common pattern, however (Figure 4). For comparison, ab initio calculations have been made for a simple model system, the BH_4^- anion with and without the electrostatic perturbation of a Li^+ cation.[61] The calculations were limited to nuclear configurations with C_{3v} symmetry (15, 16). The deviations from T_d symmetry are then conveniently described[62] in terms of symmetry-adapted linear combinations of B–H bond lengths (r_i) and HBH bond angles (θ_{ij}):

$$S_1(A_1) = (r_1 + 3r_2 - 4r_0)/2 = t$$

$$S_{3a}(T_2) = \sqrt{3}(r_1 - r_2)/\sqrt{2} = u$$

$$S_{4a}(T_2) = \sqrt{3}(\theta_{12} - \theta_{23})/\sqrt{2} = v \qquad (3)$$

The deformation energy of the isolated BH_4^- anion was calculated up to cubic terms as a function of the symmetry coordinates t, u, and v, which permits various constraint paths to be constructed (Figure 9). The effect of the electrostatic perturbation was calculated by minimizing the energy with respect to r_1, r_2, and θ_{12}, with the Li^+ cation at fixed distances on either side of the anion; this gives the response path II, which lies between two constraint paths, III (obtained by constraining the u coordinate), and IV (by constraining the v coordinate). Of these three paths, the response path II is much the most similar to the experimental distribution of sample points for tetrahedral anions in different crystalline environments (Figure 4).

In summary, scattergrams of experimental structural data (Figures 1, 3, 4, and 5) may be interpreted as minimum-energy paths or as response paths. In the first interpretation, the correlations express a property characteristic solely of the structural fragment being investigated; in the second they express also effects of the environments that are imposed on the structural

(61) O. Eisenstein and J. D. Dunitz, *Isr. J. Chem.*, **19**, 292 (1980).
(62) P. Murray-Rust, H. B. Bürgi, and J. D. Dunitz, *Acta Crystallogr., Sect. B*, **B34**, 1787 (1978).
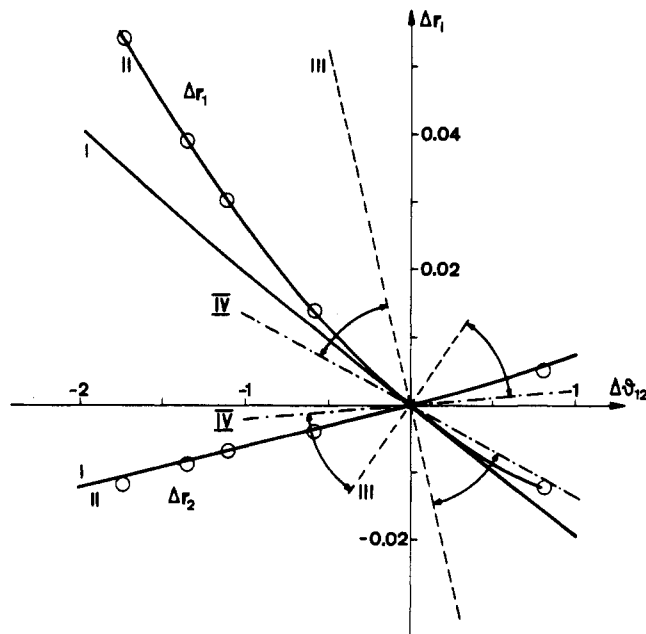

Figure 9. Dependence of Δr_1, Δr_2 (Å), and $\Delta \theta_{12}$ (deg) for BH_4^- anion as expressed by various paths: I, regression curve from Figure 4;[28] II, calculated response path for electrostatic perturbation by Li^+ cation (15, 16); III, IV calculated constraint paths with u and v (eq 3), respectively, as constraint coordinates.

fragment. The first interpretation will be more correct for narrow, steep-sided energy valleys, the second for wide, shallow valleys and relatively strong perturbations due to the environments. Any decision between these alternative interpretations cannot be made from crystallographic data alone, but will have to rely on additional information from a variety of possible sources: ab initio or molecular mechanics calculations, force constants from vibrational analysis, rotation barriers from temperature-dependent NMR studies, etc.

Calixarenes

C. David Gutsche

Department of Chemistry, Washington University, St. Louis, Missouri 63130

The study of enzymes has occupied a central place in the physical and biological sciences for many years,

C. David Gutsche was born in La Grange, IL, in 1921. He received the B.A. from Oberlin College and the Ph.D. from the University of Wisconsin, working under the direction of W. S. Johnson. Since 1947 he has been a member of the faculty of Washington University, St. Louis, where be holds the rank of Professor. From 1970 to 1976 he served as chairman of the Department of Chemistry. His long-term research interests in diazoalkane-carbonyl reactions, ring-enlargement processes, and carbene chemistry changed in the 1970s to the areas of polyfunctional catalysts and enzyme mimics, one facet of which is portrayed in this Account.

and the catalytic prowess of these naturally occurring substances has long fascinated chemists. Only within the last two decades, however, have serious attempts been made to mimic the in vivo action of enzymes by means of simple in vitro chemical systems. Foremost among the compounds investigated for this purpose are the cyclodextrins, whose torus shape endows them with the ability to form host-guest complexes and, in certain cases, to act as powerful catalysts.[1] These compounds

Figure 1. Calix crater (right) and a calixarene (left).

have the disadvantage, however, of being available in only a limited array of sizes through the action of *bacillus macerans* on starch. Of great interest to the chemist, therefore, are totally synthetic molecules possessing an architecture similar to that of the cyclodextrins but amenable to greater variation and control. This Account deals with one such class of compounds, which has historical roots in the 19th century, but whose potential as enzyme mimics has only recently been suggested.

In 1872 Adolph von Baeyer heated aqueous formaldehyde with phenol and observed a reaction that yielded a hard, resinous, noncrystalline product.[2] However, the chemistry of the day was not sufficiently advanced to allow characterization of such materials, and the structure remained unprobed. Three decades later during the years 1905–1909, Leo Baekeland devised a process for using the phenol–formaldehyde reaction to make a tough, resilient resin (called a phenoplast), which he marketed under the name "Bakelite"[3] with tremendous commercial success. As a result, much attention was directed both in industrial and academic research laboratories to a study of the chemistry of the phenol–formaldehyde process, and a significant literature arose dealing with phenoplasts. Among these investigations were ones carried out in the 1940s and 1950s by Alois Zinke's group at the University of Graz in Austria[4-7] in connection with the "curing" phase of the process. In probing this phenomenon they treated various *p*-alkylphenols with aqueous formaldehyde and sodium hydroxide, first at 50–55 °C for 45 h, then at 110–120 °C for 2 h and, finally, in a suspension of linseed oil at 200 °C for several hours. The products of this treatment are very high melting, insoluble materials to which Zinke assigned cyclic tetrameric structures, calling them "mehrkernmethylenephenolverbindungen". Through a sequence of events recounted in ref 8 these compounds came to our attention in the 1970s as interesting prospects for enzyme
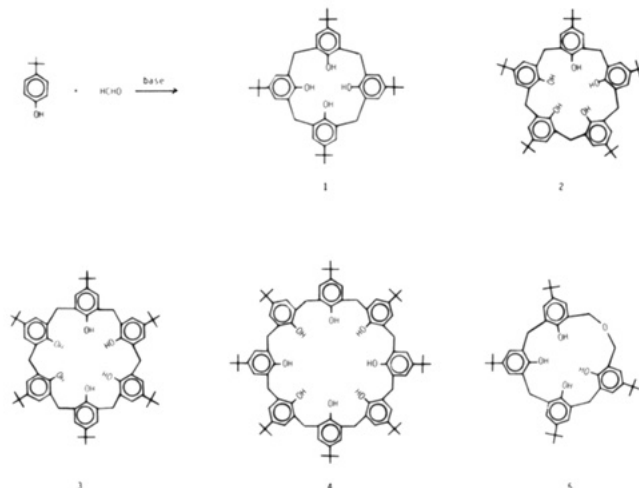
(1) Bender, M. L.; Komiyama, M. "Cyclodextrin Chemistry"; Springer-Verlag: Berlin, 1978. Saenger, W. *Angew. Chem., Int. Ed. Eng.* **1980**, *19*, 344. Breslow, R. *Acc. Chem. Res.* **1980**, *13*, 170. Tabushi, I. *Ibid.* **1982**, *15*, 66.

