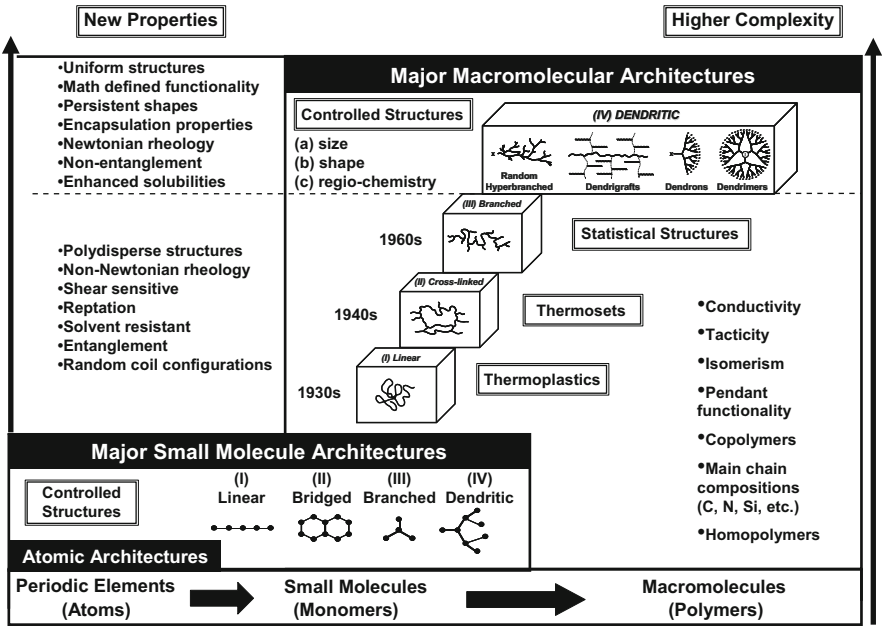


Fig. 4 Atomic small molecule and macromolecular architectures, with the emergence of new properties as a function of higher complexity

major macromolecular architectural classes are: (I) linear, (II) crosslinked/bridged, (III) branched, and (IV) dendritic/hyperbranched (as illustrated in Fig. 4). The importance of macromolecular architecture has been amply recognized by a preponderance of Nobel awards associated with the discovery of such architectural features and their consequent properties. Since Staudinger's seminal Nobel Prize in 1953, a total of ten individual scientists have now been recognized by the Nobel Committee for their contributions to polymer science (as shown in Fig. 3). These recognized contributions may be placed in the general categories noted below:

Discovery or Pioneering Characterization of the First Two Major Architectural Classes.

H. Staudinger (1953) – Discovered linear, class I architecture
P. Flory (1974) – Clarified and defined crosslinked, class II architecture

Pioneering Modification or Characterization of Linear Class I Architecture.

G. Natta, K. Ziegler (1963) – Polymerization catalyst, stereochemistry, tacticity
B. Merrifield (1984) – Controlled polypeptide sequencing, monodispersity
A. Heeger, A. MacDiarmid, H. Shirakawa (2000) – Polymer backbone conductivity
R. Grubbs, R. Schrock (2005) – Polymerization catalyst, monodispersity

History has shown that each time a major new architecture has been discovered, it has been accompanied by the emergence of a plethora of new properties,

concepts, applications, products, and activities, all of which have led to enhanced new commercial markets, quality of life, and prosperity. Since Staudinger's original discovery, a total of four major macromolecular architectures have evolved: (I) linear, (II) crosslinked, (III) branched and now (IV) dendritic topologies, as illustrated in Fig. 4.

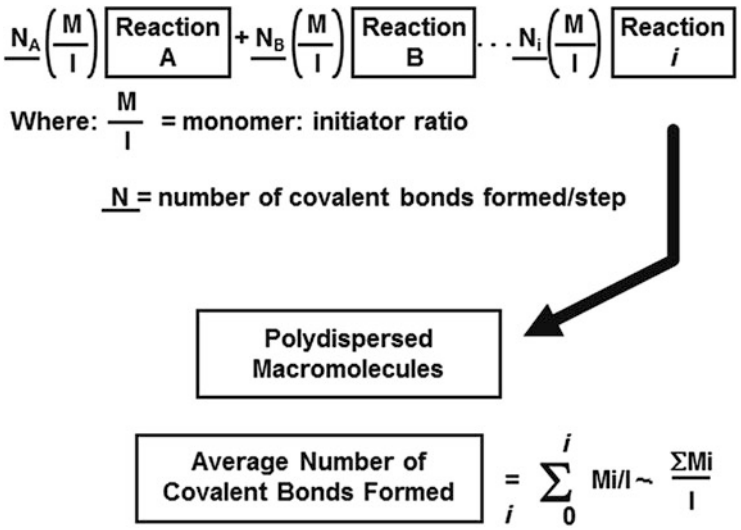
2 Traditional Polymer Chemistry

Over the past 90 years, Staudinger's macromolecular synthesis strategy has evolved based on the catenation of reactive small molecular modules (monomers). Broadly speaking, these catenations involve the use of reactive (AB-type) monomers that may be engaged to produce large molecules with polydispersed masses. Such multiple bond formation may be driven by (1) chain growth, (2) ring opening, (3) step-growth condensation, or (4) enzyme-catalyzed processes. Staudinger first introduced this paradigm in the 1920s [4, 5, 12–14] by demonstrating that reactive monomers could be used to produce a statistical distribution of one-dimensional (linear) molecules with very high molecular weights (i.e., $>10^6$ Da). As many as 10,000 or more covalent bonds may be formed in a single chain reaction of monomers. Although these macro- or megamolecules may possess nanoscale dimensions, structure control of critical macromolecular design parameters, such as size, molecular shape, spatial positioning of atoms, or covalent connectivity – other than those affording linear or crosslinked topologies – is difficult. However, substantial progress has been made in controlling dispersity by using living polymerization techniques that afford dramatic control over molecular weight and certain structural elements, as described by Matyjaszewski, Grubbs, Schrock, and others [15–19].

Traditional polymerizations usually involve AB-type monomers based on substituted ethylenes or strained small ring compounds using chain reactions that may be initiated by free radical, anionic or cationic initiators [20]. Alternatively, AB-type monomers may be used in polycondensation reactions.

Multiple covalent bonds are formed to produce each macromolecule, generally giving statistical, polydispersed structures. In the case of controlled vinyl polymerizations, the average length of the macromolecule is determined by monomer to initiator ratios. If one visualizes these polymerizations as extraordinarily long sequences of individual reaction steps, the average number of covalent bonds formed per chain may be described as shown in Scheme 1.

The first traditional polymerization strategies generally produced linear architectures; however, it was soon found that branched topologies may be formed either by chain transfer processes or intentionally introduced by grafting techniques. In any case, the linear and branched architectural classes have traditionally defined the broad area of thermoplastics. Of equal importance is the major architectural class



Scheme 1 Mathematical description of covalent bond formation as a function of AB monomer polymerization to produce linear polymers [93]. Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission

formed by the introduction of covalent (bridging) bonds between linear or branched polymeric topologies. These crosslinked (bridged) topologies were studied by Flory in the early 1940s and constitute the second major area of traditional polymer chemistry, namely, thermosets. These two broad areas of polymer science (i.e., thermoplastics and thermosets) account for billions of dollars of commerce and constitute a vast array of familiar macromolecular compositions and applications, as shown in Fig. 5.

Historically, even 50 years after Staudinger's introduction of the macromolecular hypothesis, the entire field of polymer science was viewed to consist of only the two major architectural classes: (1) linear topologies as found in thermoplastics and (2) crosslinked architectures as found in thermosets. The major focus of polymer science during the time frame spanning the 1920s to the 1970s was on unique architecturally driven properties manifested by either linear or crosslinked topologies. Based on the unique properties exhibited by these synthetic topologies, it was possible to replace many natural polymers crucial to the World War II effort. This combination of availability and properties were of utmost strategic importance [21]. During the 1960s and 1970s, pioneering investigation into long chain branching (LCB) involving polyolefins and other related branched systems began to emerge [22, 23]. More recently, intense commercial interest has been focused on new polyolefin architectures based on random long branched and dendritic topologies [24, 25]. These architectures are reportedly produced by "metallocene" and "Brookhart-type" catalysts. By the end of the 1970s, there were three major architectural polymer classes and commercial commodities associated with these topologies, as described chronologically in Fig. 6.

Thermoplastics | **Thermosets**

Class I (Linear)

•Polymer Types	Discovery	Production	Main Applications
•Poly(methyl methacrylate)	1880	1928	Plastics (Plexiglass®)
Poly(vinyl acetate)	1912	1930	Adhesive, poly(vinyl alcohol)
Poly(styrene)	1839	1930	Thermoplastics, foams
Poly(vinyl chloride)	1838	1931	Thermoplastics (synthetic fiber)
Poly(ethylene oxide)	--	1931	Thickeners, sizes
Poly(vinyl ethers)	1928	1936	Adhesives, plasticizers
Poly(hexamethylene adipamide)	1934	1938	Fibers, thermoplastics
Poly(vinylidene chloride)	1838	1939	Thermoplastics (packing films)
Poly(*N*-vinyl pyrrolidone)	--	1939	Blood plasma expander, binders
•Poly(ethylene), low density	1933	1939	Thermoplastics
Poly(ε-caprolactam)	1938	1939	Fibers, thermoplastics
Polyurethanes	1937	1940	Fibers, plastics, elastomers, foams
•Poly(acrylonitrile)	1940	1941	Fibers
Poly(tetrafluoroethylene)	1939	1950	Plastics, fibers
Poly(ethylene terephthalate)	1941	1953	Fibers, bottles
Bisphenol A polycarbonate	1898	1953	Thermoplastics
Poly(ethylene), high density	1953	1955	Thermoplastics, foams
Poly(propylene), isotactic	1954	1957	Thermoplastics, fibers
Poly(formaldehyde)	1839	1959	Thermoplastics
Aromatic polyamides	--	1961	High modulus fibers
Styrene-butadiene-styrene block copolymers		1965	Thermoplastic elastomers

Class III (Branched)

Poly(olefins), long chain branching	1980s	1990s	Elastomers, plastomers

Class II (Cross-Linked)

Polymer Types	Discovery	Production	Main Applications
Phenolic resins	**1907**	**1910**	**Thermosets (electrical insulators)**
Methyl rubbers	**1912**	**1915**	**Elastomers**
Alkyl resins	**1847**	**1926**	**Thermosets (coatings)**
Amino resins	**1915**	**1928**	**Thermosets**
Poly(butadiene)	**1911**	**1929**	**Elastomers (number Bunas)**
Poly(chloroprene)	**1925**	**1932**	**Elastomers**
Unsaturated polyesters	**1930**	**1936**	**Thermosets**
Poly(isobutylene)	**--**	**1937**	**Elastomers**
Styrene-butadiene rubbers	**1926**	**1937**	**Elastomers (letter Bunas)**
Silicone	**1901**	**1942**	**Fluids, resins, elastomers**
Epoxy resins	**1938**	**1946**	**Adhesives**
Poly(butadiene), *cis*, 1,4	**--**	**1956**	**Elastomers**

Fig. 5 Dates of discovery and production of commercial thermoplastic and thermoset polymers, organized according to their architectural class [93]. Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission

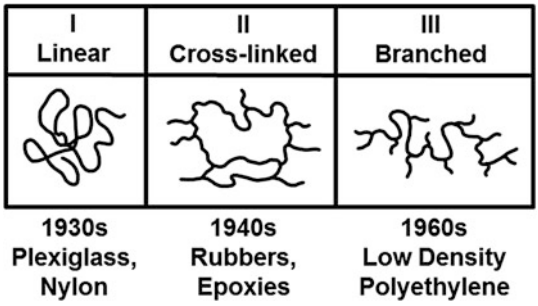


Fig. 6 Traditional macromolecular architectures, organized chronologically according to their commercial introduction

2.1 Comparison of Traditional Polymer Science with Dendritic Macromolecular Science

Covalent synthesis in traditional polymer science has evolved around the use of reactive modules (AB-type monomer) or ABR-type branch reagents that may be engaged in multiple covalent bond formation to produce large one-dimensional molecules of various lengths. Such multiple bond formation may be driven either

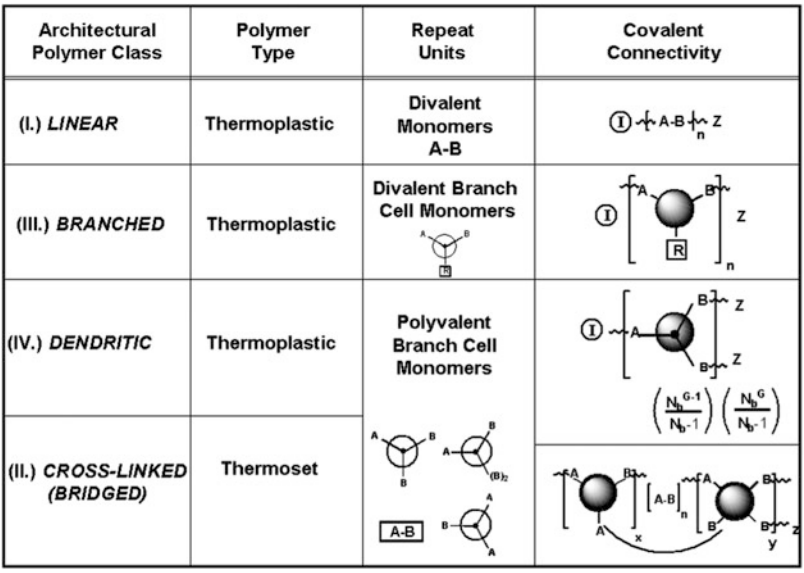


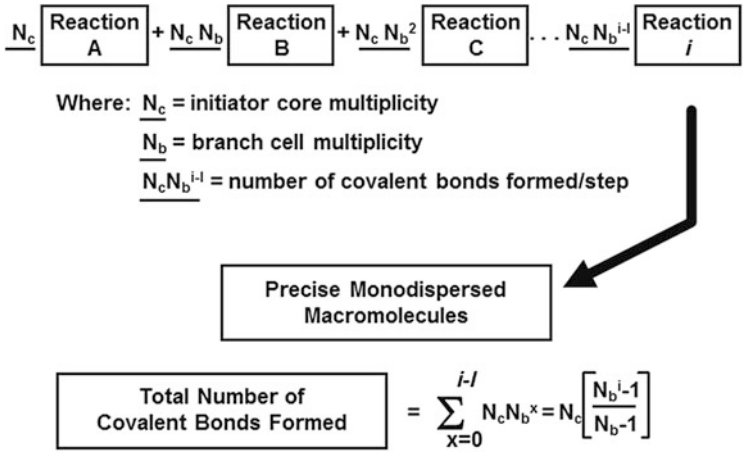
Fig. 7 Examples of architectural polymer classes (*I–IV*), polymer type, repeat units, and covalent connectivity associated with architectural class [93]. Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission

by chain reactions, ring-opening reactions, or polycondensation schemes. These propagation schemes and products are recognized as class I, linear or class III, branched architectures. Alternatively, using combinations and permutations of divalent AB-type monomers and/or AB_n, A_nB polyvalent, branch cell-type monomers produces class II, crosslinked (bridged) architectures.

A comparison of the covalent connectivity associated with each of these architecture classes (Fig. 7) reveals that the number of covalent bonds formed per step for linear and branched topology is a multiple (n = degree of polymerization) related to the monomer-to-initiator ratios. In contrast, ideal dendritic (class IV) propagation involves the formation of an exponential number of covalent bonds per reaction step (also termed G, for generation), as well as amplification of both mass (i.e., number of branch cells) and number of terminal groups per generation.

Mathematically, the number of covalent bonds formed per generation (reaction step) in the synthesis of an ideal dendron or dendrimer varies according to a power function of the reaction steps, as shown in Scheme 2. It is clear that covalent bond amplification occurs in all dendritic synthesis strategies. In addition to new architectural consequences, this feature clearly differentiates dendritic growth processes from linear covalent bond synthesis as found in traditional polymer chemistry [26].

It should be apparent that, although all major architectural polymer classes are derived from common or related repeat units, the covalent connectivity is truly discrete and different. Furthermore, mathematical analysis of the respective propagation strategies clearly illustrates the dramatic differences in structure development as a function of covalent bond formation. It should be noted that linear,



Scheme 2 Mathematical description of covalent bond formation as a function of AB_2 monomer polymerization to produce dendritic polymers [93]. Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission

branched, and dendritic topologies differ substantially both in their covalent connectivity as well as in the terminal group to initiator site ratios. In spite of these differences, these open, unlooped macromolecular assemblies clearly manifest thermoplastic polymer-type behavior in contrast to the looped, bridged connectivity associated with crosslinked, thermoset systems. In fact, it is now apparent that these three "open assembly" topologies (i.e., linear, branched, and dendritic) represent a graduated continuum of architectural intermediacy between thermoplastic and thermoset behavior, as will be described later (Sect. 3.2).

In summary, classical polymer science has provided facile access to a vast variety of polydispersed nanoscale structures, with some control over topology, composition, and flexibility or rigidity. More recent advances, however, involving "living polymerization" strategies [18, 19, 27] have produced substantially enhanced control over macromolecular size distribution and dispersity. That withstanding, dendritic macromolecular chemistry still remains the major strategy and route to unparalleled control over topology, composition, size, mass, shape, and functional group placement. These features and properties truly distinguish the many successful nanostructures found in nature [28] and as such are of keen interest as synthetic nanomaterials and for many applications in nanomedicine.

3 The Dendritic State

3.1 History

The origins of the present three-dimensional (3D), dendritic branching concepts can be traced back to the initial introduction of infinite network theory by Flory [29–32]

and Stockmayer [33, 34]. In 1943, Flory introduced the term "network cell," which he defined as the most fundamental unit in a molecular network structure [35]. To paraphrase the original definition, it is the recurring branch juncture in a network system as well as the excluded volume associated with this branch juncture. Graessley [36] took the notion one step further by describing ensembles of these network cells as micronetworks. Extending the concept of Flory's statistical treatment of Gaussian-coil networks, analogous species that are part of an open, branched or dendritic organization are known as "branch cells" and "dendritic assemblies."

Statistical modeling by Gordon et al. [37, 38], Dusek [39], Burchard [40] and others reduced such branched species to graph theory designed to mimic the morphological branching of trees. These dendritic models were combined with cascade theory [41, 42] mathematics to give a reasonable statistical treatment for network-forming events at that time.

The growth of branched and dendritic macromolecules in the sol phase of a traditional crosslinking process may be thought of as geometric aggregations of various branch cells or dendritic (network) assemblies, as described above. Beginning as molecular species, they advance through the dimensional complexity hierarchy to oligomeric, macromolecular, megamolecular, and ultimately to infinite network macroscale systems. The intermediacy of dendritic architecture in this continuum will be discussed later (Sect. 3.2). Traditional network-forming systems (e.g., epoxy resins, urethanes, polyesters) progress through this growth process in a statistical, random fashion. The resulting infinite networks may be visualized as a collection of unequally segmented Gaussian chains between *f*-functional branch junctures, crosslinks (loops), and dangling terminal groups.

More recently, non-traditional polymerization strategies have evolved to produce a fourth new major polymer architectural class, now referred to as "dendritic polymers" [43]. This new architectural polymer class consists of four major subsets: (1) random hyperbranched, (2) dendrigrafts, (3) dendrons and (4) dendrimers. Dendrimers, the most extensively studied subset were discovered by the Tomalia group while in The Dow Chemical Company laboratories (1979) and represent the first example of synthetic, macromolecular dendritic architecture [43, 44]. First use of the term "dendrimer" appeared in preprints for the first SPSJ International Polymer Conference, held in Kyoto, Japan in 1984 [45]. The following year, a full article in *Polymer Journal* [46] (Fig. 8) described the first preparation of a complete family of Tomalia-type poly(amidoamine) (PAMAM) dendrimers ($G = 1$–7) and their use as precise, fundamental building blocks to form poly (dendrimers) or so-called "starburst" polymers. These poly(dendrimers) are now referred to as "megamers" [47, 48] and are described in more detail later in Sect. 6.4.3. Other pioneers in the dendritic polymer field include Vogtle, Newkome, Frechet, Majoral, and others. These historical contributions have been reviewed recently [52] .

This article will overview the dendritic architectural state, its unique architecturally driven properties, its role relative to traditional polymer science, and describe the many enabling features that dendrimers are expected to offer to the emerging nanotechnology revolution.

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A New Class of Polymers: Starburst-Dendritic Macromolecules

D. A. TOMALIA,* H. BAKER, J. DEWALD, M. HALL,
G. KALLOS, S. MARTIN, J. ROECK,
J. RYDER, and P. SMITH

*Functional Polymers/Process and *The Analytical Laboratory,*
Dow Chemical U.S.A., Midland, Michigan 48640, U.S.A.

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ABSTRACT: This paper describes the first synthesis of a new class of topological macromolecules which we refer to as "starburst polymers." The fundamental building blocks to this new polymer class are referred to as "dendrimers." These dendrimers differ from classical monomers/oligomers by their extraordinary symmetry, high branching and maximized (telechelic) terminal functionality density. The dendrimers possess "reactive end groups" which allow (a) controlled moelcular weight building (monodispersity), (b) controlled branching (topology), and (c) versatility in design and modification of the terminal end groups. Dendrimer synthesis is accomplished by a variety of strategies involving "time sequenced propagation" techniques. The resulting dendrimers grow in a geometrically progressive fashion as shown: Chemically bridging these dendrimers leads to the new class of macromolecules—"starburst polymers" (*e.g.*, $(A)_n$, $(B)_n$ or $(C)_n$).

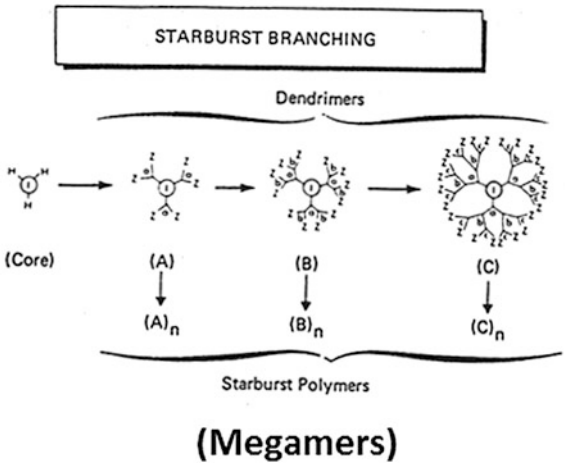


Fig. 8 Abstract of the first full article describing the synthesis of a complete family of dendrimers [55]

3.2 A Fourth Major New Architectural Polymer Class

Dendritic topology has now been recognized as a fourth major class of macromolecular architecture [49–51]. The signature for such a distinction is the unique repertoire of new properties manifested by this class of polymers [9, 26, 52–56]. Numerous synthetic strategies have been reported for the preparation of these materials, and

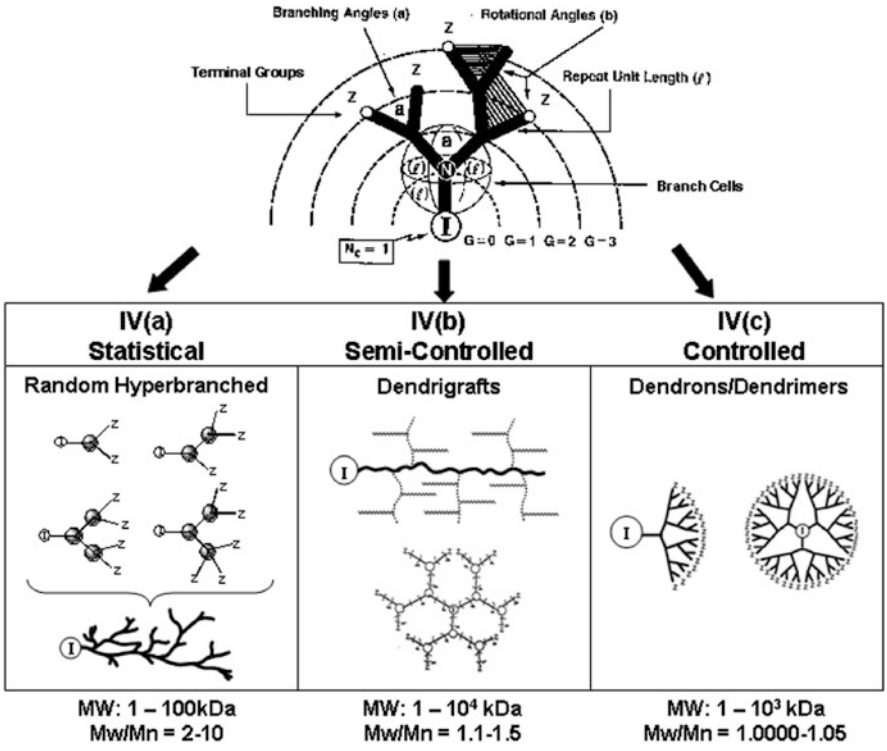


Fig. 9 Branch cell structural parameters: *a* branching angle, *b* rotation angle, *l* repeat unit length, *Z* terminal group, *I* molecular reference marker or core. Dendritic subclasses derived from branches: *IVa* random hyperbranched, *IVb* dendrigrafts, and *IVc* dendrons/dendrimers [93]. Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission

have led to a broad range of dendritic structures. Currently, this architectural class namely, Dendritic (IV) consists of three dendritic subclasses: (IVa) random hyperbranched polymers, (IVb) dendrigraft polymers, and (IVc) dendrons/dendrimers (Fig. 9). The order of this subset, from IVa to IVc, reflects the relative degree of structural control present in each of these dendritic architectures.

All dendritic polymers are open covalent assemblies of branch cells. They may be organized as very symmetrical, monodispersed arrays, as is the case for dendrimers, or as irregular polydispersed assemblies that typically define random hyperbranched polymers. As such, the respective subclasses and the level of structure control are defined by the propagation methodology used to produce these assemblies, as well as by the branch cell construction parameters. The branch cell parameters are determined by the composition of the branch cell monomers, as well as by the nature of the "excluded volume" defined by the branch cell. The excluded volume of the branch cell is determined by the length of the arms, the symmetry, rigidity/flexibility, as well as the branching and rotation angles involved within each of the branch cell domains. As shown in Fig. 9, these dendritic arrays of

branch cells usually manifest covalent connectivity relative to some molecular reference marker (I) or core. As such, these branch cell arrays may be very non-ideal and polydispersed (e.g. $M_w/M_n \cong 2$–10), as observed for random hyperbranched polymers (IVa), or very ideally organized into highly controlled core–shell type structures, as noted for dendrons/dendrimers (IVc) ($M_w/M_n \cong$ 1.01–1.0001 and less). Dendrigraft (arborescent) polymers reside between these two extremes of structure control, frequently manifesting rather narrow polydispersities of $M_w/M_n \cong 1.1$–1.5, depending on their mode of preparation.

3.3 Dendritic Polymer Subclasses

3.3.1 Random Hyperbranched Polymers

Flory first hypothesized dendritic polymer concepts [32, 30], which are now recognized to apply to statistical or random hyperbranched polymers. However, the first experimental confirmation of dendritic topologies did not produce random hyperbranched polymers but rather the more precise, structure-controlled, dendrimer architecture [43, 44, 46, 55]. This work was initiated nearly a decade before the first examples of random hyperbranched polymers were confirmed independently by Gunatillake, Odian et al. [57], as well as by and by Kim and Webster [58, 59] in 1988. At that time, Kim and Webster coined the popular term "hyperbranched polymers" that has been widely used to describe this subclass of dendritic macromolecules. Hyperbranched polymers are typically prepared by polymerization of AB_x monomers. When x is 2 or more, polymerization gives highly branched random polymers, as long as A reacts only with B from another molecule. Reactions between A and B from the same molecule result in termination of polymerization by cyclization. This approach produces hyperbranched polymers with a degree of polymerization n, possessing one unreacted A functional group and $[(x-1)_n + 1]$ unreacted B terminal groups. In a similar fashion, copolymerization of A_2 and B_3 or other such polyvalent monomers can give hyperbranched polymers [60, 61] if the polymerization is maintained below the gel point by manipulating monomer stoichiometry or limiting polymer conversion. Random hyperbranched polymers are generally produced by the one-pot polymerization of AB_x-type monomers or macromonomers involving polycondensation, ring opening, or polyaddition reactions. Hence, the products usually have broad, statistical molecular weight distributions, much as observed for traditional polymers. Over the past decade, literally dozens of new AB_2-type monomers have been reported, leading to an enormously diverse array of hyperbranched structures. Some general types include poly(phenylenes) obtained by the Suzuki coupling [58, 59]; poly (phenylacetylenes) prepared by the Heck reaction [62]; polycarbosilanes, polycarbosiloxanes [63], and poly(siloxysilanes) by hydrosilylation [64]; poly(ether ketones) by nucleophilic aromatic substitution [65]; and polyesters [66] or polyethers [67] by polycondensations or by ring-opening polymerization [68].

