3782 J. Am. Chem. Soc. **1981**, *103*, 3782-3792

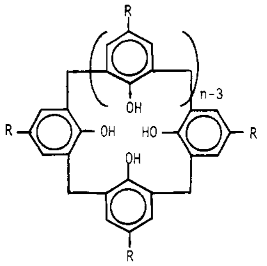
Calixarenes. 4. The Synthesis, Characterization, and Properties of the Calixarenes from *p-tert*-Butylphenol

C. David Gutsche,* Balram Dhawan, Kwang Hyun No, and Ramamurthi Muthukrishnan

Contribution from the Department of Chemistry, Washington University, St. Louis, Missouri 63130. *Received December 15, 1980*

Abstract: The condensation of *p-tert*-butylphenol with formaldehyde to form cyclic oligomers has been investigated as part of a program concerned with the synthesis of enzyme model catalysts. The product of this condensation has been shown to comprise four identifiable materials which, because of their shape, have been named *calixarenes* (Greek *calix*, chalice; *arene*, indicating the incorporation of aromatic rings). The distribution of these materials in the product depends on the conditions of the condensation. From a one-step process involving *p-tert*-butylphenol, paraformaldehyde, and a trace of base in refluxing xylene a cyclic octamer, i.e., *p-tert*-butylcalix[8]arene (**2**), can be isolated in yields as high as 64%. With a larger amount of base a cyclic hexamer, i.e., *p-tert*-butylcalix[6]arene (**3**), becomes the major product, isolable in 74% yield when rubidium hydroxide is used. From a three-step process involving *p-tert*-butylphenol, aqueous formaldehyde, and base followed, at a later stage, by strenuous heating, a cyclic tetramer, i.e., *p-tert*-butylcalix[4]arene (**4**), can be isolated in 20–25% yield. From the mixture produced in the one-step process it is also possible to isolate, in varying amounts, a *p-tert*-butylbishomooxacalix[4]arene (**14**). The structures of these materials have been established by elemental analyses, osmometric and mass spectral molecular weight determinations, and ^{1}H NMR and ^{13}C NMR measurements. In addition, the *p-tert*-butylcalix[4]arene has been synthesized by a stepwise procedure involving the preparation of a hydroxymethylated linear tetramer which undergoes acid-catalyzed converstion to the cyclic compound. The influence of reaction conditions, including concentration, reactant ratios, solvents, bases, and heating rates, on the composition of the product has been investigated. The mechanism of formation, the ^{1}H NMR spectral characteristics, and the complex-forming ability of the calixarenes are briefly discussed.

Attempts to construct in vitro systems that mimic the in vivo catalytic activity of enzymes have led chemists to give increasing attention to compounds that contain cavities of sufficient diameter and depth to form host–guest complexes, such complexes constituting the first intermediate in enzyme-model processes. However, there are relatively few compounds presently known and available that are nonpeptide in composition and that possess the molecular architecture appropriate fro the inclusion of organic compounds within a cavity. Certainly, the best known of this limited group are the cycloamyloses (cyclodextrins). The cyclohexa- and cycloheptaamyloses, in particular, have been well studied and have been shown to form complexes with a wide variety of compounds and to operate in a catalytic capacity in certain instances.[1] Far less well-known is a class of [1_n]metacyclophanes comprising cyclic arrays of phenolic residues attached by methylene groups at the positions ortho to the hydroxyl groups (**1**) that have an architecture roughly comparable to that of the cycloamyloses. The cyclic tetramers of this group (**1**, $n = 4$) have been named in a variety of ways. Zinke[2] called them "cyclischen Mehrkernmethylenephenolverbindungen", Hayes and Hunter[3] named them "cyclic tetranuclear novolaks". Cornforth and coworkers[4] referred to them as "tetrahydroxycyclotetra-*m*-benzylenes", and Chemical Abstracts has systematically named them as 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-25,26,27,28-tetrols (Ring Index No. 6485). For convenience of written and verbal discussion, however, we have chosen to call them *calixarenes* (Greek *calix*, chalice; *arene*, indicating the incorporation of aromatic rings), 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 prefixes. Thus, a cyclic tetramer derived from *p-tert*-butylphenolic and methylene units (e.g., **1**, $n = 4$) will most simply by designated as a *p-tert*-butylcalix[4]arene. Adopting the numbering scheme recommended by Chemical Abstracts;[5] however, this same compound is more systematically named as 5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetrahydroxycalix[4]arene.



1

The existence of the calixarenes was brought to our attention over 15 years ago by colleagues at the Petrolite Corporation who, in studying the composition of the bothersome precipitates that sometimes interfere with their plant production of resins from para-substituted phenols and paraformaldehyde, recognized a similarity between these precipitates and some compounds reported by Zinke.[6] A laboratory simulation of the Petrolite process, developed by Dr. John Munch,[7] involves refluxing a mixture of a para-substituted phenol, paraformaldehyde, and a very small amount of concentrated aqueous base in a hydrocarbon solvent such as xylene for several hours. This "one-step" process yielded high-melting, insoluble compounds possessing properties resembling those reported by Zinke[2,8,9] who used a more elaborate process that involved treating para-substituted phenols with aqueous formaldehyde and sodium hydroxide first at 50–55 °C for 45 h, then at 110–120 °C for 2 h, acidifying at this stage, and, finally, suspending the resinous material in linseed oil and heating at 220 °C for several hours. The material obtained by Zinke from *p-tert*-butylphenol, for example, was described as platelets decomposing above 300 °C and having such limited solubility in

---

(1) Bender, M. L.; Komiyama, M. In "Bioorganic Chemistry"; van Tamelen, E. E., Ed.; Academic Press: New York, 1977; Vol. 1, p 35; Griffiths, D. W.; Bender, M. L. In "Advances in Catalysis"; Eley, D. D.; Pines, H.; Weisz, P. B., Eds.; Academic Press: New York, 1973; Vol. 23, p 209.

(2) Zinke, A.; Kretz, R.; Leggewie, E.; Hössinger, K. *Monatsh. Chem.* **1952**, *83*, 1213.

(3) Hayes, B. T.; Hunter, R. F. *Chem. Ind.* **1956**, 193; *J. Applied Chem.* **1958**, *8*, 743.

(4) Cornforth, J. W.; D'Arcy Hart, P.; Nicholls, G. A.; Rees, R. J. W.; Stock, J. A. *Br. J. Pharmacol.* **1955**, *10*, 73

(5) We are indebted to Dr. Kurt L. Loening of Chemical Abstracts Services for his guidance in questions concerning the nomenclature of these compounds.

(6) Zinke, A.; Ziegler, E. *Ber. Dtsch. Chem. Ges.* **1944**, *77B*, 264.

(7) We are indebted to Dr. John Munch of the Petrolite Corporation, St. Louis, MO, for making this information available to us and for his continuing and helpful interest in the problem.

(8) Zinke, A.; Zigeuner, G.; Hössinger, K.; Hoffmann, G. *Monatsh. Chem.* **1948**, *79*, 438.

(9) Zinke, A.; Ott, R.; Garrana, F. H. *Monatsh. Chem.* **1958**, *89*, 135.

0002-7863/81/1503-3782$01.25/0

organic solvents that a molecular-weight determination was not possible. The corresponding product from *p*-octylphenol, however, yielded an acetate that was sufficiently soluble for a molecular weight determination, and the value obtained agreed with that calculated for a cyclic tetramer. From this, tetrameric structures were inferred for all of the compounds obtained by Zinke from para-substituted phenols and formaldehyde, including those from *p-tert*-butylphenol, *p-tert*-amylphenol, *p*-octylphenol, *p*-cyclohexylphenol, *p*-benzylphenol, and *p*-phenylphenol. The absence of stated yields for the materials for which elemental analyses, melting points, and, in one case, a molecular weight were reported led to the tacit assumption that the *only* products formed are the cyclic tetramers. That more than one material can be isolated in some instances, however, was discovered by Cornforth and co-workers[4] who separated the products from the reactions of formaldehyde with *p-tert*-butylphenol and with *p*-octylphenol into higher-melting and lower-melting compounds in both cases. On the basis of the intuitively appealing and logical idea that *only* cyclic tetramers are likely products,[10] Cornforth et al. postulated that the lower- and higher-melting compounds are conformational isomers. The concept of conformational isomers for the cyclic tetramers, which had been adumbrated by Megson[11] and by Ott and Zinke,[12] was made explicit by Cornforth who pointed out that four discrete forms can exist (which we shall refer to as the "cone", "partial cone", "1,2-alternate", and "1,3-alternate" conformations). Molecular-weight determinations of the lower-melting products and of the acetates of both the lower-and higher-melting products appeared to be in agreement with a cyclic tetrameric structure, and X-ray crystallographic measurements were interpreted as being compatible with this premise. Temperature-dependent ^{1}H NMR studies,[13,14] however, have shown the premise that both products are cyclic tetramers to be untenable, the rate of cone–cone inversion (or, minimally, cone $\rightleftarrows$ 1,2-alternate or cone $\rightleftarrows$ 1,3-alternate transformations) being on the order of 100 s^{-1}. Thus, the first hint emerged that the Zinke products might contain something in addition to cyclic tetramers, and it is with this possibility that the present paper deals.

Although our attention had been drawn to the calixarenes in the middle 1960's, these compounds did not engage our interest as potential enzyme models until a decade later when the present work commenced. Starting with the same assumptions as our predecessors, we considered the products from the para-substituted phenol-formaldehyde reactions to be pure cyclic tetramers, and this seemed to be substantiated by the elemental analyses and ^{1}H NMR, ^{13}C NMR, and mass spectra, and even by some of the osmometric molecular weight determinations. As work progressed, however, it became increasingly apparent that we were not dealing with single entities but with mixtures,[15] and we also came to realize that small differences in the conditions of the phenol–formaldehyde condensation reaction seemed to have a significant infludence on the nature of the product, as judged by its melting range. As a consequence the optimistic results reported in 1975[16] gave way to a more pessimistic perception of the reaction. Not, though, until yet another pair of researchers had succumbed to the notion that pure cyclic tetramers are formed. In 1977 Patrick and Egan[17] described the preparation of the five calixarenes that we had previously reported.[16] When we repeated these preparations, using the Munch conditions and the Patrick–Egan conditions (i.e., potassium *tert*-butoxide in place of KOH and tetralin in place of xylene), we discovered considerable variation between the products, as shown in Table I. Futher examination of the IR spectra of the products revealed small but persistent differences (e.g., well-resolved bands at 800 and 780 cm^{-1} in some preparations but only a shoulder at 800 cm^{-1} along with a well-resolved band at 780 cm^{-1} in others), and silylation followed by thin-layer chromatography indicated the presence of more than one compound in every instance. That the trimethylsilyl derivatives were not simply conformational isomers[18] was demonstrated by removing the trimethylsilyl groups by hydrolysis and obtaining two or more compounds. With this revelation it was decided to carry out a more careful investigation of the calixarene-forming reaction. *p-tert*-Butylphenol was chosed for this study because it appeared to provide materials more amenable to separation and purification than those from the other phenols. The remainder of this account, therefore, deals primarily with the reaction of *p-tert*-butylphenol and formaldehyde under various conditions.

Table I. Comparison of the Crude Products from Para-Substituted Phenols and Formaldehyde via the KOH/Xylene and Potassium *tert*-Butoxide/Tetralin Methods

	KOH/xylene method		potassium *tert*-butoxide/ tetralin method			
	present results		lit. results[17]		present results	
R	%	mp, °C	%	mp, °C	%	mp, °C
p-methyl	44	318–326	54	370–375	61	364–368
p-tert-butyl	77	361–372	54	342–344	36	396–398
p-phenyl	68	385–390	81	340–350	53	385–389
p-methoxy	58	330–350	92	380–385	85	340–344
p-carbomethoxy	72	370–380	32	380–390	77	370–380

Isolation and Identification of the Products Obtained by the One-Step Method. The "standard" one-step procedure (Munch method) consists of heating for 4 h a mixture containing *p-tert*-butylphenol, paraformaldehyde, and potassium hydroxide in the approximate ratio of 45:75:1 in a xylene solution that is approximately 1.3 M in phenol, using a Dean and Stark trap to remove the water that is formed. In a typical reaction, the xylene-insoluble product is a colorless solid, mp 360–370 °C, obtained in ca. 75% yield (see Table I). Recrystallization from chloroform affords glistening needles in 40–50% yield, melting sharply anywhere from 400–401 °C to 411–412 °C, depending on the particular sample. (It is possible that the melting point is sensitive to trace amounts of metal ions). The osmometric molecular weight that is observed for this mateiral is 1300, which is very close to the value of 1296 calculated for a cyclic octamer. However, we originally interpreted this as arising from an association dimer, because the mass spectrum shows a moderately strong signal at m/e 648, which is the molecular weight calculated for the cyclic tetramer. But, small signals at m/e values higher than this consistently appeared in the mass spectrum and suggested that the 648 signal might not arise from the monocation of the

---

(10) Space-filling molecular models indicate that a cyclic trimer is a considerably strained molecule, and the formation of higher cyclic oligomers such as pentamers, hexamers, etc., would appear to be less likely on entropic grounds.

