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The Early History of Calixarene Chemistry*

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Abstract. The history of calixarene chemistry from the mid-thirties until 1978 is described.

Key words: History of chemistry, calixarenes, Zinke, Ziegler, Hönel.

1. Introduction

Fifty years ago, in 1944, Alois Zinke and Erich Ziegler presented the constitution (Figure 1) of a cyclic tetramer, obtained in two steps from *p-tert*-butylphenol and formaldehyde and which is called today *p-tert*-butylcalix[4]arene, in *Berichte der Deutschen Chemischen Gesellschaft* [1] and in a review [2]. They had already described the synthesis of this compound (or was it the calix[8]arene?) in 1941 without, however, assigning a structure to it [3]. In 1941 they wrote: "Die erhaltenen Produkte sind offenbar ziemlich hochmolekular, denn vorläufige, mit dem Acetylderivat ausgeführte Molekulargewichtsbestimmungen ergaben einen Durchschnittswert von 1725. Es dürfte sich um Verbindungen (oder ein Gemisch von Verbindungen) handeln, die aus etwa 8 Butylphenolkernen aufgebaut sind. Ätherartige Struktur scheint nicht vorzuliegen, denn Versuche, eine Spaltung mit Bromwasserstoff zu erreichen, verliefen negativ." According to present knowledge [4, 5] it is very likely that Zinke and Ziegler indeed had the acetyl derivative of the octamer at hand in 1941. But why did they propose the calix[4]arene structure in 1944 (without giving further experimental evidence for this conclusion)? Before answering this question we should take a short look at the circumstances of the discovery, the *curricula vitae* of Zinke and Ziegler, and of a third person (whose name has been mentioned in connection with calixarene chemistry so far only in footnotes [6]): Herbert Hönel.

2. People, Time, and Circumstances

Graz, the second-largest city of Austria, is located in the south-eastern part of the country, about 50 km away from the Slovenian and Hungarian borders, respectively. Since Graz is somewhat off the beaten track, the city is not so well known to tourists as, for instance Vienna, Salzburg and Innsbruck. However, its university

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* This paper is dedicated to the commemorative issue on the 50th anniversary of calixarenes.

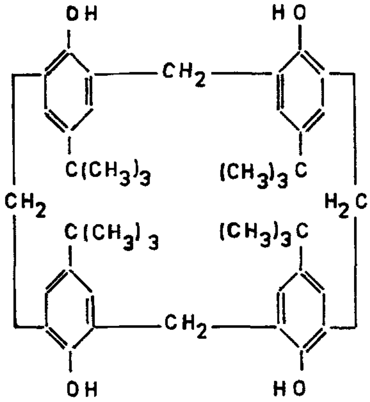


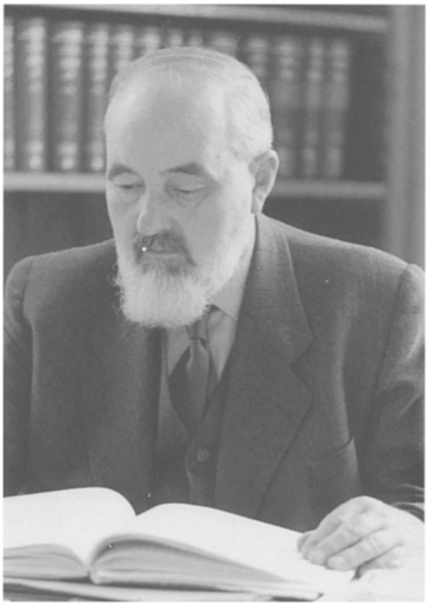
Fig. 1. Calix[4]arene as shown in Ref. [1, 2].

was founded more than 400 years ago and five Nobel prize winners have worked here. The names of Fritz Pregel (who developed the microanalysis of organic compounds), Otto Loewi (the pharmacologist who discovered acetylcholine as a neurotransmitter) and Erwin Schrödinger, the physicist, should be familiar to every chemist.