New advances beyond the traditional AB_2 Flory-type, branch cell monomers have been reported by Fréchet and coworkers [69, 70]. They introduced the concept of latent AB_2 monomers, referred to as self-condensing vinyl polymerizations (SCVP). These monomers, which possess both initiation and propagation properties, may follow two modes of polymerization: polymerization of the double bond (i.e., chain growth) and condensation of the initiating group with the double bond (i.e., step growth). Recent progress involving the derivative process of self-condensing, ring-opening polymerizations (SCROP) has been reviewed by Sunder et al. [71]. In addition, the use of enhanced processing techniques such as pseudo chain growth by slow monomer addition [72], allow somewhat better control of hyperbranched structures [71].

3.3.2 Dendrigraft Polymers

Dendrigraft polymers are the most recently discovered and currently the least understood subset of dendritic polymers. The first examples were reported in 1991 independently by Tomalia et al. [73] and Gauthier et al. [74]. Whereas traditional monomers are generally employed in constructing dendrimers, reactive oligomers or polymers are used in protect–deprotect or activation schemes to produce dendrigrafts. Consequently, dendrigraft polymers are generally larger structures than dendrimers, grow much faster, and amplify surface groups more dramatically as a function of generational development. Both hydrophilic [e.g., poly(oxazolines) and poly(ethyleneimines)] and hydrophobic (e.g., polystyrenes) dendrigrafts were reported in these early works. These first methodologies involved the iterative grafting of oligomeric reagents derived from living polymerization processes in various iterative "graft-on-graft" strategies. By analogy to dendrimers, each iterative grafting step is referred to as a generation. An important feature of this approach is that branch densities, as well as the size of the grafted branches, can be varied independently for each generation. Furthermore, by initiating these iterative grafting steps from either a point-like core or a linear core it is possible to produce spheroidal and cylindrical dendrigrafts, respectively. Depending on the graft densities and molecular weights of the grafted branches, ultrahigh molecular weight dendrigrafts (e.g., $M_w > 104$ kDa) can be obtained at very low generation levels (e.g., $G = 3$). Dramatic molecular weight enhancements vis-à-vis other dendrimer propagation methodologies are possible using dendrigraft techniques [75]. Further elaboration of these dendrigraft principles allowed the synthesis of a variety of core–shell-type dendrigrafts, in which elemental composition as well as the hydrophobic or hydrophilic character of the core were controlled independently [74].

In general, the above methodologies have involved convergent-type grafting principles whereby preformed, reactive oligomers are grafted onto successive branched precursors to produce semicontrolled structures. Compared

to dendrimers, dendrigraft structures are less controlled since grafting may occur along the entire length of each generational branch, and the exact branching densities are somewhat arbitrary and difficult to control. More recently, both Gnanou [76, 77] and Hedrick [78, 79] have developed approaches to dendrigrafts that mimic dendrimer topologies by confining the graft sites to the branch termini for each generation. These methods involve so-called "graft from" techniques and allow better control of branching topologies and densities as a function of generation. Topologies produced by these methods are reminiscent of the dendrimer architecture. Since the branch-cell arms are derived from oligomeric segments, the products are referred to as polymeric dendrimers [22, 78, 79]. These more flexible and extended structures exhibit unique and different properties compared to the more compact traditional dendrimers. Fréchet, Hawker, and coworkers [80] have utilized the techniques of living polymerization and a staged polymerization process (in which latent polymerization sites are incorporated within growing chains) to produce dendrigrafts of mixed composition and narrow polydispersity.

Another exciting development has been the emerging role that dendritic architecture is playing in the production of commodity polymers. A recent report by Guan et al. [24] has shown that ethylene polymerizes to dendrigraft polyethylene (*dendri*-polyethylene) at low pressures, in contrast to high-pressure conditions which produce only simple branched topologies. This occurs when using late-transition metal or Brookhart catalysts. Furthermore, these authors also state that small amounts of *dendri*-poly(ethylene) architecture may be expected from analogous early-transition-metal metallocene catalysts.

3.3.3 Dendrons and Dendrimers

Dendrons and dendrimers are the most intensely investigated subset of dendritic polymers. In the past decade, over 6,000 literature references have appeared dealing with this unique class of structure-controlled polymers. The word "dendrimer" is derived from the Greek words *dendri-* (tree-branch-like) and *meros* (part of), and was coined by Tomalia, et al. about 20 years ago in the first full paper on PAMAM dendrimers [45, 46]. Since this early disclosure, over 125 dendrimer compositions (families) and 1,100 dendrimer surface modifications have been reported. The two most widely studied dendrimer families are the Fréchet-type polyether compositions and the Tomalia-type PAMAM dendrimers. PAMAM dendrimers constitute the first dendrimer family to be commercialized, and represent the most extensively characterized and best-understood series at this time [55].

Dendrimer Synthesis: Divergent and Convergent Methods

In contrast to traditional polymers, dendrimers are unique core–shell structures possessing three basic architectural components (Fig. 10): a core, an interior of shells (generations) consisting of repeating branch-cell units, and terminal

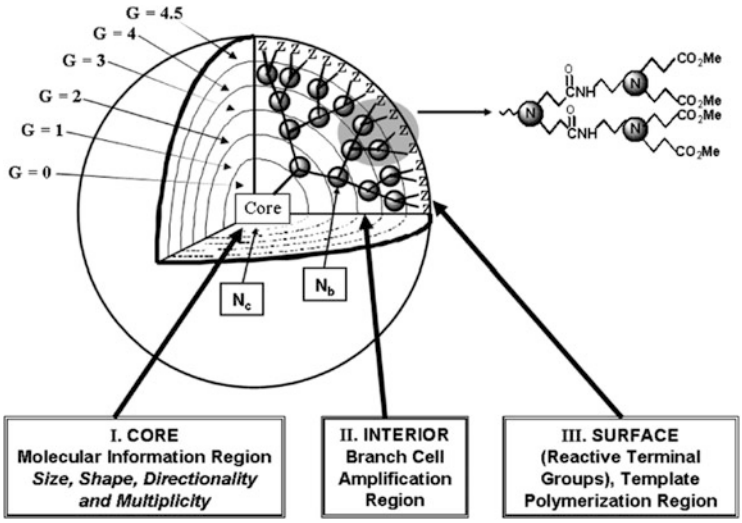
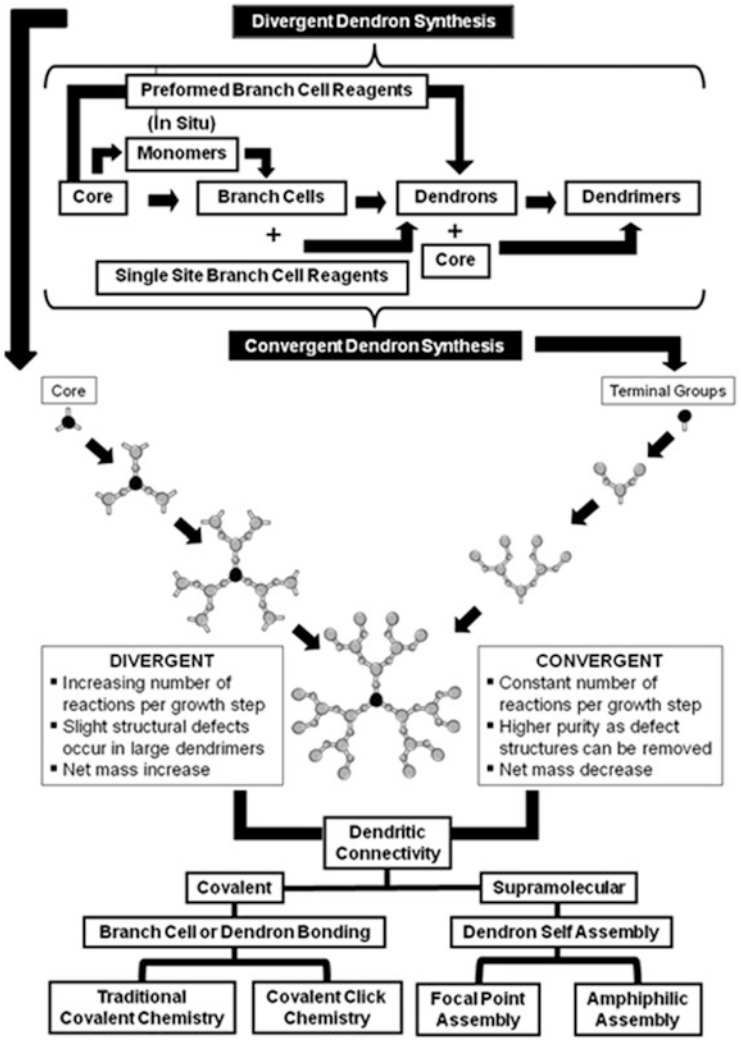


Fig. 10 Three-dimensional projection of dendrimer core–shell architecture for $G = 4.5$ poly (amidoamine) (PAMAM) dendrimer showing principal architectural components: (*I*) core, (*II*) interior, and (*III*) surface [93]. Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission

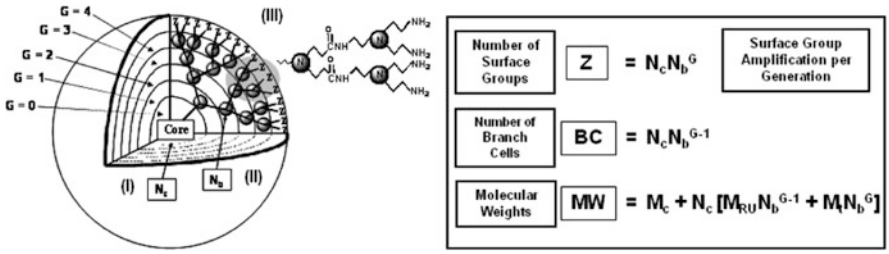
functional groups (the outer shell or periphery). In general, dendrimer synthesis involves divergent or convergent hierarchical assembly strategies that require the construction components shown in Scheme 3. Within each of these major approaches there may be variations in methodology for branch-cell construction or dendron construction. Many of these issues, together with experimental laboratory procedures, have been reviewed elsewhere [81–83].

PAMAM dendrimers are synthesized by the divergent approach. This methodology involves in situ branch-cell construction in stepwise, iterative stages around a desired core to produce mathematically defined core–shell structures. Typically, ethylenediamine (core multiplicity $N_c = 4$), ammonia ($N_c = 3$), or cystamine ($N_c = 4$) may be used as cores and allowed to undergo reiterative, two-step reaction sequences. These sequences consist of: (1) an exhaustive alkylation of primary amines (Michael addition) with methyl acrylate, and (2) amidation of amplified ester groups with a large excess of ethylenediamine to produce primary amine terminal groups (Fig. 10). This first reaction sequence on the exposed core creates $G = 0$ (i.e., the core branch cell), wherein the number of arms (i.e., dendrons) anchored to the core is determined by N_c. Iteration of the alkylation–amidation sequence produces an amplification of terminal groups from one to two with the in situ creation of a branch cell at the anchoring site of the dendron that constitutes $G = 1$. Repeating these iterative sequences (Fig. 10) produces additional shells (generations) of branch cells that amplify mass and terminal groups according to the mathematical expressions shown in the box in Fig. 11). It is apparent that both the core multiplicity (N_c) and branch cell multiplicity (N_b) determine the precise number of terminal groups and mass amplification as a function of generation.



Scheme 3 Strategies for dendrimer synthesis [52]. Copyright: Cambridge University Press

One may view those generation sequences as quantized polymerization events. The assembly of reactive monomers [44, 84], branch cells [9, 55, 56], or dendrons [55, 85, 86] around atomic or molecular cores, to produce dendrimers according to divergent or convergent dendritic branching principles, has been well demonstrated. Such systematic filling of molecular space around cores with branch cells as a function of generational growth stages (branch-cell shells) – to give discrete, quantized bundles of nanoscale mass – has been shown to be mathematically predictable [10, 11, 26]. Predicted molecular weights have been confirmed by mass spectrometry [87–90] and other analytical methods [9, 52, 91, 92]. Predicted



Gen	No. of NH_2 Surface Groups	Molecular Formula	MW	Hydrodynamic Diameter (nm)
0	4	$C_{24}H_{52}N_{10}O_4S_2$	609	1.5
1	8	$C_{64}H_{132}N_{26}O_{12}S_2$	1,522	2.2
2	16	$C_{144}H_{292}N_{58}O_{28}S_2$	3,348	2.9
3	32	$C_{304}H_{612}N_{122}O_{60}S_2$	7,001	3.6
4	64	$C_{624}H_{1252}N_{250}O_{124}S_2$	14,307	4.5
5	128	$C_{1264}H_{2532}N_{506}O_{252}S_2$	28,918	5.4
6	256	$C_{2544}H_{5092}N_{1018}O_{508}S_2$	58,140	6.7
7	512	$C_{5104}H_{10212}N_{2042}O_{1020}S_2$	116,585	8.1

Z = monomer-shell-saturation level, N_c = core (cystamine) multiplicity, N_b = branch-cell (BC) multiplicity, G = generation.

Fig. 11 Dendritic branching mathematics for predicting the number of dendrimer surface groups, number of branch cells, and molecular weight. Calculated values are for [ethylenediamine core] *dendri*-poly(amidoamine) series with nanoscale diameters

number of branch cells, number of terminal groups, and molecular weight as a function of generation for an ethylenediamine-core ($N_c = 4$) PAMAM dendrimer are shown in Fig. 11. It should be noted that the molecular weight approximately doubles as one progresses from one generation to the next. The number of surface groups and branch cells amplify mathematically according to a power function, thus producing discrete, monodispersed structures with precise molecular weights and a nanoscale diameter enhancement, as described in Fig. 11. These predicted values are routinely verified by mass spectrometry for the earlier generations (i.e., $G = 4$–5); however, with divergent dendrimers, minor mass defects are often observed for higher generations as congestion-induced de Gennes dense packing begins to take effect [9, 52, 93, 94].

4 Dendrimer Features of Interest to Nanoscience

Dendrimers may be viewed as unique, information processing, nanoscale devices. Each architectural component (core, interior, and surface) manifests a specific function, while at the same time defining properties for these nanostructures as they are grown generation by generation. For example, the core may be thought of as the molecular information center from which size, shape, directionality, and multiplicity are expressed via the covalent connectivity to the outer shells. Within the interior, one finds the branch cell amplification region, which defines the type

and amount of interior void space that may be enclosed by the terminal groups as the dendrimer is grown. Branch cell multiplicity (N_b) determines the density and degree of amplification as an exponential function of generation. The interior composition and amount of solvent-filled void space determines the extent and nature of guest–host (endoreceptor) properties that are possible within a particular dendrimer family and generation. Finally, the surface consists of reactive or passive terminal groups that may perform several functions. With appropriate functionality, they serve as a template polymerization region as each generation is amplified and covalently attached to the precursor generation. The surface groups may also serve as passive or reactive gates controlling entry or departure of guest molecules from the dendrimer interior. These three architectural components determine the physical and chemical properties, as well as the overall size, shape and flexibility of the dendrimers. It is important to note that dendrimer diameters increase linearly as a function of the number of shells or generations added, whereas the terminal functional groups increase exponentially as a function of generation. This dilemma enhances "tethered congestion" of the anchored dendrons, as a function of generation, due to the steric crowding of the end groups. As a consequence, lower generations are generally open, floppy structures, whereas higher generations become robust, less-deformable spheroids, ellipsoids, or cylinders depending on the shape and directionality of the core.

Tomalia-type PAMAM dendrimers are synthesized by the divergent approach. This methodology involves in situ branch cell construction in stepwise, iterative stages (i.e., $G = 1, 2, 3 \ldots$) around a desired core to produce mathematically defined nanoscale core–shell structures. Typically, ethylenediamine ($N_c = 4$) or ammonia ($N_c = 3$) are used as nucleophilic cores and are allowed to undergo reiterative two-step reaction sequences involving: (1) exhaustive alkylation of primary amines (Michael addition) with methyl acrylate and (2) amidation of amplified ester groups (Fig. 10) with a large excess ethylenediamine to produce primary amine terminal groups.

This first reaction sequence on the exposed dendron (Fig. 12) creates $G = 0$ (i.e., the core branch cell), wherein the number of arms (i.e., dendrons) anchored to the core is determined by N_c. Iteration of the alkylation/amidation sequence produces an amplification of terminal groups from one to two, with the in situ creation of a branch cell at the anchoring site of the dendron that constitutes $G = 1$. Repeating these iterative sequences produces additional shells (generations) of branch cells that amplify mass and terminal groups according to the mathematical expressions described in Fig. 11.

As early as 2001, Nobel Laureate Prof. B. Sharpless popularized a modular approach to organic synthesis that he referred to as "click chemistry" [95, 96]. This strategy was defined in the context of four major organic reaction categories:

1. Addition of nucleophiles to activated double bonds (i.e., Michael addition chemistry)
2. "Non-aldol"-type carbonyl chemistry (i.e., formation of amides, hydrazones, etc.)

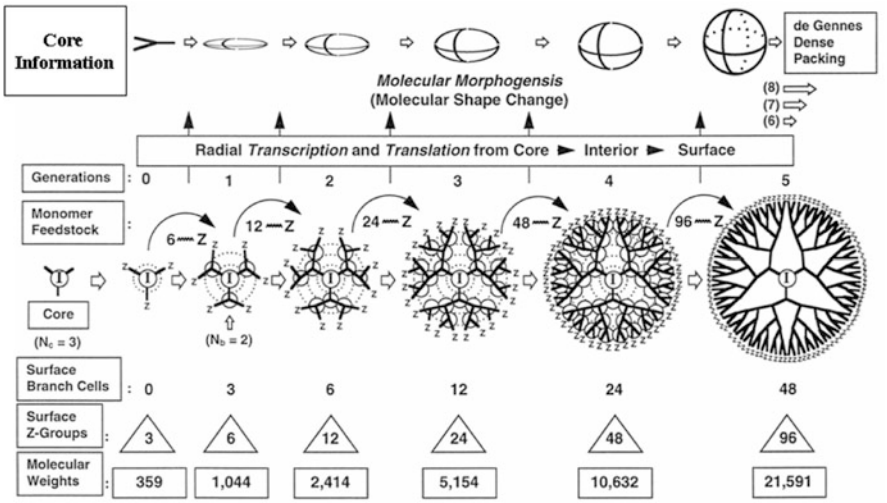


Fig. 12 Comparison of molecular shape change, two-dimensional branch cell amplification, number of surface branch cells, number of surface Z groups, and molecular weight as function of generation for $G = 0$–6 [93]. Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission

3. Nucleophilic ring opening of strained heterocyclic electrophiles (i.e., aziridines, epoxides, etc.)
4. Huisgen-type 1,3-dipolar cycloaddition of azides to alkynes

It should be noted that the first three reaction categories of click chemistry, as described above, were used by Tomalia [9, 46] and Vögtle [97] as preferred iterative synthetic routes to the first reported examples of dendrimers and low molecular weight cascade molecules, respectively.

In 1968, Huisgen [98] reported the facile, high yield, chemoselective cycloaddition of organic azides with alkynes to form covalent 1,4-disubstituted 1,2,3-triazole linkages. More recently, Sharples and colleagues [96, 99] have shown that terminal alkynes may be catalyzed by Cu^{1+} salts in an orthogonal fashion to form the corresponding triazoles in very high yields. Because of the high chemoselectivity of these reactions, they may be selectively performed in the presence of a wide variety of competing or parallel reactions and/or functionalities without interference. These features make this approach very attractive for dendrimer syntheses. Click chemistry based on these copper-catalyzed Huisgen reactions has been used recently to synthesize dendrimers [99–101], dendronized linear polymers [102], and other dendritic architectures [103].

It is apparent that both the core multiplicity (N_c) and branch cell multiplicity (N_b) determine the precise number of terminal groups and mass amplification as a function of generation. One may view those generation sequences as quantized polymerization events. The assembly of reactive monomers [9, 44], branch cells [9, 55, 56], or dendrons [55, 85, 86] around atomic or molecular cores to produce

dendrimers according to divergent or convergent dendritic branching principles has been well demonstrated. Such systematic filling of space around cores with branch cells, as a function of generational growth stages (branch cell shells), to give discrete, quantized bundles of mass has been shown to be mathematically predictable (Fig. 11) [10, 11, 26]. Predicted molecular weights have been confirmed by mass spectroscopy [87–89] and other analytical methods [9, 85, 91, 92, 104]. Predicted numbers of branch cells, numbers of terminal groups, and molecular weights as a function of generation for an ethylenediamine-core ($N_c = 4$) PAMAM dendrimer are shown in Fig. 12. It should be noted that the molecular weights approximately double as one progresses to the next generation. The number of surface groups and branch cells amplify mathematically according to a power function, thus producing discrete, monodispersed structures with precise molecular weights and nanoscale diameter enhancement, as described in Fig. 11. These predicted values are routinely verified by mass spectroscopy for the earlier generations (i.e., $G = 4$–5); however, with divergent dendrimers, minor mass defects are often observed for higher generations as congestion-induced de Gennes dense packing begins to take affect (Fig. 12).

4.1 Dendrimer Shape Change: A Nanoscale Molecular Morphogenesis

As illustrated in Fig. 12, dendrimers undergo congestion-induced molecular shape changes from flat, floppy conformations to robust spheroids, as first predicted by Goddard and coworkers [84]. Shape change transitions were subsequently confirmed by extensive photo-physical measurements, pioneered by Turro and coworkers [105–108] and solvatochromic measurements by Hawker et al. [109]. Depending upon the accumulative core and branch cell multiplicities of the dendrimer family under consideration, these transitions were found to occur between $G = 3$ and $G = 5$. Ammonia-core, PAMAM dendrimers ($N_c = 3$, $N_b = 2$) exhibited a molecular morphogenesis break at $G = 4.5$, whereas the ethylenediamine-core PAMAM dendrimer family ($N_c = 4$, $N_b = 2$) manifested a shape change break at around $G = 3$–4 [84] and the Fréchet-type convergent dendrons ($N_b = 2$) at around $G = 4$ [109]. It is readily apparent that increasing the core multiplicity from $N_c = 3$ to $N_c = 4$ accelerates congestion and forces a shape change at least one generation earlier. Beyond these generational transitions, one can visualize these dendrimeric shapes as nearly spheroidal or slightly ellipsoidal core–shell architectures. Studies by Tomalia and colleagues [110] as well as Schluter and colleagues [111] have shown that the cylindrical or rod-shaped dendrimers are routinely formed by dendronizing traditional linear polymers. These new constructs derived from linear polymer backbones are pendant dendrons and are referred to as “architectural copolymers” [52].

4.2 de Gennes Dense Packing: A Nanoscale Steric Phenomenon Not Observed in Traditional Polymers

As a consequence of excluded volume associated with the core, interior, and surface branch cells, steric congestion is expected to result due to tethered core connectivity. Furthermore, the number of dendrimer surface groups, Z, amplifies with each subsequent generation. This occurs according to geometric branching laws, which are related to core multiplicity (N_c) and branch cell multiplicity (N_b). These values are defined by the following equation:

$$Z = N_c N_b{}^G$$

Since the radii of the dendrimers increase in a linear manner as a function of generation number G, whereas the surface cells amplify according to $N_c N_b{}^G$, it is implicit from this equation that generational reiteration of branch cells ultimately will lead to a so-called dense-packed state.

As early as 1983, de Gennes and Hervet [43, 112] proposed a simple equation, derived from fundamental principles, to predict dense-packed generation for PAMAM dendrimers. It was predicted that at this generation, ideal branching can no longer occur because available surface space becomes too limited for the mathematically predicted number of surface cells to occupy. This produces a "closed geometric structure." The surface is "crowded" with exterior groups that, although potentially chemically reactive, are sterically prohibited from participating in ideal dendrimer growth.

This "critical packing state" does not preclude further dendrimer growth beyond this point in the genealogical history of the dendrimer preparation. On the contrary, although continuation of dendrimer step-growth beyond the dense-packed state cannot yield structurally ideal, next generation dendrimers, it can nevertheless occur, as indicated by further increases in the molecular weight of the resulting products. Predictions by de Gennes [112] suggested that the PAMAM dendrimer series should reach a critical packing state at $G = 9$–10. Experimentally, we observed a moderate molecular weight deviation from predicted ideal values beginning at $G = 4$–7 (Fig. 13). This digression became very significant at $G = 7$–8 and as dendrimer growth was continued to generation 12 [94]. The products thus obtained are of "imperfect" structure because of the inability of all surface groups to undergo further reaction. Presumably, some of these surface groups remain trapped or are sterically encumbered under the surface of the newly formed dendrimer shell, yielding a unique architecture possessing two types of terminal groups. This new surface group population will consist of both those groups that are accessible to subsequent reiteration reagents and those that will be sterically screened. The total number of these groups will not, however, correspond to the predictions of the mathematical branching law, but will fall between the value that was mathematically predicted for the next generations

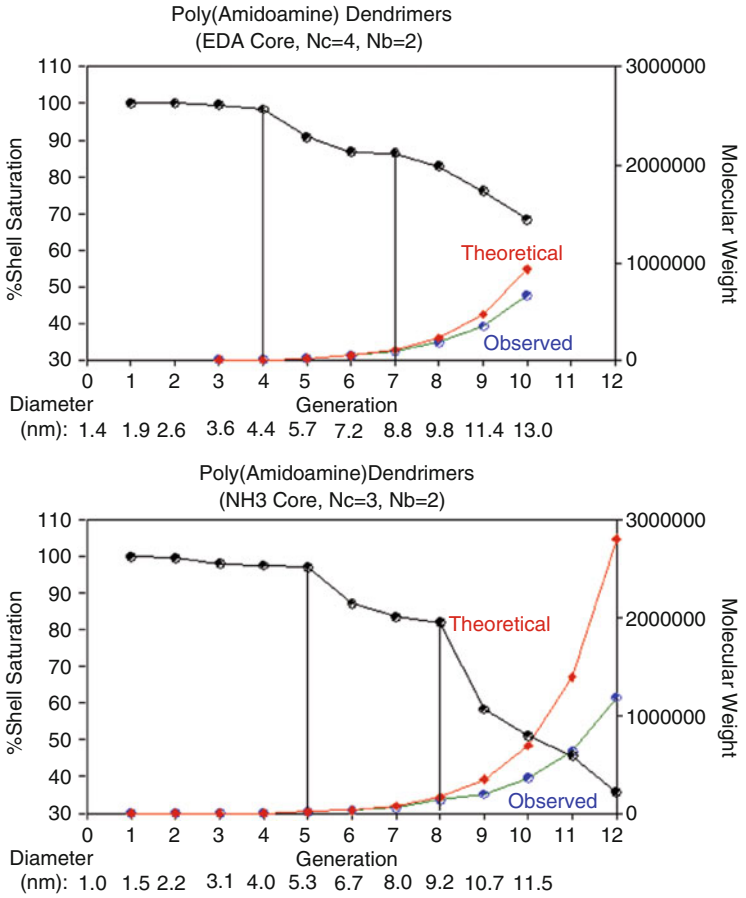


Fig. 13 (**a**) Comparison of theoretical and observed molecular weights and percentage shell filling for ethylenediamine-core poly(amidoamine) (PAMAM) dendrimers as a function of generation for $G = 1$–10. (**b**) Comparison of theoretical and observed molecular weights and percentage shell filling for NH_3-core PAMAM dendrimers as a function of generation for $G = 1$–12 [93]. Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission

(i.e., $G + 1$) and that expected for the precursor generation. Thus, a mass-defective dendrimer "generation" is formed.

Dendrimer surface congestion can be appraised mathematically as a function of generation, from the following simple relationship:

$$A_z = \frac{A_D}{N_Z}\alpha\frac{r^2}{N_c N_b^G}$$

where A_z is the surface area per terminal group Z, A_D the dendrimer surface area, N_z the number of surface groups Z per generation, and r the dendrimer radius. This relationship predicts that at higher generations, the surface area per Z group

becomes increasingly smaller and experimentally approaches the cross-sectional area or van der Waals dimension of the surface groups Z. The generation G thus reached is referred to as the "de Gennes dense-packed generation" [9, 26, 55]. Ideal dendritic growth without branch defects is possible only for those generations preceding this dense-packed state. This critical dendrimer property gives rise to self-limiting dendrimer dimensions, which are a function of the branch cell segment length (l), the core multiplicity N_c, the branch cell juncture multiplicity N_b, and the steric dimensions of the terminal group Z (Fig. 10). Whereas the dendrimer radius r in the above expression is dependent on the branch cell segment lengths l, large l values delay this congestion. On the other hand, larger N_c and N_b values and larger Z dimensions dramatically hasten it.