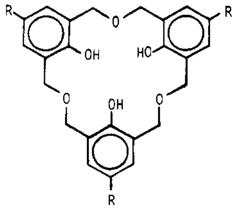
(11) Megson, N. J. L. *Oesterr. Chem. Z.* **1953**, *54*, 317.

(12) Ott, R.; Zinke, A. *Oesterr, Chem. Z.* **1954**, *55*, 156.

(13) Happel, G.; Mathiasch, B.; Kämmerer, H. *Makromol. Chem.* **1975**, *176*, 3317.

(14) Munch, J. H. *Makromol. Chem.* **1977**, *178*, 69.

(15) Hultzsch K. [*Coat. Plast. Prepr. Pap. Meet.* (*Am. Chem. Soc. Div. Org. Coat. Plast. Chem.* **1966**, *26*, 121] states that the products from the para-substituted phenol–formaldehyde reactions are mixtures of condensates of different ring sizes which are separated only with difficulty." The nature



of this mixture was not described, however, except to indicate that the smallest unit which could be isolated was the trinuclear compound in which the bridges are CH_2OCH_2.

(16) Gutsche, C. D.; Kung. T. C.; Hsu, M-L. Abstracts of the 11th Midwest Regional Meeting of the American Chemical Society, Carbondale, IL, 1975, *no.* 517.

(17) Patrick, T. B.; Egan, P. A. *J. Org. Chem.* **1977**, *42*, 382: *Ibid.* **1978**, *43*, 4280.

(18) Although the calix[4]arene has been shown to be conformationally mobile,[13,14] replacement of the hydrogen of the hydroxyl groups with larger moieties such as trimethylsilyl or acetyl curtails this mobility and makes possible the existence of stable conformational isomers.

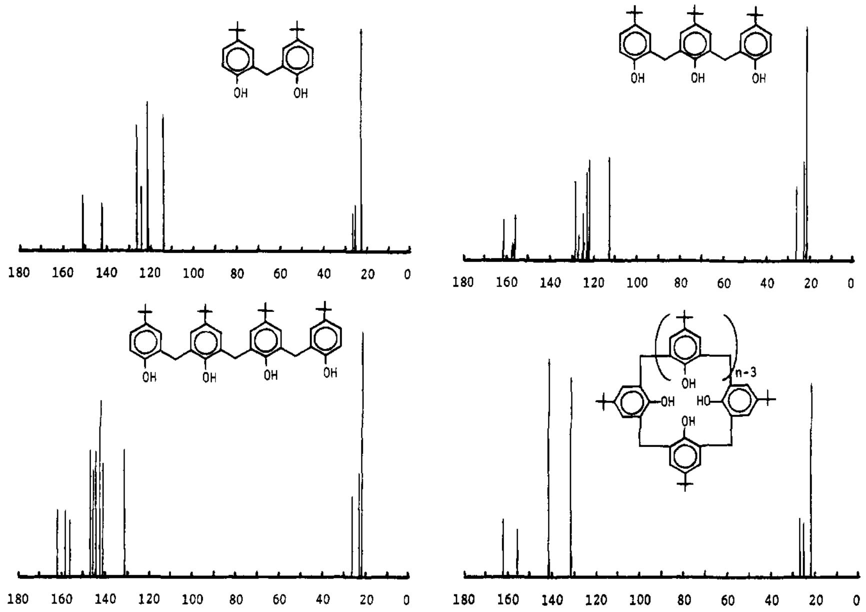
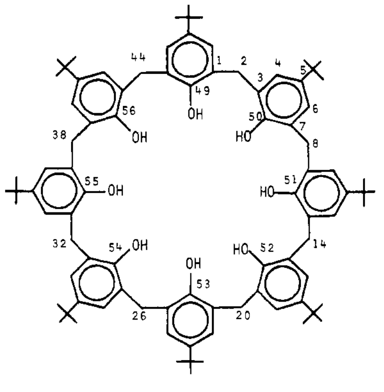


Figure 1. ^{13}C NMR spectra of linear oligomers and the 412 °C material from the condensation of *p-tert*-butylphenol and formaldehyde.

parent molecule. This was confirmed when a completely trimethylsilylated derivative was prepared which showed a very strong signal at m/e 1872 (corresponding to a cyclic octamer) and a moderately strong signal at m/e 936 (corresponding either to a tetramer resulting from cracking of the octamer or to the dication of the octamer). Both the ^1H NMR and the ^{13}C NMR spectra of the 412 °C compound are compatible with a cyclic oligomeric structure. The ^{13}C NMR spectrum, for example, shows only four resonances for aromatic carbons, whereas considerably more complex spectra are observed for acyclic oligomers[19] (where the number of nonequivalent aromatic carbons is greater than four), as illustrated in Figure 1. Still another hallmark of the cyclic oligomer is the unusually high melting point; as Zinke[2] and Kämmerer and co-workers[20] have demonstrated, the cyclic compounds generally melt above 300 °C and their acyclic counterparts below 250 °C.

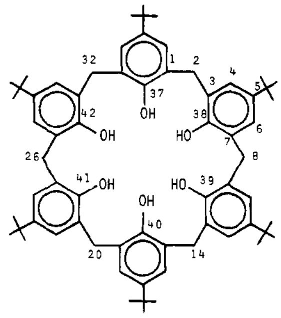
All of the data cited for the 412 °C compound are compatible with a cyclic octameric structure, viz., *tert*-butylcalix[8]arene (**2**).



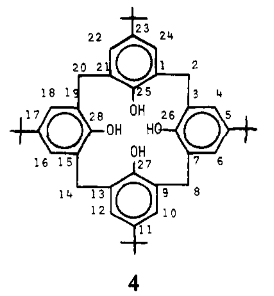
2

The remarkable similarity of the ^1H NMR spectrum of this material and that of authentic cyclic tetramer (vide infra), however, suggested the possibility that the cyclic octamer might actually consist of a pair of cyclic tetramers covalently bonded to each other in some fashion. The most obvious mode of bonding would be via a methylene group attached to the meta position of the aromatic rings or to the hydroxyl groups (i.e., $ArCH_2Ar$, $ArCH_2OAr$, or $ArOCH_2OAr$ linkages). However, a careful inspection of the ^1H NMR spectrum failed to reveal any evidence for an "extra" methylene group, and when the cyclic tetramer was treated with paraformaldehyde and base in boiling xylene for 4 h, most of the product consisted of recovered starting material, and no cyclic octamer was detected. Thus, the bulk of the evidence strongly supports structure **2**.[21] Additional, though somewhat indirect, evidence for the cyclic octameric structure is provided by the reaction of the 412 °C compound with a limiting amount of 2,4-dinitorchlorobenzene, which yields a compound whose properties are commensurate with a structure in which the ratio of calixarene to 2,4-dinitrophenyl moiety is 8:1.[22]

Concentration of the filtrate from which the *tert*-butylcalix[8]arene was crystallized yielded a second material melting at 380–381 °C. Elemental analysis and ^1H NMR and ^{13}C NMR spectra are compatible with a cyclic structure, and mass spectral measurements and osmometric molecular weight determinations on the compound as well as its trimethylsilyl derivative provide convincing support for a cyclic hexamer (**3**). Osmometric measurements reported earlier[23] on the trimethylsilyl derivative gave values closer to those of a pentamer, but more recent measurements using a better osmometer show that both the trimethylsilyl and acetyl derivatives give values commensurate with a hexamer.



3



4

As reported earlier,[24] the presence of two additional compounds in the product from the "standard" one-step method can be de-

---

[19] We are indebted to Dr. Jack Ludwig. Petrolite Corporation, St. Louis, MO, for the spectra of the acyclic oligomers.

[20] Kämmerer, H.; Happel, G.; Caesar, F. *Makromol. Chem.* **1972**, *162*, 179.

[21] A single-crystal X-ray crystallographic analysis of the 412 °C material has been carried out by Andreetti and co-workers (private communication from Professor G. D. Andreetti) which confirms the cyclic octameric structure.

[22] Muthukrishnan, R.; Gutsche, C. D. *J. Org. Chem.* **1979**, *44*, 3962.

[23] Gutsche, C. D.; Muthukrishnan, R. *J. Org. Chem.* **1978**, *43*, 4905.

[24] Gutsche, C. D.; Muthukrishnan, R.; No, K. H. *Tetrahedron Lett.* **1979**, 2213.

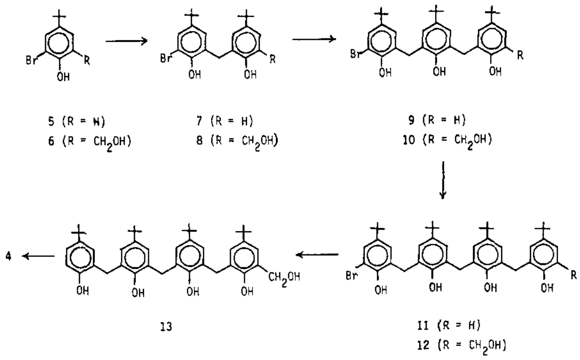
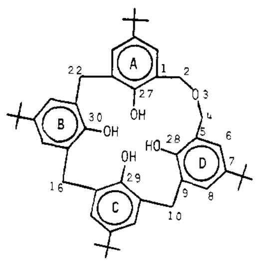


Figure 2. Stepwise synthesis of *p-tert*-butylcalix[4]arene.

tected, and by varying the overall concentration and the relative ratios of the reactants, the amounts of these materials can be increased to isolable proportions. One of them has a melting point of 344–346 °C, an elemental analysis and ^1H NMR and ^{13}C NMR spectra compatible with a cyclic structure, and a molecular weight based both on mass spectral and osmometric measurements compatible with a tetramer (**4**). An independent synthesis of *p-tert*-butylcalix[4]arene has been reported by Kämmerer and co-workers[25] and has also been carried through in our laboratories. It follows the method which was first worked out by Hayes and Hunter[3] and subsequently improved by Kämmerer et al.,[13,20,26] as outlined in Figure 2. Our synthesis, which differs from that of Kämmerer only in the use of bromine instead of chlorine as the blocking group, yields a compound identical in properties with those of the 344–346 °C compound isolated from the one-step reaction, and it shows no depression in melting point when admixed with the substance from that source. The definitive proof of structure of this compound has recently been provided by an X-ray crystallographic determination carried out by Andreetti and co-workers[27] who showed that the low-melting material prepared by the Cornforth modification of the Zinke procedure (vide infra) is a cyclic tetramer containing a molecule of occluded toluene (used as the crystallizing solvent).

The fourth compound present in the one-step product prepared by the "standard" procedure was isolated as colorless needles which did not have a sharp melting point but decomposed in the vicinity of 350 °C. An elemental analysis of this material is compatible with a $C_{45}H_{58}O_5$ formula, the molecular weight as determined by mass spectra and by osmomentry has a value of 678, the ^1H NMR spectrum shows two methylene resonances in the ratio of 3:2, the ^{13}C NMR spectrum confirms the presence of two types of methylene carbons and incates the presence of 12 nonequivalent aromatic carbon atoms, and the IR spectrum shows an absorption characteristic of an $ArCH_2$–O bond. All of these data are compatible with a structure in which four *p-tert*-butylphenol groups are joined in a cyclic array in which three of the bridges are CH_2 groups and the fourth bridge is a CH_2OCH_2 unit. We have designated the resulting compound as a *b*ishomooxacalix[4]arene (**14**) (i.e., two additional atoms and oxygen in place of a carbon).