Alois Zinke was born in 1892 in the small village of Bärnbach, located 20 km west of Graz, where his father was a director of a glass factory. At the age of ten he was sent to high school ('Landesoberrealschule') in Graz, and he stayed in that city for the rest of his life. He continued his studies at the 'Technische Hochschule' of Graz, but after two years he changed to the University where he received his Ph.D. in 1915 under the tutelage of Roland Scholl. He was assistant at the chemical institute from 1914 to 1922. In 1920 he became 'Privat-Dozent' (unpaid lecturer) in organic chemistry, and in 1922 he was appointed Professor at the 'Technische Hochschule' in Graz, but only three years later he returned to the university as 'außerordentlicher Professor'. In 1941 he became full professor and director of the Institute of Organic and Pharmaceutical Chemistry of the University, a position he held until his death in 1963 [7].

Zinke's contribution to organic chemistry include research on natural resins, e.g. the isolation of siaresinol and sumaresinol acids which he showed to be triterpenes. Most of his research, however, was devoted to highly condensed aromatic ring systems (today called PAHs), particularly perylene. He became acquainted with these ring systems during his work on alizarines with R. Scholl, and interestingly, the last three papers he published in the 'sixties also dealt with 'perylene and its derivatives', namely parts 64–66 of this series.

However, for about two decades – from 1936 to 1956 – Zinke devoted a large part of his research to exploring the chemistry of phenol-formaldehyde resin formation. This excursion into a new field of research brought about – among many other most valuable results – the discovery of calix[*n*]arenes. We will come back to this point.



Alois Zinke, 1892–1963.

Erich Ziegler was born in Marburg at the river Drau in 1912. This city is located 70 km south of Graz, and was incorporated into the territory of Yugoslavia after the First World War in 1919. In 1923 the family moved to Graz. His father had decided that Erich Ziegler should become a druggist, but during his apprenticeship he was so much attracted by chemistry that in 1933 he enrolled for chemistry at the university of Graz. He joined Zinke's group just at the time when the phenol-formaldehyde project started. He obtained his Ph.D. in 1938 with a thesis on the reaction products of cresols with formaldehyde. He worked as an unpaid assistant for Zinke until he obtained a formal appointment in 1940. He was called up to the army from August 1939 to February 1940, and again from January 1942 to March 1944. The last 18 months of this period he spent in various army hospitals, since he had been seriously injured during the war in Russia. I mention these circumstances also as one explanation of the long interval between the first and second publication on cyclic phenol-formaldehyde products by Zinke and Ziegler, referred to in the introduction.

Ziegler's further academic career progressed smoothly: after his dismissal from the army, he completed his habilitation with his inaugural lecture as 'docent' (the experimental work had already been completed before 1942). He worked for some time still in the field of phenolic alcohols, and investigated especially their reactions with aromatic diazonium salts. In the early 'fifties his interest turned to heterocyclic chemistry (he published more than 200 papers in a series 'Synthesis of Heterocycles'), and made Graz a well-known center of heterocyclic chemistry. In 1963, after the death of Alois Zinke, his mentor and finally his good friend, he became full professor and director of the Institute of Organic Chemistry. Zinke and Ziegler had both planned a new building for the institute, but it was not before the spring of 1969 that it was ready for occupancy. Ten years later, Ziegler had to retire for health reasons, but until about 1990 he visited the institute regularly, worked in the laboratory and published papers in his new fields of interest: the reactivity of the C=N double bond, the chemistry of betaines, S- and N-ylids. He died on March 27, 1993 [8].

Erich Ziegler, 1912–1993.

