

## Topics in Calixarene Chemistry

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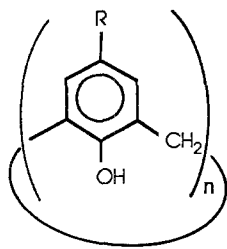
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**Abstract.** Several facets of calixarene chemistry have been investigated including the mechanism of their formation by the base-induced condensation of phenols and formaldehyde, procedures for introducing functional groups onto the 'upper rim' and 'lower rim' of calixarenes, the conformational behavior of calixarene oxyanions, the formation of complexes in aqueous and nonaqueous systems, and the application of calixarenes as catalysts.

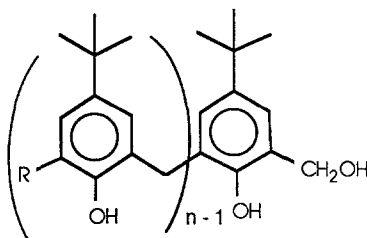
**Key words.** Calixarenes, calixarene oxyanions, conformation, complex formation, catalysis.

### 1. Mechanism of Formation of Calixarenes

Calixarenes, represented by the general structure **1**, comprise a family of macrocyclic compounds that can be prepared by the base-induced reaction of certain *p*-substituted phenols with formaldehyde. When hydroxymethylated compounds of the general structure **2** with *n* ranging from 1–4 and R = H or CH<sub>2</sub>OH are used



**1**



**2**

instead of phenols the mixture of calixarenes produced is independent of the starting material and dependent mainly on the reaction conditions, suggesting that a mobile equilibrium exists between various oligomeric precursors to the calixarenes. In a reaction carried out under mild conditions and monitored at various stages it was determined that the initially formed cyclic product is the cyclic octamer and that only under more strenuous conditions is it converted to the cyclic tetramer. This sequence of events is attributed to the existence of the linear oligomer **2** ( $n = 4$ , R = CH<sub>2</sub>OH) in a 'zig-zag' conformation [2] which must undergo a

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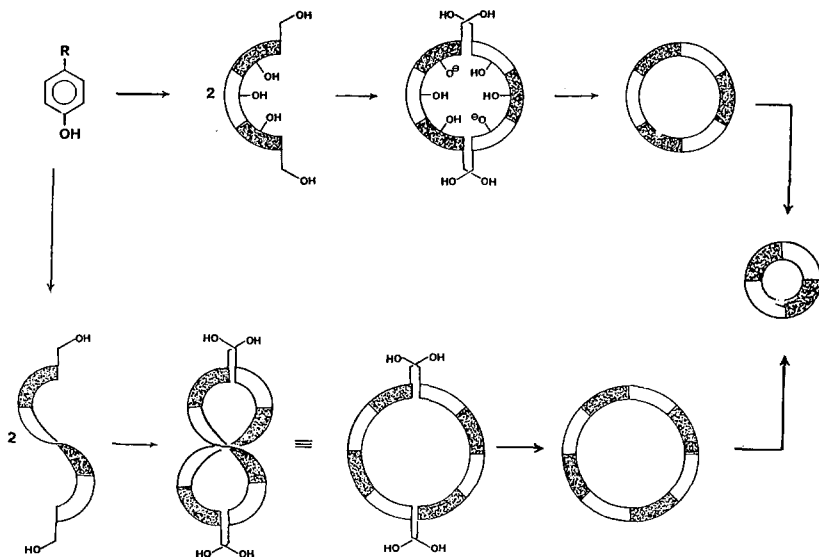


Fig. 1. Pathways of the one-step calixarene formation.

conformational change in order to cyclize. However, it can associate via intermolecular hydrogen bonding to a 'hemicalix[8]arene' in which a circular array of hydrogen bonds is present in essentially the same orientation as in the cyclic octamer [3] thus predisposing this intermediate to undergo conversion to the cyclic tetramer, as illustrated in Figure 1. In similar fashion, cyclic hexamer formation is attributed to the association of a pair of linear trimers to form a 'hemicalix[6]arene'. Among the unanswered questions in the one-step formation of calixarenes is (a) why the reaction is so extremely sensitive to the identity of the *p*-substituent, only *tert*-butylphenol or closely related phenols providing useful yields of pure calixarene and (b) why the odd-numbered calixarenes are formed in so much smaller an amount than the even-numbered calixarenes.