14

Table II. Composition (%) of the Cyclic Oligomeric Product from *p-tert*-Butylphenol and Formaldehyde via the One-Step (Munch and Patrick-Egan Conditions) and the Three-Step (Zinke and Cornforth Conditions) Methods

	one-step		three-step	
Cyclic Oligomer	KOH/ xylene	KOBu^t/ tetralin	linseed oil	dowtherm
p-tert-butylcalix[8]arene (**2**)	45	37	26	23
p-tert-butylcalix[6]arene (**3**)	9.5	14		
p-tert-butylcalix[4]arene (**4**)	9	14	6	25.5
p-tert-butylbis-homooxacalix[4]arene (**14**)	32.5			

Comparison of the Products from the One-Step (Munch Type) and the Three-Step (Zinke Type) Methods. To compare the composition of the mixtures obtained from the one-step method (Munch and Patrick-Egan conditions) and the three-step method (Zinke and Cornforth conditions), we established a product isolation protocol which involves TLC and ^1H NMR analysis coupled with crystallization and chromatographic separations. When applied to the material obtained by the one-step "standard" procedure (i.e., KOH/xylene), the composition was indicated to be 45% cyclic octamer, 9.5% cyclic hexamer, 9% cyclic tetramer, and 32.5% bishomo compound, accounting for 96% of the starting material as cyclic oligomeric product. The chromatographic separation also yielded a fraction containing a small amount of other substances, probably acyclic oligomers. When the same isolation protocol was applied to the material obtained by the one-step procedure using potassium *tert*-butoxide and tetralin the composition was indicated to be 37% cyclic octamer, 14% cyclic hexamer, and 14% cyclic tetramer. The remaining 35% of product could not be identified and probably consisted of acyclic oligomers. Thus, these conditions appear to give approximately the same amounts of octamer, hexamer, and tetramer as the Munch conditions but little, if any, of the bishomo compound.

The three-step method (Zinke type) involves low-temperature (55 °C), medium-temperature (120 °C), and high-temperature (220 °C) treatment. Analysis of the material using the original Zinke conditions (i.e., linseed oil for the final thermal step) indicated it to contain 26% cyclic octamer and 6% cyclic tetramer. There was no evidence for the formation of cyclic hexamer or the bishomo compound in the fractions that were investigated; the ethyl acetate triturates and the linseed oil fractions were not examined for their contents. Analysis of the material obtained using the Cornforth conditions (i.e., Dowtherm for the final thermal step) indicated it to contain 23% cyclic octamer and 25.5% cyclic tetramer. Here, also, there was no evidence for cyclic hexamer or the bishomo compound. These data are summarized in Table II. An unpublished modification of the Cornforth procedure[28] was investigated wherein the final thermal step is carried out without a solvent, the solid resin simply being heated at 180–220 °C and 1-mm pressure for 2 h. In our hands this procedure yielded rather small amounts of a cyclic oligomeric mixture comprising cyclic octamer and cyclic tetramer, and it appeared to offer no advantage over the other procedures.

Effects of Variations in Reaction Conditions in the One-Step and Three-Step Methods. The discrepancies in the yields and melting points of the products prepared by the same method in two different laboratories, as pointed out in Table I, is not unusual with these reactions. Indeed, it has been noted on numerous occasions that different workers in our own laboratories frequently obtain quite different results although using procedures that are ostensibly identical, and considerable variation in results are noted even by the same worker carrying out a given reaction several times. Although we have yet to determine all of the factors that control the product composition in these reactions, experiments carried out with different concentrations, reactant ratios, solvents, bases, and heating rates have shown that the reaction is susceptible

---

(25) Kämmerer, H.; Happel, G.; Böhmer, V.; Rathay, D. *Monatsh. Chem.* **1978**, *109*, 767.

(26) Kämmerer, H.; Happel, G. *Makromol. Chem.* **1978**, *179*, 1199.

(27) Andreetti, G. D.; Ungaro, R.; Pochini, A. *J. Chem. Soc., Chem. Commun.* **1979**, 1005.

(28) We are indebted to Sir John Cornforth and Dr. Gordon A. Nicholls for making this information available to us.

(29) Pedersen, C. J. *J. Am. Chem. Soc.* **1967**, *89*, 7017.

Table III. Condensation of *p-tert*-Butylphenol and Paraformaldehyde in the Presence of High Concentrations of Alkali Metal Hydroxides

alkali hydroxide	cation diameter,[29] Å	hexamer, %	octamer, %
LiOH	1.36		60
NaOH	1.94		23
KOH	2.66	56	
RbOH	2.94	74	
CsOH	3.34	40	5

in greater or lesser degree to all of these influences.

Experiments with a variety of bases, using the "standard" one-step method in which the ratio of phenol/paraformaldehyde/base is approximately 45:75:1, showed that sodium hydroxide, potassium hydroxide, and cesium hydroxide all give essentially the same product mixture in which the cyclic octamer is the major component but that lithium hydroxide is considerably less effective. The divalent metal hydroxides magnesium hydroxide and calcium hydroxide are completely ineffective, giving almost quantitative recovery of starting material. Barium hydroxide induces a reaction but yields what appears to be a mixture of linear oligomers. When the amount of base is increased so that the ratio of phenol/paraformaldehyde/base is approximately 2:4:1, however, interesting differences between the alkali metal bases are revealed. With potassium hydroxide, rubidium hydroxide, or cesium hydroxide as the base in the condensation, the cyclic hexamer is the major product. Particularly good yields of very pure product are obtained with rubidium hydroxide, making *p-tert*-butylcalix[6]arene a very readily accessible compound. Whether the high yields of cyclic hexamer are the result of a "template" effect is conjectural. Measurements on space-filling models of the calixarenes indicate that the shortest transannular distance between the surfaces of the oxygen atoms is ca. 0.8 Å in the cyclic tetramer, ca. 2.0–2.9 Å in the cyclic hexamer, and as high as 4.5 Å in the cyclic octamer. The cyclic tetramer is a rigid molecule, and there is very little possibility for variation in the diameter of the opening that is established on the "bottom" of the molecule by the cyclic array of hydroxyl groups. The cyclic hexamer, however, is moderately flexible and appears to be capable of establishing openings anywhere between 2.0 and 2.9 Å in diameter. The cyclic octamer is very flexible, and in its most expanded conformation it has an opeing that is 4.5 Å or more in diameter. Thus, the cyclic hexamer does, indeed, seem to be the oligomer most capable of encompassing a metal cation, and the crystal ionic radii of potassium and rubidium ions, as shown in Table III, suggest that they should be the ones to fit most comfortably.

The solvent in the one-step method serves the double purpose of supporting the reaction of formaldehyde and phenol in the first phase of the process to form hydroxymethylated oligomers and providing the necessary temperature to induce the cyclization of these oligomers in the second phase of the process. Only the latter aspect was investigated in a set of reactions in which toluene, xylene, and tetralin were compared. A reaction carried out in refluxing toluene (bp 110 °C) yielded only a trace of cyclic oligomers, and the product appeared to consist mainly of linear oligomers. A reaction carried out in refluxing xylene (bp ca. 140 °C) yielded a product, as described above, containing cyclic octamer, hexamer, tetramer, and bishomo compound. A reaction carried out in refluxing tetralin (bp 207 °C) yielded a product containing cyclic octamer, hexamer, and tetramer but almost no bishomo compound. Thus, the absence of bishomo compound in all but the product from the "standard" one-step process can be attributed to the higher boiling solvents which either prevent its formation or promote its conversion to other materials (vide infra). It had been hoped that different solvents might significantly alter the octamer/tetramer ratio, but this appears not to be the case.

Two variations in the Cornforth modification of the three-step method were invesitgated in the hope of improving the yield of cyclic tetramer. In one case the initial incubation at 50–55 °C was omitted and the aqueous phenol–formaldehyde solution was simply heated for 2 h at 110–120 °C, neutralized, and then subjected to the Dowtherm treatment. The product in this case yielded 22.5% of octamer and 18.5% of tetramer. In the second case the reaction was carried out with *p-tert*-butylphenol, aqueous formaldehyde, aqueous sodium hydroxide, and diphenyl ether (equivalent to Dowtherm) heated first at 100 °C for 2 h and then at 220 °C for 2 h (without the neutralization step). The product in this case yielded 43% of hexamer and 10% of tetramer, thus resembling the product of the one-step method when a large amount of base is used.

In order to test the effect of differences in rates of heating, a pair of reactions was carried out by the one-step method in which one mixture was heated as quickly as possible to reflux and the other was slowly raised from room temperature to reflux over a period of 2 h; each reaction mixture was heated at reflux for 4 h. The results from the rapidly heated reaction mixture are those already noted, viz., 45% cyclic octamer, 9.5% cyclic hexamer, 9% cyclic tetramer, and 32.5% bishomo compound. The slowly heated reaction mixture yielded 58% cyclic octamer, 7% cyclic hexamer, 10% cyclic tetramer, and 7.5% bishomo compound. Thus, the most striking difference is in the amount of bishomo compound formed, the amounts of the other three cyclic oligomers being quite comparable for the two procedures.

Acetates and Trimethylsilyl Ethers of the Calixarenes. Zinke was the first to prepare the acetates of the calixarenes, and on the basis of a Rast molecular-weight determination on the acetate from the *p*-octylphenol/formaldehyde condensation product, he postulated cyclc tetrameric structures. Cornforth repeated and modified the Zinke procedure for the condensation of *p-tert*-butylphenol and formaldehyde, and he obtained a low-melting compound (mp 330–332 °C) and a high-melting compund (mp 380 °C). From the former, which is clearly established as the cyclic tetramer, Cornforth obtained an acetate with mp 247–250 °C upon treatment with acetic anhydride and sodium acetate. This appears to be identical with the compound that we have obtained from the cyclic tetramer (**4**) which, when treated with acetic anhydride and sodium acetate, yields an acetate with mp 278–281 °C.[30] However, when **4** is treated with acetic anhydride and sulfuric acid, a different compound is obtained, with mp 383–386 °C. On the basis of the elemental analyses, the ^{1}H-NMR spectra (which show a lower ratio for the $(CH_3)_3C/CH_3CO$ resonances for the 278–281 °C acetate than for the 383–386 °C acetate), and the IR spectra (which show an OH stretching band at 3550 cm^{-1} for the 278–281 °C acetate but no absorption in this region for the 383–386 °C acetate), it is probable that the 278–281 °C acetate is the triacetate of *p-tert*-butylcalix[4]arene and the 383–386 °C acetate is the tetraacetate of *p-tert*-butylcalix[4]arene.

The cyclic hexamer (**3**) and the cyclic octamer (**2**) were converted by the acetic anhydride/sulfuric acid procedure to the hexaacetate of *p-tert*-butylcalix[6]arene and the octaacetate of *p-tert*-butylcalix[8]arene, respectively, with mp 360–362 °C and 353–354 °C. The acetate of Cornforth's high-melting compound from the *p-tert*-butylphenol/formaldehyde condensation melts as 332–333 °C and is probably the octaacetate of *p-tert*-butylcalix[8]arene, as suggested by the data cited in Table II. The acetate obtained by Zinke from this same condensation reaction is simply reported to darken above 290 °C, so it is uncertain as to which of the calixarene acetates it corresponds.

By means of standard silylation procedures using hexamethyldisilazane and chlorotrimethylsilane,[31] the cyclic hexamer (**3**) and the cyclic octamer (**2**) are easily converted to the corresponding hexakis(trimethylsilyl) and octakis(trimethylsilyl) derivatives in reasonably good yields. The cyclic tetramer (**4**), however, gives only recovered starting material under these conditions. When a recently reported method[32] using chloro-

---

(30) Most of the melting points of the calixarenes observed in our laboratory are 15–30 °C higher than those reported in the literature for what appear to be identical compounds. It is uncertain whether this is due to differences in the purity of the samples or to differences in the methods for measuring these rather high melting points.

(31) Langer, S. H.; Connell, S.; Wender, I. *J. Org. Chem.* **1958**, *23*, 50.

(32) Olah, G. A.; Gupta, B. G. B.; Narang, S. C.; Malhotra, R. *J. Org. Chem.* **1979**, *44*, 4272.

trimethylsilane and lithium sulfide was employed, a product was obtained that was much more chloroform-soluble than the starting material and which, on the basis of the ^1H NMR spectrum of the crude material, appears to be a bis(trimethylsilyl) derivative. Attempts to purify this material by recrystallization, however, yielded only the parent cyclic tetramer. The considerably greater crowding of the hydroxyl groups in the cyclic tetramer as compared with the higher cyclic oligomers undoubtedly is responsible for the greater difficulty in forming derivatives from *p-tert*-butylcalix[4]arene.

