Chapter 1
History of Cyclodextrins

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Abstract Cyclodextrins are cyclic oligosaccharides obtained by enzymatic degradation of starch. They are remarkable macrocyclic molecules that have led major theoretical and practical advances in chemistry, biology, biochemistry, health science, and agriculture. Their molecular structure is composed of a hydrophobic cavity that can encapsulate other substances to form inclusion complexes through host-guest interactions. This unique feature is at the origin of many applications. Cyclodextrins and their derivatives have a wide variety of practical applications in almost all sectors of the industry, including pharmacy, medicine, foods, cosmetics, chromatography, catalysis, biotechnology, and the textile industry.

Villiers published the first reference to cyclodextrins in 1891. Since the beginning of the twentieth century, major researchers, such as Schardinger, Pringsheim, Karrer, Freudenberg, French, Cramer, Casu, Bender, Saenger, Nagai, Szejtli, and Pitha, have paved the history of the cyclodextrins. Several time periods have marked their history. After their discovery and characterization from 1891 to 1911, there has been a period of doubt and disagreement from 1911 to 1935. Then, the 1935–1950 exploration period was marked by structural results on the "Schardinger dextrins." In 1949, Cramer introduced the cyclodextrin-based nomenclature. Research between 1950 and 1970, the period of maturation, focused on conformations and spectroscopic data of cyclodextrins and their inclusion complexes, with applications in catalysis and as enzyme models. Finally, the period of use has been ongoing since 1970 and has seen cyclodextrins find many industrial applications. Cyclodextrins have then found many industrial applications, initially in the pharmaceutical and food sectors. In 1984, the first chromatographic columns were commercialized. At that time, many cyclodextrin-based catalysts were developed for biomimetic

chemistry and other applications such as artificial enzymes. Currently, more than 2000 publications on cyclodextrins are published each year.

In this chapter, we present a historical overview of the discovery, development, and applications of cyclodextrins.

Keywords History · Schardinger dextrins · Discovery · Production · Separation · Native cyclodextrins · Development · Inclusion complexes · Applications

1.1 Introduction

Figure 1.1 shows that cyclodextrins occur in many daily products such as an ibuprofen tablet, a nonsteroidal anti-inflammatory drug, a whooping cough vaccine, a curative antidote, a hair loss solution, a stop smoking aid, toothpastes, shampoo, colognes, a deodorant toilet, razors, a turmeric-based food supplement, a butter, a mayonnaise, fish sausages, modified steaks, a horseradish powder, mustard sauces, a sweetener, honey, a cinnamon extract, green tea without bitterness, vanilla coffee, clarified fruit juices, chewing gums, chromatographic columns, biopesticides, catalysts, tubular materials, a curtain, cosmetotextiles, an ink, a detergent, a bioflocculant for swimming pool, or a bioadsorbent for water treatment.

Fig. 1.1 Commercial products containing cyclodextrins in our daily lives

Cyclodextrins are cyclic oligomers obtained from the enzymatic degradation of starch. They are one of the most remarkable macrocyclic molecules with significant impacts in our daily lives. Cyclodextrins have a particular structure composed of a hydrophobic cavity that can encapsulate other substances to form inclusion complexes through host-guest interactions. This characteristic feature is at the origin of many applications. Today, all industrial sectors are concerned, e.g., pharmaceuticals, cosmetics, food, hygiene and toiletries, biotechnology, medical, radiology, agrochemistry, catalysis, packaging, textile industry, nanotechnology, and soil and water treatment.

The French pharmacist Villiers published the first reference to cyclodextrins in 1891 (Villiers 1891a, b, c, d). Since the beginning of the twentieth century, Schardinger, Pringsheim, Karrer, Freudenberg, French, Cramer, Casu, Bender, Saenger, Nagai, Szejtli, and Pitha have marked the history of cyclodextrins (Szejtli 1998; Loftsson and Duchêne 2007; Kurkov and Loftsson 2013; Crini 2014; Morin-Crini et al. 2015; Crini et al. 2018).

The first important period on the history of cyclodextrins, from 1891 to 1911, covers their discovery by Villiers, and their characterization and chemistry by Schardinger (Thoma and Stewart 1965; Caesar 1968; Clarke et al. 1988; Szejtli 1998). In 1891, Villiers discovered a crystalline dextrin from the *Bacillus amylobacter* digest of potato starch, which he named *cellulosine*. At the beginning of the last century, Schardinger also observed the formation of two crystallized products during his investigations of food spoilage, which he called crystallized dextrin-α and crystallized dextrin-β. Schardinger gave the first detailed description of the preparation and separation of these two dextrins. He was also the first to isolate the strain of bacteria responsible for dextrin formation, i.e., *Bacillus macerans*. However, from 1911 to 1935 came a period of doubt and disagreement, in particular between the groups of Pringsheim and Karrer, although they published numerous studies on the composition, properties, and chemistry of the crystallized dextrins (Crini 2014).

It was not until the mid-1930s that research on dextrins developed again. The exploration period from 1935 to 1950 was marked by the numerous results obtained by Freudenberg and French on the structure of the "Schardinger dextrin" molecules. In 1935, Freudenberg was the first to develop a relatively simple method for the obtention and purification of the two Schardinger dextrins. Freudenberg also suggested in 1936 a cyclic structure for α-dextrin and β-dextrin, which was confirmed in 1938. In the 1940s, French proposed that Schardinger dextrins be called cycloamyloses and described new protocols for the preparation of cycloamyloses with high purity. In 1942, Hudson discovered the enzyme in *Bacillus macerans* responsible for the conversion of starch into dextrins, and the same year, French published the exact molecular weights of the cyclohexaamylose and cycloheptaamylose, i.e., α-dextrin and β-dextrin, respectively. In 1948, Freudenberg discovered γ-dextrin or cyclooctaamylose, and 1 year later, Cramer, his PhD student, introduced the cyclodextrin-based nomenclature. From 1950 onward, this terminology was increasingly used although the nomenclature of cyclodextrins remained a subject of debate until the end of the 1990s.

The period between 1950 and 1970, known as the period of maturation of notions, focused on inclusion complexes with Cramer's work in the foreground. At the beginning of the 1950s, French finally demonstrated the chemical cyclic structures of cycloamyloses. In 1953, Cramer gave the basis for supramolecular catalysis involving cyclodextrins, and the same year, with Freudenberg and Plieninger, he published the first patent concerning the applications of cyclodextrins in pharmaceutical formulations. In 1956, Cramer introduced and detailed the notion of an *inclusion complex*. From that time on, the interest in cyclodextrins increased. During the maturation period, the works of Casu on the conformation and spectroscopic characterization of cyclodextrins were acknowledged to have brought an important contribution. At the same time, much attention was also focused on their use for catalysis and as enzyme models, and one name stands out in particular in the enzymology and catalysis by cyclodextrins: Bender (Crini 2014). Nonetheless, until the mid-1970s, the three main native cyclodextrins, i.e., α-, β-, and γ-cyclodextrins, available only in small quantities, were long considered as just laboratory curiosities (Thoma and Stewart 1965; Caesar 1968; Kainuma 1984; Clarke et al. 1988). In the way of industrial development, the three main obstacles were their price, e.g., in 1975 1 kg of β-cyclodextrin had a price of about 1500 $ (Szejtli 1982a), their presumed toxicity (French 1957a), and the lack of sufficient knowledge of these substances (Szejtli 1982a). In addition, very few researchers were convinced of the industrial potential of cyclodextrins.

The 1970s were marked by two important events: firstly, several manufacturers started to produce and to commercialize cyclodextrins; at that time, due to improvements in the production of cyclodextrins, their prices have dropped significantly. Secondly, the first toxicological studies had established that β-cyclodextrin administrated orally was a harmless substance. As a result, this has led to spectacular progress. From then on, the period of use began and cyclodextrins found many industrial applications. During this period of utilization, four names stand out: Saenger, Szejtli, Nagai, and Pitha. In the mid-1970s, pharmaceutical and food applications started to appear and rapidly gained ground, especially in Japan (Hamada et al. 1975; Szejtli 1977; Pitha et al. 1983; Uekama and Otagiri 1987; Frömming and Szejtli 1994). In 1980, Saenger published the first comprehensive review about the potential industrial applications of cyclodextrins (Saenger 1980). The first International Cyclodextrin Symposium organized by Szejtli took place in Budapest in 1981, and 1 year later, he wrote the first comprehensive cyclodextrin book (Szejtli 1982a). At that time, many interesting catalysts based on cyclodextrins were also constructed for biomimetic chemistry and other processes of interest such as artificial enzymes (Breslow 1979; Breslow and Dong 1998). Both from an academic and industrial point of view, the number of communications then started to increase exponentially, as did the filing of patents.

In the mid-1980s, cyclodextrins were produced in large quantities and commercialized at a reasonable price, i.e., 10–15 $/kg (Szejtli 1982a). Other industrial applications have become possible. In 1984, the first chromatographic columns were marketed (Armstrong 1984; Ward and Armstrong 1986, 1988; Armstrong and Jin 1989). Since then, an increasing interest in cyclodextrins and their possible

applications has existed (Duchêne 1987, 1991; Szejtli 1988). An abundant scientific literature has built up since the 1980s. Currently, every year, more than 2000 publications, including articles and book chapters, are devoted to cyclodextrins (Cyclodextrin News, CycloLab Ltd., Hungary). Nowadays, these molecules still fascinate researchers and industrials.

The objective of this chapter is to describe historical landmarks of the discovery, exploration, and utilization of cyclodextrins. We also present some highlights of their early industrial applications. To this end, an extensive list of data from about 500 original publications has been compiled. Although this historical chapter cannot hope to be exhaustive, it does highlight the work of those researchers who have contributed to the knowledge of cyclodextrins throughout the 129 years of its history.

1.2 Discovery and First Chemical Studies of Cyclodextrins

1.2.1 Discovery: 1891–1911

During experiments on the degradation and reduction of carbohydrates under the action of ferments, Antoine Villiers, a French pharmacist and chemist, was the first to observe in 1891 the formation of unwanted crystals with particular properties, i.e., the formation of cyclodextrins. Among various Villiers' biographies, those by French (1957a), Thoma and Stewart (1965), Caesar (1968), Szejtli (1998), Loftsson and Duchêne (2007), Kurkov and Loftsson (2013), Crini (2014), and Morin-Crini et al. (2015) deserve particular mention.

Studying the degradation and reduction of carbohydrates, Villiers showed how easy it was to transform starch to yield "novel crystalline dextrins" with particular properties under the action of ferments. He first obtained a small amount of crystalline dextrins from digests of *Bacillus amylobacter*, i.e., *Clostridium butyricum*, on potato starch under certain conditions (Villiers 1891a, b): 50 g potato starch in 1 L of water at 100 °C subsequently seeded with *Bacillus amylobacter* and incubated for several days in an oven at 40 °C. Villiers presented his results to the French *Académie des Sciences* in February 1891 (Fig. 1.2). At that time, the dextrins, previously discovered in 1821, were the degradation products and/or the intermediate decomposition products of starch through heating. For Villiers, his dextrins were degradation products of starch. When purified by fractional precipitation, the crystals presented very different optical rotation properties and were difficult to hydrolyze any further. Iodine stains red those dextrins that had a high optical activity, and the intensity of the stain decreased with the optical activity. The butyric ferment caused the transformation of the starch directly into dextrin without the involvement of intermediates such as diastases secreted by the ferment. Later, Villiers considered his dextrins as the intermediate decomposition products of starch (Villiers 1891b). Villiers also obtained *un curieux sous-produit*, i.e., a curious by-product, in small

CHIMIE ORGANIQUE. — *Sur la transformation de la fécule en dextrine par le ferment butyrique*. Note de M. **A. Villiers**.

« Ayant entrepris l'étude de l'action des ferments figurés sur les hydrates de carbone, dans des conditions diverses, je donnerai ici les premiers résultats relatifs à l'action du *ferment butyrique* (*Bacillus amylobacter*) sur la fécule de pomme de terre.

» Il est facile de transformer la matière amylacée en dextrine sous l'action de ce ferment.

Fig. 1.2 Extract of the first proceedings of the French *Académie des Sciences* of February 1891 where Villiers described the action of the butyric ferment *Bacillus amylobacter* on potato starch

CHIMIE ORGANIQUE. — *Sur la fermentation de la fécule par l'action du ferment butyrique*. Note de M. **A. Villiers**.

« J'ai montré dernièrement (*Comptes rendus*, février 1891, p. 435) que la fécule de pomme de terre peut, dans des conditions déterminées, fermenter sous l'action du *Bacillus amylobacter*, les produits principaux de cette fermentation étant constitués par des dextrines.

» Il se forme en même temps, mais en très petite quantité, soit environ 3^{gr} pour 1000 de fécule, un hydrate de carbone qui se sépare en beaux cristaux radiés, au bout de quelques semaines, dans l'alcool ayant servi à la précipitation des dextrines. Ces cristaux renferment de l'eau et de l'alcool de cristallisation, la proportion de ce dernier étant très faible, environ 4 pour 100. Au contact de l'air, ils deviennent opaques, en perdant de l'alcool et absorbant de l'eau, sans que leur poids varie d'une manière notable. En les dissolvant dans une assez grande quantité d'eau chaude, on obtient, par refroidissement, de petits cristaux brillants, inaltérables à l'air, dont la composition est représentée par un multiple de la formule

$$C^{12}H^{10}O^{10} + 3HO.$$

Fig. 1.3 Extract of the second proceedings of the French *Académie des Sciences* of June 1891 where Villiers described the chemical composition of two novel crystalline dextrins which he named *cellulosines*

quantities after several weeks of incubation: 3 g of this carbohydrate was obtained as crystals after bacterial digestion of 1000 g of starch. This new substance was found in the alcohol that was used for the precipitation of dextrins (Villiers 1891b).

In a second proceedings of the French *Académie des Sciences* of June 1891 (Fig. 1.3), Villiers described the chemical composition of the novel highly crystalline dextrin having a composition between that of starch and that of dextrin (Villiers 1891c). In air, the crystals, containing water and alcohol of crystallization (the proportion of the latter is rather small, about 4%), became opaque. They lose alcohol

and absorbed water without any change in weight. After purification in large amount of hot water, Villiers obtained small brilliant crystals, most probably β-cyclodextrin, and determined the chemical composition of this crystalline carbohydrate. He gave the first empirical formula: $[(C_6H_{10}O_5)_2 + 3H_2O]$. Its solubility in water at room temperature was low but raised with temperature. The white crystals with a very slight sweetness showed extremely high optical activity, much higher than those of certain dextrins formed under the action of the butyric ferment. Villiers then considered this novel substance as an isomer of starch (Villiers 1891c, d). By manipulating the experimental conditions, Villiers obtained two distinct crystalline dextrins, most probably α-cyclodextrin and β-cyclodextrin, having a composition represented by a multiple of the formula $[(C_6H_{10}O_5) + 3H_2O]$. Villiers noted again that the white crystals with a very slight sweetness showed extremely high optical activity. Pursuing his experiments, he observed that the two dextrins, always considered as isomers of starch, were almost insoluble in water, soluble in alcohol, non-fermentable, and acid resistant, and they could also be converted into ethers under the action of acid chlorides. Villiers finally concluded that the properties of these two particular dextrins were very clearly different from those of the various saccharides and polysaccharides known at the time and proposed the name of *cellulosines* due to the similarities with cellulose, e.g., with "regard to difficulty of acid hydrolysis" (Villiers 1891c, d).

At the beginning of the 1900s, Heinrich Robert Koch, a famous German physician and microbiologist, who received a Nobel Prize in 1905, remained unconvinced by Villiers' conclusions (Crini 2014). In Koch's opinion, Villiers used "primitive bacteriological techniques and probably impure cultures." This was also pointed out by Schardinger (1904). Later, French (1957a) indicated that "Villiers used impure cultures but his digests contained sufficient *Bacillus macerans* to account for the small amount of crystalline dextrin obtained."

The recognition to cyclodextrins is attributed to Franz Schardinger, an Austrian chemist and bacteriologist. Schardinger is the first Great Scientist who has left its mark on the history of these oligosaccharides. He is considered the "Founding Father" of cyclodextrin (Szejtli 1982a; Crini 2014).

At the beginning of the last century, Schardinger also observed the formation of dextrins during his investigations of resistant microorganisms that can lead to food poisoning (Fig. 1.4). Like other researchers at that time, Schardinger studied these dextrins with the expectation that they would shed some light on the synthesis and degradation of starch. In 1903, Schardinger discovered that a type of extremely heat-resistant microorganism was able to dissolve starch and form crystalline by-products (Schardinger 1903a), remarkably similar to *cellulosines* reported by Villiers. Using the iodine test, Schardinger distinguished two types of *krystallisiertes dextrins* which he called crystallized dextrin A and crystallized dextrin B. The B form resembled Villiers' cellulosine. Indeed, the chemical behavior and the physical constants given by Schardinger for his substance agree very well with those of the dextrin previously described by Villiers. Schardinger found that it was possible to isolate pure fractions with a maximum yield of 30% crystallized dextrins from starch, the main form obtained being always dextrin B. *Krystallisiertes dextrins*

Zeitschrift
für
Untersuchung der Nahrungs- und Genußmittel,
sowie der Gebrauchsgegenstände.

Heft 19. 1. Oktober 1903. 6. Jahrgang.

Über thermophile Bakterien aus verschiedenen Speisen und Milch,
sowie über einige Umsetzungsprodukte derselben in kohlenhydrathaltigen Nährlösungen, darunter krystallisierte Polysaccharide (Dextrine) aus Stärke.

Von

Franz Schardinger.

Mitteilung aus der K. K. Allgemeinen Untersuchungsanstalt für Lebensmittel in Wien.

Im vergangenen Jahre hatte die hiesige Anstalt die Frage der Zulässigkeit des Genusses längere Zeit hindurch warm aufbewahrter Speisen zu prüfen, wobei sich im Verlaufe der Untersuchung beachtenswerte mikrobiologische Funde ergaben, über die im nachstehenden eingehender berichtet werden soll. Auf Grund der Forschungsergebnisse über thermophile Bakterien konnte es keinem Zweifel unterliegen, daß bei der in Betracht kommenden Temperatur zwischen 50—60° bakterielles Leben überhaupt möglich ist, es war also zunächst festzustellen, ob in den Speisen derartige Keime vorhanden und welcher Art die von ihnen veranlassten Zersetzungen sind, soweit eine Feststellung in letzter Beziehung derzeit möglich ist.

Fig. 1.4 First page of the article published by Schardinger on dextrins in 1903

were first considered as the degradation products of starch through heating (Schardinger 1903a). Schardinger also managed to isolate the strain of bacteria responsible for the degradation of starch – he called it *strain II* (Schardinger 1903b). He observed that this heat-resistant organism had considerable starch-fermenting power. When sub-cultured on starch, *strain II* broke down starch, giving an alcohol-insoluble "soluble starch" together with crystallized dextrin A (fine hexagonal plates) and crystallized dextrin B (stout prismatic crystals). Schardinger also observed that with time, the activity of the *strain II* microorganism decreased. Indeed, he was unsuccessful in maintaining a culture of *strain II* which had the characteristic starch-degrading activity.

In 1904, Schardinger isolated a new microorganism, considered as "an accidental contaminant," which he first called *Rottebacillus I* owing to its action on potato starch, i.e., it produced acetone and ethyl alcohol by fermentation of carbohydrate media (Schardinger 1904). The name *Rottebacillus I* was used to express the fact

Bacillus macerans, ein Aceton bildender Rottebacillus.

[Mitteilung aus der k. k. Untersuchungsanstalt für Lebensmittel in Wien.]

Von **Franz Schardinger.**

Ueber die durch den genannten Mikroben bewirkte Acetongärung wurde bereits in No. 8 der Wiener klinischen Wochenschrift, Jahrg. 1904 berichtet. Die Ergebnisse fortgesetzter Studien über diese Gärung und die Verrottung pflanzlicher Gebilde sollen im nachfolgenden einem weiteren Leserkreise unterbreitet werden.

Fig. 1.5 Abstract of the article published in the journal *Wiener Klinische Wochenschrift* by Schardinger on *Bacillus macerans* in 1904

the microorganism was able to form both acetone and ethyl alcohol. Several months later, Schardinger used the Latin term *Bacillus macerans* to name his microbe, i.e., *macerare*, to rot (Fig. 1.5). This bacillus was able to give the same crystalline dextrins as before, which he designated as *krystallisiertes polysaccharides*, i.e., crystallized polysaccharides, considered then as the intermediate decomposition products of starch (Schardinger 1904). Using the characteristic reaction that starch derivatives show with iodine, Schardinger proposed a distinction between a "crystallized amylose" and a "crystallized amylodextrin." The yields obtained were tenfold those reported by Villiers. To explain this result, Schardinger suggested that, in the conditions of sterilization described by Villiers, the bacillus used was "probably not pure" (Schardinger 1904). One year later, Schardinger was also the first to observe that different starchy substrates differed in their behavior with *Bacillus macerans*, especially in the yields obtained (Schardinger 1905).

1.2.2 The Foundation of the Cyclodextrin Chemistry

Schardinger is acknowledged as being the first to lay down the basis of the cyclodextrin chemistry (French 1957a; Thoma and Stewart 1965; Szejtli 1998). Indeed, he was the first researcher to describe the fundamental properties of *cellulosines*, to introduce the terms crystallized α-dextrin and crystallized B-dextrin, to isolate the microorganism able to synthesize the enzyme that catalyzes the degradation of starch into crystallized dextrins, to hypothesize that the crystallized substances were cyclic "polysaccharides," and also to suggest their ability to form complexes.

Between 1905 and 1911, Schardinger made several important observations (Schardinger 1903a, b, 1904, 1905, 1909, 1911). He observed that *cellulosines* were often formed in starch-based media containing putrefying microorganisms. The formation of the two crystallized dextrins depended on the type of bacteria digesting starch. The distinction between the two forms was always made through their ability to form complexes of different colors with iodine. Schardinger also studied the chemistry of the two dextrins, pointing out their lack of reducing power and hydrolysis to reducing sugar. Dextrins were non-reducing to copper reagents and

non-fermentable by yeast. Schardinger also reported their behavior in the presence of alcohols, chloroform, ether, and iodine solution. He used the complexes with these solvents as a means of precipitation of dextrins (Schardinger 1911). This was the first indication of the ability of dextrins to form "inclusion" complexes (Crini 2014). Finally, Schardinger proposed empirical formulae of dextrins. However, he did not propose a structure for his crystallized dextrins and also did not attempt their molecular-weight determinations. It will take another 20 years before the cyclic nature of Schardinger dextrins will be recognized. Professor Schardinger decided to stop his research into dextrins in 1911, and as a conclusion he wrote: "I realize that still very many questions remain unsolved; the answer to these I must leave to another, who, owing to more favorable external conditions, can deal with the subject more intensively."

In the 24 years following Schardinger's final paper (Schardinger 1911), the field of research on crystallized dextrins was dominated by the groups of Pringsheim and Karrer. Pringsheim is recognized as the first researcher to have published prolifically on dextrins. However, the works were repetitive, marred by frequently contradictory results and by even hot debate between the two groups (French 1957a; Szejtli 1998; Crini 2014; Morin-Crini et al. 2015).

1.3 Historical Landmarks in the Exploration of Cyclodextrins: From 1911 to 1970

1.3.1 Nomenclature

In 1891, cyclodextrin was initially called *cellulosine* by Villiers because he assumed that the novel crystalline substance, obtained from digests of *Bacillus amylobacter*, was *une sorte de cellulose*, i.e., a kind of cellulose (Crini 2014).

In 1903, Schardinger reported the formation of two *krystallisiertes dextrins* during his investigations of food spoilage, which he called crystallized dextrin A and crystallized dextrin B, because most of their properties were similar to the already known partial degradation products of starch, i.e., the dextrins (Schardinger 1903a, b). One year later, the *krystallisiertes dextrins*, considered as the intermediate crystallized decomposition products/by-products of starch, were designated by the term *krystallisiertes polysaccharides*, i.e., crystallized polysaccharides (Schardinger 1904). Pursuing his investigations on the structure of starch, Schardinger then introduced a distinction between a *crystallized amylose* for dextrin A and a *crystallized amylodextrin* for dextrin B, because, for him, there was an analogy between his dextrins and amylose and amylodextrin, especially with respect to their iodine color reactions (Schardinger 1905, 1907). Finally, Schardinger considered that these names were inappropriate and thus decided to rename it *crystallized dextrin*-α and *crystallized dextrin*-β (Schardinger 1911).