## 2. 'Upper-rim' Functionalization Procedures

Functionalized calixarenes are of interest as potential catalysts, and considerable effort has been directed to the attachment of various entities onto both the 'upper' and 'lower' rims of the cyclic oligomers. 'Upper rim' functionalization has been achieved by aluminum chloride-catalyzed debutylation followed by functional group introduction via the electrophilic substitution route [4], the *p*-Claisen rearrangement route [5], and the *p*-quinonemethide route. The last of these methods, illustrated in Figure 2, involves the condensation of a debutylated calixarene (**3**) with formaldehyde and any of a wide variety of dialkylamines to give Mannich bases (**4**). Quaternization of **4** (e.g. with MeI) to give **5** followed by treatment with two equivalents of a nucleophile (the first equivalent acting as a base) provides good yields of products of structure **6** where Nu can be a variety of functions including OR, CN, CH(CO<sub>2</sub>Et)<sub>2</sub>, CH(NO<sub>2</sub>)(CO<sub>2</sub>Et), SR, and N<sub>3</sub>. Weak nucleophiles (e.g. imidazole or 2-nitrophenoxide) fail to react, and very strong nucleophiles (e.g.

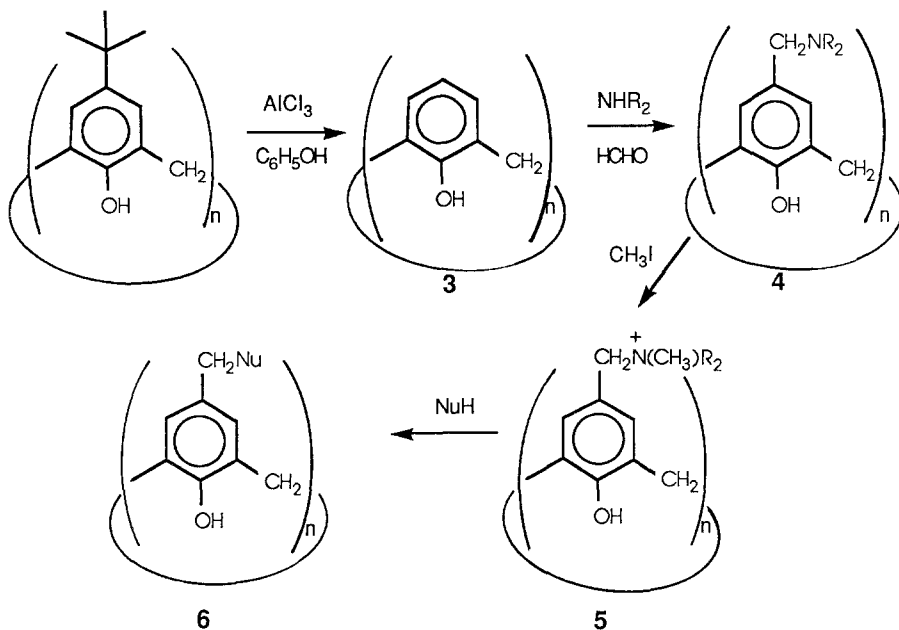


Fig. 2. *p*-Quinonemethide route to functionalized calixarenes.

acetylides, hydride) give mixtures in which some of the reaction involves displacement on nitrogen.

### 3. 'Lower-rim' Functionalization of Calixarenes

The OH groups at the 'lower-rim' of the calixarenes provide a ready handle for the introduction of substituents, and numerous esters and ethers have been made in this laboratory and elsewhere. The arylation of calix[4]arenes has now been studied in some detail using the aryl halides shown in Table I. The conformations of the products have been determined by  $^1\text{H}$  NMR measurements. The product mixtures

Table I. Product composition from the arylation of *p*-allylcalix[4]arene and *p*-*tert*-butylcalix[4]arene with *p*-substituted  $\text{ArCOCl}$ .

<i>p</i> -R group of of $\text{ArCOCl}$	$\sigma_{\text{para}}$	Product	
		<i>p</i> -allylcalix[4]arene	<i>p</i> - <i>tert</i> -butylcalix[4]arene
$\text{OCH}_3$	-0.27	1,3-alt	cone (90%); 1,3-alt (5%)
$\text{C}(\text{CH}_3)_3$	-0.20	1,3-alt	cone (80%); 1,3-alt (20%)
$\text{CH}_3$	-0.17	1,3-alt	cone (90%); 1,3-alt (5%)
H	0.0	1,3-alt	cone (98%); 1,3-alt (trace)
Br	0.23	1,3-alt	cone
CN	0.66	cone	cone
$\text{NO}_2$	0.76	cone	cone

