for another 20 min, after which time the excess borohydride was destroyed by the addition of 2 N HCl until the pH had reached 2.0. $(NH_4)_2SO_4$ was added to the saturation point, and the solution was extracted with three 300-mL aliquots of Et_2O. The combined organics were dried, filtered, and concentrated (in vacuo), affording a yellow oil. This procedure was repeated 7-8 times with each of the labeled substrates. The combined crude product mixtures were partially purified by flash chromatography (6 in. × 20 mm; 5:1, petroleum ether/EtOAc). Incubations of substrates labeled at C-2 and at C-4 afforded 12.5 and 7.0 mg, respectively, of impure 3-[2-$^2H_1$]decyn-1-ol. These alcohol samples were contaminated with ca. 25-30% (by GC) of 3-decen-1-ol (from reduction of 2,3-decadienoyl-NAC). Even after further purification of a sample by HPLC (19:1, hexane/EtOAc; 1.0 mL/min; 4.6 × 250 mm silica gel column; effluent monitored using a Knauer differential refractometer), GC analysis of the product from the incubation of substrate labeled at C-2 showed the presence of both 3-decen-1-ol (15%) and 3-decyn-1-ol (81%). Accordingly, HPLC purification was not ordinarily employed, and the olefinic impurities were carried through the remainder of the derivatization process.

In a prior control experiment, a mixture of 3-decynoyl-NAC (13 mg) and 2,3-decadienoyl-NAC (34 mg) was dissolved in 20 mL of THF, and this solution was further diluted with 20 mL of ^2H_2O and 20 mL of 1.0 M KPO_4 (pH 7.0, in 99.8% ^2H_2O). This solution was cooled and treated with $NaBH_4$ as described above. Extraction of the reaction mixture was followed by purification by flash chromatography, affording 2.5 mg of a mixture of alcohols, identified by GC analysis as 3-decyn-1-ol, (*E*)-3-decen-1-ol, and (*Z*)-3-decen-1-ol. Owing to difficulty in separating these alcohols from one another, a ^2H NMR spectrum was run on the mixture. No incorporation of deuterium from the medium was observed.

Reduction of Chirally Labeled 3-[2-$^2H_1$]Decyn-1-ol. 3-[2-$^2H_1$]Decyn-1-ol (12.5 mg, from incubation of substrate labeled at C-2) was reduced to 1-[2-$^2H_1$]decanol by homogeneous hydrogenation in benzene solution, in the presence of $(Ph_3P)_3RhCl$.[30] The course of the reaction was followed by GC. When the reaction was complete, the mixture was filtered through a plug of silica gel, which was rinsed with a 4:1 mixture of petroleum ether/Et_2O. Concentration of the filtrate in vacuo gave 13.2 mg of labeled 1-decanol, as a light yellow oil. This material was used without further purification.

Oxidation of Chirally Labeled 1-[2-$^2H_1$]Decanol. Labeled 1-[2-$^2H_1$]-decanol (13 mg; 0.083 mmol) was oxidized to 1-[2-$^2H_1$]decanoic acid by Sharpless's procedure.[31] After 2 h, the color of the reaction mixture had changed from black to light green. An aliquot was removed for GC analysis, which showed complete conversion of the alcohol to the corresponding acid. The reaction mixture was then extracted 3 times with CH_2Cl_2. The combined organics were carefully concentrated, and the black residue was taken up in Et_2O and filtered through a plug of silica gel. Concentration of the filtrate in vacuo gave 7.0 mg of labeled acid, as a white solid. This was esterified without further purification.

Esterification of Chirally Labeled [2-$^2H_1$]Decanoic Acid (from Incubation of C-2 Labeled Substrate) to Methyl (*S*)-α-Hydroxybenzeneacetate (Methyl Mandelate). The methyl mandelate ester of chirally labeled 1-[2-$^2H_1$]decanoic acid (7.0 mg) was made by the method described by Parker.[32] Following flash chromatographic purification, 6.5 mg of labeled ester was obtained, as a clear colorless oil: ^1H NMR (CCl_4) δ 0.9 (t, J = 6 Hz, 3 H, CH_3), 1.05-1.9 (m, 14 H, CH_2), 2.4 (t, J = 8 Hz, 1 H, $CH_2CHDCOO$), 3.7 (s, 3 H, $COOCH_3$), 5.77 (s, 1 H, Ar $CH(OCOR)COOCH_3$), 7.36 (m, 5 H, Ar H); ^2H NMR (benzene; see Figure 2a) δ 2.27 (s, ca. 0.64 D, *pro-R* CHDCOO), 2.16 (s, ca. 0.36 D, *pro-S* CHDCOO).

Conversion of Chirally Labeled 3-[2-$^2H_1$]Decyn-1-ol (from Incubation of C-4 Labeled Substrate) to the Decanoic Acid Ester of Methyl Mandelate. Labeled 3-[2-$^2H_1$]decyn-1-ol (6 mg), derived from incubation of 2,3-[4-^2H]decadienoyl-NAC with AAI, was converted to the corresponding methyl mandelate ester by the procedure described above, except that unlabeled 3-decyn-1-ol (6 mg) was added as carrier. The yield of labeled ester was 8 mg. ^1H NMR (CCl_4) δ 0.9 (t, J = 6 Hz, 3 H, CH_3), 1.05-1.9 (m, 14 Hz, CH_2), 2.4 (t, J = 8 Hz, 1 H, $CH_2CHDCOO$), 3.7 (s, 3 H, $COOCH_3$), 5.78 (s, 1 H, Ar $CH(OCOR)COOCH_3$), 7.36 (m, 5 H, Ar H); ^2H NMR (benzene; see Figure 2b) δ 2.16 (s, ca. 0.67 D, *pro-S* CHDCOO), 2.25 (s, ca. 0.33 D, *pro-R* CHDCOO).

Acknowledgment. We gratefully acknowledge the NSF-supported Southern California Regional NMR facility (at Cal Tech) for high-field ^2H NMR spectra and the NIH for generous financial support, via Grant GM 26074. We also thank Prof. Jon Clardy and Dr. Cun-heng He (Cornell University) for solution of the crystal structure of the chiral allene, Dr. Bruce Coxon (National Bureau of Standards) for plotting the spectra shown in Figure 2, and Prof. Anthony Ponaras (Catholic University) for helpful discussions.

(46) Cahn, R. S.; Ingold, C. K.; Prelog, V. *Experientia* **1956**, *12*, 81-94.
(47) Cahn, R. S.; Ingold, C. K.; Prelog, V. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 385-415.

Calixarenes. 13. The Conformational Properties of Calix[4]arenes, Calix[6]arenes, Calix[8]arenes, and Oxacalixarenes

C. David Gutsche* and Lorenz J. Bauer

Contribution from the Department of Chemistry, Washington University, St. Louis, Missouri 63130. *Received February 14, 1985*

Abstract: The [1$_n$]metacyclophanes known as calixarenes, obtainable in ring sizes containing 4-8 aryl moieties in the macrocyclic array, are conformationally flexible in varying degrees. We have studied the conformational characteristics of these molecules by means of temperature-dependent ^1H NMR measurements. On the basis of the data that have been obtained, preferred conformations are suggested, and the energies of activation for conformational inversion are assigned. It is found that the $\Delta G^{\ddagger}$ values in nonpolar solvents such as chloroform and benzene are somewhat higher than those in semipolar solvents such as acetone and acetonitrile and considerably higher than those in pyridine. The ^1H NMR data are commensurate with a "cone" conformation for the cyclic tetramers and cyclic pentamers, a "winged" or "hinged" conformation for the cyclic hexamers, and a "pleated-loop" conformation for the cyclic octamers. The conformational implications of the temperature-dependent ^1H NMR behavior of a cyclic pentamer, a cyclic heptamer, a dihomooxacalix[4]arene, a tetrahomodioxacalix[4]arene, and a hexahomotrioxacalix[3]arene are also discussed.