Mechanism of Formation of Cyclic Oligomers. Base-catalyzed reactions of *p-tert*-butylphenol and formaldehyde have been shown to yield, inter alia, hydroxymethyl derivatives of monomers[33] and dimers.[2] The mechanism of formation of the dimer and higher oligomers was suggested by Hultzsch and Schiemann[34] to involve quinonemethide intermediates, but this has been questioned[35] because of the high temperatures that are required to generate quinonemethides from compounds such as *o*-(methoxymethyl)phenol.[36] However, it is known that oxy Cope rearrangements occur far more readily with anions than with the corresponding neutral compounds,[37] so conversion of *o*-(hydroxymethyl)phenolates to *o*-quinonemethides may, indeed, occur under much milder conditions. The mixtures from which the calixarenes eventually form probably contain linear oligomers in which the ortho,ortho bridges are CH_2 groups as well as CH_2OCH_2 groups, in various combinations. Conversion of the components of this mixture to calixarenes occurs, almost certainly, in the thermal phase of the reaction. To study the thermal reaction, Zinke and co-workers[38,39] used *o,o'*-bis(hydroxymethyl)-*tert*-butylphenol as a starting material. They observed that at 155 °C water splits out and a high-molecular-weight (1420) polyether (seven to eight ether groups) is formed and that when this is heated to still higher temperatures formaldehyde splits out, ether groups are lost, and uncharacterized compounds of somewhat lower molecular weight are formed. In the present work, the monitoring of a condensation carried out by the one-step method indicates that comparable reactions occur under these conditions. Noting the ^1H NMR spectrum in the region between δ 3.0 and 5.0 ppm, after 10 min of reaction time, resonances at δ 4.7 (characteristic of $ArCH_2OH$ methylene) and δ 4.4 (characteristic of $ArCH_2OCH_2Ar$ methylene) were observed. Intially, the δ 4.7 resonance was more intense, but after 30 min the two resonances were of equal intensity; by 40 min the δ 4.4 resonance was the stronger; and by 1 h the δ 4.7 resonance had almost disappeared. Appearing after about 40 min was a resonance at δ 3.9 (characteristic of $ArCH_2Ar$ methylene), and this continued to slowly grow until the termination of the reaction after 4 h (at which time the δ 4.4 and δ 3.9 resonances were approximately equal in intensity, reflecting the presence of calixarenes and bishomocalixarene in the final product).

The concurrent formation of calixarenes and bishomocalixarene in the one-step method suggests the possibility that the bishomo compound might be an obligatory precursor of the calixarenes. This, however, appears not to be the case, for when a sample of the *p-tert*-butylbishomooxacalix[4]arene (14) is heated in xylene alone, no reaction occurs, and when it is heated in xylene in the presence of base, only a very slow and partial transformation takes place, producing a mixture of cyclic octamer, hexamer, and tetramer. Heating to a higher temperature in tetralin is more effective in transforming the bishomo compound, but the product contains only trace amounts of cyclic octamer, hexamer, and tetramer, the major component being a material that fails to move from the origin in the TLC analysis (which suggests that it is a linear polymer of considerable length). v. Euler and co-workers[40] observed the formation of a tetrahomobisoxacalix[4]arene in 6–10% yield by heating bis(2-hydroxy-3-(hydroxymethyl)-5-methyl)methane for 30 min at 150 °C, and Kämmerer and Dahm[41] reported the isolation of the corresponding octahomotetraoxacalix[4]arene.

Too little is yet known about the composition of the mixture from which the cyclic oligomers are produced and of the chemistry of these components to provide the basis for a convincing reaction mechanism. From the present studies it appears that the bishomo compound is *not* a major precursor of the calixarenes, suggesting that the monohydroxymethylated linear oligomers are the more likely candidates. The preponderance of the even-numbered calixarenes may indicate that cyclodimerization rather than cyclization is a major pathway, but more data are necessary before this can be supported or refuted.

Properties of the Calixarenes. Kämmerer and co-workers, in a series of papers,[13,20,25,26,42,43] have studied the properties of the calixarenes prepared by the multistep synthesis of Hayes and Hunter.[3] Their data provide a useful comparison with the data on the compounds obtained in the present study by the one-step and three-step methods. Of particular interest are the IR stretching frequencies of the OH groups and the ^1H NMR characteristics of the CH_2 groups.

The stretching frequencies of the OH groups of the calixarenes appear at unusually low frequency, and this is attributed to the very strong intramolecular hydrogen bonding that the cyclic structures facilitate. For a series of cyclic oligomers Kämmerer observed the following OH stretching frequencies: cyclic tetramer, 3180 cm^{-1}; cyclic pentamer, 3290 cm^{-1}; cyclic hexamer, 3170 cm^{-1}; cyclic heptamer, 3155 cm^{-1}. In the present work the observed values are as follows: *p-tert*-butylcalix[4]arene, 3160 cm^{-1}; *p-tert*-butylbishomooxacalix[4]arene, 3300 cm^{-1}; *p-tert*-butylcalix[6]arene, 3150 cm^{-1}; *p-tert*-butylcalix[8]arene, 3200 cm^{-1}. It is interesting to note that in both series three of the four compounds show the OH stretching frequency between 3150 and 3200 cm^{-1}, while the fourth member shows it near 3300 cm^{-1}. In the Kämmerer series it is the pentamer that is exceptional, and in our series it is the bishomo compound; molecular models suggest that these two compounds are approximately equivalent in flexibility and that both are more flexible than the tetramer. What is unexpected, however, is that the higher oligomers, viz., the hexamer, heptamer, and octamer, all show OH stretching frequencies that are indicative of very strong intramolecular hydrogen bonding, suggesting a degree of inflexibility comparable to that of the tetramer.

Temperature-dependent ^1H NMR studies carried out by Kämmerer and co-workers[13] on the *p-tert*-butylcalix[4]arene synthesized by the multistep method and by Munch[14] on a *p-tert*-octylcalixarene synthesized by the one-step method have shown that at temperatures above room temperature the CH_2 hydrogens appear as a sharp singlet but that below room temperature they appear as a well-resolved pair of doublets. These observations are rationalized in terms of conformational inversion (i.e., cone $\rightleftarrows$ cone, cone $\rightleftarrows$ 1,2-alternate, and/or cone $\rightleftarrows$ 1,3-alternate transformations in the case of the cyclic tetramer) which, if slow on the NMR time scale, will show the CH_2 hydrogens chemically shifted and coupled but which, if rapid on the NMR time scale, will show the CH_2 hydrogens in an averaged environment. The similarity of the results reported by Kämmerer and by Munch seems to indicate that both experimenters were dealing with a cyclic tetramer. However, our observation that the cyclic octamer behaves in a similar fashion casts some doubt on this conclusion and suggests that the Munch studies might actually have involved

---

(33) Ullmann, F.; Brittner, K. *Ber. Dtsch. Chem. Ges.* **1909**, *42*, 2540.

(34) Hultzsch, I.; Schiemann, G. *Ber. Dtsch. Chem. Ges.* **1942**, *75*, 363.

(35) Wegler, R.; Herlinger, H. In "Methoden der Organischen Chemie (Houben-Weyl)", XIV/2; Makromolekulare Stoffe, Georg Thieme Verlag: Stuttgart, 1963; p 257.

(36) Gardner, P. D.; Sarrafizadeh, H.; Brandon, R.L. *J. Am. Chem. Soc.*, **1959**, *81*, 5515.

(37) Evans, D. E.; Golob, A. M. *J. Am. Chem. Soc.* **1975**, *97*, 4765. Thies, R. W.; Shih, H. J. *J. Org. Chem.* **1978**, *43*, 1050.

(38) Zinke, A.; Ziegler, E.; Hontschik, I. *Monatsh. Chem.* **1948**, *78*, 317.

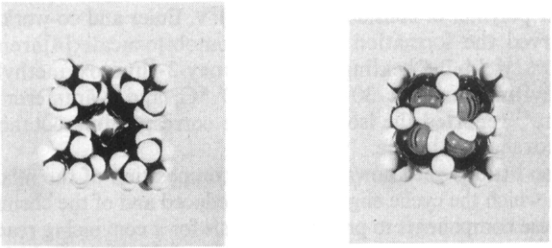
(39) Zinke, A.; Hontschik, I. *Monatsh. Chem.* **1948**, *78*, 327.

(40) v. Euler, H.; Adler, E.; Bergstrom, B. *Ark. Kemi Mineral. Geol.* **1941**, 14B, No. 25; *Ibid.* **1941**, *14B*, No. 30; v. Euler, H., *Angew. Chem.* **1941**, *54*, 458.

(41) Kämmerer, H.; Dahm, M. *Kunsts-Plast* (*Solothurn, Switz*) **1959**, *6*, 20.

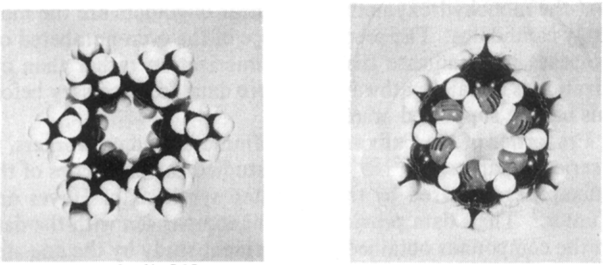
(42) Böhmer, V.; Chhim, P.; Kämmerer, H. *Makromol. Chem.* **1979**, *180*, 2503.

(43) Kämmerer, H.; Happel, G. *Makromol. Chem.* **1980**, *181*, 2049.



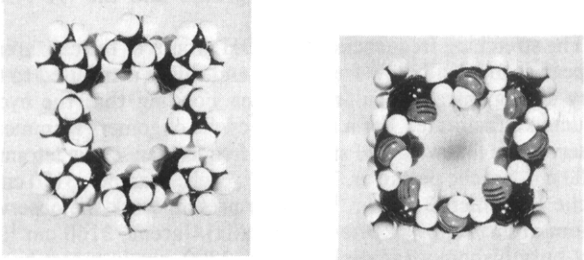
p-tert-butylcalix[4]arene (top view)

p-tert-butylcalix[4]arene (bottom view)



p-tert-butylcalix[6]arene (top view)

p-tert-butylcalix[6]arene (bottom view)



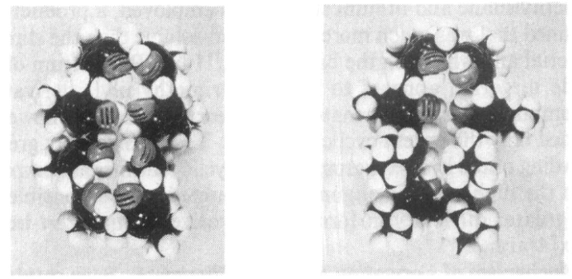
p-tert-butylcalix[8]arene (top view)

p-tert-butylcalix[8]arene (bottom view)

Figure 3. Space-filling molecular models of the cyclic tetramer, hexamer, and octamer in the "open" conformation.

the *p-tert*-octylcalix[8]arene. That the cyclic octamer should show this ^{1}H-NMR behavior is quite extraordinary, for molecular models indicate that it should be a far more flexible molecule than the cyclic tetramer. Possibly, the molecule exists in a transannularly "pinched" conformation which maximizes the intramolecular hydrogen bonding to give a structure that is approximately equivalent to a pair of cyclic tetramers fused to each other. Space-filling models of the cyclic tetramer, hexamer, and octamer in the "open" conformation are shown in Figure 3; those for the cyclic octamer in transannularly "pinched" conformations are shown in Figure 4. Of the two "pinched" conformations, designated as syn-cone/cone and anti-cone/cone conformations, the latter appears to allow somewhat more effective intramolecular hydrogen bonding between the OH groups. A more detailed study of the NMR characteristics of the calixarenes will be reported in a subsequent paper.

Since oure long-range goals with the calixarenes revolve around their ability to capture other molecules, the observation of this phenomenon is of especial interest. *p-tert*-Butylcalix[4]arene shows a striking ability to form complexes with a variety of small molecules, occluding chloroform, benzene, and toluene with great tenacity. Only after prolonged heating at high temperatures and low pressures is it possible to completely remove these compounds from the calixarene. That the occluded molecules are inside the calix is strongly indicated by the X-ray crystallographic determination[27] of the toluene complex of *p-tert*-butylcalix[4]arene which clearly shows the toluene to be in the middle of the structure. *p-tert*-Butylbishomooxacalix[4]arene shows a similar tendency to form 1:1 complexes with small molecules such as chloroform and methylene chloride. *p-tert*-Butylcalix[6]arene, somewhat surprisingly, forms a very stable complex that contains one molecule of chloroform and two molecules of methanol. Upon heating at high temperature under vacuum, one molecule of methanol can be removed and then the second molecule, but the molecule of chloroform is retained even after 144 h at 257 °C and 1-mm pressure. The hexaacetate of the cyclic hexamer shows similar behavior, occluding two molecules of chloroform which can be removed in stepwise fashion only under very strenuous conditions. *p-tert*-Butylcalix[8]arene, on the other hand, appears to form only very labile complexes from which the occluded material can be removed simply by drying at room temperature and atmospheric pressure. Attempts to discern strong complex formation between the cyclic octamer and a wide variety of organic compounds have been without success. A more detailed study of the formation of calixarene complexes will be reported at a later date.



syn-Cone/cone Conformation

anti-Cone/cone Conformation

Figure 4. Space-filling molecular models of the syn-cone/cone and the anti-cone/cone forms of *p-tert*-butylcalix[8]arene in the transannularly "pinched" conformations.