While Zinke had never heard about the future of his cyclic phenol-formaldehyde products, Ziegler was informed about 'calixarenes' by Hermann Kämmerer from Mainz, Germany. Ziegler had given a lecture in Mainz on February 4, 1954, with the title 'Über cyclische Phenol-Formaldehyd-Kondensate' [9]. This was at a time when he had already abandoned research in this area. Nevertheless, Ziegler regularly received reprints of Kämmerer's work in this field, and they exchanged Christmas letters for the rest of Ziegler's life.

As indicated in the introduction, we must mention the name of a third person, who initiated the work on phenol-formaldehyde chemistry in Graz. Herbert Hönel [10] was born in Graz in 1890, where he obtained his Ph.D. in chemistry in 1913. After the First World War, in which he took part as a soldier, he found employment in 1919 at the 'Chemische Fabriken Dr. K. ALBERT' in Biebrich on the river Rhine, Germany, where he first came into contact with the synthesis and production of polymers. It was certainly a lucky chance (for both of them) when in 1926 Otto Reichhold [11], director of the largest Austrian varnish and coatings company, met this most talented chemist, and gave him an adequate position in his company. Hönel's first patents dealt with 'oil-reactive phenolic resins' and with 'terpene phenolic resins'. Within a short time he became a renowned pioneer in the field of plastics and coatings. From 1928 till 1939 he crossed the Atlantic several times to work for REICHHOLD in the United States as well. Hönel's success in research and development were cornerstones for the foundation of the 'BECKACITE-Kunstharzfabriken' in 1934 in Vienna and Hamburg, and factories with similar production lines in France and Great Britain. During the war he worked in Hamburg and Vienna.

After the war, he returned to the city where he was born. Alois Zinke provided him with a small laboratory in the basement of the institute of organic chemistry where he continued his studies on water-soluble resins. At the end of the war, when supplies of raw materials became short, he had already produced a coating material for protecting iron from rusting. This material, however, was only good enough in times of war. Then he became really obsessed with the idea of water-soluble resins. The reasons for this goal were clear: the high price of organic solvents, the danger in handling because of their flammability, health and environmental hazards. In 1948 he was co-founder of a small coatings company in Graz. Though in the beginning the company had to produce the material by conventional methods, Hönel gave the company the name 'VIANOVA-Kunstharz AG', indicating that 'new ways' were on the program. To make the story brief: the breakthrough came at the end of the 'fifties, and in the 'sixties all major car makers in Europe, such as Volkswagen, FIAT, Renault etc., used coatings produced under patents and licenses of VIANOVA. Because of their solubility in water the materials developed at VIANOVA could also be modified to serve in the electrolytic deposition of films on metals, a further big success. For many years now two modern research buildings of VIANOVA (which belongs to the HOECHST group today) have been located just 500 m away from the main building of the University of Graz. Hönel himself received many honors, including the Dr. h.c. rer.nat. from this university. He died in June of 1990, some months after the celebration of his 100th birthday.

Before dealing with the discovery of calixarenes, some remarks should be made on the circumstances under which these investigations took place. The time between the two World Wars was a very hard one for Austria (which means the part that remained from the Austrian Empire). This was especially true for the universities and was felt most in experimental disciplines. From 1917 to 1943 Anton Skrabal was head of the chemistry department in Graz. His main research interests were in the field of physical chemistry, especially kinetics. In 1878, when the new chemistry building was completed, it was the most modern one in Europe [12, 13]. Due to Skrabal's interests and his nature, substantial investments in equipment and modernization of the laboratories did not take place (with the exception of a small additional building for physical chemistry in 1927). Electric light was not introduced to the laboratories until 1943, when it had already become an utmost necessity because (due to shortages of rare earth materials) incandescent Welsbach mantles for gaslight illumination were no longer available during the War. In other words, working was only possible from 9 a.m. to 3 p.m. during the winter months!