(2) von Baeyer, A. *Ber.* **1872**, *5*, 25, 280, 1094.

(3) Numerous accounts of the history of phenol–formaldehyde resins are available, including Baekeland, L. H. *Indust. Eng. Chem.* **1913**, *5*, 506. Carswell, T. S. "Phenoplasts"; Interscience: New York, 1947. Gillis, J.; Oesper, R. E. *J. Chem. Ed.*, **1964**, *41*, 224.

(4) Zinke, A.; Ziegler, E. *Ber.*, **1944**, *77B*, 264.

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

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

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

(8) Gutsche, C. D.; Dhawan, B.; No, K. H.; Muthukrishnan, R. *J. Am. Chem. Soc.* **1981**, *103*, 3782.

Figure 2. Products from the base-catalyzed condensation of *p-tert*-butylphenol and formaldehyde.

mimic building. Perceiving a similarity between the shapes of these cyclic tetramers and a type of Greek vase known as calix crater (Figure 1), we suggested[9] that they be called "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 in the aromatic rings by appropriate prefixes. Thus, a cyclic tetramer derived from *p-tert*-butylphenolic and methylene units is most simply designated as a *p-tert*-butylcalix[4]arene.[10]

Zinke[6] and all subsequent workers with the calixarenes have noted their propensity to form molecular complexes with smaller molecules, a direct consequence of the presence of cavities in the calixarenes. The enzymes are known to possess cavitated active sites, where complex formation with substrate occurs as the first step in the catalytic process. Thus, the calixarenes are particularly attractive compounds for attempting to construct in vitro systems that mimic the in vivo catalytic activity of the enzymes.

Isolation and Characterization of the Calixarenes

Zinke reported that *p*-methyl-, *p-tert*-butyl-, *p*-amyl-, *p*-octyl-, *p*-cyclohexyl-, *p*-benzyl-, and *p*-phenylphenol condense with formaldehyde to yield high-melting materials, all of which were assumed to be cyclic tetramers on the basis of a molecular weight determination on the acetate of the product from *p*-octylphenol.[6] The tacit assumption that a single product is formed in every instance was later negated by Sir John Cornforth and co-workers[11] at Oxford University who isolated higher and lower melting compounds from the condensations of formaldehyde with *p-tert*-butylphenol and with *p*-octylphenol. These workers assumed that

(9) 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. Gutsche, C. D.; Muthukrishnan, R. *J. Org. Chem.* **1978**, *43*, 4905.

(10) Adopting the numbering scheme recommended by Chemical Abstracts, this compound is more systematically named as 5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetrahydroxycalix[4]arene. It can also be named as a cyclophane (the calixarenes are classed as [1$_n$]metacyclophanes) or by systematic *Chemical Abstracts* nomenclature, viz. 5,11,17,23-tetra-*tert*-butylpentacyclo[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-tetrol.
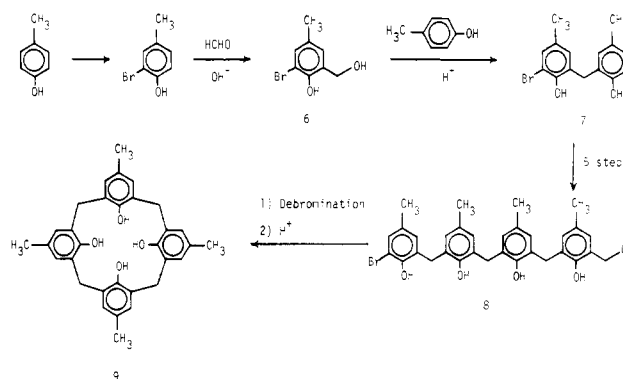
(11) Cornforth, J. W.; Hart, P. D'A.; Nicholls, G. A.; Rees, R. J. W.; Stock, J. A. *Br. J. Pharmacol.* **1955**, *10*, 73.

the pairs of compounds isolated in each case were conformational isomers of the cyclic tetramers. However, this interpretation was subsequently invalidated by Hermann Kämmerer and co-workers at the University of Mainz, Germany[12,13] and by John Munch of the Petrolite Corporation of St. Louis[14] whose dynamic ^{1}H NMR studies showed that rapid conformational interconversion occurs at room temperature.

The recent work by our group[8] has revealed that mixtures comprising cyclic oligomers of *various ring sizes* are generally obtained. In the most thoroughly studied example,[8] we have shown that the condensation of *p-tert*-butylphenol and formaldehyde yields cyclic tetramer **1**, cyclic hexamer **3**, cyclic octamer **4**, and the dihomooxa compound **5** (Figure 2). The presence of small amounts of cyclic pentamer **2**[15a] and cyclic heptamer[15b] has also been recently demonstrated. All of these structures are in complete agreement with chemical, spectral, and analytical data; compounds **1–4** have been definitively established by single crystal X-ray crystallography by the Andreetti, Ungaro, and Pochini group at the University of Parma, Italy.[16–18] Figure 3 shows "top" and "bottom" views of the space-filling molecular models (CPK models) of the calixarenes in their "expanded" conformations, the *p*-phenyl compounds being chosen because their depth more clearly illustrates the relative cavity sizes. Also shown for comparison is β-cyclodextrin.

In the course of our work we discovered that the yield of several of the products from the *p-tert*-butylphenol/formaldehyde condensation can be maximized by appropriate choice of reaction conditions. A modification of the Zinke procedure produces the cyclic tetramer in 30–35% yield; a procedure developed by the Petrolite group[19] produces the cyclic octamer in ca. 65% yield; a modification of the Petrolite procedure produces the cyclic hexamer in ca. 75% yield. Thus, the even-numbered calixarenes in the *p-tert*-butyl series are easily available in large quantity. It appears that this may be one of just a few special cases, however. The closely related *p-tert*-amylphenol and *p*-(1,1,3,3-tetramethylbutyl)phenol (i.e., *p*-octylphenol) behave in a comparable fashion, but all other *p*-alkylphenols that we have investigated fail to yield any cyclic tetramer and yield the cyclic hexamer and octamer only in difficultly purifiable form.[20] *p*-Heteroatom-substituted phenols behave even more capriciously and yield products that have not yet been successfully purified and characterized.[21]

(12) Kämmerer, H.; Happel, G.; Caesar, F. *Makromol. Chem.* **1972**, *162*, 179.

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

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

(15) (a) Ninagawa, A.; Matsuda, H. *Makromol. Chem., Rapid Commun.* **1982**, *3*, 65. (b) Nakamoto, Y.; Ishida, S. *Ibid.* **1982**, *3*, 705.

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

(17) Andreetti, G. D.; Ungaro, R.; Pochini, A. *J. Chem. Soc., Chem. Commun.* **1981**, 533.

(18) Coruzzi, M.; Andreetti, G. D.; Bocchi, V.; Pochini, A.; Ungaro, R. *J. Chem. Soc., Perkin Trans. 2* **1982**, 1133.

(19) Buriks, R. S.; Fauke, A. R.; Munch, J. H. U.S. Patent 4 259 464, 1981.

