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C. D. Gutsche
The Calixarenes

K. N. Raymond, G. Müller and
B. F. Matzanke
Complexation of Iron by Siderophores
A Review of Their Solution and
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Y. Kobayashi and I. Kumadaki
Valence-Bond Isomers of Aromatic
Compounds

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Natural Vibrational Raman Optical Activity

Structural Chemistry

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With Contributions by
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The Calixarenes

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1 Introduction

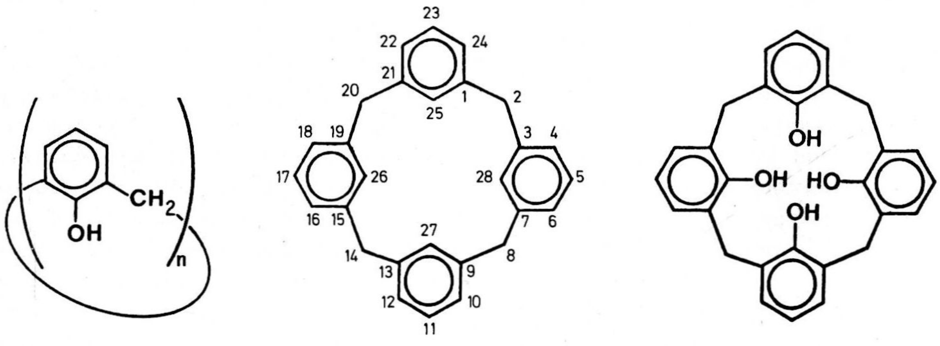
The synthesis of compounds containing cavities of molecule-sized dimensions has captured the attention of numerous chemists in recent years, and this area of organic chemistry is acquiring the status of a recognizable and expanding subdiscipline. The principal reason for the burgeoning interest in these compounds is their imputed, and in some instances demonstrated, ability to form inclusion complexes, *i.e.* to participate in what has been variously described as "host-guest" chemistry [1] or "receptor-substrate" chemistry [2]. This review deals with certain [1_n]metacyclophanes possessing basket-like shapes, particular attention being given to those members which have been named "calixarenes" [3,4].

2 Nomenclature of the Calixarenes

The compounds discussed in this review are represented by the general structure *1*. In the IUPAC system of nomenclature [5], a specific member of this group (as represented by structure *2*) is named

pentacyclo[19.3.1.$1^{3,7}$.$1^{9,13}$.$1^{15,19}$]octacosa-1(25),3,5,7(28),
9,11,13(27),15,17,19(26),21,23-dodecaene ,

and it is numbered as shown in Fig. 1. An alternative nomenclature for this type of ring structure was suggested by Cram and Steinberg [6,7] according to which *2* is named as [1.1.1.1]metacyclophane. Several research groups have reported syntheses of the tetrahydroxy derivatives of *2* (as represented by structure *3*) and have named them in various ways. Zinke and coworkers [8] called these compounds "cyclischen Mehrkernmethylene-phenolverbindungen", Hayes and Hunter [9] named them "cyclic tetranuclear novolaks", and Cornforth and coworkers [10] referred to them as "tetrahydroxycyclotetra-*m*-benzylenes. For convenience of written and verbal discussion



1 *2* *3*

Fig. 1. Poly-aryl *m*-methylene-bridged macrocyclic compounds

we have chosen to call them "calixarenes" (Greek, *calix*, chalice; arene, indicating the incorporation of aromatic rings in the macrocyclic array), specifying the size of the macrocycle by a bracketed number inserted between *calix* and *arene* and specifying the nature and position of substitution on the aromatic rings by appropriate numbers and descriptors [11)].

The structures and numbering for five types of calixarenes containing intraannular hydroxyl groups [12)] which figure prominently in the following sections of this review are shown in Fig. 2. The cyclic tetramer composed of *p-tert*-butylphenol units and methylene units, for example, is named 5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetrahydroxycalix[4]arene; in abbreviated fashion it will be referred to as *p-tert*-butylcalix[4]arene.