Additional physical evidence supporting the development of congestion as a function of generation is shown in the composite comparison of dendrimer nanoperiodic property patterns as illustrated in Sect. 6.5.2. Plots of intrinsic viscosity [η] [9, 113], density z, surface area per Z group (A_z), and refractive index n as a function of generation clearly show maxima or minima at $G = 3$–5, paralleling computer-assisted molecular-simulation predictions [84, 114], as well as extensive photochemical probe experiments reported by Turro and coworkers [105–108].

Clearly, this de Gennes dense-packed congestion would be expected to contribute to (1) sterically inhibited reaction rates and (2) sterically-induced stoichiometry [9]. Each of these effects was observed experimentally at higher generations. The latter would be expected to induce dendrimer mass defects at higher generations, which we have used as a diagnostic signature for appraising the de Gennes dense packing effect.

Theoretical dendrimer mass values were compared to experimental values by performing electrospray and MALDI-TOF mass spectrometry analysis on the respective PAMAM families (i.e., $N_c = 3$ and 4) [88]. Note that there is essentially complete shell filling for the first five generations of the NH_3-core PAMAM series ($N_c = 3$, $N_b = 2$) (Fig. 13b). A gradual digression from theoretical masses occurs for $G = 5$–8, followed by a substantial break (i.e., $\Delta = 23\%$) between $G = 8$ and 9. This discontinuity in shell saturation is interpreted as a signature for de Gennes dense packing. It should be noted that shell saturation values continue to decline monotonically beyond this breakpoint to a value of 35.7% of theoretical at $G = 12$. A similar trend is noted for the ethylenediamine-core PAMAM series ($N_c = 4$, $N_b = 2$); however, the shell saturation inflection point occurs at least one generation earlier (i.e., $G = 4$–7, see Fig. 13a). This suggests that the onset of de Gennes dense packing may be occurring between $G = 7$ and 8. Recent work by Halperin, Schluter and coworkers [111] describes a simple yet elegant strategy for detecting the onset of de Gennes dense packing by UV labeling dendrimer surfaces with the Sanger reagent, as a function of generation, and monitoring signal regression as an indication of congestion and dense packing. This protocol provides a photolabeling technique that corroborates mass spectrometry data, as shown in Fig. 13.

Unique features offered by the "dendritic state" that have no equivalency in classical polymer topologies are found almost exclusively in the dendron/dendrimer subset and to a slightly lesser degree in the dendrigrafts. They include:

1. Nearly complete nanoscale size and mass monodispersity
2. The ability to control congestion, shape, and nanocontainer/scaffolding properties as function of generation
3. Mathematically defined exponential amplification and functionalization of dendrimer surface chemistry
4. Nanoscale dimensions and shape mimicry of proteins
5. Dendrimer interior guest–host encapsulation properties for both inorganic and organic guests

These features are captured to some degree with dendrigraft polymers; however, they are either absent or present to a vanishing small extent for random hyperbranched polymers.

5 Unique Quantized Dendrimer Properties

5.1 Critical Nanoscale Design Parameters

The structure-controlled features manifested by dendrons/dendrimers, such as: size, shape, surface chemistry, flexibility/rigidity, elemental composition, and architecture, have provided a unique window to a new systematic concept for unifying nanoscience and will be described later in Section 6. These nanolevel structure-controlled features are referred to as "critical nanoscale design parameters" (CNDPs).

5.1.1 Controlled Nanoscale Monodispersity

The monodispersed nature of dendrimers has been verified extensively by mass spectroscopy, size exclusion chromatography, gel electrophoresis, and transmission electron microscopy (TEM) [55, 115]. As is always the case, the level of monodispersity is determined by the skill of the synthetic chemist, as well as the isolation or purification methods utilized. In general, convergent methods produce the most nearly isomolecular dendrimers. This is because the convergent growth process allows purification at each step of the synthesis and eliminates cumulative effects due to failed couplings [85, 116]. Appropriately purified, convergent dendrimers are probably the most precise synthetic macromolecules that exist today.

As discussed earlier, mass spectroscopy has shown that PAMAM dendrimers produced by the divergent method are very monodisperse and have masses consistent with predicted values for the earlier generations (i.e., $G = 0$–5) (Fig. 13). Even at higher generations, as one enters the de Gennes dense packed region, the molecular weight distributions remain very narrow (i.e., 1.05) and consistent, in spite of the fact that experimental masses deviate substantially from predicted theoretical values. Presumably, de Gennes dense packing produces a very regular and dependable effect that is manifested by the observed narrow molecular weight distribution.

5.1.2 Controlled Nanoscale Shapes and Container or Scaffolding Properties

Systematic shape and unimolecular container or scaffolding behavior appears to be a nano-periodic property that is specific to each dendrimer family or series. These properties are determined by the size, shape, and multiplicity of the construction components used for the core, interior, and surface of the dendrimer (Fig. 12). Higher multiplicity components and those that contribute to "tethered congestion" will hasten the development of more rigid shapes, container properties, and less flexible surface scaffolding as a function of generation.

5.2 Amplification and Functionalization of Dendrimer Surface Groups

Dendrimers within a generational series can be expected to present their terminal groups in at least three different modes, namely, flexible, semi-flexible, or rigid functionalized scaffolding. Based on mathematically defined dendritic branching rules (i.e., $Z = N_c N_b{}^G$), the various surface presentations become more congested and rigid as a function of increasing generation level. It is implicit that this surface amplification can be designed to control gating properties associated with unimolecular container development. Furthermore, dendrimers may be viewed as versatile nanosized objects that can be readily surface-functionalized with a vast array of chemical and application features. Presently, well over 1,000 diverse surface functionalities have been attached to dendrimer surfaces [52]. The ability to control and engineer these parameters provides an endless list of possibilities for utilizing dendrimers as modules for nanodevice design [11, 48, 50, 117]. Recent reviews have begun to focus on this area [118–122].

5.3 Nanoscale Dimensions and Shapes Mimic Those of Proteins

In view of the extraordinary structure control and nanoscale dimensions observed for dendrimers, it is not surprising to find extensive interest in the use of dendrimers as globular protein mimics. Based on their systematic, dimensional length scaling properties and electrophoretic/hydrodynamic [91, 92] behavior, they are widely recognized as artificial proteins [48, 123]. Substantial effort has been focused recently on the use of dendrimers for "site isolation" mimicry of proteins [9], enzyme-like catalysis [124], viral capsid mimicry [125] and other biomimetic applications [48, 126], drug delivery [119, 123, 127, 128], surface engineering [129], and light harvesting [130, 131]. These fundamental properties have in fact

led to their commercial use as globular protein replacements for gene therapy, immunodiagnostics [132, 133], and a variety of other biological applications [52].

6 Dendrimers: Window to a New Nano-periodic System for Defining and Unifying Nanoscience

> "Science will continue to advance regardless of disputes over priorities. However, confusion and disagreement over common scientific language and standards can plunge a discipline into chaos. Such was the case for 19th century traditional chemistry before the emergence of Mendeleyev's Periodic Table of the Elements (1869)." From *Mendeleyev's Dream – The Quest for the Elements* by P. Strathern [134].

Clearly the need for a unifying system and framework that provides a central dogma with predictive capabilities for a priori design assessment as well as for defining risk/benefit boundaries remains an urgent challenge for nanotechnology [135]. Historically, a similar challenge existed for traditional chemistry in the early nineteenth century. Prior to the emergence of a central dogma and a common scientific language, traditional chemistry was viewed as an empirical discipline, which was transformed into a precise, predictive science only after the advent of atomic/molecular theory, established stoichiometries, and the emergence of well-defined periodic property patterns as first described by Mendeleev in 1869 [134].

It is from this perspective that the National Science Foundation (NSF) sponsored a workshop entitled "Periodic patterns, relationships and categories of well-defined nanoscale building blocks" in 2007 [136]. This seminal workshop evolved an embryonic consensus that subsequently led to a proposed concept for defining and unifying nanoscience based on the integration of traditional chemistry "first principles" with certain critical hierarchical design parameters (CHDPs) [137, 138]. These CHDPs include size, shape, surface chemistry, flexibility/rigidity, composition, and architecture and appear to be conserved and transferred as a function of complexity (illustrated in Fig. 14).

These highly conserved CHDP transformations were first reported for a wide range of divergent, structure-controlled dendrimer syntheses as early as 1990 [9]. These syntheses provided a remarkable window for observing CHDP-dependent structure control related to divergent dendrimer synthesis. This structure control and information transfer was observed from the atomic scale (critical atomic design parameters, CADP), i.e., 10^{-11} m $\rightarrow$ molecular/subnanoscale (critical molecular design parameters, CMDP), i.e., 10^{-10} m $\rightarrow$ nanoscale level (critical nanoscale design parameters, CNDP), i.e., 10^{-9} m, as shown in Fig. 15. Furthermore, it became readily apparent that these CHDPs defined discrete, reproducible hierarchical periodic property patterns. These patterns were uniquely different at each of these hierarchical levels. In essence, the predictions of Nobel Laureate physicist, P.W. Anderson in 1972 were observed to be fulfilled [139]. Simply stated, as one breaks hierarchical symmetry by advancement with well-defined building blocks to higher structural complexity, the whole becomes not only more than, but very different from the sum of its parts. As a consequence, one should expect to

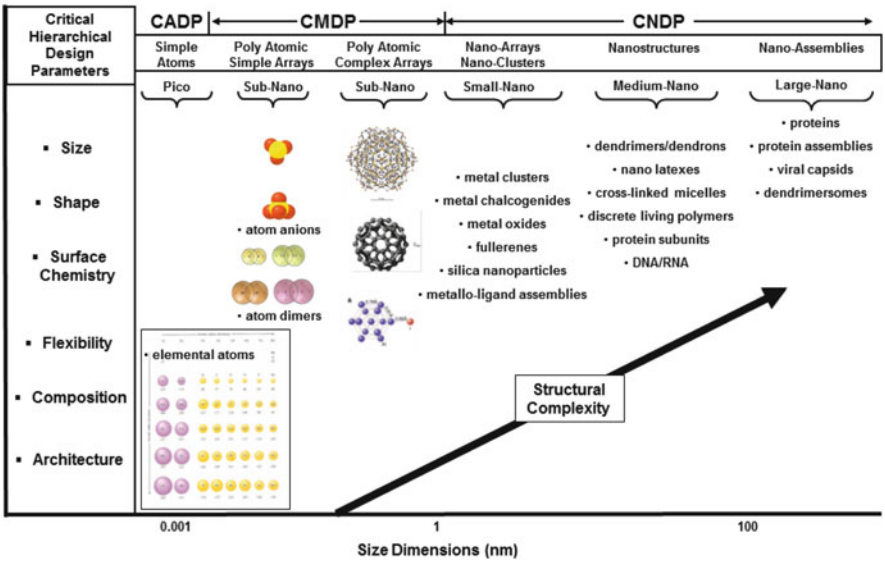


Fig. 14 Structural control of critical hierarchical design parameters (CHDPs), namely, size, shape, surface chemistry, flexibility/rigidity, composition, and architecture, required for bottom-up synthesis of higher nanostructural complexity manifesting atom mimicry

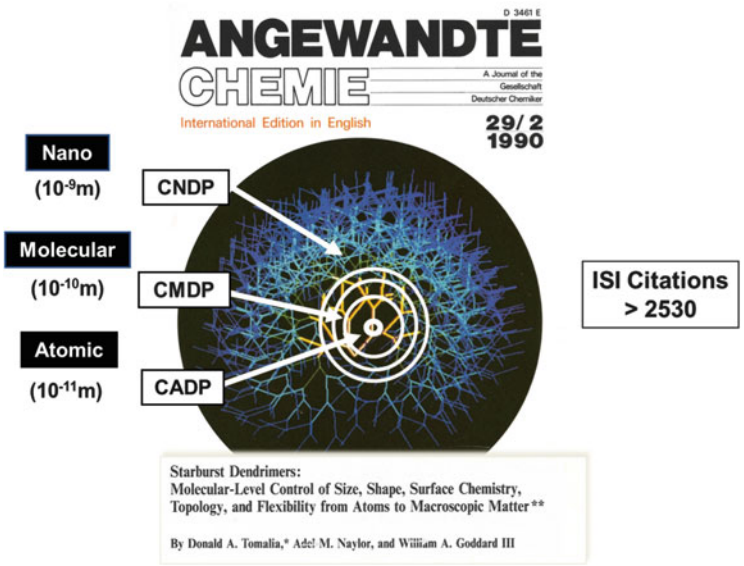


Fig. 15 Front cover of Angew Chem Int Ed Engl (1990), 29:138–175 first describing structural control of critical hierarchical design parameters (CHDP) from atoms to macroscopic matter observed during the divergent syntheses of all dendrimers [9]. Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission

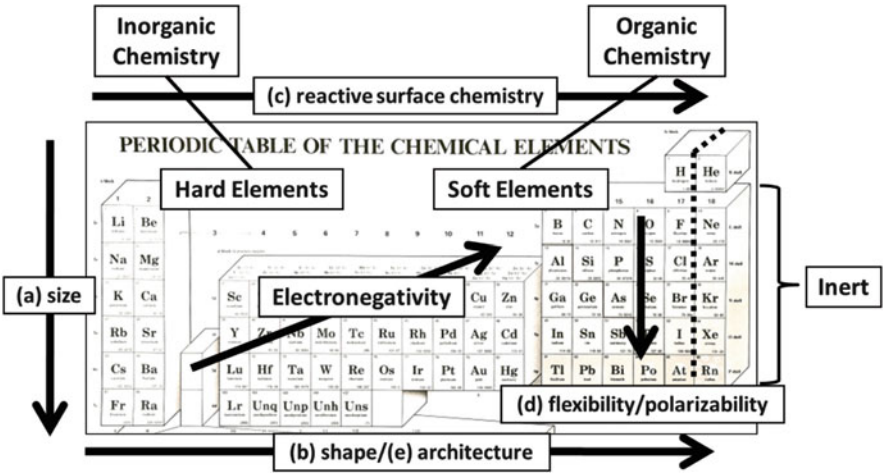


Fig. 16 Critical atomic design parameters (CADPs): structure-controlled (*a*) size, (*b*) shape, (*c*) surface chemistry, (*d*) flexibility/polarizability, (*e*) architecture, and (*f*) elemental composition [94]

observe totally new emerging nanomaterial properties and patterns that are unprecedented and uncharacteristic compared to the less complex hierarchical precursors and building blocks involved in their construction.

6.1 Elemental Picoscale Periodicity Derived from CADPs

It is generally accepted that very specific amounts and arrangements of quantized subatomic building block constituents (i.e., particles such as electrons, protons, and neutrons) are involved in the production of all known atomic elements. The unique quantities and ratios of these self-assembling subatomic building blocks, by definition, determine the discrete and unique physico-chemical properties of each atomic element. As a consequence, each atomic element possesses a unique list of CADPs that allows them to be reproducibly defined and structure-controlled as a function of CADPs such as size, shape, surface chemistry, flexibility (i.e., polarizability), elemental composition (i.e., number of protons, neutrons, and electrons), and architecture. As such, these CADP-derived picoscale building blocks are observed to manifest discrete and unique intrinsic properties individually, as well as very familiar periodic property relationships when compared to each other. These elemental periodic property trends or patterns based on CADPs provide the invaluable predictive value and are the very essence of Mendeleev's Periodic Table, as illustrated in Fig. 16.

6.2 *Chemists and Physicists Are Developing a Mutual Consensus on Nanoscale Atom Mimicry and Superatoms*

Recent dialogue sparked by a plenary presentation to the American Physical Society in early 2012 [140] has led to the realization that both chemists and physicists have been thinking and working in parallel worlds concerning the general concept of nanoscale atom mimicry, nanoscale superatoms, and nanoclusters [141]. Although physicists have focused primarily on atom mimicry associated with hard particle, metal cluster-type electron orbital behavior, chemists have been more interested in heuristic nanoscale atom mimicry based on well-defined nanovalency, nanosterics, nanostoichiometries, and similar issues. Many of these features and properties have been associated with discrete soft nanoparticles such as dendrimers, proteins, viral capsids, DNA and RNA, nanolatexes, polymeric micelles, and monodispersed synthetic polymers.

It is now recognized and generally accepted, that more complex, large nanoscale collections (i.e., 10^3 times larger than atoms) of discretely organized atoms may manifest many physico-chemical and building block features that are reminiscent of individual atoms [142, 143]. These chemically bonded or supramolecularly assembled collections of atoms are generally homogeneous and monodisperse entities that exhibit well-defined size (i.e., mass), shape, surface chemistry (i.e., valency), flexibility/rigidity, atomic composition, and architecture. They are often referred to as nanoscale "superatoms," [142–145] atom equivalents [146], or heuristic "atom mimics" [121, 137, 138, 147, 148].

A superatom is defined as any cluster of atoms that seems to exhibit the properties of elemental atoms. An early example of a hard superatom was the observed clustering of sodium atoms, when cooled from vapor, to preferentially form a magic number of cluster atoms (i.e., 2, 8, 20, 40, 58, etc.). The first two magic numbers (i.e., 2 and 8) are recognized as the number of electrons required to fill the first and second shells, respectively. Thus, superatom mimicry is related to the free electrons in the cluster that appear to occupy a new set of orbitals that are defined by the entire group of atoms involved in the cluster, rather than each individual atom separately. Superatoms appear to behave chemically in a way that will allow them to have a closed shell of electrons in this new cluster orbital counting scheme. Many examples of hard superatoms involving metal atom clusters have been reported by pioneering physicists such as Khanna, Castleman and coworkers [143, 144], and others [149].

This atom cluster behavior has also been observed and referred to by others as "nanoscale atom mimicry," [137, 138], wherein certain heterogeneous, soft, non-metal atom clusters appear to exhibit combining patterns that produce well-defined stoichiometries and closed-shell-type behavior that is normally associated with naked, elemental atoms. More specifically, this nanoscale atom mimicry was noted in the 1990s [10, 11] for analogous soft superatoms such as dendrimers. For example, dendrimers possessing unfilled outer monomer shells were observed to be highly autoreactive, leading to dimer or oligomer formation. In contrast, ideal outer

shell saturated dendrimers behaved like noble gas atomic elements and did not exhibit this autoreactivity. In fact this nanoscale atom mimicry constituted a primary hypothesis upon which a new nano-periodic system for unifying nanoscience was proposed [137]. More specifically, it provided a fundamental paradigm for explaining why many well-defined nanoscale building blocks (i.e., both soft and hard nano-elements) were observed to combine in well-defined stoichiometries. These soft and hard nano-elements have been observed to produce extensive libraries of literature-documented chemically bonded nanocompounds and supramolecularly derived nano-assemblies, as will be described later.

These superatoms or atom mimics appear to fulfill a pivotal role as nanoscale building blocks, much as elemental atoms function at the pico- or subnanoscale level. As such, these poly(atomic) structures or entities have been classified and referred to as "nano-element categories" [137, 138]. Furthermore, these nano-element categories have been shown to form stoichiometric nanocompounds or assemblies that exhibit well-defined intrinsic nano-periodic property patterns in much the same way as atomic elements and their compounds.

In the context of this perspective and using "traditional chemistry first principles" initiated by Lavoisier, Dalton, Mendeleev and others, a new systematic framework for unifying and defining nanoscience was proposed. Just as the nineteenth century first principles led to a central paradigm and a periodic system for traditional elemental atom and small molecule chemistry, it was proposed that a similar nano-periodic system might be defined for discrete, well-defined nanomodules at the nanolevel (Fig. 17).

The initial nano-periodic framework of nano-elemental categories should be viewed as a "works in progress". This framework is expected to be expanded and better articulated with time, just as Dalton's original list of atomic elements has grown from 23 in 1808 to now over 117 known atomic elements [150]. The current system is based on 12 nano-element categories, which are differentiated equally into two main groups consisting of six categories each: (1) hard nano-element categories (i.e., inorganic modules) and (2) soft nano-element categories (i.e., organic modules). The inorganic-like, hard nano-element categories are arbitrarily designated as [H-1] metal nanoclusters, [H-2] metal chalcogenide nanocrystals, [H-3] metal oxide nanocrystals, [H-4] silica nanoparticles, [H-5] fullerenes, and [H-6] carbon nanotubes. The organic-like, soft nano-element categories include [S-1] dendrons/dendrimers, [S-2] nano-latexes, [S-3] polymeric micelles, [S-4] proteins, [S-5] viral capsids, and [S-6] RNA/DNA (Fig. 18). Single units of these various elements (i.e., chemically bonded or supramolecularly assembled modules) are 1–100 nm in at least one dimension, contain between 10^3 and 10^9 atoms with masses of 10^4–10^{10} Da. In order to be included as a nano-element category, each type of nanomaterial had to exhibit:

1. Discrete, well-defined monodispersity (i.e., >90% monodisperse as a function of size or mass)
2. Exist as well-defined nanostructures, assemblies, or collections of units that mimic or behave like atoms

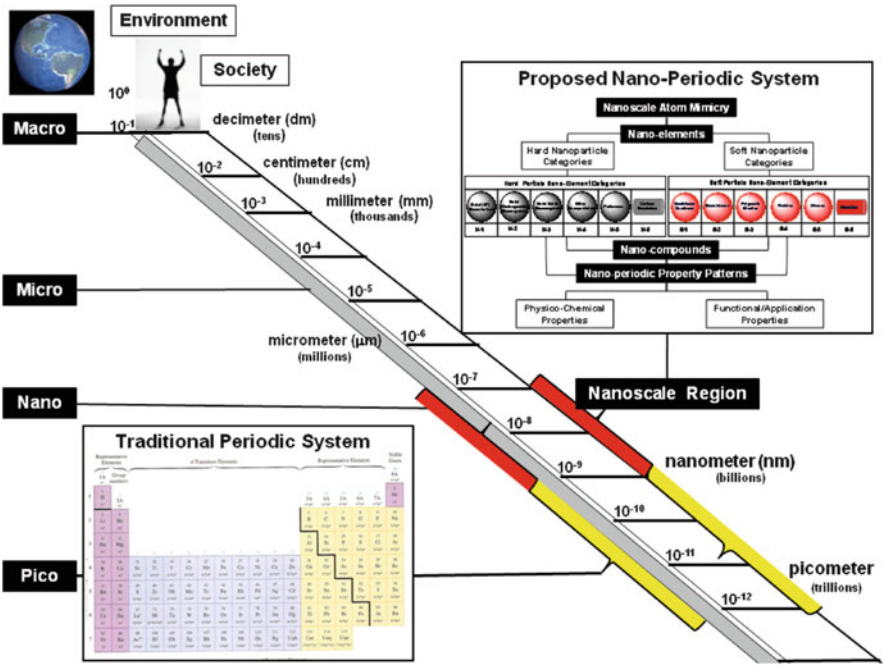


Fig. 17 Hierarchical dimensions influenced by the traditional elemental periodic system and the proposed nano-periodic system [138]

3. Exhibit well-defined stoichiometries (i.e., quantitative constants) and mass-combining ratios when reacting or assembling with each other
4. Exhibit discrete, nano-periodic property patterns as a function of one or more of their CNDPs (i.e., size, shape, surface chemistry, flexibility/rigidity, elemental composition, or architecture)

From this basic list of 12 nano-element categories, a nano-element road map leading to three combinatorial libraries of nanocompounds and nano-assemblies can be envisioned, namely, [hard-hard], [hard-soft], and [soft-soft] types as illustrated in Fig. 18. These nanocompounds and nano-assemblies can be characterized analytically by the proportion of each of these 12 basic nano-elements they contain, based on their discrete bonding/assembly capacities, valencies, stoichiometries, and mass-combining ratios. Many examples of these stoichiometric nanocompounds and assemblies are already documented in the literature and are described in more detail elsewhere [137, 138].

As described above, a fourth feature anticipated by this new nano-periodic system was the expectation that members of these hard and soft nano-elemental categories, as well as their nanocompounds and assemblies would be expected to manifest certain well-defined nano-periodic property patterns. These property patterns were expected to be dependent on one or more of their CNDPs. Just as atomic

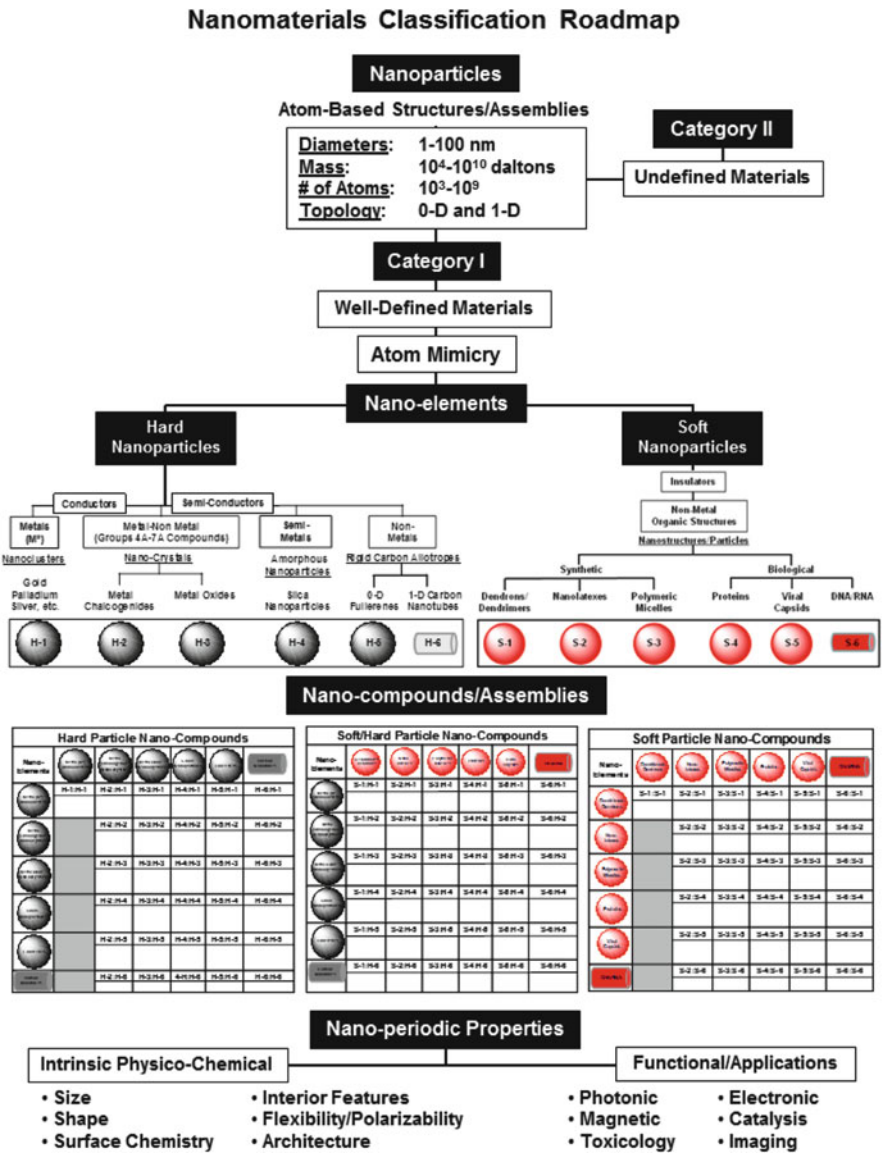


Fig. 18 Concept overview: Using first principles and step logic that led to the "central dogma" for traditional chemistry, the criteria of nanoscale atom mimicry was applied to category I-type, well-defined nanoparticles. This produced 12 proposed nano-element categories, which were classified into six hard particle and six soft particle nano-element categories. Chemically bonding or assembling these hard and soft nano-elements leads to hard:hard, soft:hard or soft:soft types of nanocompound categories, many of which have been reported in the literature . Based on the discrete, quantized features associated with the proposed nano-elements and their compounds, an abundance of nano-periodic property patterns related to their intrinsic physico-chemical and functional/application properties have been observed and reported in the literature [137]. Copyright: Springer

element periodic property patterns have been shown to be dependent on their intrinsic CADPs (Fig. 16) and are routinely utilized for predictive purposes in traditional small-molecule chemistry, it was hoped that similar relationships and behavior would be observed at the nanoscale level.

Recently, first steps toward the fulfillment of this expectation have been realized by publication of the first "Mendeleev-like nano-periodic tables" for predicting the self-assembly modes of soft nano-element modules. More specifically, the self-assembly properties of soft nano-elements such as amphiphilic dendrons (i.e., [S-1] nano-elements) were systematically investigated by Percec, Rosen and colleagues [151]. They reported a prediction accuracy for resulting self-assembled structures of 85–90% based on the a priori use of dendron CNDPs. These issues will be described later in Section 6.6.3.