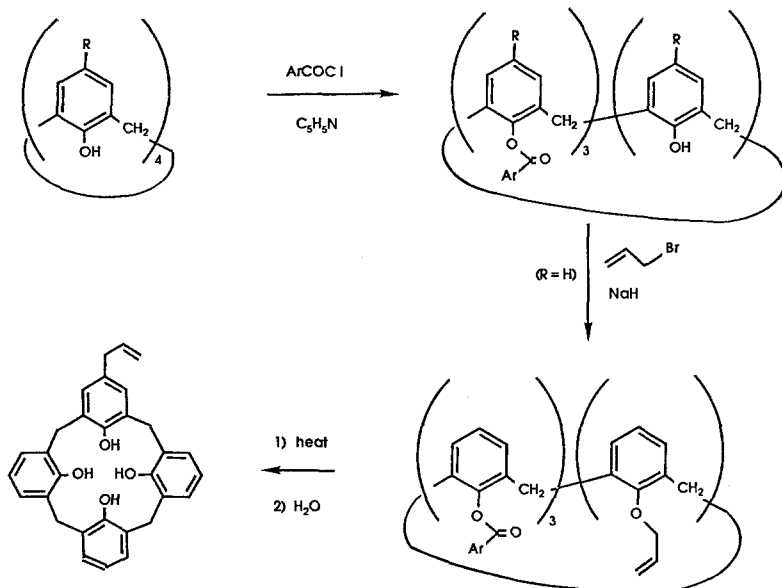


Fig. 3. Synthesis of *p*-monoallylcalix[4]arene via the tribenzoate.

indicated in Table I are interpreted as the result of a competition between the rate of conformational interconversion and the rate of derivatization, the slower the former and the more rapid the latter the more likely will be the formation of the cone conformer as the major product.

Solvent effects are shown to play a part in the reaction. For example, the use of pyridine in place of THF provides a means for obtaining triaroylates from calix[4]arenes and makes available a starting material for the preparation of 'upper-rim' mono-functionalized calix[4]arenes [6], as shown in Figure 3.

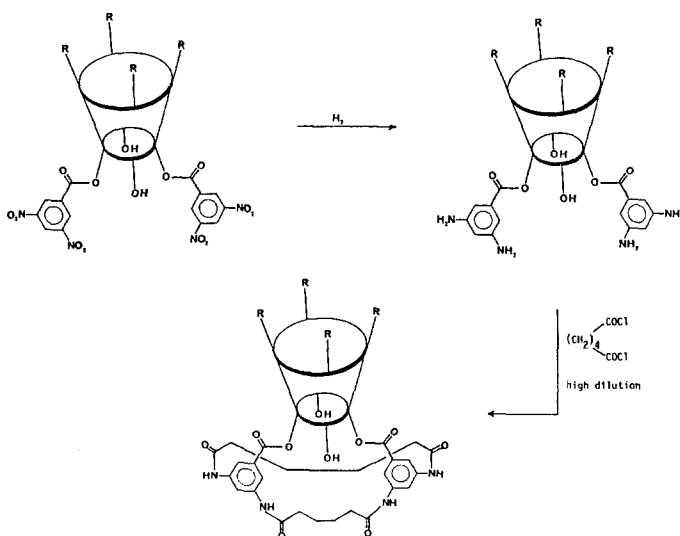


Fig. 4. Synthesis of a 'double cavity' calixarene.

Steric effects are shown to affect the outcome of the arylation reaction as illustrated, for example, by the reaction with 3,5-dinitrobenzoyl chloride which affords an excellent yield of a di-arylate and provides a starting material for the synthesis of a 'double cavity' calixarene, as illustrated in Figure 4.

#### 4. Conformational Behavior of Calixarene Oxyanions

Treatment of a DMSO solution of a calix[4]arene with incremental amounts of *n*-butyllithium generates solutions that have been analyzed by means of  $^1\text{H}$  NMR and  $^7\text{Li}$  NMR with the results shown in Figure 5. In both cases spectral changes are observed until four equivalents of base have been added, at which point the spectra remain essentially invariant upon addition of more base. The conformational identity of the various species can be established by inspection of the  $\delta$  3–5 ppm region of the  $^1\text{H}$  NMR spectra which arises from the  $\text{CH}_2$  protons, a pair of doublets signifying a cone conformation, two sets of pairs of doublets signifying a partial cone conformation, and a singlet signifying a 1,3-alternate conformation. Inspection of Figure 6 reveals that the mono- and tetra-anions are cone conformers and the tri-anion is a partial cone conformer. The spectrum of the system generated from two equivalents of base, however, is best interpreted as a superposition of the spectra of the mono- and tri-anions, suggesting that a dianion is unstable and disproportionates to equal amounts of these anions. These conclusions are corroborated by the  $^7\text{Li}$  NMR spectra which show single resonances for the mono- and tetra-anions, a three line spectrum for the tri-anion, and a spectrum for the system containing two equivalents of base that is the superposition of the spectra of the mono- and tri-anions.