(20) The report by Patrick, T. B.; Egan, P. A. *J. Org. Chem.* **1977**, *42*, 382 that cyclic tetramers are obtained from *p*-methyl-, *p-tert*-butyl-, *p*-phenyl-, *p*-methoxy-, and *p*-carbomethoxyphenol under conditions closely resembling those of the Petrolite process must be discounted for lack of adequate experimental foundation.
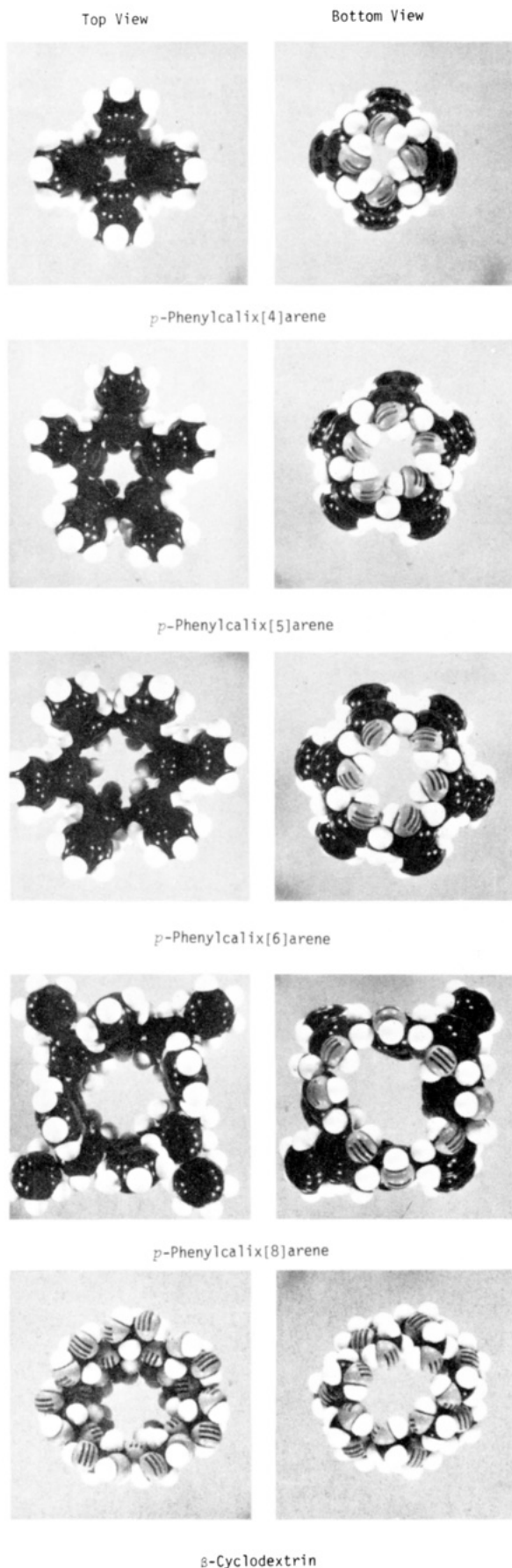
(21) Chen, S. I., unpublished observations.

Scheme I
Ten-Step Synthesis of *p*-Methylcalix[4]arene[22]

Scheme II
Stepwise Synthesis of *p*-Phenylcalix[4]arene[29]
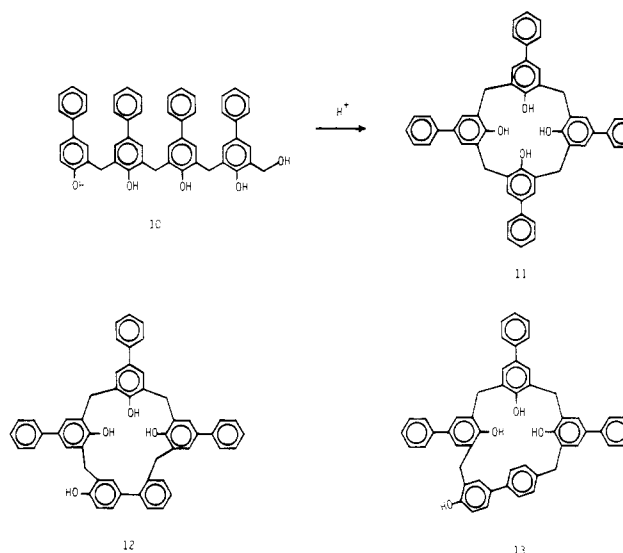
Stepwise Synthesis of the Calixarenes

In 1956 Hayes and Hunter[22] devised a 10-step synthesis of *p*-methylcalix[4]arene. Starting with *p*-cresol, they protected one of the *o*-positions by bromination and then sequentially added methylene groups by base-induced hydroxymethylation and aryl groups by acid-catalyzed arylation. The *o*-bromo-*o'*-hydroxymethyl linear tetramer thus obtained was debrominated and then cyclized, as illustrated in Scheme I. Curiously, no comparison of the Hayes and Hunter product with the Zinke product was reported, although the Hayes and Hunter synthesis seems to have been generally accepted as implicit proof for the Zinke tetrameric structure. Over the last 10 years the Kämmerer group has exploited and improved the Hayes and Hunter synthesis, demonstrating its potential in the preparation of a series of methyl- and *tert*-butyl-substituted calixarenes, including cyclic tetramers, pentamers, hexamers, and heptamers.[12,13,23–28]

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

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

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

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

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

(27) Kämmerer, H.; Happel, G. *Monatsh. Chem.* **1981**, *112*, 759.

(28) Kämmerer, H.; Happel, G.; Mathiasch, B. *Makromol. Chem.* **1981**, *182*, 1685.

Top View   Bottom View

p-Phenylcalix[4]arene

p-Phenylcalix[5]arene

p-Phenylcalix[6]arene

p-Phenylcalix[8]arene

β-Cyclodextrin

Figure 3. Space-filling molecular models of *p*-phenylcalixarenes and β-cyclodextrin. The *p*-phenyl rather than the *p-tert*-butyl substituent has been chosen to more clearly show the proportions of the cavities. All of the models were photographed to the same scale.

Scheme III
Convergent, Stepwise Synthesis of Calix[4]arene[25]
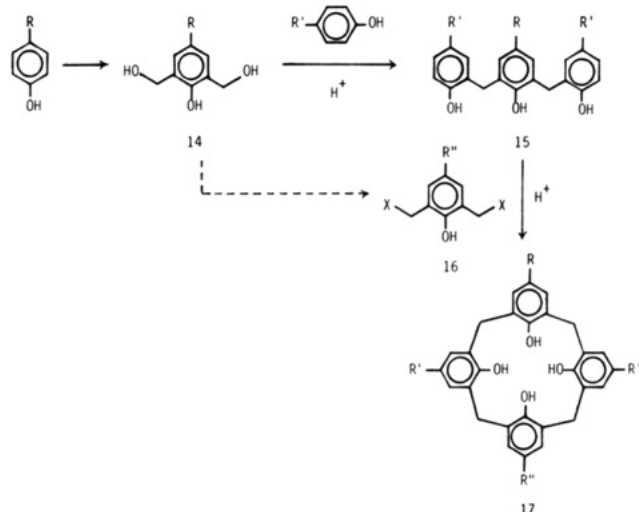
The Hayes and Hunter synthesis has serious drawbacks; it is long and tedious and affords the final product in very modest yield. An illustrative example is the synthesis of *p*-phenylcalix[4]arene, which we carried out to ascertain whether this compound is present in the Zinke or Petrolite products.[29] The hydroxymethylations and arylations proceeded in only fair yield, and the cyclization generated three products, as shown in Scheme II. One of these is the desired *p*-phenylcalix[4]arene (11), and the other two are postulated to be isomeric cyclic tetramers resulting from cyclization into the other reactive sites of the terminal phenyl moiety, viz., 12 and 13. The overall yield of each of these materials is under 0.5%, making this a less than ideal synthesis of compounds for enzyme mimic studies.

Recognizing the deficiencies in the Hayes and Hunter synthesis, the Kämmerer group[25] has explored a more convergent approach that retains much of the flexibility of the sequential stepwise approach. It involves the condensation of a linear trimer with 2,6-bis(halomethyl)phenol, as illustrated in Scheme III. Although short, it suffers from quite low yields in the cyclization step, which range from 10 to 15% in the best cases and down to 2–7% in the more interesting cases in which a mixture of alkyl, bromo, and nitro functions are incorporated as R groups.[30]

We have devised another convergent synthesis that retains some of the functional group flexibility of the Hayes and Hunter method and that gives sufficiently high yields to make calixarenes available for enzyme mimic studies.[31] In a four-step sequence (Scheme IV) a *p*-substituted phenol (e.g., *p*-phenylphenol) is treated with formaldehyde under controlled conditions to produce the bis(hydroxymethyl) dimer 18; the dimer is condensed with two equivalents of a *p*-substituted phenol (e.g., *p-tert*-butylphenol) to yield the linear

(29) Gutsche, C. D.; No, K. H. *J. Org. Chem.* **1982**, *47*, 2708.