6.3 Atom Mimicry: Nanoscale Superatoms and Atom Equivalents

6.3.1 Quantized Aufbau Components: Electrons, Atoms, and Monomer Units

The selection process for various category I-type, hard and soft particle nano-elements (Fig. 18) was based on certain heuristic or experimentally demonstrated atom mimicry features. Earlier general atom mimicry comparisons were made based on the similarity of core–shell architecture exhibited by atoms and dendrimers [10, 11]; however, more detailed working examples that include (inorganic) hard metal nanoclusters are as illustrated in Fig. 19. In descending order, analogous (i.e., heuristic) aufbau components (i.e., electron, Au atoms, and β-alanine monomer units) leading to core–shell picoscale (atoms) and nanoscale hard matter (Au nanoclusters) and soft matter (dendrimers), respectively, are compared. This comparison illustrates aufbau component mimicry and quantized features required to produce core–shell-type structures at two diverse hierarchical dimensional levels. Well-defined sizes, atomic/molecular masses, and outer-shell saturation values (n) are inextricably connected to specific electron shell, atom shell, or monomer shell (generation) levels in each case. Such atom mimicry is clearly demonstrated for hard nanoparticle gold clusters and soft nanoparticle dendrimers. Similar architectural motif patterns may be observed to a lesser or greater degree in the pervasive core–shell taxonomy observed for all proposed nano-element categories, as described elsewhere [137, 138].

Seminal work by Schmid [152, 153] and Rao [154] has shown that fundamental core–shell metal nanoclusters (i.e., Au and Pd) with magic numbers of metal atoms (i.e., 13, 55, 147, 309, 561, and 1,415) corresponding to closed atom shells 1, 2, 3, 4, 5, and 7, respectively, do indeed exist. As noted by Schmid, they are substantially more robust when ligand-stabilized [155]. Furthermore, they can be prepared

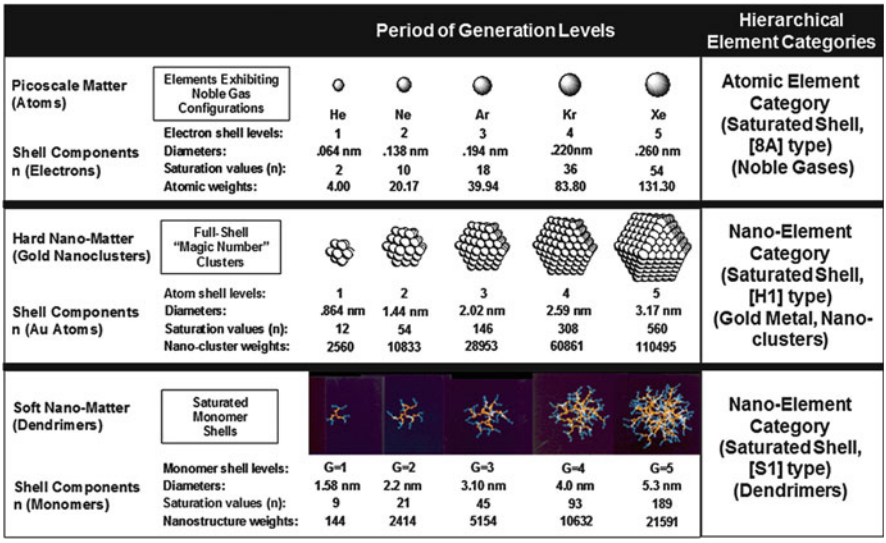


Fig. 19 Comparison of atomic picoscale particles, hard nanoparticles, and soft nanoparticles. Center image Hard Matter. Reprinted from [155] with permission from Elsevier

routinely as monodisperse modules by chemical means [152, 156–159]. Wilcoxon et al. [160] have shown that these closed, metal nanocluster, core–shell assemblies can be isolated, analyzed and characterized using high pressure liquid chromatography (HPLC) methodologies. It is also noteworthy, that these basic hard particle nanomodules exhibit pervasive nano-periodic self-assembly features by organizing into giant, self-similar core–shell nanocrystals that are invariant to scaling [154]. Similar nano-periodic, self-assembly properties have also been noted for soft nanoparticles such as dendrimers [46, 161, 162] and are described later in Sect. 6.6.3.

6.3.2 Heuristic Comparison of Autoreactive Surface Chemistry Associated with Unsaturated Outer Shells in Atomic Elements and in Dendrimers

Without the benefit of quantum mechanics or electronic theory, nineteenth century chemists determined that an atom's reactivity was associated with electron occupancy levels residing between the shell saturation levels that completed each period [134, 163, 164]. Furthermore, these elements combined with precise valencies and stoichiometries to give compounds with predictable combining mass ratios. As shown in Fig. 20, traditional chemistry recognizes that the noble gas configurations are associated with inertness due to their saturated outer electron shells. They do not exhibit any autoreactivity, unlike atomic elements penultimate to the noble gases that contain unsaturated outer electron shells. As such, halogen elements such as chlorine exhibit autoreactivity and exist as chlorine atom dimers. It should be noted in the far right column that ideal dendrimer structures (i.e., $G = 1$–5) possessing

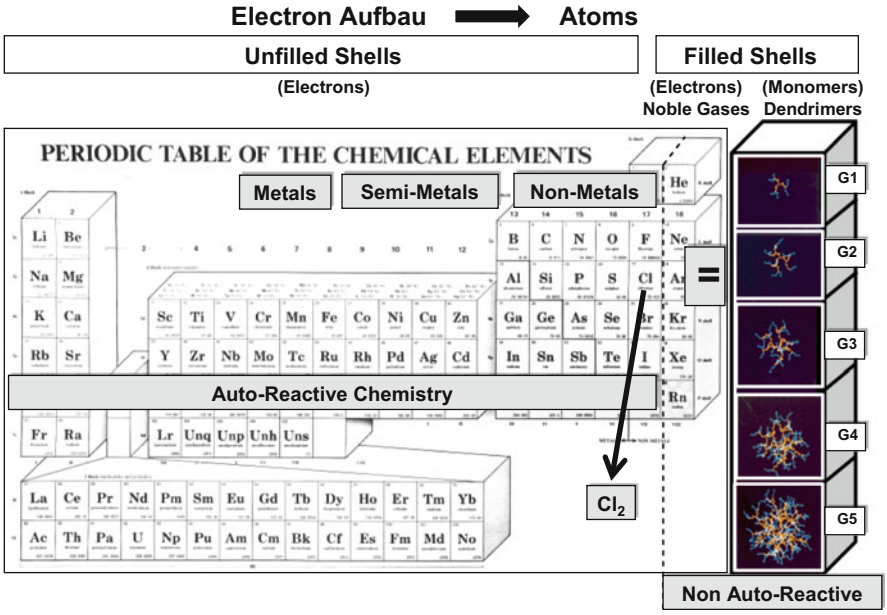


Fig. 20 Mendeleev periodic table, displaying horizontal autoreactive elements (i.e., chlorine dimer) in respective periods (1, 2, 3...) penultimate to the *vertical column* of non-autoreactive noble gases. *Far right column* displays ideal theoretical, shell-saturated PAMAM dendrimers ($G = 1, 2, 3,...$) as heuristic non-autoreactive nanoscale analogs of inert, noble gas elements. In the case where $G = 2$, shell-saturated dendrimer structure is equivalent to argon at the atomic level

saturated outer monomer shells are compared heuristically to the respective atomic element noble gases.

In a similar fashion, as illustrated in Fig. 21, dendrimers possessing an unfilled outer monomer shell are found to be very autoreactive and combine to form dimers, etc. reminiscent of halogens (or more specifically chlorine). As such, it should be apparent that the $G = 2$ dendrimer possessing an unsaturated outer monomer shell behaves as a superatom analogue of chlorine. This dendrimer species, possessing an unsaturated monomer shell penultimate to the saturated ideal dendrimer structure, may proceed to form a dimeric nanocompound (i.e., megamer) by interdendrimer reactions or simply by combining intramolecularly to produce a macrocyclic site. In contrast, so-called ideal dendrimers in the far right column are heuristically analogous to atomic-level inert gas configurations. These ideal, outer-shell-saturated dendrimers possess saturated outer shell level monomer values commensurate with mathematically defined shell saturation values, as described earlier (Fig. 11).

These saturated outer monomer shell dendrimers are not autoreactive with each other or reagents possessing common surface functionality (i.e., either nucleophilic or electrophilic moieties, respectively). In summary, as illustrated in Fig. 22, this outer shell autoreactivity has been observed not only with atomic elements but also

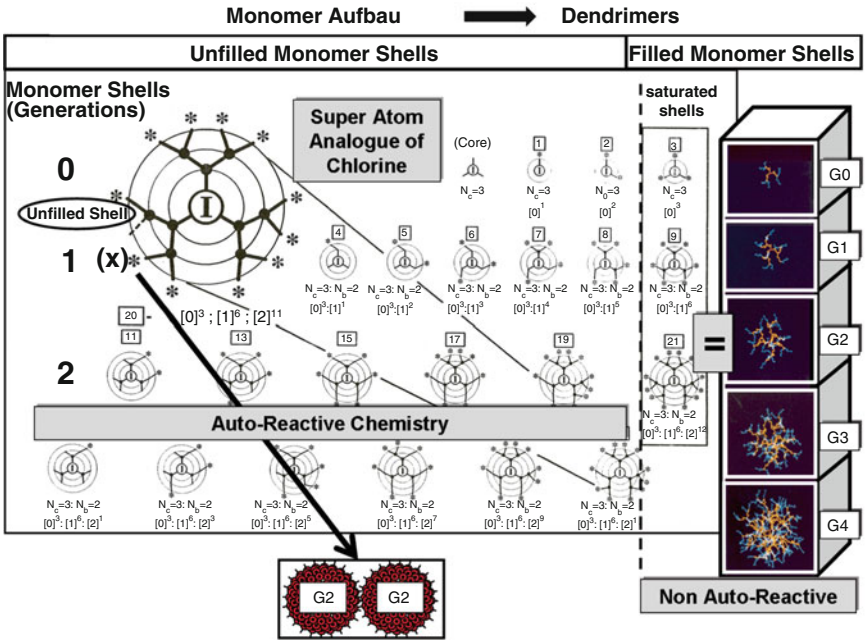


Fig. 21 Heuristic dendrimer-based periodic table based on monomer shell filling. Monomer aufbau stages (i.e., $G = 0$–4) mimic respective electron shell-filling stages in atoms. Autoreactive dendrimer species reside penultimate to the outer-shell-saturated *stick configurations* mimicking noble gas elements. These unfilled shell species are autoreactive, producing $G = 2$ dimers, wherein dendrimer species possessing 20 monomer units represent a "superatom" analog of elemental chlorine. The 21-monomer, shell-saturated analog is a $G = 2$ dendrimer mimicking argon. Molecular simulations of ideal, outer-shell-saturated dendrimer generations (i.e., $G = 0$–4) (*far right column*) are shown next to the core–shell (i.e. shell-saturated) *stick configurations*

with dendrimers [10, 11], as well as with their related core–shell (tecto)dendrimers [48, 165]. In the case of atomic elements (i.e., far left column) outer electron shell saturation is fulfilled by autoreaction to produce an elemental dimer. In the middle column, the penultimate dendrimer species to the saturated ideal dendrimer structure presents an isolated functional group (i.e., amine or ester) in the outer monomer shell that may react with a co-reactive functional group (i.e., amine or ester) on the surface of a neighboring dendrimer to give dimer formation [10, 11]. Therefore, these two nanoscale dendrimer scaffoldings that combined to form dimer appear to be heuristically mimicking elemental atoms and, as such, are individually referred to as "soft superatoms" [141]. As illustrated in Fig. 22, core–shell tecto(dendimers) were also observed to follow an analogous autoreactivity pattern associated with unsaturated outer dendrimer shells [48, 165].

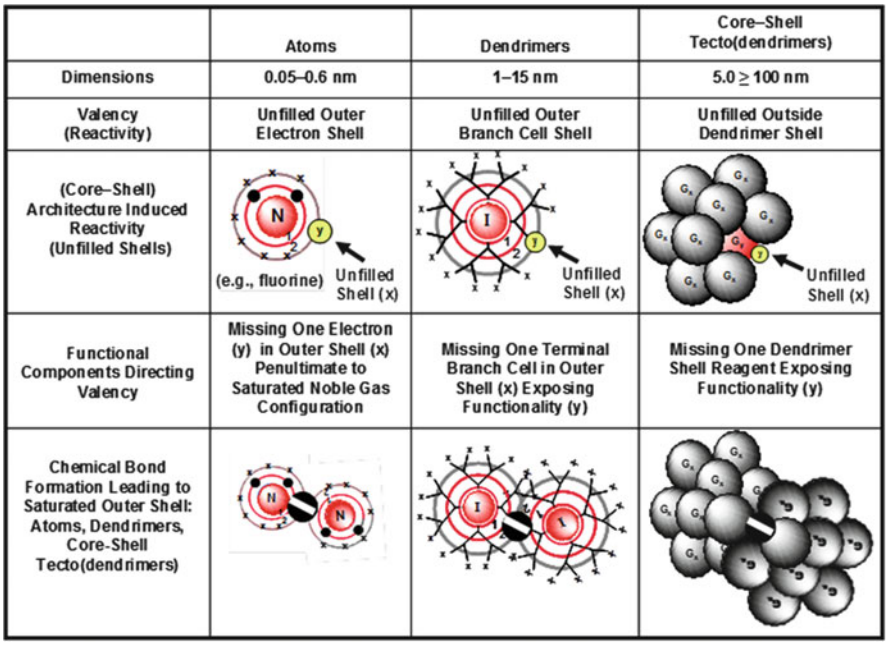


Fig. 22 Quantized module reactivity patterns at the subnanoscale level (i.e., atoms), lower nanoscale level (i.e., dendrimers), and higher nanoscale level, i.e., core–shell tecto(dendrimers) involving outer unsaturated electron, monomer, or dendrimer principle valence shells [137] Copyright: Springer

6.3.3 Heuristic Comparison of Valency and Symmetry Features Shared by Atoms and Spheroidal Nanomodules

At the picoscale level, valence shell electron pair repulsion (VSEPR) theory is a widely recognized theoretical model that proposes the geometric arrangement of terminal atoms or groups of atoms surrounding a central atom in a covalent compound or charged ion. The concept is based solely on the repulsion of the electron pairs present in the valence shell of the central atom. The premise of VSEPR is that the valence electron pairs surrounding an atom mutually repel each other and therefore adopt an arrangement that minimizes this repulsion. In essence, the utilization of space by the valence electrons surrounding the central atom is defined by these charge repulsion events and ultimately determines the shape and molecular geometry of the resulting bonded structure. The number of electron pairs surrounding an atom, both bonding and non-bonding, is called its steric number. VSEPR theory mainly involves predicting the arrangement of electron pairs surrounding one or more central atoms in a molecule that are bonded to two or more other atoms. The geometry of these central atoms in turn determines the ultimate architecture or shape of the structure [166], as shown in Fig. 23a.

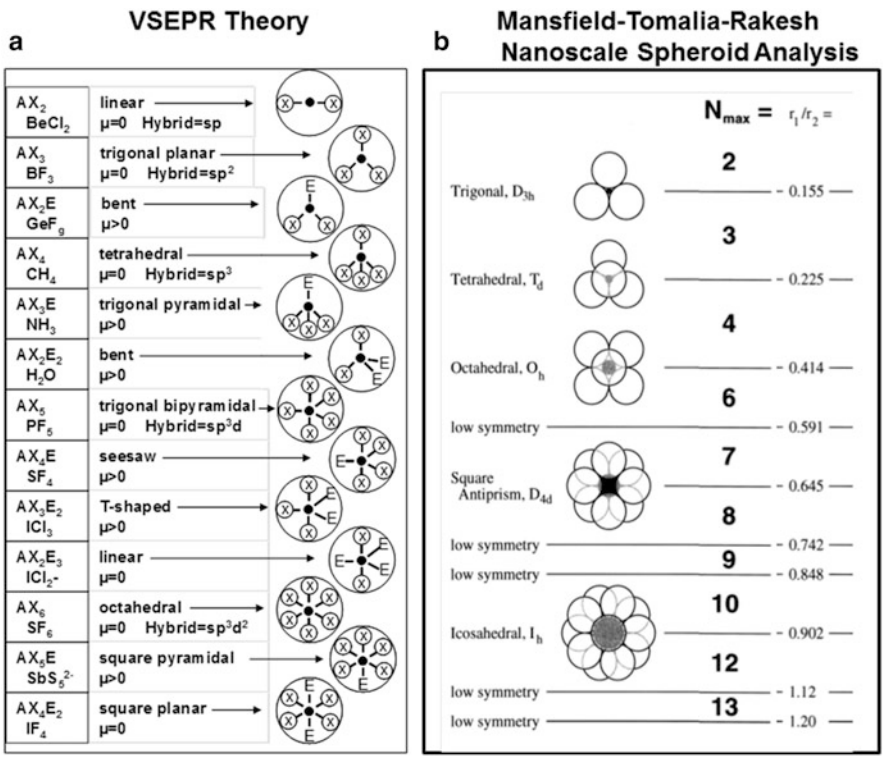


Fig. 23 Heuristic comparison of valency and symmetry features shared by (**a**) atoms [166] and (**b**) spheroidal nanomodules [121, 137, 167]. *VSEPR* valence shell electron pair repulsion [52]. Copyright: Cambridge University Press

For example, when two electron pairs surround the central atom, their mutual repulsion is minimal when they lie at opposite poles of the central sphere. Therefore, the central atom is predicted to adopt a linear geometry. If three electron pairs surround the central atom, their repulsion is minimized by placing them at the vertices of a triangle centered on the atom. Therefore, the predicted geometry is trigonal. Similarly, for four electron pairs, the optimal arrangement is tetrahedral, for five electron pairs it is trigonal bipyrimidal, for six electron pairs it is octahedral, etc., thus defining a wide range of defined symmetries and geometries, as illustrated in Fig. 23a. Essentially, all of these geometries are manifestations of core–shell (i.e. nucleus–electron) relationships, which yield reproducible geometries defining one of the important CADPs for atoms, namely shape. These features are in turn translated into shape-defining features, which are conserved in the resulting molecular structure. Now consider a similar analysis at the nanoscale level using the space-filling features of spheroids (Fig. 23b). At the nanoscale level, similar heuristic core–shell relationships have been analyzed mathematically using spheroids. More importantly, these relationships have also been demonstrated

experimentally using spherical dendrimers to produce core–shell tecto(dendrimers) and are described later (see Sects. 6.3.3 and 6.4.3).

Mathematically [167], these core–shell relationships have been analyzed as a function of the ratio of the core spheroid (r_1) and shell spheroid (r_2) radii [167], wherein the core spheroid size is systematic increased relative to the shell spheroid. Quite remarkably, this treatment produces many important symmetries and geometries that appear to mimic those observed for atoms at the picoscale level in the context of the VSEPR theory. For example, at an r_1/r_2 value of 0.155, a valence of 3 shell spheroids and a trigonal geometry (D_{3h}) is observed. At values for $r_1/r_2 = 0.255$–0.414, one observes a valency of 4 with tetrahedral (T_h) symmetry, and at $r_1/r_2 = 0.255$ one observes a valency of 8 with octahedral (O_h) symmetry (see also Sect. 6.4.3). In essence, these valencies and geometries represent space-saturated values around core atoms or core spheroids, respectively. These space saturation values around a core may be engineered by simply tuning the relative core and shell radii. This provides a powerful and useful strategy for defining valency for all surface-reactive spheroidal nano-objects. It can be seen that when the core reagent is small and the shell reagent is large, only a very limited number of shell-type reagents can be attached to saturate the space surrounding the core (i.e., $r_1/r_2 = 0.155$–1.20). Quite remarkably, when $r_1/r_2 = 1$, as would be the case for metal nanoclusters, a valency of 12 and an icosahedral (I_h) symmetry is observed (see Fig. 21 and Sect. 6.4.3). This is consistent for core–shell-type metal nanoclusters (i.e., gold nanoclusters), as reported by Schmidt et al. [152, 153] (Fig. 19). However, when $r_1/r_2 \geq 1.20$ more space surrounding the core allows the attachment of more spheroidal shell reagents p to discrete saturation values (N_{max}). This saturation value (N_{max}) is discrete and can be determined from the general expression described by the Mansfield–Tomalia–Rakesh equation [167] (described later in Sect. 6.4.3).

6.4 *Combining Soft and Hard Nano-element Categories to Create Combinatorial Libraries of Nanocompounds and Nano-assemblies*

6.4.1 Recent Literature Examples Fulfilling and Verifying Atom Mimicry and Superatom Behavior by Forming 3D Nanoscale Lattices, Nanocompounds, and Nano-assemblies Reminiscent of Atomic Elements

Very recently, important examples describing the chemical combination and assembly of these proposed hard and soft nano-element categories (i.e., superatoms) as described in Fig. 24 have now appeared in the literature and are referred to as "nanoscale atom mimicry" at the nanoscale. In each case, our early concept has been fulfilled and validated by these authors, who have referred to these nanoscale

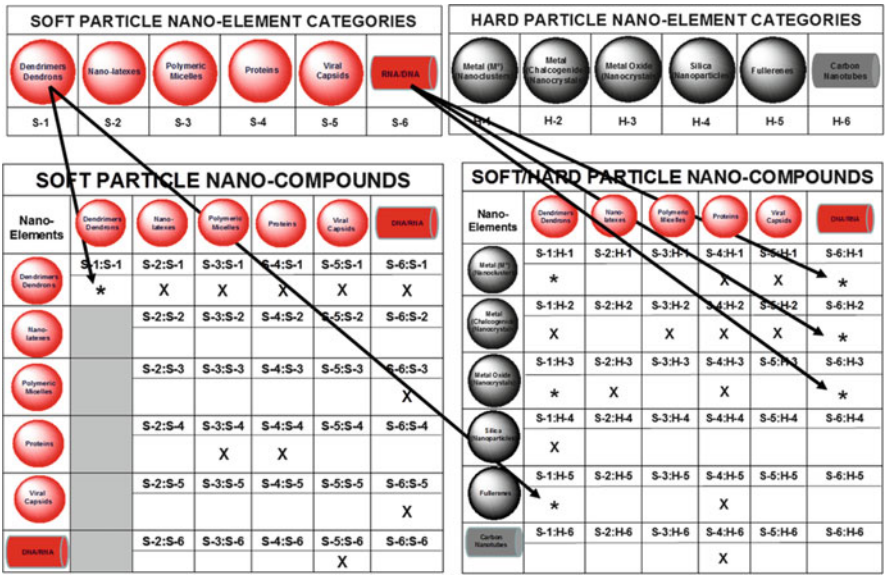


Fig. 24 Proposed hard and soft particle nano-element categories and combinatorial libraries of possible nanocompounds. Nanocompounds indicated by an *asterisk* are described in the text (Sect. 6.4). Nanocompounds indicated by *X* have been reported in the literature and described elsewhere [138]

building blocks as "atom equivalents" (i.e., Mirkin and coworkers [146]) or "nanoscale atoms" (i.e., Roy, Brus and coworkers [168]). In the first case, Mirkin and coworkers [146] have reported the assembly of metal nanoclusters [H-1], metal chalcogenide nanocrystals (quantum dots) [H-2], and metal oxide nanocrystals [H-3] using complementary DNA [S-6] to give [H-1:(S-6)*n*], [H-2:(S-6)*n*], or [H-3:(S-6)*n*] type 3D nanoscale unit cell lattices. Quite remarkably, these nanoscale unit cell lattices mimic inorganic salt lattices formed from atomic elements. In the second case, Roy et al. [168] have shown that by combining fullerene (C_{60}) [H-5] (i.e., 0.71 nm) with various metal chalcogenide nanocrystals [H-2] (i.e., 0.85–0.92 nm), a solid-state material is formed that they described as a "super atomic relative" of the cadmium iodide (CdI_2) structure type. Furthermore, they stated that the constituent clusters (i.e., [H-5] and [H-2]) interacted electronically to produce a magnetically ordered phase at low temperature, akin to atoms in a solid-state compound.

Both soft matter (organic) and hard matter (inorganic) categories of these quantized nanomodules have been proposed and referred to as soft and hard nano-element categories, respectively. These nano-element categories (see Figs. 18 and 24) were proposed on the basis of selection criteria and assumptions described elsewhere [137, 138]. Furthermore, these first 12 soft and hard nano-element categories, designated [S-*n*] and [H-*n*], respectively, have been reported to

form a wide range of soft particle and soft-hard particle nanocompounds and assemblies. Both the nano-elements and their nanocompounds are widely recognized to exhibit new emerging properties and nano-periodic property patterns [137, 138]. Leading references to these literature examples (designated by X in the combinatorial nanocompound library in Fig. 24) are described in greater detail elsewhere [137]. This account will focus only on several selected examples of nanocompound formation (designated by an asterisk in Fig. 24) that involve either chemical reactions or supramolecular, self-assembly interactions between dendrons/dendrimers and/or other nano-element categories. For example, self-assembling certain [S-1]-type amphiphilic dendrons, according to Percec and colleagues. [169], produces vast libraries of stoichiometric spherical or cylindrical supramolecular dendrimers $[S\text{-}1]_n$.

These assemblies may be viewed as nanocompounds/assemblies of the [S-1]-type nano-element category, much as S_8 is viewed to be a molecular compound of the atomic element sulfur. Combining dendrimers with other dendrimers has produced core–shell tecto(dendrimers), i.e., [S-1:(S-1)*n*]-type core–shell nanocompounds with well-defined stoichiometries. Similarly, covalent grafting of linear poly(ethyleneglycol)s produces discrete [S-1:(S-3)*n*]-type core–shell compounds . On the other hand, covalent attachment of fullerenes produced precise [S-1:(H-4)*n*]-type core–shell structures. Combining dendrimers with metal nanoclusters has produced a variety of unique, i.e., [(H-1)*n*:(S-1)] and [(S-1):(H-1)*n*], core–shell-type nanocompounds, as designated in Fig. 24. Specific literature examples of these proposed nanocompounds/assemblies will be described in the remaining sections of this review.

6.4.2 $(Dendrons)_n\ [S\text{-}1]_n$: Self-Assembly into Supramolecular Spherical or Cylindrical Dendrimer-Type Nanocompounds and Nano-assemblies

Perhaps some of the most compelling examples of precise stoichiometric [S-1]-type nano-assemblies are the enormous libraries of spherical and cylindrical supramolecular dendrimers (i.e., supramolecular megamers) reported by Percec and colleagues [151, 169, 170]. Percec's amphiphilic dendrons have been shown to exhibit heuristic atom mimicry features reminiscent of atomic elements, namely, precise mass-combining ratios and unique emerging properties. Just as atomic elements such as phosphorous and sulfur aggregate into discrete P_4 and S_8 clusters, respectively [171], so do appropriately functionalized Percec dendrons (Fig. 25). Whereas earlier Zimmerman-type dendron self-assemblies [172, 173] have generally involved small, single-digit aggregation numbers, many of Percec's dendrons self-assemble into supramolecular dendrimers requiring large double-digit aggregation numbers. For example, the number of dendrons leading to hollow, spherical supramolecular dendrimers involved aggregation numbers of 72–155 [170]. Recently, a remarkably large supramolecular dendrimer derived from

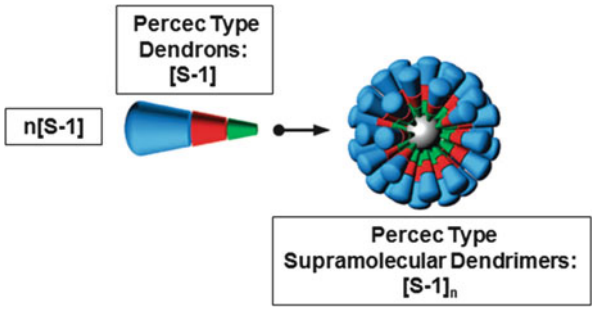


Fig. 25 Self-assembly of Percec-type amphiphilic dendrons (i.e., [S-1]-type nano-elements) into spherical supramolecular dendrimers (i.e., $[S\text{-}1]_n$, where n = discrete, stoichiometric aggregation number that ranges between 72 and 155 for various $[S\text{-}1]_n$-type stoichiometric nanocompounds and nano-assemblies) [170]. Copyright: 2008 American Chemical Society

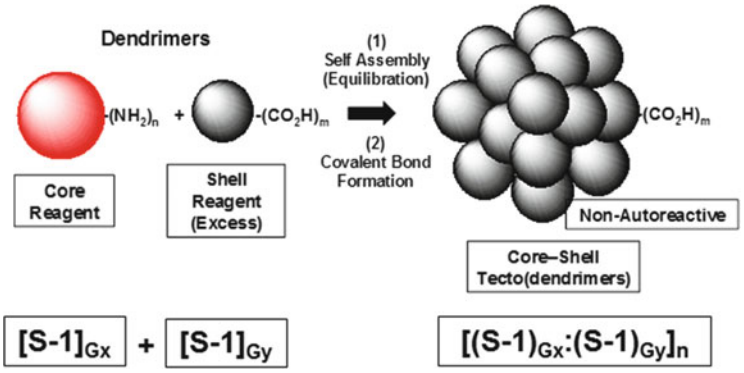


Fig. 26 The saturated-shell architecture approach to covalent megamer synthesis. All surface dendrimers are terminated with carboxylic acid [165]

(770)-dendrons (i.e., 1.73×10^6 g/mol) has been reported [151]. This giant supramolecular dendrimer completes a continuum that has been defined between small filled and large hollow dendrimers, all of which appear to be defined by the primary structure of the precursor dendrons.