3 Synthesis and Characterization of the Calixarenes

3.1 Arene-Aldehyde Condensations

3.1.1 Base-Catalyzed Condensation of *p*-Substituted Phenols and Formaldehyde

In 1872 Baeyer heated aqueous formaldehyde with phenol and observed a reaction which yielded a hard, resinous, noncrystalline product [13)]. The chemical techniques at the time were not sufficiently advanced to allow characterization of such materials, however, and the structure remained unknown. Three decades later Baekeland devised a process for using this phenol-formaldehyde reaction to make a tough, resiliant resin (called a phenoplast) which he marketed under the name "Bakelite" [14)] with tremendous commercial success. As a result, considerable industrial and academic attention was focused on phenol-formaldehyde processes, and a significant literature arose dealing with phenoplasts. Among these investigations were ones carried out by Zinke and coworkers in connection with the "curing" phase of the process [8,15–19)]. In the investigation of this phenomenon they treated various *p*-substituted phenols with aqueous formaldehyde and sodium hydroxide, first at 50–55 °C, then at 110–120 °C for 2 hours and, finally, in a suspension of linseed oil at 200 °C for several hours. From *p*-methyl, *p-tert*-butyl, *p-tert*-amyl, *p*-(1,1,3,3-tetramethylbutyl), *p*-cyclohexyl, *p*-benzyl, and *p*-phenylphenol very high-melting, highly insoluble materials were obtained, all of which were postulated to be cyclic tetramers, *i.e.* calix[4]arenes of structure *4* in Fig. 2. The tacit assumption that a single product is formed in every instance was later shown to be incorrect by Cornforth and coworkers [10)] who isolated higher- and lower-melting compounds from the condensations of formaldehyde with *p-tert*-butylphenol and *p*-(1,1,3,3-tetramethylbutyl)phenol (often referred to in the calixarene literature as *p*-octylphenol). Cornforth's conclusion that the materials were conformational isomers of the calix[4]arenes, however, was subsequently invalidated by Kämmerer and coworkers [20,21)] and by Munch [22)] whose temperature dependent ^{1}H NMR studies showed that rapid conformational interconversion occurs at room temperature. Finally, the recent work of Gutsche and coworkers [23)] has revealed that mixtures comprising cyclic oligomers of *various ring size* are generally obtained in these condensation reactions. In the most thoroughly studied example [3,23–28)] it has been shown that the condensation of *p-tert*-butyl-