Calixarenes, which are [1$_n$]metacyclophanes, can be obtained in ring sizes ranging from 4 to 8 aromatic residues[1] by base-induced condensation of certain para-substituted phenols and formaldehyde. The smallest members of the series, the calix[4]arenes, can exist in several conformations, as first adumbrated by Megson[2] and Ott and Zinke[3] and subsequently made explicit by Cornforth.[4] Space-filling (Corey-Pauling-Koltun) molecular

(1) For reviews of the calixarenes see: Gutsche, C. D. *Acc. Chem. Res.* **1983**, *16*, 161. Gutsche, C. D. "Topics in Current Chemistry"; Boschke, F. L., Ed.; Springer-Verlag, 1984; Vol 123, p 1.

(2) Megson, N. R. L. *Oesterr. Chem. Ztg.* **1953**, *54*, 317.
(3) Ott, R.; Zinke, A. *Oesterr. Chem. Ztg.* **1954**, *55*, 156.

0002-7863/85/1507-6052$01.50/0

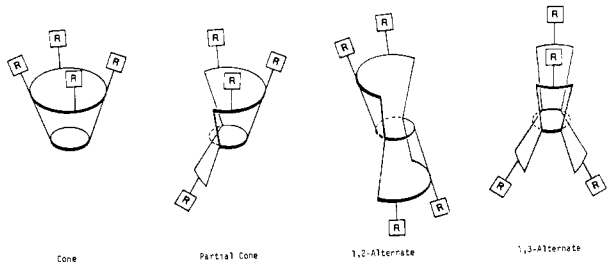
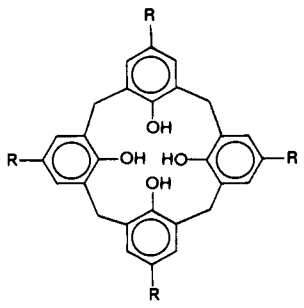


Figure 1. Conformations of the calix[4]arenes.

models support the validity of this idea and indicate that the conformational flexibility of the calixarenes might be expected to increase with increasing ring size. Temperature-dependent ^{1}H NMR studies of the calix[4]arenes,[5,6] and the calix[8]arenes,[6,7] however, have shown that this is not necessarily the case: the calix[4]arenes and calix[8]arenes show almost identical behavior in nonpolar solvents. On the other hand, calix[5]arenes, calix[6]arenes, and calix[7]arenes, as well as the oxacalixarenes, behave in a more expected fashion and appear to be more flexible molecules. The purpose of the present work is to expand on the data in the literature to provide a basis (a) for determining the shape of the preferred conformation of each of the calixarenes and (b) for correlating the conformational behavior of the calixarenes with their para substituents and with the solvent.

Conformational Properties of the Calix[4]arenes (1). Cornforth and co-workers[4] pointed out that four discrete forms of the calix[4]arenes can exist, which we have designated as the "cone", "partial-cone", "1,2-alternate", and "1,3-alternate" conformations,[8] as shown in Figure 1. Interconvertibility among these conformers



I

has been demonstrated by temperature-dependent ^{1}H NMR measurements, first by Kämmerer and co-workers[5] and more recently by our group.[8] The resonance signal of greatest utility in these studies is that arising from the methylene hydrogens; in chloroform solution it appears as a singlet above room temperature and as a pair of doublets below room temperature[5-7] (see Figure 3). It is inferred from these data that the calix[4]arenes prefer the cone conformation but that inversion of the cone takes place fairly rapidly at room temperature (ca. 150 sec^{-1}). X-ray crystallographic studies of the calix[4]arenes[9,10] provide unequivocal evidence that these compounds do, indeed, exist in the cone conformation in the solid state. This conformational preference is a consequence of the hydroxyl groups which make possible very strong intramolecular hydrogen bonding, as indicated by the unusually low stretching frequency of the OH bonds in the infrared spectrum (ca. 3150 cm^{-1}). Space-filling molecular models support the idea that the cone conformation is perfectly constituted to facilitate what has been referred to as circular "flip-flop" hydrogen bonding[11] (see Figure 4). Analogous metacyclophanes lacking OH groups at positions 25, 26, 27, and 28 of the calix[4]arene system (e.g., the calixarenes obtained from the acid-catalyzed condensation of resorcinol and benzaldehyde[12] in which the eight OH groups are near the upper rim of the calix) as well as the calixarenes obtained from chloromethylmesitylene and $AlCl_3$[13] have been shown to prefer 1,3-alternate-like conformations. The present study employs conventional methods to analyze the temperature-dependent ^{1}H NMR data and to determine barriers to conformational inversion for a number of para-substituted calix[4]arenes in several solvents. The rate of inversion at the coalescence temperature was calculated from the expression[14] $k_{coalescence} = \pi(\Delta\nu^2 + 6J^2)^{1/2}/(2^{1/2})$ where $\Delta\nu$ is the difference in chemical shift between the centers of the two doublets arising from the methylene protons, and J is the coupling constant. Substituting this value into the Eyring rate equation gives the expression

$$\Delta G^{\ddagger} = RT \ln \left(\frac{6.62 \times 10^{12}}{k_{coalescence}} \right)$$

Table I. Coalescence Temperatures, Methylene Shift Positions, and Free Energies of Activation for the Conformational Inversion of the Calix[4]arenes (**1**) at 100 MHz

para substituent	deuterated solvent	T_c, °C	methylene shifts, Hz H(A)	methylene shifts, Hz H(B)	$\Delta G^{\ddagger}$, kcal/mol
tert-butyl	chloroform	52	425	350	15.7
	bromobenzene	43	423	337	15.2
	toluene	39	425	324	14.9
	carbon disulfide	36	427	351	14.9
	benzene	35	423	336	14.8
	pyridine	15	472	360	13.7
hydrogen	chloroform	36	425	352	14.9
	bromobenzene	23	434	333	14.1
	toluene	18	416	314	13.9
	benzene	15	420	327	13.8
	acetonitrile	0	411	346	13.3
	acetone	−5	418	361	13.1
	pyridine	−22	478	345	11.8
phenyl	chloroform	44	443	373	15.3
	bromobenzene	36	433	353	14.9
	acetone	8	435	389	13.8
	pyridine	−2	521	378	12.8
allyl	chloroform	37	420	343	15.0
	acetone	5	413	352	13.5
	acetonitrile	2	409	343	13.3
tert-octyl[a]	chloroform	30	427	350	14.6
	bromobenzene	24	426	344	14.3
	toluene	28	423	325	14.4
	pyridine	−13	467	371	12.4
tert-amyl	chloroform	27	423	350	14.5
	bromobenzene	25	427	338	14.3
	toluene	36	424	322	14.8
isopropyl	chloroform	33	426	350	14.8
	bromobenzene	32	430	334	14.6
	toluene	30	428	322	14.4
benzoyl	chloroform	33	435	370	14.9
hydroxyethyl	chloroform	44	422	343	15.3
	acetone	18	428	307	13.8
dichlorodi-*tert*-butyl	chloroform	38	423, 420	347, 343	15.0
bromo	pyridine	2	492	350	13.0

[a] *tert*-Octyl is the designation used for 2,2,4,4-tetramethylbutyl.