Experimental Section[44]

Preparation of Cyclic Oligomers. 5,11,17,23,29,35,41,47-Octa-*tert*-butyl-49,50,51,52,53,54,55,56,-octahydroxycalix[8]arene (2). Following the Munch procedure, a slurry of 27.8 g (0.18 mol) of *p-tert*-butylphenol, 9.0 g (0.30 mol) of paraformaldehyde, and 0.4 mL (0.004 mol) of 10 N KOH in 150 mL of xylene was refluxed in an inert atmosphere with efficient stirring for 4 h in a 500-mL flask equipped with a Dean and Stark water collector. After 30 min all of the solid had gone into solution, and after 1 h a white precipitate began to separate. The reaction mixture was refluxed for 4 h, cooled, and filtered. The solid product was washed, in succession, with 100-mL portions of toluene, ether, acetone, and water and was then dried and recrystallized from chloroform to afford 20.4 g (64%) of the *tert*-butylcalix[8]arene (**2**) as colorless, glistening needles: mp 411–412 °C; IR (KBr) 3230 cm^{-1}; ^{1}H NMR (pyridine-d_5) δ 9.6 (s, 1, ArOH), 7.14 (s, 2, ArH), 4.3 (br d, 1, CH_2), 3.4 (br d, 1, CH_2), 1.24 (s, 9, $C(CH_3)_3$); ^{13}C NMR ($CDCl_3$) δ 162 (30%, Ar), 156 (25%, Ar), 141 (100%, Ar), 131.5 (92%, Ar), 26.5 (30%, Ar*C*H$_2$Ar), 24 (17.5%, *C*(CH$_3$)$_3$), 21 (89%, C(*C*H$_3$)$_3$); osmometric M_r ($CHCl_3$, 37 °C), 1300 (calcd[47] 1298); R_f[44] 0.75.

Anal. Calcd for $C_{88}H_{112}O_8$: C, 81.44; H, 8.70. Found: C, 81.46; H, 8.70. A solution of 0.65 g (0.5 mmol) of the *tert*-butylcalix[8]arene in 4 mL of pyridine was mixed with an excess of hexamethyldisilazane (1 mL) and trimethylchlorosilane (0.5 mL) and heated under reflux in an atmosphere of nitrogen for 2 h. The solution was cooled, and the pyridine was removed under reduced pressure to leave a gummy residue, which solidified upon trituration with methanol. Chromatography on silica gel

---

(44) Boiling points are uncorrected. Melting points of all compounds melting above 250 °C were taken in sealed and evacuated capillary tubes on a Mel-Temp apparatus (Laboratory Devices, Cambridge, MA) using a 500 °C thermometer calibrated against a thermocouple (accuracy, ±1 °C). Infrared (IR) spectra were determined on a Perkin-Elmber Infracord, a Perkin Elmer 457, or a Perkin-Elmer 283B spectrometer. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Hitachi–Perkin-Elmer R-24B spectrometer, and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a JEOL FX-100 spectrometer. Chemical shifts are reported as δ values in parts per million relative to tetramethylsilane (δ 0.0) as an internal standard. Mass spectra[45] were obtained on a Varian MAT 311A instrument. Osmometric molecular weight determinations[46] were made on a Wescan Model 232A apparatus, using concentrations of ca. 10^{-3} M in $CHCl_3$. Microanalyses were carried out by Industrial Testing Laboratories, St. Louis, MO. Thin-layer chromatographic (TLC) analyses were carried out on silica gel plates (adsorbant thickness 250 μm), using $CHCl_3$ (3 parts)/hexane (4 parts) as the eluting agent.

(45) We are indebted to Ralph Fuhrhop of the Monsanto Co., St. Louis, MO, for carrying out the mass spectral determinations.

(46) We are indebted to Alice Gutsche for carrying out the osmometric molecular weight determinations.

(47) The calculated osmometric molecular weights are based on the following atomic weights: C, 12.01; Cl, 35.45; H, 1.01; O, 16.00; Si, 28.09.

using a hexane/CH_2Cl_2 eluant yielded 0.55 g (61%) of material that showed only a single spot on TLC. Recrystallization from hexane/acetone yielded colorless needles of the **octakis(trimethylsilyl) derivative of *tert*-butylcalix[8]arene**: mp 358–360 °C; IR (KBr) 1251 and 841 cm^{-1} (C–Si stretching); ^1H NMR (CCl_4) δ 6.86 (m, 2, ArH), 3.83 (br s, 2, CH_2), 1.20 (s, 9, $C(CH_3)_3$), –0.02 (s, 9, $Si(CH_3)_3$); ^{13}C NMR ($CDCl_3$) δ 148.2 (10%, Ar), 141.7 (19%, Ar), 128.8 (43%, Ar), 124.4 (28%, Ar), 32.8 (15%, CH_2), 31 (very weak, $C(CH_3)_3$), 30.3 (100%, $C(CH_3)_3$), 0.8 (53%, $Si(CH_3)_3$); osmometric M_r ($CHCl_3$, 37 °C), 1889 (calcd[47] 1875); mass spectrum (EI, 90 eV), *m/e* 1872 (100, octamer), 936 (13, tetramer or dication of octamer).

Anal. Calcd for $C_{112}H_{176}Si_8O_8$: C, 71.74; H, 9.46. Found: C, 71.90; H, 9.59. A 2.0-g (1.54 mmol) sample of *tert*-butylcalix[8]arene was treated with 50 mL of acetic anhydride and 2 drops of concentrated H_2SO_4, and the mixture was heated at reflux for 2 h. Upon cooling, a colorless solid precipitated from the dark-brown solution. This was separated by filtration and recrystallized from acetic anhydride to yield 1.2 g (48%) of the **octaacetate of *tert*-butylcalix[8]arene** as glistening crystals: mp 353–354 °C; IR (KBr) 1765 cm^{-1} (C=O stretching); ^1H NMR ($CDCl_3$) δ 6.94 (s, 2, ArH), 3.62 (br s, 2, CH_2), 1.93 (s, 3, $OCOCH_3$), 1.28 (s, 9, $C(CH_3)_3$); osmometric M_r ($CHCl_3$, 37 °C), 1636 (calcd[47] 1634).

Anal. Calcd for $C_{104}H_{128}O_{16}$: C, 76.47; H, 7.84. Found: C, 76.34; H, 7.89.

5,11,17,23,29,35-Hexa-*tert*-butyl-37,38,39,40,41,42-hexahydroxycalix[6]arene (3). This compound can be isolated from the mother liquor of the crystallization of the xylene-insoluble fraction described in the preceding procedure. It is prepared in better yield, however, by the following procedure. A slurry of 10.0 g (0.066 mol) of *p-tert*-butylphenol, 4.0 g (0.133 mol) of paraformaldehyde, and 6 mL of 5 N rubidium hydroxide in 100 mL of xylene was refluxed in an inert atmosphere with efficient stirring for 4 h in a 500-mL flask equipped with a Dean and Stark collector. The cooled reaction mixture was filtered, and the solid that was obtained was suspended in 300 mL of $CHCl_3$ and shaken with 100 mL of 1 N HCl. The organic layer was separated, washed with water, dried over anhydrous Na_2SO_4, and concentrated to 100 mL. Addition of methanol caused the precipitation of a solid, which was removed by filtration to give 7.85 g (73%) of colorless product, mp 380–381 °C. Recrystallization from $CHCl_3$ or $CHCl_3/CH_3OH$ produced a white solid with the same melting point of 380–381 °C: IR (KBr) 3400 (shoulder, OH stretching), 3150 cm^{-1} (OH stretching); ^1H NMR (CD_2Cl_2) δ 10.2 (s, 1, ArOH), 7.10 (s, 2, ArH), 3.88 (s, 2, CH_2), 1.25 (s, 9, $C(CH_3)_3$; ^{13}C NMR ($CDCl_3$) δ 147.2 (15%, Ar), 144.2 (15%, Ar), 126.9 (40%, Ar), 126.1 (65%, Ar), 34.0 (17%, $ArCH_2Ar$), 33.1 (25%, $C(CH_3)_3$), 31.4 (100%, $C(CH_3)_3$); osmometric M_r ($CHCl_3$, 37 °C), 1131 (calcd[47] for $C_{66}H_{84}O_6{\cdot}CHCl_3{\cdot}CH_3OH$, 1125); mass spectrum (FI, 3 kV), *m/e* 972 (100), 973 (67) [calcd for cyclic hexamer: 972 (100), 973 (72)]; R_f[44] 0.63.

Anal. Sample dried at 140 °C for 48 h at 1 mm: Calcd for $C_{66}H_{84}O_6{\cdot}CHCl_3{\cdot}2CH_3OH$: C, 72.25; H, 8.11. Found: C, 71.79; H, 7.64. Sample dried at 207 °C for 48 h at 1 mm: Calcd for $C_{66}H_{84}O_6{\cdot}CHCl_3{\cdot}CH_3OH$: C, 72.72; H, 7.93. Found: C, 72.56; H, 7.78. Sample dried at 257 °C for 144 h at 1 mm: Calcd for $C_{66}H_{84}O_6{\cdot}CHCl_3$: C, 73.76; H, 7.79. Found: C, 73.80; H, 7.98.

Evaporation of the solvent from the xylene-soluble portion left a residue which was shown by TLC to contain a small amount of the cyclic octamer, some cyclic hexamer, along with linear oligomers from which no pure material could be obtained by recrystallization.

The **hexakis(trimethylsilyl) derivative of *tert*-butylcalix[6]arene** was prepared as described above for the cyclic octamer and obtained as glistening crystals after recrystallization from $CHCl_3/CH_3OH$: mp 410–412 °C; IR (KBr) 1251 and 841 cm^{-1} (C–Si stretching); ^1H NMR ($CDCl_3$) δ 7.21 (m, 2, ArH), 3.9 (br s, 1.33, CH_2), 3.35 (br s, 0.66, CH_2), 1.48 (s, 3, $C(CH_3)_3$), 1.14 (s, 6, $C(CH_3)_3$), 0.31 (s, 6, $Si(CH_3)_3$), –0.8 (s, 3, $Si(CH_3)_3$); osmometric M_r ($CHCl_3$, 37 °C), 1403 (calcd[47] 1406); mass spectrum (FI, 2 kV), *m/e* 1404 (100), 1405 (107) [calcd for hexamer: 1404 (100), 1405 (122)].

Anal. Calcd for $C_{84}H_{132}Si_6O_6$: C, 71.79; H, 9.40. Found: C, 71.94; H, 9.34.

The **hexaacetate of *tert*-butylcalix[6]arene** was prepared as described above for the cyclic octamer by treating the calixarene with acetic anhydride and H_2SO_4. The crude product, obtained in quantitative yield, was recrystallized from $CHCl_3/CH_3OH$ to give white platelets: mp 360–362 °C (dec); IR (KBr) 1765 cm^{-1} (C=O stretching); ^1H NMR ($CDCl_3$) δ 7.2–6.7 (br s, 2, ArH), 3.8–3.4 (br s, 2, CH_2), 2.3–1.5 (br, s, $OCOCH_3$), 1.2 (s, 9, $C(CH_3)_3$); osmometric M_r ($CHCl_3$, 37 °C) on sample dried for 48 h at 140 °C (1 mm), 1442 (calcd[47] for $C_{78}H_{96}O_{12}{\cdot}2CHCl_3$, 1464).

Anal. Sample dried at 140 °C for 48 h at 1 mm: Calcd for $C_{78}H_{96}O_{12}{\cdot}2CHCl_3$: C, 65.75; H, 6.71; Cl, 14.56. Found: C, 65.93; H, 6.80; Cl, 14.33. Sample dried at 207 °C for 48 h at 1 mm: Calcd for $C_{78}H_{96}O_{12}{\cdot}CHCl_3$: C, 70.64; H, 7.22. Found: C, 70.35; H, 7.30. Sample dried at 257 °C for 144 h at 1 mm: Calcd for $C_{78}H_{96}O_{12}{\cdot}{}^1/{}_2CHCl_3$: C, 73.42; H, 7.52. Found: C, 73.76; H, 7.76.