In the mid-1910s, the German chemist and biochemist Hans Pringsheim used the name of *krystallisiertes polyamylosen*, i.e., crystallized polyamyloses, distinguishing two series, the α-series of dextrins containing 2n D-glucose units per molecule and the β-series containing 3n D-glucose units per molecule. Four substances, i.e., α-diamylose, α-tetraamylose, α-hexaamylose, and α-octaamylose, were included in the α-series of dextrins, while the β-series only contained two substances, i.e., β-triamylose and β-hexaamylose. Indeed, for Pringsheim, the Schardinger dextrins arose through the bacterial depolymerization of starch to the fundamental units: the amylose fraction being broken down into the α-series of dextrins, i.e., polyamyloses, and the amylopectin fraction being degraded to the β-series (French 1957a; Thoma and Stewart 1965; Caesar 1968; Szejtli 1998; Morin-Crini et al. 2015). Pringsheim also used the terms of α-amylosan, α-allo-amylosan, and α-iso-amylosan and β-amylosan, β-allo-amylosan, and β-iso-amylosan for α-dextrin and β-dextrin, respectively (Crini 2014). At the same time, the Swiss chemist Paul Karrer also introduced the notion of series of crystallized dextrins. Like Pringsheim, Karrer was convinced that the α-series of dextrins was composed of at least four distinct substances differing in molecular size. However, he disagreed with the subdivision of the β-series into triamylose and hexaamylose. For Karrer, these two products were identical. In addition, Karrer regarded maltose as the fundamental unit of the whole of the starch molecule, while Pringsheim considered the polyamyloses as the basic units of the starch molecule (French 1957a; Thoma and Stewart 1965; Caesar 1968; Szejtli 1998; Morin-Crini et al. 2015). Like Pringsheim, Karrer also used the amylosan-based terminology (Crini 2014).

In the 1920s, as a tribute of the pioneering work of Schardinger, the German chemist Karl Johann Freudenberg called them "Schardinger dextrins" and referred to these compounds as α-dextrin and β-dextrin (French 1957a; Thoma and Stewart 1965; Caesar 1968; Szejtli 1998; Loftsson and Duchêne 2007; Kurkov and Loftsson 2013; Morin-Crini et al. 2015) and later as pentaosan and hexaosan, respectively (Crini 2014). For many years, cyclodextrins were called "Schardinger dextrins" in his honor, almost up to the 1970s, or also sometimes simply as dextrins (Szejtli 1998). Schardinger dextrins were subsequently named "cycloamyloses" by the American chemist Dexter French in 1942 (French and Rundle 1942), "cycloglucanes" by Freudenberg in 1943 (Freudenberg 1943), and finally "cyclodextrins" in 1949 by the German chemist Friedrich Cramer, a pupil of Freudenberg (Cramer 1949). The model of "cycloamyloses" was constructed from glucopyranose units in the boat conformation. For French, α-dextrin, β-dextrin, and γ-dextrin must be called cyclohexaamylose, cycloheptaamylose, and cyclooctaamylose, respectively, the Greek prefix to the "amylose" corresponding to the degree of polymerization, i.e., indicating the number of glucose units in the ring (French and Rundle 1942). However, at that time, Freudenberg claimed that "this new nomenclature was inappropriate and ambiguous" (Freudenberg 1943). Again, in 1947, Freudenberg wrote: "It appears to be premature to rename the α-dextrin cyclohexa-amylose and the β-dextrin cycloheptа-amylose" (Freudenberg et al. 1947a, b). In 1943, Freudenberg proposed the cycloglucane-based nomenclature, e.g., cyclohexaglucane α(1→4), cycloheptaglucane α(1→4), and cyclooctaglucane α(1→4) for α-dextrin, β-dextrin,

and γ-dextrin, respectively (Freudenberg 1943). During the mid-1940s, there was another system in current use (Crini 2014). In the alternate system, the number of residues in the cyclic polymer was indicated by prefixing a Greek letter to the series name. Since the smallest known cycloamylose was a hexamer, it was assigned the prefix α. The cyclic heptatose, octaose, etc. were referred to, respectively, as β, γ, etc. The first system introduced by French was however preferred because it was more descriptive of the structures.

At the end of the 1940s, Cramer first proposed the cyclo-based nomenclature for the nomenclature of the Schardinger dextrins, e.g., (6-ose)-cyclo, (7-ose)-cyclo, and (8-ose)-cyclo for α-, β-, and γ-dextrins, respectively. For the first time in 1949, Cramer introduced the term cyclodextrin. This name was included in the title of his PhD dissertation entitled *Die Cyclodextrine aus Stärke* (Cramer 1949). For Cramer, the term of cyclodextrin must be used to refer to cyclic oligosaccharides made up of 6, 7, or 8 units of D-glucose joined by α-(1 → 4) linkages termed α-, β-, and γ-cyclodextrin, respectively. Because of its relative brevity, the term cyclodextrin was soon accepted, but the nomenclature of cyclodextrins remained a subject of debate until the end of the 1990s (Szejtli 1998; Loftsson and Duchêne 2007; Kurkov and Loftsson 2013; Crini 2014; Morin-Crini et al. 2015). Indeed, at that time, several laboratories proposed clarifications of the nomenclature of cyclodextrins because the term cyclodextrin only specified the nature of the sugars but did not give any information on the bonding between them. Thus, the name cyclomaltohexaose was suggested in 1997. This name is composed of first the term cyclo followed by a term indicating the type of linkage, i.e., malto for glucose unit bound by α-(1→4) linkages, and the number of sugar units with the ending ose, i.e., hexa for 6 or hepta for 7. This final term, present in cyclomaltohexaose, implies a free anomeric center, which is not present in cyclodextrins. Both the terms cyclodextrins and cyclomaltooligosaccharides were used (Crini 2014).

Other nomenclatures have also been proposed. For instance, α-cyclodextrin was named cyclohexakis-(1→4)-α-D-glycosyl or cyclo-α-(1→4)-glucohexaoside. The term of the glycosyl residue is preceded by the type of linkage between brackets, which in turn is preceded by the term cyclo plus an indication of the number, i.e., cyclohexakis, etc. The literature uses all of these nomenclatures. Nevertheless, the cyclodextrin-based nomenclature is still the most widely used in literature today. The nomenclature for large-ring cyclodextrins, i.e., LR-CDs with a degree of polymerization between 9 and >100, is more simple: each molecule is designated by an abbreviation CDn where *n* indicates the number of glucose units in the macrocycle, e.g., CD14 (boat-like structure) composed of 14 glucose units (Morin-Crini et al. 2015; Assaf et al. 2016; Sonnendecker and Zimmermann 2019a, b; Sonnendecker et al. 2018, 2019).

1.3.2 Native Cyclodextrins

Schardinger recognized only dextrin-α and dextrin-β, while Freudenberg obtained γ-dextrin in 1948, although previously regarded by him as a cyclic heptasaccharide (Freudenberg and Cramer 1948). Two years later, Freudenberg elucidated the structure of γ-dextrin (Freudenberg and Cramer 1950). The same year, using partial acid hydrolysis and enzyme digestion followed by X-ray measurements and paper chromatography, French also elucidated the structure of γ-dextrin, first named *cycloöctaamylose* and later cyclooctaamylose (French et al. 1950b). This dextrin was composed of eight glucose residues symmetrically arranged in a ring and linked together by α-1,4-glucosidic bonds. In the late 1950s, French and co-workers had established the molecular weight, the exact chemical structure, the dimensions, and the types of bonding in the three cycloamyloses, cyclohexaamylose, cycloheptaamylose, and cyclooctaamylose, i.e., α-dextrin, β-dextrin, and γ-dextrin, respectively (French and McIntire 1950; Norberg and French 1950; French et al. 1950a, b).

In 1948, the first indications of the existence of higher homologues of dextrins were published by Freudenberg and his young student Cramer (Freudenberg and Cramer 1948). Two years later, French also suggested the possible existence of cycloamyloses containing more than 8 glycosyl units (Norberg and French 1950; French et al. 1950b). The same year, Akiya and co-workers claimed the "discovery of new series of cyclic oligosaccharides" similar to the Schardinger dextrins, containing more than 8 glucose units (Akiya and Watanabe 1950a, b, c; Akiya and Okui 1951). Later, Caesar (1968) reported that these "new" compounds were the α- and β-dextrins. In fact, the existence of larger homologues of cycloamyloses was clearly demonstrated a decade later by French. In 1957, French discovered delta-dextrin or δ-dextrin and epsilon-dextrin or ε-dextrin, containing 9 and 10 units of glucose, respectively (French 1957a, b). He proved their existence using radioautography and chromatography measurements. However, French elucidated their structures only in 1965 (French et al. 1965). At that time, French also wrote: "there is no obvious reason why the series should stop here" (French 1957a), suggesting the existence of cycloamyloses with 11 and 12 units of glucose, i.e., ξ-dextrin or zeta-dextrin and η-dextrin or eta-dextrin, respectively. In the beginning of the 1960s, French continued to study cycloamyloses with a larger ring. His objective was to develop a fractionation method for isolation of larger homologues of cycloamyloses after extensive β-amylase digestion to hydrolyze maltooligosaccharides. In 1961, the existence of cycloamyloses with 11 and 12 units of glucose is confirmed using radioautography (Pulley and French 1961), and 4 years later, he was the first to propose a fractionation method for their isolation (French et al. 1965). The structure and the dimensions of ξ-dextrin and η-dextrin are reported. French finally introduced the notion of Schardinger dextrin series, "a Schardinger dextrin family" (French et al. 1965). The same year, Thoma and Stewart (1965) also published similar results, and the discovery of ξ-dextrin and η-dextrin is attributed to them (Caesar 1968; Szejtli 1998; Loftsson and Duchêne 2007).

French's results had for many years been regarded as dubious since they were not able to experimentally distinguish the large cyclodextrins from branched derivatives. As late as 1988, Szejtli expressed his doubts, in his monograph *Cyclodextrin Technology*, to whether cyclodextrins larger than γ-cyclodextrin exist (Szejtli 1988). In fact, higher cyclic cyclodextrins than the three native cyclodextrins, reported in the 1960s, were probably so-called branched derivatives such as branched diglucosyl-cyclodextrins. When a section of the amylopectin molecule containing a branching point was incorporated into a cyclic structure, one or two glucosyl or maltosyl side chains were attached by α-(1→6) linkages to the ring formed (Frömming and Szejtli 1994). During the production of native cyclodextrins, these branched cyclodextrins were also produced. It was only during the mid-1990s that the existence of the large cyclodextrins has been fully proven (Miyazawa et al. 1995; Endo et al. 1997, 1999; Larsen 2002; Qi et al. 2004; Taira et al. 2006; Crini 2014).

1.3.3 Cyclodextrin Chemistry

For over 20 years, Pringsheim and his various collaborators penned an abundant literature on dextrins. Indeed, Pringsheim is considered to be the first researcher to have published prolifically on their preparation and chemistry (Pringsheim and Langhans 1912; Pringsheim and Eissler 1913, 1914; Pringsheim 1915, 1919, 1922, 1924, 1925, 1926, 1927, 1928a, b, 1931a, b, 1932; Pringsheim and Lichtenstein 1916; Pringsheim and Persch 1921, 1922; Pringsheim and Dernikos 1922; Pringsheim and Goldstein 1922, 1923; Pringsheim and Beiser 1924, 1932; Irvine et al. 1924; Pringsheim and Leibowitz 1924, 1925a, b, 1926a, b; Pringsheim and Steingroever 1924, 1926; Pringsheim and Wolfsohn 1924; Pringsheim and Schapiro 1926; Pringsheim and Meyersohn 1927; Irvine et al. 1929; Pringsheim et al. 1930, 1931a, b). However, these studies suffered from numerous errors due to the use of dextrins that were not pure and to problems arising from separation of the fractions and from the use of unsuitable analytical methods, e.g., determination of the masses by cryoscopy (Freudenberg and Jacobi 1935; Samec and Blinc 1941; French 1957a; Thoma and Stewart 1965; Caesar 1968). In 1935, Freudenberg dismissed the work of Pringsheim as practically valueless, since "most of it was based upon work with dextrin mixtures and upon serious misconceptions relating to the structural principles of high polymers" (Freudenberg and Jacobi 1935). French (1957a) also wrote: "Pringsheim's literature was voluminous but much of it was repetitive, controversial, or based on erroneous concepts."

From 1910, Pringsheim repeated Schardinger's experiments. He reported higher yields of β-dextrin from glycogen crude preparations of amylopectin, and this is the reason why he postulated that amylose was polymerized α-diamylose and amylopectin and glycogen were polymerized β-triamylose. Like Schardinger, Pringsheim observed that the relative proportions of α- and β-dextrins depended on the different substrates used (Pringsheim and Langhans 1912). Pringsheim described the

chemical behavior of dextrins and their properties, in agreement with the previous results published by Schardinger. The dextrins were soluble in water but insoluble in alcohol, ether, and chloroform. They do not reduce Fehling's solution. To precipitate the dextrins, different solvents including benzene, toluene, xylene, bromobenzene, nitrobenzene, and petroleum ether were proposed (Pringsheim and Eissler 1913, 1914; Pringsheim 1915; Pringsheim and Lichtenstein 1916). Pringsheim confirmed that the simplest means to distinguish between the α- and β-dextrins was the iodine reaction (Pringsheim 1922; Pringsheim and Dernikos 1922). Pringsheim was the first to study the halogen complexes of dextrins (Pringsheim and Wolfsohn 1924; Pringsheim and Schapiro 1926). The first methylated β-dextrin was also obtained by his group: 43.6% of degree of methylation as against 45.6% required by theory. The compound was crystallized from ether (Pringsheim and Goldstein 1923). Several data can also be found referring to the preparation of dextrin derivatives including acetates, nitrates, and ethers (Pringsheim 1927, 1928a, b, 1931b; Pringsheim and Meyersohn 1927; Irvine et al. 1929; Pringsheim et al. 1930, 1931a, b; Pringsheim and Beiser 1932). However, all Pringsheim's data are essentially of historic interest (Samec and Blinc 1941; French 1957a; Thoma and Stewart 1965; Caesar 1968; Szejtli 1982a; Crini 2014). From 1920 to 1925, Karrer also contributed greatly to the knowledge of the chemistry of the Schardinger dextrins (Thoma and Stewart 1965; Caesar 1968; Szejtli 1998; Crini 2014). Karrer published several important works on dextrins (Karrer 1920, 1921, 1922, 1923, 1925; Karrer and Nägeli 1921a, b; Karrer et al. 1921, 1922; Karrer and Bürkin 1922). Like Schardinger and Pringsheim, Karrer studied the crystallized dextrins with the expectation that they would shed some light on the features of starch. In 1921, Karrer published the first conclusions on the acetolysis of α-dextrin and β-dextrins. He demonstrated that this reaction gave essentially the same excellent yield of maltose as starch or maltose itself gives, when treated similarly (Karrer 1921; Karrer and Nägeli 1921a, b; Karrer et al. 1921). Karrer also investigated the interactions between dextrins and ions such as barium, sodium, and potassium (Karrer 1922; Karrer and Bürkin 1922; Karrer et al. 1922). In 1925, Karrer summarized the whole of his works and conclusions on dextrins in a famous comprehensive book (Karrer 1925).

Between 1911 and 1935, epoch called by Crini (2014) the "period of doubt," other researchers have also published interesting works on the chemistry of the Schardinger dextrins (Biltz 1913; Biltz and Truthe 1913; Freudenberg and Ivers 1922; Miekeley 1930, 1932; Ulmann 1932, Ulmann et al. 1932; Hess et al. 1933). Miekeley (1930, 1932) published experimental data on the chemical composition of dextrins, which complemented those of Pringsheim. In 1933, Ulmann's group observed that the α-dextrin-ethanol complex had two different crystal modifications which could be interconverted. This was the first observation that a same guest may form different crystal structures with the same dextrin (Hess et al. 1933). However, this period did nothing to stimulate the development of Schardinger dextrins, considered as by-products of starch degradation. So, the work on cyclodextrins reported before 1935 was of little consequence (Samec and Blinc 1941; Thoma and Stewart 1965; Caesar 1968; Szejtli 1998; Crini 2014). This can be explained by the fact that researchers used

incompletely separated fractions and based too much reliance on cryoscopic measurements of molecular weights, which led to many anomalous results.

From 1935 to 1950, epoch called by French (1957a) the "maturation period," the works of Freudenberg on the chemistry of the Schardinger dextrins were acknowledged to have made an important contribution to the cyclodextrin science (Freudenberg and Jacobi 1935; Freudenberg and Rapp 1936; Freudenberg et al. 1936, 1938, 1939, 1947a, b; Freudenberg and Meyer-Delius 1938, 1939; Freudenberg 1939, 1943; Freudenberg and Cramer 1948, 1950). Indeed, Freudenberg is recognized as a pioneer in this domain (Thoma and Stewart 1965; Caesar 1968). As far back as 1922, Freudenberg was the first researcher to focus on the chemical modification of dextrins, in particular of tosylated residues (Freudenberg and Ivers 1922). Later, the Schardinger dextrins were oxidized by iodite, "probably by a glycol-cleavage reaction" (Freudenberg 1934). Enzymatic hydrolysis gave no trace of a sugar unit other than *D*-glucose (Freudenberg and Jacobi 1935). During the hydrolysis of dextrins, Freudenberg also observed an increase in rotation due to hydrolysis of the β-linkage. During acetolysis, the dextrins were shown to be more nearly similar to starch than to compounds of the levoglucosan type. Using a cryoscopic method for the determination of molecular weights, Freudenberg reported (erroneously) the number of glucose units that the Schardinger dextrins contained: five for A-dextrin and six for β-dextrin (Freudenberg and Jacobi 1935). In 1936, Freudenberg confirmed that enzymatic hydrolysis gave no trace of a sugar unit other than D-glucose. He also reported that methylation studies failed to reveal the presence of any *D*-glucose units, concluding that glucose was the only product of acid hydrolysis of dextrins (Freudenberg and Rapp 1936). The following pieces of experimental evidence were also published: (i) the rate of hydrolysis of dextrins in 51% sulfuric acid was too low for there to be any labile β-linkages present; (ii) the Schardinger dextrins were non-reducing, that is, they did not have a reducing chain termination; and (iii) methylation studies on dextrins gave no products than 2,3,6-*O*-methyl-*D*-glucose (Freudenberg and Rapp 1936). The same year, Freudenberg prepared fully methylated α- and β-dextrins and finally demonstrated that 2,3,6-tri-methylglucose was the only product of methylation of dextrins followed by hydrolysis (Freudenberg et al. 1936). Later, acetate derivatives of the dextrins were proposed and characterized for the first time (Freudenberg et al. 1947a, b). In 1955, Freudenberg published a detailed description of the chemistry of the three main cyclodextrins (Freudenberg 1955), and in 1962, he summarized all his results (Freudenberg 1962).

Between 1942 and 1950, French published numerous important contributions on the chemistry of the Schardinger dextrins (French and Rundle 1942; Rundle and French 1943; Bates et al. 1943; French et al. 1948, 1949a, b, 1950a, b, 1954; French and McIntire 1950; Norberg and French 1950). Very quickly, like Freudenberg, French became a pioneer in the understanding of their chemistry (Thoma and Stewart 1965; Caesar 1968; Szejtli 1998; Crini 2014). French showed that the Schardinger dextrins, being cyclic, had no non-reducing end group and they were extremely resistant to alpha-type amylases. Using data from periodate oxidation and methylation reactions, he demonstrated that Schardinger dextrins could not be open-chain compounds. Periodate oxidation was slow with Schardinger dextrins in

comparison with that of straight-chain amylodextrin. French published protocols for the methylation of Schardinger dextrins and showed that 2,3,6-tri-methylglucose was the only product of methylation of cycloamyloses followed by hydrolysis (French et al. 1950b), in agreement with the previous results published by Pringsheim (Pringsheim 1924, 1925, 1926; Pringsheim and Beiser 1924) and Freudenberg (Freudenberg and Meyer-Delius 1938; Freudenberg et al. 1938). French also published solubility data on cycloamyloses, especially in presence of organic liquids. Solubility data of dextrins in water at room temperature were as follows: α-dextrin 14.5 g/100 mL, β-dextrin 1.8 g/100 mL, and γ-dextrin 23.2 g/100 mL (French et al. 1949a). Using data from periodate oxidation and methylation reactions, French definitively demonstrated that Schardinger dextrins could not be open-chain compounds and they were regarded as conical cylinders (French and McIntire 1950; Norberg and French 1950; French et al. 1950a, b). At that time, Schardinger dextrins were also found to be rather anomalous structures with interesting complexing properties when compared with the linear oligosaccharides. French indeed suggested for the first time the fact that cycloamyloses were capable of forming particular complexes. The nature of the complexes between halogen and Schardinger dextrins, particularly the iodine complexes, depended much on the amount of the halides added. However, the cavity of dextrins was referred to as hydrocarbon in nature by French. This result has been definitively abandoned in 1965 with the advent of the modern conformational theory.

1.3.4 Molecular Structure of Schardinger Dextrins

Schardinger was the first to hypothesize that the crystalline substances were "cyclic polysaccharides" (Schardinger 1907, 1909, 1911). However, he never managed to elucidate their structure.

In 1920, Karrer was the first to suggest that the dextrins were made up of several components (Karrer 1920), and 1 year later, he proved it using detailed acetolysis data (Karrer 1921; Karrer and Nägeli 1921a, b; Karrer et al. 1921). In 1923, Karrer was also the first to propose that dextrins are composed of maltose units only joined by α-(1→4) glucosidic linkages (Karrer 1923, 1925), although Pringsheim (1922, 1924) remained unconvinced by Karrer's conclusions. Figure 1.6 is a schematic illustration of two glucopyranose units of a dextrin molecule showing details of the α-(1→4) glucosidic/glycosidic linkage and the numbering systems employed to describe the glucopyranose rings. Later, Miekeley (1930, 1932) also came to the same conclusions as Karrer. In 1926, Pringsheim is finally convinced by Karrer's conclusions (Pringsheim 1926) although he continued to regard the polyamyloses as the basic units of the starch "molecule" (Pringsheim 1928a, 1931a). However, just like Schardinger, Karrer, and Miekeley, Pringsheim failed to elucidate the cyclic structure of the dextrins.

From 1934 for a period of approximately 25 years, the main contributions toward the molecular structure and size of the Schardinger dextrins were developed by

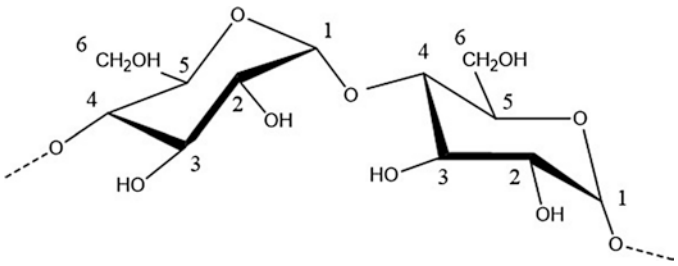


Fig. 1.6 Schematic illustration of two glucopyranose units of a dextrin molecule showing details of the α-(1→4) glycosidic linkage and the numbering systems employed to describe the glucopyranose rings

Freudenberg (Freudenberg 1934, 1939, 1943, 1955, 1957a, b; Freudenberg and Jacobi 1935; Freudenberg and Rapp 1936; Freudenberg et al. 1936, 1938, 1939, 1947a, b, 1953; Freudenberg and Meyer-Delius 1938, 1939; Freudenberg and Cramer 1948, 1950). From 1922, Freudenberg was attracted by Schardinger dextrins since he wanted to obtain information on the degradation products of starch to be able to elucidate its structure (Freudenberg and Ivers 1922). For Freudenberg, Schardinger dextrins were first laboratory curiosities and/or unwanted by-products of starch degradation (Freudenberg 1934), and their chain molecules were intermediate between maltose and starch with non-reducing end groups. Indeed, it is only at the end of the 1930s that Freudenberg concluded that the dextrin-α and dextrin-β molecules were cyclic. In 1935, α-dextrin was considered as a mixture of chain molecules containing 4–5 *D*-glucose units (Freudenberg and Jacobi 1935). Using results of constructing molecular models with the monomer units in a boat rather than a chain conformation, the dextrins were lined with a hydrocarbon interior. One year later, studying the nature of the glycosidic bonds, Freudenberg showed that the dextrins gave rotation-time curves closely parallel to those given by starch and the rigid models such as Kekulé model did not allow free rotation about the individual bonds (Freudenberg and Rapp 1936). The presence of a *Konstellation*, i.e., a ring conformation, is suggested, and in 1936, Freudenberg hypothesized that A-dextrin and β-dextrin have a cyclic structure (Freudenberg et al. 1936). During 2 years, he tried to prove it. On the basis of results obtained from methylation reactions and enzymatic hydrolysis of the dextrins, Freudenberg came, in 1938, to the "same conclusion" as Schardinger, Karrer, Pringsheim, and Miekeley, concerning the cyclic chemical structure of A-dextrin and β-dextrin (Freudenberg and Meyer-Delius 1938; Freudenberg et al. 1938). Ten years later, Freudenberg and his doctoral student Cramer finally demonstrated his conclusion using optical activity data (Freudenberg and Cramer 1948). Schardinger dextrins had a cyclic structure composed of maltose units bound together by α-(1→4) glycosidic linkages. At that time, both French and Borchert also confirmed the cyclic structure of dextrins by X-ray crystallography (French et al. 1948; Borchert 1948). However, although Freudenberg had determined for the first time the correct chemical structure for the Schardinger dextrins, the number of D-glucosyl residues that he gave for the α- and β-dextrin

rings, i.e., five and six, respectively, using a cryoscopic method were incorrect. The correct values were determined by French using both X-ray diffraction and crystal density measurements.