(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) Kämmerer, H.; Happel, G.; Caesar, F. *Makromol. Chem.* **1972**, *162*, 179. Happel, G.; Mathiasch, B.; Kämmerer, H. *Ibid.* **1975**, *176*, 3317.
(6) Gutsche, C. D.; Bauer, L. J. *Tetrahedron Lett.* **1981**, 4763.
(7) Munch, J. H. *Makromol. Chem.* **1977**, *178*, 69.
(8) Gutsche, C. D.; Dhawan, B.; Levine, J. A.; No, K. H.; Bauer, L. J. *Tetrahedron* **1983**, *39*, 409.
(9) Andreetti, G. D.; Ungaro, R.; Pochini, A. *J. Chem. Soc., Chem. Commun.* **1979**, 1005.
(10) Andreetti, G. D.; Pochini, A.; Ungaro, R. *J. Chem. Soc., Perkin Trans. 2* **1983**, 1773.
(11) Saenger, W.; Betzel, C.; Brown, C. M. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 883. Saenger, W.; Betzel, C.; Hingerty, B.; Brown, G. M. *Nature (London)* **1982**, *296*, 581. Saenger, W. *Ibid.* **1979**, *279*, 343.
(12) Högberg, A. G. S. *J. Am. Chem. Soc.* **1980**, *102*, 6046. Högberg, A. G. S. *J. Org. Chem.* **1980**, *45*, 4498.
(13) Bottino, F.; Montaudo, G.; Maravigna, P. *Ann. Chim.* (*Rome*) **1967**, *57*, 972.
(14) Kurland, R. S.; Rubin, N. B.; Wise, W. B. *J. Chem. Phys.* **1964**, *40*, 2426.

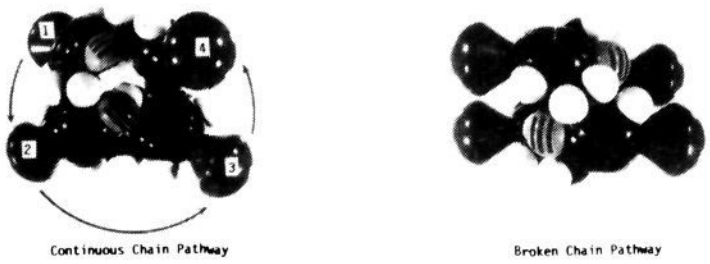


Figure 2. Space-filling models of the intermediate states for the continuous-chain and broken-chain pathways for inversion between cone conformations.

The results obtained from these measurements are shown in Table I where the coalescence temperature (T_c), the downfield shifts of the methylene protons (measured from the center of each of the doublets), and the free energy of activation for the inversion are recorded for each calixarene and solvent combination.

The data in Table I for the calix[4]arenes show that the barriers to inversion vary only slightly as the para substituent changes from isopropyl to *tert*-butyl to *tert*-amyl to *tert*-octyl; the highest value in chloroform (15.7 kcal/mol) is observed for the *tert*-butyl compound and the lowest value (14.5 kcal/mol) for the *tert*-amyl compound. Two para substituents that might have been expected to have a significant effect failed to do so; *p*-hydroxyethyl groups (which have the potential for intramolecular hydrogen bonding) and *p*-benzoyl groups (space-filling molecular models suggesting the capability of face-to-face association) changed the conformational mobility to a negligible extent. The insensitivity of the inversion barrier to the steric bulk of the para substituent is commensurate with what is thought to be the molecular motion involved in the process, i.e., a rotation of the aryl rings in a direction that brings the OH groups through the center of the annulus of the calixarene ring system, placing the para substituents away from the annulus.

A more subtle para-substituent effect, one that may have a steric component, arises from the possibility of complexation between calixarene and solvent. *p-tert*-Butylcalix[4]arene crystallizes from a number of solvents (e.g., toluene or chloroform) with a solvent molecule held in the cavity (an endo-calix complex), as indicated by X-ray crystallographic studies;[9] on the other hand, calix[4]arene, which has a hydrogen as the para substituent, is solvent free in the solid state.[10] The difference in the conformational inversion barrier between *p-tert*-butylcalix[4]arene and calix[4]arene (1.0 kcal/mol in chloroform solution, 1.1 kcal/mol in benzene solution, and 1.3 kcal/mol in toluene solution) might, therefore, be the result of the tighter complex that the *tert*-butylcalix[4]arene forms with the solvent in which it is dissolved. For both *p-tert*-butylcalix[4]arene and calix[4]arene the order of complexing ability toward nonpolar solvents decreases in the order: chloroform > bromobenzene > toluene > benzene. On the other hand, *p*-isopropylcalix[4]arene, *p-tert*-amylcalix[4]arene, and *p-tert*-octylcalix[4]arene show only very small differences in inversion barriers in this series of solvents.

In more polar solvents such as acetone and acetonitrile an appreciable decrease in the inversion barrier is observed which becomes even greater in the basic, hydrogen-bonding solvent pyridine. We postulate that the major effect of these solvents, particularly pyridine, is to disrupt the intramolecular hydrogen bonding, which is the primary force responsible for the preference of the calixarene to assume the cone conformation. For conformational inversion to occur it is necessary that the intramolecular hydrogen bonding be interrupted to some extent. The pathway envisaged by Kämmerer and co-workers[5] for this process invokes the formation of the 1,3-alternate conformation as an intermediate, a species that can then revert either to the original cone conformation or to its mirror image (i.e. the "inverted-cone" conformation). This mechanism, which we call the "broken-chain" pathway, requires the total disruption of the hydrogen bonding in the circular array of the initial cone conformation, although it can be regained between two of the hydroxyls when the 1,3-alternate conformation has been reached. As an alternative we suggest a "continuous-chain" pathway in which the aryl groups

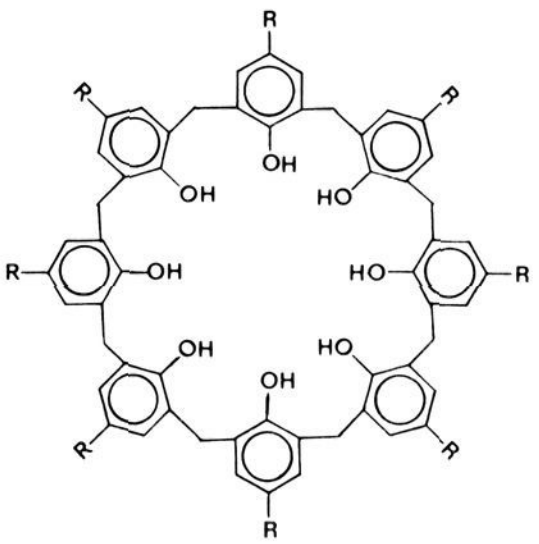
Table II. Coalescence Temperatures, Methylene Shift Positions, and Free Energies of Activation for the Conformational Inversion of the Calix[8]arenes (**2**) at 100 MHz

para substituent	deuterated solvent	T_c, °C	methylene shifts, Hz H(A)	methylene shifts, Hz H(B)	$\Delta G^{\ddagger}$, kcal/mol
tert-butyl	chloroform	53	433	351	15.7
	bromobenzene	43	433	337	15.1
	toluene	36	432	320	14.7
	carbon disulfide	32	430	337	14.6
	benzene	33	431	330	14.6
	acetone[a]	−48			~10.6
	pyridine[b]				<9
hydrogen	pyridine				<9
phenyl	pyridine				<9
tert-octyl	chloroform	43	437	351	15.2
	bromobenzene	38	431	348	15.0
	toluene	23	433	328	14.1
	pyridine[b]				<9
tert-amyl	chloroform	59	434	351	16.0
	bromobenzene	53	427	338	15.6
	toluene	36	423	324	14.8
isopropyl	chloroform	38	433	350	15.0
	bromobenzene	31	435	339	14.6
	toluene	20	433	322	13.9

[a] Completely resolved spectrum not observed because of poor solubility at this temperature. [b] The resonance remained a somewhat broadened singlet; no coalescence temperature was observed.

swing through the annulus in sequence, leading to an activated complex that resembles a skewed 1,2-alternate conformation, as illustrated in Figure 2. Although some hydrogen bond stretching is necessary and the complete disruption of one hydrogen bond is perhaps required to reach this intermediate state, space-filling models provide some support for the idea that an almost continuous hydrogen bonded system can be maintained throughout the process with only slight distortions of bond angles. The continuous chain mechanism also provides a reasonable explanation for the conformational inversion of the calix[8]arenes, as discussed in the following section.