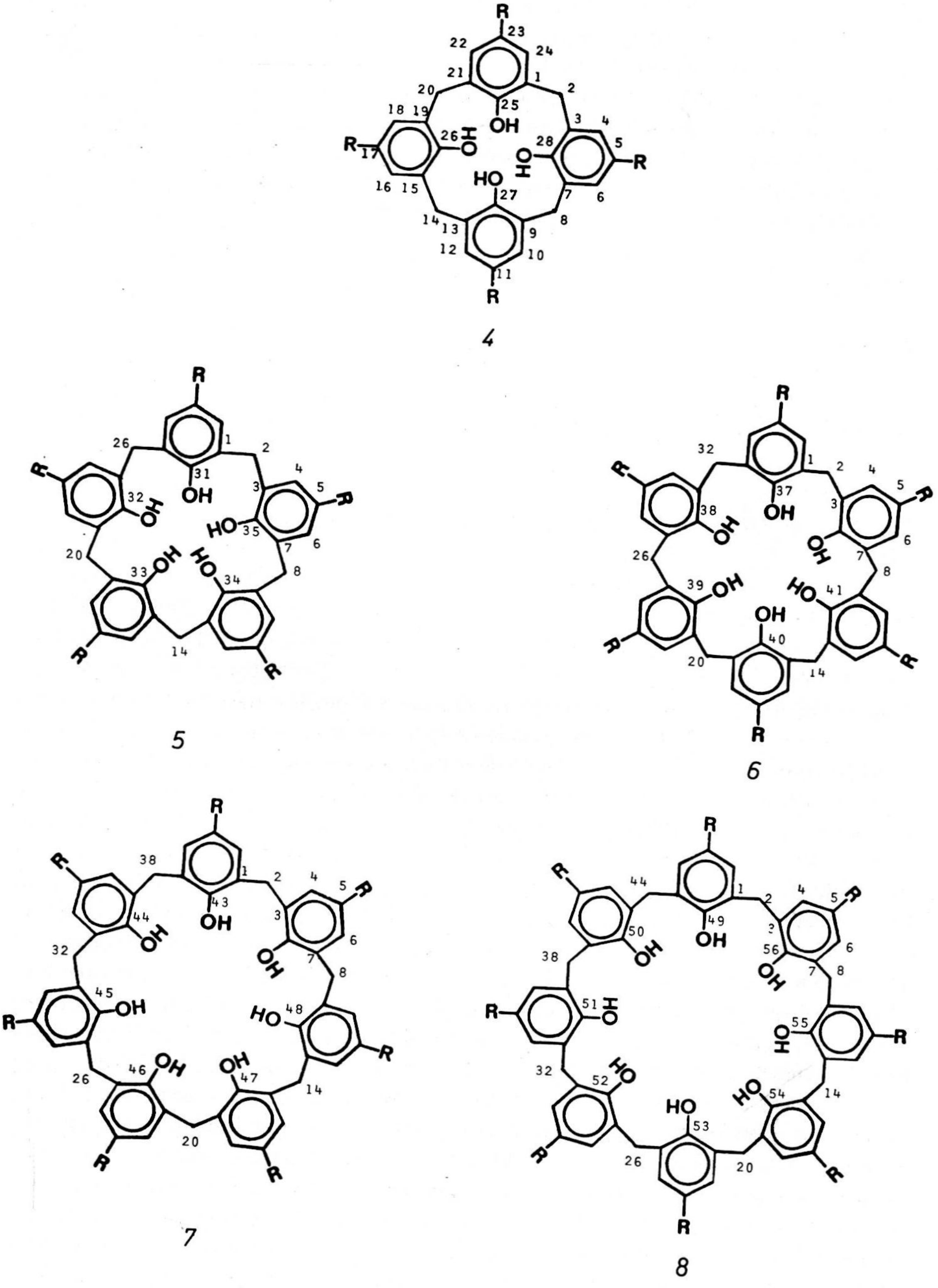
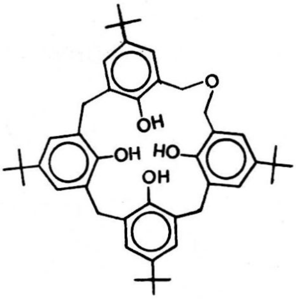


Fig. 2. Structures and numbering of intraannularly-hydroxylated calix[n]arenes

phenol and formaldehyde yields cyclic tetramer (*4*, R = *tert*-Butyl), cyclic hexamer (*6*, R = *tert*-Butyl), and cyclic octamer (*8*, R = *tert*-Butyl) as the major products as well as small amounts of cyclic pentamer [26] (*5*, R = *tert*-Butyl) and cyclic heptamer [27] (*7*, R = *tert*-Butyl) under some conditions. In addition, *p-tert*-butyldihomooxacalix[4]arene (*9*) is formed in ponderable quantity in certain cases [23,24,28]. The structures of the cyclic oligomers in the *p-tert*-butyl series have been well established. All are in complete agreement with chemical, spectral, and analytical data; and definitive structure proofs via x-ray crystallography have been provided for compounds *4* (R = *tert*-butyl) [29], *4* (R = 1,1,3,3-tetramethylbutyl) [30], *5* (R = *tert*-Butyl) [31], *5* (R=H) [32], *6* (R = *tert*-Butyl) [33], and *8* (R = *tert*-Butyl) [34].