Between 1942 and 1965, French also contributed greatly to the molecular structural knowledge of the Schardinger dextrins, or, as he preferred to call them, cycloamyloses (Caesar 1968; Szejtli 1998; Crini 2014). Very quickly, French became a pioneer in the understanding of their structure, publishing an impressive number of results on cycloamyloses which are still used as references today (French and Rundle 1942; Rundle and French 1943; Bates et al. 1943; French et al. 1948, 1949a, b, 1950a, b, 1954; French and McIntire 1950; Norberg and French 1950; French 1957a, b, 1960, 1962; Bailey and French 1957; Thoma and French 1958, 1959, 1960, 1961; James et al. 1959; Thoma et al. 1959; Whelan et al. 1960; Pulley and French 1961; Robyt and French 1964; French and Abdullah 1965; French et al. 1963, 1965). French's first work concerned the molecular weights of the Schardinger dextrins, considered as cyclic molecules in agreement with the previous results published by Freudenberg (Freudenberg and Meyer-Delius 1938; Freudenberg et al. 1938). French and Rundle (1942), using the X-ray diffraction technique and crystal density measurements, determined the molecular weights of α-dextrin and β-dextrins and discovered the exact number of glucose units per dextrin, i.e., six and seven, respectively, in disagreement with the results published by Freudenberg and Jacobi (1935). French and Rundle demonstrated that molecular weights were integral multiples of the value 162.1 for a glucose residue. They concluded that the X-ray diffraction technique was better suited to the determination of the molecular weights of high molecular weight crystalline substances since impurities, such as solvent of crystallization and inorganic ash, were of minor importance (French and Rundle 1942). In this paper, French also suggested that Schardinger dextrins were cyclic "macromolecules," formed from starch polysaccharide (French and Rundle 1942). They were non-reducing "D-glucopyranosyl polymers" containing 6, 7, or 8 units linked by α-*D*-(1→4) bonds, in agreement with the results published by Karrer (1923) and Miekeley (1932). In each cycloamylose "macromolecule," the *D*-glucose units were in the C1 conformation. Schardinger dextrins were then regarded as cylinders (French and Rundle 1942). However, Freudenberg did not agree with this point of view (Freudenberg 1943).

French pointed out three interesting features: (1) as a consequence of the C-1 conformation of the glucopyranose units, all the secondary hydroxyl groups were located on one side of the cylinder, whereas all the primary hydroxyl groups were located on the opposite side of the cylinder; (2) the interior of the cylinder consisted only of a ring of C-H groups, a ring of glucosidic oxygens, and another ring of C-H groups; and (3) the interior of the cavity was relatively apolar compared to water (French and Rundle 1942; Rundle and French 1943; Bates et al. 1943; French et al. 1948, 1949a, b). Freudenberg claimed again that all the structural and conformational conclusions of French were ambiguous due to "the use of products that were not pure" (Freudenberg et al. 1947a, b). One year later, Freudenberg and Cramer concurred with French's results, after studying the X-ray measurements of Borchert (1948) and also his optical rotation data, publishing similar interpretations

(Freudenberg and Cramer 1948; Cramer 1949). In 1950, French, studying the periodate oxidation of the three cycloamyloses, finally concluded that all three molecules had a cyclic structure in which each *D*-glucose unit was linked to the next by an α-*D*-(1→4)-glucosidic bond, and the interior of the cavity was apolar (French and McIntire 1950; Norberg and French 1950; French et al. 1950b). Schardinger dextrins were then regarded rather as conical cylinders than cylinders, in agreement with Cramer's suggestion. Another interesting feature is made by French: γ-dextrin was "a noncoplanar, more flexible structure," and therefore, it was the "most soluble of the three dextrins." Later, cycloamyloses were finally regarded as truncated cones or "capsules" by French (French 1957a), in agreement with the results published by Cramer (Cramer 1952, 1953, 1956; Dietrich and Cramer 1954).

Cramer also contributed greatly to the molecular structural knowledge of the Schardinger dextrins. In 1948, the young student Cramer published his first result on Schardinger dextrins (Freudenberg and Cramer 1948). Using optical activity, Cramer demonstrated the cyclic nature of α- and β-dextrins. The same year, he discovered γ-dextrin and suggested that the three dextrins possessed an apolar cavity. One year later, Cramer received his PhD at Heidelberg University, under the supervision of Freudenberg (Cramer 1949). He introduced the cyclodextrin-based nomenclature, demonstrated the cyclic nature of cyclodextrins using optical activity data, and showed that the three cyclodextrins had different internal diameters and each cavity was filled with water molecules (Cramer 1949). His doctoral work was then published between 1951 and 1952 (Cramer 1951a, b, c, 1952), adding to the previous results of Freudenberg but mostly "confirming those of French" on the physical (cavity size) and chemical (reactivity) properties, the structure, and chemistry of cyclodextrins. For instance, investigating the configuration at the anomeric centers by hydrolytic methods, Cramer came to the same conclusions as Karrer (1923), Miekeley (1932), and French (French and Rundle 1942) as to the existence of α-(1→4) glucosidic/glycosidic linkages. Cramer also published for the first time a variety of other interesting features. Studying the molecular size of the three dextrins, he showed that a same dextrin could exist in different crystal forms. Cramer then discovered the toroidal form of the cyclodextrin molecules, considering cyclodextrins as truncated cones or "capsules" rather than cylinders, like previously reported by French (French et al. 1948, 1949a, b). The numbering system employed to describe the glucopyranose rings, reported in Fig. 1.5, was then accepted, and Cramer schematized his conclusions on the chemical structure of α-, β-, and γ-cyclodextrins by the two schemes reported in Fig. 1.7. Cramer finally concluded that cyclodextrins were non-reducing oligosaccharides containing 6, 7, or 8 units linked by α-*D*-(1→4) bonds, having both hydrophobic and hydrophilic regions. On the side where the secondary hydroxyl groups were situated, the diameter of the cavity was larger than on the side with the primary hydroxyls, since free rotation of the latter reduced the effective diameter of the cavity. Figure 1.8 illustrates the hydrophobic and hydrophilic regions of an α-dextrin "capsule" (Cramer 1953, 1956; Dietrich and Cramer 1954).

In 1965, both Casu et al. (1965) and Hybl et al. (1965) confirmed the conclusions published by French and Cramer on the cyclic structure of cyclodextrin and its

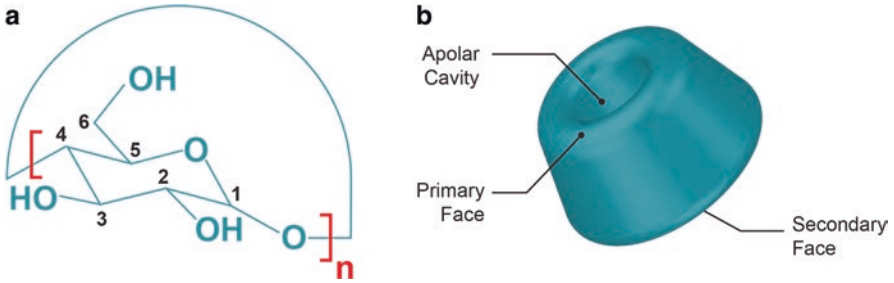


Fig. 1.7 Schematic representations of the (**a**) general chemical structure for cyclodextrins (n = number of glucose units; n = 6, 7, and 8 for α-, β-, and γ-cyclodextrin, respectively) and (**b**) their particular structure showing the apolar cavity of a cyclodextrin "capsule" or torus

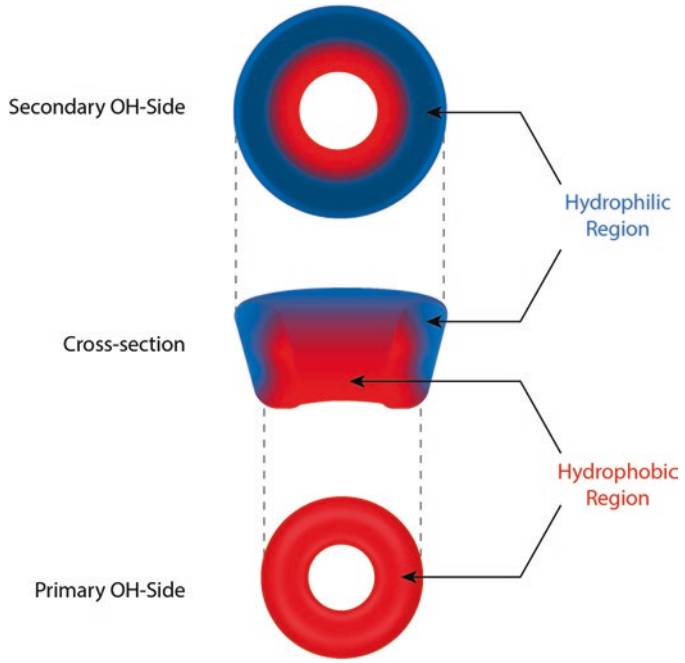


Fig. 1.8 Schematic representation of a dextrin "capsule" showing the hydrophobic and hydrophilic regions

features, using NMR spectra in dimethylsulfoxide solution and using X-ray crystallography of the α-cyclodextrin-potassium acetate complex, respectively. Their results clearly demonstrated that (i) all the glucose residues of cyclodextrins were in the ^{4}C1 chair conformation; (ii) the cavity was lined by the hydrogen atoms and the glycosidic oxygen bridges, respectively; and (iii) the nonbonding electron pairs of the glycosidic oxygen bridges were directed toward the inside of the cavity,

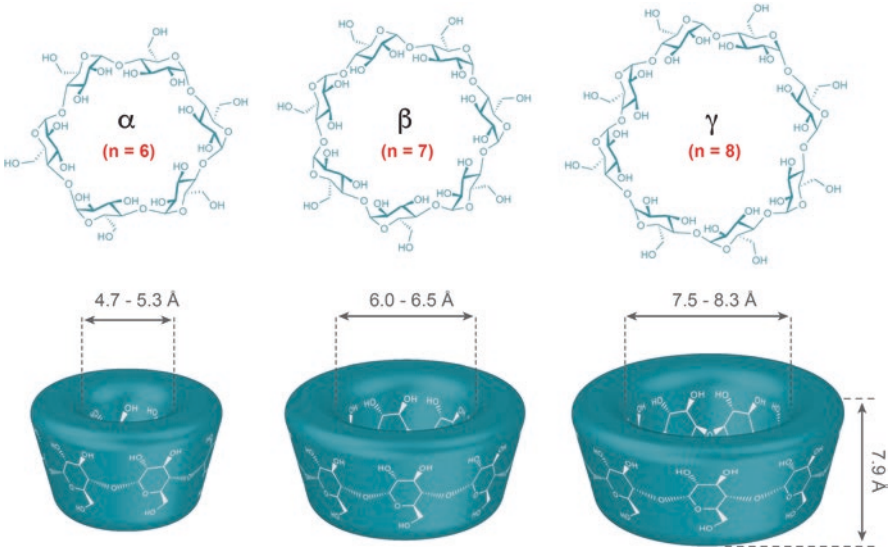


Fig. 1.9 Schematic representations of the chemical tridimensional structure and dimensions for α-, β-, and γ-cyclodextrins (*n* = 6, 7, and 8, respectively) accepted in the 1960s

producing a high electron density. The schematic diagram of two glucopyranose units of a cyclodextrin molecule showing details of the α-(1→4) glycosidic linkage reported in Fig. 1.6 and the schematic representations of the chemical tridimensional structure and dimensions (Fig. 1.9) for α-, β-, and γ-cyclodextrin are finally accepted at the mid-1960s. Later, a more precise study of the conformation of α-cyclodextrin in solution was made by Saenger's group using NMR spectroscopy (Wood et al. 1977). All six glucose units had identical conformations and the molecule had hexagonal symmetry. The secondary hydroxyl groups, which were located in one side of the torus of cyclodextrins, formed hydrogen bond with the secondary hydroxyl groups of contiguous glucose units, in agreement with the previous conclusions published by Casu et al. (1965) and by Hybl et al. (1965). In the cyclodextrin molecule, a complete secondary belt was formed by hydrogen bonds, making it a rigid structure. This was proposed to explain the fact that, among the three native cyclodextrins, β-cyclodextrin had the lowest solubility (Wood et al. 1977). The hydrogen belt was incomplete in the α-cyclodextrin molecule, and γ-cyclodextrin was a noncoplanar, more flexible structure, confirming the results published by French and McIntire (1950). At the beginning of the 1960s, French indicated the possible existence of "a Schardinger dextrin family," describing the structure of δ-dextrin, ε-dextrin, ξ-dextrin, and η-dextrin containing 9, 10, 11, and 12 glucose units, called larger homologues of cycloamyloses (Pulley and French 1961; French et al. 1965). These larger dextrins were not regular cylinder-shaped structures. Indeed, they were collapsed and their real cavity was even smaller than the γ-dextrin (Fig. 1.10).

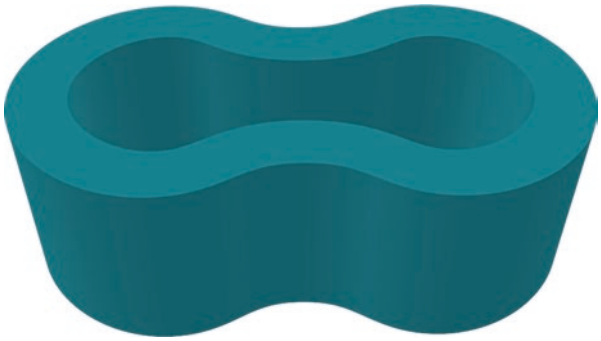


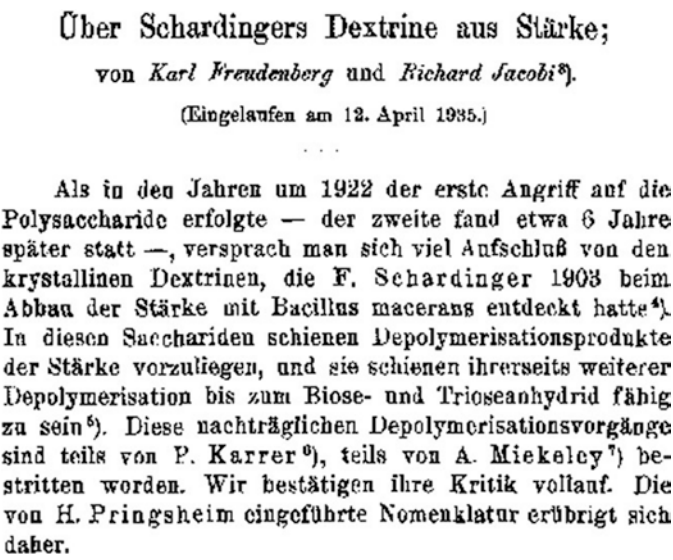
Fig. 1.10 Collapsed cylinder structure of δ-dextrin

1.3.5 Preparation and Separation of Schardinger Dextrins

Between 1905 and 1911, Schardinger studied the first preparation, fractionation/separation, and purification of the two *cellulosines* (Schardinger 1905, 1907, 1909, 1911). In 1911, he published the first fractionation and purification scheme of the dextrins. Later, both Freudenberg, French, and Cramer published other important schemes: see the references French (1957a) and Thoma and Stewart (1965).

The dextrins were synthesized from several sources of starch, e.g., potatoes, rice, and wheat, and bacteria, e.g., the formation of dextrins depended on the type of bacteria digesting starch. About 25–30% of the starch was converted to crystalline dextrins depending on these parameters. The yield was tenfold those reported by Villiers (Schardinger 1907). Schardinger also based his method of separation on the ease of crystallization of the β-dextrin from water and its low solubility, about 1.5% at room temperature, followed by precipitation of the α-dextrin from the mother liquor by the addition of alcohol. Schardinger' protocol was modified by Lange in 1925 who introduced trichloroethylene as a precipitating agent for the crystalline dextrins (Lange 1925). This protocol is described in detail in Pringsheim's book (Pringsheim 1932).

In 1935, Freudenberg and his student Jacobi described a method for the synthesis of Schardinger dextrins with high purity (Freudenberg and Jacobi 1935) (Fig. 1.11). Freudenberg is indeed recognized as the first to prepare almost pure dextrins with high yields (Thoma and Stewart 1965; Caesar 1968; Clarke et al. 1988; Szejtli 1998; Crini 2014). Freudenberg improved the separation of dextrins and produced a scheme based not only on solubility differences of the dextrins themselves, as initially proposed by Schardinger, but also on the differences in solubilities and rates of crystallization of their acetates (Freudenberg and Jacobi 1935). However, the protocol was difficult since it involved many acetylation and saponification reactions. During more than 10 years, this protocol was studied and modified, and in 1947, Freudenberg's group described the first scheme for the isolation of pure fractions of dextrins using bromobenzene as precipitant: α-dextrin did not precipitate, while β-dextrin and γ-dextrin were readily precipitated (Freudenberg et al. 1947a,



Über Schardingers Dextrine aus Stärke;

von *Karl Freudenberg* und *Richard Jacobi*[3].

(Eingelaufen am 12. April 1935.)

. . .

Als in den Jahren um 1922 der erste Angriff auf die Polysaccharide erfolgte — der zweite fand etwa 6 Jahre später statt —, versprach man sich viel Aufschluß von den krystallinen Dextrinen, die F. Schardinger 1903 beim Abbau der Stärke mit Bacillus macerans entdeckt hatte[4]. In diesen Sacchariden schienen Depolymerisationsprodukte der Stärke vorzuliegen, und sie schienen ihrerseits weiterer Depolymerisation bis zum Biose- und Triosean hydrid fähig zu sein[5]. Diese nachträglichen Depolymerisationsvorgänge sind teils von P. Karrer[6], teils von A. Miekeley[7] bestritten worden. Wir bestätigen ihre Kritik vollauf. Die von H. Pringsheim eingeführte Nomenklatur erübrigt sich daher.

Fig. 1.11 First page of the article of Professor Freudenberg published in 1935 where he described a method for the synthesis of Schardinger dextrins with high purity

b). This scheme was comprehensively discussed by French (1957a). In 1950, Freudenberg and Cramer also confirmed the possible existence of dextrins with 9 or 10 glucose units, identified during the preparation of α-, β-, and γ-dextrins (Freudenberg and Cramer 1950). However, these findings were only substantiated a decade later by French (Pulley and French 1961).

French was also among the early researchers, along with Freudenberg, to focus on improving the production of dextrins. French became a pioneer in the preparation of the compounds in a very pure state. Knowing the works of the group of Hudson on the enzymolysis conditions which affected the yield and proportion of the dextrins (Tilden and Hudson 1939, 1942; Tilden et al. 1942; McClenahan et al. 1942; Wilson et al. 1943) and using his own results on the solubilities of Schardinger dextrins (French et al. 1949a), French proposed in 1949 a new protocol for the separation and purification of dextrins (French et al. 1949b), which did not require the acetylation and saponification steps used by Freudenberg. Treatment of starch with the amylase of *Bacillus macerans* gave crude starch digests containing the three cycloamyloses, i.e., ~60% α-dextrin, ~20% β-dextrin, and ~ 20% γ-dextrin, together with small amounts of higher cycloamyloses. Moreover, the protocol permitted the facile separation of pure dextrins by differential precipitation using specific precipitants such as bromobenzene and propan-1-ol (French et al. 1949b). Later, French showed that high temperature cellulose column chromatography was one of the most effective methods for the quantitative analysis of mixtures of cycloamyloses (Pulley and French 1961; French et al. 1965). This method was required in connection with the production of cycloamyloses since these products were simultaneously produced from starch together with the higher series of cycloamyloses. In 1961,

French also reported the preparation, isolation, and partial characterization of large cyclodextrins with 9, 10, 11, and 12 glycosyl units in the macrocycle (Pulley and French 1961), identified during the preparation of α-, β-, and γ-dextrins like Freudenberg.

In the mid-1950s, Cramer also investigated the enzymatic production of cyclodextrins, their separation and purification, and characterization (Cramer 1955, 1956; Cramer and Steinle 1955; Cramer and Henglein 1957a, b). Cramer described an easy protocol to separate α-, β-, and γ-cyclodextrins from the digest by selective precipitation using appropriate organic compounds and optimize parameters, e.g., pH = 6 and temperature = 40 °C (Cramer 1956). The three cyclodextrins are precipitated by addition of a tetrachloroethylene-tetrachloroethane mixture, followed by the addition of *p*-cumene. α-Cyclodextrin was isolated by selective precipitation with cyclohexane, β-cyclodextrin with fluorobenzene, and γ-cyclodextrin with anthracene. Cramer explained his results by the difference in the sizes of cavities of the three cyclodextrins and concluded that the superiority of his method over previous procedures, particularly those of French, resided in the technical ease and the completeness of precipitation.

To summarize, during the periods of reaching maturity from 1935 to 1950 and of exploration from 1950 to 1970, the separation and the purification of the mixture were difficult (Crini 2014; Crini et al. 2018). The period of reaching maturity was also marked by several contradictory results, due, at least in part, to differences in the protocols used for the preparation of Schardinger dextrins and dubious purity of the samples (Thoma and Stewart 1965; Caesar 1968; Szejtli 1998). The work during these periods was even marred by hot debate between the different laboratories, especially those of Freudenberg and Cramer and of French. In addition, in the early 1950s, researchers had not fully realized the potential of cycloamyloses and had little faith in their complexation properties (Szejtli 1998). The three main cyclodextrins were considered just laboratory curiosities difficult to produce. In 1963, French was the first to propose the preparation of cycloamyloses on a larger-than-laboratory scale (French et al. 1963). However, at the end of the 1960s, French concluded that "cycloamyloses were very promising molecules although they remained very expensive products, available only in small amounts as fine chemicals, and also toxic."

1.3.6 The Action of Amylases on Cycloamyloses

Up to 1939, the Schardinger dextrins were known only as products of the bacterial breakdown of starch. For Freudenberg's opinion, *Bacillus macerans* was able to transform starch structure into cyclic and linear breakdown products, and starch was based upon a cyclic Schardinger nucleus with side branches which would be broken in the bacterial breakdown (Fig. 1.11). During the same period, Tilden and Hudson (1942), studying the bacteria that produced the dextrins, also concluded that the resulting Schardinger dextrins were derived from some basic configuration

pre-existing in the starch "molecule." Similar conclusions were published by Kerr (1942, 1943), Myrbäck (1942), and Samec (1942).