Temperature-dependent NMR measurements of solutions containing calix[4]arenes provide a means for measuring rates of conformational interconversion;

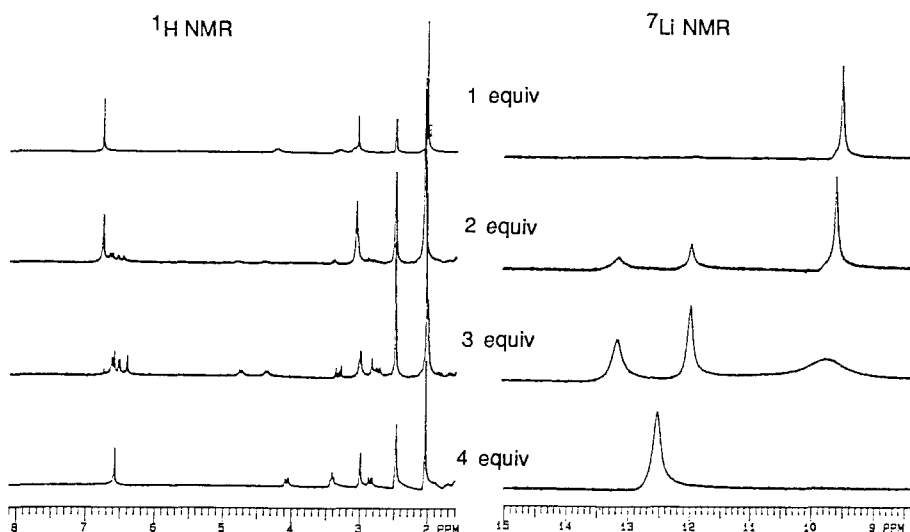


Fig. 5.  $^1\text{H}$  NMR and  $^7\text{Li}$  NMR spectra of lithium oxyanions of calix[4]arenes.

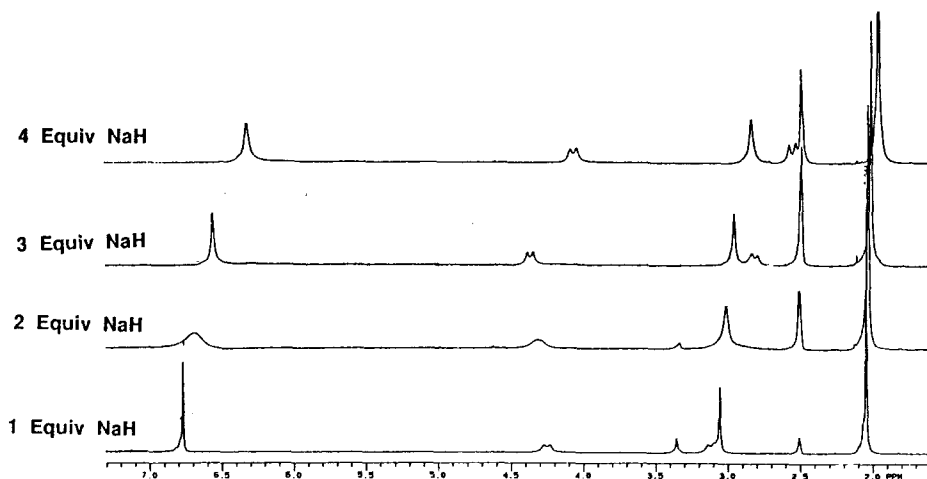


Fig. 6.  $^1\text{H}$  NMR spectra of the sodium oxyanions of calix[4]arenes.