Conformational Properties of the Calix[8]arenes (2). The remarkable similarity between the temperature-dependent ^{1}H NMR spectra of the calix[4]arenes and the calix[8]arenes has been discussed in earlier papers in this series,[1,6] a similarity that delayed the structural characterization of the cyclic octamers for a number of years. The much larger annulus of the calix[8]arenes, the



2

possibility of 16 "up-down" conformations, and the numerous other conformations in which one or more aryl rings project "out" would appear to make these more flexible and complicated than the calix[4]arenes. Yet, in nonpolar solvents the cyclic octamers possess temperature-dependent ^{1}H NMR spectra almost identical with those of the cyclic tetramers (see Figure 3), and the barriers to conformational inversion differ by only a fraction of a kcal/mol, as shown in Table II. In an earlier paper[6] we explained this in terms of a "pinched" conformation for the cyclic octamer, a form in which the molecule puckers to create two pairs of circular arrays

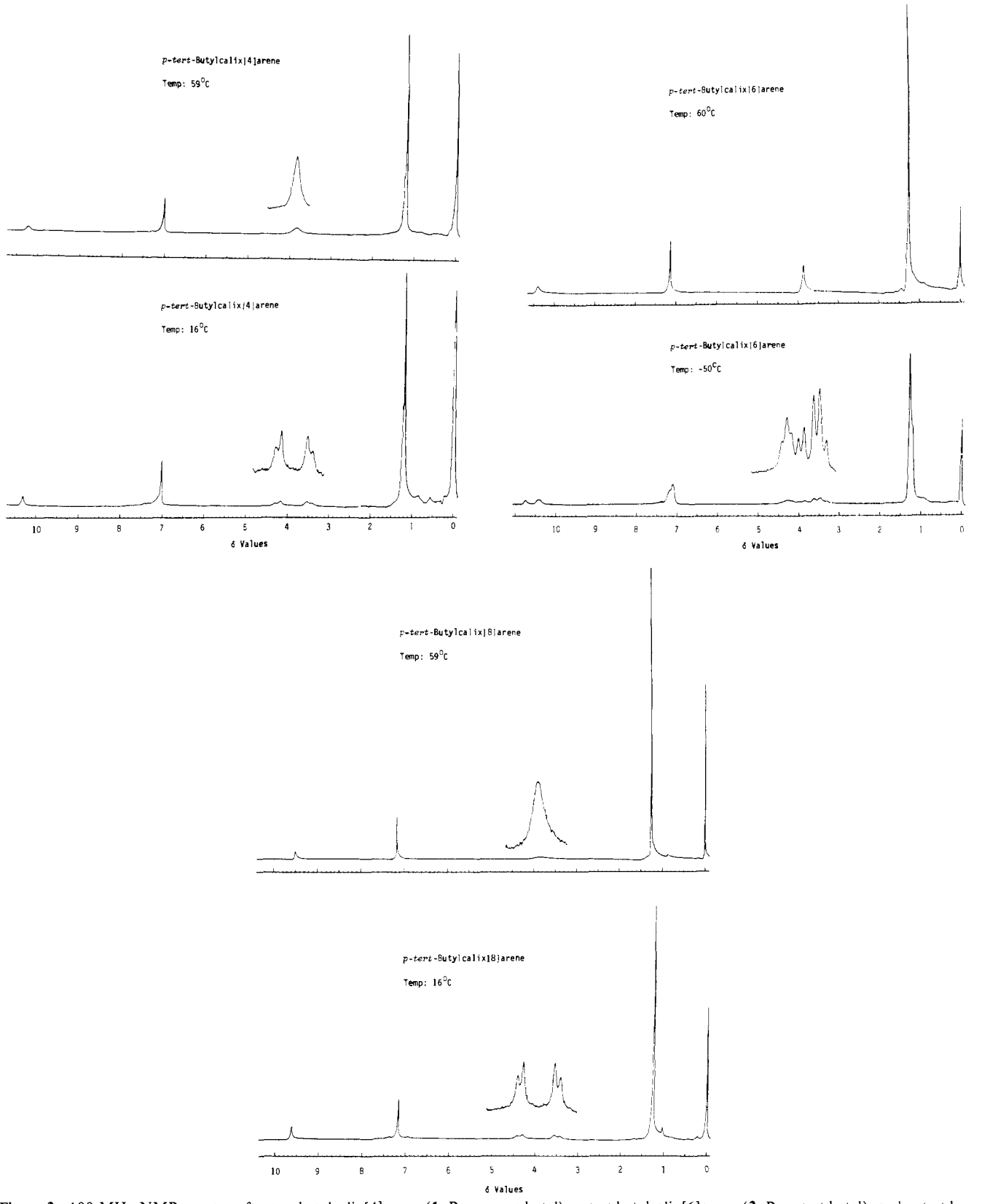


Figure 3. 100-MHz NMR spectra of *p-tert*-butylcalix[4]arene (**1**, R = *p-tert*-butyl), *p-tert*-butylcalix[6]arene (**3**, R = *tert*-butyl), and *p-tert*-butylcalix[8]arene (**2**, R = *tert*-butyl) in $CDCl_3$ solution above and below the coalescence temperatures.

of hydrogen bonds with four OH groups in each array. A recent X-ray crystallographic structure determination of *p-tert*-butylcalix[8]arene,[15] however, shows that in the solid state the molecule exists in an essentially flat form which we have named the "pleated-loop" conformation. Space-filling molecular models show that the pleated-loop conformation is perfectly constituted to facilitate circular flip-flop hydrogen bonding (see Figure 4). Although it is possible, and indeed under certain conditions quite likely, that the conformation in solution is different from that of the solid state, we think that the temperature-dependent ^1H NMR behavior of the cyclic octamer in solution may be best interpreted

(15) Gutsche, C. D.; Gutsche, A. E., Karaulov, A. I. *J. Inclusion Phenom.*, in press.