6.4.3 Dendrimer$_{(G)}$-(Dendrimer$_{(G)}$)$_n$ [S-1$_{(G)}$:(S-1$_{(G)}$)$_n$] Core–Shell-Type Nanocompounds

Covalent, saturated-shell, nanocompounds (Fig. 26) can be prepared by a two-step approach involving, firstly, self-assembly of an excess of carboxylic acid-terminated dendrimers (i.e., shell reagent) around a limited amount of amine-terminated dendrimer (i.e., core reagent) in the presence of LiCl to form a

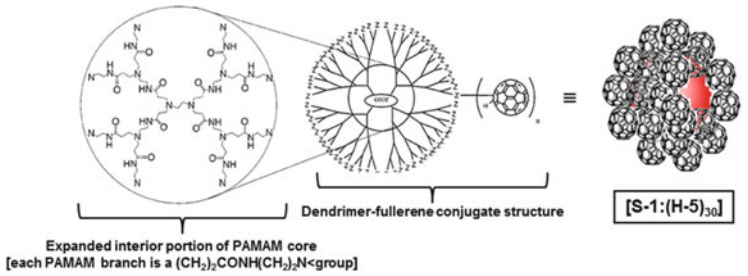


Fig. 27 Core–shell architecture of the PAMAM core:fullerene shell [S-1:(H-5)$_{30}$] type of nanocompound. *Z* indicates terminal –NH_2 or –NH– groups on the PAMAM dendrimer core component of the core–shell nanocompound [177]

charge-neutralized dendriplex. This was followed by covalent amide bond formation between the core and dendrimer shell reagents using a carbodiimide reagent [165, 174, 175]. The resulting nanocompounds are outer shell saturated, core–shell tecto(dendrimers). They have also been referred to as "covalent megamers" and are prime examples of precise polydendrimer cluster structures that are reminiscent of metal nanoclusters (Fig. 19). These structures may be mathematically predicted by the Mansfield–Tomalia–Rakesh equation [121, 167] (see Sect. 6.5.3) and have been unequivocally verified by experimental mass spectrometry, gel electrophoresis, and atomic force field microscopy (AFM) [121, 174–176].

6.4.4 Dendrimer-(Fullerene)$_n$ [S-1:(H-5)$_n$] Core–Shell-Type Nanocompounds

Covalent, stoichiometric [dendrimer core:fullerene shell] nanocompounds were readily formed by allowing a [core:1,2-diaminoethane];(4→2); {*dendri*-poly (amidoamine)-$(NH_2)_{64}$} ($G = 4$) PAMAM dendrimer to react with an excess of buckminsterfullerene (C_{60}) [177]. In the presence of an excess of C_{60}, only 30 C_{60} moieties bonded to the dendrimer surface to produce a well-defined, stoichiometric [dendrimer (core):fullerene (shell)$_n$] nanocompound, i.e., [S-1:(H-5)$_{30}$] core–shell-type as shown in Fig. 27. These structures were characterized extensively by MALDI-TOF, thermogravimetric analysis (TGA), UV–vis spectroscopy, and Fourier transform infrared (FTIR) spectroscopy. Such nanocompounds exhibited new fullerene-like solubility and photo-properties by readily generating singlet $^1O_2$ in either aqueous or organic solvents. However, they offered other unique features such as larger size and nanocontainer-type properties that would normally be associated with the dendrimer core interior.

6.5 *Nano-periodic Physico-Chemical Property Patterns*

6.5.1 Historical Picoscale, Atomic Element Periodic Patterns Contributing to Emergence of Mendeleev's Periodic Table

The emergence of Mendeleev's Periodic Table (1869) classifying the fundamental elemental building blocks of the universe, provided a central idea or dogma for a new science. Much like the axioms for geometry, Newtonian physics, and Darwinian biology, the area of traditional chemistry now had a central idea (dogma) upon which this discipline could be systematically defined, unified, and grown. However, history shows that many minor, yet important, documented periodic property patterns were required for the elements that ultimately contributed to the final consolidation and framework for Mendeelev's Periodic Table [178]. A small sampling of these well-known minor periodic element property patterns is given below:

- Elemental chemical and physical properties repeated in a series of periodic intervals as a function of atomic weight both horizontally and vertically [166]
- Valency in the early elements appeared to increase as a function of atomic weight
- Newland's "law of octaves" [134, 166]
- Dobereiner's "law of triads" [134, 166]
- De Chancourtois' "telluric screw," which demonstrated periodic property patterns that appeared to repeat or become similar after every 16 atomic weight units

In a similar fashion, analogous nano-periodic property patterns are accumulating. Many have been documented in the literature and are described briefly in Sect. 6.4.2. There is no doubt that collectively these nano-periodic property patterns will eventually evolve into a grand, encompassing framework that should be expected to define an ultimate version of a Mendeelev-like nano-periodic system. A small sampling of examples is presented in the following section.

6.5.2 Intrinsic Dendrimer-Based Periodic Patterns of Chemical Reactivity and Physical Size

Intrinsic viscosity [η] is a physical property (expressed in dL/g), which in essence is the ratio of volume to mass. As the generation number increases and transition occurs to a spherical shape, the volume of a spherical dendrimer increases in cubic fashion while its mass increases exponentially; hence, the value of [η] must decrease once a certain generation is reached. This prediction has now been confirmed for many different dendrimer families [9, 116, 179]. Because of this feature, the soft particle dendron/dendrimer-based, [S-1]-type nano-elements are unique macromolecules that exhibit completely different physico-chemical properties (i.e., nano-periodic property patterns) compared to compositionally

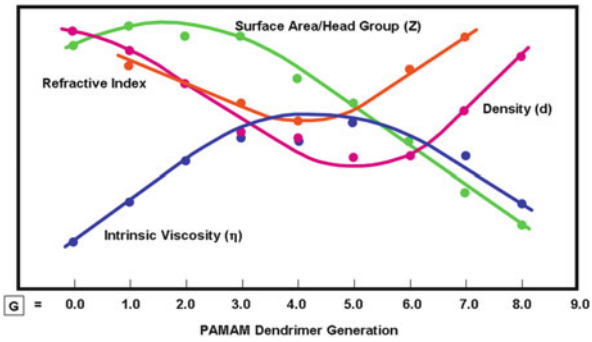


Fig. 28 Comparison of surface area per Z head group, refractive index, density (d) and viscosity (η) as a function of generation for $G = 1$–9 [9, 93]. Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission

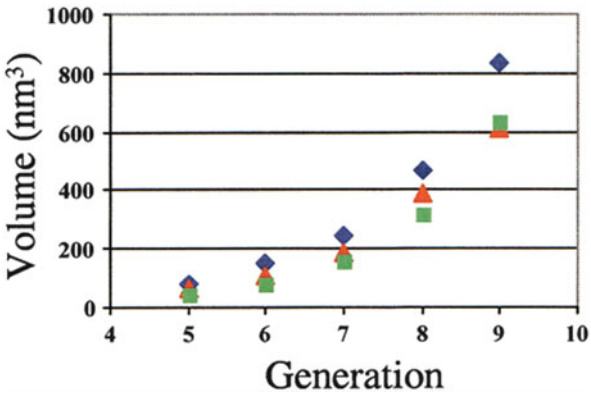


Fig. 29 Molecular volume of PAMAM dendrimers as a function of generation and pH. Dendrimer samples were deposited on mica from solutions of pH = 1 (*diamonds*) and pH = 6 (*triangles*). The *squares* depict the theoretical volumes for generations 5-9 based on known molecular weights and estimated densities [174]. Copyright: 2002 American Chemical Society

isomeric traditional linear, crosslinked, or branched polymers. This is largely due to the dendritic architecture that induces congestion properties. These properties emerge as a function of generational growth (Figs. 28 and 29) to produce unprecedented nano-periodic property patterns that are intrinsic and uniquely characteristic of dendrons and dendrimers.

Dendrimer-based intrinsic viscosities [η] initially increase in a classical fashion as a function of molar mass (i.e., generation), but dramatically decline beyond a critical generation due to a congestion-induced shape change. A dendrimer shape change occurs from an extended, compressible, floppy configuration in the early generations (i.e., $G = 0$–3) to more rigid globular shapes in the later generations (i.e., $G = 4$–10) (Fig. 28). In effect, for the Tomalia-type PAMAM series at critical generations (i.e., $G = 3$–4 and higher) the dendrimer acts more like an Einstein spheroid [9, 84, 114].

The dendrimer density z (atomic mass units per unit volume) clearly minimizes between generations 4 and 5. It then begins to increase as a function of generation due to the increasingly larger, exponential accumulation of surface groups. Since refractive indices are directly related to density parameters, their values minimize and parallel the above density relationship.

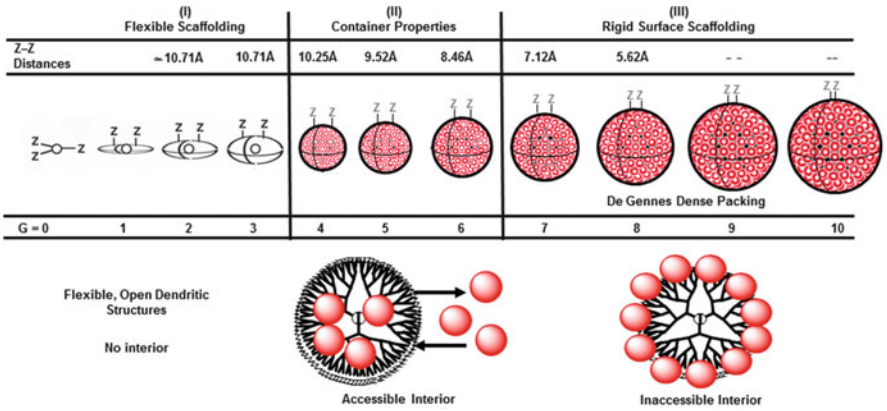


Fig. 30 Congestion-induced dendrimer shape changes (*I*, *II*, *III*) with development of nanocontainer properties for a family of [core:1,2-diaminoethane];(4→2); *dendri*-poly (amidoamine)–$(NH_2)_Z$} ($G = 0$–10) PAMAM dendrimers with core multiplicity $N_c = 4$ and branch cell multiplicity $N_b = 2$. Distances between Z surface groups are shown as a function of generation [138]

Plots of intrinsic viscosity [η], density (d), surface area per Z group (A_z) and refractive index as a function of generation clearly show intrinsic maxima or minima at $G = 3$–5 for this Tomalia-type PAMAM dendrimer series. These data corroborate computer-assisted molecular-simulation predictions [9, 180], as well as extensive photochemical probe experiments reported by Turro et al, and others [55, 105–108, 181].

Atomic force microscopy studies by Betley et al. [174] clearly demonstrated that dendrimers exhibit well-defined, monodispersed molecular volumes as a function of generation and pH, as shown in Fig. 29.

The dendrimer radius (r) is dependent on the branch cell segment length l, such that large l values delay congestion. On the other hand, larger N_c and N_b values and larger Z dimensions dramatically enhance congestion. These congestion properties are unique for each dendrimer family; wherein, N_c and N_b determine the generation levels within a family that will exhibit nano-encapsulation properties. Higher N_c and N_b values predict that lower generation levels will produce appropriate surface congestion properties, to manifest encapsulation features as shown in Fig. 30.

These congestion issues are consistently observed universally as periodic patterns characteristic of all dendrimer families including so-called giant redox active metallo-dendrimers recently reported by Astruc and coworkers [182].

6.5.3 Spheroidal Valency Defined by Nanosterics

Clearly, these fundamental dendrimer properties illustrate the unique and intrinsic nano-periodic property patterns manifested by this soft matter, [S-1]-type

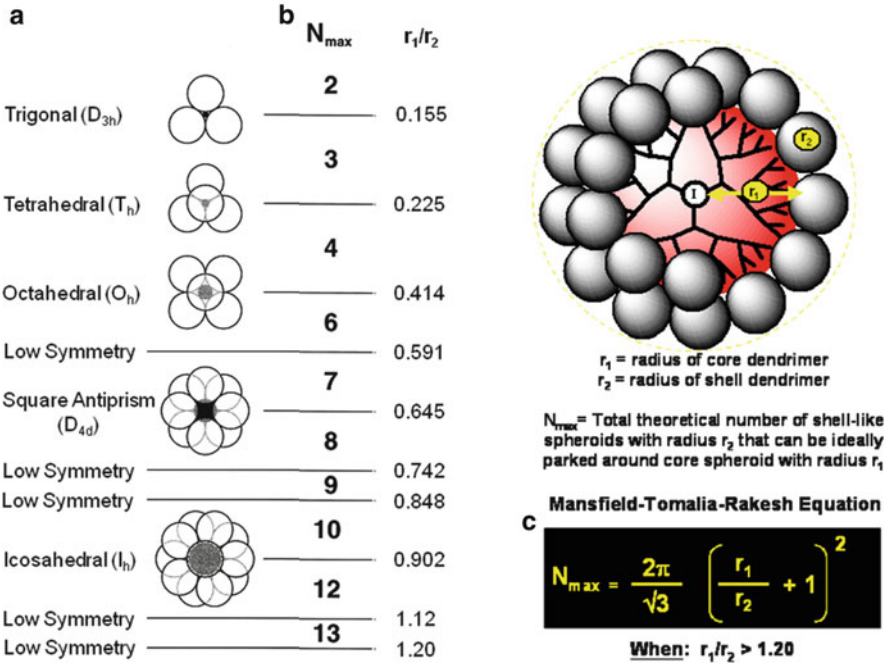


Fig. 31 (**a**) Symmetry properties of core–shell tecto(dendrimer) structures when $r_1/r_2 < 1.20$. (**b**) Sterically induced stoichiometry (SIS) defined shell capacities (N_{max}), based on the respective core and shell radii, when $r_1/r_2 < 1.20$. (**c**) Mansfield–Tomalia–Rakesh equation for calculating the maximum shell-filling value (capacity) (N_{max}), when $r_1/r_2 > 1.20$ [121, 138, 167]

nano-element category. Many other nano-periodic property patterns have been documented for the behavior, assembly, and reactions of dendrimers with other dendrimers, as well as with other well-defined nano-element categories. For example, work on this soft matter, [S-1]-type nano-element category [121, 167, 175] has demonstrated that mathematically defined, periodic size properties of spheroidal dendrimers can determine the chemical reactivity patterns with other dendrimers. These reactivity patterns, based on the relative sizes of a targeted dendrimer cores and dendrimer shell components, strongly influence the assembly of precise dendrimer clusters (i.e., core–shell (tecto)dendrimers). Mathematical relationships (i.e. the Mansfield–Tomalia–Rakesh equation) predict dendrimer cluster saturation levels (i.e., magic numbers for dendrimer shells) as a function of the core dendrimer size relative to the size of the shell dendrimers that are being used to construct the dendrimer cluster (Fig. 31) [167, 183]. These periodic property patterns and magic shell relationships are reminiscent of those observed for the self-assembly of [H-1]-type metal nanocrystals; wherein, the predicted number of touching spheroids for the first shell surrounding a central core metal atom is 12 when $r_1/r_2 = 1.00$. This is a well-known value (i.e., 12 atoms) for the first shell of all core–shell metal atom self-assemblies [152, 154, 156] (see Fig. 19).

6.6 *First Steps Towards a "Central Dogma" for Synthetic Nanochemistry: Dendrimer-Based Nanochemistry*

One of the highest priority challenges and barriers hindering continued progress of the international nanoscience technology movement is the absence of a "central paradigm and a Mendeleev-like periodic system" for unifying and defining nanoscience.

Historically, the development of such a central paradigm and systematic framework was absolutely critical for the seminal transformation in the early nineteenth century of an empirical alchemy movement to a systematic, highly predictable scientific discipline recognized as traditional small-molecule chemistry [134].

As described in this chapter and elsewhere, substantial progress has been made toward resolving this challenge by the introduction of a systematic, unifying framework based on the first principles of traditional chemistry [137, 138]. In review, this concept was inspired by the pervasive heuristic "atom mimicry" behavior observed for a broad range of monodisperse, well-defined nanoparticle categories [137, 138]. Ample evidence has now emerged that supports the premise that CADPs such as size, shape, surface chemistry, flexibility/rigidity, composition, and architecture may be conserved and translated hierarchically from the picoscale to the nanoscale level if suitable structure-controlled, bottom-up synthesis strategies are employed [137]. These conserved features were first observed with well-defined bottom-up structure-controlled, soft nanoparticles such as dendrons, dendrimers, and dendronized polymers [138, 151, 169]. An abundance of literature data has now shown that at least 12 categories of both soft and hard nano-elements (i.e., SNE, HNE) exhibit atom mimicry features and pervasive nano-periodic property patterns or trends related to their CNDPs. Hard and soft nanomodule categories (i.e., atom collections of 10^3–10^9 atoms) have been shown to behave heuristically like "nanosized superatoms" by exhibiting remarkably well-defined stoichiometries and mass-combining ratios to form covalent nanocompounds and non-bonding nano-assemblies. Furthermore, as predicted in the original concept paper [137] and described briefly in this chapter, both the hard and soft nano-element categories (designated [HNE-n] and [SNE-n]), as well as their resulting nanocompounds and assemblies appear to manifest both physico-chemical and functional/ application property trends reminiscent of Mendeleev-like property patterns normally associated with the atomic elements (Fig. 32).

We now examine recent progress reported by Percec, Rosen and colleagues [151] that has clearly demonstrated the first working examples of predictive, Mendeleev-like nano-periodic tables. These Percec nano-periodic tables clearly demonstrate a priori predictions for the mode of [S-1]-type amphiphilic dendron self-assembly into supramolecular dendrimers with 85–90% accuracy. Quite remarkably, as proposed in the original concept [137], these self-assembly modes may be accurately predicted based on simply knowing the CNDPs (size, shape, surface chemistry, and flexibility) for the amphiphilic dendron primary structure, as will be described in the next section.

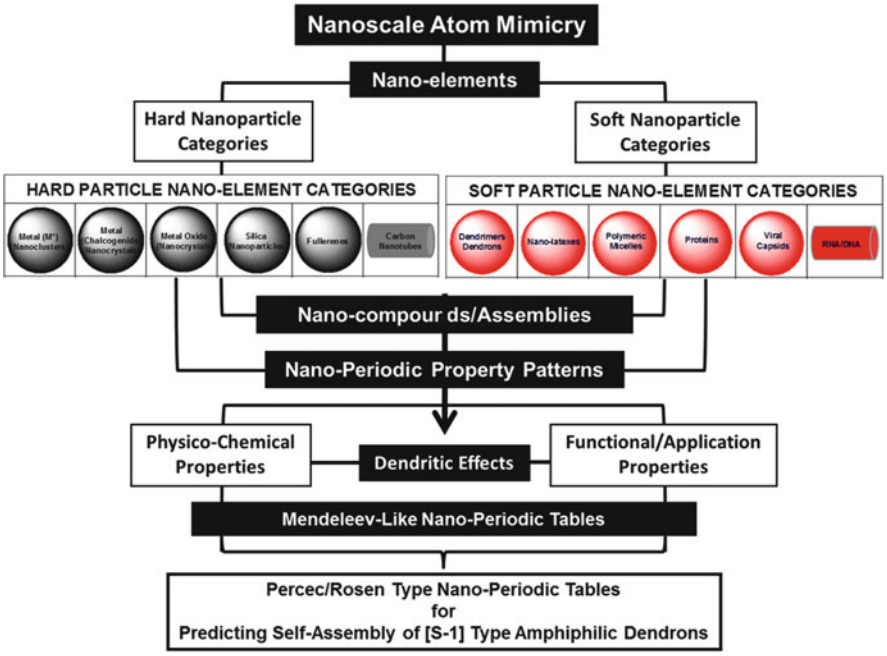


Fig. 32 The first examples of Mendeleev-like nano-periodic tables have recently fulfilled the predictions for expected nanoscale property patterns and trends [137, 138]. Percec and Rosen [151] have reported the first three nano-periodic tables for predicting the self-assembly patterns for [S-1]-type amphiphilic dendrons, with predictive accuracies of 85 to >90%, based on knowledge of the primary dendron CNDPs, namely, size, shape, surface/apex chemistry, and flexibility/rigidity [94].

6.6.1 Percec's Quest for Synthetic Mimicry of Biological Quasi-equivalence with [S-1]-Type Amphiphilic Dendrons

As early as 1992, Percec et al. [184] compared the similarity of supramolecular nanocylinders obtained from his amphiphilic dendrons with the supramolecular assembly of protein subunits to produce the cylindrical viral capsids that surround RNA in the tobacco mosaic virus (TMV). More recently, Percec [185] reviewed the historical inspiration provided by Klug's seminal Nobel work on the structure of TMV [186, 187]. Percec was able to show unequivocally that dendrons behave much like protein subunits to produce a rich variety of cylindrical and spherical supramolecular dendrimers that exhibit quasi-equivalency, much as noted in many viral capsids. Based on accelerated design strategies involving synthetic amphiphilic dendrons, Percec et al. [188–191] were able to demonstrate the quasi-equivalent mimicry of biological systems by using retrostructural analysis [191] of their periodic and quasi-periodic supramolecular dendrimer assemblies, as

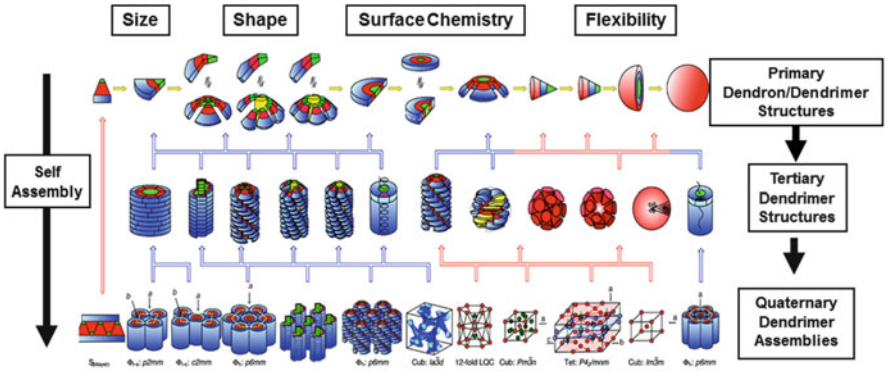


Fig. 33 Dependency of self-assembly patterns leading to tertiary and quaternary dendron assemblies on primary structure-controlled dendron CNDPs such as size, shape, surface/apex chemistry, and flexibility [151]. Copyright: 2009 American Chemical Society

outlined in Fig. 33. This remarkable comparison corroborates and documents many dendron libraries and other examples of dendron/dendrimer-based "protein mimicry" [192–194].

6.6.2 Tobacco Mosaic Virus as a Compelling Example of a Supramolecular Core–Shell Nanocompound [S-6:$(S\text{-}4)_{2130}$] Exhibiting Well-Defined Stoichiometry: Self-Assembly of an [S-4]-Type Protein Subunit Shell Around an [S-6]-Type ss-RNA Core

More than three decades ago, important stoichiometric, self-assembly relationships were noted by Klug [186, 187, 195] between the single-stranded (ss)-RNA core and the self-assembling protein subunits in the formation of tobacco mosaic viruses. The stoichiometric relationship between the viral core and the viral capsid was carefully documented by X-ray studies. This work rigorously demonstrated that exactly 2,130 protein subunits assembled to form a viral capsid shell around an ss-RNA core to produce tobacco mosaic virus of 18 nm diameter, 300 nm length, and helical symmetry. Elucidation of this self-assembly process together with the unprecedented characterization of this viral assembly by X-ray analysis garnered the Nobel Prize for A. Klug in 1982. In the context of the systematic nano-periodic concept [137], this viral construct may be viewed as a supramolecular, stoichiometric core–shell [S-6:$(S\text{-}4)_{2130}$]-type nano-assembly as described in Fig. 34.

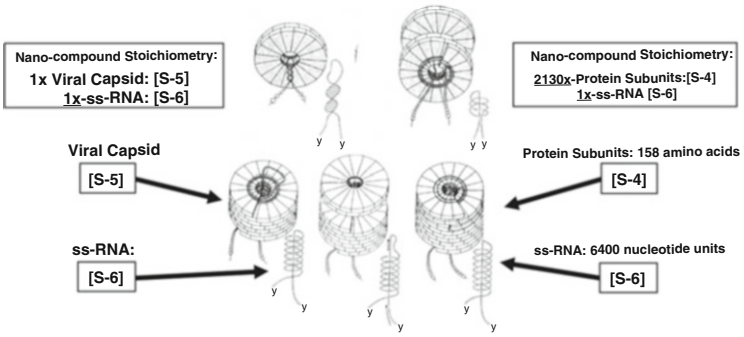


Fig. 34 Tobacco mosaic virus (TMV): an example of a well-defined nanocompound [S-6: $(S\text{-}4)_{2130}$] consisting of an ss-RNA (core) and protein subunits (shell), with nanoscale dimensions of 18 nm diameter and 300 nm length, and a helical symmetry [195, 206]. Reproduced with permission from the Society for General Microbiology

6.6.3 A Library of Amphiphilic Dendron Self-Assembly Directed by the CNDPs

Inspired by Klug's work on TMV, the Percec group synthesized and analyzed innumerable libraries of self-assembling amphiphilic dendrons [169]. For each library, the dendron primary structures were compared to the tertiary structures of the self-assembled supramolecular dendrimers and the quaternary structure of the crystal lattices. A sampling of these libraries reveals primary dendron structures derived from AB_2; 3,4-dendrons, AB_2; 3,5-dendrons, and AB_3; 3,4,5-dendrons, to mention a few [151]. A typical library for an AB_2; 3,4-disubstituted biphenyl dendron family is characterized as a function of dendron CNDPs such as generation (size), surface or apex chemistry, shape, and flexibility (as shown in Fig. 35). These analyses clearly showed that important dendron parameters such as (1) the molecular solid angle (α') of the dendron, (2) the morphology (shape) of the supramolecular dendrimer, and (3) the aggregation number (μ) (i.e. supramolecular dendrimer stoichiometry) varied in a predictive manner to reveal important self-assembly patterns as a function of dendron generation. It should be noted that very precise reproducible stoichiometries were observed for these dendron self-assemblies, as evidenced by their discrete aggregation numbers, namely, $[S\text{-}1]_n$ (Fig. 35).

For example, these library analyses revealed interesting patterns such as an increase in the generation number causes a change in molecular solid angle (α') and typically a transition from lamellar to columnar and spherical assemblies. Increasing the generation number does not necessarily increase the diameter of the supramolecular dendrimer, but generally reduces the aggregation number (μ) or number of dendrons required to form a supramolecular sphere or the cross-section of a supramolecular column. Deviations from these patterns usually indicate the formation of hollow core supramolecular dendrimers or other novel mechanisms of

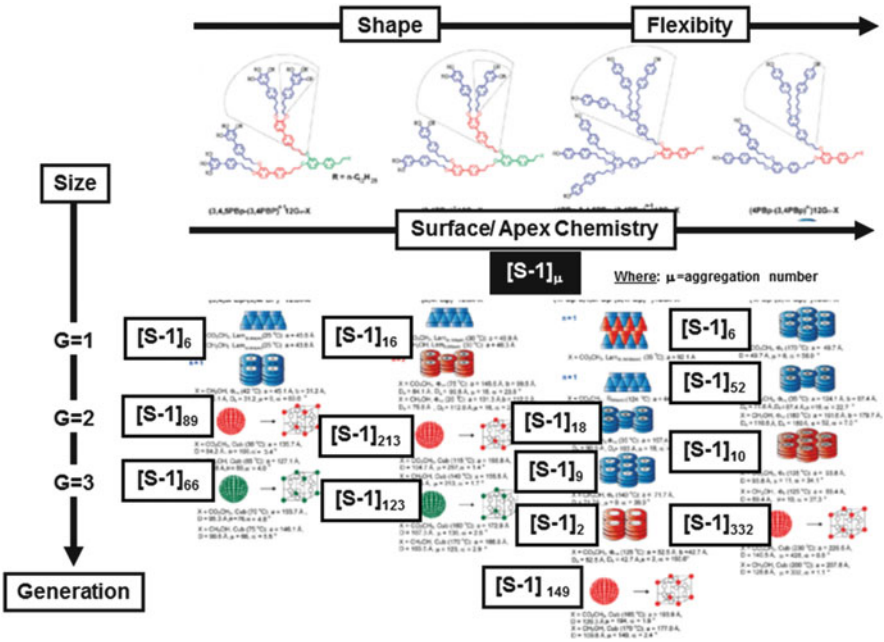


Fig. 35 Structural and retrostructural analysis of supramolecular dendrimers $[S\text{-}1]_{\mu}$ derived from the self-assembly library of AB_2; 3,4-disubstituted biphenyl type amphiphilic dendrons; [S-1] [151, 169]. Copyright: 2009 American Chemical Society

self-assembly. Generally, AB_3; 3,4,5-trisubstituted libraries exhibit more spherical structures as compared to AB_2; 3,4-disubstituted dendron libraries.