Using this concept, Freudenberg was the first scientist to investigate the enzymatic production of dextrins and to propose a first mechanism of action for *Bacillus macerans* (Freudenberg et al. 1938, 1939; Freudenberg and Meyer-Delius 1938, 1939; Freudenberg 1939). This mechanism indicated that the dextrins were preformed within the starch macromolecules (Freudenberg 1939), in agreement with the results of Hudson' group (Tilden and Hudson 1939). However, Freudenberg did not agree with the generally accepted point of view at that time concerning the nature of the bonding of the *D*-glucose units, and he rapidly abandoned this mechanism. Using the helical model of the structure of starch proposed by Hanes (1937) and the α-*D* nature of the glucose units, Freudenberg proposed a second mechanism based on a transglucosylation reaction (Fig. 1.12). He suggested that the enzyme involved was able to degrade the helical structure of the starch, i.e., the amylose fraction, and that there ensued a rearrangement of the glucose units which were then able to form a ring structure (Freudenberg et al. 1939; Freudenberg and Meyer-Delius 1939). Because of the helical arrangement, the first and fifth or sixth

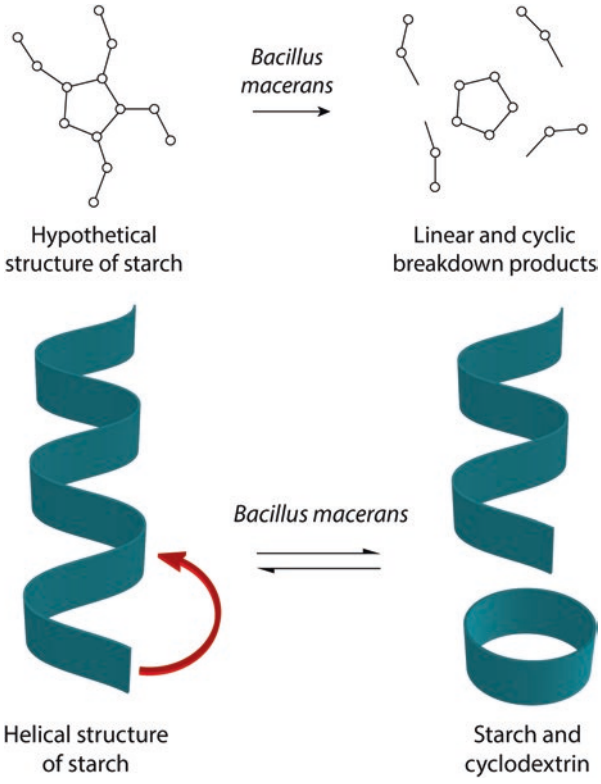
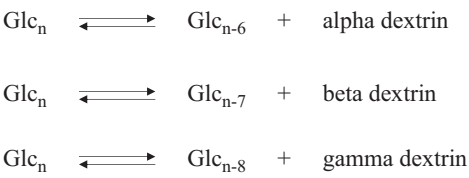


Fig. 1.12 Freudenberg's initial (above) and final (below) model of formation of Schardinger dextrins/cyclodextrin; adapted from Freudenberg (1939)



Scheme 1.1 Reactions proposed by Freudenberg (1939) to explain the formation of dextrins (Glc = a *D*-glucose or a *D*-glucosyl residue)

D-glucosyl residues were situated close to one another and were able to unite to form rings of five or six D-glucose units. The reactions proposed by Freudenberg to explain the formation of dextrins are given in Scheme 1.1 (Freudenberg 1939). Freudenberg concluded that the cyclodextrins were not preformed in starch "molecule" but that formation was made possible by the helicity of the starch chain. However, he was unable to prove this mechanism. It would be confirmed a few years later by French using chromatography (French et al. 1954) and later by Takeo and Kuge (1969) using X-ray crystallography.

From the 1940s, numerous research groups worked on the bacteria that produced the dextrins (Myrbäck 1938, 1942, 1949a, b; Samec and Blinc 1939, 1941; Myrbäck and Ahlborg 1940; Blinc 1941, 1942; Samec 1942; Tilden and Hudson 1939, 1942; Tilden et al. 1942; Kerr 1942, 1943, 1949; Kerr and Severson 1943; Wilson et al. 1943; Myrbäck and Gjorling 1945; Cori and Cori 1946; French et al. 1948; Kerr and Cleveland 1949; Hale and Rawlins 1951). However, the discovery of the enzyme in *Bacillus macerans*, responsible for the conversion of starch into dextrin, is attributed to Tilden and Hudson. In 1939, Tilden and Hudson isolated a cell-free enzyme preparation from *Bacillus macerans*, i.e., *Acrobacillus macerans*, that had the ability to convert starch into crystalline dextrins with interesting yields, ~55%, (Tilden and Hudson 1939). They introduced the name of cycloamylose glucanotransferase, i.e., CGTase or cyclodextrin glucanotransferase. Prior to this discovery, dextrins were made using live cultures of *Bacillus macerans*. In 1942, the authors proposed the following protocol (Tilden and Hudson 1942; Tilden et al. 1942): they cultivated *Bacillus macerans* on sterilized potato slices or on a medium containing 5% oatmeal, in presence of 2% calcium carbonate; after 2–3 weeks of cultivation at 37–40 °C, the cell mass was recovered by filtering or centrifuging; the filtrate contained the enzyme in an activity of 0.7 units/mL, which was separated either by freeze-drying or, after concentration, by precipitation with acetone. Their results mainly showed that it was essential to determine the optimal culturing conditions for the production of the enzyme and the optimal pH, temperature, and fermentation time for enzyme activity for effective use of the enzyme. Later, Hale and Rawlins (1951) also attained similar yields of the enzyme on a scale of 20 L in 10–12 days in an aerated culture. Tilden and Hudson were also the first to propose a simple protocol for purifying the amylase of *Bacillus macerans* using both precipitation by acetone, adsorption, and dialysis steps (Tilden and Hudson 1942; Tilden et al. 1942). The enzyme purified had an activity 140 times that of the initial enzyme solution and was able to convert 1000 times its weight of starch in 30 min at 40 °C.

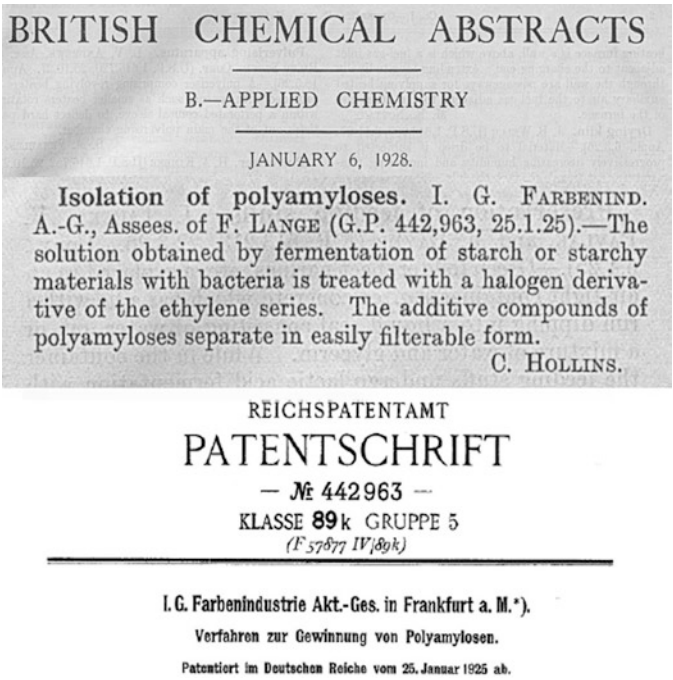
Since Tilden and Hudson's discovery of *Bacillus macerans* cycloamylose glucanotransferase, effort was devoted to working out methods for cyclodextrin

production and the details of the mechanism. These two researchers also laid down the basis of the enzymology of dextrins, and their findings were validated and used for over 30 years. Myrbäck and Gjorling (1945) and Cori and Cori (1946) also confirmed that the enzyme which catalyzed the degradation of starch into dextrins was mainly produced by bacillus strains. These two groups were the first to describe the action mechanism involved in the enzyme synthesis of Schardinger dextrins and to point out that the rate of hydrolysis of dextrins was much slower in its initial phase than later on. In addition, the authors noted that, after a few days, the Schardinger dextrins formed under the action of *Bacillus macerans* gradually disappeared. This was also observed by Kneen and Beckord (1946), by French (French et al. 1948), and later by Hale and Rawlins (1951). The explanation was given by French which introduced the reversibility of the action of the enzyme (French et al. 1948). In 1948, French's group proposed a mechanism of action based on a transglucosylation reaction to interpret the formation of dextrins by *Bacillus macerans* (French et al. 1948). Their results demonstrated that *Bacillus macerans* was capable of producing a glycosidic exchange reaction between maltose and cyclohexaamylose which resulted in the formation of higher weight saccharides, confirming the concept of glycosidic exchange introduced by Cori and Cori (1946). French pointed out that the enzyme performed three transglucosylation reactions involving cyclization, coupling, and disproportionation, as well as a hydrolysis reaction. This mechanism proposed by French and detailed in his comprehensive review (French 1957a) was only demonstrated in the 2000s (Lee and Robyt 2001; Qi et al. 2004). In 1950, Akiya and co-workers also proposed a mechanism of action and claimed the "discovery" of a new strain of *Bacillus macerans* (Akiya and Watanabe 1950a, b, c), although Hudson's group have previously shown that all examined strains of *Bacillus macerans* were capable of forming Schardinger dextrins (Tilden and Hudson 1939, 1942; Tilden et al. 1942).

1.3.7 The First Schardinger Dextrin-Related Patents

The first patent on Schardinger dextrins was registered in 1925 by the German Fritz Lange for *IG Farbenindustrie* (Fig. 1.13). This patent entitled *Verfahren zur gewinnung von polyamylosen* focused on the isolation of polyamyloses (Lange 1925).

Freudenberg, Cramer, and Plieninger filed the first industrial cyclodextrin-related patent in 1953, called "Method for preparation of inclusion compounds of physiologically active organic compound" (Freudenberg et al. 1953). The patent described the most important aspects of the applications of cyclodextrins in drug formulations (Fig. 1.14). The authors detailed specific effects that could be achieved by complexation of drugs with cyclodextrin complexation such as enhancement of solubility of poorly soluble drugs, protection of easily oxidizable substances against atmospheric oxidation, reduction of the loss of highly volatile substances, etc. In 1987, Cramer wrote: "At that time, I saw the first possibilities for a technology transfer and I took a patent. This, unfortunately, never found any industrial application" (Cramer 1987).



BRITISH CHEMICAL ABSTRACTS

B.—APPLIED CHEMISTRY

JANUARY 6, 1928.

Isolation of polyamyloses. I. G. Farbenind. A.-G., Assees. of F. Lange (G.P. 442,963, 25.1.25).—The solution obtained by fermentation of starch or starchy materials with bacteria is treated with a halogen derivative of the ethylene series. The additive compounds of polyamyloses separate in easily filterable form.

C. Hollins.

REICHSPATENTAMT

PATENTSCHRIFT

— № 442963 —

KLASSE 89k GRUPPE 5

(F 57877 IV/89k)

I. G. Farbenindustrie Akt.-Ges. in Frankfurt a. M.*).

Verfahren zur Gewinnung von Polyamylosen.

Patentiert im Deutschen Reiche vom 25. Januar 1925 ab.

Fig. 1.13 Extract of the British Chemical Abstracts announcing the first patent on polyamyloses filed by Lange in 1925

The potential use of cyclodextrins in pharmaceuticals had been launched. It was not till the 1970s and 1980s though that the first industrial-scale applications in pharmacy appeared (Szejtli 1998; Loftsson and Duchêne 2007; Morin-Crini et al. 2015).

1.3.8 Cyclodextrins as Models

Cramer knew everything about cyclodextrins, publishing an impressive number of results over a period of 25 years on their preparation, separation, characterization, structure, properties, chemistry, biochemistry, and their potential application in pharmacy, catalysis, and enzymology (Freudenberg and Cramer 1948, 1950; Cramer 1949, 1951a, b, c, 1952, 1953, 1954, 1956, 1961; Freudenberg et al. 1953; Cramer and Steinle 1955; Cramer and Henglein 1956, 1957a, b; Cramer and Dietsche 1958, 1959a, b; Lüttringhaus et al. 1958; Cramer and Kampe 1962, 1965; Cramer and Hettler 1967; Cramer et al. 1967, 1969).

In 1953, Cramer was the first to show the catalytic role that cyclodextrins could play in chemical reactions through a key-lock interaction similar to that of an enzyme-substrate complex (Cramer 1953). Later, Cramer gave the basis for supramolecular catalysis involving cyclodextrins (Cramer and Dietsche 1958, 1959a;

Erteilt auf Grund des Ersten Überleitungsgesetzes vom 8. Juli 1949
(WiGBl. S. 175)

BUNDESREPUBLIK DEUTSCHLAND

AUSGEGEBEN AM
5. NOVEMBER 1953

DEUTSCHES PATENTAMT

PATENTSCHRIFT

№ 895 769

KLASSE 12o GRUPPE 27

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Dr. Karl Freudenberg, Heidelberg,
Dr. Friedrich Cramer, Heidelberg-Schlierbach und
Dr. Hans Plieninger, Heidelberg
sind als Erfinder genannt worden

Knoll A.-G. Chemische Fabriken, Ludwigshafen/Rhein

Verfahren zur Herstellung von Einschlußverbindungen physiologisch wirksamer organischer Verbindungen

Patentiert im Gebiet der Bundesrepublik Deutschland vom 26. August 1951 an
Patentanmeldung bekanntgemacht am 5. März 1953
Patenterteilung bekanntgemacht am 24. September 1953

Es ist bereits bekannt, Additionsverbindungen von organischen Stoffen herzustellen, die die zweite Komponente in den Hohlräumen ihres Molekülis oder Kristallgitters einschließen. So sind z. B. Additionsverbindungen von Desoxycholsäure, Harnstoff und von den Schardinger-Dextrinen bekannt, die die verschiedensten Stoffe eingeschlossen enthalten. Diese Additionsverbindungen, die treffender als Einschlußverbindungen bezeichnet werden, weil sie die eingeschlossenen Komponenten in getarnter Form enthalten, haben die Eigenschaft der Schwerlöslichkeit.

Während bisher bei den Schardinger-Dextrinen Addukte nur mit sauerstofffreien, physiologisch indifferenten, halogenhaltigen Kohlenwasserstoffen, insbesondere der aromatischen Reihe, und mit höheren Alkoholen bekannt waren, wurde nunmehr gefunden, daß diese Dextrine auch mit beliebigen, insbesondere mit physiologisch wirksamen Stoffen Einschlußverbindungen bilden. Diese neuen Addukte zeichnen sich ebenfalls durch Schwerlöslichkeit und meist damit verbundene protrahierte Wirkung, durch Beständigkeit gegen Körpersäfte, durch Geschmacksverbesserung und durch Lagerungsbeständigkeit aus.

Die neuen Addukte werden dadurch hergestellt, daß man konzentrierte wäßrige Lösungen der Schardinger-Dextrine mit den Einschlußkomponenten vereinigt. Zu diesem Zweck wird die heiß gesättigte, wäßrige Dextrinlösung mit der Einschlußkomponente versetzt und darauf allmählich erkalten gelassen. Nach einer anderen Ausführungsform des Verfahrens wird die gesättigte wäßrige Dextrinlösung mit der suspendierten Einschlußkomponente durchgeschüttelt. Man kann auch so vorgehen, daß man die wäßrige Dextrinlösung mit einer Lösung der Einschlußkomponente in einem mit

Fig. 1.14 First page of the first patent concerning the applications of cyclodextrin in pharmaceutical formulations filed by Karl Freudenberg, Friedrich Cramer, and Hans Plieninger in 1953

Cramer 1961; Cramer and Kampe 1962, 1965). For instance, he reported a cyclodextrin-accelerated reaction studying the hydrolysis of ethyl *p*-chloromandelate in the presence of α-cyclodextrin (Cramer and Dietsche 1958). Cyclodextrins can also be used as an asymmetric agent (Cramer 1961; Cramer and Kampe 1962, 1965). The potential use of cyclodextrins in catalysis and supramolecular chemistry had been launched. The first reports of their potential use as enzyme models were also attributed to Cramer. Enzyme-substrate interactions can be established either by non-covalent bond such as hydrogen bonding or van der Waals forces or by a covalent bond. When a covalent bond is formed, the cyclodextrin established a

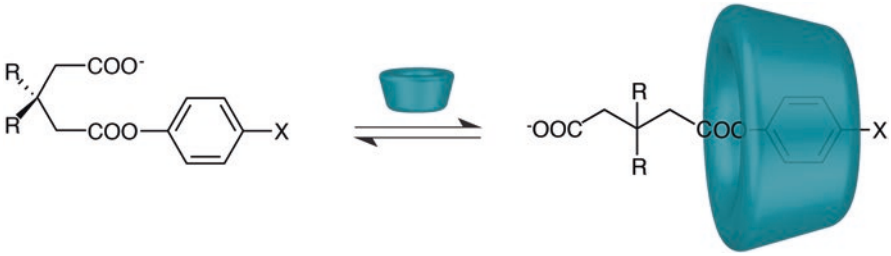

Fig. 1.15 Mechanism proposed during the hydrolysis of 3,3-disubstituted phenyl-glutarate via intramolecular catalysis; the presence of cyclodextrin suppressed this intramolecular catalysis

covalent bond with some entering or leaving component, e.g., in the case of ester hydrolysis. This process was called covalent catalysis. The model of non-covalent catalysis was inclusion complex catalysis, introduced by Cramer (1953) and later studied in detail by Bender (van Etten et al. 1967a, b; Griffiths and Bender 1973). An interesting example is given in Fig. 1.15. The hydrolysis of 3,3-disubstituted phenyl-glutarate proceeded via intramolecular catalysis. This was suppressed by cyclodextrin inclusion complex formation. The stabilizing effect depended on the cyclodextrin concentration according to the hyperbolic curve of the Michaelis-Menten enzyme kinetics. The reaction rate reached a minimum value when all the ester molecules were complexed. The hydrolysis was also independent of the pH; consequently cyclodextrin was only a binding site and was not involved directly in the reaction mechanism.

At the end of the 1950s, the numerous fundamental studies of French also led to growth in the interest in cycloamyloses not only as model enzymes but also as aroma-stabilizing agents for the food industry (Thoma and French 1958; Thoma et al. 1959; French et al. 1963), even though at the time, industrial application of cycloamyloses was still not considered feasible. This last point was only clarified in the 1970s. In the 1960s, Bender reported that cycloamyloses had a great potential for acid-base catalysis similar to that of naturally occurring enzymes. His numerous works made the creation of artificial enzymes possible. Bender, studying cycloamyloses-catalyzed reactions, showed that cycloamyloses can accelerate or decelerate various kinds of reactions including oxidation, hydrolysis, decarboxylation, nitrosation, and isomerization. The reaction rates depended on the cycloamylose used and the kind and stability of the inclusion compound formed. The first review on the phenomenon of cycloamylose catalysis has been published in 1973 by Bender (Griffiths and Bender 1973). This comprehensive review also summarized the developments in the chemistry of cycloamyloses and its derivatives used as enzyme models. It was updated by Bender in 1978 (Bender and Komiyama 1978). Cycloamylose-catalyzed reactions were classified in two categories: (i) covalent catalysis in which cycloamyloses catalyze reactions via the formation of covalent intermediates and (ii) non-covalent catalysis in which cycloamyloses provide their cavities as apolar or sterically restricted reaction fields without the formation of any covalent intermediates. Bender pointed out that non-covalent catalysis by

cycloamyloses might be the result of either a solvent effect or of a conformational effect, e.g., in decarboxylation and stereoselective reactions. Bender is recognized as the initiator of the era of biomimetic chemistry, including artificial enzymes, molecular recognition, and bio-inspired reactivity (see his famous book: Bender and Komiyama (1978)).

1.3.9 Complex Formation and Inclusion Compounds

In 1938, Freudenberg suggested, for the first time, the hydrophobicity of the inner surface of the dextrin and noted how dextrins had the ability to form complexes due to their cyclic structure (Freudenberg and Meyer-Delius 1938; Freudenberg et al. 1938). The dextrins exhibited a complexing capacity which was discussed in connection with the blue starch/iodine complex. For the first time, the ability of Schardinger dextrins to form complexes was suggested. To explain these complexes, Freudenberg was the first to show the involvement of hydrophobic forces in the formation of the complexes (Freudenberg 1939; Freudenberg and Meyer-Delius 1939; Freudenberg et al. 1939). Originally, however, Freudenberg was convinced that the dextrins and the amylose helix were lined with a hydrocarbon interior, and thus the cavity of the dextrins has been referred to as hydrocarbon in nature (Thoma and Stewart 1965; Caesar 1968; Clarke et al. 1988; Szejtli 1998; Crini 2014; Morin-Crini et al. 2015; Crini et al. 2018).

Cramer was recognized not only for having introduced the cyclodextrin-based nomenclature but mostly for his important work on inclusion complexes, although they were only fully acknowledged at the end of the 1970s (Crini 2014). In 1949, in his PhD dissertation entitled *Die cyclodextrine aus Stärke*, Cramer evoked for the first time the fact that the three native cyclodextrins, considered as cylinders with different internal diameters, were able to accommodate molecules of different sizes: this was the first indication on their ability to form "inclusion" complexes (Cramer 1949). Two years later, Cramer published his first results on the complexes (Cramer 1951a, b, c, 1952). For instance, he observed that a number of dyes showed characteristic changes in their absorption spectra in aqueous solutions of the cyclodextrins (Cramer 1952). Between 1952 and 1954, Cramer discovered that the toroidal form of the cyclodextrin molecules, regarded as truncated cones, enabled them to accept various molecules inside their cavity (Cramer 1952, 1953; Dietrich and Cramer 1954). He was the first to demonstrate the hypotheses Schardinger put forward at the beginning of the nineteenth century on their ability to form complexes. In 1952, Cramer adopted the term *einschlussverbindungen*, i.e., inclusion compound, to characterize a complex (Cramer 1952), and later he also used the terms "occlusion compound" and "molecular encapsulation" (Cramer and Dietsche 1959a). In 1953, he registered his first patent where he highlighted the fact that "the formation of an inclusion complex could modify the physical, chemical and biological characteristics of a guest molecule such as a drug" (Freudenberg et al. 1953). The inclusion phenomena and the term *einschlussverbindungen* were however used by Schlenk in 1950 for the first time (Schlenk et al. 1955; French 1957a; Szejtli 1982a; Crini

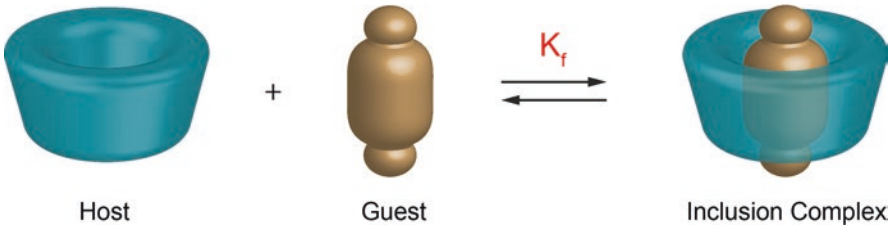

Fig. 1.16 Inclusion phenomena between a cyclodextrin molecule (the host) and an organic molecule (the guest) to form inclusion complexes; K_f is the formation constant

2014). The term "inclusion compound" has been coined to describe the positional relationship of two components which form certain types of crystals. These components were designated as host and guest, again in reference to the solid state (Schlenk et al. 1955; Schlenk and Sand 1961).

In 1956, Cramer introduced the notion of "inclusion complex" (Cramer 1956). He considered the interior of the cavity as a lipophilic microenvironment into which a non-polar hydrophobic molecule can "slide" (Fig. 1.16). The guest was maintained within the cavity by non-covalent forces, which were thus weak and enable the whole system to be reversible. Cramer showed that formation of an inclusion complex was the result of an association/dissociation equilibrium between the free guest and the free host and the complex. This was governed by a constant, denoted formation constant, K_f. The higher its value, the more stable the inclusion is, and the less dissociation that occurred. Cramer then conducted important research between 1955 and 1965 on the inclusion phenomena (Cramer 1956, 1961; Cramer and Henglein 1956; Cramer and Dietsche 1959a, b; Cramer and Kampe 1962, 1965). He studied in detail the molecular dispositions of numerous guest organic compounds in the cyclodextrin cavity in solution by the use of UV-visible and circular dichroism experiments, in order to demonstrate the formation of inclusion complexes. These experiments also permitted to calculate the formation constant or dissociation constant of the different complexes.

Figure 1.17 shows the two possible penetration pathways for benzoic acid, phenol, and methylated benzoic acids. α-Cyclodextrin complexes with phenol and benzoic acid guests in the head first position were more stable than in the tail first position, while β-cyclodextrin complexes with the same guests preferred the tail first position. A substituted benzene ring with a van der Waals radii of about 6.8 Å could only penetrate into the ring of a β-cyclodextrin molecule (diameter cavity: 7.5 Å) either "head first" or "bottom first" but never crosswise. The stability of the complex was proportional to the hydrophobic character of the substituents (Cramer and Henglein 1956; Cramer and Dietsche 1959a, b; Cramer 1961). In the 1970s, this was also demonstrated by van Hooidonk and Breebaart-Hansen (1970, 1972), Harata and Uedaira (1975), and later Szejtli (1982a) using the same methods, i.e., UV-visible spectroscopy and circular dichroism. Demarco and Thakkar (1970) were the first in a pioneering work to demonstrate the formation of inclusion complexes

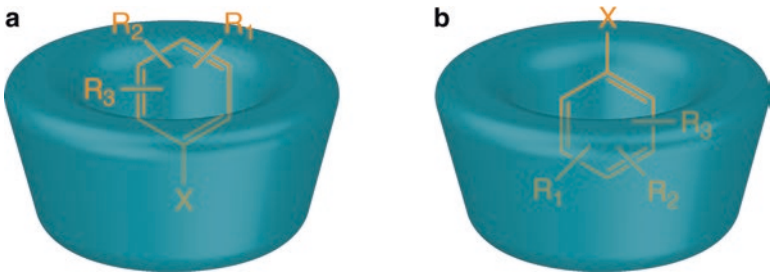

Fig. 1.17 Two possible penetration pathways (a, head first; b, right, tail first) for benzoic acid, phenol, and methylated benzoic acids (X = COOH or OH; R_1, R_2, R_3 = H or CH_3)

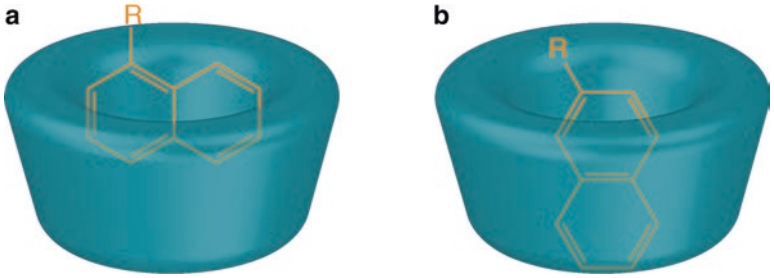

Fig. 1.18 (**a**) Equatorial inclusion of a 2-substituted naphthalene and (**b**) axial of a 1-substituted naphthalene. (Adapted from Harata and Uedaira 1975)

between several organic substances studied by Cramer and β-cyclodextrin using NMR spectroscopy.