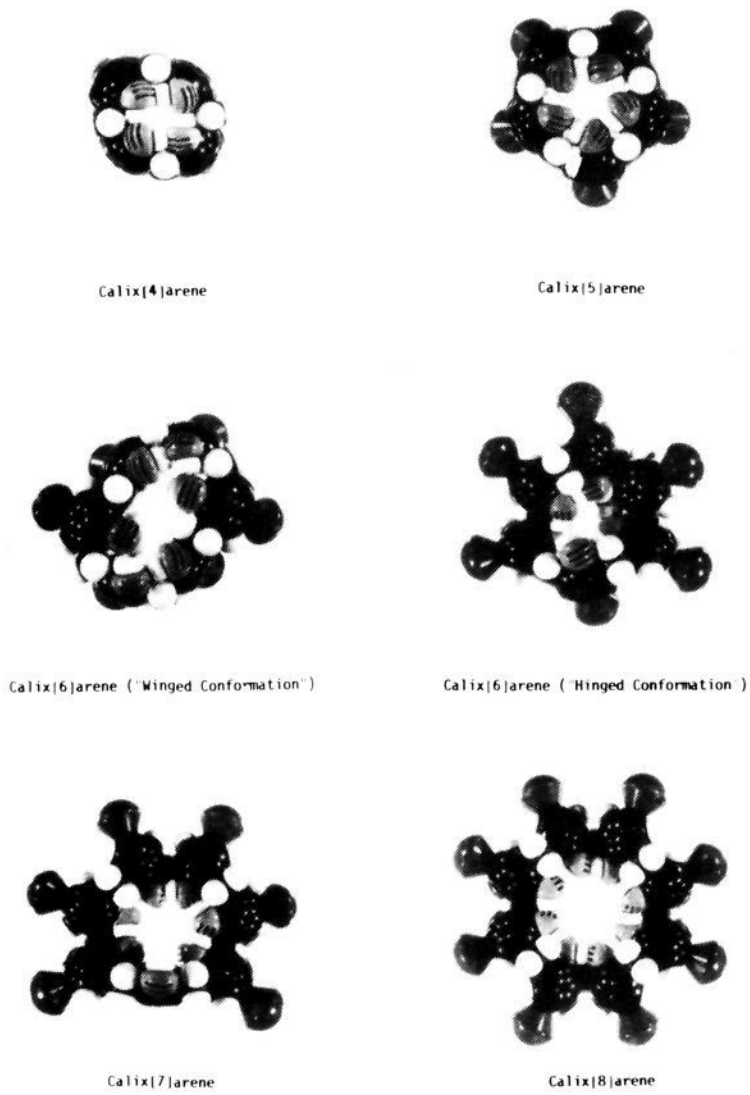
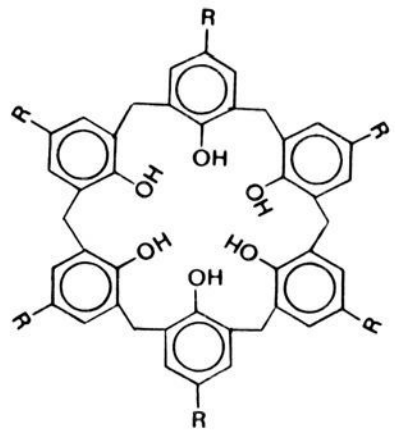


Figure 4. Space-filling molecular models of calix[4]arene, calix[5]arene, calix[6]arene, calix[7]arene, and calix[8]arene, showing the arrangements of the intramolecularly hydrogen bonded hydroxyl groups.

in terms of this conformation. Although the pleated-loop conformation of the cyclic octamer and the cone conformation of the cyclic tetramer appear to be rather different types of structures, both have "circular" hydrogen bonded arrays, and the relation of the methylene hydrogens to the rest of the molecule is virtually the same in both compounds. The interconversion between a pleated-loop conformation of the cyclic octamer and its mirror image form can occur in a continuous-chain fashion similar to that which we have postulated for the interconversion between the cone conformations of the cyclic tetramer. If one accepts this hypothesis, there remains the problem of explaining the qualitative and quantitative similarities of the inversion barriers of the cyclic octamer and cyclic tetramer in nonpolar solvents, i.e., in both series the inversion barriers decrease in the following order: chloroform > bromobenzene > toluene > benzene. Since a compound in the pleated-loop conformation lacks a cavity and would not be expected to form endo-calix complexes comparable to those postulated for compounds in the cone conformation, it is possible that the solvent phenomenon may arise from something other than endo-calix-type host–guest complexation.

The effect of polar solvents on the conformational behavior of the calix[8]arenes has been attributed to a disruption of the intramolecular hydrogen bonding[6] that maintains the pleated-loop conformation, pyridine being particularly effective in this respect. In this case, the structural differences between the calix[4]arenes and calix[8]arenes play a decisive role: the tetramer experiences much less structural perturbation because of its inherently less flexible macrocyclic ring system. Thus, although the intramolecular hydrogen bonding is disrupted in both cases, the cone conformation of the cyclic tetramers remains a relatively stable entity whereas the pleated-loop conformation of the cyclic octamer does not. That a greater structural change occurs in the case of the cyclic octamer is suggested by a comparison of the chemical shift differences of cyclic octamer vs. cyclic tetramer, viz. in chloroform the differences are 0.02 for the *tert*-butyl, 0.05 for the methylene, and 0.15 for the aromatic proton resonances, whereas in pyridine they are 0.14 for the *tert*-butyl, 0.13 for the methylene, and 0.37 for the proton resonances. This topic is discussed in greater detail in a latter paper of this series.[16]

Conformational Properties of the Calix[6]arenes (3). The cyclic hexamers can exist in eight "up–down" conformations as well as numerous others in which one or more of the aryl groups projects outward from the average plane of the molecule. Tempera-



3

ture-dependent ^{1}H NMR measurements indicate that in nonpolar solvents the cyclic hexamers are more flexible than either the cyclic tetramers or the cyclic octamers, the coalescence temperature in chloroform being 11 °C for the *p-tert*-butyl compound. Also, the low-temperature spectra are more complex, as shown in Figure 3. The methylene resonances of the cyclic hexamer appear as a complex envelope of eight peaks with shifts of δ 4.47, 4.33, 4.19, 4.03, 3.90, 3.65, 3.51, and 3.31 downfield from Me_4Si in a pattern that can be interpreted as arising from three sets of overlapping pairs of doublets. The three downfield peaks, which form the left-hand half of two sets of doublets, are in an approximately 1:2:1 ratio (the distortion is due to second order coupling effects) and are separated by a distance corresponding to the normal methylene coupling constant of ca. 13 Hz. Proceeding upfield, the next two peaks, which form the left-hand half of the remaining doublet, are in an approximately 1:1 ratio with a separation of 13 Hz. The last three peaks, which form the right-hand halves of three sets of doublets, are in an approximately 2:3:1 ratio with a separation of 13 Hz. Selective decoupling experiments confirm these assignments. The *tert*-butyl resonances appear as a pair of singlets at δ 1.28 and 1.16 in a 2:1 ratio, and the hydroxyl resonances appear as two broad peaks in a 2:1 ratio. These patterns are commensurate with a winged conformation (as illustrated in Figure 4) in which the molecule transannularly pinches in a fashion that places two of the aryl groups in "out" positions and the other four in up and/or down positions. Space-filling molecular models of this conformation show that the six hydroxyl groups form two clusters of three in which circular flip-flop hydrogen bonding might be possible, although the O–H–O angle is very acute. Another form that allows a similar pair of triplet OH group clusters is illustrated in Figure 4 and is referred to as the "hinged" conformation in which three contiguous aryl groups are up and the other three are down. Although X-ray crystallographic data are now available for the cyclic tetramers, cyclic pentamers, and cyclic octamers, none have yet been reported for a cyclic hexamer in the free phenolic form. Crystal structures for two of the ethers of cyclic hexamers have recently been obtained[17,18] which show that two of the aryl rings do, indeed, assume an out position. However, this observation has little relevance to the conformation of the parent calixarene, because hydrogen bonding plays no role in determining the conformation of the ether derivatives.

Since the low-temperature spectrum of *p-tert*-butylcalix[6]arene shows a pair of *tert*-butyl resonances as well as the several sets of methylene resonances, the barrier to conformational inversion can be calculated from coalescence temperatures in the manner described above. In chloroform solution the coalescence tem-

(16) Bauer, L. J.; Gutsche, C. D. *J. Am. Chem. Soc.*, following paper in this issue.
(17) Ungaro, R.; Pochini, A.; Andreetti, G. D.; Domiano, P. *J. Inclusion Phenom.* **1985**, *3*(1), 35.
(18) Lin, L.-g.; Stanley, G. S.; Gutsche, C. D., unpublished observations.