5,11,17,23-Tetra-*tert*-butyl-25,26,27,28-tetrahydroxycalix[4]arene (4). Following the Cornforth procedure, 10 g of *p-tert*-butylphenol was mixed with 10 mL of 3 N NaOH and 9.7 g of 37% formaldehyde solution. The mixture was heated at 50–55 °C for 45 h and then at 110–120 °C for 2 h to give a yellow solid. This was stirred with 100 mL of 1 N HCl for 1 h to neutralize the base, and the solid was removed by filtration, washed with water, and dried in an oven at 110–120 °C for 30 min. This material was mixed with 70 g of Dowtherm or diphenyl ether and heated to 210–220 °C for 2 h in an atmosphere of nitrogen, vigorous frothing commencing at ca. 130 °C. The reaction mixture was cooled, treated with 150 mL of ethyl acetate, and filtered to yield 5.47 g of a white solid, which was indicated by TLC to contain cyclic tetramer accompanied by smaller amounts of cyclic octamer and, possibly, cyclic hexamer. This material was treated with 75 mL of toluene, heated at reflux for 30 min, and filtered hot to give 1.48 g of cyclic octamer (mp 407–409 °C after recrystallization from $CHCl_3$; 85% recovery). Upon cooling, the toluene solution deposited crystals which were recrystallized from toluene to give 2.75 g (25%) of *tert*-butylcalix[4]arene as white plates: mp 344–346 °C; IR (KBr) 3160 cm^{-1} (OH stretching); ^1H NMR ($CDCl_3$) δ 9.6 (s, 1, ArOH), 7.08 (s, 2, ArH), 4.3 (br d, 1, CH_2), 3.55 (br d, 1, CH_2), 1.26 (s, 9, $C(CH_3)_3$); ^{13}C NMR ($CDCl_3$)[48] δ 146.6 (40%, Ar), 144.4 (40%, Ar), 127.7 (86%, Ar), 125.8 (82%, Ar), 34.8 (29%, $C(CH_3)_3$), 32.7 (29%, CH_2), 31.4 (100%, $C(CH_3)_3$); osmometric M_r ($CHCl_3$, 37 °C), 645 (calcd[47] 649); mass spectrum (EI, 90 eV), *m/e* 648 (100), 649 (48), 650 (13) (calcd for M, M + 1, M + 2: 100%, 48.4%, 12.2%) R_f[44] 0.53.

Anal. Sample dried at 207 °C for 48 h at 1 mm: Calcd for $C_{44}H_{56}O_4{\cdot}C_7H_8$: C, 82.70; H, 8.64. Found: C, 82.59; H, 8.78. Sample dried at 257 °C for 144 h at 1 mm: Calcd for $C_{44}H_{56}O_4{\cdot}{}^1/{}_2C_7H_8$: C, 82.13; H, 8.64. Found: C, 81.99; H, 8.88.

A 1.5-g sample of **4** was treated with 37.5 mL of acetic anhydride and 2 drops of concentrated H_2SO_4. The mixture was heated under reflux for 2 h and poured into 300 mL of ice–water, and the precipitate was separated by filtration to yield 1.1 g of a brown solid. Several crystallizations from acetic acid gave 0.76 g (42%) of the **tetraacetate of *p-tert*-butylcalix[4]arene** as a colorless, crystalline solid: mp 383–386 °C with softening at 330–340 °C; IR (KBr) 1760 cm^{-1} (C=O stretching); ^1H NMR ($CDCl_3$) δ 7.2 and 6.8 (s, 8, ArH), 3.6 (br s, 8, CH_2), 2.3, 2.1, and 1.9 (s, 15, $COCH_3$ and CH_3CO_2H), 1.4, 1.35, and 1.1 (s, 36, $C(CH_3)_3$). The sample for analysis was dried at 140 °C for 24 h at 1 mm.

Anal. Calcd for $C_{52}H_{64}O_8{\cdot}CH_3CO_2H$: C, 73.97; H, 7.76. Found: C, 73.79; H, 7.87.

A 1.0-g sample of **4** was treated with 10 mL of acetic anhydride and 0.5 g of sodium acetate. The mixture was heated under reflux for 2 h and poured into 100 mL of ice–water, and the precipitate was separated by filtration and crystallized 3 times from acetic acid to give 0.46 g (38%) of the **triacetate of *p-tert*-butylcalix[4]arene** as a white, crystalline solid: mp 278–281 °C; IR (KBr) 3550 (OH stretching), 1755 cm^{-1} (C=O stretching); ^1H NMR δ 7.2–6.7 (m, 8, ArH), 3.8–3.1 (m, 8, CH_2), 2.3–1.8 (m, 12, $COCH_3$ and CH_3CO_2H), 1.4–1.0 (m, 36, $C(CH_3)_3$). The sample for analysis was dried at 140 °C for 24 h at 1 mm.

Anal. Calcd for $C_{50}H_{62}O_7{\cdot}CH_3CO_2H$: C, 74.82; H, 7.91. Found: C, 74.44; H, 8.06.

7,13,19,25-Tetra-*tert*-butyl-27,28,29,30-tetrahydroxy-2,3-bishomo-3-oxacalix[4]arene (14). Following essentially the same procedure as that described above for the preparation of the cyclic octamer, 6.0 g (0.04 mol) of *p-tert*-butylphenol, 2.50 g (0.08 mol) of paraformaldehyde, and 0.1 mL (0.0005 mol) of 5 N KOH were suspended in 50 mL of xylene, and the mixture was heated at reflux for 4 h. The xylene-insoluble fraction consisted mainly of the cyclic octamer, as described above. The xylene-soluble fraction was placed in a round-bottomed flask, and the xylene was removed under reduced pressure to leave a brown sludge. This was heated overnight at 90 °C and 1-mm pressure to remove all volatile materials, and the residual brown solid was recrystallized several times from CH_2Cl_2/CH_3OH to yield 1.34 g (20%) of colorless, fine needles: mp ~350 °C (dec); IR (KBr) 3300 (OH stretching), 1076 cm^{-1} (aliphatic C–O stretching); ^1H NMR ($CDCl_3$) δ 9.60 (s, 2, OH on rings B and C), 8.92 (s, 2, OH on rings A and D), 7.3–6.8 (m, 8, ArH), 4.60 (3, 4, $ArCH_2OCH_2Ar$ between rings A and D), 3.85 (s, 6, $ArCH_2Ar$), 1.26 (s, 36, $C(CH_3)_3$); ^{13}C NMR ($CDCl_3$) δ 151.3 (12%, Ar), 147.5 (15% Ar), 144.9 (8%, Ar), 143.7 (9%, Ar), 142.2 (4%, Ar), 139.2 (3%, Ar), 128.2 (21%, Ar), 127.5 (17%, Ar), 126.4 (23%, Ar), 126.0 (24%, Ar), 125.3 (21%, Ar), 122.4 (15%, Ar), 34.0 (12%, $ArCH_2OCH_2Ar$), 32.8 (8%, $C(CH_3)_3$), 31.4 (21%, $ArCH_2Ar$), 31.3 (100%, $C(CH_3)_3$); osmo-

---

(48) We are indebted to Mr. Lorenz. J. Bauer for obtaining this spectrum.

metric M_r ($CHCl_3$, 37 °C), 681 (calcd[47] 679); mass spectrum (EI, 90 eV), *m/e* 678 (100), 679 (54), 680 (16) (calcd for M, M + 1, M + 2, 100%, 49.5%, 13.2%); R_f[44] 0.45.

Anal. Calcd for $C_{45}H_{58}O_5 \cdot CH_2Cl_2$: C, 72.34; H, 7.80; Cl, 9.30. Found: C, 73.06; H, 8.06; Cl, 10.17.

Treatment of the compound described above with acetyl chloride in pyridine yielded the **tetraacetate of the bishomooxa compound** as colorless crystals after three recrystallizations from 95% ethanol: mp 282–287 °C; IR (KBr) 1762 cm^{-1} (C═O stretching); osmometric M_r ($CHCl_3$, 37 °C) 868 (calcd[47] 847).

Anal. Calcd for $C_{53}H_{66}O_9 \cdot H_2O$: C, 73.60; H, 7.87. Found: C, 73.59; H, 7.70.

Comparison of the One-Step and Three-Step Methods for Preparing Calixarenes. Complete Analysis of the Product Mixture from the One-Step Method (Munch Conditions). A 10-g sample of *p-tert*--butylphenol, 5 g of paraformaldehyde, and 0.16 mL of 10 N KOH in 50 mL of xylene was refluxed for 4 h as described above. the xylene-insoluble fraction consisted of 7.25 g of an almost colorless powder, which was indicated by TLC to contain the octamer as the major component accompanied by some cyclic hexamer and tetramer. Recrystallization from $CHCl_3$ yielded 4.25 g (39%) of the cyclic octamer, mp 400–404 °C, which gave a single spot on TLC. The filtrates from this recrystallization were combined with the xylene-soluble portion of the reaction mixture, and the solvent was removed by evaporation to give 7.73 g of crude material which, on the basis of the relative intensities of the ^1H NMR resonances at ca. δ 4.4 ($ArCH_2OCH_2Ar$) and 3.8 ($ArCH_2Ar$), was estimated to contain 55% of the bishomo compound (**14**). A 130-mg portion of this material was chromatographed on a 15 mm × 35 cm column containing 13–14 g of silica gel (SILICAR CC-4 Special, Mallinckrodt Chemical Co) which was eluted with $CHCl_3$/hexane (3:4). Fractions were collected in 10-mL portions, giving the following results: fractions 3–5 contained 8.0 mg (6.15%) of cyclic octamer, fraction 6 contained 4.1 mg (3.2%) of a mixture of cyclic octamer and hexamer, fractions 7–12 contained 30.2 mg (23.3%) of a mixture of cyclic hexamer and tetramer, fraction 13 contained 2.3 mg (1.8%) of a mixture of cyclic tetramer and bismo compound, fractions 14–26 contained 57.9 mg (44.5%) of the bishomo compound, and fractions 32–33 contained 27.5 mg (21.5%) of a mixture probably containing linear oligomers and, possibly, some unreacted starting material (total recovery 130 mg (100%)). Assuming the mixed fractions to be 1:1 in composition, the total yields of products can be calculated to be 4.85 g (45%) of cyclic octamer, 1.02 g (9%) of cyclic hexamer, 0.97 g (9%) of cyclic tetramer, and 3.51 g (32%) of bishomo compound, accounting for 95% of the starting material.

Analysis of the Product Mixture from the One-Step Method (Patrick–Egan Conditions). A 10-g sample of *p-tert*-butylphenol, 6.6 g of paraformaldehyde, and 1.75 g of potassium *tert*-butoxide were added to 135 mL of tetralin, and the mixture was heated in an oil bath at 200 °C for 5 h in an apparatus equipped with a Dean and Stark trap to remove the water that was formed. From the cooled reaction mixture 6.5 g (60%) of a white solid was removed by filtration and was indicated by TLC to contain cyclic octamer, hexamer, and tetramer. After trituration with 40 mL of cold methanol to remove some sticky, soft material and any vestiges of tetralin, the residue was boiled with 100 mL of toluene and filtered hot. The hot toluene-insoluble fraction amounted to 4.3 g (40%) and was shown by TLC to contain cyclic octamer and hexamer. This was triturated with 100 mL of 1 N HCl, dissolved in 150 mL of hot $CHCl_3$ which was then dried with Na_2SO_4, and concentrated to 100 mL. On cooling, 1.81 g (17%) of the octamer separated, and this was recrystallized from $CHCl_3$ to give 1.74 g of pure cyclic octamer. The mother liquor was concentrated, and methanol was added to turbidity, affording 1.95 g (18%) of a white solid which was indicated by TLC to be ca. 1:2 mixture of cyclic octamer and hexamer. Attempts to separate this mixture by crystallization failed. From the cooled toluene solution, 1.15 g (11%) of white solid precipitated, which was indicated by TLC to be mostly cyclic tetramer mixed with some cyclic octamer. This was stirred with 25 mL of $CHCl_3$, filtered, and crystallized from toluene to give 0.75 g (7%) of pure cyclic tetramer. The tetralin-soluble fraction was evaporated to dryness under vacuum, the residue was extracted with 20 mL of hexane which was then refrigerated, and the precipitate was removed by filtration to yield 2.56 g (24%) of a white solid which was indicated by TLC to be a mixture of cyclic octamer, hexamer, and tetramer. Crystallization from toluene gave 0.315 g (3%) of pure cyclic tetramer, and evaporation of the mother liquor followed by recrystallization from $CHCl_3$ gave 0.35 g (3%) of pure octamer along with a mixture that could not be separated. From these data it can be calculated that the total product contains approximately 3.49 g (32%) of cyclic octamer, 2.15 g (20%) of cyclic hexamer, and 1.85 g (17%) of cyclic tetramer, accounting for 69% of the starting material.

Analysis of the Product Mixture from the Three-Step Method (Zinke Conditions). A 10-g sample of *p-tert*-butylphenol, 9.7 g of 37% formaldehyde solution, and 10 mL of 3 N NaOH was maintained at 50–55 °C for 45 h. The mixture was cooled and acidified with 100 mL of 1 N HCl, and the pasty mass was washed with water and heated in an oven at 110–120°C for 2 h. To the cooled solid 50 g of linseed oil was added, and the mixture was heated for 2 h at 220 °C. It was then cooled and triturated with 150 mL of ethyl acetate, and the remaining solid was thoroughly washed with 150 mL of CH_3OH to leave 5.7 g (53%) of material. This was boiled with 150 mL of toluene and filtered hot to leave 3.7 g of colorless solid, which was recrystallized from $CHCl_3$ to yield 2.82 g (26%) of cyclic octamer, mp 409–411 °C. Concentration of the toluene produced 1.25 g of a white solid which was shown by TLC to be a mixture of cyclic octamer and tetramer. Recrystallization from toluene yielded 0.65 g (6%) of cyclic tetramer, mp 344–346 °C. No attempt was made to investigate the composition of the linseed oil-soluble fraction.