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Although the structures of the cyclic oligomers from the base-catalyzed condensation of *p-tert*-butylphenol and formaldehyde are now well understood, there is considerable confusion in the older literature concerning these compounds. As early as 1912 Raschig postulated the existence of cyclic compounds in Bakelite products [35], but Baekeland pointed out [36] that "we must not forget that one hypothesis is about as easy to propose as another as long as we are unable to use any of the methods for determining molecular size and molecular constitution". Not until three decades later did evidence begin to accumulate in support of cyclic oligomers as condensation products of phenols and formaldehyde. In 1941 Zinke and Ziegler [15] described a product which they obtained in good yield from a base-catalyzed condensation of *p-tert*-butylphenol and formaldehyde. It was stated to have a melting point above 340 °C and to form an acetate that had a molecular weight of 1725. No structure was suggested for this product, but in retrospect it seems quite certain that what these workers had isolated was *p-tert*-butylcalix[8]arene (*8*, R = *tert*-Butyl). Three years later Zinke and Ziegler again described a *p-tert*-butylphenol/formaldehyde condensation product [16], prepared under somewhat different and more carefully detailed conditions than those previously described, to which they assigned a cyclic *tetrameric* structure (*4*, R = *tert*-Butyl). However, they stated that molecular weight data could not be obtained, because neither the parent compound nor its acetate were sufficiently soluble. Thus, the cyclic tetrameric structure seems to have been based more on intuition than on solid data, cyclic tetrameric structures being "in the air" at the time. For example, Niederl and McCoy [37] claimed to have obtained a *p*-methylcalix[4]arene from an acid-catalyzed condensation of *p*-cresol with 2,6-*bis*-(hydroxymethyl)-4-methylphenol, repeating the work of Koebner [38] who had assigned a linear trimeric structure to this product. But, Koebner's contention was ultimately sustained [39,40], and it is quite certain that a cyclic tetramer is *not* formed under these conditions. Zinke and coworkers continued the investigation of the products of the base-catalyzed reactions of *p*-substituted phenols and formaldehyde and in 1952 published data on the products from the seven phenols cited above. They reported a molecular weight of 873 for the acetate of the product from *p*-octylphenol and formaldehyde, in agreement with a cyclic tetrameric structure. Thus, it was assumed that all of the other *p*-substituted phenol/formaldehyde products were also cyclic tetramers.

The first suggestion that the Zinke products were not pure entities came from Cornforth's experiments [10] in which he isolated mixtures from the condensations of *p-tert*-butylphenol and *p*-octylphenol with formaldehyde. The high-melting compounds were designated as HBC and HOC, respectively, and the low-melting compounds as LBC and LOC. Although the molecular weights of all of these compounds and/or their acetates seemed to be in agreement with a cyclic tetrameric structure and although preliminary x-ray crystallographic data seemed also to support this contention, more recent work [20–23,29,30,34] indicates that only the low-melting compounds (LBC and LOC) possess this structure. The high melting compounds (HBC and HOC) are now known to be the cyclic octamers [23,41]. Other workers, including the author of this review, also succumbed to the intuitively appealing and logical assumption that the products of the base-catalyzed condensation of *p*-substituted phenols and formaldehyde must possess cyclic tetrameric structures. Using a condensation procedure devised by chemists of the Petrolite Corporation, Gutsche and coworkers [42] reported the preparation of "cyclic tetramers" from *p*-methyl-, *p-tert*-butyl-, *p*-phenyl-, *p*-methoxy-, and *p*-carbomethoxyphenol with formaldehyde. Using a slightly modified version of the Petrolite procedure, Patrick and Egan [43] condensed the same five phenols and also imputed cyclic tetrameric structures to all of the products [44]. Subsequent experiments by Gutsche et al. [23,45,46], however, have shown that in none of these condensations is the cyclic tetramer a major product and that in most instances it is present in such low amounts as to be nonisolable. The Petrolite procedure [47], devised to simulate the factory production of phenol/formaldehyde resins for the manufacture of surfactant compounds, consists of refluxing a *p*-substituted phenol, paraformaldehyde, and a trace of 50% sodium hydroxide in xylene for several hours (the Patrick-Egan modification substitutes potassium *tert*-butoxide for sodium hydroxide and tetralin for xylene). The cooled reaction mixture deposits copious amounts of an insoluble product which, in the case of the *p-tert*-butylphenol reaction, is now known to be almost entirely cyclic octamer. Thus, from *p-tert*-butylphenol crystalline *p-tert*-butylcalix[8]arene (*8*, R = *tert*-Butyl) can be obtained in yields of 60–70%, making it a readily available cyclic oligomer.