For those readers who are not familiar with European history: Austria did not exist between March 1938 and May 1945. When the University of Graz became 'Reichsuniversität' in 1938 about one third of the academics (among them Loewi and Schrödinger), and one third of the students had to leave the university. Though the 'Third Reich' highly esteemed chemistry in general this brought no real and lasting improvement to the chemistry department in Graz. Quite to the contrary: the outbreak of the War robbed Zinke of his talented coworkers (Ziegler, Hanus) in the field of phenol-formaldehyde chemistry and left him with a few female graduate students. These were, in short, the conditions and circumstances under which the calixarenes were born.

3. The Discovery of Calixarenes

In 1936, Herbert Hönel supported by Otto Reichold, asked Alois Zinke, whom he had known from his student days, to act as a consultant for the BECKACITE Co., Hamburg–Vienna, in the field of phenol-formaldehyde resins, a proposal which Zinke obviously could not refuse. He started work immediately, together with his two assistants Franz Hanus and Erich Ziegler. After the war, Hanus [14] left the university and Richard Zigeuner joined Zinke's group. At that time, however, competition was strong in this field. There were already several research groups working in the area: those of H. v. Euler and E. Adler [15], K. Hultsch [16], M. Köbner [17], and N. J. L. Megson [18], to name just a few.

Right from the start Zinke planned a comprehensive study of chemical processes involved in the curing (= hardening) of phenol-formaldehyde resins. Thus, the series he published received the title 'Zur Kenntnis des Härtungsprozesses von Phenol-Formaldehyd-Harzen'. The first paper [19] appeared in 1939 [20], the last contribution [21], number XXVIII in this series, in 1958 [22]. In the industrial production of phenolic resins not only phenol itself but also alkylphenolss, and mixtures thereof, are valuable parts of the recipes, Zinke used *ortho* and/or *para* substituted alkylphenols as model compounds. Also, 2- and 4-chlorophenol and 2,4-dichlorophenol were employed to block reactive sites in order to simplify the first reaction steps. The work performed in Graz has certainly added much to our current knowledge of the constitution of phenol-formaldehyde resins as well as of the intermediates and the mechanisms leading to them (these results may be found in appropriate reviews [2, 18, 23] and monographs [16, 24–26]). The discovery of cyclic oligomers had never caused too much excitement in Graz. They fitted nicely in the general picture they were drawing, created much work (in establishing their molecular weight), but were a kind of a dead end insofar as they would not polymerize further.

Nevertheless, the story leading to the discovery is quite interesting. One of the reasons is that the same story was duplicated some 30 years later in the U.S.A., as we will see. In their first papers Zinke and his coworkers had described that the benzylalcohols formed from phenols lead to dibenzylethers (which had also been found by Euler and others), and that these ethers can decompose on heating to give the corresponding diarylmethane derivatives and one equivalent of formaldehyde is liberated (benzaldehydes and the corresponding methylphenols are other reaction products, especially if chlorinated phenols are used as starting material [3]). In their first paper of 1941 in which the preparation of an cyclic oligomer from *p-tert*-butylphenol was reported [3] they described the fact that the sodium salt of 2-hydroxy-3,5-dimethyl-benzylalcohol (*m*-xylenolalcohol) gave the corresponding diphenylmethane derivative (with loss of formaldehyde and water) within four weeks if kept at room temperature. From this observation they concluded 'that the curing process of phenolalcohols can be influenced by the presence of alkali'.

Zinke had been informed by BECKACITE-Kunstharzfabrik that during the curing process of technical resols [27] clear solutions in dry oils or other inert solvents could only be obtained if scrupulously alkali-clean material was used. The technical handling of a product where sludges are precipitating is of course unpleasant (thinking of pipes and valves), and also the customer might have problems and will complain. So the information from BECKACITE (so to speak, Hönel) was also combined with a request to have a look into this matter. For whatever reason (maybe there was a hint from Hönel?), the resol obtained from *p-tert*-butylphenol was studied first. Anyway, this phenol proved to be an excellent choice. When Erich Ziegler heated 50 g of this resol – prepared in the usual way from the phenol, aqueous formaldehyde (35%), and 3N sodium hydroxide solution – in linseed oil he obtained a brownish waxy material which yielded 20 g of crystalline glistening material after washing with ethyl acetate. The product could be recrystallized from tetrachloromethane and from benzene [3] or a chlorobenzene–ethanol mixture [1].