Analysis of the Product from the Three-Step Method (Cornforth Conditions). As described above, a 10-g sample of *p-tert*-butylphenol gave 5.47 g of a Dowtherm-insoluble, ethyl acetate-insoluble fraction which could be separated into 1.48 g (13.7%) of the cyclic octamer and 2.75 g (25%) of the cyclic tetramer. Removal of the Dowtherm under vacuum left a black paste, which was extracted with 15 mL of hexane. The precipitate that formed upon refrigerating the hexane solution was removed by filtration and consisted of 3.15 g (29%) of a white solid which was indicated by TLC to contain cyclic octamer, hexamer, and tetramer. This was treated with 50 mL of toluene, heated to reflux, and filtered hot to yield a product which was indicated by TLC to contain two compounds. Recrystallization from $CHCl_3$ afforded 1.17 g (11%) of the cyclic octamer. From the cooled toluene solution 0.6 g of material precipitated which was a mixture that could not be separated by recrystallization.

Studies of the Reaction Variables in the One-Step and Three-Step Methods. Effect of the Identity of the Base.[49] The "standard" one-step method (Munch conditions) was used as described above, in which 6 g of *p-tert*-butylphenol, 2.5 g of paraformaldehyde, and 0.1 mL of 5 N base in 50 mL of xylene was refluxed for 4 h and worked up to yield xylene-insoluble and xylene-soluble products which were assayed by TLC. The products obtained with NaOH, KOH, or CsOH appeared to be very similar to one another in composition, indicating that the cations in these cases have little effect on the composition of the product mixture. Lithium hydroxide, on the other hand, was much less effective and yielded only 0.34 g (5%) of xylene-insoluble material and 5.63 g (87%) of xylene-soluble material which was shown by TLC to consist mainly of starting compound accompanied by small amounts of cyclic octamer, hexamer, tetramer, and bishomo compound. Recrystallization of the xylene-insoluble material from CH_2Cl_2/CH_3OH yielded 0.22 g (3%) of bishomo compound. Similarly $Mg(OH)_2$ (added as 0.0292 g of solid along with 0.1 mL of water) and $Ca(OH)_2$ (added as 0.0536 g of solid along with 0.1 mL of water) were ineffective, giving only recovered starting material in 95% and 96% yields, respectively. In contrast, $Ba(OH)_2$ (added as 0.0968 g of solid along with 0.1 mL of water) induced a reaction, but the product did not contain cyclic oligomers. No precipitate formed during the course of the reaction, and evaporation of the xylene gave material which was indicated by TLC to contain some starting material but a greater amount of a slower-moving component which is postulated to be a mixture of linear oligomers. The only nonhydroxide base investigated was K_2CO_3, which gave a 73% yield of xylene-insoluble material closely resembling that produced with NaOH, KOH, or CsOH.

Effect of Boiling Point of Solvent in the One-Step Method (i.e., Tetralin Instead of Xylene). The "standard" one-step method (Munch conditions) was used as described above, in which 10 g of *p-tert*-butylphenol, 5 g of paraformaldehyde, and 0.16 mL of 10 N KOH in 50 mL of tetralin (bp 207 °C) was refluxed for 4 h. The cooled mixture was filtered, and the white solid that was collected was washed with 10 mL of ethyl acetate and then added to 100 mL of toluene and refluxed for 30 min. Filtration of the hot solution left 4.15 g of colorless material that was twice recrystallized from $CHCl_3$ to yield 3.60 g (33%) of cyclic octamer, mp 409–411 °C. The toluene solution was concentrated to 50 mL and cooled, whereupon 1.25 g of a white solid separated. This was collected by filtration and shown by TLC to be a mixture of octamer and tetramer. It was triturated with hot $CHCl_3$, and the 1.06 g of residue was crystallized from toluene to give 1.0 g (9%) of cyclic tetramer, mp 344–346 °C. The filtrates from these recrystallizations were combined with the tetralin-soluble fraction, and the solvent was removed under reduced pressure to give 8.6 g of a colorless solid. Chromatographic separation of a 100-mg sample of this material on a silica column, as described above, indicated it to contain 8% cyclic octamer, 10% cyclic hexamer,

---

(49) We are indebted to Mr. Elliot Kaplan for carrying out these experiments.

16% cyclic tetramer, and 2% bishomo compound; the remaining material eluted much more slowly than the cyclic oligomers and presumably is polymeric in nature. From these data it can be calculated that the total yields are 40% cyclic octamer, 8% cyclic hexamer, 22% cyclic tetramer, and 1.5% bishomo compound.

Effect of Boiling Point of Solvent in the Three-Step Method (i.e., Xylene Instead of Dowtherm). The Cornforth modification of the three-step method was used as described above, in which a mixture of 10 g of *p-tert*-butylphenol, 9.7 g of 37% formaldehyde solution, and 10 mL of 3 N NaOH was heated for 45 h at 50–55 °C, neutralized with 100 mL of 1 N HCl, and heated for 2 h at 110–120 °C. The product resulting from this treatment was mixed with 50 mL of xylene and refluxed 4 h. From the cooled solution a white solid was removed by filtration, washed with 15 mL of methanol, and triturated for 30 min with boiling toluene to leave 4.7 g of material which, when crystallized from $CHCl_3$, afforded 3.35 g of cyclic octamer. From the toluene-soluble fraction 0.55 g of cyclic tetramer was obtained after recrystallization from $CHCl_3$. The filtrates from these recrystallizations were added to the xylene-soluble fraction, the solvent was removed by evaporation to give 7.09 g of solid material, and chromatography of a 100-mg aliquot indicated the composition to be 13% cyclic octamer, 10% cyclic hexamer, and 10% cyclic tetramer. From these data it can be calculated that the total yields are 39.5% cyclic octamer, 7% cyclic hexamer, and 12% cyclic tetramer.

Effect of the Rate of Heating in the One-Step Method. In the "standard" one-step method (Munch conditions), the mixture of *p-tert*-butylphenol, paraformaldehyde, base, and xylene is placed in an oil bath at 160–165 °C and rapidly taken to reflux. In the comparison experiment, the mixture was slowly taken from room temperature to reflux over a period of 2 h and heating then continued for 4 h at reflux temperature. The xylene-insoluble material from this procedure amounted to 9.5 g (88%) and was indicated by TLC to contain cyclic octamer, hexamer, tetramer, and only a small amount of bishomo compound. Two recrystallizations from $CHCl_3$ afforded 5.4 g (49%) of cyclic octamer, mp 408–410 °C. The filtrates from these recrystallizations were added to the xylene-soluble fraction, and the solution was evaporated to dryness. The residue was boiled with 200 mL of $CHCl_3$ and filtered hot, and the insoluble residue was then recrystallized from toluene to give 0.525 g (5%) of cyclic tetramer, mp 343–345 °C. The filtrates were again combined, and the solvent was removed by evaporation to leave 4.5 g of residue, a 100-mg aliquot of which was chromatographed on silica gel and shown to contain 19% cyclic octamer, 16% cyclic hexamer, 12.5% cyclic tetramer, and 18% bishomo compound; the remainder was polymeric material. On the basis of these data it can be calculated that the total yields are 58% cyclic octamer, 7% cyclic hexamer, 10% cyclic tetramer, and 7.5% bishomo compound.

Multistep Synthesis of *tert*-Butylcalix[4]arene (4). 2-(3-Bromo-5-*tert*-butylsalicyl)-4-*tert*-butylphenol (7). 2-Bromo-4-*tert*-butylphenol (**5**), prepared in 91% yield by treatment of *p-tert*-butylphenol with bromine in $CHCl_3$ and CCl_4, was treated with aqueous NaOH and 37% formaldehyde solution at 50 °C for 20 h to yield a crude product containing 2-bromo-4-*tert*-butyl-6-(hydroxymethyl)phenol (**6**), which was used in the next step without purification. A mixture of 71.3 g of **6** and 710 g of *p-tert*-butylphenol was heated with 2 mL of concentrated HCl at 110 °C for 20 h. After removal of the excess *p-tert*-butylphenol by steam distillation, the residue was dried and purified by recrystallization from $CHCl_3$/hexane to give 68.9 g (61%) of a colorless powder: mp 142–143 °C; IR (KBr) 3390 and 3210 (OH stretchings), 880 (1,2,3,5-tetrasubstituted benzene), 800 cm^{-1} (1,2,4-trisubstituted benzene); ^1H NMR (CCl_4) δ 7.20–6.60 (m, 5, ArH), 7.20 (br, 2, OH), 3.87 (s, 2, CH_2), 1.25 (s, 18, $C(CH_3)_3$); TLC ($CHCl_3$/hexane (9:1)), R_f 0.30.

Anal. Calcd for $C_{21}H_{27}BrO_2\cdot{}^1/_6\,C_6H_{14}$: C, 65.13; H, 7.22. Found: C, 65.61; H, 7.15.

3-(3-Bromo-5-*tert*-butylsalicyl)-5-*tert*-butyl-2-hydroxybenzyl Alcohol (8). A solution of 2.01 g of **7** in 1.54 mL of 20% aqueous NaOH was mixed with 3 mL of 37% formaldehyde in an ice bath. After the system was flushed with N_2 several times, the reaction mixture was stirred at 50 °C for 16 h and then diluted with cold water and acidified by passing CO_2 through it. The precipitate was collected by filtration, washed with water several times, dried in vacuum overnight, and recrystallized from CCl_4/petroleum ether (bp 35–60 °C) to give 1.66 g (77%) of colorless powder: mp 112 °C; IR (KBr) 3460–3200 (OH stretching), 880 cm^{-1} (1,2,3,5-tetrasubstituted benzene); ^1H NMR (CCl_4) δ 7.25–6.87 (m, 4, ArH), 5.75 (br s, 3, OH), 4.70 (s, 2, CH_2), 1.22 ppm (two s, 18, $C(CH_3)_3$); TLC ($CHCl_3$/ethyl ether (9:1)), R_f 0.53.

Anal. Calcd for $C_{22}H_{29}BrO_3\cdot{}^1/_6C_6H_{14}$: C, 63.44; H, 7.19. Found: C, 63.42; H, 7.23.

2-[3-(3-Bromo-5-*tert*-butylsalicyl)-5-*tert*-butylsalicyl]-4-*tert*-butylphenol (9). A mixture of 16.52 g of **8** and 203 g of *p-tert*-butylphenol was heated in an oil bath until the mixture started to melt. At this point 5 mL of concentrated HCl was added dropwise over a period of 30 min. Refluxing was continued for 7 h, the excess *p-tert*-butylphenol was removed by steam distillation, and the crude product was dried and recrystallized from toluene/petroleum ether (bp 35–60 °C) to give 19.83 g (91%) of a colorless powder: mp 208–209 °C; IR (KBr) 3230 (OH stretching), 880 (1,2,3,5-tetrasubstituted benzene), 800 cm^{-1} (1,2,4-trisubstituted benzene); ^1H NMR (acetone–d_6) δ 7.25–6.70 (m, 7, ArH), 7.00 (br s, 3, OH), 3.93 (d, 4, CH_2), 1.20 (s, 27, $C(CH_3)_3$); TLC ($CHCl_3$/ethyl ether (9:1)), R_f 0.79.

Anal. Calcd for $C_{32}H_{41}BrO_3$: C, 69.43; H, 7.46. Found: C, 69.67; H, 7.39.

3-[3-(3-Bromo-5-*tert*-butylsalicyl)-5-*tert*-butylsalicyl]-5-*tert*-butyl-2-hydroxybenzyl Alcohol (10). A solution of 6.50 g of **9** in 10 mL of 10% aqueous NaOH was mixed with 10 mL of 37% formaldehyde in an ice bath. The reaction mixture was flushed several times with N_2, stirred for 16 h at 50 °C, diluted with cold water, and acidified by passing CO_2 into it. The crude product was separated by filtration, washed several times with water, dried in a vacuum oven, and recrystallized from toluene/petroleum ether (bp 35–60 °C) to give 5.51 g (80%) of a colorless powder: mp 177–178 °C; IR (KBr) 3260 (OH stretching), 870 cm^{-1} (1,2,3,5-tetrasubstituted benzene); ^1H NMR (acetone-d_6) δ 7.24–6.95 (m, 6, ArH), 7.25 (s, 4, OH), 4.81 (s, 2, CH_2OH), 3.95 (two s, 4, CH_2), 1.21 (s, 27, $C(CH_3)_3$); TLC ($CHCl_3$/ethyl ether (9:1)), R_f 0.54.