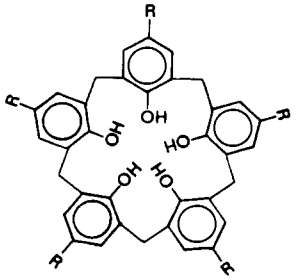
Table III. Coalescence Temperatures and Free Energies of Activation for the Conformational Inversion of the Calix[6]arenes (**3**) at 100 MHz

para substituted	deuterated solvent	T_c, °C	$\Delta G^{\ddagger}$, kcal/mol
tert-butyl	chloroform	11	13.3
	bromobenzene	−12	13.0
	acetone[a]	−40	11.1
	pyridine[a]	−54	9.0
hydrogen	chloroform	3	13.2
	acetone[a]	−49	~9.5
	pyridine[a]	−70	<9
tert-octyl	chloroform	12	13.6
allyl	chloroform	−2	13.0

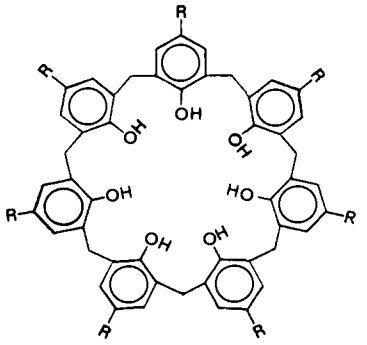
[a] Completely resolved spectra not observed because of limited solubility.

perature for the *tert*-butyl groups is −14 °C, corresponding to a free energy of activation for inversion of 13.3 kcal/mol; the coalescence temperature for the methylene resonances is 11 °C, corresponding to a free energy of activation for inversion of 13.0 kcal/mol. These values, which agree quite closely, are approximately 2 kcal/mol lower than those for the inversion barrier of *p-tert*-butylcalix[4]arene as well as *p-tert*-butylcalix[8]arene, reflecting the greater flexibility of the cyclic hexamer. As shown by the data in Table III, para substituents have little influence on the inversion barrier of the cyclic hexamers, and the effects of nonpolar solvents differ in the same order as in the cyclic tetramers and cyclic octamers. Again, pyridine lowers the coalescence temperature by a considerable amount; the barrier to inversion for the cyclic hexamer in pyridine falls between that of the cyclic tetramer and cyclic octamer.

Conformational Properties of the Calix[5]arenes (4) and Calix[7]arenes (5). The calixarenes containing odd numbers of aryl rings are much less accessible from "one-step" syntheses, although Ninagawa and Matsuda[19] have reported the isolation of small amounts of *p-tert*-butylcalix[5]arene and Nakamoto and Ishida[20] the isolation of small amounts of *p-tert*-butylcalix[7]arene from condensations of *p-tert*-butyphenol and formaldehyde. Our attempts to use these procedures for synthesis, however, have met with limited success, and only the cyclic pentamer has been obtained in an amount sufficient for NMR study. Its ^{1}H NMR



4



5

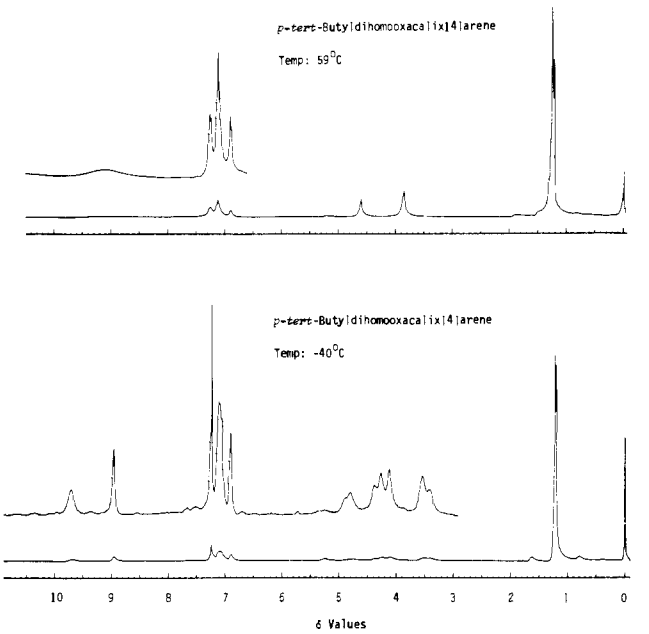


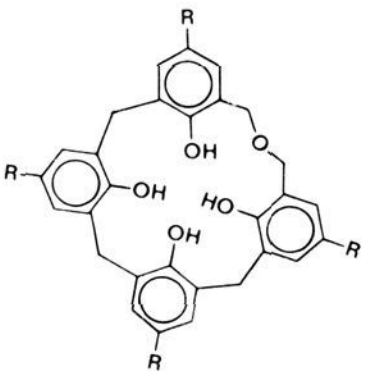
Figure 5. ^{1}H NMR spectrum of *p-tert*-butyldihomooxacalix[4]arene (**6**, R = *t*-Bu) in $CDCl_3$ at 100 MHz.

spectrum in chloroform at room temperature shows a broad singlet for the methylene hydrogens at δ 3.76 that resolves into a pair of doublets at lower temperature, the coalescence temperature of −2 °C corresponds to an inversion barrier of 13.2 kcal/mol. Kämmerer and co-workers[21] have reported similar values for a calix[5]arene (containing *tert*-butyl and methyl groups) that was synthesized by a stepwise method. This value is 2.5 kcal/mol lower than that of the corresponding cyclic tetramer and 0.2 kcal/mol higher than that of the corresponding cyclic hexamer, indicating a conformational flexibility very close to that of the latter. The conformation, however, is probably more similar to that of the cone form of the cyclic tetramer than the winged form of the cyclic hexamer. Space-filling molecular models show that a cone conformation is nicely constituted to allow a circular array of five intramolecularly hydrogen bonded hydroxyl groups (see Figure 4). X-ray crystallographic studies of *p-tert*-butylcalix[5]arene[17] and calix[5]arene[22] show that in the solid state the compounds are in a slightly distorted cone conformation and a symmetric cone conformation, respectively. The difference between the solid-state conformations of these two compounds can probably be attributed to the fact that calix[5]arene crystallizes as a 2:1 complex with acetone whereas *p-tert*-butylcalix[5]arene is reported to be solvent free.

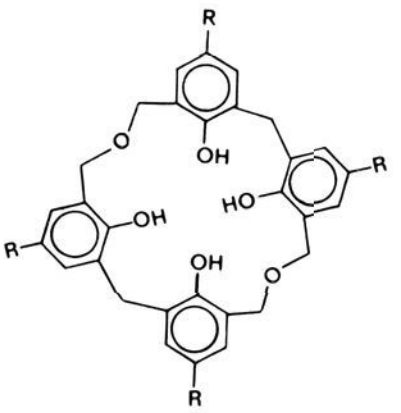
A temperature-dependent ^{1}H NMR study of a calix[7]arene has been reported by Kämmerer and co-workers[23] for a compound synthesized by a stepwise method. They observed a singlet for the methylene resonances in chloroform solution at room temperature and a pair of doublets at low temperature. The coalescence temperature of −10 °C corresponds to an inversion barrier of 12.3 kcal/mol. This indicates that the cyclic heptamer is the most flexible of the known calixarenes, probably a consequence of (a) the odd number of aryl groups, making it impossible to assume the pleated-loop conformation of the cyclic octamer or the winged conformation of the cyclic hexamer and (b) the large annulus, precluding a strongly hydrogen bonded cone conformation. Space-filling molecular models of the heptamer show that six of the aryl residues can easily form a continuous "pleated ribbon" but that considerable torsional strain is necessary to bring the seventh aryl residue into the ribbon to make it a loop. The temperature-dependent ^{1}H NMR data are probably commensurate

(19) Ninagawa, A.; Matsuda, H. *Makromol. Chem., Rapid Commun.* **1982**, *3*, 65.
(20) Nakamoto, Y.; Ishida, S. *Makromol. Chem., Rapid Commun.* **1982**, *3*, 705.
(21) Kämmerer, H.; Happel, G.; Mathiasch, B. *Makromol. Chem.* **1981**, *182*, 1685.
(22) Coruzzi, M.; Andreetti, G. D.; Bocchi, V.; Pochini, A.; Ungaro, R. *J. Chem. Soc., Perkin Trans. 2* **1982**, 1133.
(23) Kämmerer, H.; Happel, G. *Makromol. Chem.* **1980**, *181*, 2049.