Briefly: apart from the two articles mentioned already in the introduction [1, 3] Zinke published three more papers concerning cyclic oligomers obtained from *p*-substituted phenols and formaldehyde in 1948 [28], 1952 [29], and his final paper in 1958 [21]. The *para* substituents (besides *tert*-butyl) were the methyl, phenyl, benzyl, cyclohexyl, *tert*-pentyl, and 1,1,3,3-tetramethylbutyl group. Cryoscopic molecular weight determinations in camphor or naphthalene with the latter compound (which showed good solubility) gave values in excellent agreement with the tetrameric structure [29]. Since none of the original specimens have been saved in Graz (though many of these compounds were prepared by students in the undergraduate courses of organic synthesis in the 'fifties on a multigram scale, as the author of this article remembers) it is very hard to say today which of these samples were pure tetramers [5]. Moreover, in none of the papers is the exact amount of alkali employed defined. Today it is well known that this is one of the most important factors for the outcome of the reaction [30–32]. Usually it was just stated that the resols [27] were precipitated with dilute hydrochloric (!) or acetic acid and washed. Only in one case [33] is it stated: "das durch schwaches Ansäuern mit verd. Essigsäure abgeschiedene und mit wenig Wasser *nicht alkalifrei gewaschene* Produkt wird durch Erhitzen auf 120° vorgehärtet und . . . " A successful repetition of Zinke's procedures outside of his laboratory was certainly not easy, as the general part of the papers, remarks and references had to be studied. Therefore, it is not surprising that just a few years after the most detailed paper of 1952 (with the molecular weight determination), John Cornforth (an Australian chemist working in Britain who obtained the Nobel Prize in 1975 for his work on enzyme-catalyzed reactions) isolated a pair of compounds in each case when repeating the preparation of two of Zinke's tetramers [34]. We shall come back to this point shortly in the section on 'The Zinke Paradigm'.

In 1981 Gutsche [31] published a paper for the preparation of *p-tert*-calix[4]-arene which he thought to be a 'foolproof' procedure. In 1986 [32] he had to admit that not only others, but also people from his own laboratories had difficulties in duplicating this foolproof procedure. He could pinpoint the frequently observed failure in the instruction given to neutralize the finely ground solid 'precursor' (in former days called resols) with aqueous HCl. The ingenious idea of Gutsche was then [32] to completely omit these washings and to add just the necessary (small) amount of NaOH in the very beginning, and so to run through the reaction in a one pot manner (removing the water after some time, adding the diphenyl ether to allow pyrolysis at 250°C). This procedure has now been published in *Organic Syntheses* [35] together with preparations of *p-tert*-butylcalix[6]arene [36], and -calix[8]arene [37].

The question (mentioned in the introduction) of why Zinke and Ziegler gave their first cyclic oligomer a tetrameric structure (Figure 1) in 1944 (though an exact molecular weight determination was not published before 1952) has not yet been answered. One reason which has been put forward by Gutsche [6, 38], namely that they saw the paper of J. Niederl [39] on calix[4]resorcinols, can be ruled out. Due to the circumstances described above, there were no American chemistry journals or *Chemical Abstracts* available in Graz during the War. Niederl's paper [39] was first quoted by Zinke in his papers of 1948 [28] and 1952 [29], and there he gave a wrong year (1936) in the references. However, before 1958 Zinke must have had a Niederl product at hand since, in his last paper [21], he described its degradation with nitric acid to styphnic acid (2,4,6-trinitroresorcinol). The reason for putting forward the tetrameric structure must have been more intuitive, and caused by the fear that his competitors would present this formula soon. I think that the two main reasons for this assignment were (a) Hans v. Euler's [40] publication in 1941 of a cyclic diether containing four phenolic nuclei, and it could be expected that Euler would soon come up with a carbocyclic tetramer, and (b) the porphins! In the 'thirties Hans Fischer had synthesized several porphins and written two books on the chemistry of pyrroles [41]. At that time it was a generally accepted rule that pyrrole and phenols (especially those with a *para* substituent where only the two *ortho* positions are available) show a similar reactivity towards electrophiles.