Anal. Calcd for $C_{33}H_{43}BrO_4$: C, 67.92; H, 7.38. Found: C, 67.80; H, 7.46.

2-[3-[3-(3-Bromo-5-*tert*-butylsalicyl)-5-*tert*-butylsalicyl]-5-*tert*-butylsalicyl]-4-*tert*-butylphenol (11). A mixture of 5.83 g of **10** and 65 g of *p-tert*-butylphenol was heated in an oil bath at 110–120 °C until it started to melt and was then treated in two portions with 8 mL of concentrated HCl. After refluxing the mixture for 6 h, the excess *p-tert*-butylphenol was removed by steam distillation, and the residue was crystallized from toluene/petroleum ether (bp 35–60 °C) to give 5.64 g (79%) of a colorless powder: mp 155 °C; IR (KBr) 3230 (OH stretching), 880 (1,2,3,5-tetrasubstituted benzene), 800 cm^{-1} (1,2,4-trisubstituted benzene); ^1H NMR (acetone-d_6) δ 7.35–6.87 (m, 9, ArH), 3.92 (two s, 6, CH_2), 3.05 (br s, 4, OH), 1.23 ppm (s, 36, $C(CH_3)_3$); TLC ($CHCl_3$/hexane/ethyl ether (3:3:1)), R_f 0.79.

Anal. Calcd for $C_{43}H_{55}BrO_4$: C, 72.15; H, 7.74. Found: C, 71.95; H, 7.76.

3-[3-[3-(3-Bromo-5-*tert*-butylsalicyl)-5-*tert*-butylsalicyl]-5-*tert*-butylsalicyl]-5-*tert*-butyl-2-hydroxybenzyl Alcohol (12). A suspension of 2.00 g of **11** in 20 mL of methanol cooled in an ice bath was mixed with 1.01 mL of 20% aqueous NaOH and 3 mL of 37% aqueous formaldehyde. After flushing the system several times with N_2, the reaction mixture was stirred at 50 °C for 58 h. It was then added to ice-cold water and acidified by passing CO_2 through the suspension, and the precipitate was collected, dried, and recrystallized from CH_3OH containing a few drops of hexane to give 1.40 g (67%) of a colorless powder: mp 165–167 °C (dec); IR (KBr) 3270 (OH stretching), 880 cm^{-1} (1,2,3,5-tetrasubstituted benzene); ^1H NMR (acetone-d_6) δ 7.24–7.08 (m, 8, ArH), 4.89 (br s, 5, OH), 4.71 (s, 2, CH_2OH), 3.89 (two s, 6, CH_2), 1.21 (two s, 36, $C(CH_3)_3$); TLC ($CHCl_3$/hexane/ethyl ether (5:5:1)), R_f 0.41.

Anal. Calcd for $C_{44}H_{57}BrO_5\cdot 2H_2O$: C, 67.60; H, 7.80. Found: C, 67.31; H, 7.53.

3-[3-[3-(5-*tert*-Butylsalicyl)-5-*tert*-butylsalicyl]-5-*tert*-butylsalicyl]-5-*tert*-butyl-2-hydroxybenzyl Alcohol (13). A solution of 2.00 g of **12** in 30 mL of methanol and 1.2 mL of 20% aqueous KOH was flushed with H_2 several times and then treated with 0.7 g of Raney nickel (W-2) catalyst.[50] The reaction mixture was stirred at room temperature until the calculated amount of H_2 had been absorbed (~4 h), and the catalyst was then removed by filtration and the filtrate neutralized by passing CO_2 through it. Removal of the precipitate by filtration and recrystallization from ethyl ether/petroleum ether (bp 35–60 °C) gave 1.41 g (78.5%) of a colorless powder: mp 190–192 °C; IR (KBr) 3160 (br, OH stretching), 880 (1,2,3,5-tetrasubstituted benzene), 790 cm^{-1} (1,2,4-trisubstituted benzene); ^1H NMR (acetone-d_6) δ 7.45–6.80 (m, 9, ArH), 4.78 (s, 2, CH_2OH), 3.89 (s, 6, CH_2), 3.07 (br s, 5, OH), 1.21 (s, 36, $C(CH_3)_3$); TLC ($CHCl_3$/hexane/ethyl ether (5:5:3)), R_f 0.48.

Anal. Calcd for $C_{44}H_{58}O_5$: C, 79.24; H, 8.77. Found: C, 79.42; H, 8.88.

5,11,17,23-Tetra-*tert*-butyl-25,26,27,28,-tetrahydroxycalix[4]arene (4). Following the Kämmerer modification[25] of the procedure of Hayes and Hunter,[3] a solution of 0.669 g of **13** in 125 mL of acetic acid was added dropwise at the rate of 5 drops/min to a mixture of 1.5 L of acetic acid and 5 mL of concentrated HCl in a system flushed with N_2. Every 5 h an additional 5 mL of HCl was added and the reaction mixture was

---

(50) Mozingo, R. "Organic Synthesis", Collect. Vol. 3; Wiley: New York, 1955; p 181.

refluxed for 25 h. The acetic acid was then removed by distillation at reduced pressure, and the precipitate that formed was separated by filtration and dissolved in 70 mL of boiling CHCl$_3$. The CHCl$_3$ was concentrated to 10 mL, and the precipitate that deposited from the ice-cooled solution was separated by filtration and recrystallized twice from CHCl$_3$ to give 0.552 g (85%) of white plates, mp 341–343 °C, the ^{1}H NMR, ^{13}C NMR, and mass spectra of which were identical with those of the sample prepared from *p-tert*-butylphenol and paraformaldehyde in the one-step procedure, as described above. A mixture of the materials from these two sources showed no depression in melting point.

Miscellaneous Experiments. Base-Induced Reaction of 2,6-Bis(hydroxymethyl)-4-*tert*-butylphenol (16) via Munch Conditions. A 2.5-g sample of 2,6-bis(hydroxymethyl)-4-*tert*-butylphenol [mp 64–65 °C after several recrystallizations; shows single spot on TLC (lit.[51] mp 74–75 °C)] and 0.04 mL of 10 N KOH were added to 12.5 mL of xylene, and the mixture was heated at reflux for 4 h in an inert atmosphere. From the cooled reaction mixture, 1.4 g (73%) of a solid separated which TLC analysis indicated to contain cyclic octamer, hexamer, tetramer, and bishomo compound, with the cyclic octamer being the major constituent. Crystallization from CHCl$_3$ yielded 0.75 g (39%) of pure cyclic octamer, mp 409–411 °C. The filtrate from the crystallization was combined with the xylene-soluble fraction, and the solvent was removed by evaporation to leave 1.1 g (57%) of material which was indicated by ^{1}H NMR inspection of the resonances at δ 4.4 and 3.8 to contain ~60% of the bishomo compound along with the cyclic octamer, hexamer, and tetramer. Trituration and recrystallization from various solvents yielded an additional 0.75 g (4%) of cyclic octamer, 0.035 g (2%) of cyclic tetramer, 0.145 g (7.5%) of bishomo compound, and 0.110 g (6%) of a mixture along with 0.6 g (31%) of a solid residue.

Base-Induced Reaction of 2,6-Bis(hydroxymethyl)-4-*tert*-butylphenol (16) via Cornforth Conditions. A 5.0-g sample of 2,6-bis(hydroxymethyl)-4-*tert*-butylphenol[51] was mixed with 0.1 mL of 10 N KOH and heated at 110–120 °C. The mixture quickly melted and after 1 h began to resolidify and foam. A TLC analysis at this stage indicated that a small amount of cyclization to cyclic octamer, hexamer, tetramer, and bishomo compound had already occured, and a ^{1}H NMR analysis showed that the number of CH$_2$OCH$_2$ linkages was equal to the number of ArCH$_2$Ar linkages. The solid material was dissolved in 35 g of Dowtherm and heated to 200–220 °C for 2 h in an atmosphere of N$_2$. The cooled residue was then treated with 80 mL of ethyl acetate, and the resulting precipitate was separated by filtration and washed with 30 mL of methanol to yield 1 g of a solid which was indicated by TLC to be a mixture of hexamer and tetramer. Trituration with hot toluene left 0.225 g (6%) of cyclic hexamer undissolved, and upon cooling the toluene 0.56 g (14.5%) of cyclic tetramer, mp 340–342 °C, was deposited. From the Dowtherm-soluble fraction there was obtained, by a series of triturations and crystallizations, an additional 0.5 g (13%) of cyclic hexamer, mp 372–374 °C, and 0.21 g (5.5%) of cyclic tetramer.

Action of Base on *tert*-Butylcalix[4]arene (4). A 100-mg sample of cyclic tetramer (4) and 0.04 mL of 10 N KOH were added to 4 mL of xylene, and the mixture was heated at reflux for 4 h. The reaction mixture was assayed by TLC and shown to contain only trace amounts of substances other than the starting material. A CHCl$_3$ solution of the product was washed with 5 mL of 1 N HCl, and the CHCl$_3$ was evaporated and the residue recrystallized from toluene to give 70 mg (70%) of colorless solid, mp 342–344 °C, which showed no depression in melting point when admixed with starting material.

Action of Base on *tert*-Butylcalix[6]arene (3). A 100-mg sample of cyclic hexamer (3) was treated in the manner described above for the cyclic tetramer and gave similar results. The recoverd material, after recrystallization from CHCl$_3$/methanol, consisted of 78 mg (78%) of colorless solid, mp 373–375 °C, identical with starting material.

Thermolysis of *tert*-Butylbishomooxacalix[4]arene (14). A 110-mg sample of bishomo compound (14) was added to 1 g of Dowtherm, and the mixture was heated at 210–220 °C for 2 h in an atmosphere of N$_2$. To the cooled mixture 5 mL of ethyl acetate was added, causing the precipitation of a small amount of material which was indicated by TLC analysis to contain trace amounts of cyclic octamer, hexamer, and tetramer and large amounts of a substance which remained at the origin. TLC analysis of the ethyl acetate-soluble fraction indicated it to contain cyclic octamer, hexamer, tetramer, unreacted starting material, linear oligomers (probably), and a significant fraction which remained at the origin. A comparable experiment in which xylene instead of Dowtherm was used yielded unreacted starting material as the major product. However, when xylene along with a small amount of KOH was used (i.e., Munch conditions), a small amount of conversion of **14** to cyclic octamer, hexamer, and tetramer was noted.

Acknowledgment. We are indebted to the National Science Foundation for early support of this work via Grant GP-41420 and to the National Institutes of Health for continuing support via Grant GM-23534. We are also indebted to Drs. T. C. Kung and M-L. Hsu for their splendid research efforts during the embryonic phases of the project, out of which the present work emerged.

---

(51) Hanus, F.; Fuchs, E. *J. Prakt. Chem.* **1939**, *153*, 327.

Gas-Phase Acid-Induced Nucleophilic Displacement Reactions. 4. A Stereochemical Probe for the Existence and the Relative Stability of Cyclic Halonium Ions in the Gas Phase[1]

Giancarlo Angelini and Maurizio Speranza*

Contribution from the Laboratorio di Chimica Nucleare del C.N.R., Area della Ricerca di Roma, 00016 Monterotondo Stazione, C.P. 10, Rome, Italy. *Received November 14, 1980*

Abstract: A comprehensive investigation on the existence and the relative stability of gaseous three-membered cyclic butene halonium ions was carried out by establishing the stereochemistry of the acid-induced displacement by nucleophiles such as H$_2$O, H$_2$S, etc., on a number of positively charged intermediates. The latter were obtained in the gas phase from the reaction of radiolytic formed Brønsted (CH$_5^+$ and C$_2$H$_5^+$) and Lewis (C$_2$H$_5^+$ and CH$_3$FCH$_3^+$) acids with 2,3-dihalobutanes. The stereoisomeric distribution of the neutral 3-halobutan-2-ols (or thiols) formed in these processes strongly implies the intermediacy of cyclic 2,3-butene halonium ions, whose stability in the gas phase depends on the nature of the halogen involved, increasing in passing from Cl to Br. No evidence for the occurrence of stable cyclic 2,3-butene fluoronium ions was obtained by the same procedure. Other factors, namely the strength of the radiolytic gaseous acid "catalysts" and the configuration of the starting dihalobutane, were found to play a role in determining the stereochemistry of the substitution processes investigated. A close correspondence does exist between the present results and those from strictly related mass spectrometric and condensed phase investigation.

Since their first recognition as elusive intermediates in the trans addition of halogens to alkenes,[2] three-membered cyclic alkenehalonium ions [I] excited considerable interest,[3] especially in relation to the study of adjacent group participation in solvolytic

0002-7863/81/1503-3792$01.25/0