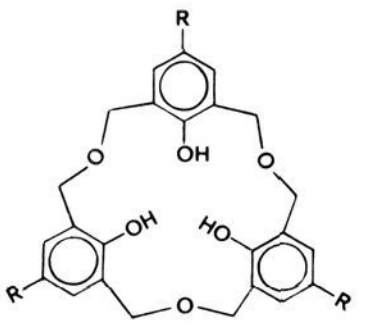
with a quasi-centrosymmetric structure,[24] and it is predicted that the X-ray structure will show the compound to be an almost planar array in which one of the aryl groups is only slightly out of the average plane. The strain necessary to achieve this conformation, however, is reflected in the considerably greater ease with which the cyclic heptamer interconverts with its mirror image conformation.



6



7



8

Conformational Properties of the Oxacalixarenes (6–8).[25] The substitution of a methylene bridge ($-CH_2-$) of a calixarene by a dimethyleneoxa bridge ($-CH_2OCH_2-$) to give a dihomooxacalixarene (**6**) increases the size of the annulus of the molecule; the resulting increased conformational mobility is reflected in the temperature-dependent ^1H NMR spectrum. As shown in Figure 5, the methylene resonances of **6** are broad singlets at δ 4.61 (arising from CH_2OCH_2) and δ 3.77 (arising from $ArCH_2Ar$) at room temperature that resolve at lower temperature into eight lines (two sets of pairs of doublets at δ 4.83, 4.33 with J = 12.0 Hz arising from CH_2OCH_2 and δ 4.21, 3.51 with J = 13 Hz arising from $ArCH_2Ar$).[26] The coalescence temperatures of −8 and −2 °C, respectively, for these sets of methylene resonances correspond to free energies of activation for the conformational inversion of 12.9 and 13.0 kcal/mol. These values are ca. 2.7 kcal/mol lower than that for *p-tert*-butylcalix[4]arene. At −60 °C the downfield set of doublets changes into a broad singlet which at −90 °C appears to be resolved into two new sets of resonances, viz. a pair of doublets at approximately the same position as the higher temperature set of doublets and an AB quartet displayed around the center of the original set of doublets. This second conformational inversion also affects the OH resonances, the room temperature peak at δ 9.75 splitting at −62 °C into a peak at δ 10.0 and another at δ 9.50. The conformational barrier for the process is ca. 10.3 kcal/mol. To explain this behavior it is postulated that in addition to the "cone-to-cone" interconversion which accounts for the higher of the two conformational barriers, a second flexing occurs which involves "inside" and "outside" forms

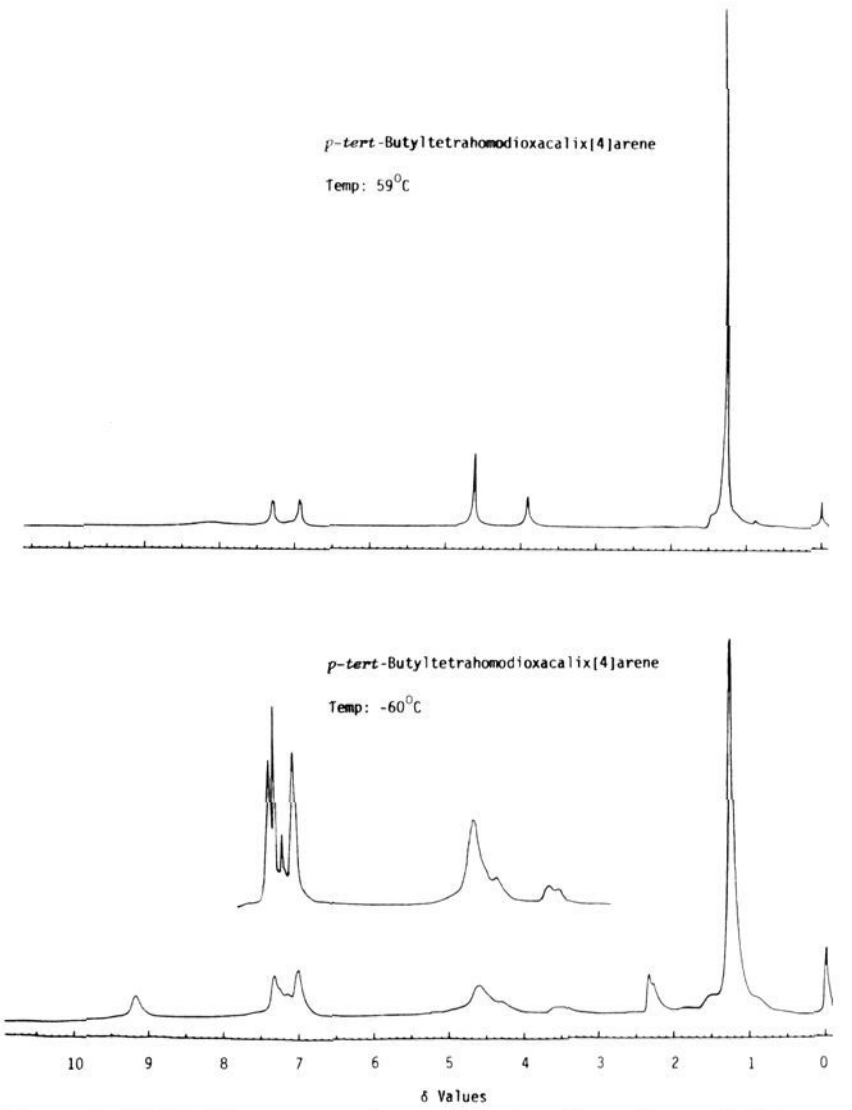


Figure 6. ^1H NMR spectrum of *p-tert*-butyltetrahomodioxacalix[4]arene (**7**, R = *t*-Bu) in $CDCl_3$ solution at 100 MHz.

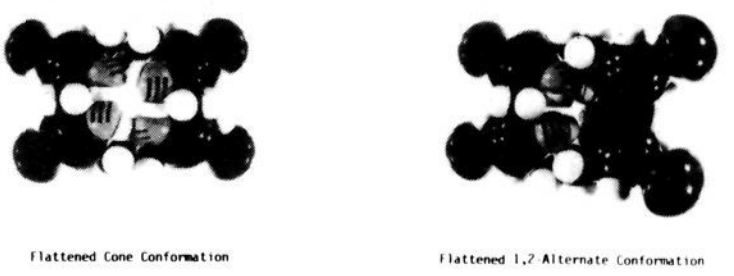


Figure 7. Space-filling molecular models of the flattened-cone and flattened-1,2-alternate conformations of the tetrahomodioxacalix[4]arene (**7**) ring system.

of the CH_2OCH_2 bridge and accounts for the lower of the conformational barriers. Two of the four hydroxyl groups would be expected to be differentially affected by the proximity of the CH_2OCH_2 oxygen, thus accounting for the two OH peaks at low temperatures.

In pyridine solution the coalescence temperature for the conformational inversion of **6** falls to −32 °C, corresponding to a free energy barrier of 10.0 kcal/mol. The decrease in the barrier of 3 kcal/mol from that observed in $CHCl_3$ is only slightly greater than that for *p-tert*-butylcalix[4]arene, suggesting that the role of intramolecular hydrogen bonding is approximately the same in the two systems. The rotational barrier for **6** is higher than that for the cyclic hexamer, indicating that the dihomooxa ring system is inherently less flexible than that of the cyclic hexamer.