Another interesting example was the complex between β-cyclodextrin and naphthalene substituted in position 1 or 2 (Fig. 1.18). The modification of the circular dichroism that occurred depended on the geometry of both the host and the guest molecules. A positive circular dichroism band implied axial inclusion, i.e., along the Cn symmetry axis, whereas a negative band signified equatorial inclusion, i.e., perpendicular to the Cn axis (Cramer 1961; Cramer and Kampe 1962, 1965). Later, Szejtli (1982a) also indicated that the sign and intensity of the induced Cotton effects were quite sensitive to the orientation of the guest chromophore in the cyclodextrin cavity. If the electric dipole moment coincided with the axis of the cyclodextrin, a positive Cotton effect was observed. When they were perpendicular to each other, a negative Cotton effect was observed. The circular dichroism spectra of 1- and 2-naphthols were therefore quite different: the naphthalene ring in one case was accommodated crosswise and in the other case lengthwise in the cyclodextrin cavity. In the complexes of 2-naphthalenes, the inclusion was axial (Harata and Uedaira 1975; Szejtli 1982a) (Fig. 1.18).

Cramer concluded that the preferred position for the guest compound inside the cavity depended on steric interactions, due to the chemical structure and geometry of each guest compound. The complex was strong when there was size

complementarity between the guest and the cyclodextrin cavity. In solution, two main components of the driving forces of the process are suggested: the first was the presence of repulsive forces between the included water molecules and the apolar cavity, and the second was the presence of repulsive forces between the bulk water and the apolar organic guest. Cramer also indicated that hydrogen bonding between the guest and the cyclodextrin was of only minor importance as a driving force for complex formation (Cramer 1956). The stability of cyclodextrin inclusion complexes was due to a favorable change in enthalpy during the inclusion process. However, later, Cramer also considered that a complex was stabilized not only by van der Waals forces but also by hydrogen bonds (Cramer and Kampe 1965; Cramer et al. 1967).

In 1958, Cramer was the first to propose a scheme for the preparation of so-called catenanes, compounds consisting of two rings connected to each other without chemical bond, by using cyclodextrin complexes (Lüttringhaus et al. 1958). Figure 1.19 shows the structural scheme of catenanes and the principle of their attempted preparation. Incorporating a dithiol with sufficiently long chain into cyclodextrin, and oxidizing the two protruding terminal SH groups to give an -S-S- bridge, a catenane was formed. These molecules were studied in the 1990s and proposed for the synthesis of supramolecular materials, scaffolds and templates, and in biomimetism (Nepogodiev and Stoddart 1998). In 1959, Cramer observed that, in the case of guest molecules that cannot be totally included by a single molecule, a second cyclodextrin molecule may bind: this was the first observation of 2:1 complexes in solution (Cramer and Dietsche 1959a, b). Figure 1.20 illustrates the association of free cyclodextrin and substrate to form various substrate-cyclodextrin complexes. Depending on the respective size of the guest and host molecules, one guest molecule can interact with one or two (or more) cyclodextrins, i.e., host-guest complexes 1:1 and 2:1, or two (or more) guest molecules can interact with one cyclodextrin or two (or more), i.e., host-guest complexes 1:2 and 2:2.

In 1967, Cramer comprehensively discussed all the possible penetration pathways and the effect of substituents on the stability of the inclusion complexes (Cramer and Hettler 1967). The same year, he gave the first scientific explanation to

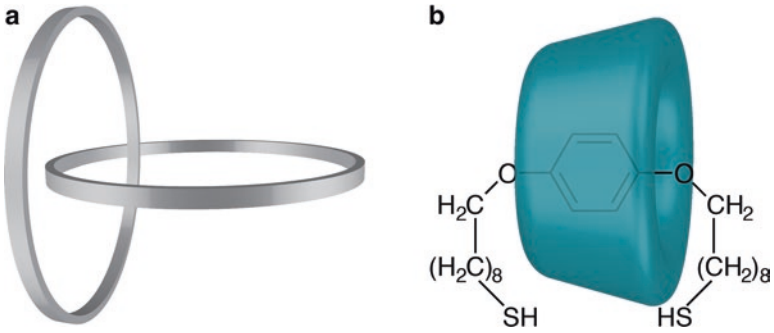

Fig. 1.19 (**a**) Structural scheme of catenanes and (**b**) principle of their attempted preparation. (Adapted from Lüttringhaus et al. 1958)

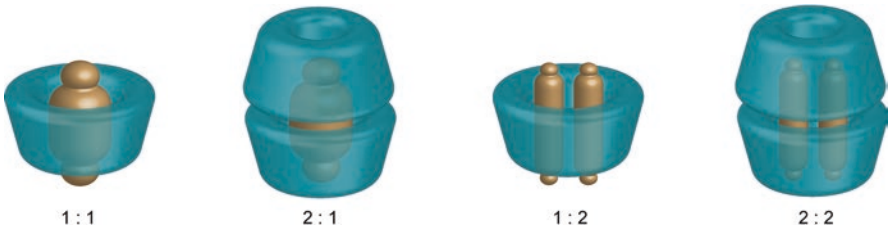

Fig. 1.20 Association of free cyclodextrin and substrate to form various substrate-cyclodextrin complexes

explain the mechanism of formation of an inclusion complex between a substrate and a cyclodextrin molecule both in solution and solid state (Cramer et al. 1967). To explain the formation of an inclusion complex, Cramer introduced five elementary steps: (1) the substrate approaches the cyclodextrin molecule; water molecules escape from the cyclodextrin cavity and acquire a new energy level, corresponding to that of the gaseous state; the van der Waals interactions and the number of hydrogen bonds decrease, whereas the degrees of freedom of translation and rotation of the freed water molecules increase; (2) the guest molecule becomes released from the layer of water that envelops it and also acquires a different state; the layer of water becomes dispersed and rearranges; (3) the guest molecule, considered to be in a perfect gas state, enters the cavity, and the complex formed is stabilized by van der Waals forces and/or hydrogen bonds; (4) the expelled water molecules are rearranged and form hydrogen bonds between each other; and (5) the structure of the water is restored around the part of the substrate that remains in contact with the solvent and that is integrated into the hydration shell around the CD. Cramer finally concluded that the most important property of cyclodextrins was the ability to establish specific interactions, i.e., molecular encapsulation, with various types of molecules through the formation of non-covalently bonded entities such as hydrophobic interactions, van der Waals forces, and hydrogen bonding (Cramer and Hettler 1967; Cramer et al. 1967). Cramer's work on inclusion complexes established much of our modern understanding of the behavior of cyclodextrins during complexation and remains a commonly cited source to this day.

At the same time as Cramer, French also studied the formation of inclusion complexes and showed that evidence for a guest inclusion into the cycloamylose cavity may be proved by analytical techniques such as UV-visible absorption spectrophotometry, optical rotatory dispersion, circular dichroism, and X-ray measurements (Thoma and French 1958, 1959, 1960, 1961; James et al. 1959; Thoma et al. 1959). The guests studied were the same as that of Cramer such as phenol, benzoic acids, or iodine. For instance, in 1958, French showed that absorption spectroscopy was an interesting method to determine the dissociation constant of the inclusion complex between cycloamylose and iodine (Thoma and French 1958). The values of dissociation constant could be easily obtained from the observed change in absorbance and the concentration of cycloamylose added according the Benesi-Hildebrand method. For French, the driving forces for complex formation included solvent

effects, van der Waals forces, and hydrogen bonds. One year later, French demonstrated that X-ray diffraction was also a powerful method to study the inclusion complexes between iodine and cycloamyloses (James et al. 1959). French also observed that, because of their structure, some guests can be included in one or two cycloamylose molecules, and depending on the cavity size, it was a different part of the guest molecule that can be included. This was clearly demonstrated in the 1970s by NMR spectroscopy (Szejtli 1982a).

Later, Lichtenthaler and Immel (1996) demonstrated, using molecular modelling, the need for compliance between hydrophobic host surfaces and hydrophobic domains in the cyclodextrin cavity. This striking tendency to optimize the reciprocal concurrence of lipophilic as well as hydrophilic domains at the guest-host interface may accordingly be concluded to be an important if not the decisive element in orienting the guest into the cavity and in determining the stability of the complex, particularly in cases where the guest is devoid of polar groups. This was the first study showing the importance of the reciprocal interplay of such interactions.

1.3.10 The First Reviews on Schardinger Dextrins

Relatively few reviews of cyclodextrins were published during the period from 1911 to 1970 as recently reported by Crini et al. (2018). The first review of Schardinger dextrins was published in German by Pringsheim in 1931 in a chapter entitled *Dextrine: Charakteristik, Gewinnung und Eigenschaften* and published in his book *Die polysaccharide* (Pringsheim 1931a). Pringsheim also published an English version in 1932 in another book *The Chemistry of the Monosaccharides and of the Polysaccharides* (Fig. 1.21). This mini-revue, entitled "The dextrins: Characteristics, Sources, and Properties," summarized the works of Schardinger on dextrins but mostly his own works (Pringsheim 1932).

Later, the dextrins were described in German by Samec and Blinc in a review dated 1941 and entitled "*Die Neuere Entwicklung der Kolloidchemie der Stärke*," in which they concluded that, "because of the use of impure dextrins, the work performed prior to about 1935 was judged to be of little consequence" (Samec and Blinc 1941). In 1954, an interesting brief overview on cyclodextrins was published by Cramer in his famous book on inclusion complexes entitled *Einschlussverbindungen* (Cramer 1954). However, the very first state of the art on the subject was only published by French in 1957 in a special volume of the journal *Advances in Carbohydrate Chemistry*. French wrote up an excellent fundamental review of over 70 pages with 159 references, entitled "The Schardinger Dextrins," where he described the history of Schardinger dextrins, their characteristics, chemistry and derivatives, and biochemical properties (French 1957a). French divided their history into two general periods, their discovery between 1891 and 1935 and their maturity from 1935 to 1950. Transfer reactions due to the *Bacillus macerans* action were also critically reviewed by French. In 1965, Thoma and Stewart also published a comprehensive review on the characteristics of *Bacillus macerans*

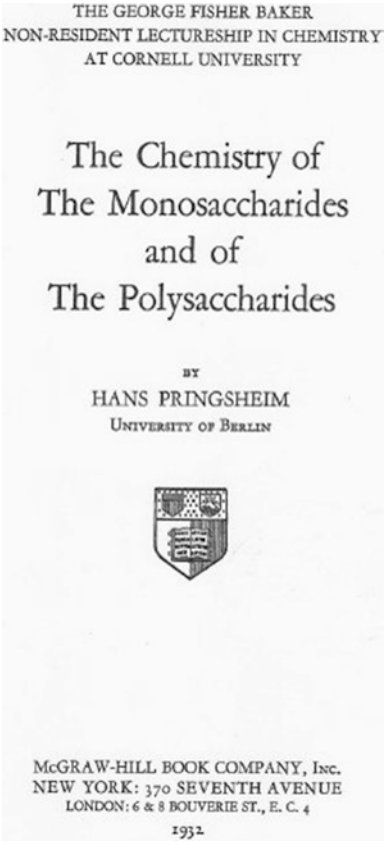

Fig. 1.21 Cover of Pringsheim's book published in 1932 where Professor Hans Pringsheim summarized the works of Professor Schardinger

amylase (Thoma and Stewart 1965). Three years later, Caesar summarized the use of cycloamyloses as models for enzymes (Caesar 1968).

1.3.11 Toxicological Considerations

Pringsheim was the first to conduct several biological tests to determine whether the dextrins were physiologically available either to plants or animals (Pringsheim and Müller 1922; Hoesslin and Pringsheim 1923; Pringsheim 1928b, 1931a). Pringsheim studied the absorption and metabolism of dextrins in rats, pigs, and humans. Polyamylose, probably α-cyclodextrin, administered in a dose of 50 g to diabetic persons, did not cause any change in the urinary glucose level, and no polyamylose was found in the feces (Pringsheim and Müller 1922). Hoesslin and Pringsheim (1923) fed polyamylose to starved rabbits and guinea pigs. No glycogen synthesis was detected in the liver 3 h after administration. Pringsheim suggested that polyamylose was metabolized in the rat. His experiments also showed that the

Schardinger dextrins were not fermentable and hence not utilized by yeast (Pringsheim 1928b). In 1931, for the treatment of diabetes, Pringsheim concluded: "α-dextrin directly utilized would be a suitable source of energy for diabetics since it only occasionally cause nausea and there is no noticeable increase in urine sugar" (Pringsheim 1931a).

However, in 1957, French wrote: "It would appear that the Schardinger dextrins exhibit a toxic effect, possibly by virtue of their remarkable complexing ability, and in any case, the suggestion of Professor Pringsheim that they be used as an energy source by diabetics looks risky" (French 1957a). Indeed, the first studies carried out by him in the rat led to the conclusion that Schardinger dextrins presented a certain toxicity (French 1957a). In the same paper, it is noted that "In unpublished attempts to investigate the ability of animals to utilize Schardinger dextrins, B.H. Thomas and D. French fed rats a diet in which a part of the carbohydrate was supplied by higher purified β-dextrin. The animals refused to eat the test diet except in very small quantities and within a week all animals on the ration were dead. Postmortem examination did not reveal the cause of death" (French 1957a). Their experiments indeed showed that the rats refused to eat food containing highly refined dextrins except in very small quantities. In spite of the small doses, rat mortality was 100% within a week of introducing "highly purified" β-dextrin into the diet (French 1957a). However, in these studies, experimental conditions, such as the purity of dextrins, the number of rats treated, or the existence of a control group, were not mentioned. Later, Szejtli suggested that one of the hypotheses was traces of solvent remaining in the dextrins which the rats could have smelt (Szejtli 1982a, 1988; Frömming and Szejtli 1994). This was the only result of French's that posed a problem and which led to extensive debate of the toxicity of the cycloamyloses (French 1957a), and most importantly this result deterred many scientists from developing cycloamylose-containing products for human use. The observations and conclusions drawn by French were only refuted much later following studies with the same animal model (Andersen et al. 1963; Lach and Cohen 1963; Lach and Chin 1964; Szejtli et al. 1980a; Chow and Karara 1986).

1.3.12 Other Works During the Period from 1911 to 1970

Other historical landmarks on the discovery of cyclodextrins published by other researchers during the period from 1911 to 1970 are reported in Table 1.1 (Thoma and Stewart 1965; Caesar 1968; Szejtli 1998; Loftsson and Duchêne 2007; Kurkov and Loftsson 2013; Crini 2014; Morin-Crini et al. 2015; Crini et al. 2018).

Table 1.1 Selected historical landmarks in the discovery of cyclodextrin during the period from 1911 to 1970

Year	Main results, achievements, or events	Reference(s)
1922	Amylose is converted into a diamylose, i.e., Schardinger's α-dextrin Amylopectin is converted into a triamylose, i.e., Schardinger's β-dextrin	Pictet and Jahn (1922)
1925	The first patent is registered by IG Farbenindustrie	Lange (1925)
1930	Chemical composition of dextrins The work of Schardinger on α-dextrin is demonstrated Like Karrer, Miekeley also suggests that the existence of alpha diamylose is doubtful The acetylation reaction of alpha tetraamylose, whether catalyzed by pyridine or an acid, always gives alpha tetraamylose acetate, rather than alpha diamylose acetate	Miekeley (1930)
1930	Description of the characteristics of *Bacillus macerans*	Zacherov (1930)
1932	Molecular size of α-dextrin The first attempt to determine the molecular weight of dextrins using osmotic-pressure measurements	Ulmann et al. (1932), Ulmann (1932)
1932	The existence of α-1,4-glucosidic linkages is confirmed	Miekeley (1932)
1933	Chemical modification of α-dextrin α-Dextrin ethanol complex has two different crystal modifications which could be interconverted: Ulmann's group is the first to observe that a same guest may form different crystal structures with the same dextrin	Hess et al. (1933)
1939	The enzyme in *Bacillus macerans* responsible for the conversion of starch into dextrin is discovered by Hudson's group Relationship between the constitution of the Schardinger dextrins and that of starch A mechanism of formation is suggested Different starchy substrates differ in their behavior with *Bacillus macerans* in regard to the total yields of Schardinger dextrins and to the relative proportions of α- and β-dextrins	Tilden and Hudson (1939)
1942	The discovery of the amylase "Schardinger dextrinogenase" is confirmed by Hudson's group Description of a simple protocol for purifying the amylase of *Bacillus macerans* First description of the extracellular amylase produced by *Bacillus polymyxa* The ratio of α- to β-dextrin changes during the enzymolysis of starch The name of cyclodextrin glucanotransferase or CGTase is introduced Schardinger dextrins are derived from some basic configuration pre-existing in the starch molecule With Tilden, Hudson lays down the basis of the enzymology of dextrins	Tilden and Hudson (1942), Tilden et al. (1942), McClenahan et al. (1942), Wilson et al. (1943)
1942	Acid modification of corn starch leads to greatly reduced yields of Schardinger dextrins	Kerr (1942)

(continued)

Table 1.1 (continued)

Year	Main results, achievements, or events	Reference(s)
1943	Both the groups of Kerr and Hudson show that the amylose fraction of starch gives much higher yields of Schardinger dextrins, up to about 70%, than does the amylopectin fraction *Bacillus macerans* is capable of transfer reactions involving only α-*D*-(1→4) glucosidic bonds of linear or cyclic compounds	Kerr (1942, 1943), Wilson et al. (1943)
1945	The reducing values and amounts of fermentable sugars gradually increase during enzymolysis of starch with *Bacillus macerans* amylase The total dextrin yield increases to a maximum and then declines to practically zero as the reducing value increased Description of the action mechanism involved in the enzyme synthesis of Schardinger dextrins	Myrbäck and Gjorling (1945)
1946	Transglycosylase mechanism in enzymic synthesis of Schardinger dextrins	Cori and Cori (1946)
1948	The cyclic structure of dextrins is confirmed by X-ray crystallography: α-dextrin has an orthorhombic unit cell with 24 *D*-glucose residues per cell; one molecule of β-dextrin has 7 *D*-glucose residues; the crystal for γ-dextrin is not identified, but a pseudo-cell is obtained which contains 16 *D*-glucose residues, in harmony with an 8-membered ring	Borchert (1948)
1948	Synthesis of cyclodextrins containing nitrates and their characterization using X-ray data The first reliable molecular-weight determinations of crystallized dextrins based upon colligative properties	Gruenhut et al. (1948)
1950	"Discovery" of a new strain of *Bacillus macerans* "Discovery" of homologues of Schardinger dextrin containing more than 8 glucose units	Akiya and Watanabe (1950a, b, c)
1950	Introduction of German term *einschlussverbindungen*, literally inclusion compounds	Schlenk et al. (1955)
1950	The stoichiometry of an inclusion compound in solution can be determined by a slope ratio method	Harvey and Manning (1950)
1951	Cycloamylose glucanotransferases are detected in various microorganisms	Hale and Rawlins (1951)
1953	The first simple protocol for the purification of the Schardinger dextrinogenase enzyme	Schwimmer (1953)
1954	The first study on a specific modification of cyclodextrin: tosylation reaction; the previous results reported by Freudenberg in the 1920s are confirmed	Lautsch et al. (1954)
1961	The first study on cyclodextrin-fatty acid complexes In presence of organic molecules, solubility decreases owing to complex formation, in agreement with Cramer's results In the case of ethanol and propanol, there is a maximum on the concentration-solubility curve: The dependence of the solubility of β-cyclodextrin on the ethanol concentration is highlighted	Schlenk and Sand (1961)

(continued)

Table 1.1 (continued)

Year	Main results, achievements, or events	Reference(s)
1961	Acylated β-cyclodextrins are proposed as stationary phases in gas-liquid chromatography Materials are used for the separation of olefins, aldehydes, alcohols, and esters The separation however does not involve inclusion	Sand and Schlenk (1961), Schlenk et al. (1962)
1963	Only the signal of a single kind of anomeric proton in the NMR spectrum of γ-cyclodextrin is reported, suggesting that all glucose units are similar	Rao and Foster (1963)
1964	The first infrared spectra of four different hydrates of α-cyclodextrin Casu suggests for the first time that the glucopyranose rings possess the C1 chair conformation	Casu (1964), Casu and Reggiani (1964, 1966), Casu et al. (1964)
1964	The ability of cycloamyloses to form inclusion complexes is dependent on the presence of water An inhibitory effect of β-cyclodextrin on the hydrolysis of benzocaine is reported for the first time	Lach and Chin (1964)
1964	The first application of α-cyclodextrin as reagent for detection in thin-layer chromatography	Kaufmann and Wessels (1964)
1965	The cavity of cyclodextrins has definitively no hydrocarbon character	Thoma and Stewart (1965)
1965	The first NMR spectra of α-cyclodextrin and β-cyclodextrin Using NMR data, Casu confirms that (i) the D-glucopyranose units in cyclodextrins and in maltose possess the C1 chair conformation; (ii) β-cyclodextrin possesses a perfect rigid structure; (iii) the secondary hydrogen bond belt in α-cyclodextrin is incomplete; and (iv) the primary and secondary hydroxyl groups have a similar conformation in both the dissolved and the crystalline state Casu is the first to suggest the existence in water of hydrogen bonds between the secondary hydroxyl groups	Casu et al. (1965)
1965	The first determination of the structure of the complex between α-cyclodextrin and potassium acetate using three-dimensional X-ray data: a channel-type complex is formed in the crystalline state of the complex; the contact is established between one secondary and one primary hydroxyl edges Using X-ray data, the authors demonstrate that (i) all the glucose residues of cyclodextrins are in the C1 chair conformation; (ii) the change in crystallinity as function of dehydration is reflected in the X-ray diffraction pattern; and (iii) the secondary hydrogen bond belt in α-cyclodextrin is incomplete	Hybl et al. (1965)
1965	Classification of complexes based on their phase-solubility profiles	Higuchi and Connors (1965)
1965	The first insoluble resins from the epichlorohydrin reaction with cyclodextrins	Solms and Egli (1965)

(continued)

Table 1.1 (continued)

Year	Main results, achievements, or events	Reference(s)
1966	The complete oxidation of all primary hydroxyl functions of α- and β-cyclodextrins is reported Using chemical experiments and NMR data, Casu demonstrates the existence in water of hydrogen bonds between the secondary hydroxyl groups Intramolecular hydrogen bonding renders the secondary hydroxyl groups in cyclodextrins more resistant to hydrogen exchange	Casu (1966)
1967	The first recognition on the fundamental role of cyclodextrins in enzymology and catalysis	Van Etten et al. (1967a, b)
1967	α- and β-cyclodextrins are separated on a column made of cellulose: the method is suitable for both analytical and preparative purposes and provides highly purified products	Lammers (1967)
1968	The degree of substitution of partially methylated cyclodextrins is determined using NMR spectroscopy First detailed discussion of the conformations of methylated and acetylated cyclodextrins	Casu et al. (1968a, b, c)
1968	The water content of cyclodextrins can be determined by gas chromatography Using gas chromatography and elementary analysis, a crystalline β-cyclodextrin hydrate is found to have the composition $C_{42}H_{70}O_{35}$ 12 ± 0.5 H_2O Temperature dependence of the solubility in water, determined by refractometry, is reported	Wiedenhoff and Lammers (1968)
1968	For large-scale manufacture of Schardinger dextrins, sago starch is proposed	Caesar (1968)
1969	Gas-liquid chromatography is proposed as direct and accurate method for the analysis of cycloglycosyltransferase products The method is also used for the quantitative assay of mixtures containing α-, β-, and γ-cyclodextrins	Beadle (1969)
1969	The enzyme involved in the mechanism of action of *Bacillus macerans* is able to degrade the helical structure of starch X-ray crystallography is an interesting method to elucidate the structure of cyclodextrins and their complexes: inclusion complex formation results in important changes in the X-ray powder diagrams of cyclodextrins The transglucosylation reaction is confirmed by X-ray crystallography The first NMR spectrum of γ-cyclodextrin	Takeo and Kuge (1969)

(continued)

Table 1.1 (continued)

Year	Main results, achievements, or events	Reference(s)
1970	Cyclodextrins should be regarded as truncated cones NMR data confirm that the hydrogen atoms H3 and H5 direct toward the interior of the cavity while the hydrogen atoms H1, H2, and H4 locate on its exterior, in agreement with the C1 chair conformation of glucose units The hydrogen atoms H3 and H5 are considerably shielded when guest molecules are accommodated within the cavity, while the other hydrogen atoms show only a marginal shift By measuring changes in the chemical shift, the coupling constant, the nuclear Overhauser effect, and the relaxation times of components, it is possible to determine geometrical relationships between host and guest and their dynamic features in aqueous solution	Demarco and Thakkar (1970)
1970	The 1H-NMR spectra of γ-cyclodextrin in DMSO-d_6 at 25 °C and 80 °C show that the hydroxyl protons are shifted downfield relative to the values for both α- and β-cyclodextrins: this indicates that hydrogen bonds are stronger in γ-cyclodextrin than in β-cyclodextrin Assignments of the NMR signals for the individual protons in peracetylated cyclodextrins	Takeo and Kuge (1970)
1970	Detailed conformational studies on cycloamyloses using conformation-energy maps Cyclodextrins should be regarded as a truncated cone Hydrogen bonds are stronger in γ-cyclodextrin than in β-cyclodextrin Hydrogen bonding between the C2 and C3 hydroxyls results in a lowering of energy by 20 kcal/Mol in α-cyclodextrin and of 30 kcal/Mol in β-cyclodextrin Cycloamyloses having fewer than six α-*D*-glucopyranosyl residues are not possible because of steric reasons	Sundararajan and Rao (1970)

1.4 Historical Landmarks in the Development of Cyclodextrins: From 1970 Until Now

1.4.1 Production of Cyclodextrins

At the mid-1970s, industrial-scale production really started (Horikoshi 1979). Indeed, several manufacturers started to produce and to market cyclodextrins, e.g., Nihon Shokuhin Kako, Japan; Sanraku Ocean Co. Ltd., Japan; Toyo Joso, Japan; and Chinoin, Hungary. The first pilot plant at Nihon Shokuhin Kako firm, Japan, started up in 1978 with a production capacity of about 20 tons per year (Sicard and Saniez 1987). However, cyclodextrins were expensive.