e.g. in the case of the cone conformation a pair of doublets (from  $\text{CH}_2$  protons) indicates an interconversion that is slow on the NMR time scale, a singlet indicates an interconversion that is fast, and a broad signal characterizes the coalescence temperature  $T_c$ . The coalescence temperature for the mono-anion is *ca*  $90^\circ\text{C}$ , while the tri- and tetra-anions show no hint of coalescence at  $140^\circ\text{C}$ . To test the premise that a lithium cation is complexed by a calix[4]arene in crown ether-like fashion, a similar study was carried out with sodium as the cation, with the results shown in Figure 6. As in the lithium system, the mono- and tetra-anions exist in the cone conformation. In contrast, however, the tri-anion appears to exist in the cone rather than the partial cone conformation, and the system generated from two equivalents of base does not appear to be a mixture of the mono- and tri-anions. A temperature-dependent study of the sodium system showed that it is more conformationally mobile than the lithium system. For example,  $T_c$  for the tetra-anion is only  $80^\circ\text{C}$ . To further explore the relation between conformational mobility of the oxyanions and the size of the cation, the potassium tetra-anion was generated; its  $T_c$  was determined to be even lower, at  $20^\circ\text{C}$ .

These studies have been extended to the calix[6]arenes, which also have been observed to show changes in the  $^1\text{H}$  NMR spectra as incremental amounts of strong base, up to six equivalents, are added to a DMSO solution. With the calix[6]arene systems the spectra are considerably more complex than those of the calix[4]arenes, and conformational assignments are much more difficult to make. However, a comparison of the temperature-dependent behavior of the lithium and sodium oxyanions of the calix[6]arenes indicates that the sodium system is less conformationally mobile and suggests that here, also, a crown ether-like complexation of the metal ion may be occurring. The annulus of the calix[6]arene system is complementary in size to the sodium cation, while that of the calix[4]arene is complementary in size to the lithium cation.

## 5. Aqueous Solution Complexation of Organic Molecules

The *p*-quinonemethide method of functionalization has made carboxyl and amino-containing calixarenes available in all of the ring sizes 4–8, thus allowing the complexation behavior of these compounds in dilute aqueous base and acid to be measured. The guest molecules used were naphthalene, anthracene, pyrene, fluoranthene, and perylene (left-hand column in Figure 7), and the association constants for complex formation of these hydrocarbons with the various calixarenes are shown in Figure 7. The similarity in  $K_{\text{assoc}}$  values of the carboxy and amino calixarenes for a given hydrocarbon and a given ring size suggests that the site of complexation is not proximate to these functional groups but involves the hydroxyl end of the system (referred to in Section 3 as the ‘lower rim’). There is, in fact, a rough correlation between the size of the guest aromatic hydrocarbon and the size of the opening of the ‘lower rim’.

## 6. Non-aqueous Complexation of Organic Molecules

The interaction of calixarenes with amines in acetonitrile solution has been studied in some detail [7] and it has been postulated that a two-step sequence takes place in which a proton is transferred from the calixarene to the amine, producing a calixarene anion and an ammonium ion, followed by ion-pairing between these species. Toward most other types of organic molecules in organic solution, however, the simple calixarenes or calixarene derivatives have shown little tendency to form


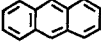
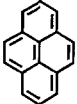
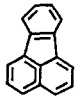
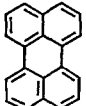
	Carboxy Calixarene				Amino Calixarene			
	$n = 5$	$n = 6$	$n = 7$	$n = 8$	$n = 5$	$n = 6$	$n = 7$	$n = 8$
	$3.7 \times 10^3$	$3.7 \times 10^3$	$3.9 \times 10^3$	$6.1 \times 10^2$	$3.3 \times 10^3$	$4.5 \times 10^3$	$3 \times 10^3$	$1.1 \times 10^3$
	$9.1 \times 10^3$	$1.3 \times 10^4$	$1.1 \times 10^4$	$< 10^2$	$9 \times 10^3$	$1.6 \times 10^4$	$8.3 \times 10^3$	$< 10^2$
	$< 10^2$	$< 10^2$	$1.1 \times 10^4$	$4.4 \times 10^4$	$< 10^2$	$< 10^2$	$9 \times 10^3$	$3.6 \times 10^4$
	$4 \times 10^3$		$3.6 \times 10^3$	$1.4 \times 10^4$	$2 \times 10^3$	$4 \times 10^3$	$3 \times 10^3$	$1.5 \times 10^4$
	$< 10^2$	$< 10^2$	$9 \times 10^3$	$8.4 \times 10^3$	$< 10^2$	$< 10^2$	$1 \times 10^4$	$1 \times 10^4$

Fig. 7. Complexation of aromatic hydrocarbons in aqueous solution by carboxy and amino calixarenes.