4. The Zinke Paradigm

Thomas Kuhn, a philosopher and historian of science wrote: "A scientific paradigm is created by an achievement that is sufficiently unprecedented to attract an enduring group of adherents away from competing modes of scientific activity and is sufficiently open ended to leave all sorts of problems for the redefined group of practitioners to resolve" [42]. In 1989 C. David Gutsche presented a lecture with the title 'Calixarenes: paradoxes and paradigms in molecular baskets' at a symposium; this lecture appeared in print in *Pure and Applied Chemistry* the following year [38]. Since this journal and Gutsche's book of 1989 *Calixarenes* [5] are readily available, the further 'early' history of calixarene chemistry will be dealt with in a nutshell.

In the mid-fifties the 'Zinke cyclic tetramer paradigm' [38] became well known to chemists working in the field of phenol-formaldehyde chemistry. In addition, Hayes and Hunter [43] presented in 1956/1958 a stepwise synthesis of methylcalix[4]arene, and – although no direct comparison with a specimen obtained via the Zinke procedure had been carried out – the identity was assumed. The Hayes and Hunter synthesis was later used and largely extended by H. Kämmerer [44]. But before this, as already mentioned before, Sir John Cornforth [34] had repeated Zinke's experiments with two *p*-substituted phenols and had obtained two pairs of compounds, high melting and lower melting species. Because X-ray experiments did not give unequivocal results Cornforth proposed that the phenolic nuclei could not rotate round the bonds joining them to the methylene groups, thus giving rise to diastereoisomers. H. Kämmerer [45] demonstrated in 1955, using temperature-dependent ^{1}H-NMR, that the cyclic tetramers were much more flexible than was assumed earlier by using space filling molecular models. (But this did not solve the question of structure for the second set of compounds obtained by Cornforth. It is known today that these products were the calix[8]arenes.)

Before the '*Early* History of Calixarene Chemistry' finally ended, the Zinke paradigm worked once more. This event is known as the 'Petrolite Chapter' [5, 38]. The PETROLITE Corporation was founded in 1916 and is located in Webster Groves, Missouri, not far from St. Louis, and thus not far from Washington University, St. Louis, C. D. Gutsche's working place. Its original products were demulsifiers for resolving crude oil emulsions. In the 'fifties, a Petrolite demulsifier was introduced onto the market which was made by reacting *p-tert*-butylphenol and formaldehyde under alkaline catalysis, then further oxyalkylating this intermediate with ethylene oxide. The intermediate was first assumed to be an open chain oligomer. Soon, however, the PETROLITE Co. encountered the same technical troubles with insoluble sludges in their product as had been the case at the BECKACITE Co. in the mid-thirties. The problem was brought to a group of chemists of the PETROLITE research laboratories. One of these chemists, J. H. Munch, around 1972 developed [46] a rather brief method of preparing large amounts of glistening crystals from a *p*-substituted phenol and paraformaldehyde in boiling xylene in the presence of some concentrated aqueous potassium hydroxide. (This method is very similar to the procedure now presented in *Organic Syntheses* [37] for the preparation of *p-tert*-butylcalix[8]arene!). Searching the literature, the PETROLITE chemists found the facts concerning the cyclic tetramers mentioned already, and concluded that their products must be the Zinke substances, although their method of preparation was quite different from the Zinke–Conforth procedure. Patents regarding this preparation of 'calix[4]arenes' were filed in 1976/77.