(30) In a similar vein G. H. Hakimelahi and co-workers (*Helv. Chim. Acta* **1982**, *65*, 1221, 1264) have reported the synthesis of *p*-chlorocalix-[4]arene and *p*-chlorocalix[3]arene in 65–71% yield by the acid-catalyzed condensation of the linear dimer from *p*-chlorophenol and formaldehyde with the *bis*(hydroxymethyl)linear dimer and 4-chloro-2,6-bis(hydroxymethyl)phenol, respectively. Attempts in our laboratory to reproduce theses results have not yet been successful; whether this procedure affords a viable alternative to the ones discussed in this Account remains to be ascertained.

(31) No, K. H.; Gutsche, C. D. *J. Org. Chem.* **1982**, *47*, 2713.
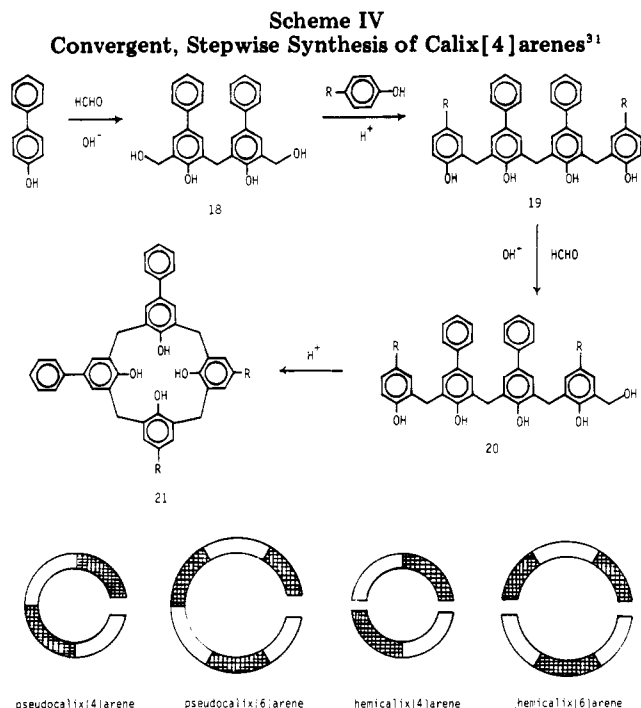
Scheme IV
Convergent, Stepwise Synthesis of Calix[4]arenes[31]

Figure 4. Stylized representations of pseudocalixarenes and hemicalixarenes.

tetramer 19 (e.g., R = *t*-Bu); and the dimer is mono-hydroxymethylated to yield 20 (e.g., R = *t*-Bu) and then cyclized to the calix[4]arene 21 (e.g., R = *t*-Bu). Although the overall yield is only ca. 10%, the starting materials are cheap and the workup and purification procedures are generally simple and straightforward. If improvements in the selective hydroxymethylation step could be realized, the synthesis would excel the Zinke "one-flask" method not only with respect to flexibility but also with respect to yield as well.

Physical Properties of the Calixarenes

The calixarenes are characterized by much higher melting points and lower solubilities in common organic solvents than their acyclic counterparts. The majority melt well over 300 °C (*p-tert*-butylcalix[8]arene, for example, melts at 412 °C), and only two cases of lower melting points have been reported, viz., the mixed *p*-methyl-*p-tert*-butylcalix[5]arenes, which melt around 260 °C.[28] The calixarenes show concentration-independent OH stretching absorptions in the infrared at unusually low frequency, generally in the 3150–3200 cm⁻¹ region indicative of very strong intramolecular hydrogen bonding. Only the calix[5]arenes and the dihomooxacalix[4]arenes (that possess cavities with dimensions very close to those of the calix[5]arenes) show OH stretching absorption at slightly higher frequency indicative of somewhat looser intramolecular hydrogen bonding. It is interesting that the acyclic analogues also show OH stretching absorptions at low frequency,[32] suggesting that they are coiled to form "pseudocalixarenes" or intermolecularly associated to form "hemicalixarenes" (Figure 4).

The Kämmerer group has reported the infrared, ultraviolet, NMR, and mass spectral data for a variety of calixarenes carrying *p*-methyl and *p-tert*-butyl substitutes;[23-28] the publications from this group should be
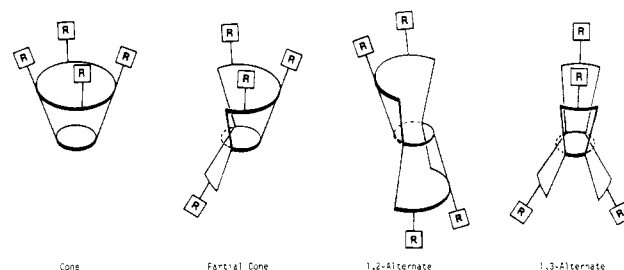
Figure 5. Conformations of the calix[4]arenes.

consulted for specific details.

Molecular Complexes of the Calixarenes

Many of the calixarenes form crystalline complexes with a variety of small molecules. For example, *p-tert*-butylcalix[4]arene forms complexes with chloroform, toluene, and pyridine;[8] *p-tert*-butylcalix[5]arene forms complexes with isopropyl alcohol[15] and acetone;[18] *p-tert*-butylcalix[6]arene forms a complex containing chloroform and methanol;[8] *p-tert*-butylcalix[8]arene forms a complex with chloroform[8]; *p-tert*-butyldihomooxacalix[4]arene forms a complex with methylene chloride.[8] The tenacity with which the guest molecule is held varies widely within this group. Whereas the cyclic octamer loses chloroform upon standing a few minutes at room temperature and atmospheric pressure, the cyclic hexamer retains some chloroform even after heating for 6 days at 257 °C and 1 mm pressure. That the guest molecule is located *within the calix* of the host molecule is indicated by the X-ray crystallographic pictures of the cyclic tetramer[16] and cyclic pentamer complexes.[18] Derivatives of the calixarenes also frequently show a marked tendency to form complexes. For example, the tetraacetate of *p-tert*-butylcalix[8]-arene retains methanol, chloroform, and ethyl acetate far more tightly than does the parent compound.[33]

Conformationally Mobile Calixarenes

The possibility of conformational isomerism in the calix[4]arenes was adumbrated by Megson[34] and Ott and Zinke[35] and was made explicit by Cornforth[11] who pointed out that four discrete forms can exist. We shall refer to these as the "cone", "partial cone", "1,2 alternate", and "1,3 alternate" conformations (Figure 5). That these conformations are readily interconvertible was first shown by the Kämmerer group, which carried out dynamic ¹H NMR studies of *p*-alkylcalix[4]arenes prepared by the stepwise procedure.[12,13] Observing the resonances arising from the ArCH₂Ar methylene hydrogens of the calix, they noted that above room temperature the pattern is a sharp singlet while below room temperature it is a pair of doublets (Figure 6). This can be interpreted in terms of a "cone" conformation interconverting rapidly on the NMR time scale at the higher temperature and slowly at the lower temperature. From the coalescence temperature of ca. 45 °C it is calculated that the rate of interconversion is ca. 100 s⁻¹.

A similar study was reported in 1977 by Munch[14] using calixarene prepared by the Petrolite method from *p*-octylphenol. Almost identical results were obtained, and this appeared to provide excellent proof for the

(32) Cairns, T.; Eglinton, G. *Nature (London)* 1962, *196*, 535.