strong complexes. For example, the tetra-(*p*-nitrobenzoyl) ester of calix[6]arene was considered to be a likely candidate, because CPK models indicated it to contain a long trench into which an aromatic hydrocarbon might fit. This compound, prepared by treating a calix[4]arene with an excess of NaH and *p*-nitrobenzoyl chloride, was shown by  $^1\text{H}$  NMR studies to possess the conformation pictured in Figure 8. Solutions of the tetra-ester in  $\text{CHCl}_3$  containing naphthalene or anthracene, however, showed no change in the resonance lines of the hydrocarbons, and a closer investigation of the  $^1\text{H}$  NMR characteristics of the tetra-ester, using transient NOE techniques, reveals that it probably exists in a form in which the aromatic moieties is tipped inward to fill the crevice created by the other aromatic moieties, thus excluding external guest molecules.

In contrast, 'double cavity' calixarenes, synthesized as described in Section 3, show a significant tendency to form complexes in organic solvents. In particular, they appear to interact with acidic compounds, as illustrated by the data in Figure 9 for carboxylic acids and in Figure 10 for phenols, where the magnitudes of the changes in chemical shifts of the resonances of the guest molecule are taken as a measure of the degree of complexation. Even molecules as weakly acidic as acetonitrile show significant  $^1\text{H}$  NMR shifts in the presence of the 'double cavity' calixarene, as illustrated by the data in Figure 11. Moderate complexation (shifts *ca* 0.05 ppm) was observed with ethanol, *n*-butanol, phenol, bromophenol, nitrobenzene, and  $\text{CH}_2\text{Cl}_2$ . Weak or no complexation (shifts less than 0.02 ppm) was observed with aniline, benzene, acetone, toluene, bromobenzene, adiponitrile, quinuclidine, collidine, ethyl cyanoacetate, and ethyl nitroacetate. That the apparent degree of complexation is not directly proportional to the acid strength of the guest is shown by a variety of comparisons. For example, isobutyric acid shows less

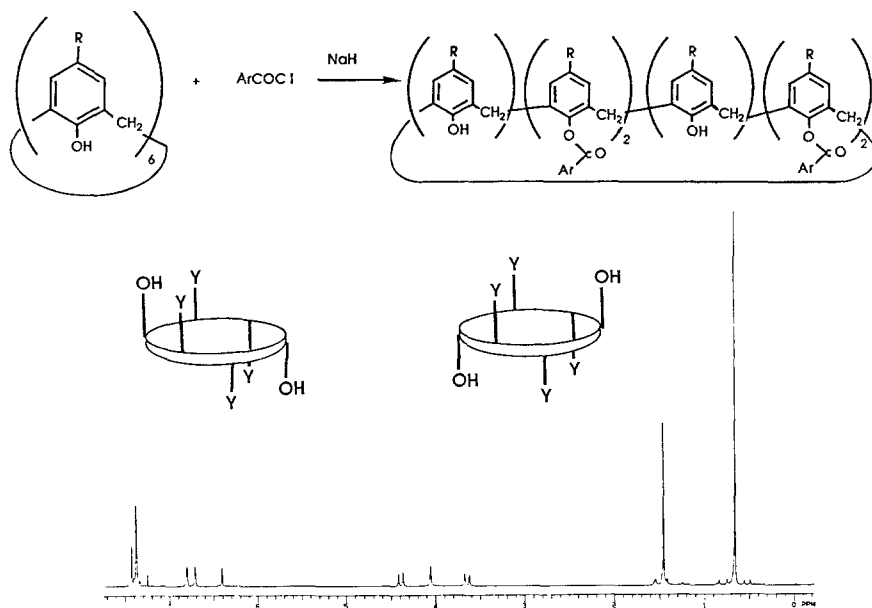


Fig. 8. Conformation of tetra-(*p*-nitrobenzoyloxy)-calix[6]arenes.