Furthermore, it was shown by Percec and coworkers [151] that simply by knowing the four CNDPs (size, shape, surface chemistry, and flexibility) of the primary dendron structure, one could predict self-assembly patterns leading to tertiary and quaternary structures with greater than 85–93% accuracy, as shown in Fig. 36.

6.6.4 First Nano-periodic Tables for Predicting Amphiphilic Dendron Self-Assembly to Supramolecular Dendrimers Based on the CNDPs

Like proteins, the primary structures of the amphiphilic dendrons determine their tertiary structure. As such, Percec has compared dozens of his AB_2- and AB_3-derived dendron libraries in an effort to determine trends or "nano-periodic self-assembly patterns" as proposed by others [137]. Percec's seminal comparison produced the first three Mendeleev-like, predictive nano-periodic tables for the self-assembly of aryl ether dendrons [151]. The first of these nano-periodic tables is shown in Fig. 36.

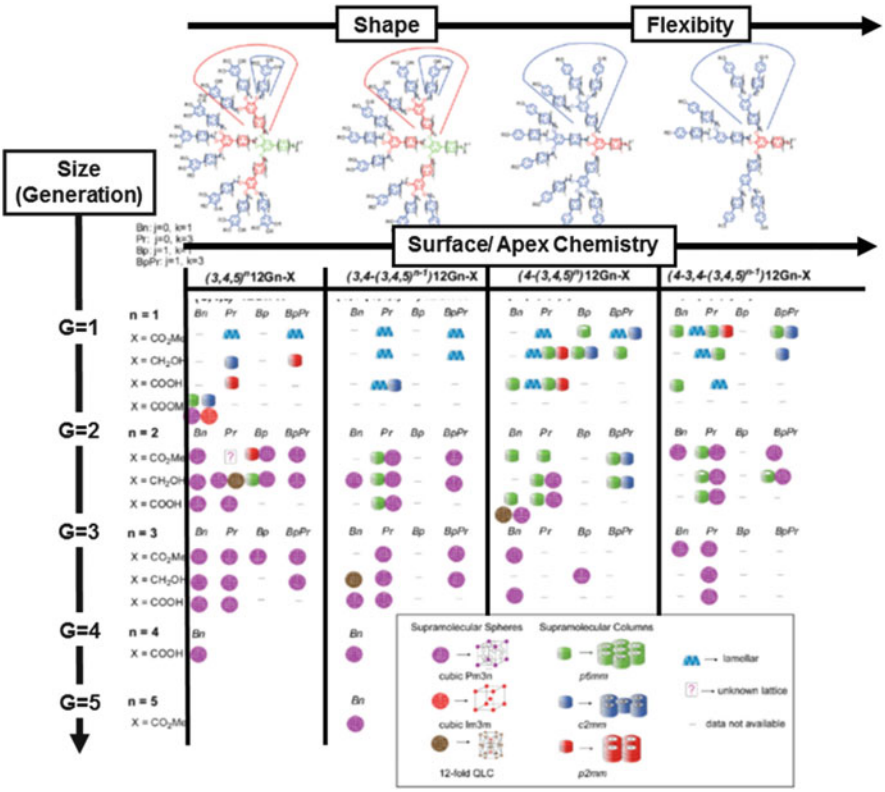


Fig. 36 Nano-periodic table I: Primary dendron structures [S-1] versus 3D supramolecular dendrimer structures $[S\text{-}1]_\mu$ for all libraries of AB_3 supramolecular dendrimers. *Bn* benzyl ether, *Pr* phenylpropylether, *Bp* biphenyl-4-methyl ether, *BpPr* biphenylpropyl ether [151]. Copyright: 2009 American Chemical Society

The three nano-periodic tables summarize the tertiary and quaternary structures that are formed for similar primary dendron structures, but using different dendron building blocks. They provide predictive nano-periodic tables that describe general trends in the sequence–structure relationship (i.e., primary → secondary → tertiary → quaternary structures). Furthermore, they identify clustered regions where specific structures will be found. The supramolecular dendrimer structures formed may be classified into lamellar, columnar, or spherical morphologies by analogy to β-sheets, helical structures of fibrillar proteins, and the pseudo-spherical structure of globular proteins. In all three nano-periodic tables, $G = 1$ dendrons behave similarly and exhibit a high proportion of lamellar and columnar structures, including hollow columnar structures.

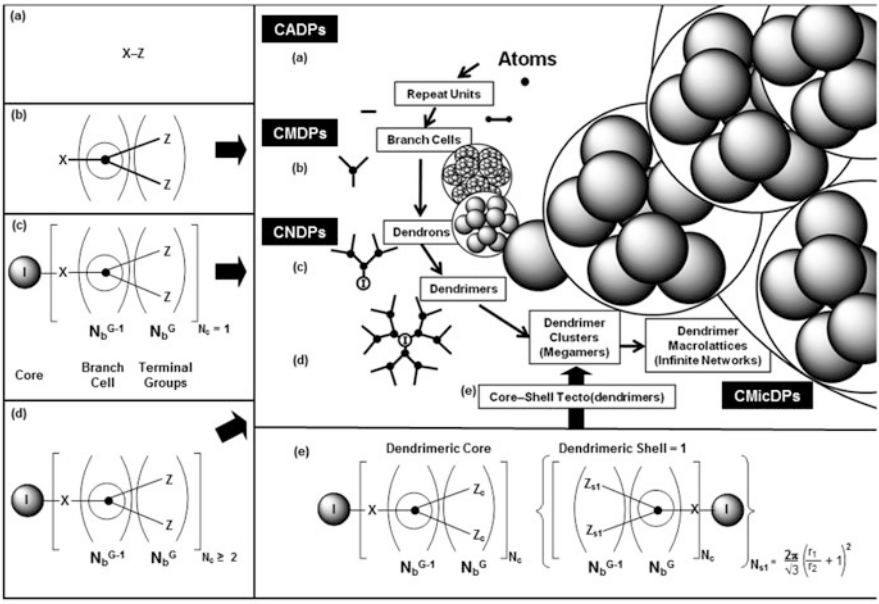


Fig. 37 Mathematically defined, bottom-up aufbau roadmap for constructing and transferring CADP → CMDPs to produce CNDP-conserved nanoscale [S-1]-type nano-element category complexity [94]

6.6.5 Aufbau Intermediates Involved in the Dimensional Enhancement of Soft Nano-element [S-1] Category Complexity

As stated earlier, the "central dogma" for traditional soft and hard matter chemistry emerged from the first initiatives of Lavoisier, Dalton, and others in the early nineteenth century. It was initially focused on the simple combinatorial bonding of atoms to form small molecules (i.e., monomers, branch cell monomers), much as illustrated in Fig. 37. Synthetic soft matter chemistry, initiated by Wöhler, witnessed steady progress throughout the nineteenth and twentieth century toward more complex molecular structures and architectures, including dendrons and dendrimers. The aufbau process for bottom-up construction of such well-defined soft matter, nano-element category [S-1]-type structures (i.e., dendrons and dendrimers) by covalent bonding and non-bonding supramolecular strategies is outlined in this section, as illustrated earlier in Scheme 3.

Essentially, all other proposed hard-soft nano-element categories (Fig. 18) evolve from aufbau strategies that allow the control and conservation of critical hierarchical design parameters (CHDPs) from the atomic to the nanoscale level (i.e., CADP → CMDP → CNDP). Nature has already evolved very exquisite aufbau strategies for synthesizing other important soft matter nano-element categories such as proteins [S-4], viral capsids [S-5], and DNA/RNA [S-6].

It is noteworthy, that an "aufbau roadmap" leading to the dendron/dendrimer soft nano-element category [S-1] can be mathematically defined from the atomic and small molecule dimensional levels. It is apparent that that this aufbau strategy is dependent on conserved CADPs and CMDPs to produce precise mathematically defined covalent structures such as linear and branch cell monomers (Fig. 37). When assembled according to well-defined divergent or convergent dendritic amplification principles, they produce precise mathematically defined covalent dendron, dendrimer, or core–shell tecto(dendrimer) structures (Fig. 26). Presumably, analogous mathematical relationships exist for Percec-type self-assembling dendrons to produce supramolecular dendrimers (as described in Fig. 25).

7 Conclusions

In summary, polymer science has progressed and advanced dramatically in the 60 years that have lapsed since Herman Staudinger was recognized for his revolutionary macromolecular hypothesis in 1953. Most notable, has been the enormous impact that Staudinger's paradigm has had on international commerce and enhancement of the human condition. This influence has been so substantial that the twentieth century has been referred to as the "plastic's century" [196]. The explosive activity during the twentieth century in the field of polymer science has been directly connected to the many important new emerging properties these materials have presented to society in such diverse areas as transportation, shelter, clothing, food, and healthcare, to mention a few. There is no doubt that these new properties were driven by emergence of the four major architecture classes, namely, (I) linear, (II) crosslinked, (III) branched, and (IV) dendritic polymers. Based on their macromolecular physico-chemical properties and low cost of production, the first three major macromolecular architectures (I–III) have constituted the bulk of all commercial polymer products used by society. Since feedstocks for these three early macromolecular architectures have been based primarily on non-renewable petroleum and fossil fuels, the impact of these materials has not been totally positive for society or the environment. As such, many new commercial polymer platforms have turned to renewable or biodegradable feedstocks and polymer compositions.

In contrast, the fourth major architectural class, namely, dendrimers/dendritic polymers have been found to be more suited for very important, but smaller volume, markets such as catalysis, electronics, diagnostics, protein mimics, and nanomedicine to mention a few. In that regard, using strictly abiotic methods, it has been widely demonstrated over the past decade that dendrimers [52, 55] can be routinely constructed with a control that rivals the structural regulation found in biological systems. The close scaling of size [123, 197], shape, and quasi-equivalency of surfaces [188, 189, 198] observed between nanoscale biostructures and various dendrimer families/generational levels are both striking and provocative [54, 123, 188, 189, 197–201]. These remarkable similarities suggest a broad

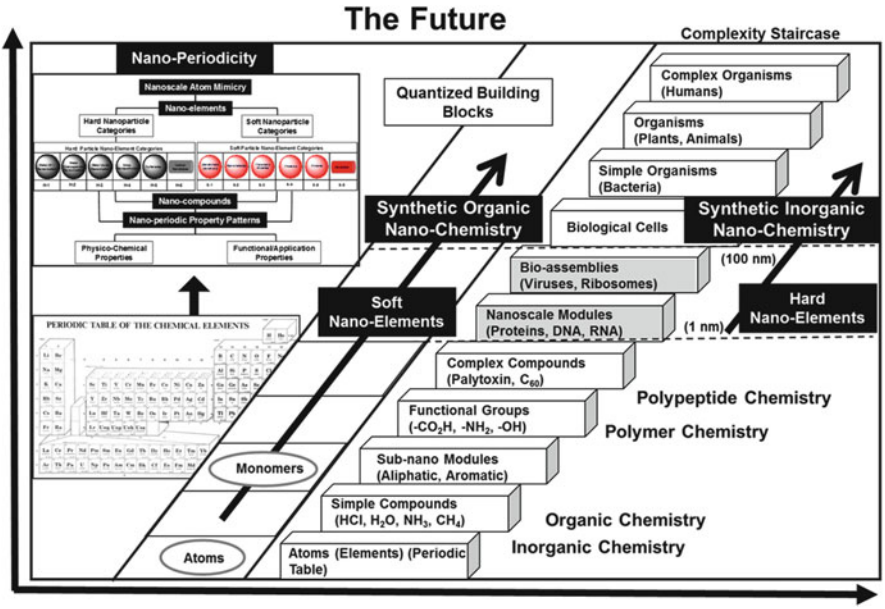


Fig. 38 Traditional scientific disciplines and the expected new nano-periodic system or framework and new scientific disciplines (i.e., synthetic organic and inorganic nanochemistry) as a function of the hierarchical building block [52]. Copyright: Cambridge University Press

strategy based on rational biomimicry as a means for creating a repertoire of structure-controlled, size- and shape-variable dendrimer assemblies. Successful demonstrations of such a biomimetic approach has proved it to be a versatile and powerful synthetic strategy for systematically accessing virtually any desired combination of size, shape, and surface chemistry in the nanoscale region. Future extensions will involve combinational variation of dendrimer module parameters such as families (interior compositions), surfaces, generational levels, or architectural shapes (i.e., spheroids, rods, etc.).

In conclusion, it is hoped that the remarkable features described for the dendritic state throughout this account will provide fresh new perspectives and positive expectations for continued growth in the field. There is enormous optimism for the emergence of entirely new, unprecedented properties and applications based on the hybridization of these quantized dendrimer nanosized building blocks with other similar quantized soft and hard nano-building blocks. Quite remarkably, convergence of the dendritic state with the world of nanoscience has already inspired a unique perspective and scientific window to a new concept and systematic framework for unifying and defining nanoscience [136–138]. Recent reports by Percec, Rosen and colleagues [151, 169] have provided the first steps toward fulfillment of this nano-periodic concept by predicting a priori nano-periodic self-assembly property patterns for dozens of amphiphilic dendrons. These Percec–Rosen tables are Mendeleev-like in that they have accurately predicted

nano-periodic property patterns for dendron self-assembly by simply using nano-periodic CNDP concept criteria. More recent work by chemists such as Mirkin and colleagues [146], Roy, Brus and colleagues [168] and physicists such as Khanna, Castleman and colleagues [143, 144, 202, 203], and others [204, 205] are fulfilling and validating the nano-periodic concept based on atom mimicry and nanoscale superatoms by documenting very sophisticated examples of hard/hard, hard/soft and soft/soft nanocompounds and nano-assemblies and their new properties. Continued progress in this area will undoubtedly lead to a deeper understanding of this proposed nano-periodic paradigm, which unifies both soft and hard nanomatter, as well as providing a more scientifically grounded basis for the emergence and future growth of two important scientific disciplines: stoichiometric synthetic organic nanochemistry and synthetic inorganic nanochemistry (Fig. 38).

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Helical Polymers for Efficient Enantiomer Separation

Yoshio Okamoto

Abstract The separation of enantiomers by high-performance liquid chromatography (HPLC) using the helical polymers mainly synthesized in my group over the past 40 years is described. In 1979, a one-handed helical poly(triphenylmethyl methacrylate) (PTrMA) was synthesized by asymmetric anionic polymerization. This is the first example of the asymmetric synthesis of a one-handed helical polymer, and the polymer exhibited an unexpected high chiral recognition to many racemates. A practically useful chiral stationary phase (CSP) for HPLC was developed by coating the polymer on silica gel. In 1982, the CSP was commercialized as the first chiral column based on a chiral polymer. Following this study, various helical polymers have been synthesized for use as CSPs by many researchers including ourselves and, in many cases, the helical structure of the polymers has played an important role in chiral recognition. In 1984, we found that cellulose trisphenylcarbamate coated on silica gel showed a very high chiral recognition and afforded a very useful CSP. Among the many phenylcarbamate derivatives of cellulose and amylose, the tris(3,5-dimethylphenylcarbamate)s show very attractive abilities. Today, these polysaccharide-based CSPs are most frequently used to analyze or preparatively separate chiral compounds.

Keywords 3,5-Dimethylphenylcarbamate · Chiral recognition · Chiral stationary phase · Enantioseparation · Helix

Y. Okamoto (✉)
Nagoya University, Furo-cho, Chikusa-ku, Nagoya 464-8603, Japan

Polymer Materials Research Center, Harbin Engineering University, Harbin, China
e-mail: okamoto@apchem.nagoya-u.ac.jp

Contents

1 Introduction 392
2 Enantiomer Separation by HPLC 393
3 Molecular-Type CSPs 393
4 Polymer-Type CSPs 395
5 Polymethacrylates 396
6 Polyacrylamides and Polymethacrylamides 398
7 Polyacetylenes 399
8 Poly(α-amino acids) and Polyamides 401
9 Other Synthetic Polymers 401
10 Natural Polymers and Their Derivatives 401
10.1 Cellulose Derivatives 402
10.2 Amylose Phenylcarbamates 404
10.3 Other Carbamate Derivatives of Cellulose and Amylose 405
10.4 Chiral Recognition Mechanism 406
10.5 Other Polysaccharide Derivatives 408
11 Recent Situation Regarding Chromatographic Chiral Separations 408
12 Preparative Separation 410
13 Concluding Remarks 410
References 411

1 Introduction

In 1848, Louis Pasteur succeeded in the first separation (resolution) of enantiomers by the direct crystallization of racemic sodium tartrate. He and coworkers also established other separation methods, including the crystallization of diastereomeric salts and the kinetic resolution of racemic hydrolyzable substrates using enantioselective biocatalysts such as enzymes. However, during his studies, it was impossible to perform the resolution of enantiomers by column chromatography because the chromatographic separation method had not yet been developed. The first baseline separation of enantiomers by liquid chromatography was attained for racemic amino acids using the ligand exchange method by Davankov in 1971 [1], and thereafter, many chiral stationary phases (CSP) for high-performance liquid chromatography (HPLC) have been developed [2, 3]. Today, this method of enantiomer separation has become very practical not only for analyzing chiral compounds, but also for obtaining pure enantiomers. The CSPs are classified into two categories. The first is molecular-type CSPs based on small molecules capable of chiral recognition and the second is polymer-type CSPs based on optically active polymers. Among more than one hundred commercially available CSPs, the polymer-type CSPs with a helical conformation are most frequently used [4–6]. This chapter mainly describes the polymer-type CSPs with helical structures developed in my group [7].

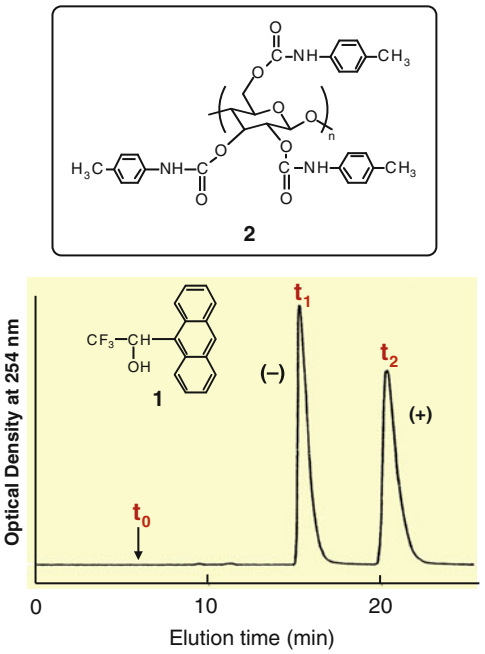


Fig. 1 Resolution of racemic alcohol **1** on cellulose tris-(4-methylphenylcarbamate) **2**

2 Enantiomer Separation by HPLC

Figure 1 shows the chromatogram of the HPLC resolution of a chiral alcohol **1** on cellulose tris(4-methylphenylcarbamate) (**2**) as a CSP. The enantiomers are completely resolved, showing elution times t_1 and t_2. The elution time (t_0) for a non-retained compound, 1,3,5-tri-tert-butylbenzene, is also shown. Based on this result, the retention factors, k_1 and k_2, are obtained as $k_1 = (t_1 - t_0)/t_0$ and $k_2 = (t_2 - t_0)/t_0$, and the separation factor α, which is correlated with the degree of chiral recognition, i.e., $k_2/k_1 = (t_2 - t_0)/(t_1 - t_0) = 1.48$. The separation factor α is correlated with the energy difference between the interactions of the enantiomers with CSP by $-RT\ln\alpha = \Delta(\Delta G)$ and this value is −0.24 kcal/mol when $\alpha = 1.48$. Usually, when $\alpha = 1.2$, it is sufficient for baseline separation, which corresponds to $\Delta(\Delta G) = -0.11$ kcal/mol. With a very small energy difference, complete separation of the enantiomers is attained.

3 Molecular-Type CSPs

Some typical molecular-type CSPs are shown in Fig. 2 [8]. Most CSPs are linked to silica gel. For chiral recognition, these CSPs employ various types of molecular interactions, such as coordination to metal ions, hydrogen bonding,

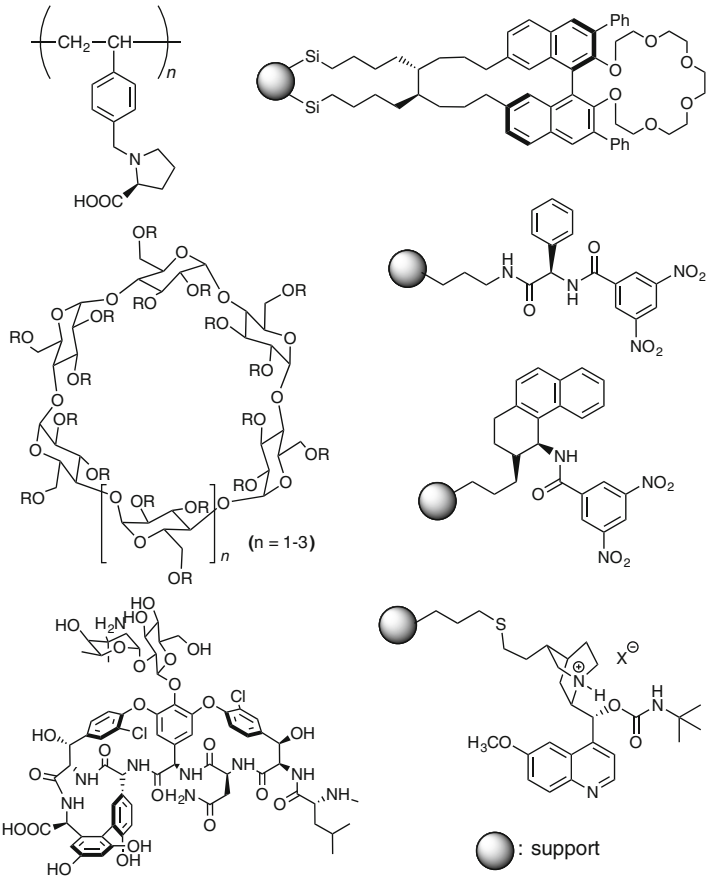


Fig. 2 Structures of molecule-type CSPs. Reprinted by permission from the American Chemical Society [8]

dipole–dipole interaction, charge-transfer interaction, π–π interaction, inclusion into cyclic compounds, and ionic interactions. The recognition of a CSP is usually similar to that of the chiral compounds used as a CSP. Therefore, the mechanism of chiral recognition on a CSP is often explained by the spectroscopic analysis of the interaction between the chiral compound and a racemate. In these CSPs, a very high recognition or α value can be obtained if a racemate or analyte fits to a CSP. On the other hand, one CSP can cover the separation of rather limited numbers of racemates, and sometimes the selection of a suitable CSP is not easy.

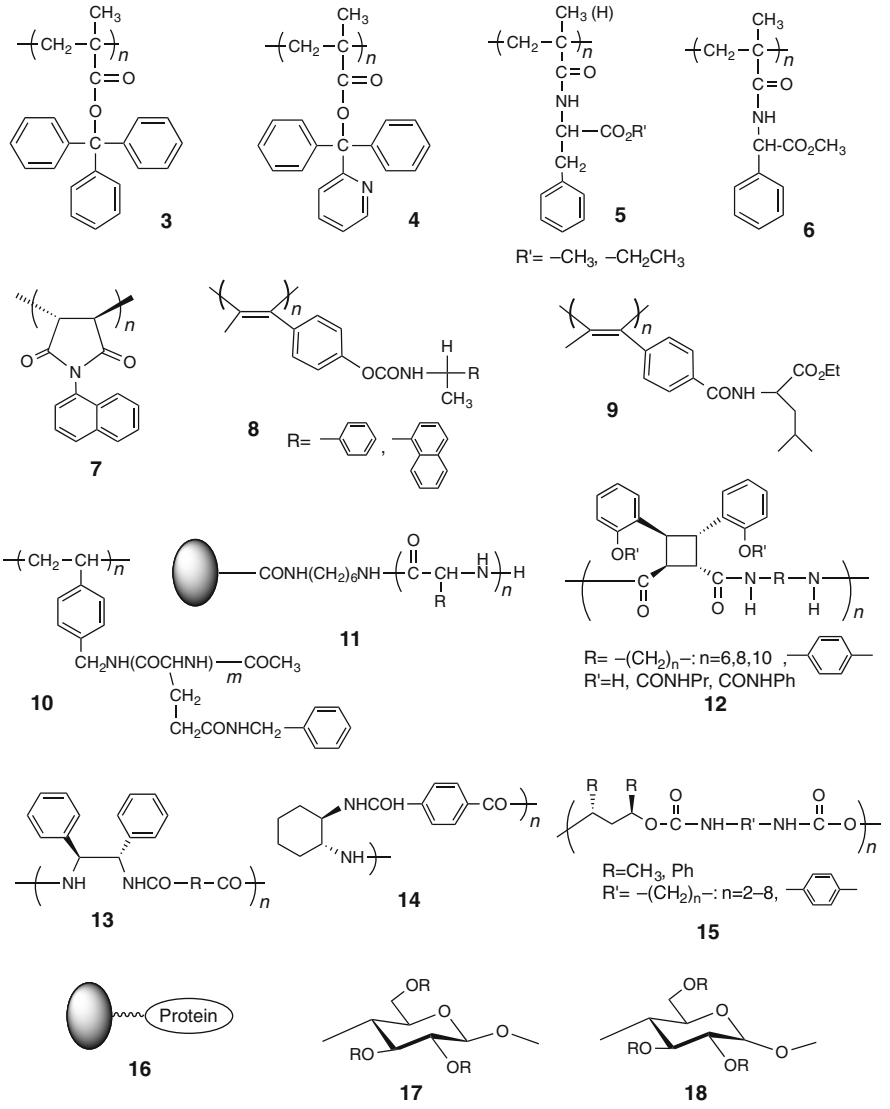


Fig. 3 Structures of polymer-type CSPs

4 Polymer-Type CSPs

Figure 3 shows examples of the polymer-type CSPs [4, 5, 8]. Various chiral polymers including polymethacrylates (**3**,**4**), poly[(meth)acrylamides] (**5**,**6**), polymaleimide (**7**), polyacetylenes (**8**,**9**), poly(α-amino acid) (**10**,**11**), polyamides (**12**–**14**), polyurethane (**15**), proteins (**16**), and polysaccharide derivatives (**17**,**18**) have been evaluated as CSPs.

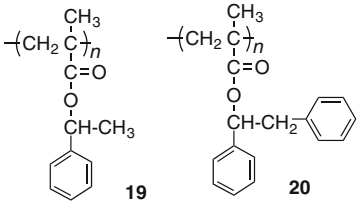


Fig. 4 Polymethacrylates **19** and **20** with chiral side chains

Chiral recognition of the polymer-type CSPs is often influenced by the higher-order structure of the polymers. Consequently, the stereoregularity of a polymer structure is an important factor in controlling the chiral recognition ability of the polymer-based CSPs.

5 Polymethacrylates

The polymethacrylates (**19**,**20** in Fig. 4) with optically active side chains, such as the 1-phenylethyl group or 1,2-diphenylethyl group, show very low chiral recognitions even with a high stereoregularity [9]. This result suggests that simple optically active polymethacrylates cannot be used as CSPs with a high chiral recognitions. On the other hand, one-handed helical polymethacrylates **3** and **4** exhibit much higher chiral recognitions.

Triphenylmethyl methacrylate (TrMA) is a unique monomer, which affords a highly isotactic polymer (PTrMA) even by a radical process, and the polymer with more than a 95% triad isotacticity can be obtained by the anionic polymerization with butyllithium (BuLi) [10]. In 1979, we found that optically active PTrMA is formed during the anionic polymerization of TrMA with the complex of (−)-sparteine-*n*-BuLi at −78°C (Fig. 5) [11, 12]. This is the first example of helix-sense-selective polymerization preferentially producing a stable one-handed helical polymer through the polymerization process. The results clearly indicated that the existence of a stable helical polymer even in solution is possible on a vinyl polymer without chiral side groups. The helical structure is maintained due to the steric hindrance of the bulky triphenylmethyl groups. Therefore, when the ester groups are hydrolyzed with an acid, the optical activity of the polymer disappears.