(33) Dhawan, B., unpublished observations.
(34) Megson, N. R. L. *Oesterr. Chem. Z.* 1953, *54*, 317.
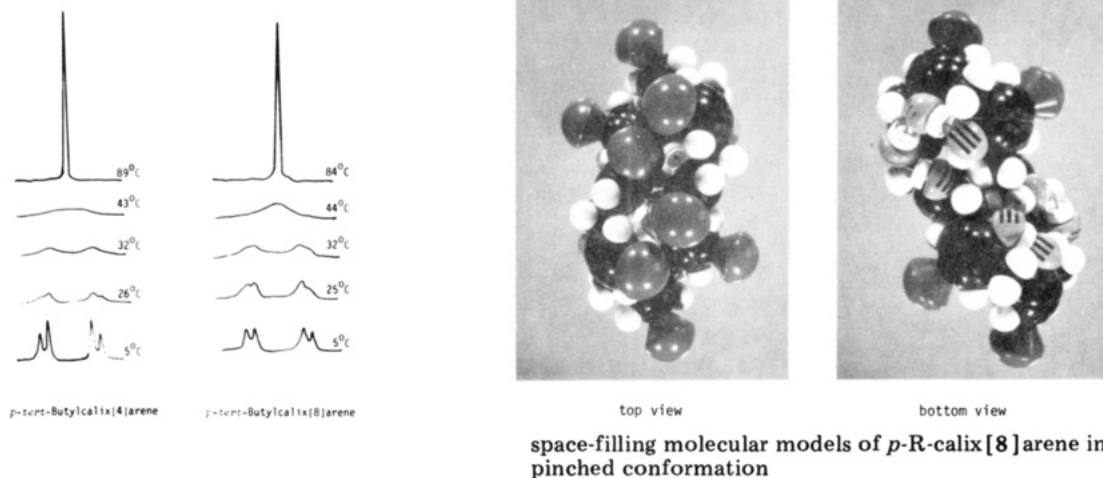(35) Ott, R.; Zinke, A. *Oesterr. Chem. Z.* 1954, *55*, 156.

space-filling molecular models of *p*-R-calix[8]arene in
pinched conformation

Figure 6. ¹H NMR spectra of *p-tert*-butylcalix[4]arene and *p-tert*-butylcalix[8]arene at various temperatures; space-filling molecular models of *p-tert*-butylcalix[8]arene in "pinched" conformation.

cyclic tetrameric structure of the Munch compound. It seemed inconceivable that the quite rigid calix[4]arene and a larger, presumably more flexible, calix[8]arene might manifest the same dynamic ¹H NMR behavior. Yet, that is precisely what occurs. In 1981 Gutsche and Bauer[36] showed that *authentic* samples of *p-tert*-butylcalix[4]arene and *p-tert*-butylcalix[8]arene do, indeed, show virtually identical dynamic ¹H NMR behavior in CDCl₃ and C₆D₅Br (Figure 6). In pyridine-d_5, however, a difference emerges; whereas the calix[4]arene resolves into a pair of doublets at lower temperatures, the calix[8]arene shows only a singlet resonance, even at −90 °C. The similarity of the dynamic ¹H NMR spectra in the nonpolar solvents is ascribed to intramolecular hydrogen bonding, which makes the cyclic octamer behave, quite fortuitously, as though it were a cyclic tetramer as the result of a "pinched conformation" that has the superficial aspect of a pair of tetramers "stuck" together. The type of hydrogen bonding present in the calix[4]arenes has been referred to as "circular" by Saenger[37] who has suggested that circularity confers a special stability on the system. The cyclic octamer, by "pinching" transannularly, can assume a conformation containing two such circularly hydrogen bonded arrays, each containing four OH groups. A necessary corollary to this postulate, however, is that a pseudorotation is operative, which averages the CH₂ *groups* at a rate that is fast on the NMR time scale at the temperatures at which the dynamic NMR studies are conducted, i.e.
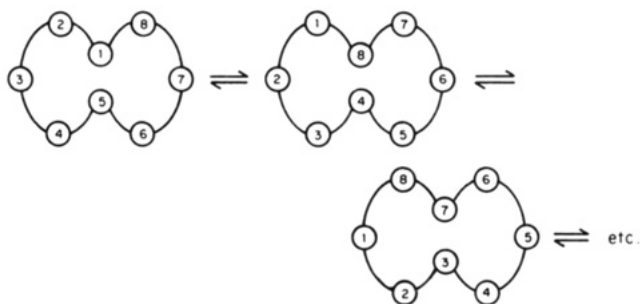
In their systematic study of calixarenes synthesized by the stepwise method, the Kämmerer group has in-

vestigated the dynamic ¹H NMR behavior of cyclic pentamers[28] and heptamers[26] in addition to the cyclic tetramers.[12,13] They found that the $\Delta G^\ddagger$ values for the inversion of the cyclic pentamer (12.1 kcal/mol) and cyclic heptamer (12.2 kcal/mol) are comparable, although both are considerably lower than that of the cyclic tetramer (15.7 kcal/mol). The dynamic ¹H NMR behavior of the calix[6]arenes[38] indicates that they resemble the calix[8]arenes in assuming a "pinched" conformation in nonpolar solvents, leading to circular hydrogen bond arrays containing three OH groups. The result is to force the system into a conformation in which the aryl groups in the 1-and 4-positions project outward like a pair of wings perpendicular to the aryl groups in the 2-, 3-, 5-, and 6-positions, which are colinear, forming a channel into which other molecules might comfortably fit (Figure 7).

Conformationally Immobile Calixarenes

D. J. Cram has defined a "cavitand" as a *synthetic* compound containing an "enforced cavity"[39] large enough to engulf ions or other molecules.[40] The calix[4]arenes are synthetic compounds and they have the capacity to entrap other molecules. They do not have *enforced* cavities, however, because they are conformationally mobile. To make them cavitands it is necessary to "fix" them in either a "cone" or a "partial cone" conformation. One way for accomplishing this is to replace the hydrogens of the hydroxyl functions with larger groups. When transformation between conformations occurs, an aryl group rotates around the C-2/C-6 axis in a direction that brings the OH groups through the center of the macrocyclic ring. Space-filling models (CPK models) indicate that while OH groups provide little hindrance to this process, larger groups can make the transformation impossible. We have studied the process of conformational fixing by this means in some detail.[41]

Acetylation of **22a** yields a tetraacetate fixed in the "1,3-alternate" conformation.[42] This result was antic-

(36) Gutsche, C. D.; Bauer, L. J. *Tetrahedron Lett.* **1981**, 4763.
(37) Saenger, W. *Nature* (*London*) **1979**, *279*, 343.

(38) Bauer, L. J., unpublished observations.
(39) Helgeson, R. C.; Mazaleyrat, J.-P.; Cram, D. J. *J. Am. Chem. Soc.*
1981, *103*, 3929.
(40) Cram, D. J. *Science* (*Washington, D.C.*) **1983**, *219*, 1177.
(41) Gutsche, C. D.; Dhawan, B.; Levine, J. A.; No, K. H.; Bauer, L.
J. *Tetrahedron* **1983**, *39*, 409.