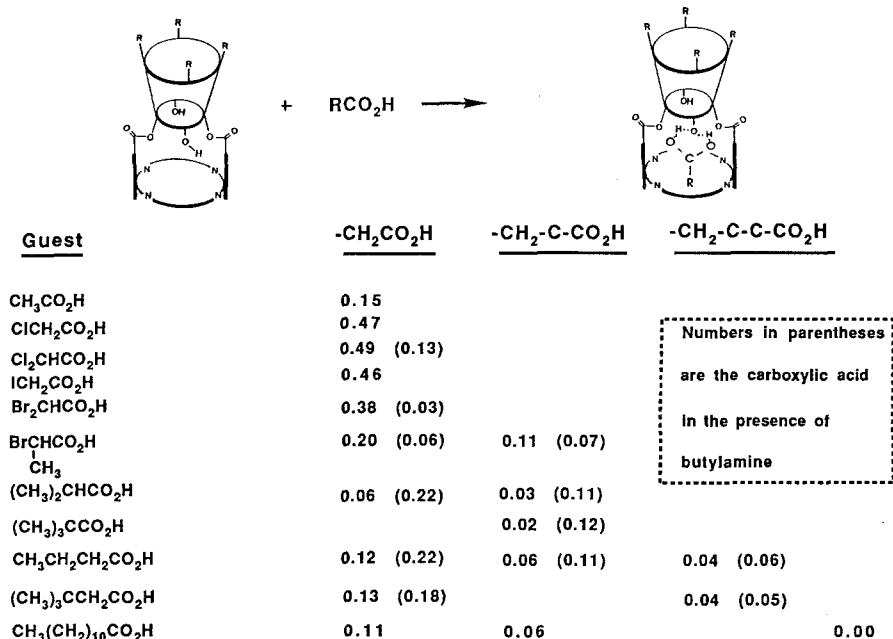


Fig. 9. Complexation of a 'double cavity' calixarene with carboxylic acids.

<u>Guest</u>	<u>H<sub>ortho</sub></u>	<u>H<sub>meta</sub></u>	<u>H<sub>para</sub></u>
Phenol	0.04	0.05	0.06
<i>o</i> -Nitrophenol	0.01 (0.02)	0.02 (0.02)	0.02 (0.02)
<i>m</i> -Nitrophenol	0.02 (0.09); 0.03 (0.12)	0.13 (0.08)	0.25 (0.13)
<i>p</i> -Nitrophenol	0.04 (0.14)	0.10 (0.08)	
2,4-Dinitrophenol	0.00	0.01; 0.03	
2,5-Dinitrophenol	0.01	0.02	0.00
Picric Acid		0.04	

Numbers in parentheses are the phenol in the presence of butylamine

Fig. 10. Complexation of a 'double cavity' calixarene with phenols.

interaction than acetic acid, and *m*-nitrophenol and *p*-nitrophenol show a stronger interaction than *o*-nitrophenol, 2,4-dinitrophenol, or picric acid. To explore this phenomenon in greater detail <sup>1</sup>H NMR relaxation values (*T*<sub>1</sub>) were measured for the 'double cavity' calixarene in the presence of several carboxylic acids as well as *m*-nitrophenol, with the results shown in Figure 12. These values were compared with those of the guest molecule both in the absence of the calixarene and in the presence of butylamine, to which a proton transfer occurs. In the case of butyric acid the *T*<sub>1</sub> values are significantly lower in the presence of the calixarene than in the presence of butylamine, whereas this is not true with pivalic acid,

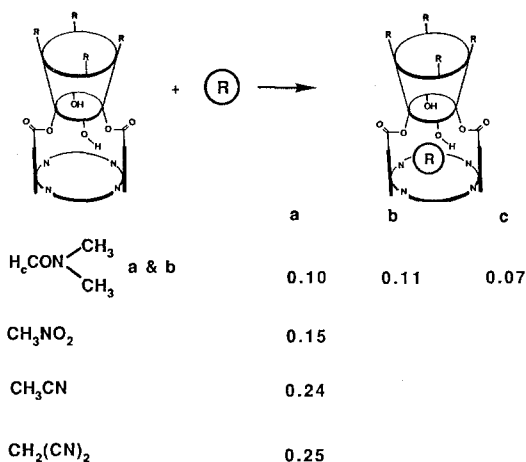


Fig. 11. Complexation of a 'double cavity' calixarene with small molecules.

indicating that butyric acid forms a complex while pivalic acid does not. The  $^1\text{H}$  NMR chemical shift data indicating *m*-nitrophenol forms a complex are corroborated by the  $T_1$  measurements, which show values that are considerably lower than those of the uncomplexed guest and also lower than those of the guest in the presence of butylamine.