The polymerization of TrMA is more precisely controlled with chiral ligands (+)- and (−)-2,3-dimethoxy-1,4-bis(dimethylamino)butane (DDB) to give an almost completely one-handed helical polymer with a narrow molecular weight distribution (Fig. 6). An analogous helical polymer (PDPyMMA) can be obtained from diphenyl-2-pyridylmethyl methacrylate (DPyMMA) [13], but this polymer shows a helix–helix inversion when its molecular weight is low [14]. No helical polymer was obtained from the less bulky monomer, 1,1-diphenylethyl methacrylate (DPEMA) [15].

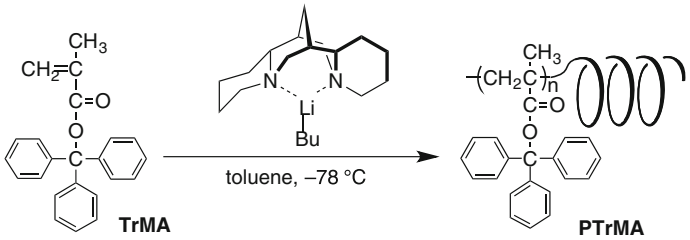


Fig. 5 Helix-sense-selective polymerization of triphenylmethyl methacrylate (TrMA) with (−)-sparteine-*n*-BuLi complex. Reprinted by permission from Chemical Society of Japan [5]

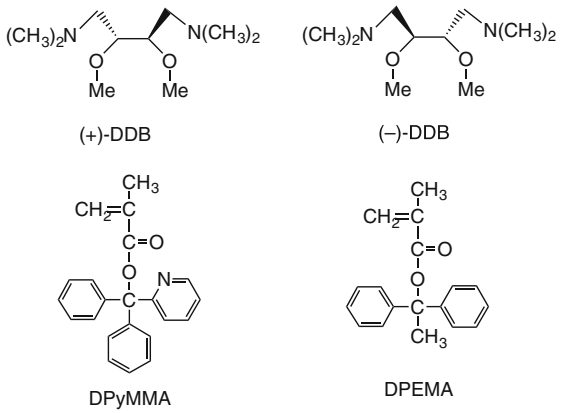


Fig. 6 Structures of (+)- and (−)-2,3-dimethoxy-1,4-bis(dimethylamino)butane (DDB), diphenyl-2-pyridylmethyl methacrylate (DPyMMA), and 1,1-diphenylethyl methacrylate (DPEMA)

The one-handed helical PTrMA exhibited an unexpected high chiral recognition when used as a CSP in liquid chromatography [16]. Because PTrMA with a degree of polymerization (DP) above 100 is insoluble in solvents, the polymer was ground into small particles and then packed into an HPLC column. The packed column could resolve many racemates using methanol as the eluent [17]. However, the column was unable to be used for a long time because the insoluble PTrMA was brittle and caused clogging of the end filter of the HPLC column. This defect was overcome by coating macroporous silica gel having rather large pores with a soluble PTrMA with a lower DP of ca. 50 [18]. The PTrMA adsorbed on the silica gel did not come off the silica gel and could be stably used as a CSP. In 1982, the column was commercialized as the first synthetic polymer-based chiral column, CHIRALPAC OT, from Daicel. The column could resolve many racemates, particularly stereochemically interesting aromatic compounds, as shown in Fig. 7.

One of the weak points of the PTrMA is the fact that the trityl ester is not strong enough and slowly solvolized in methanol, which is often used as the eluent in HPLC. The ability of the column gradually deteriorated and, therefore, it was requested that the methanol be completely replaced with hexane. The one-handed

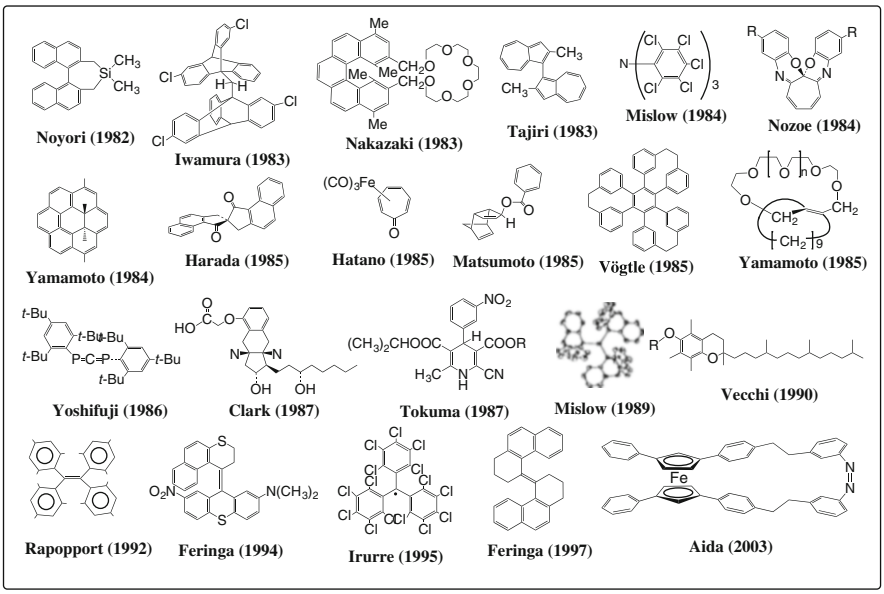


Fig. 7 Compounds resolved on poly(triphenylmethyl methacrylate) PTrMA column

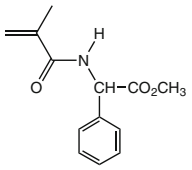
helical PDPyMMA also shows an analogous chiral recognition with a slightly higher durability against solvolysis by methanol [19].

6 Polyacrylamides and Polymethacrylamides

Blacshke and coworkers synthesized various poly(meth)acrylamide (**5**, **6**) gels through the radical copolymerization of (meth)acrylamides bearing optically active side groups, with ethylene diacrylate as a crosslinker, and used the gels for the resolution of many racemic pharmaceuticals by column chromatography [20]. The authors pointed out that the structure constructed during the polymerization plays a key role in the chiral recognition of the gels. Therefore, when the same chiral side groups were attached onto a poly(acryloyl chloride) gel, the obtained gel exhibited a much lower chiral recognition.

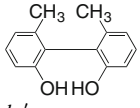
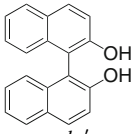
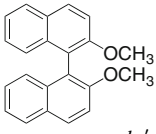
We synthesized chiral polymers with different tacticities by the radical polymerization of the optically active methacrylamide **21** (Fig. 8) in the absence and presence of a Lewis acid, $Yb(OTf)_3$ [21]. The polymerization without the Lewis acid at $-20°C$ afforded the syndiotactic polymer with a triad tacticity *mm*/*mr*/*rr* = ~0/13/87, whereas in the presence of the Lewis acid, the isotactic polymer with *mm*/*mr*/*rr* = 87/13/~0 was obtained. These two tactic polymers exhibited different chiral recognitions as the CSPs in HPLC, as shown in Table 1. The isotactic polymer could not resolve any of the three racemates, although two racemates were resolved on the highly syndiotactic polymer. In the isotactic

Fig. 8 Structure of methacrylamide **21**



21

Table 1 Enantioseparation of racemates on poly((R)-**21**)[a]

						
Tacticity (*mm*/*mr*/*rr*)	k_1'	α	k_1'	α	k_1'	α
~0/13/87	1.62 (+)	1.48	2.51 (−)	1.14	2.01 (−)	~1
6/29/65	1.22 (+)	1.31	2.32 (−)	~1	1.64 (−)	~1
87/13/~0	0.66 (+)	~1	2.26 (−)	~1	0.67 (−)	~1

[a]Flow-rate, 0.1 mL/min; column, 2.0 (internal diameter) × 250 mm; eluent, hexane/2-propanol (70:30). The signs in parentheses show the optical rotation of the first eluted enantiomer. Printed by permission from the Chemical Society of Japan [5]
k_1' retention factor, α separation factor

polymer, the polar amide groups may stay inside of the polymer chain due to helical conformation and cannot sufficiently interact with the racemates, as suggested by the smaller retention factors.

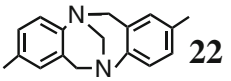
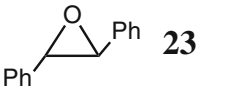
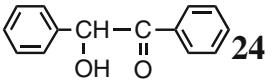
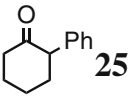
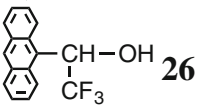
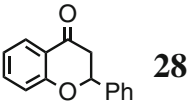
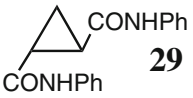
7 Polyacetylenes

Stereoregular polyacetylenes have been attracting great attention due to the characteristic features based on their helical structure and the conjugated main chain [22, 23]. The dynamic structure change in the helical polymers is particularly attractive. Stereoregular polyacetylenes with the *cis*-transoidal structure have been synthesized by rhodium catalysts from various acetylene derivatives.

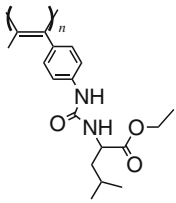
We synthesized the polyphenylacetylene derivatives **8** shown in Fig. 3 with a *cis*-transoidal structure as a CSP for HPLC [22]. The stereoregular **8** resolved several racemates including Tröger base derivatives and *trans*-stilbene oxide. We confirmed that polyphenylacetylene **8** with a stereoirregular main chain structure exhibited a very poor chiral recognition and could not resolve the above racemates, indicating that the main chain regularity is a key factor for having a high chiral recognition.

The important role of the helical structure of the polyphenylacetylene derivatives has also been confirmed for **9** (shown in Fig. 3), which has an amide linkage at the 4-position. This L-leucine-based CSP coated on silica gel could resolve all of the racemates **22**–**29** (Table 2) when the polymer was coated on silica gel from a methanol–chloroform (3:7) solution [23]. However, the CSP coated from

Table 2 Resolution of racemates **22**–**29** on polyphenylacetylene derivative **9**: influence of coating solvents on silica gel[a] [23]

	Coating solvents			
	MeOH/$CHCl_3$		THF	
Racemates	k_1'	α	k_1'	α
 **22**	0.33(+)	1.26	0.16(+)	~1
 **23**	0.31(+)	2.19	0.22(+)	1.24
 **24**	0.70(+)	1.25	1.55	1.00
 **25**	0.78(−)	1.13	0.29(−)	~1
 **26**	5.55(+)	1.15	3.84	1.00
$Co(acac)_3$ **27**	0.38	1.15	0.29(+)	~1
 **28**	0.85(−)	1.12	0.31	1.00
 **29**	0.87(+)	1.98	1.45	1.00

[a]Column, 0.20 (internal diameter) × 25 cm; eluent, hexane-2-propanol (95/5). The signs in parentheses show the optical rotation of the first eluted enantiomer
k_1' retention factor, α separation factor



30

Fig. 9 Structure of polyphenylacetylene derivative **30**

a THF solution showed a much lower recognition. This big difference is ascribed to the different polymer structures, depending on the solvents. The role of the amide linkage between L-leucine and the phenyl group is also important, because the derivative **30** (Fig. 9) with a urea linkage showed a very poor resolution ability, even if the CSPs were prepared under various conditions.

Several optically active polyacetylenes have also been evaluated as solid membranes for separating enantiomers [24].

8 Poly(α-amino acids) and Polyamides

Poly(α-amino acid)s (**10** and **11** in Fig. 3) are expected to show attractive chiral recognition due to their helical conformation. However, so far, a high chiral recognition has not yet been reported [25]. Saigo and coworkers reported optically active polyamides (**12** and **13** in Fig. 3) with attractive structures [26, 27]. These CSPs can separate polar compounds using hydrogen bonding as the main interaction. The chiral recognition ability of **12** clearly depends on the number of methylene groups, and an odd–even effect was observed. Compound **12** with an even number of methylene groups showed a higher recognition. We then synthesized a polyamide **14** derived from (−)-1,2-*trans*-diaminocyclohexane [28]. The polyamide **14** with the 1,4-phenylene residue showed a better chiral recognition than the polyamides derived from the same diamine and α,ω-dicarboxylic acids, HOOC-$(CH_2)_n$-COOH.

9 Other Synthetic Polymers

The N-substituted maleimide derivative (**7** in Fig. 3) is the monomer that can produce an optically active polymer by asymmetric polymerization with chiral initiators such as (−)-sparteine-*n*-BuLi [29]. The monomeric unit of the polymer is chiral if the polymerization proceeds in *trans*-addition by predominantly forming either an (*R*,*R*) or (*S*,*S*) center. The polymer **7** with a high optical activity exhibits a chiral recognition [30].

Various optically active polyurethanes **15** were also synthesized from chiral diols and various diisocyanates to be used as CSPs [31]. The polyurethanes derived from aliphatic diisocyanates show better chiral recognitions than those from aromatic diisocyanate.

10 Natural Polymers and Their Derivatives

Some enzymes are well known to show high chiral recognitions and have been used as asymmetric catalysts in organic synthesis. A few proteins, such as bovine serum albumin, α_1-acid glycoprotein, and ovomucoid, have also been used as CSPs for HPLC [32–34]. These CSPs can resolve many chiral drugs. Protein-based CSPs are often not stable because they change their conformation depending on the conditions such as solvents and temperature. The proteins contain many different

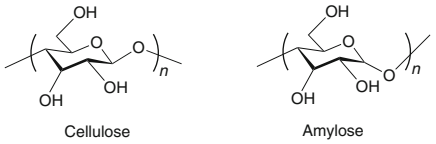


Fig. 10 Structures of cellulose and amylose

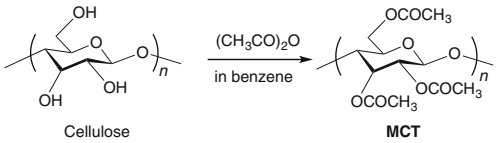


Fig. 11 Synthesis of microcrystalline cellulose triacetate (MCT)

adsorbing sites and the contents of the effective sites may not be high, which means that the CSPs are not suitable for the preparative separation of racemates. These are the weak points of the protein-based CSPs.

Polysaccharides, such as cellulose and amylose (Fig. 10), are the most abundant polymers on the earth and are known to have a chiral recognition ability. In 1951, Kotake resolved some amino acid derivatives by paper chromatography [35]. However, their abilities and mechanical properties are not adequate for use as CSPs in HPLC. Fortunately, polysaccharides are readily modified to esters and carbamates by the reaction with acid chlorides and isocyanates, respectively, and these derivatives show very attractive chiral recognitions based on their helical conformations.

10.1 Cellulose Derivatives

10.1.1 Cellulose Esters

In 1973, Hesse and Hagel reported an interesting cellulose ester, "microcrystalline cellulose triacetate" (MCT, Fig. 11), which was synthesized under heterogeneous conditions without dissolving the product in order to maintain the crystalline structure based on the natural cellulose [36]. MCT can resolve many compounds, particularly aromatic compounds (Fig. 12). The chiral recognition sites derived by the crystalline structure of the native cellulose can discriminate these racemates. This chiral recognition of MCT is significantly changed by the dissolution of MCT in a solvent, as pointed out by Hesse. For instance, the Tröger base (**22** in Table 2) is completely resolved on the MCT, whereas on the CSP coated on silica gel from a MCT solution, the Tröger base is poorly resolved with the reversed elution order of enantiomers. This result clearly indicates that the higher order structure of the polymers is important for efficient chiral recognition.

Cellulose derivatives alone are rather difficult to use as CSPs in HPLC because the derivatives do not have sufficient strength for high compression during HPLC. This defect can be overcome by coating them on macroporous silica gel. In 1984, Daicel and my group also found that cellulose benzoate coated on silica gel affords an attractive CSP [37, 38], and the ability as a CSP is much improved by

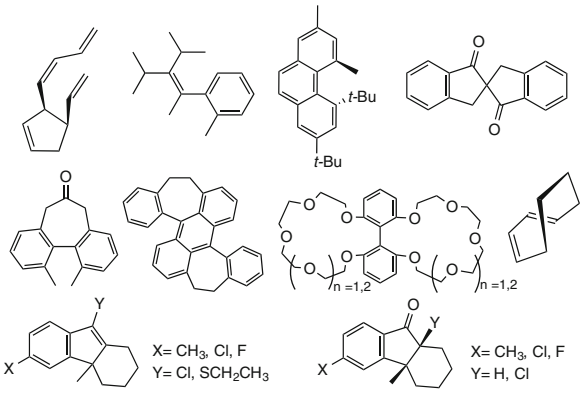
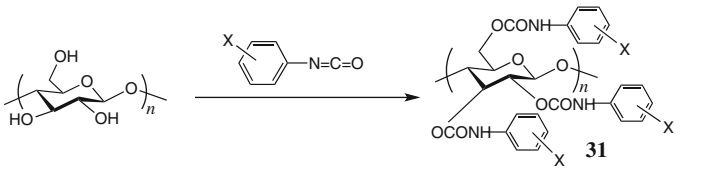


Fig. 12 Compounds resolved on microcrystalline cellulose triacetate. Reprinted by permission from Chemical Society of Japan [5]



X =

a:	H	**l:**	4-Ph_3C	**w:**	3,4-$(CH_3)_2$	**ah:**	2-Cl-6-CH_3
b:	4-CH_3	**m:**	4-F	**x:**	3,5-$(CH_3)_2$	**ai:**	3-Cl-2-CH_3
c:	4-C_2H_5	**n:**	4-Cl	**y:**	2,6-$(CH_3)_2$	**aj:**	3-Cl-4-CH_3
d:	4-$(CH_3)_2CH$	**o:**	2-Cl	**z:**	3,4,5-$(CH_3)_3$	**ak:**	4-Cl-2-CH_3
e:	4-$(CH_3)_3C$	**p:**	3-Cl	**aa:**	3,5-Cl_2	**al:**	4-Cl-3-CH_3
f:	4-CH_3O	**q:**	4-Br	**ab:**	3,4-Cl_2	**am:**	3-F-4-CH_3
g:	4-C_2H_5O	**r:**	4-I	**ac:**	2,6-Cl_2	**an:**	4-F-3-CH_3
h:	4-$(CH_3)_2CHO$	**s:**	4-CF_3	**ad:**	3,5-F_2	**ao:**	5-F-2-CH_3
i:	4-PhO	**t:**	4-NO_2	**ae:**	3,5-$(CF_3)_2$	**ap:**	3-F-5-CH_3
j:	4-$(CH_3)_3Si$	**u:**	2-CH_3	**af:**	2-Cl-4-CH_3	**aq:**	3-Cl-5-CH_3
k:	4-Ph	**v:**	3-CH_3	**ag:**	5-Cl-2-CH_3	**ar:**	3-Br-5-CH_3

Fig. 13 Cellulose trisphenylcarbamate derivatives. Printed by permission from Chemical Society of Japan [5]

introducing a methyl group on the benzoate [39]. The ability of these benzoate derivatives is dependent on the coating conditions on the silica gel, which can influence the higher order structure of the polymers.

10.1.2 Cellulose Phenylcarbamates

In 1984, we also reported that cellulose trisphenylcarbamate (**31a** in Fig. 13) coated on silica gel shows an excellent chiral recognition for many racemates and affords a

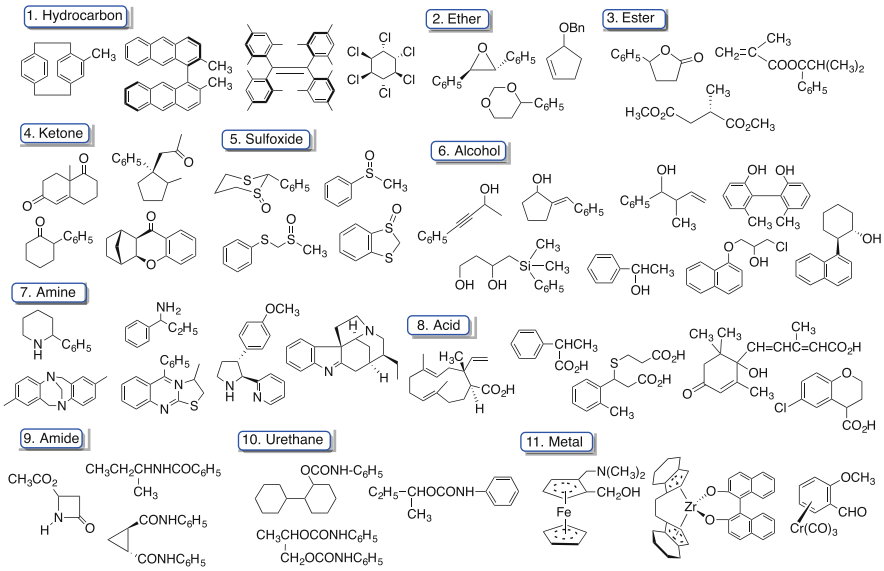


Fig. 14 Racemates resolved on 3,5-demethylphenylcarbamate (**31x**)

practically useful chiral CSP [40]. This finding encouraged us to synthesize a series of phenylcarbamate derivatives, as exemplified in Fig. 13. The chiral recognition of these derivatives depends very much on the substituents, and all the derivatives show more or less different recognitions. Among the many derivatives, 3,5-dimethylphenylcarbamate (**31x**, commercial name Chiralcel OD) is one of the most attractive [41]. This can resolve most types of compounds if they are soluble in a hexane–alcohol mixture [42–45]. Examples of the racemates resolved on **31x** are shown in Fig. 14. Today, Chiralcel OD is one of the most popular CSPs, as will be explained in Sect. 11. Basic and acidic compounds can also be directly resolved using suitable eluents containing an amine, such as diethylamine, and an acid, such as trifluoroacetic acid, respectively [46, 47].

10.2 Amylose Phenylcarbamates

Amylose has also been derivatized into various phenylcarbamates and evaluated as CSPs in HPLC [48, 49]. Again, 3,5-dimethylphenylcarbamate (**32**, Fig. 15) is one of the most useful derivatives and has been commercialized as Chiralpak AD from Daicel. Chiral recognition of the amylose derivative is rather complimentary to that of **31x**, and many compounds that are difficult to resolve on **31x** can be resolved on the amylose derivative **32**. With these two 3,5-methylphenylcarbamates, nearly 80% of 500 racemates have been resolved by my group [43].

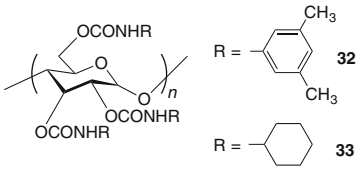
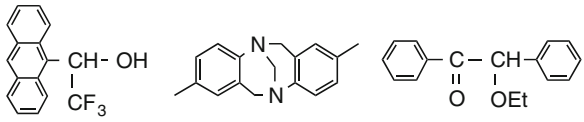


Fig. 15 Structures of amylose 3,5-dimethylphenylcarbamate (**32**) and cyclohexylcarbamate (**33**)



a **b** **c**

Separation factors (α) in the resolution of racemates (**a**-**c**) on **33**

racemates	α_{HPLC}	α_{TLC}
a	1.32	1.22
b	2.54	2.00
c	3.89	2.72

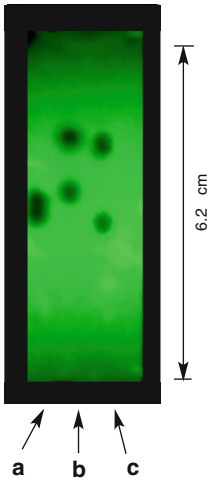


Fig. 16 TLC resolution of racemates *a–c* on amylose triscyclohexylcarbamate (**33**). Reprinted with permission of American Chemical Society [51]

10.3 Other Carbamate Derivatives of Cellulose and Amylose

Although the simple alkylcarbamates, such as the methyl- and ethylcarbamates of cellulose and amylose, show a poor chiral recognition, the cyclohexylcarbamates (**33** in Fig. 15) have characteristic abilities and can resolve many racemates [50]. Phenylcarbamates are difficult to be used as CSPs in thin layer chromatography (TLC), because aromatic groups obstruct the detection. Because the cyclohexyl derivatives have no aromatic group, they are usable as the CSP in TLC, as shown in Fig. 16. There is a rather good correlation between the HPLC and TLC resolutions, although HPLC exhibits a slightly better resolution.

Most carbamate derivatives usually have the same substituents on the 2-, 3- and 6-positions of the glucose unit. The synthesis of the derivatives with regioselectively different substituents has also been examined [51–53], and some of them exhibit a characteristic chiral recognition.

Chiral recognition of the benzylcarbamate derivatives (**34**, **35** in Fig. 17) of cellulose and amylose is of interest from the view point of the influence of the carbamate groups on the chiral recognition [54]. For both the cellulose and amylose

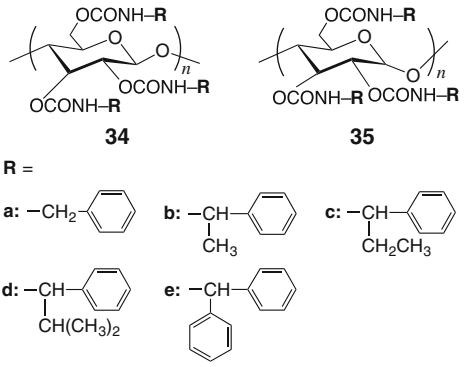


Fig. 17 Benzylcarbamate derivatives **34a–e** and **35a–e** of cellulose and amylose, respectively. Reprinted by permission from Chemical Society of Japan [5]

derivatives, only the derivatives **34b** and **35b** with a methyl substituent and **34c** and **35c** with an ethyl substituent on the benzyl carbon have good chiral recognition ability and resolve many of the racemates **22–29** shown in Table 2. The benzylcarbamate itself and the derivatives with larger isopropyl and phenyl substituents do not resolve most of the racemates **22–29**. To attain a good chiral recognition, a specific size of the carbamate group seems necessary. The polysaccharide derivatives with carbamate groups that are too small or too large may not have a regular helical structure, as will be discussed in Sect. 10.4. The cellulose derivatives **34b** and **34c** with a high ability form lyotropic liquid crystalline phases at high concentrations, while the other cellulose derivatives with a lower ability do not, suggesting that **34b** and **34c** have a rather rigid helical conformation, which seems essential to attain a high chiral recognition.

Because the **34b** and **35b** derivatives contain a chiral 1-phenylethyl group, its chirality influences their recognition. For the cellulose derivative **34b**, the *R*-isomer shows a slightly higher chiral recognition than the *S*-isomer, but for the amylose derivative **35b**, which can more efficiently resolve most of the racemates **22–29** than the cellulose derivatives, the *S*-isomer shows a much higher chiral recognition [54]. Derivative **35b** has been commercialized as Chiralpak AS.