Top View   End View   Bottom View

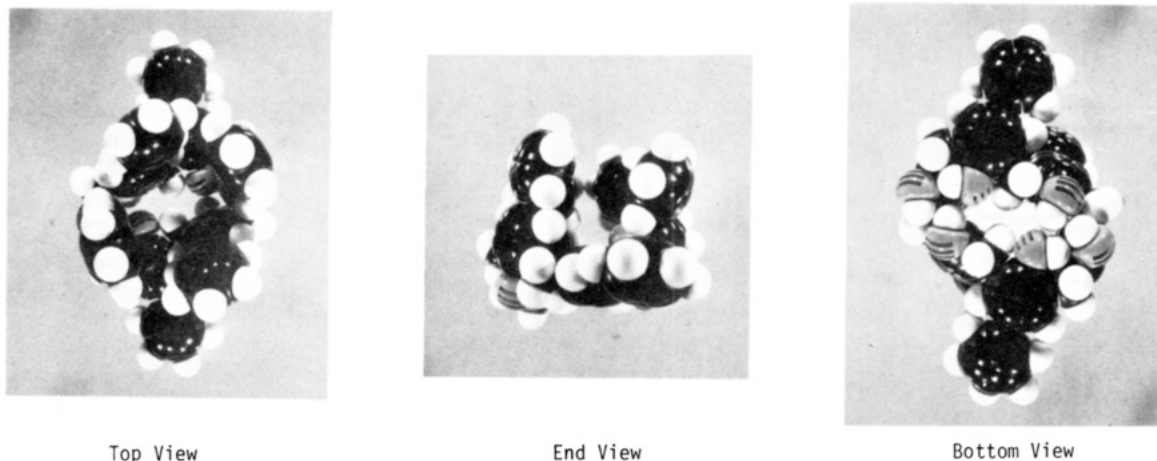**Figure 7.** "Winged" conformation of *p*-phenylcalix[6]arene.

ipated from the observation that the octaacetates of the octahydroxycalix[4]arenes[43] obtained by the acid-catalyzed condensation of resorcinol with aldehydes[44] are fixed in a "1,3-alternate-like" conformation.[45,46] Further investigation, however, has shown that the "1,3 alternate" conformation is rare among derivatives of the tetrahydroxycalix[4]arenes and that the "partial cone" and "cone" conformations are generally favored. For example, **22b** yields a tetraacetate (**23b**) fixed in a

a, R = H
b, R = *t*-Bu
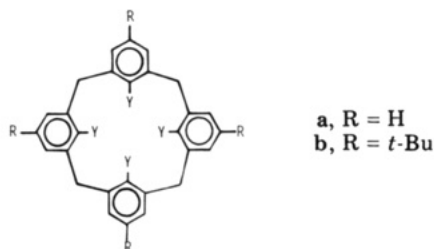
22, Y = OH; **23**, Y = OAc; **24**, Y = OMe; **25**, Y = OEt;
26, Y = OCH$_2$CH=CH$_2$; **27**, Y = PhCH$_2$O; **28**, Y = SiMe$_3$

"partial-cone" conformation, a result that has been verified by X-ray crystallography.[47] Methylation and ethylation of **22a** and **22b** and allylation of **22a** yield the corresponding ethers **24a**, **24b**, **25a**, **25b**, and **26a** in the "partial cone" conformation.[48] Allylation of **22b**, however, yields **26b** in the "cone" conformation, and benzylation of **22a** and **22b** and trimethylsilylation of **22b** yield the corresponding derivatives in the "cone"

conformation.[49] In only two instances to date have mixtures of conformational isomers been obtained upon derivatization. One of these is the acetylation of **21** (R = *t*-Bu), which yields a "1,3 alternate" and two "partial cone" conformers.[50] Trimethylsilylation of this same material, on the other hand, yields only a single compound, which possesses the "cone" conformation.

The particular derivatizing agent used may affect the structure as well as the conformation of the product. For example, treatment of **22a** and **22b** with methyl iodide and NaH in a THF–DMF solution yields the tetramethyl ethers; treatment of **22b** with dimethyl sulfate in the presence of BaO–Ba(OH)$_2$ in DMF yields the trimethyl ether; and treatment of **22b** with excess diazomethane for an extended period yields the monomethyl ether.[51] In similar fashion, treatment of **22b** with benzyl bromide and NaH in THF–DMF yields the tetrabenzyl ether, while treatment of **22b** with benzyl tosylate yields the dibenzyl ether. A "flattened partial cone" conformation is assigned to the trimethyl ether, and a "flattened 1,3 alternate" conformation is assigned to the monomethyl and dibenzyl ethers. The trimethyl and monomethyl ethers are conformationally less mobile than the tetramethyl ethers,[48] a result that is ascribed to intramolecular hydrogen bonding arising from the free hydroxyl group(s) in the molecules. The derivatization reactions of the calix[4]arenes present a somewhat clouded picture from the standpoint of conformational predictability, and work is underway to try to clarify it. It is apparent, though, that the "partial cone" and "cone" conformations are generally preferred and that, by appropriate choice of reagent and reaction conditions, a given system can be fixed in either of these conformations. This represents a particularly propitious facet of the calixarenes, for not only does it bring them into the fold of cavitands but it provides a means for contouring the cavity by design.

Although the calix[8]arenes resemble the calix[4]arenes with respect to conformational mobility, their ester and ether derivatives show no conformational fixation,

(42) The patterns of the ^{1}H NMR and ^{13}C NMR resonances are different for each of the four conformations of the symmetrically substituted calix[4]arenes, providing an easy and accurate method for establishing conformational identity.
(43) The resorcinol–aldehyde condensation products, obtained by Michael, A., *Am. Chem. J.* **1883**, *5*, 338, were first assigned cyclic tetrameric structures by Niederl, J. B.; Vogel, H. J. *J. Am. Chem. Soc.*, **1940**, *62*, 2512.
(44) Högberg, A. G. S. *J. Am. Chem. Soc.* **1980**, *102*, 6046.
(45) Nilsson, B. *Acta Chem. Scand.* **1968**, *22*, 732. Palmer, K. J.; Wong, R. Y.; Jurd, L.; Stevens, K. *Acta Crystallogr. Sect. B* **1976**, *B32*, 847.
(46) The octahydroxycalix[4]arenes have recently been shown to be convertible to cavitands by Moran, J. R.; Karbach, S.; Cram, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 5826.
(47) Rizzoli, C.; Andreetti, G. D.; Ungaro, R.; Pochini, A. *J. Mol. Struct.* **1982**, *82*, 133.
(48) The tetramethyl ethers **24a** and **24b** are more conformationally mobile than would be predicted by inspection of the CPK models; at room temperature the ^{1}H NMR spectra show only a broad resonance for the methylene hydrogens, quite analogous to the parent calixarenes; this sharpens to simple patterns at elevated temperature and to more complex patterns at lower temperature, commensurate with a "partial-cone" conformation. This behavior provides a good example of the fact that hard, space-filling models tend to overestimate the barriers to conformational changes.

(49) The trimethylsilyl derivative of **22a** has been obtained only as an oil and is not yet well characterized.
(50) The C_s symmetry of **21** (R = *t*-Bu) gives rise to six conformers; viz., one "cone", two "partial cone", two "1,2 alternate", and one "1,3 alternate".
(51) This compound was originally ascribed a dimethyl ether structure (see ref 41), but an X-ray crystallographic determination recently carried out in the Washington University laboratories by Professor G. G. Stanley shows it to be a monomethyl ether.

Scheme V
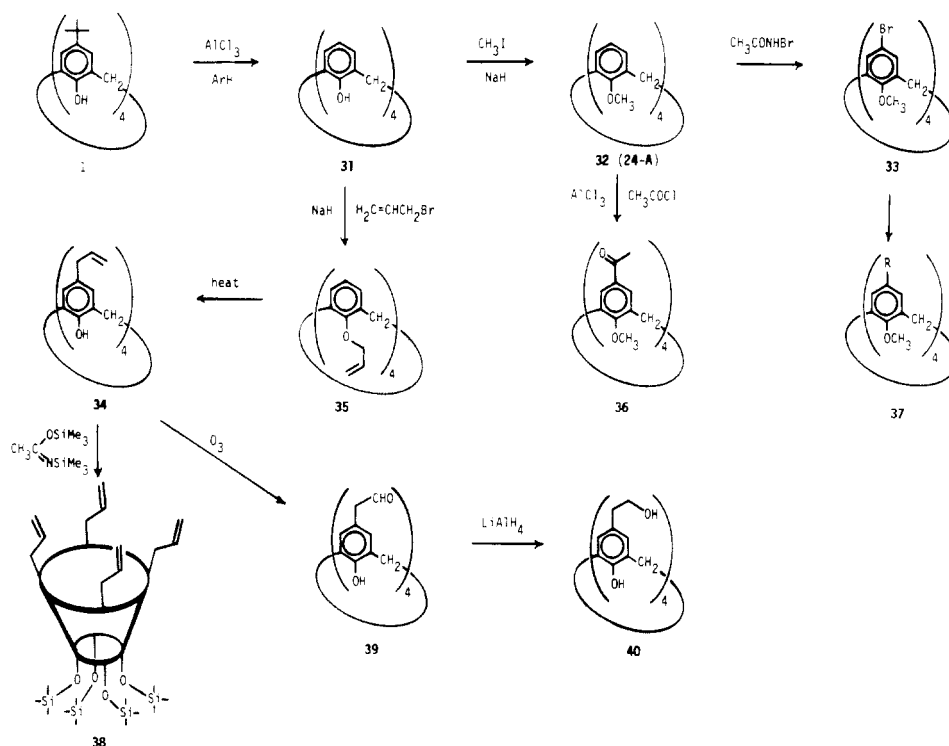
even at low temperatures. Clearly, the derivatives of the calix[8]arenes can exist in an "expanded" conformation with an annulus large enough for groups even as big as trimethylsilyl to pass through without hindrance. The calix[6]arenes occupy an intermediate position. The derivatives are more conformationally mobile than those of the calix[4]arenes, but at low temperatures the system may be fixed in a conformation resembling the "winged" form of the parent calix[6]arene, as judged from the ^{1}H NMR patterns.