Guest		$T_1$ (neat)	$T_1$ ( with calixarene)	$T_1$ (with butylamine)
$\text{CH}_3\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$	$\text{H}_a$	2.71	0.62	1.32
	$\text{H}_b$	3.03	0.61	1.50
	$\text{H}_c$	2.73	0.80	1.85
$(\text{CH}_3)_3\text{CCO}_2\text{H}$		2.50	1.81	1.45
$\text{CH}_3(\text{CH}_2)_5\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$	$\text{H}_a$	1.26	0.47	0.59
	$\text{H}_b$	1.29	0.49	0.87
	$\text{H}_{\text{CH}_3}$	2.42	1.23	2.00
$\text{CH}_3(\text{CH}_2)_8\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$	$\text{H}_a$	1.19	0.58	0.66
	$\text{H}_b$	1.32	0.50	1.05
	$\text{H}_c$	2.57	1.87	2.26
	$\text{H}_a$	4.11	1.48	2.88
	$\text{H}_b$	5.00	1.60	2.76
	$\text{H}_c$	4.27	1.67	3.37
	$\text{H}_d$	4.86	3.23	4.38

Fig. 12.  $T_1$  values for guest molecules, free and complexed with a 'double cavity' calixarene.

Since the most basic group in the calixarene is the amide moiety, the  $pK_{BH}$  of which would be expected to be quite low, the interaction with acids is unlikely to involve complete proton transfer. Hydrogen bond formation, combined with van der Waals interactions between host and guest, are probably responsible for the association. The initial concept of the 'double cavity' calixarene considered it to be a molecule in which the 'lower cavity' is established by the macrocyclic tetraamide ring, complex formation involving the insertion of the guest molecule through this annulus so as to bring its polar end proximate to the phenolic groups, as suggested in Fig. 9. The  $^1H$  NMR spectrum of the 'double cavity' calixarene, however, shows a pair of resonances from N—H, and an NOE experiment indicates that one (or two?) of the amides is proximate to an OH group. A CPK model conformationally adjusted to accommodate these data shows a cavity not in the bottom of the molecule but at the side of the molecule. It is hoped that X-ray crystallography of the 'double cavity' calixarene will allow an accurate assignment of the detailed architecture of this molecule.

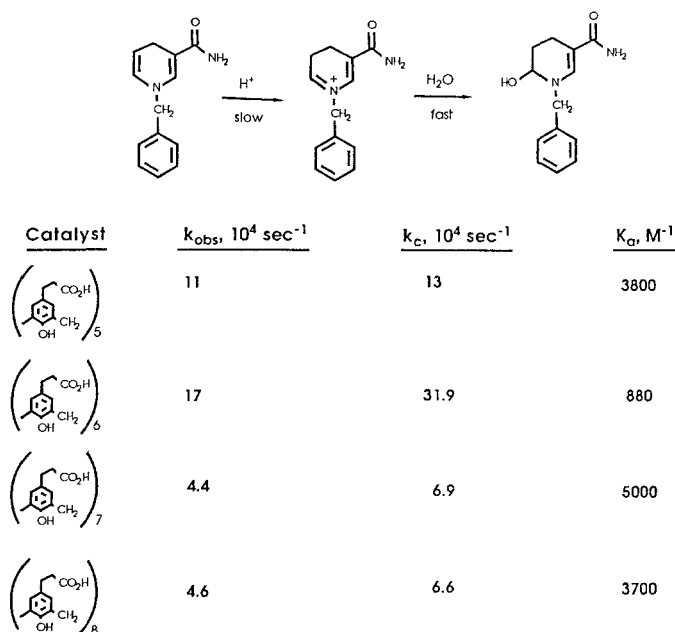


Fig. 13. Catalysis of the hydration of a dihydropyridine.

## 7. Catalysis of the Hydration of a Dihydropyridine

Shinkai and coworkers [8] have prepared the water soluble hexasulfonate of calix[6]arene and have shown that it enhances the rate of the acid-catalyzed addition of water to *N*-benzylidihydronicotinamide. With the water soluble carboxy calixarenes now available by the procedure described in Section 2 it is of interest to compare these with the sulfonate and also to ascertain the effect of ring size on the catalysis. The observed rates of hydration, the values of the catalytic constant  $k_c$ ,

and the values of the association constant  $K_a$  for carboxycalix[n]arenes with  $n = 5-8$  are shown in Figure 13. The greatest catalysis is observed for the cyclic hexamer, the rates dropping off as the ring is made smaller or larger than six aromatic moieties. Carboxycalix[4]arene shows no catalysis whatsoever. Although carboxycalix[6]arene shows a significant level of catalysis it is less effective than the sulfonatocalix[6]arene, for which Shinkai obtained a catalytic constant of 131 and an association constant of 564. The difference can probably be attributed to the greater acid strength of the arenesulfonate groups, in keeping with Shinkai's rationalization of the catalysis as a complexation-polarization phenomenon.

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