10.4 Chiral Recognition Mechanism

The possible molecular structures of cellulose trisphenylcarbamate **31a**, its 3,5-dimethyl derivative **31x**, and amylose tris(3,5-dimethylphenylcarbamate) **32** are shown in Fig. 18. Both cellulose derivatives have left-handed 3/2 helical structures [55], whereas the amylose derivative has a left-handed 4/3 helical structure [56]. The structure of cellulose tris(3,5-dimethylphenylcarbamate) **31x** is clearly different from that of **31a**. The high chiral recognition of **31x** is ascribed to the two methyl groups. In addition to the steric effect of the two methyl groups, their electron-donating effect can influence the polarity of the carbamate residue, which may allow the derivative to have a stiffer helical structure. The derivatives

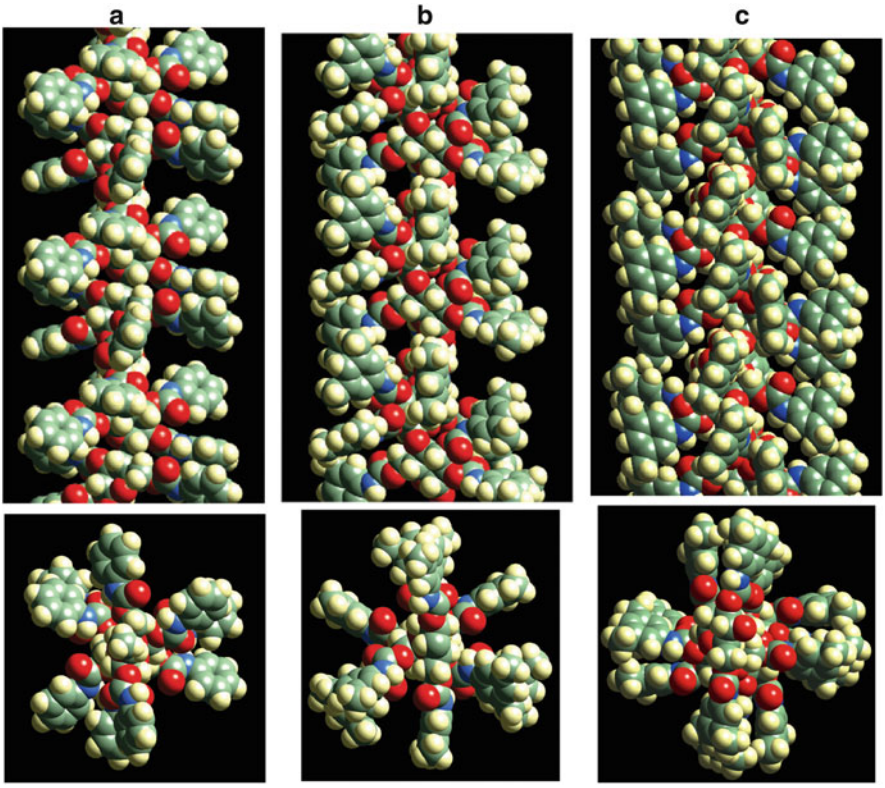


Fig. 18 Molecular structures of (**a**) cellulose trisphenylcarbamate (**31a**), (**b**) cellulose tris (3,5-dimethylphenylcarbamate) (**31x**), and (**c**) amylose tris(3,5-dimethylphenylcarbamate) (**32**). Printed with permission of Chemical Society of Japan (**a**, **b**) [56] and American Chemical Society (**c**) [57]

have a rather polar helical groove along the polymer chain. Many polar racemates can interact with the helical polymers inside of the groove through molecular interactions such as hydrogen bonding, dipole–dipole interactions, π–π interactions, and hydrophobic interactions. The latter two interactions must also play an important role in the separation of nonpolar compounds, which are also often efficiently resolved on the phenylcarbamates. The interaction inside the groove seems important for efficient chiral recognition because the cellulose phenylcarbamate derivatives with a polar substituent at the 4-position, like the nitro group, exhibit a very poor chiral recognition [41]. The polar substituents existing on the outside of the polymer chain may strongly interact with racemates to prevent them from going into the groove.

As shown in Fig. 18, the structure of the amylose derivative **32** is quite different from that of the cellulose derivatives. Because of this significant difference, the chiral recognitions of **31x** and **32** are rather complimentary and, therefore, racemates that cannot be resolved on **31x** can often be resolved on **32**, and vice versa.

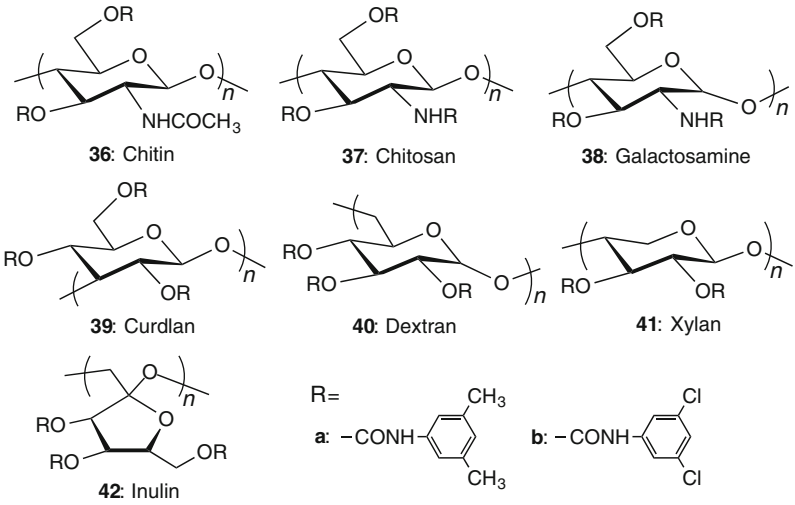


Fig. 19 3,5-Dimethylphenylcarbamates and 3,5-dichlorophenylcarbamates of polysaccharides **36**–**42**. Reprinted by Permission from Chemical Society of Japan [5]

For the derivatives soluble in $CHCl_3$, a detailed discussion on the mechanism of the chiral recognition is made possible by the NMR spectral measurements in this solvent [57, 58]. Other methods have also been used to understand the mechanism of chiral recognition by the polysaccharide derivatives [59].

10.5 Other Polysaccharide Derivatives

Besides the cellulose and amylose derivatives, other polysaccharides such as chitin (**36**), chitosan (**37**), galactosamine (**38**), curdran (**39**), dextran (**40**), xylan (**41**), and inulin (**42**) were evaluated as 3,5-dimethylphenylcarbamates and 3,5-dichlorophenylcarbamates (Fig. 19) [60, 61]. In most cases, these derivatives showed lower chiral recognition abilities than those of the corresponding cellulose and amylose derivatives. However, some racemates are better resolved on the chitin and chitosan derivatives.

11 Recent Situation Regarding Chromatographic Chiral Separations

Figure 20 depicts the recent situation regarding the determination and separation methods of chiral compounds, as published in the Journal of The American Chemical Society (JACS) in 2010 and 2012. In these years, JACS published nearly

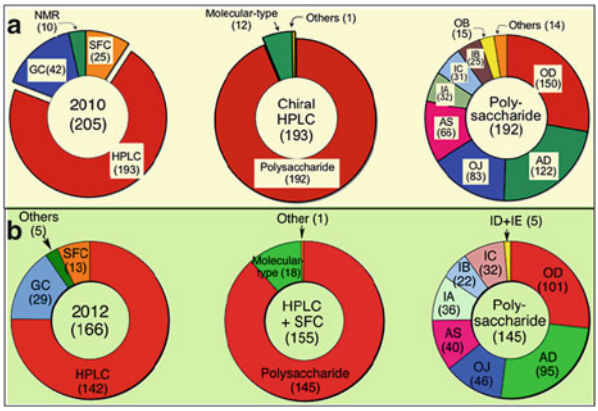


Fig. 20 Methods for determination of enantiomeric excess reported in Journal of The American Chemical Society in 2010 (*a*) and 2012 (*b*). Left circle: Methods for e.e. determination. Middle circle: CSPs for HPLC and SFC. Right circle: Polysaccharide-based CSPs. OD: cellulose 3,5-dimethtylphenylcarbamate, AD: amylase 3,5-dimethylphenylcarbamate, OJ: cellulose 4-methylbenzoate, AS: amylase (S)-l-phenylethylcarbamate, IA: immobilized AD, IB: immobilized OD, IC: immobilized cellulose 3,5-dichlorophenylcarbamate

3,000 papers; of these, 205 papers in 2010 and 166 papers in 2012 reported the determination of enantiomeric excess (e.e.) or separation of chiral compounds. Before 2007, there were three main methods for e.e. determination: HPLC, gas chromatography (GC), and NMR [6]. The NMR method is becoming less popular, probably because of its low sensitivity and accuracy. Recently, supercritical fluid chromatography (SFC) with supercritical carbon dioxide as the main eluent has been used in place of HPLC. Many CSPs for HPLC can also be used for SFC. The properties of supercritical carbon dioxide are rather similar to those of normal alkanes, such as hexane. Therefore, many chiral compounds can be resolved by SFC as well as by HPLC. Among these methods, HPLC is the most popular and nearly 75% of the chiral separations have been performed by this method. Polysaccharide derivatives have been mainly used as the CSPs. The polysaccharide-based CSPs were commercialized by Daicel in 1984, mainly based on our work, in which the chiral packing materials (CPM) were prepared by coating the polysaccharide derivatives on silica gel. These include Chiralcels OB, OD, and OJ, and Chiralpaks AD and AS (see Fig. 20) and, more recently, these derivatives have successfully been immobilized without significantly changing the properties of the polysaccharide derivatives on the surface of silica gel [62–65]. These CPMs include Chiralpaks IA, IB, and IC, and allow us to use any solvents that cannot be used for coated-type CPMs. The immobilized CPMs seem to be becoming more popular. Anyhow, it is clear that in the past decades, the polysaccharide-based CPMs have been significantly contributing to the research on chiral compounds.

12 Preparative Separation

Concerning the large-scale preparative separation of enantiomers, we can use the simulated-moving bed (SMB) system. This chromatographic system is useful for the separation of two components and has been used in industry to purify sugars using ion-change resins as stationary phases. Fortunately, enantiomers are two components and, therefore, we can readily use this industrial system for the separation of chiral compounds using the polysaccharide-based CPMs. Several chiral drugs or intermediates have been industrially resolved by SMB using the polysaccharide-based CPMs [66]. A CPM suitable for preparative resolution has also been developed as an organic–inorganic hybrid material [67]

13 Concluding Remarks

In 1979, we found that a vinyl polymer, PTrMA, with a stable one-handed helical structure can be directly synthesized through the asymmetric anionic polymerization of TrMA by the (−)-sparteine-BuLi complex in toluene. This is the first example of the asymmetric synthesis of a helical polymer and proved that such a helical polymer can stably exist without optically active side groups. The helical PTrMA exhibited an unexpected high chiral recognition of many racemates, particularly stereochemically interesting compounds. In 1982, the chiral column was commercialized as the first chiral column based on an optically active polymer. As described in this chapter, following this study, many helical polymers were synthesized for evaluation as CSPs for HPLC, and it became clear that to attain high chiral recognitions, regular helical structures of the polymer chains is very important. Besides the synthetic polymers, we also extended our studies to polysaccharide derivatives. In 1984, we found that cellulose trisphenylcarbamate with a helical conformation functions as an excellent CSP when coated on silica gel. This finding had been extended to many other carbamate derivatives and other polysaccharides, including amylose. Among the many polysaccharide derivatives we synthesized, the 3,5-dimethylphenylcarbamates of cellulose and amylose are currently the most popular CSPs; with these four or five polysaccharide-based CSPs, nearly 90% of the chiral compounds can be resolved. The contribution of these CSPs to the research and development of chiral compounds, including many drugs, has been remarkable. The high abilities of these CSPs are closely related to their rather rigid helical structures.

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Index

A
Adaptation, 155
Adaptive constitutional networks (ACNs), 166
Adaptive polymer networks, 166
Addition polymerization, 133
Alanylglycine (AlaGly) dyads, 202
Alkylidene biscyclopentadiene, 213
Amino acids, 181, 392, 401
  hydrazides, 162
  noncanonical, 199, 201
Amphiphilic benzyl ether dendrons, 181
Amylopectin, 152
Amylose, 391, 402
Amylose phenylcarbamates, 404
Anthracene, 212
Aquaporin, transmembrane protein mimics, 188
Archimedean solids, 236
Atom mimicry, 321, 353
Au nanoclusters, 357
Autoreactivity, surface chemistry, 358
Azides, Staudinger reduction, 177
Azidohomoalanine (Aha), 207
Azidonorleucine (Anl), 208

B
Baekeland, Leo H., 65
Bakelite, 65, 90
Benzothiadiazole (BTZ), 314
Benzyl ether, 182
Berthelot, Pierre Eugene Marcellin, 67
Berzelius, Jacob., 67, 325
Beta sheet, 202, 302, 377
Bioactive molecules, 249
Biodynamers, 162
Bioinspired materials, 21
Biological mimics, 173
Biomedicine, 250
Biopolymers, 295
Biphenylmethyl ether, 182
Biphenylpropyl ether, 182
4,4'-Bipyridinium (BIPY), 271
Block copolymers, 183, 249
BONCAT (bio-orthogonal noncanonical amino acid tagging) method, 207
Bonding, directional, 229
Bovine serum albumin (BSA), 305, 401
Branch cells, 333
Braun, Dietrich., 62
Brookhart-type catalysts, 329
Buckminsterfullerene, 367
Bühl, Alfons, 109
Buna, 122
Burchard, Walther., 32, 151, 333
Butadiene, 54, 57, 84, 300

C
Cantow, Hans-Joachim., 21, 33, 34, 40, 174–177
Caoutchouc, 69
Carbon double bonds, 93
Carothers, Wallace Hume., 9, 25, 52, 83, 106
Car tires, 92, 96
Catenanes, polyhedral, 221
Cellophane, 65
Celluloid, 64, 90
Cellulose, 23, 391, 402
  regenerated, 64
Cellulose esters, 402
Cellulose nitrate, 64

Cellulose phenylcarbamates, 403
Cellulose triacetate, microcrystalline (MCT), 402
Cellulose tris(3,5-dimethylphenylcarbamate), 406
Cellulose trisphenylcarbamate, 391, 403
Chain stiffness, 152
Chain-folded lamellar crystals, 201
Chemical warfare, 87
Chiral packing materials (CPM), 409
Chiral recognition, 391, 406
Chiral stationary phase, 391
Chirality, 263
Cholesterol, 190
Circular dichroism (CD), 182, 187, 267
Cisplatin, 254
Coil–globule transition, 306
Colloid theory, 68, 100
Columnar stacks, 311
Condensation polymerization, 133
Conformational memory, 298
Constitutional dynamic chemistry, 155
Constitutional networks/dynamic networks (CDNs), 155, 166
Continuous wave (CW) EPR, 307
Coordination complex, supramolecular, 229
Copolypeptides, 302
Copper-catalyzed azide-alkyne 1,3-dipolar cycloaddition (CuAAC) click reaction, 279
Crick, Francis H C., 13, 15, 178, 217, 325
Critical hierarchical design parameters (CHDPs), 378
Critical nanoscale design parameters (CNDPs), 348
Critical packing state, 345
Cuboctahedron, 236
Curdran, 408
Cyclobis(paraquat-*p*-phenylene) ($CBPQT4^{+}$), 274
Cyclopentadiene, 211
Cyclopentadithiophene (CDT), 314
Cyclophosphamide, 253

D

Dalmatian insect powder, 45
Defence chemistry, 121
de Gennes dense packing, 345
Dendrigraft polyethylene (*dendri*-polyethylene), 337
Dendrigrafts, 333, 337
Dendrimers, 179, 321, 333, 338
  shape change, 344
  surface congestion, 346
Dendrimersomes, 190
Dendritic assemblies, 333
Dendritic effects, 321
Dendronized polymers, 179, 295, 306
Dendrons, 333, 338
  self-assembling, 179
Dextran, 408
Diels–Alder reaction, 213
Dimethoxy-1,4-bis(dimethylamino)butane (DDB), 396
Dimethylphenylcarbamate, 391, 404
Dinaphtho[38]crown-10 (DN38C10), 274
1,5-Dioxynaphthalene (DNP), 271, 274
Dipeptides, dendritic, 188
Diphenylethyl methacrylate (DPEMA), 396
Diphenyl-2-pyridylmethyl methacrylate (DPyMMA), 396
Diplatinated phenanthrene, 234
Directional bonding, 245
Diypridyl iodonium ligand, 233
DNA, 200
  branched, 217
  nanotechnology, 221
  programmability, 223
  recombinant, 199
  structural, 217
Dodecahedron, 236
Donor–acceptor, charge transfer interactions, 271
  stacks, 275
Double helix, 178, 218, 324
Double quantum (DQ) solid-state NMR, 297
Doxorubicin, 251, 254
5-Doxylstearic acid (5-DSA), 305
Drug carrier system, 250, 254
Duranes, 212
Dynamers, 155
Dynamic covalent chemistry (DCC), 157
Dynamic materials, 155
Dynamic non-covalent chemistry (DNCC), 157
Dynamics, 295

E

Elastin-like polypeptides (ELPs), 309
Electrocyclization, 187
Electron–electron double resonance (DEER), 305
Electron paramagnetic resonance (EPR) spectroscopy, 295
Enantioseparation, 391

Ethylene bonds, saturation, 102
Excluded volume effects, 152, 335
Explosives, 64, 87, 122–124, 379

F
Fatty acids (FA), 304
Feynman, Richard., 16
Field-effect transistor (FET) hole mobilities, 315
Finkelmann, Heino., 34
Fischer, Emil., 43, 46, 68, 107, 127
Flory, Paul J., 44, 62, 149, 327, 336
Foldamers, 271
Formaldehyde, 25
Freiburg Center for Interactive Materials and Bioinspired Technologies (FIT), 35
Freiburg Materials Research Center (FMF), 34
Fritschi, Jakob., 71, 102
Fullerenes, 354, 364, 367

G
Galactosamine, 408
Galalith, 64, 90, 92
Galectins, 192
Gamma-gauche effect, 297
Gaussian-coil networks, 333
Gel permeation chromatography, 26, 267
Gels, macro-/supramolecular, 201, 205
viscoelastic behavior, 205
Glycodendrimersomes, 192
Glycodynamers, 162
Glycogen, *p*-iodobenzoyl derivative, 26
Goodman, Murray., 266
Gronski, Wolfram., 34

H
Haber, Fritz., 11, 14, 45, 55, 87, 102
Happy oligorotaxanes, 286
Hard/soft nanoelements, 321
Heidegger, Martin., 13, 28, 56, 108, 119
Helix–coil/helix–helix transition, 186
Helixes, 263, 391
Hemoglobin, 25, 66, 200, 257
Hexabenzocoronene (HBC), 311
Hexacatenane, 223
Hexagons, 234
High-performance liquid chromatography (HPLC), 391
Hirohito, Emperor., 139, 173, 178
History of chemistry, 61
History of materials, 61
Huisgen cycloaddition, 246
Human serum albumin (HSA), 304
Husemann, Elfriede., 4, 26, 30–43, 151
Hydration, 205
Hydrogen bonding, 155
Hydrorubber, 102
N-(2-Hydroxypropyl)methacrylamide, 251,
Hyperbranched polymers, 336
Hyperbranching, 153

I
Icosahedron, 236
I.G. Farben Industries, 39
Imine formation, 155
Immerwahr, Clara., 55
Immerwahr, Paul., 55
Initiators, 93, 134
Insecticides, 45
Intelligence and curiosity, 1
π–π interactions, 271
International Historic Chemical Landmark, 21, 22
Intrinsic viscosity, 26
Intrinsically disordered proteins (IDPs), 304
Inulin, 408
p-Iodobenzoyl glycogen, 26,
Isomerism, 326
Isoprene, 11, 22, 54, 56, 84, 92, 104

J
Janus dendrimers, 190
Japan, 132, 139, 173
Jolles, Georges., 16

K
Karlsruhe, 11, 53
Ketenes, 94
Klatte, Fritz., 65, 83
Klug, Aaron., 179, 180, 374, 375
Knoll, Max., 26
Krebs, Hans., 1, 12–14
Krebser, Adolf., 71–75
Krische, Wilhelm., 64
Kuhn, Thomas S., 17
Kuhn, Werner., 26
Kuhn–Mark–Houwink–Sakurada, 26

L
Laccase, 147
Lamellar crystals, 201
Lautenschläger, Ludwig Carl., 56
Lectins, 192
Lectures, macromolecular concepts, 139
Leucine zipper, 205
Lifson, Shneior., 267
Light scattering, 152
Lipmann, Fritz., 13
Liposomes, 190
Liquid crystals, anisotropy, 34
  smectic, 203
Long chain branching (LCB), 329
Lüttringhaus, Arthur., 41

M
Macromolecular Manifesto, 81, 89, 91
Macromolecules, 2, 21, 22, 44, 61, 81
Magic angle spinning (MAS), 297
Magnetic resonance (MR), 296
Majority rule, 269
Mao, Chengde., 223
Mark, Hermann Franz., 7, 26, 39, 51, 102, 263
Mark–Houwink, 26, 148
Mason, Thomas., 201
Matrix proteins, extracellular, 201, 206
Mechanically interlocked molecules (MIMs), 271
Mechanostereochemistry, 271, 272
Megamers, 333
Memory, 298
Mendeleev-like nano-periodic tables, 357
Metal–ligand bonds, 232
Metallacages, 229
  prismatic, 238, 241
Metallacycles, 229
  squares, 233
Metallocenes, 329
Metastyrene, 56, 63, 69
Methacrylamide, 399
Meyer, Kurt H., 51, 55, 99, 102
Micelles, 2, 100, 134, 249
Mie, Gustav., 25
Miniemulsion polymerization, 309
Molecular biology, 199
Molecular colloid, 100
Molecular isomerism, 326
Molecular squares, 233
Molecule, 66
Monodispersity, nanoscale, 348
Monomers, 24, 92, 213
Morawetz, Herbert., 8, 43, 44, 62, 267
Mulder, Gerardus Johannes., 66
Mülhaupt, Rolf., 21, 34, 153
Multi-arm junctions, 222
Multi-furan, 212
Multi-maleimide, 212
Myoglobin, 257

N
Nanocompounds/assemblies, 321, 363
Nanomedicine, 16
Nanoperiodic system, 321
Nanoscale monodispersity, 348
Nanosterics, 370
Nanotechnology, 217
Natta, Giulio., 25, 200, 264, 296, 327
Neocarzinostatin (SMANCS), 252
Nobel Prize in Chemistry 1953, 2, 81
Non-canonical amino acids, 199
Nuclear magnetic resonance (NMR), 295
  crystallography, 314
Nuclear Overhauser effect (NOE), 314
Nucleic acids, 199
Nucleotides, 218
Nucleus independent chemical shift (NICS), 297
Nylon, 83, 92, 106, 125, 133, 147, 266

O
Okamoto, Yoshi., 267, 391
Oligoethyleneglycol (OEG), 307
Oligo-pseudorotaxanes, 288
Oligorotaxane foldamers, 281
Organic field-effect transistors (OFETs), 313
Organic light-emitting diodes (OLEDs), 313
Organic photovoltaic (OPV) cells, 313
Oswald, Wolfgang., 46
Ovomucoid, 401

P
Paclitaxel, 254
Parkesine, 64
PEG-*b*-poly(aspartate), 254
PEG-*b*-poly(L-lysine), 253
Peptide mimics, 181
Percec dendrons, 365
Perylene bis(diimide)s (PBIs), 313
Perylenediimide (PDI), 311
Phenylpropyl ether, 182
Phosphines, Staudinger reduction, 177

Phospholipids, 190
Piano-stool metal centers, 235
Plastics, 61, 66
  chemistry, 81
Platinum-pyridyl-carboxylate, 241
Platonic solids, 236
Pleiadene, 212
Plexiglas/Perspex, 83
Poison gas, 124
Polanyi, Michael., 68
Polyacetylenes, 395, 399
Polyacrylamides, 398
Polyamides, 395, 401
Polycarbosilanes, 336
Polycarbosiloxanes, 336
Polyelectrolytes, 271
Polyesters, 211
Polyglucoside, 69
Polyhedra supramolecular, 236
Polyion complex (PIC) micelles, 255
Polyisocyanates (nylon 1), 266
Polyisoprene, 12, 22, 56, 71
Polyisoprene, catalytic hydrogenation, 22
Polymaleimide, 395
Polymer, Berzelius., 66
Polymer research, 81
Polymer sciences, 21, 39
Polymer–drug conjugates, 249, 251
Polymeric micelles, 249
Polymeric vesicles, 249
Polymerization, reversible, 211
Polymers, 21, 61
Polymersomes, 190, 257
Polymethacrylamides, 395, 398
Polymethacrylates, 395
Polyoxymethylene (paraformaldehyde), 69, 94, 100
Polypeptides, 295
  periodic, 201
  self-assembly, 302
Polyphenylacetylenes, 186
Polypropylene, isotactic, 265
Polypseudorotaxanes, 279
Polysaccharides, 395
Polystyrenes, 9, 91, 96, 102, 264, 337
Polyurethanes, 92, 133, 395, 401
Polyvinyl alcohol (PVA) fiber, 148
Polyvinylchloride, 65, 91
Poly(*n*-alkylmethacrylates), 299
Poly(amide)s, 50
Poly(amidoamine) (PAMAM), dendrimers, 333
Poly(α-amino acid), 395, 401
Poly(γ-benzyl-L-glutamate) (PBLG), 203, 302
Poly(dendrimers), 333
Poly(divinyl ether-co-maleic anhydride) (DIVEMA), 250
Poly(ether ketones), 336
Poly(ethylene glycol) (PEG), 252
  linear, 365
Poly(ethylene oxide)-*b*-poly(propylene oxide)-*b*-poly(ethylene oxide), 254
Poly(ethylene sulfonate), 250
Poly(ethyleneoxide)-conjugated lipids, 190
Poly(α,L-glutamic acid), 203
Poly(hydroxypropyl methacrylamide) (PHPMA), 251
Poly(*n*-hexyl isocyanate), 266
Poly(3-hexyl thiophene) (P3HT), 314
Poly(*N*-isopropylacrylamide) (PNiPAAm), 306
Poly(phenylacetylenes), 336
Poly(phenylenes), 336
Poly(propylene), 296
Poly(siloxysilanes), 336
Poly(styrene-*co*-maleic acid/anhydride), 252
Poly(triphenylmethyl methacrylate) (PTrMA), 391, 398
Priesner, C., 26, 27, 91, 103, 106, 107, 117
Prisms, trigonal., 242
Protein synthesis, 199
Proteins, 199
  dynamics/flexibility, 304
Pseudorotaxane foldamers, 273
Pyrethroids, 24
Pyrethrum, 45
Pyrolysis, 11

R

Random hyperbranched polymers, 336
Recombinant DNA, 199
Reichstein, Tadaeus., 24
Responsibility in science, 1
Reversible polymerization, 211
Rhombicuboctahedron, 236
Rod-like polymers, 203
Röhm, Otto., 83
Rotaxanes, 271
  foldamers, 278
Roth, Klaus., 13
Rubber, 3, 11, 24, 107, 200
  hydrogenation, 102
  synthetic (Kautschuk), 57
Ruska, Ernst., 26
Ruska, Helmut., 26
Ruzicka, Leopold., 24, 59, 125

S
Schaffner, Ruth., 215
Schmierenchemie (goo chemistry), 28
Schneider, Hans-Adam., 34
Schulz, Günter Victo., 26
Self-assembly, 173, 179
  coordination-driven, 229, 245
  information-directed, 217
  multicomponent, 240
  post-self-assembly functionalization, 245
Self-condensing ring-opening polymerizations (SCROP), 337
Self-condensing vinyl polymerizations (SCVP), 337
Self-healing, 232
Sergeants and soldiers effect, 269
Shastri, Prasad, 33, 34
Shellac, 65
Side-chain liquid crystal polymers, 180
Simulated-moving bed (SMB) system, 410
Slichter, W P., 296
Small-angle X-ray scattering (SAXS), 303
Sociopolitics, 1
Solutions, properties, 151
  viscoelastic behavior, 205
Sparteine-*n*-BuLi, 401
Spitteler, Adolf., 64
Squares, molecular, 233
Starburst polymers, 333
Start reaction, 93
Staudinger, Dora (Dorothea)., 23, 53, 89, 110
Staudinger effect, 139, 140
Staudinger index, 26, 135
Staudinger, Hermann, 1
Staudinger, Magda., 3–15, 23, 26, 31, 33, 40–44, 89, 109, 126–144,174, 177, 178
Staudinger reaction, 135, 177, 178
Stealth liposomes, 191
Stereochemistry, 263
Stereoisomerism, 326
Stick model, 104
Sticky ends, 217, 223
Structure, 295
Styrene, 54, 63, 91, 264
Superatoms, 321, 353
Supercritical fluid chromatography (SFC), 409
Supramolecular chemistry, 155
Supramolecular coordination complexes (SCCs), 229, 231
Supramolecule-to-supramolecule transformation, 243

T
Tactic polymers, 263
Tautomerism, 51, 326
Teramoto, Akio., 267
Tetrakis(*n*-butylthiomethyl)benzene, 234
Tetramethylpiperidineoxyl (TEMPO), 307
Tetrapyridyl porphyrin, 242
Thiele, Johannes., 84
Titanocene, 233
Tobacco mosaic virus (TMV), 373
Transmembrane proteins, 190
Transmission electron microscopy (TEM), 26
Triangles, 234
Triphenylmethyl methacrylate (TrMA), 396
Tris(3,5-dimethylphenylcarbamate)s, 391
Tropoelastin, 310
Typhus, 45

U
Ultracentrifugation, 26, 200
Ultraviolet phase contrast microscopy, 26
Urushi lacquer, 147
Urushiol, 147

V
Valence shell electron pair repulsion (VSEPR), 361
Valences, 95
  secondary, 101
Vesicles, 190, 249
Vinyl chloride, 65
Vinylon, 148
Viscosity law, 25, 104
Vorländer, Daniel., 84
Vulcanisation, 92

W
Watson, James D., 13, 15, 178, 217, 325
Wegner, Gerhard., 39
Wide-angle X-ray scattering (WAXS), 300
Wieland, Heinrich., 23, 69, 97
Williams, Charles Greville., 92
Williams–Landel–Ferry (WLF) equation, 300
Willstädter, Richard., 45, 56, 84, 97, 102, 116, 135

X
X-ray diffraction, 25
Xanthogenate, 65
Xylan, 408

Z
Ziegler, Karl., 200, 265, 327
Ziegler–Natta catalysts, 265
Zipper proteins, 204