Another way to reduce the conformational mobility of the calixarenes is to bridge two or more regions of the molecule. Currently under investigation[52] is the synthesis of 29 as a building block for the construction
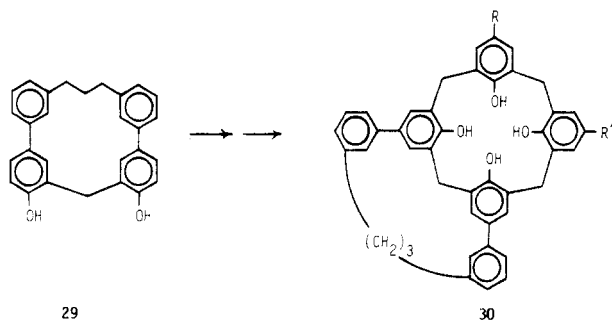
of 30 via the convergent method outlined in Scheme IV. Although 30 allows conformational mobility in the *p*-R and -R′ moieties, complete inversion between cone conformations is not possible. Thus, if R and R′ are different, the calix[4]arene can exist in nonracemizable enantiomeric forms.

Calixarenes Carrying Functional Groups

If calixarenes are to serve as enzyme mimics it is necessary that they carry functional groups of various types. The *p-tert*-butylcalixarenes serve as admirable

precursors for functional group introduction, for the *p-t*-Bu groups can be easily removed by trans-alkylation.[53] When *p-tert*-butylcalix[4]arene (1) is de-*tert*-butylated, compound 31 is obtained in good yield and is amenable to functionalization in the *p*-position. For example, bromination of the tetramethyl ether (32) of calix[4]arene proceeds smoothly, affording a material that, by lithiation followed by carbonation, yields *p*-carboxycalix[4]arene (37, R = CO$_2$H) or, by cyanation, yields *p*-cyanocalix[4]arene (37, R = CN).[54] In similar fashion, Friedel–Crafts acylation of 32 yields *p*-acetylcalix[4]arene (36).[55] Perhaps the most interesting functionalization sequence is the one involving the conversion of 31 to the tetraallyl ether (35), which, when heated in diethylaniline, undergoes a multiple para Claisen rearrangement to afford *p*-allylcalix[4]-arene (34) in excellent yield.[56] Trimethylsilylation of 34 fixes the compound in the "cone" conformation, producing a functionalizable calixarene 38 containing an enforced cavity. The synthetic potential of 34 is illustrated by its ozonolysis to *p*-(2-oxoethyl)calix[4]-arene (39) and subsequent reduction to *p*-(2-hydroxy-ethyl)calix[4]arene (40). Reaction sequences similar to those shown in Scheme V for *p-tert*-butylcalix[4]arene are also applicable to *p-tert*-butylcalix[6]arene and *p-tert*-butylcalix[8]arene, thus making functionalized calixarenes available in a variety of ring sizes.

Calixarenes as Metal Ion Transport Agents

The ability of the calixarenes to transport metal ions through hydrophobic liquid membranes has been studied by Reed Izatt and co-workers at Brigham Young Univeristy.[57] Although calixarenes 1, 3, and 4

(52) Bailey, D. L., unpublished observations.

(53) See Tashiro, M. *Synthesis*, 1979, 921 for general references, and Böhmer, D.; Rathay, H.; Kämmerer, H. *Org. Prep. Proced. Int.* 1979, 113 for a closely analogous example.
(54) Pagoria, P. F., unpublished observations
(55) Lin, L. G., unpublished observations.
(56) Gutsche, C. D.; Levine, J. A., *J. Am. Chem. Soc.* 1982, *104*, 2652.

Scheme VI

30 - - - - →

41

CH$_2$CH$_2$CH$_2$ bridge

bottom of partial calix

OCH$_2$CO$_2$H groups
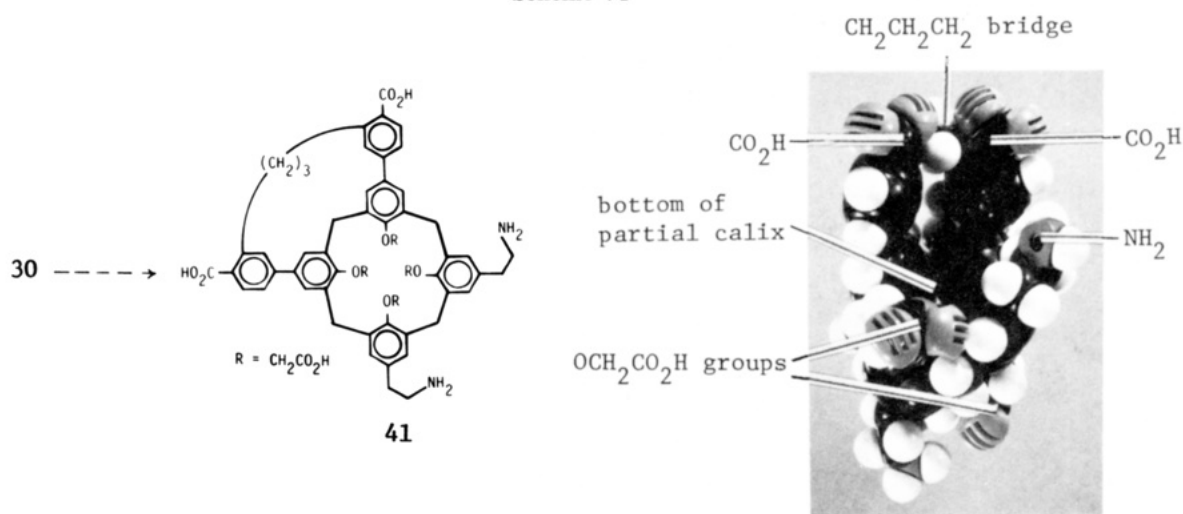
Space filling molecular model of compound **41** in the partial cone conformation