David Gutsche, having been a consultant to PETROLITE Corporation since 1949 [47] was informed about Munch's method in 1972 [46]. At that time, Gutsche had become interested in bioorganic chemistry and considered that Zinke's tetramers should be interesting candidates as enzyme mimics because of their basket-like shape. R. Ott and Zinke had already published the picture of a space-filling molecular model in a cone form, having the four hydroxyl groups close together, in 1954 [48]. Gutsche presented his results concerning the synthesis of five cyclic tetramers at two symposia in 1975 [49]. At these occasions he also coined the name CALIXARENES, although the name did not appear in print before 1978 [4]. It must have been an unpleasant surprise to Gutsche to see the results (exactly the same five examples) he had presented orally, published by a participant (Timothy Patrick) at one of the meetings two years later [50], obviously without the consent of the group at Washington University, as indicated by a rather short excuse [51]. Furthermore, these compounds were made commercially available by Parish Chemical Co., Provo, Utah [52]. The answer from Gutsche came one year later as a short communication to the editor of the *Journal of Organic Chemistry* [4]. The summary of this paper says: "The products obtained from the base-catalyzed condensation of formaldehyde with several *para*-substituted phenols have been shown to be mixtures of two or more components which appear to be cyclic oligomers with five or more aromatic units in the cyclic array." In this paper Gutsche used ^{1}H- and ^{13}C-NMR, osmotic molecular weight determination and mass spectrometry, as well as derivatization techniques to obtain trimethylsilyl derivatives, and TLC separation. As pointed out by Gutsche much later [38]: "One of the most powerful destroyers of paradigms is a new instrumental technique." So the Zinke paradigm found an end in 1978, and the modern times of calixarene chemistry began.

5. Conclusion

Though Gutsche's paper of 1978 [4] certainly was an incisive work in calixarene chemistry, much remained to be done to clarify the situation. In this paper, Gutsche had claimed that no calix[4]arenes were formed by the direct method. However, he had studied only the products obtained by Munch's procedure and the small modification thereof by Patrick. No comparison was made with a compound prepared according to the Zinke (or Cornforth) procedure or by the stepwise synthesis of Hayes–Hunter [43] or Kämmerer [45, 53]. This missing link was provided in a very extensive contribution in 1981 [31]. In this paper Gutsche showed that he could obtain the *tert*-butylcalix[4]arene in 20–25% yield (accompanied by smaller amounts of cyclic octamer) following the Cornforth modification of Zinke's procedure. It should be mentioned that he also repeated the multistep synthesis of Hayes–Hunter, and Kämmerer, respectively (with only minor modifications), and finally proved the identity of both products in this fine piece of work [31]. From Gutsche's investigations, including the analysis of the product mixtures obtained under different reaction conditions, it is now known that calix[8]arenes are formed by the direct method in the presence of a low concentration of alkali (0.03 equiv. with respect to the phenol), and at the relatively low temperature of boiling xylene; calix[6]arenes are obtained as the major product at the same temperature, but using nearly a tenfold amount of alkali (0.3 equiv.); and finally calix[4]arenes are obtained with low alkali concentration (0.045 equiv.) but at rather high temperature, boiling diphenyl ether (b.p. 250°) being the preferred solvent. Under these conditions *p-tert*-butyl[4]calixarene can now be prepared in 61% yield, according to *Organic Syntheses* [35] "pure enough for further use". From these pieces of evidence it is obvious that the Zinke products must have been in general the tetramers (low alkali concentration, rather high temperature), maybe contaminated with small amounts of the octamers. Therefore "to Zinke should go the true parentage" of calixarene chemistry, as noted by Gutsche [54].

* *Note added in proof:* The 'term ZINKE ZIEGLER Synthesis of Calixarenes' has recently been added to the vocabulary of Organic Name reactions [55].

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