The first to believe in the possibilities of industrial production and the multiple applications of cyclodextrins was probably Szejtli, a Hungarian carbohydrate chemist who organized the cyclodextrin technology in Hungary in the 1970s (Szejtli 1988, 1998). Among the list of prestigious researchers who have contributed to the

development of cyclodextrins, Szejtli played a fundamental role as eminent scientist, visionary, and entrepreneur, creating, in 1989, a private company, CycloLab Ltd., totally devoted to cyclodextrins. Without Szejtli, the feasible production of cyclodextrins on an industrial scale probably would not be as advanced as it is today.

In the mid-1980s, advancements in biotechnology led to drastic improvements in the production and purification of cyclodextrins. Cyclodextrins were then produced in large quantities with high purity and marketed at a reasonable price, and as a result, more industrial applications have become possible. In addition, this period from 1970 to 1980 was also marked by another important event: the first toxicological studies had established that β-cyclodextrin administrated orally was a harmless substance. Pharmaceutical, food, chromatographic, and cosmetic applications started to appear and rapidly gained ground. Since then, an increasing interest in cyclodextrins as raw materials and their possible applications has existed (Szejtli 1982a, 1988; Duchêne 1987, 1991).

1.4.2 Mechanism of Inclusion Complexes

In the mid-1970s, several researchers such as Saenger, a pupil of Cramer, Bender, and Szejtli pursued and reformulated the interpretations made by Cramer on the mechanisms of formation of inclusion complexes.

On the basis of the mechanism proposed in 1967 by Cramer, Saenger gave in 1976 three important explanations for the formation of an inclusion complex with α-cyclodextrin in aqueous solution (Saenger et al. 1976): (1) the guest molecule directly replaces the water molecules in the cavity; (2) the cyclodextrin molecules absorb the energy of the water molecules retained in the cavity and take on a relaxed conformation; in this state, the water molecules can be easily substituted by another guest; and (3) the guest becomes associated with the outer surface of the cyclodextrin and only enters the cavity once it has absorbed the activation energy, i.e., transfer of the conformation from a state of high energy of the cyclodextrin-water complex to a state of lower energy of the cyclodextrin-guest molecule complex. Saenger introduced the notion of the release of the tension energy within the α-cyclodextrin molecule upon formation of the complex. This relief of strain in the cyclodextrin ring contributed to the enthalpy of association and to the stabilization of the inclusion complex. In water, the α-cyclodextrin was in a strained, high-energy conformation, and that, when another guest molecules displaced the water, thus forming an inclusion complex, a conformational change of the cyclodextrin molecule occurred, transforming the α-cyclodextrin structures into an unstrained, relaxed state. This was demonstrated using detailed X-ray diffraction studies. A scheme of inclusion-complex formation involving relief of strain energy and release of high-energy water is proposed (Fig. 1.22). This scheme shows the possible pathways of α-cyclodextrin inclusion complex formation in aqueous solution. Owing to the inclusion of water, the ring of cyclodextrin is distorted, only four of the six possible hydrogen bonds are formed, and introducing a suitable guest molecule, the ring is

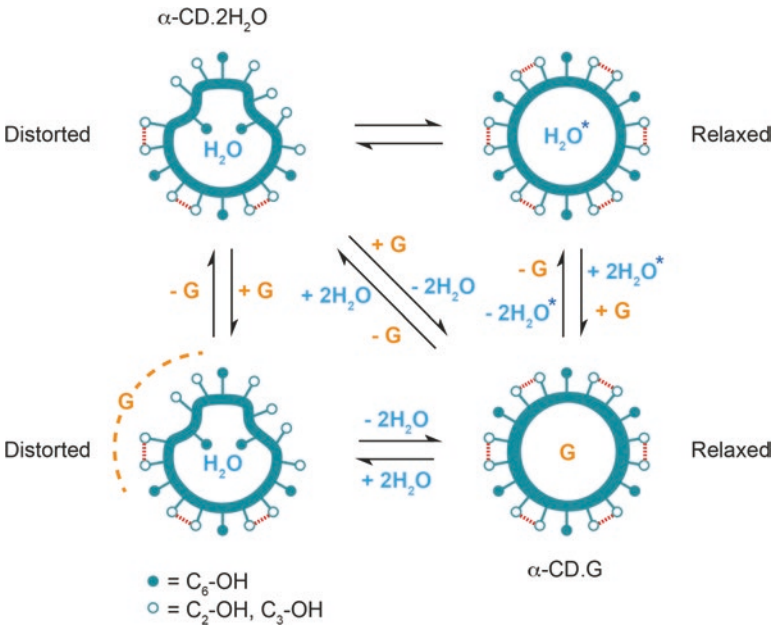

Fig. 1.22 Saenger's theory of formation of α-cyclodextrin complexes in aqueous solution: G, guest; H_2O^*, activated water. Hydrogen bonds are marked by dashed lines. (Adapted from Saenger et al. 1976)

relaxed. Later, Saenger showed that, in the cases of β- and γ-cyclodextrins, the strain energy relief mechanism did not seem to be operative and the cyclodextrin-water adducts were not strained (Lindner and Saenger 1978). In 1980, Saenger published a thorough state of the art of inclusion complexes, including his own interpretations (1980).

In 1978, Bender elucidated the mechanism of formation of the complexes developed by Saenger. He pointed out that the complexation involved hydrophobic interactions, like that of Saenger 2 years before. The driving force of inclusion is "an example of an atypical hydrophobic interaction" (Bender and Komiyama 1978). Bender proposed the fact that the complexation reaction involved a gain in enthalpy and a loss of entropy. The further the guest molecule penetrated into the cyclodextrin cavity, the greater was the change in enthalpy, and the higher was the stability of the complex. Moreover, the greater was the apolarity of the guest, the more this phenomenon was marked. The previous explanation that Bender offered to explain the favorable enthalpy change was that the empty cyclodextrin contained water molecules that were unable to form their full complement of hydrogen bonds to adjacent water molecules, and thus might be considered to enthalpy rich (Griffiths and Bender 1973). The inclusion of a guest "would then displace this high energy water from the cyclodextrin cavity, leading to a net increase in solvent-solvent hydrogen bonds and a favorable enthalpy of association."

In 1982, in his first book on cyclodextrins, Szejtli pursued and reformulated all the interpretations made by Cramer, Saenger, and Bender on the mechanism of formation of inclusion complexes (Szejtli 1982a). The gain in enthalpy is then explained by the spontaneous arrival of the guest, displacing active water molecules retained in the non-polar cavity of the cyclodextrin in aqueous solution. Szejtli illustrated his conclusions using a schematic representation of cyclodextrin inclusion complex formation (Fig. 1.23). In this famous figure, *p*-xylene is the guest molecule, and the small circles represent the water molecules which are repulsed both by the hydrophobic potential guest and the hydrophobic cavity of the truncated cyclodextrin cylinder (Szejtli 1978; Szejtli et al. 1979). The three main conclusions were as follows: (1) the guest molecule, less polar than water, directly replaced the water molecules in the cavity; these water molecules were in an unfavorable energy state owing to the polar-apolar interactions and were thus easily displaced by more suitable molecules; (2) the cyclodextrin molecules absorbed the energy of the water molecules retained in the cavity; and (3) the organic guest dissolved in water entered in the cavity because it had a preference for hydrophobic environment.

Szejtli supported the idea that, although van der Waals interactions and hydrogen bonding played an important role, the main force behind the formation of the complexes was the stabilizing reduction of the whole system's energy on the replacement of the high enthalpy water molecules in the cavity, by hydrophobic molecules leading to apolar-apolar bonding. He proposed that this bonding was too weak to be alone responsible for the higher stability of the complex and showed the parallel occurrence of steric interactions. Indeed, Szejtli demonstrated in various publications that the preferred position for the guest compound inside the cavity also depended on steric interactions. He concluded that the complexation phenomenon results from a multitude of interactions between the three components of the system cyclodextrin-substrate-solvent leading to a state that is more thermodynamically stable overall (Szejtli 1995). In the 1990s, there was a general agreement in the literature that during the formation of an inclusion complex, a whole set of intermolecular interactions come into play and that each one has its own role in the overall process.

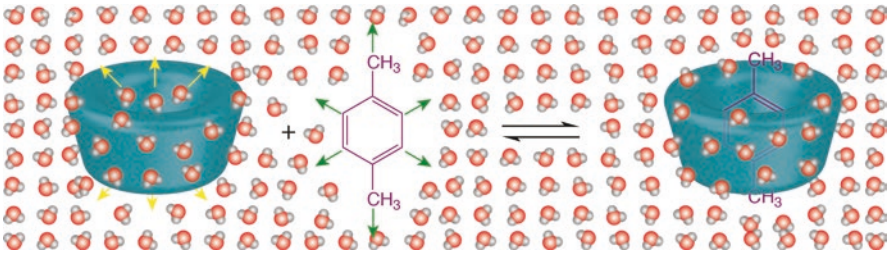

Fig. 1.23 Formation of an inclusion complex between *p*-xylene, the guest, and a cyclodextrin molecule; water molecules are repulsed by the hydrophobic potential guest. (Adapted from Szejtli (1978) and Szejtli et al. (1979)

1.4.3 Inclusion Phenomena and Its Effects

Since Cramer's discovery of inclusion phenomena, effort was devoted to physical and chemical properties of inclusion complexes and their consequences. Indeed, his results were not only of fundamental interest but also of industrial interest, and in the 1970s, this interest has grown considerably. Numerous works showed that inclusion of a guest active ingredient molecule in a host cyclodextrin molecule was a real molecular encapsulation, and the resulting inclusion complex superstructure had new physicochemical properties, stability, solubility, and also better therapeutic efficacy. So, several technological characteristics used in pharmacy could also be advantageously modified.

Rapidly, the pharmaceutical industry understood the advantages of using cyclodextrins. Szejtli (1982a, 1988) summarized them in six points:

1. The modification of the physicochemical properties of the guest molecule: e.g., liquid compounds can be transformed into crystalline, compressible forms; substances with low solubility in water become more soluble after complexation; the rate of dissolution of poorly soluble substances can also be increased; certain unpleasant tastes can be eliminated; smell can also be covered by complex forming; the color of certain substances can be altered since inclusion can change the spectral properties of the guest; etc.
2. The modification of the chemical activity of the guest: e.g., reactive substances can be protected by inclusion reducing the risks when they are mixed with other substances; chemical reactions can be carried out selectively, the cyclodextrins playing the role of catalysts; etc.
3. The stabilization of substances sensitive to light or to oxygen, etc., e.g., protection of active ingredients against oxidation, heat-promoted decomposition, or light-induced reactions.
4. The uptake of volatile substances: e.g., volatile drug can be stabilized without losses through evaporation; storage and handling of certain toxic substances such as pesticides can be improved; savings can be made on the quantity of substance required owing to reduced evaporation; etc.
5. The complexation, extraction, and transport of pollutants.
6. Several technological advantages, e.g., stable, standardized compositions, simple dosage and handling of dry powders, reduced packing and storage costs, and also saving of energy and manpower.

1.4.4 Large Cyclodextrins

Although the existence of cyclodextrins with over 8 glucose units is described and studied for the first time in the 1950s by Freudenberg, French, and Cramer, it was only in the middle of the 1990s that the cyclodextrins containing 9, 10, 11, and 12 units of glucose, called large-ring cyclodextrins, were studied in any depth

(Miyazawa et al. 1995; Endo et al. 1997, 1999; Larsen 2002; Taira et al. 2006). The difficulties to purify them and the low yields prevented their study until then. Using specific enzymes and/or particular experimental conditions, some works also reported the existence of cyclodextrins of over 100 glucose units (Terada et al. 1997; Koizumi et al. 1999; Qi et al. 2004). Larsen (2002) published the first interesting review on large cyclodextrins.

1.4.5 First Comprehensive Reviews on Cyclodextrins

From a fundamental point of view, an abundant scientific literature has built up since the 1970s. Indeed, a large number of generalist reviews, book chapters and books, and articles and patents have been published on practically all the aspects of cyclodextrins. Crini et al. (2018) recently reported that in the periods 1961–1985 (~24 years), 1986–2000 (~14 years), and 2001–2015 (~14 years), 2654, 18,856, and 42,284 cyclodextrin-related publications have been published, respectively, so many that it would not be feasible to cite them all. For this, readers should refer to the library database "Cyclodextrin News" from CycloLab Ltd. (Hungary) which is a periodical collecting all the cyclodextrin works, i.e., articles, reviews, proceedings, patents, conferences, and lectures, through different disciplines, i.e., chemistry, biology, health science, agriculture, nanotechnology, etc. This database is searchable until 2018, when it was turned into a blog and stopped collecting literature. Table 9 shows the first comprehensive reviews and book chapters on cyclodextrins during the period 1957–1998.

As already stated, the very first comprehensive review on cyclodextrins was published by French in 1957 (French 1957a). French's state of the art was continued a few years later by Kainuma (1984) and Clarke et al. (1988). Research on the action of *Bacillus macerans* on starch before 1980 was comprehensively reviewed by Kainuma. Clarke et al. discussed topics on detection, thermodynamics, and kinetics of complex formation from a literature survey of 182 previous papers. In 1980, Saenger published the very first review of industrial applications of cyclodextrins (Saenger 1980). In a very well-cited review published in the journal *Chemical Reviews*, Szejtli wrote: "Cyclodextrins can be consumed by humans as ingredients of drugs, foods, or cosmetics" (Szejtli 1998). In this review, Szejtli, pursuing the history of cyclodextrins written by French, divided the chemical and industrial developments of cyclodextrins into three stages, the discovery period from 1891 to 1935, the exploratory period in 1935–1970, and the utilization period from 1970 to the present day. The history was then updated later by Loftsson and Duchêne (2007) and by Crini (2014). Other fundamental reviews published in the period 1970–1990 are reported in Table 1.2.

Table 1.2 The first comprehensive reviews and book chapters on cyclodextrins during the period 1970–1998

Title	References
Cycloamyloses as catalysts	Griffiths and Bender (1973)
Some application possibilities of cyclodextrins in pharmaceutical industries	Szejtli (1977)
Application of cyclodextrin glycosyltransferase	Okada (1979)
Biomimetic chemistry in oriented systems	Breslow (1979)
Cyclodextrin inclusion-compounds in research and industry	Saenger (1980)
Inclusion compounds in chromatography	Smolková-Keulemansová and Krysl (1980)
Cyclodextrins as stationary phases in chromatography	Smolková-Keulemansová (1982)
Cyclodextrins in food, cosmetics and toiletries	Szejtli (1982b)
Synthesis of chemically modified cyclodextrins	Croft and Bartsch (1983)
Starch oligosaccharides: Linear, branched, and cyclic	Kainuma (1984)
Cycloamylose-substrate binding	Bergeron (1984)
Supramolecular catalysis by cyclodextrin and macrocyclic polyether	Sirlin (1984)
Structural aspects of cyclodextrins and their inclusion complexes	Saenger (1984)
Industrial applications of cyclodextrins	Szejtli (1984)
Chiral stationary phases for high performance liquid chromatographic separation of enantiomers: a mini-review	Armstrong (1984)
Improved cyclodextrin chiral phases: A comparison and review	Ward and Armstrong (1986)
Cyclodextrins: A new group of industrial basic materials	Szejtli (1985)
Production, characterization and applications of cyclodextrins	Bender (1986)
Cyclodextrins in biotechnology	Szejtli (1986)
Cyclodextrins in drug carrier systems	Uekama and Otagiri (1987)
Inclusion complexes of the cyclomalto-oligosaccharides (cyclodextrins)	Clarke et al. (1988)
Cyclodextrin-stationary phases	Ward and Armstrong (1988)
Cyclodextrin polymers in the pharmaceutical industry	Fenyvesi (1988)
Liquid chromatographic separation of anomeric forms of saccharides with cyclodextrin bonded phases	Armstrong and Jin (1989)
HPLC separation of enantiomers and other isomers with cyclodextrin-bonded phases: rules for chiral recognition	Han and Armstrong (1989)
Cyclodextrin additives	Sybilska and Zukowski (1989)
NMR studies of cyclodextrin inclusion complex	Yamamoto and Inoue (1989)

(continued)

Table 1.2 (continued)

Title	References
Cyclodextrins in the pharmaceutical field	Bekers et al. (1991)
Hydroxypropyl-β-cyclodextrins, preparation and physicochemical properties	Szente and Strattan (1991)
Cyclodextrins and their applications in analytical chemistry	Li and Purdy (1992)
Use of cyclodextrins in capillary electrophoresis	Fanali (1993)
Medicinal applications of cyclodextrins	Szejtli (1994)
Cyclodextrins as building blocks for supramolecular structures and functional units	Wenz (1994)
Cyclodextrin derivatives in pharmaceutics	Albers and Muller (1995)
Cyclodextrin derivatives	Jicsinszky et al. (1996)
The stability of cyclodextrin complexes in solution	Connors (1997)
Cyclodextrins	Robyt (1998)
Inclusion complexes of the cyclodextrins	Lincoln and Easton (1998)
Introduction and general overview of cyclodextrin chemistry	Szejtli (1998)
Methods for selective modifications of cyclodextrins	Khan et al. (1998)
Cyclodextrin-based catenanes and rotaxanes	Nepogodiev and Stoddart (1998)
Applications of computational chemistry to the study of cyclodextrins	Lipkowitz (1998)
Complexation thermodynamics of cyclodextrins	Rekharsky and Inoue (1998)
Organic reactions mediated by cyclodextrins	Takahashi (1998)
Cyclodextrin drug carrier systems	Uekama et al. (1998)
Industrial applications of cyclodextrins	Hedges (1998)

1.4.6 First Books on Cyclodextrins

The first books devoted entirely to the chemistry of cyclodextrins and their applications were only edited in 1978 and in 1982 by Bender and Komiyama and Szejtli, respectively (Table 10). Bender and Komiyama (1978) detailed the formation of an inclusion complex and covered all the aspects of catalysis by cyclodextrins. In his first book entitled *Cyclodextrins and Their Inclusion Complexes* (296 pages with more than 650 references), Szejtli reviewed the first industrial applications of cyclodextrins in pharmacy, food industry, chromatography, and chemical industry (Szejtli 1982a). In this book, Szejtli also summarized his interpretations on the concept on inclusion complex. Other important books published in the period from 1970 to 1990, which are still considered as reference works in the cyclodextrin community, are reported in Table 1.3.

Table 1.3 The first books on cyclodextrins published in the period from 1970 to 1990

Title	Author(s)	References
Cyclodextrin chemistry	Myron Lee Bender and Makoto Komiyama	Bender and Komiyama (1978)
Cyclodextrin and Their Inclusion Complexes	József Szejtli	Szejtli (1982a)
Inclusion compounds	Jerry L. Atwood, J. Eric E. Davies and David D. MacNicol	Atwood et al. (1984)
Cyclodextrins and Their Industrial Uses	Dominique Duchêne	Duchêne (1987)
Cyclodextrin technology	József Szejtli	Szejtli (1988)
New trends in cyclodextrins and derivatives	Dominique Duchêne	Duchêne (1991)
Cyclodextrins in Pharmacy	Karl-Heinz Frömming and József Szejtli	Frömming and Szejtli (1994)

1.4.7 The Dissemination of Knowledge About Cyclodextrins

Szejtli is distinguished not only for his contribution to chemistry, biology, and technology of cyclodextrins but also for his important contribution to the dissemination of knowledge about cyclodextrins. From 1975 to 2004, Szejtli published more than 500 publications on cyclodextrins (Cyclodextrin News Database, CycloLab Ltd., Hungary), including 106 patents and more than 100 general reviews and book chapters, and has given more than 200 invited lectures throughout his career. Szejtli's comprehensive reviews are still considered as reference works in the cyclodextrin community (Szejtli 1977, 1982a, b, 1983, 1984, 1985, 1986, 1987, 1988, 1989, 1990, 1994, 1996, 1997, 1998, 2002, 2003, 2004). His name is very often cited in the bibliographic references of articles dealing with cyclodextrins.

From the point of view of the dissemination of knowledge about cyclodextrins, we should also cite the publications of Duchêne (Duchêne 1987, 1991; Duchêne and Wouessidjewe 1990a, b, 1992; Duchêne et al. 1992, 2009), Loftsson (Loftsson and Brewster 1996, 2010, 2012; Loftsson and Stefansson 1997; Brewster and Loftsson 2002, 2007; Loftsson et al. 2004, 2005; Loftsson and Duchêne 2007; Kurkov and Loftsson 2013; Jansook et al. 2018), and Szente (Szente and Strattan 1991; Szente and Szejtli 1996; Szente and Szemán 2013; Fenyvesi and Szente 2016; Fenyvesi et al. 2016; Szente and Fenyvesi 2018).

1.4.8 The First International Cyclodextrin Symposium

Realizing the exponentially increasing number of articles, chapters, and patents, Szejtli organized the first International Cyclodextrin Symposium in Budapest in 1981 (Szejtli 1982a). This first symposium was a great success, with participants coming from all over the world – more than 180 participants from 17 countries – while Szejtli

"expected 25-30 participants outside Hungary." The 63 submitted manuscripts filled a 544-page volume of proceedings published by Reidel Publishing (Szejtli 1982c). The second cyclodextrin symposium was organized in 1984 in Tokyo, Japan.

Since 1984 and Szejtli's initiative, a broad community of researchers has met every 2 years to exchange and share their works on cyclodextrins. Each symposium provides opportunities for scientists who work in several aspects of cyclodextrin research to discuss their advances in all cyclodextrin fields. The 19th International Cyclodextrin Symposium was held in 2018 in Tokyo, Japan, and the next will be organized in Sicily, Italy, in 2020. In Asia and in Europe, the cyclodextrin scientific community is also very active with the organization of meetings where academic researchers and industrials come together to present the latest achievements in the field of cyclodextrin science and technology, e.g., Asian Cyclodextrin Conferences, European Conferences, and French Cyclodextrin Days.