In the process of unravelling the intricacies of the condensation of *p-tert*-butylphenol and formaldehyde [23], it was discovered that if a stoichiometric amount of base is used in the condensation instead of the catalytic amount employed in the original Petrolite procedure the major product is the cyclic hexamer, *p-tert*-butylcalix[6]arene (*6*, R = *tert*-Butyl). Yields as high as 70–75% of pure, crystalline material can be obtained, thus making this another abundantly available cyclic oligomer. Ironically, the cyclic tetramer is the even-numbered cyclic oligomer produced in lowest yield. Employing the Zinke procedure as modified by Cornforth by the substitution of Dowtherm (a eutectic of biphenyl and diphenyl ether) for linseed oil in the final step, one can obtain *p-tert*-butylcalix[4]arene in capriciously varying yields ranging from almost nothing to as high as 45%. Considerable effort has been expended in an attempt to understand the details of this reaction, but definitive results have yet to be obtained. One of the critical steps in the Zinke-Cornforth procedure is the last one in which the solid resinous material is powdered and heated (i.e. in linseed oil or Dowtherm). With regard to this step Zinke states [19] that "we believe we have isolated such cyclized compounds by heating resoles which had been condensed as far as the ether stage and which had not been washed free from alkali". Experiments in our laboratories have shown that acid washing the finely powdered resin fails to remove all of the base (sodium content of acid-washed resin is 1.3%). Only by dissolving the resin in an organic solvent, washing the solvent with acid followed by water, and evaporating the solvent can a base-free resin be obtained. The base-free material fails to yield cyclic oligomers when heated in Dowtherm, but upon the addition of a small amount of base (0.15 equivalent, based on the starting phenol, may be the optimum quantity [48]) cyclic tetramer is formed in 25–35% yield [48,49].

The odd-numbered calixarenes are more difficult to obtain in quantity than the even-numbered calixarenes. Employing the Patrick and Egan modification of the Petrolite procedure and changing the heating sequence (55 °C for 6 hours followed by 150 °C for 6 hours) Ninagawa and Matsuda [26] obtained a mixture from which they isolated 23% cyclic tetramer, 5% cyclic pentamer, and 11% cyclic octamer. Employing the Petrolite procedure but with dioxane as the solvent and a 30 hour heating period, Nakamoto and Ishida [27] obtained a mixture containing cyclic hexamer, heptamer, and octamer from which they isolated 6% of the heptamer.

Little is known about the overall mechanism of cyclic oligomer formation. although the mechanism of the initial stages of the sequence seems fairly clear. The first chemical event is the reaction of formaldehyde (formed in the Petrolite procedures by depolymerization of paraformaldehyde) with phenol to form 2-hydroxymethyl- and 2,6-*bis*(hydroxymethyl)phenols in a base-catalyzed process, as shown in Fig. 3. Such compounds were characterized many years ago [50], obtained from the action of aqueous formaldehyde on phenol in basic solution at room temperature. Subsequent condensation between the hydroxymethylphenols and the starting phenol occurs to form linear dimers, trimers, tetramers, etc. via a pathway that might involve *o*-quinonemethide intermediates which react with phenolate ions in a Michael-like reaction, as portrayed in Fig. 4. The condensation of hydroxymethyl-