Stylized representation of compound **41** in the partial cone conformation

Aldol Product
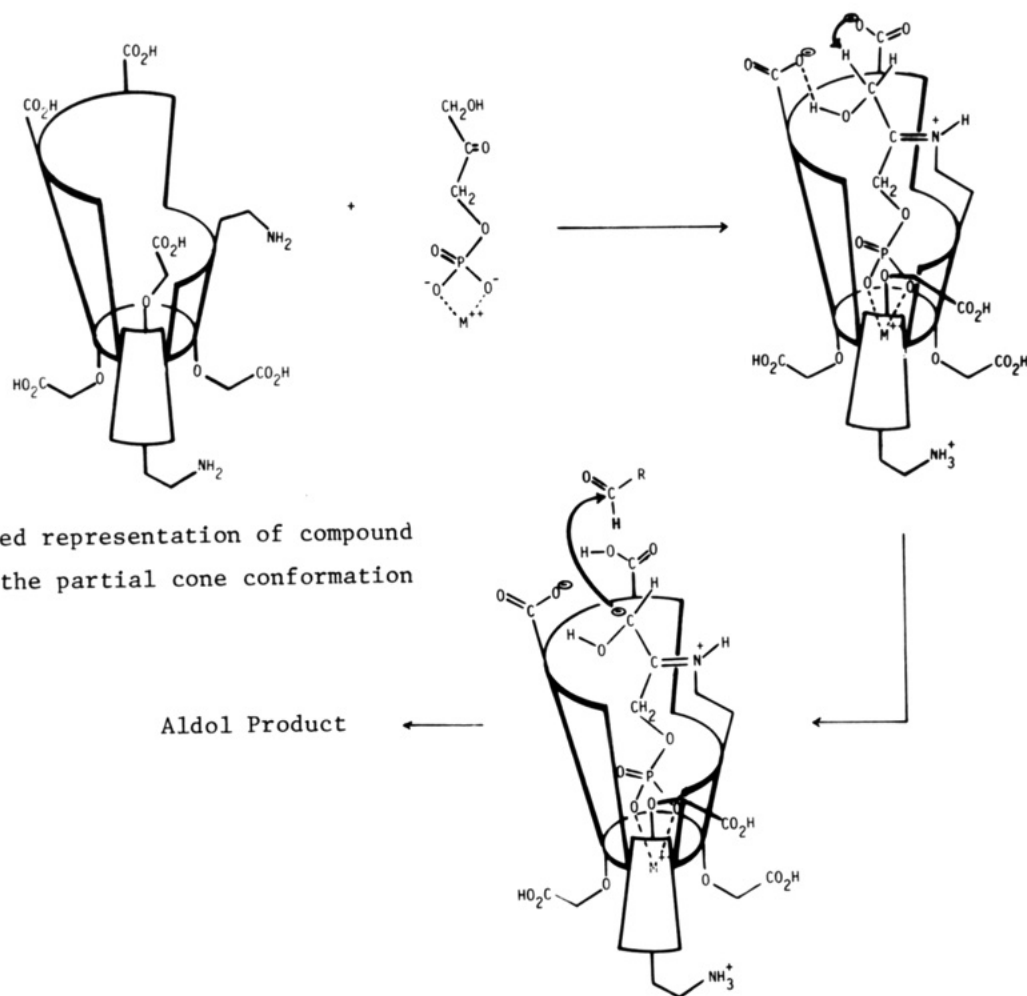
are ineffective toward cations in neutral soluion, they show considerable transport ability in basic solution. This contrasts with 18-crown-6, which is far more effective, for example, for KNO$_3$ than KOH. All three calixarenes show the greatest transport ability for Cs$^+$,

with the cyclic tetramer being the most selective but the cyclic octamer being the most effective. Control experiments with phenol and *p-tert*-butylphenol, which show little or no transport ability, indicate that the macrocyclic ring plays a critical role. Thus, the calixarenes may possess useful features as ion carriers because of their low water solubility, their ability to form *neutral* complexes with cations through loss of a proton,

(57) Izatt, R. M.; Lamb, J. D.; Hawkins, R. T.; Brown, P. R.; Christensen, J. J. *J. Am. Chem. Soc.*, in press.

and their potentiality for allowing the coupling of cation transport with the reverse flux of protons.

Calixarenes as Enzyme Mimics

Our main interest in the calixarenes focuses on their potential as enzyme mimics, and the necessary synthetic capabilities appear to now be in hand. For example, the synthesis of the conformationally semiflexible mixed calixarene **30** (R = R′ = t-Bu) is feasible, and by the types of reactions shown in Scheme V it should be possible to convert **30** to **41** (Scheme VI). Derivatization of the hydroxyl groups via ethyl α-bromoacetate at an appropriate point during this sequence would, presumably, fix the system in a "partial-cone" conformation, and hydrolysis in the last stages of the sequence would yield **41** (R = CH_2CO_2H). It is postulated that **41** might serve as an aldolase model,[58] holding in its calix a molecule of metal-atom-coordinated dihydroxyacetone phosphate in such a fashion that the keto group is proximate to the amino function (leading to Schiff base formation) and the α-hydrogens of the hydroxymethylene group are proximate to a carboxylate function (leading to proton abstraction and formation of the carbanion, shown in Scheme VI as a charge-separated enamine). Condensation with an aldehyde (glyceraldehyde phosphate in the biological reaction) can then rapidly occur at the exposed, unhindered face of the carbanion to yield the aldol product. In similar fashion, numerous other enzyme mimic systems can be envisaged in which appropriate functional groups are arrayed around the cavities provided by calixarenes either in the "cone" or "partial-cone" conformation.

The first chapters in the calixarene story, as described in this account, have dealt with the development of methods for constructing the basic frameworks, methods for controlling the conformation and contour of the calix, and methods for introducing functional groups. The chapters yet to be written must deal with the utility of the calixarenes in such applications as enzyme mimics, ion carriers, and selective complexing agents.

(58) For a brief description of the chemistry of aldolase see: Walsh, C. "Enzymatic Reaction Mechanisms"; W. H. Freeman: San Francisco, 1979; p 745. For a more extended discussion see: Horecker, B. L.; Tsolas, O.; Lai, C. Y. "The Enzymes"; Boyer, P., Ed.; Academic Press: New York, 1972; Vol. 7, p 213.

Acetylene Diethers: A Logical Entry to Oxocarbons

Fèlix Serratosa

Department de Quimica Orgànica, Facultat de Quimica, Universitat de Barcelona, Barcelona-28, Spain

Received July 23, 1982 (Revised Manuscript Received November 29, 1982)

Although oxocarbons have been known for more than 150 years and several reviews[1] and even an entire book[2] have been devoted to them in the past few years, we feel that a brief account of our recent findings on the field, directed to a more general audience, is justified. Our interest in oxocarbons came through our own work on the chemistry of acetylene diethers that we developed during the past 12 years or so.[3] Acetylene diethers may be regarded as *esters* of the first member of the series of aromatic oxocarbon dianions, $C_nO_n^{2-}$, and as the common precursors of all of the other members of the series (Table I). In this context, the story of acetylene diethers is as old as the history of organic chemistry itself, and it is strongly tied to the work of the greatest chemists of the 19th century, such as Berzelius, Wöhler, Gmelin, and Liebig, who were the first to prepare croconic and rhodizonic acids from "potassium carbonyl".[4]

Over 100 years later, in 1959, Cohen, Lacher, and Park[5] synthesized the so-called squaric acid, and, soon

Table I
Aromatic Oxocarbon Dianions $C_nO_n^{2-}$

n	name	structural formula
2	acetylenediolate	$^-O-C{\equiv}C-O^-$
3	deltate	
4	squarate	
5	croconate	
6	rhodizonate	

afterwards in 1960, West[6] realized that rhodizonate, croconate, and squarate belong to the same oxocarbon

Fèlix Serratosa was born in Barcelona, Spain, in 1925. He received the B.S. degree in Chemistry at the University of Barcelona in 1949, the Ph.D. degree from the University of Madrid in 1953, and performed postdoctoral work, from 1955 to 1957, at M.I.T. Returning to Spain, he joined the C.S. I.C. (the Spanish National Research Council) and the University of Barcelona, where he is currently Professor of Organic Synthesis. His field of interest includes organic synthesis and the chemistry of acetylenes, carbenes, ylides, and diazo ketones.

(1) G. Maas and P. Hegenberg, *Angew. Chem., Int. Ed. Engl.*, 5, 888 (1966); R. West and J. Niu in "Non-Benzenoid Aromatics", J. Snyder, Ed., Academic Press, New York, Vol. 1, p 311, 1969; R. West and J. Niu in "The Chemistry of the Carbonyl Group", J. Zabicky, Ed., Wiley-Interscience, New York, Vol. 2, p 241, 1970; A. H. Schmidt and W. Reid, *Synthesis*, 869 (1978); R. West, *Isr. J. Chem.*, 20, 300 (1980); A. H. Schmidt, *Chem. Unserer Zeit.*, 16, 57 (1982).
(2) "Oxocarbons", R. West, Ed., Academic Press, New York, 1980.