1.4.9 Cyclodextrin Derivatives

The underivatized or native β-cyclodextrin's low water solubility as showed by French in the 1940s restricted its advantage. For this reason, a number of derivatives such as hydrophilic methylated derivatives have been synthesized. Whereas the first methylated derivatives of β-cyclodextrins were studied as early as 1924 by Pringsheim and collaborators (Irvine et al. 1924), it was however not until 1969 that the alkylated cyclodextrins were comprehensively described by Gramera (1969). Indeed, in the older literature, particularly in the works of Pringsheim and Freudenberg, several methods were proposed referring to the preparation of such derivatives, but these are essentially of historic interest.

Literature on the preparation and investigation of cyclodextrin derivatives only proliferated in the 1960s. Since, numerous cyclodextrin derivatives and polymers were described, including alkylated and acylated derivatives, nitrogen- and sulfur-containing derivatives, halogenated products, and 6-deoxy derivatives. The derivatives of practical importance were the methylated and hydroxypropyl cyclodextrin derivatives in the 1980s and 10 years later the sulfobutyl ether derivatives. Casu was the first to prepare cyclodextrin derivatives such as methylated (Casu et al. 1968a, c) and acetylated (Casu et al. 1970) products. The experimental protocols were repeated in the 1980s by Szejtli (Szejtli 1982a, 1983, 1984). His work, particularly on methylated cyclodextrins, showed great promise for both human and animal use (Szejtli 1982a). Methylation could be either partial, i.e., esterification in positions 2 and 6, giving dimethyl-cyclodextrins or complete giving trimethyl-cyclodextrins. The randomized derivative called RAMEB was often used. These derivatives were much more soluble than the parent cyclodextrins, but their solubility was temperature-dependent. For this reason, hydroxypropyl cyclodextrins with high water solubility were more advantageous. However, because hydroxypropylation occurred randomly, the resulting products were not pure chemical entities but amorphous complex mixtures.

Croft and Bartsch (1983) were the first to publish a review on all the different chemically modified cyclodextrins which had been synthetized up to late 1982. In

1987, Sébille showed that cyclodextrin chemistry offered various possibilities to synthetize derivatives with different functions for various industrial uses, e.g., sulfur- and nitrogen- and imidazole- or histamine-containing derivatives, alkylated and acyl derivatives, halogenated products, polymers from cyclodextrins, etc. (Sébille 1987). By working in carefully controlled conditions, mono-, di-, and poly-substitution were possible and opened the way to several functional derivatives with catalytic or biological activity, for instance. One of the most popular derivative was mono-substituted 6-*O*-*p*-toluenesulfonyl-cyclodextrin, used as starting material to prepare modified cyclodextrins (Saenger 1980; Szejtli 1982a; Sébille 1987). Jicsinszky et al. (1996) published a comprehensive chapter (137 pages, 865 references) on cyclodextrin derivatives. In 1998, Khan et al. (1998) proposed a global schema for the modification of cyclodextrins. These two last publications are still reference today.

Thousands of derivatives containing cyclodextrin have been proposed in the literature, particularly for pharmaceutical uses. Szejtli (2004) estimated that over 15,000 derivatives had been studied. In reality, most of these derivatives will never find applications, especially for reasons of production costs and essentially lengthy and difficult synthesis involving complicated steps. Among industrially produced, standardized, and available derivatives, the most important ones are the methylated β-cyclodextrins such as RAMEB (randomly methylated-β-cyclodextrin; considered as a mixture) and DIMEB (a particular methylated cyclodextrin: heptakis(2,6-di-O-methyl-β-cyclodextrin), considered a single isomer; its solubility decreases with an increase in temperature), the 2-hydroxypropylated β-cyclodextrins or HPBCD (the real advantage of this derivative over the methylated derivatives is the lower affinity for cholesterol binding), and the sulfobutylether-β-cyclodextrins or SBEBCD (Fig. 1.24).

Brauns and Müller (1983) and Pitha (1984) registered the first patents on 2-hydroxypropyl-β-cyclodextrin. This compound called hydroxypropylbetadex was the first commonly applied cyclodextrin derivative, used as pharmaceutical excipient in drug formulations in the 1990s (Szente and Strattan 1991). Rapidly, a monograph for this substance has been published in both the US Pharmacopeia and European Pharmacopeia (Brewster and Loftsson 2002, 2007; Brewster et al. 2004). Nowadays, 2-hydroxypropyl-β-cyclodextrin is the most versatile excipient among the cyclic oligosaccharides (Malanga et al. 2016). It can be used in oral, rectal, dermal, ocular, and parenteral formulations, and several pharmaceutical products are marketed, e.g., Indocid® (eye drop), Vorzu® (tablet for fungal infection), Strepfen® (oromucosal spray with flurbiprofen), Vibativ® (i.v. infusion with telavancin), and Lubion® (injection with progesterone as active ingredient). This substance is used as excipient and/or as active component, e.g., at the end of the 2000s, it was discovered that it had beneficial effects for patients in Niemann-Pick type C disease (Liu et al. 2009). Stella and Rajewski (1992) patented the sulfobutylether-β-cyclodextrin product as a potential alternate solubilizing excipient to 2-hydroxypropyl-β-cyclodextrin. This derivative, developed by CyDex under the brand name Captisol®, was found a more efficient complex-forming host than parent cyclodextrins with no apparent toxicity and very high water solubility. Captisol® became generic worldwide in 2011, e.g., Dexolve® developed by CycloLab Ltd. (Hungary). It is used not only as a solubilizing agent but also as an osmotic agent (Puskás et al. 2015).

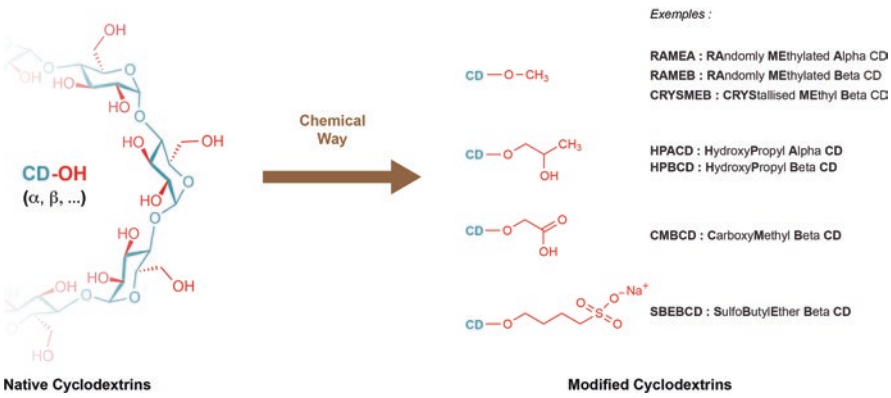

Fig. 1.24 Examples of modified cyclodextrins

In the last four decades, numerous cyclodextrin-based materials have also been synthetized. The list includes modified polymers obtained using grafting reactions (Crini and Morcellet 2002; Kozlowski and Sliwa 2010); cross-linked materials using reticulation or polymerization reaction, e.g., soluble or insoluble polymers (gels/hydrogels, beads, sponges) and fibers (Fenyvesi 1988; Armspach et al. 1999; Mocanu et al. 2001; Crini and Morcellet 2002; Crini 2005; Li 2009; Yang and Yang 2013; Aytac and Uyar 2017); functionalized materials prepared through coating or grafting such as silica beads, e.g., Cyclobond® columns, or resins (Crini and Morcellet 2002; Landy et al. 2012); and nanoporous frameworks containing cyclodextrins (Mahmud and Wilson 2016; Morin-Crini et al. 2018). These materials have been proposed for potential applications in pharmacy (Fenyvesi 1988; Van de Manakker et al. 2009; Muankaew and Loftsson 2018), chromatography (Ward and Armstrong 1988; Schneiderman and Stalcup 2000; Szejtli 2002; Vetter and Bester 2006; Xiao et al. 2012), electrophoresis (Fanali 1993; Chankvetadze 2004; Escuder-Gilabert et al. 2014), textile (Buschmann et al. 1998; Szejtli 2003; Buschmann and Schollmeyer 2004; Ammayappan and Moses 2009; Andreaus et al. 2010; Voncina 2011), supramolecular chemistry (Wenz 1994; Nepogodiev and Stoddart 1998; Schneider and Yatsimirsky 2000; Wenz et al. 2006; Schneider 2012; Zhang and Ma 2013), enzymology (Komiyama 1996; Villalonga et al. 2007; Sonnendecker and Zimmermann 2019a), food industry (Han 2005; Fenyvesi et al. 2016), and cosmetics (Buschmann and Schollmeyer 2002, 2004; Bilensoy 2011) and for environmental purposes (Gruiz et al. 2011; Morin-Crini et al. 2018; Crini et al. 2018).

1.4.10 The First Applications of Cyclodextrins

Table 1.4 shows selected historical landmarks in cyclodextrin fundamental science and applications during the period of their development, from 1970 to 1990. Since the 1990s, a large number of generalist reviews and book chapters have been published on

Table 1.4 Selected historical landmarks in cyclodextrin science during the period of their development, from 1970 to 1990

Period	Main fundamental result, achievement, or event	Reference(s)
1970	The first patent applications on cyclodextrin production at enhanced scale	Armbruster (1970)
1971	Powder X-ray diffractometry is a simple and useful method for the determination of cyclodextrin inclusion compounds in powder or microcrystalline states The diffraction pattern of an inclusion compound is clearly distinct from the superposition of each component if a true inclusion compound exists The first evidence of the possible formation of ternary complexes: a molecule, which alone does not form stable complexes with cyclodextrins, may be incorporated into the cavity when accompanied by another molecule, e.g., diethyl ether in presence of anthracene	Takeo (1971)
1972	In Hungary, Szejtli organized the cyclodextrin research laboratory which became, in 1987, the first private research institute for the technological transfer between cyclodextrin research and industry	Szejtli (1982a)
1973	The presence of two different forms of inclusion complexes in the crystalline state, i.e., channel and cage-type structures, is suggested	McMullan et al. (1973a, b)
1973	The Raman spectra of amylose and cyclodextrins are studied	Cael et al. (1973)
1973	Calorimetry is proposed to detect inclusion compound formation: thermodynamic parameters, enthalpy, and entropy changes can be obtained	Lewis and Hansen (1973)
1973	The interaction of α-cyclodextrin with certain phenol derivatives is enthalpy driven rather than entropy driven, unlike classical hydrophobic interactions which are characterized by a large positive entropy contribution	Griffiths and Bender (1973)
1975	Freeze-drying is proposed to prepare inclusion compounds in an industrial scale	Kurozumi et al. (1975)
1975	Preparation of Schardinger β-dextrin on an industrial scale by cyclodextrin glycosyltransferase of an alkalophilic *Bacillus sp*.	Matzuzawa et al. (1975)
1976	The precise geometry of an inclusion compound can be established by single-crystal X-ray structure analysis Introduction of the notion of the release of the tension energy within the cyclodextrin molecule upon formation of the complex A new concept is suggested for the first time: cyclodextrins are packed within a crystal lattice of one of two types, i.e., cage and channel structures, depending upon the size and characteristics of the guest molecules	Saenger (1976), Saenger et al. (1976)

(continued)

Table 1.4 (continued)

Period	Main fundamental result, achievement, or event	Reference(s)
1976	The first cyclodextrin-based pharmaceutical is marketed in Japan: Prostarmon E™ Ono Pharmaceutical Co. Japan authorizes the use of α-cyclodextrin and β-cyclodextrin as food additives	Szejtli (1977), Uekama and Hirayama (1978), Hirayama et al. (1980), Uekama and Otagiri (1987), Frömming and Szejtli (1994)
1977	A detailed 1H-NMR spectrum of α-cyclodextrin is given NMR data and computer simulation show that all six glucose units in α-cyclodextrin have identical conformations	Wood et al. (1977)
1977	Polarography is used to prove the formation of inclusion compounds with electroactive guests	Osa et al. (1977)
1978	Bender elucidates the mechanism of formation of the complexes developed by Saenger The complexation reaction involves a gain in enthalpy and a loss of entropy	Bender and Komiyama (1978)
1978	Japan permits the use of cyclodextrins in food products	Hashimoto (1996), Hedges (1998)
1978	Cyclodextrin inclusion compounds accommodate many water molecules in the lattice as crystal lattice These water molecules are involved in the formation of hydrogen bonding networks	Lindner and Saenger (1978)
1979	Circular dichroism spectroscopy is particularly useful to detect cycloamylose inclusion compounds in aqueous solution	Bergeron and McPhie (1979)
1980	The X-ray structural analysis of the cyclodextrin/iodine complex is detailed, showing that the iodine chain is slightly zigzag and discontinuous	Saenger (1980)
1980	The hydrolysis rate of some esters is accelerated between 10^6- and 10^7-fold by cyclodextrin if the reactive site of the guests is fixed in an optimum binding geometry with respect to the catalytic hydroxyl group of the host	Breslow et al. (1980)
1980	Two naphthalene molecules can be included within one γ-cyclodextrin cavity	Ueno et al. (1980)
1981	Three forms of hydrated α-cyclodextrin were comprehensively studied: the crystalline structures are classed in two categories, cages and channels, according to the overall appearance of the cavities	Chacko and Saenger (1981)
1981	A relationship between the position of the guests in the cavity and the changes in the ^{13}C chemical shift is proposed	Komiyama and Hirai (1981)
1981	Organization of the First International Cyclodextrin Symposium in Budapest	Szejtli (1982c)
1981	The first edible coating for food packaging	Hiroshi (1981)

(continued)

Table 1.4 (continued)

Period	Main fundamental result, achievement, or event	Reference(s)
1982	The nontoxicity of cyclodextrins by oral administration appears to be highly probable Modified cyclodextrins are interesting to improve the spatial complementarity of the host with respect to the guest and to extend molecular recognition processes	Szejtli (1982a)
1982	The detection of the inclusion compound formation using a potentiometric titration is proposed Cyclodextrins favor the non-ionized guest molecules with higher hydrophobicity, rather than the ionized ones	Connors et al. (1982)
1982	Cyclodextrin inclusion compounds in solution can be studied by Raman spectroscopy	Higuchi et al. (1982)
1983–1985	Patents on 2-hydroxypropyl-β-cyclodextrin	Brauns and Müller (1983), Pitha (1984)
1983	The Hungarian Ministry of Health approves the use of β-cyclodextrin for stabilization of natural flavors	Szejtli (1984)
1984	The strength of interaction varies with the shape of the guest: the guests that fit the cavity best give the most stable compounds Crystal structures of complexes show that, in the case of a polar guest, hydrogen bond formation stabilizes the orientation According to neutron diffraction data, water molecules are involved in the formation of hydrogen bonding networks between host/host, host-guest, or each other with a definite regularity, i.e., circular or flip-flop hydrogen bonds, to stabilize the packing modes	Saenger (1984)
1984	The first chromatographic columns are marketed	Armstrong (1984), Ward and Armstrong (1986)
1984	Szejtli demonstrated the nontoxicity of cyclodextrins by oral administration	Szejtli (1984)
1984	Cyclodextrins are extensively hydrolyzed in the human colon: the products of hydrolysis include glucose and maltooligosaccharides	Antenucci and Palmer (1984)
1988	Piroxicam-β-cyclodextrin tablets marketed by Chiesi Farmaceutici, Italy	Szejtli (1977), Uekama and Otagiri (1987), Frömming and Szejtli (1994), Hashimoto (1996)

practically all the aspects of cyclodextrins, so many that it would not be feasible to cite them all. In this section, we chose to highlight selected works on the first applications of cyclodextrins. A recent review on this topic can be found in the review by Crini et al. (2018) who summarized the literature published in the last four decades. Readers interested in cyclodextrin applications should also refer to the library database "Cyclodextrin News" from CycloLab Ltd., Hungary.

Cyclodextrins have been used in pharmaceutical industry since the 1970s (Szejtli 1977; Uekama and Hirayama 1978; Uekama and Otagiri 1987; Frömming and Szejtli 1994). With a more accurate picture of their toxicity and better

understanding of molecular encapsulation, several inclusion complexes appeared on the market (Davis and Brewster 2004; Brewster and Loftsson 2007).

In 1976, the first product, i.e., prostaglandin E2/β-cyclodextrin Prostarmon E™ sublingual tablet, was marketed in Japan (Ono Co.) (Uekama and Hirayama 1978; Hirayama et al. 1980). Prostaglandin E2, a substance with potent oxytocin-like effects, was of interest as a possible agent for the induction of labor in childbirth (Davis and Brewster 2004). However, this substance was highly unstable, and this feature complicated its formulation and development. The solution was to encapsulate it using β-cyclodextrin, resulting in a significant increase in its solid-state stability. This led to spectacular progress in pharmaceutical domain. The second prostaglandin marketed was Prostavasin®, a complex between prostaglandin E1 and α-cyclodextrin. In 1979, this product was approved for the treatment of peripheral vascular complications. Uekama's group studied the molecular motions of prostaglandin $F_{2\alpha}$-cyclodextrin inclusion compounds (Uekama and Hirayama 1978; Hirayama et al. 1980; Uekama et al. 1984). As a consequence of the inclusion, the internal motion of the ϖ-side alkyl chain of the prostaglandin is selectively reduced by α-cyclodextrin, while the internal motion around the five-membered ring, as well as the overall motion, is decreased by β-cyclodextrin. In the case of the γ-cyclodextrin inclusion compound, total motion of the prostaglandin is reduced. The inclusion of prostaglandin E_1 in γ-cyclodextrin increased its heat stability and slowed down its conversion to prostaglandin A_1 (Uekama et al. 1984). The structures proposed by Uekama's group and illustrated in Fig. 1.25 were demonstrated using NMR data (Uekama and Hirayama 1978; Hirayama et al. 1980).

Another interesting formulation was the complex β-cyclodextrin/piroxicam, used, e.g., in the treatment of acute pain of rheumatic disease. In 1988, Chiesi Farmaceutici, Italy, has put on the market this complex Brexin® or Cycladol® (Fig. 1.26). Nine years later, the first US-approved product, 2-hydroxypropyl-β-cyclodextrin/itraconazole oral solution (Sporanox® Janssen), was introduced (Fig. 1.26). Itraconazole is an orally active triazole antifungal agent to inhibit most human fungal pathogens but is practically insoluble in water at physiological pH. In 2002, two formulations containing sulfobutylether β-cyclodextrin were introduced by Pfizer in the USA and Europe: an intravenous formulation of the antifungal agent voriconazole (Vfend®) and an intramuscular dosage form for the antipsychotic agent ziprasidone (Geodon®).

All these formulations are preformed prior to be administrated. There are also some cases when the complexes are formed within the body. The best-known example is the one containing the active compound sugammadex (Bridion®): it is a modified γ-CD used as an antidote to certain curare-like muscle relaxants in anesthesia since 2008. After intravenous administration, it neutralizes steroid curare-like agents such as rocuronium and vecuronium by forming an inactive complex (Fig. 1.26) in the plasma which is then eliminated in the urine.

Actually, more than 80 pharmaceutical products can be found (CycloLab Ltd., Hungary). In these formulations, native cyclodextrins and their derivatives, such as the hydroxypropyl derivatives of β- and γ-cyclodextrins, sulfobutylether β-cyclodextrin, and maltosyl-β-cyclodextrin (this derivative might be a component of several drugs

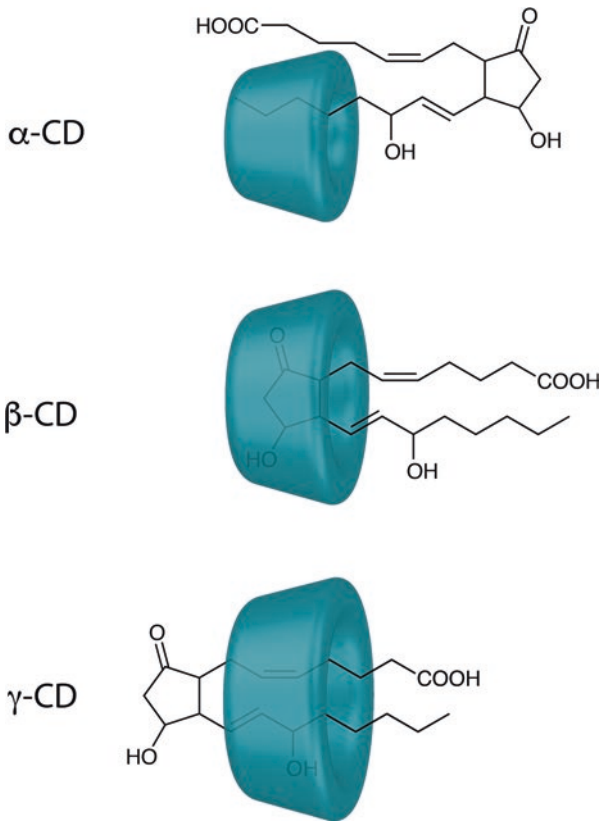

Fig. 1.25 Inclusion mode of cyclodextrin-prostaglandin $F_{2\alpha}$ inclusion compounds in aqueous solution. (Adapted from Uekama and Hirayama (1978) and Hirayama et al. (1980))

marketed in Japan, but information are scarce), are mainly used as complexing agents to increase the aqueous solubility of poorly water-soluble drugs, to increase their stability and bioavailability. Cyclodextrins are also used to replace organic solvents in parenteral and topical formulations, to reduce gastrointestinal irritation, and to increase dermal availability of drugs. Initially, cyclodextrins were mainly used in solid dosage forms for oral administration, but rapidly, other administration routes were proposed such as ocular, nasal, parenteral, rectal, or dermal route. For instance, RAMEB is included in Clorocil® eye drop (Oftalder, Portugal) and Aerodiol® nasal spray (Servier, France). Both are non-parenteral, and the latter was withdrawn from the market because of economic reasons.

Food applications also started to appear in the mid-1970s. Japan authorized the use of cyclodextrin as a food additive in 1976 (Szejtli 1982a, 1998; Vaution et al. 1987; Hedges et al. 1995; Hashimoto 1996; Hedges 1998). Powdered flavors, e.g., apple and citrus fruits; spices, e.g., horseradish wasabi and mustard; and herbs such as peppermint were marketed. Other marketed food products containing cyclodextrins or made by cyclodextrin-aided technology included chocolate (Choco Bar™), chewing gum

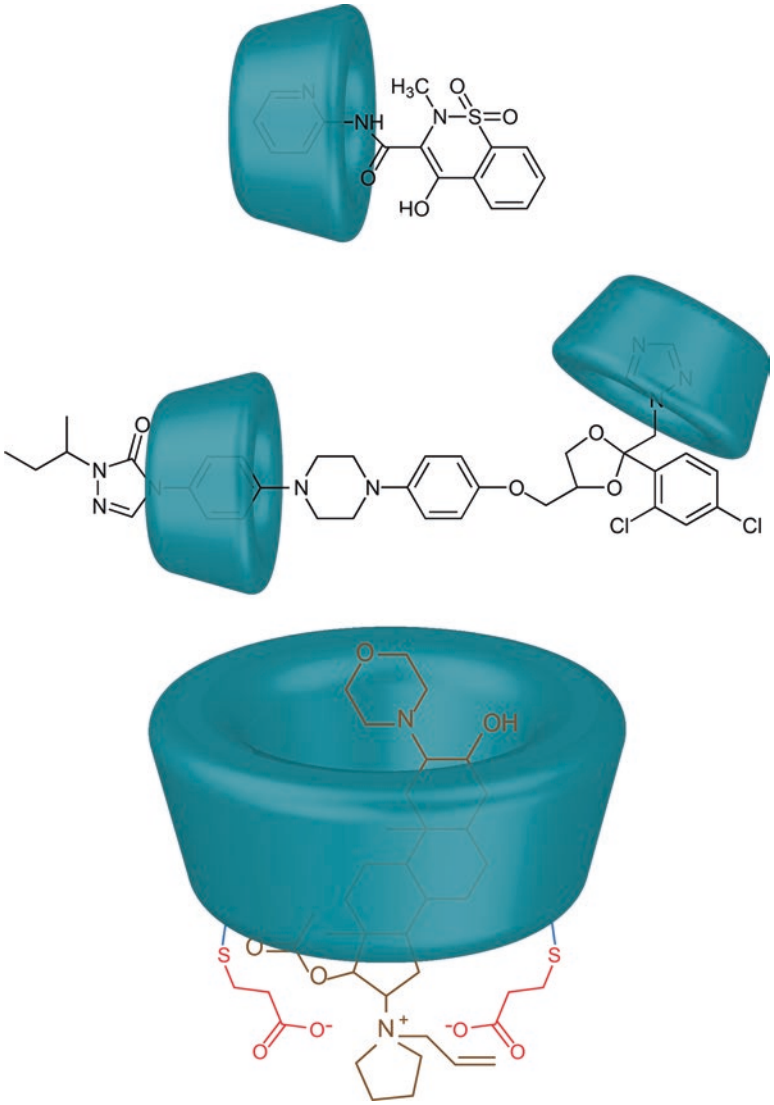

Fig. 1.26 β-cyclodextrin/piroxicam (top), 2-hydroxypropyl-β-cyclodextrin/itraconazole (middle), and sugammadex/rocuronium (bottom) complexes

(Flavono™), powdered green tea (Stick Lemon™), and dietary fibers (Hedges 1998; Hashimoto 2002). In 1992, low-cholesterol butter, prepared by mixing cyclodextrin with the melted butter, under the trade name of Balade™ was marketed in Belgium (Comini and Mentink 1991). Other low-cholesterol milk products such as cheese (Natual™, France), cream, and egg (Simply Eggs™, USA) were produced. Other examples include bubbling coffee (Nescafé®, Nestlé), beer (FlavorAktiv™, Great

Britain), and supplements. In the 2000s, the three native cyclodextrins were introduced into the generally regarded safe list of the US Food and Drug Administration for use as a food additive (Hashimoto 2002). Now the food industry, along with the pharmaceutical domain, is one of the sectors that consumes the most cyclodextrins, at least in Japan.