The flexibility of a calix[4]arene system is further increased by the substitution of a pair of methylene groups by CH_2OCH_2 groups to give a tetrahomodioxacalix[4]arene (**7**). The ^1H NMR spectrum of *p-tert*-butyltetrahomodioxacalix[4]arene in chloroform at room temperature, shown in Figure 6, displays a sharp singlet at δ 3.93 for the $ArCH_2Ar$ methylene hydrogens and another sharp singlet at δ 4.63 for the CH_2OCH_2 methylenes. At −60 °C the upfield methylene resonance resolves into a pair of doublets with centers at δ 3.54 and 4.38 (J = 14 Hz), and the downfield

(24) A pleated-loop conformation of the cyclic heptamer does not possess true centrosymmetry and might be expected to show four different sets of methylene resonances. However, the four nonequivalent sets are so similar in their chemical environment that it is likely that their NMR behavior will be almost identical, leading to a low-temperature resolved spectrum consisting simply of a pair of doublets arising from the methylene resonance.

(25) Dhawan, B.; Gutsche, C. D. *J. Org. Chem.* **1983**, *48*, 1536.

(26) Compound **6** in the cone conformation contains two sets of nonequivalent $ArCH_2Ar$ methylene groups and one or two sets (depending on the local conformation) of nonequivalent CH_2OCH_2 methylene groups, giving the possibility of as many as five sets of pairs of doublets. Accidental equivalence apparently reduces the actual number to only two.

methylene resonance remains as a broadened singlet. The coalescence temperature for the upfield methylene resonances at −24 °C corresponds to a free energy barrier of 11.9 kcal/mol. In pyridine solution the coalescence temperature is lower than −70 °C and again demonstrates the importance of intramolecular hydrogen bonding in maintaining conformational rigidity in the calixarene series. A space-filling molecular model of **7** shows that a "flattened-cone" as well as a "flattened-1,3-alternate" form maximizes the intramolecular hydrogen bonding by establishing a cyclic array that includes all four of the OH groups, as illustrated in Figure 7. Of these two conformations the flattened-cone appears to be slightly less strained. The presence of three CH_2OCH_2 bridges in a calixarene system leads to still greater conformational flexibility. The ^1H NMR spectrum of *p-tert*-butylhexahomotrioxacalix[3]arene (**8**, R = *tert*-butyl) in $CDCl_3/CS_2$ solution shows no sign of restricted rotation at any temperature down to −90 °C, indicating that this compound is the most flexible of all of the ring systems investigated in the present study.

Conclusions. The conformational flexibility of calixarenes and oxacalixarenes carrying endo-annular hydroxyl groups is determined by the size of the macrocyclic ring which, in turn, influences the nature of the intramolecular hydrogen bonding.[27] To achieve the most effective intramolecular hydrogen bonding the calix[4]arenes, dihomooxacalix[4]arenes, and calix[5]arenes adopt a cone conformation; the tetrahomodioxacalix[4]arenes probably adopt a flattened-cone conformation; the calix[6]arenes are postulated to adopt a winged or hinged conformation; the calix[7]arenes are postulated to adopt a pseudo pleated-loop conformation; and the calix[8]arenes are thought to exist in a true pleated-loop conformation. Thus, as the ring size increases, the preferred conformation of the calixarenes becomes increasingly planar. Interconversion between the mirror image forms of a particular conformation takes place with varing degrees of ease; the value for the free energy of activation for inversion in nonpolar solvents decreases in the following order: calix[4]arenes = calix[8]arenes > calix[5]arenes = dihomooxacalix[4]arenes = calix[6]arenes > calix[7]arenes > tetrahomodioxacalix[4]arenes > hexahomotrioxacalix[3]arenes. In pyridine solution the intramolecular hydrogen bonding is disrupted, and the inversion barrier becomes primarily a function of ring size, viz. the value for the free energy of activation for inversion decreases in the following order: calix[4]arenes > calix[5]arenes > dihomooxacalix[4]arenes > calix[6]arenes > tetrahomodioxacalix[4]arenes > calix[8]arenes > hexahomotrioxacalix[3]arenes. The character of the para substituent appears to play no more than a minor role in determining the magnitude of the conformational inversion barrier in these compounds.

Acknowledgment. We are indebted to the National Institutes of Health (Grant GM-23534) and to a Biomedical Science Support Grant for generous financial support of this work. We are indebted to Drs. Shou-I Chen, Balram Dhawan, Kwang H. No, Jeffery A. Levine, Lee-Gin Lin, Philip F. Pagoria, and P. K. Sujeeth for supplying most of the compounds used in this work.

Registry No. **1** (R = *tert*-butyl), 60705-62-6; **1** (R = hydrogen), 74568-07-3; **1** (R = phenyl), 60705-63-7; **1** (R = allyl), 81294-23-7; **1** (R = *tert*-octyl), 97998-54-4; **1** (R = *tert*-amyl), 77769-14-3; **1** (R = isopropyl), 97998-55-5; **1** (R = benzoyl), 97998-56-6; **1** (R = hydroxyethyl), 97998-57-7; **1** (R = dichloro, di-*tert*-butyl), 97998-59-9; **1** (R = bromo), 97998-58-8; **2** (R = *tert*-butyl), 68971-82-4; **2** (R = hydrogen), 82452-93-5; **2** (R = phenyl), 92887-20-2; **2** (R = *tert*-octyl), 98013-93-5; **2** (R = *tert*-amyl), 93503-77-6; **2** (R = isopropyl), 98013-94-6; **3** (R = *tert*-butyl), 78092-53-2; **3** (R = hydrogen), 96107-95-8; **3** (R = *tert*-octyl), 98013-95-7; **3** (R = allyl), 98013-96-8; **4** (R = *t*-Bu), 81475-22-1; **5** (R = *t*-Bu), 84161-29-5; **6** (R = *t*-Bu), 72251-68-4; **7** (R = *t*-Bu), 85097-23-0; **8** (R = *t*-Bu), 76543-12-9.

(27) Correlations between the free energy of activation for conformational inversion and the IR and NMR characteristics of the hydroxyl groups in the calixarenes are only approximate, as illustrated by the following data for the compounds in $CDCl_3$ or $CHCl_3$ solution.

	ν_{OH}, cm^{-1}	δ_{OH}	$\Delta G^{\ddagger}$, kcal/mol
calix[4]arenes	3160	10.2	15.7
calix[5]arenes	3280	8.0	13.2
calix[6]arenes	3150	10.5	13.3
calix[7]arenes	3155	10.3	12.3
calix[8]arenes	3230	9.6	15.7
dihomooxacalix[4]arenes	3300	9.0, 9.7	12.9
tetrahomodioxacalix[4]arenes	3370	9.0	11.9
hexahomotrioxacalix[3]arenes	3410	8.5	<9

Calixarenes. 14. The Conformational Properties of the Ethers and Esters of the Calix[6]arenes and the Calix[8]arenes

C. David Gutsche* and Lorenz J. Bauer

Contribution from the Department of Chemistry, Washington University, St. Louis, Missouri 63130. *Received February 14, 1985*

Abstract: Ethers and esters of calix[6]arenes and calix[8]arenes are obtainable from the parent calixarenes. We have studied their conformational behavior by means of ^1H NMR spectroscopy and have shown these compounds to be more flexible than the corresponding derivatives of the calix[4]arenes. Conformational freezing can be observed, nevertheless, particularly when the ether groups are large moieties such as trimethylsilyl. In the case of the trimethylsilyl ethers of the calix[6]arenes, conformational inversion appears to take place via a "para substituent through the annulus" route rather than the more usual "oxygen through the annulus" route.

Detailed studies of the conformational properties of the ethers and esters of the calix[4]arenes have been reported.[1,2] Because of the small annulus in the calix[4]arenes the replacement of the hydrogens of the hydroxyl function with anything larger than

0002-7863/85/1507-6059$01.50/0