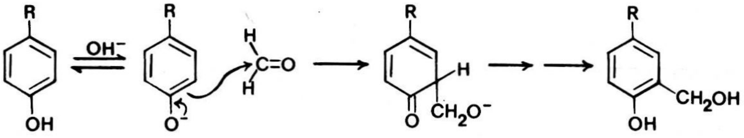

Fig. 3. Base-catalyzed hydroxymethylation of phenols

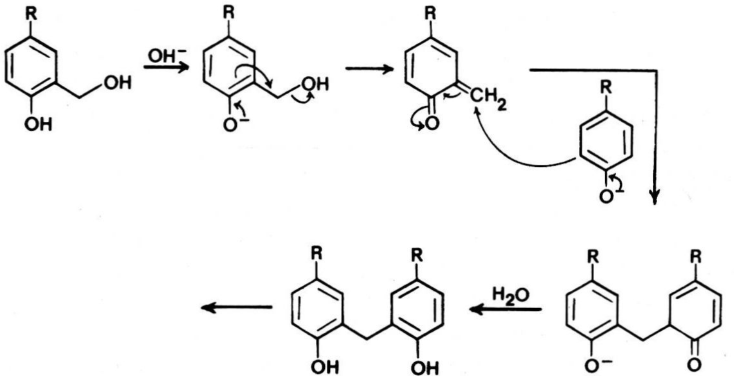

Fig. 4. Base-catalyzed formation of linear oligomers from phenols and formaldehyde

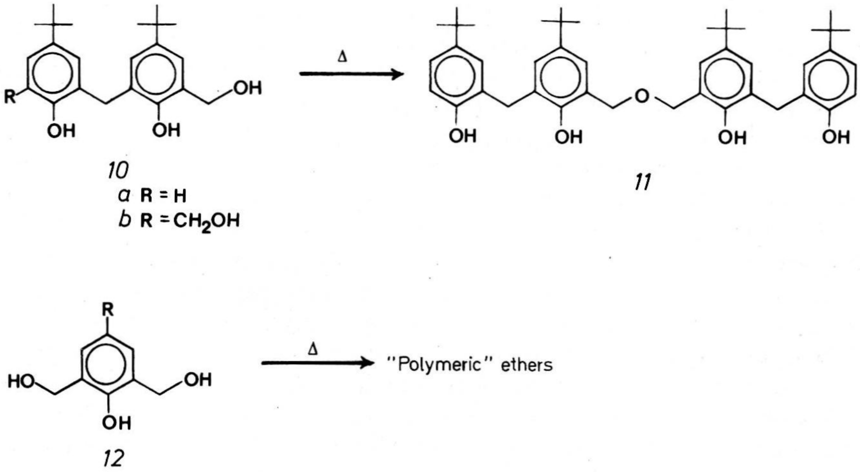

Fig. 5. Formation of dibenzyl ethers of 2-hydroxymethylphenols

phenols to form oligomers also has been shown to occur under relatively mild conditions. The possibility of quinonemethide intermediates was suggested as far back as 1912 [51] and has been promoted by Hutzsch [52], v. Euler [53], and others. However, because the formation of *o*-quinonemethides from compounds such as *o*-(methoxymethyl)phenol requires quite high temperatures (500–600 °C) [54] doubt has been cast on the validity of this premise [55]. On the other hand, it is known that oxy-Cope rearrangements occur far more readily with anions than with the corresponding neutral compounds [56], so conversion of 2-hydroxymethylphenolates to *o*-quinonemethides may, in fact, occur under the basic conditions prevailing in the reactions under discussion. Intermolecular dehydration of 2-hydroxymethylphenols to form dibenzyl ethers also occurs under the conditions of the Zinke-Cornforth and Petrolite condensation reactions, as illustrated in Fig. 5. For example, *10a* yields the ether *11* [57], and *12* ($R = CH_3$ and R = *tert*-Butyl) yields polymeric ethers [58, 59]