Hinze (1981) was the first to describe the application of cyclodextrins in analytical chemistry, focusing on their use in chromatography and purification methods. At that time, the first studies had established that cyclodextrins were interesting complexing agents, chiral selectors, and/or additives in chromatography (Smolková-Keulemansová and Krysl 1980; Hinze 1981; Smolková-Keulemansová 1982; Sybilska and Smolková-Keulemansová 1984; Krysl and Smolková-Keulemansová 1985; Li and Purdy 1992). Cyclodextrins were first proposed for thin-layer chromatography, gel electrophoresis, gas chromatography, and liquid chromatography and later for capillary electrophoresis, electrokinetic chromatography, and dialysis (Armstrong 1980, 1984; Smolková-Keulemansová and Krysl 1980; Smolková-Keulemansová 1982; Hinze 1981; Cserhati et al. 1983; Ward and Armstrong 1986; Li and Purdy 1992; Fanali 1993; Fanali et al. 1994; Schneiderman and Stalcup 2000). The first cyclodextrin-based chiral gas chromatography was published by Smolková-Keulemansová (1982).

At the beginning of the 1980s, Armstrong laid down the fundamentals of cyclodextrin-assisted separation science. Between 1980 and 1988, Armstrong and his collaborators pioneered the development and optimization of analytical methods suitable for cyclodextrin-based isomer separation. In 1984, the first chromatographic columns were marketed (Advanced Separation Technologies Inc., Whippany, NJ), and this led to spectacular progress in chromatography (Armstrong 1980, 1984; Hinze 1981; Ward and Armstrong 1986, 1988; Armstrong and Jin 1989; Han and Armstrong 1989; Menges and Armstrong 1991). These chromatographic packings consisted of cyclodextrin molecules linked to silica gel via a 6–10-atom spacer. Both the linkage and the cyclodextrin were hydrolytically stable under high-performance liquid chromatography. Easily the most popular cyclodextrin-based stationary phases were based on β-cyclodextrin, e.g., they have been shown to be very effective at resolving the enantiomers of many compounds. Subsequently, other stationary phases were developed, based on other native cyclodextrins, e.g., α- and γ-cyclodextrin, or derivatized cyclodextrins such as naphthyl-ethyl-carbamate derivative. The α-cyclodextrin and γ-cyclodextrin columns, while less broadly applicable in the reversed-phase mode than the β-cyclodextrin columns, were useful for specific applications such as the separation of enantiomers of underivatized aromatic amino acids and substituted analogues or of polycyclic aromatic compounds and steroid stereoisomers. The aromatic-derivatized cyclodextrin phases were used to separate the enantiomers of many classes of compounds including pesticides, biological compounds, drugs, and amino acids (Menges and Armstrong 1991; Mitchell and Armstrong (2004). The chiral recognition mechanisms in analytical separation sciences were reviewed by Scriba (2012). Li and Purdy (1992) and later Szente and Szemán (2013) comprehensively reviewed the application of cyclodextrins in diverse fields of analytical chemistry and covered the structural aspects of

cyclodextrins that enabled the improvement of different chromatographic separations.

The first comprehensive review on potential applications in cosmetology, toiletry, and hygiene has been published by Szejtli (1982b). This topic was later updated by Vaution et al. (1987), Hashimoto (1996, 2006), Citernesi and Sciacchitano (1995), Buschmann and Schollmeyer (2002), and Duchêne et al. (2009). In the mid-1980s, some products appear in the market although the cyclodextrins were often used without any indication of their precise role: Epicutin® TT, Chemishes Laboratorium Dr Kurt Richter, a complex between cyclodextrin and *Melaleuca alternifolia* leaf oil, used in skin care applications; Vivace®, Shiseifo Co., a powder cologne; Klorane®, Klorane Laboratories, a dry shampoo; Novoflex®, Revlon, a vitamin shampoo; Eucerin® Vital Active, Beiersdorf, a vitamin A cream; etc. In the cosmetic industry, cyclodextrin complexes were useful for modifying solubility, improving stabilization, transforming liquids into solids, preserving color, decreasing an unpleasant smell, or diminishing the odor of mercaptan used in permanent hair preparations. Cyclodextrins were used as empty capsules in dry shampoos to eliminate fatty substances such as sebum, or in toothpaste and mouthwash to remove undesirable odors (Duchêne et al. 2009).

In the 1980s, applications were found in textiles including textile finishing and functional textiles (Szejtli 1985; Hashimoto 1996; Buschmann and Schollmeyer 2002). The permanent fixation of cyclodextrin molecules offered textiles with interesting properties, e.g., the formation of body odor was reduced by the complexation, the release of perfumes from cyclodextrins was possible, etc. The first cellulose-cyclodextrin copolymer was described in 1980 by Szejtli's group. Alkali-swollen cellulose fibers were reacted with epichlorohydrin. The chemically bound cyclodextrin retained its complex-forming ability and could be loaded with chemically and/or biologically active guests such as perfumes to prepare perfumed textiles or drugs to prepare medical bandages (Szejtli et al. 1980b). For instance, Fig. 1.27 illustrates a guest exchange by a cellulose fiber containing cyclodextrin. The process consists to load the fixed cyclodextrin molecules with perfume molecules. During wearing and by sweat humidity, excreted short-chain fatty acids displace and release the perfume molecules and will be in turn entrapped (Szejtli 2003). Procter & Gamble recognized that similar effects can be achieved without chemical fixation by simple spraying of hydroxypropyl-β-cyclodextrin solution on the fabric. This odor-eliminating spray (Febreze®) has become a great success in the USA marketed since 1998 ensuring a continuous demand for cyclodextrin production. Actually, cyclodextrins play an important role in the textile industry as a tool to remove odors, e.g., encapsulation of sweat or cigarette smoke components permits to reduce the intensity of odors of clothing or furniture textiles, as showed in Fig. 1.28. The mechanism of drug release is similar from medical textiles such as antimicrobial textiles for wound dressing (Aubert-Viard et al. 2019), intraperitoneal meshes (Chai et al. 2019), and other implants (Vermet et al. 2017). CycloMesh™, a polyester visceral implant soaked in ropivacaine hydrochloride developed for slow anesthetic release and in situ activity after inguinal hernia surgery, will be soon subjected to clinical trials in France.

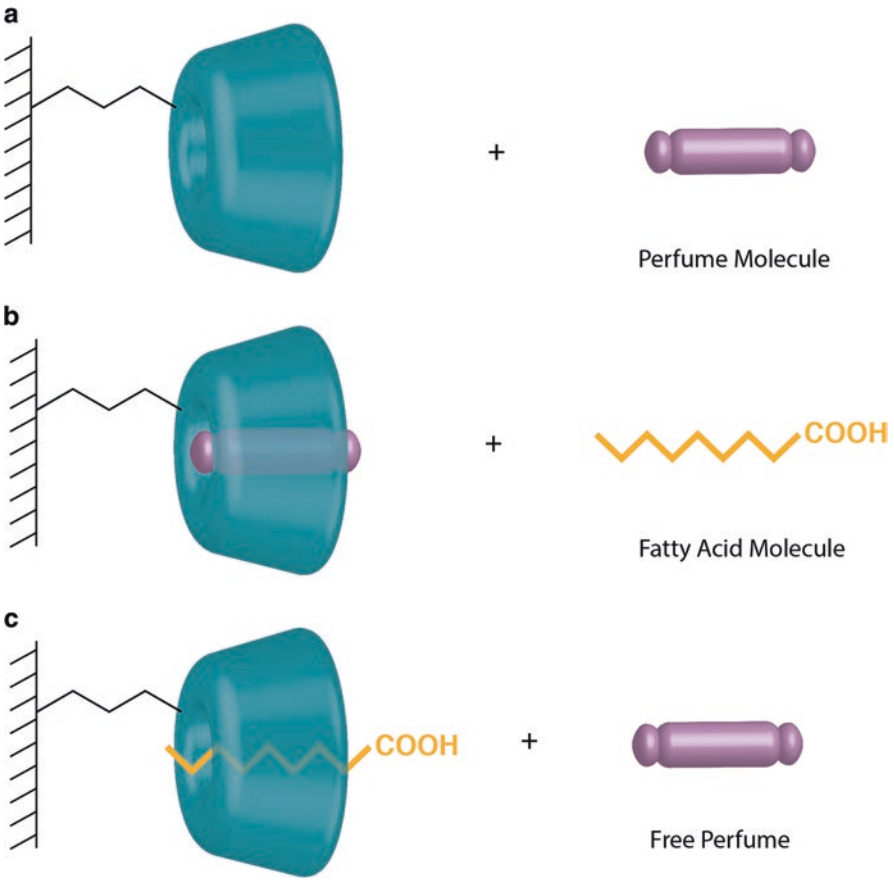

Fig. 1.27 Guest exchange by a cellulose fiber containing cyclodextrin: the process consists to load the fixed cyclodextrin molecules with perfume molecules; then during wearing and by sweat humidity, excreted short-chain fatty acids displace and release the perfume molecules and will be in turn entrapped. (Adapted from Szejtli 2003)

During the period from 1980 to 1990, manufactured products using cyclodextrins have emerged such as pesticide formulations, reproduction processes, e.g., photography and inks, tobaccos, corrosion inhibitors, industrial detergents, sterilizing agents, anti-foam agents, glues, wood treatment, etc. (Szejtli 1982a, 1984, 1988; Vaution et al. 1987). In the agricultural sector, the use of complexation by cyclodextrins has facilitated the formulation of pesticides in many ways, e.g., by enhancing water solubility and biological activity, through stabilization of labile substances, by enabling easier handling of hazardous substance, and also through the formation of crystalline substances from volatile liquids. An important feature of the cyclodextrin-formulated pesticides is the water-triggered release of the active compounds. A large number of patents concerning the use of cyclodextrins in agrochemistry were filled (Szejtli 1982a, 1984; Szente and Szejtli 1996; Morillo 2006).

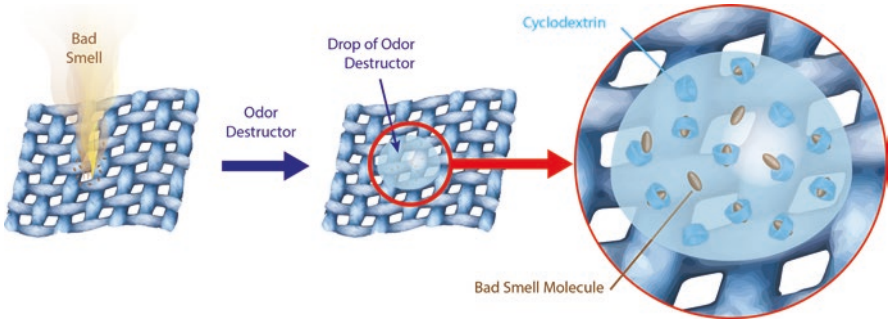

Fig. 1.28 Elimination of odors by a textile fiber containing cyclodextrin molecules either permanently fixed by chemicals bonds or just adsorbed on the fibers

1.4.11 Cyclodextrins: Trends and Outlook

Although an important number of works, patents, and products have been realized, the sector of cyclodextrin-based pharmacy continues to interest the scientific community. Cyclodextrins are still regarded as "novel" excipients, active ingredients, drug delivery vehicles, and anti-aggregation agents (Conceição et al. 2018). New formulations continue to be reported, generating new interests in medicine and biomedicine (Higashi et al. 2018; Higashi 2019; Menezes et al. 2019; Pawar and Shende 2019). The 18 ongoing clinical trials in 2019 give the promise of new marketed formulations (Cyclodextrin News, CycloLab Ltd., Hungary).

The recent research has clearly revealed that cyclodextrins cannot be considered inactive excipients any more (Arima et al. 2017). Hydroxypropyl-β-cyclodextrin was found by serendipity to be useful for slowing down the progression of Niemann-Pick type C disease, the fatal genetic disorder. Based on the promising results of the clinical trials, this cyclodextrin received orphan drug status both from Food and Drug Administration and European Drug Agency. The mechanism of action which was thought first to be based on cholesterol complexation is still under debate.

Yokoo et al. (2015) demonstrated that hydroxypropyl-β-cyclodextrin was a potential anticancer agent in leukemia. This derivative was found effective in inhibition of leukemic cell proliferation at various leukemic cell lines. It was proved to influence autophagy, a catabolic process with an essential function in the maintenance of cellular and tissue homeostasis. As solubilizing agent to increase cholesterol solubility, hydroxypropyl-β-cyclodextrin is used for prevention and treatment of atherosclerosis, a chronic inflammatory disease driven primarily by a continuous retention of cholesterol within the subendothelial space to hinder its precipitation in the form of cholesterol crystals (Zimmer et al. 2016).

Several research groups are developing special cyclodextrin derivatives with various functions, for instance, for targeted drug delivery. Folate-appended cyclodextrins are recognized by folate-receptor-expressing tumor cells; therefore they can be utilized as potent anticancer agents (Motoyama et al. 2015). Lactosyl-β-cyclodextrin

was found effective for hepatomegaly in Niemann-Pick type C disease (Maeda et al. 2019). Cyclodextrins decorated with a photosensitizer group can be used for drug delivery in phototherapy where the release of active ingredients is controlled by light (Benkovics et al. 2017). Multifunctional cyclodextrin derivatives having nitric oxide-releasing moiety in addition to the photosensitizer are efficient antimicrobial and anti-tumor agents in photodynamic therapy (Malanga et al. 2019). Many bacteria display mannose-binding lectins on their surfaces, and so mannosylated cyclodextrins are target-specific antimicrobial delivery systems to be used in fighting against antimicrobial resistance (Cutrone et al. 2018).

Another direction of recent cyclodextrin research is the design and synthesis of specific cyclodextrins tailored to the guest molecules to be entrapped. Encouraged by the extreme success of sugammadex tailored for encapturing rocuronium muscle relaxant, further cyclodextrin-based detoxicants were prepared: e.g., a cyclodextrin dimer as antidote for cyanide poisoning (Yamagiwa et al. 2014), another dimer designed for binding and removal of bisretinoid lipofuscins from the eye to prevent aging-related blindness (Nociari et al. 2014), and specially substituted cyclodextrins to catalyze the decomposition of organophosphorus chemical weapons getting importance in view of increasing terrorist threat (Müller et al. 2013). Even the social media shared the news on methyl- and hydroxypropyl-β-cyclodextrins as possible antidotes to box jellyfish venom (Lau et al. 2019). Similarly, quaternary amino β-cyclodextrin was found to bind ochratoxin A, a widely spread nephrotoxic contaminant mycotoxin, with an association constant more than 200-fold higher than that of β-cyclodextrin, making this derivative useful for decontamination of ochratoxin A-contaminated drinks (Poór et al. 2015).

Actually, fundamental research is also focusing on cyclodextrin-based nanoparticles/nanomaterials for pharmaceutical and biomedical applications and nanomedicine, e.g., molecular diagnosis, medical imaging, antifungal treatment, antimicrobial therapy, gene therapy, or tissue engineering, and on self-association of cyclodextrins for applications not only for formulation and drug delivery, and medicine, but also for materials science, supramolecular chemistry, and asymmetric catalysis (Hirakawa and Tomita 2013; Morohoshi et al. 2013; Zhang and Ma 2013; Chilajwar et al. 2014; Melotti et al. 2014; Simoes et al. 2014; Dong et al. 2015; Macaev and Boldescu 2015; Mavridis and Yannakopoulou 2015; Miller et al. 2015; Perez-Anes et al. 2015; Wu et al. 2015; Brackman et al. 2016; Junthip et al. 2016; Okano et al. 2016; Oliveri and Vecchio 2016; Ryzhakov et al. 2016; Sharma and Baldi 2016; Silva et al. 2016; Yuan and Zhang 2016; Saokham and Loftsson 2017; Egele et al. 2019; Fenyvesi et al. 2019; Hammoud et al. 2019; Kumar and Rao 2019; Neva et al. 2019; Pawar and Shende 2019; Topuz and Uyar 2019; Zhang et al. 2019a).

Nanoparticles of various compositions have been engineered in ever smaller sizes to function in both diagnostic and therapeutic capacities. They are available on a scale similar to many biological molecules and infectious agents, thereby opening the possibility of biological intervention on the molecular level (Gilmore and Colson 2011). Nanoparticle-based systems can improve bioavailability, reduce immunogenicity, modify drug metabolism, reduce toxicity, and increase the biological half-life of drugs after systemic administration. The use of cyclodextrin-based

nanoaggregates both in oral and ophthalmic drug delivery could be a promising strategy to improve the bioavailability of poorly soluble drugs (Loftsson and Stefansson 2017; Kumar and Rao 2019). Nanomaterials are also interesting because they can be formulated as oral, parenteral, topical, or inhalation dosage forms (Chilajwar et al. 2014). They can be targeted by using specific components and/or moieties, e.g., antibody-targeted cyclodextrin-based nanoparticles were developed for siRNA delivery in the treatment of myeloid leukemia (Guo et al. 2017). Various innovative ideas for the purpose-oriented design of such systems have been published, e.g., "ship-in-a-bottle" (Xu et al. 2019), modern Trojan horse (Gilmore and Colson 2011), and molecular Lego approach for the diversity-oriented synthesis of cyclodextrin analogues as scaffolds for multivalent systems (Lepage et al. 2015). Promising developments for nanoparticles are under way in emerging domains such as nutraceuticals and cosmeceuticals (Fenyvesi et al. 2016; Adeoye et al. 2017). Further contributions are also expected in the near future in bacterial resistance and chemotherapy (Carneiro et al. 2019; Zhang et al. 2019b).

Recently, Higashi et al. (2018) introduced a new concept in pharmaceutical sciences termed "supramolecular pharmaceutical sciences" which combines pharmacy domain and supramolecular chemistry. This concept is focused on the development of cyclodextrin-based supermolecules, such as polyspeudorotaxanes, polyrotaxanes, polycatenanes, and daisy chains, as active pharmaceutical ingredients used, for instance, against Niemann-Pick type C disease, leukemia, Alzheimer's disease, chronic renal failure, or sterility. These biodegradable polyrotaxanes ensure longer residence time and slow release of the cyclodextrin – mostly hydroxypropyl-β-cyclodextrin – as active ingredient. The low local concentrations result in reduced toxicity even in the case of the methylated derivatives.

The number of publications on the use of nanofibers containing cyclodextrins, e.g., prepared by electrospinning, is also growing (Celebioglu and Uyar 2012, 2013; Aytac et al. 2015, 2016; Topuz and Uyar 2019). These nanofibers are proposed as innovative products for medicine, biomedicine, and nanomedicine applications, e.g., for medical devices, tissue engineering scaffolds, stents, prosthesis, and bone implants. Most of these studies are in the proof-of-concept stage, and only a few therapeutic nanosystems/nanomaterials have been comprehensively investigated. Nanofibers are also proposed for textile and environmental applications (Celebioglu et al. 2016), e.g., innovative clothing, filtration media, and membranes.

The use of cyclodextrins for veterinary purposes seems to be a promising domain (Chiu et al. 2016). New formulations continue to be reported, e.g., Itrafungol™, Voriconazole Dexolve™, Nexterone™, Cereni™, Vetmedin™, Suvaxyn™, etc. Itrafungol™ is an antifungal containing 2-hydroxypropyl-β-cyclodextrin used as antimycotic drug in oral form in cats. Another example is Voriconazole Dexolve™, a commercial formulation containing sulfobutylether-β-cyclodextrin as an excipient, used as an antimycotic drug for veterinary and human use. Suvaxyn™ containing a sulfolipo-cyclodextrin as adjuvant is used as vaccine for the active immunization of pigs.

The global market of cyclodextrins used in food industries is continuously increasing (Fenyvesi and Szente 2016; Fenyvesi et al. 2016). The main application

is the stabilization of flavors and aromas. α-Cyclodextrin, being non-digestible, is recognized a dietary fiber with beneficial effects on digestion of fat and carbohydrates (Artiss et al. 2006). It has been marketed for body weight control in several countries. Further studies and industrial developments are expected in the near future in the following domains: functional food, nutritional supplements, nutraceuticals, wrapping materials, and packaging. One of the most promising functional food groups is those enriched in antioxidant compounds of a lipophilic nature (Fenyvesi and Szente 2016; Kfoury et al. 2016; Zarzycki et al. 2016).

Other applications have been reported in sectors such as supramolecular catalysis (Hapiot et al. 2014; Chen et al. 2019; Fernandez et al. 2019), asymmetric and stereospecific synthesis (Macaev and Boldescu 2015), click chemistry (Celebioglu et al. 2016; Hou et al. 2016), metal-organic frameworks (Rajkumar et al. 2019), agrochemistry (Campos et al. 2015; Yusoff et al. 2016), supercritical fluid chromatography (Xiao et al. 2012; West 2014), imprinting techniques (Lay et al. 2016), nanofibers (Topuz and Uyar 2019), and environment (Taka et al. 2017; Crini et al. 2018).

Research on cyclodextrins is also very active in fields such as the formulation of detergents and sugar-based surfactants (Valente and Söderman 2014), glues and adhesives (Osaki 2019), silicon industry (Grachev et al. 2019), flame-retardant formulation (Luda and Zanetti 2019), the sector of plastics for packaging or for automotive (Szente and Fenyvesi 2018), the industry of fibers and paper, soil remediation (Atteia et al. 2013; Lau et al. 2014; Madrid et al. 2019; Gruiz et al. 2019), materials for wastewater treatment (Cova et al. 2018; Morin-Crini et al. 2018; Barbosa et al. 2019), biodiesel production (Zhang et al. 2018), and hydrogen storage (Han et al. 2018).

The slide ring gels (polyrotaxane gels) found their application in the car industry and telecommunication (Ito 2017; Kashiwagi et al. 2018; Jiang et al. 2018). There are also many possibilities for the development of new textiles and cosmetic products, called cosmetotextiles (Singh et al. 2011), with advanced properties (Shende and Trotta 2019; Yao et al. 2019). Their applications seem promising.

Cosmeceuticals containing cyclodextrins also seem to be a promising domain for medicine, dermatology, and aromatherapy (Adeoye et al. 2017; Kaur et al. 2018). These products are cosmetics with pharmaceutical and therapeutic benefits.

1.5 Conclusion

In this chapter, we described historical landmarks of the discovery, exploration, and utilization of cyclodextrins, cyclic oligosaccharides obtained from the enzymatic degradation of starch and discovered serendipitously in 1891 by Villiers. Of course, this historical chapter cannot hope to be exhaustive, but it highlighted the work of those researchers who have contributed to the knowledge of cyclodextrins throughout the 129 years of its history.

Expensive to produce, the three main native cyclodextrins, i.e., α-, β-, and γ-cyclodextrins, were long considered just laboratory curiosities. Until the mid-1970s, the main obstacles were the lack of sufficient knowledge of these molecules, their high price, and also their presumed toxicity. In addition, very few researchers were convinced of the industrial potential of cyclodextrins.

As reported in this comprehensive chapter, since Villiers' discovery, several great scientists, including Schardinger, Freudenberg, Cramer, French, and Szejtli, have left their mark on the history, characterization, properties, and potential applications of these molecules over a period of 86 years, from 1903, i.e., the first paper on cyclodextrin chemistry published by Schardinger, to 1989, i.e., the creation by Szejtli of the first company totally devoted to cyclodextrins.

Since the 1980s, cyclodextrins have considerably attracted the interest of scientists and industries in different disciplines including health science, agriculture, chemistry, biochemistry, and environment. The main reason for this growing interest was their ability to form inclusion complexes with various molecules through host-guest interactions.

Today, cyclodextrins continue to offer new horizons to scientists and industrials with a wide range of possible modifications and forms for multiple classical, e.g., pharmacy, food industry, chromatography, cosmetology, and biotechnology, and emerging, e.g., biomedicine, agrochemistry, and nanomaterials, applications.

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