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Conformational and complexational characteristics of calixarenes

C. D. Gutsche, M. Iqbal, K. S. Nam, K. See, and I. Alam

Department of Chemistry, Washington University, St Louis, MO 63130

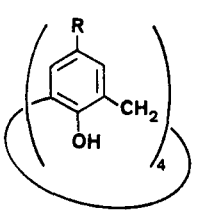
Abstract. Syntheses of functionalized calix[4]arenes have been achieved by two new routes, one involving attachment of groups in the p-positions by means of quinonemethide intermediates and the other involving attachment of groups on the oxygens by means of ester formation using functionalized aroyl chlorides. The complexation properties of calixarenes have been studied with unfunctionalized calixarenes and amines, with amino calixarenes and metal ions, and with "double cavity" calixarenes and various guest molecules. The conformational behavior of the mono-, di-, tri-, and tetra-anions of several calix[4]arenes has been studied, and it has been demonstrated that the mono- and tetra-anions exist in the cone conformation, that the tri-anion exists in the partial cone conformation, and that the di-anion partitions between the mono- and tri-anions.

SYNTHESIS OF FUNCTIONALIZED CALIXARENES

p-Quinonemethide route

Calixarenes are cavity-containing macrocyclic compounds that have attracted interest because of their potential for forming host-guest complexes and, if appropriately functionalized, acting as enzyme mimics (ref. 1). Functionalized calixarenes have previously been prepared by the direct substitution route (ref. 2) and the p-Claisen rearrangement route (ref. 3 & 4); the present work adds another procedure for introducing various groups onto the p-position of the calixarene framework.

p-tert-Butylcalix[4]arene (**1b**) can be prepared in good yield by the base-induced condensation of p-tert-butylphenol and formaldehyde (ref. 5). Aluminum chloride-catalyzed removal of the tert-butyl groups proceeds in excellent yield (ref. 3 & 4), making calix[4]-arene (**1a**) a readily available starting material. Treatment of a THF-acetic acid solution of **1a**, formaldehyde, and the appropriate secondary amine at room temp for 1 day affords the Mannich bases **2** in 70–90% yields. Quaternization of **2** with methyl iodide yields **3**, and treatment of **3** with various nucleophiles under basic conditions yields **5**, presumably via the intermediate p-quinonemethide **4** (e.g. the quaternary salt of the p-bromobenzenesulfonate of **3** undergoes no reaction when treated with cyanide under conditions that convert **3** to **5a**).



a (R = H)
b (R = t-butyl)
c (R = allyl)

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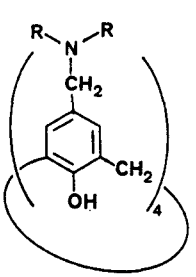

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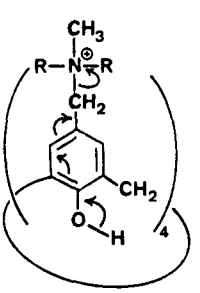

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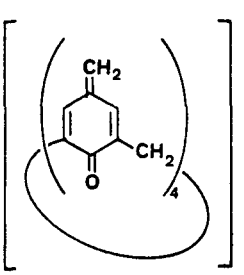

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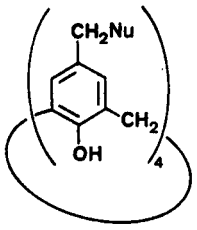
The p-quinonemethide route provides a particularly short pathway to a variety of functionalized calixarenes. For example, the preparation of p-(2-aminoethyl)calix[4]arene (**6b**) as previously described via the p-Claisen rearrangement route (ref. 3) involved oxidation of the allyl groups to aldehydes, reduction of the aldehydes to alcohols, conversion of the alcohols to bromides, replacement of the bromines with azido groups, and reduction of the azido groups to yield **6b**. This same compound has now been prepared simply by reduction of **5a**. The lower homolog, p-(aminomethyl)calix[4]arene (**6a**) is readily



a (Nu = CN)

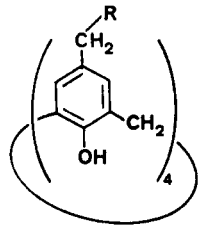
b (Nu = N_3)

c (Nu = $CH(CO_2Et)_2$)

d (Nu = $CH(CO_2Et)NO_2$)

e (Nu = H)

5



a (R = NH_2)

b (R = CH_2NH_2)

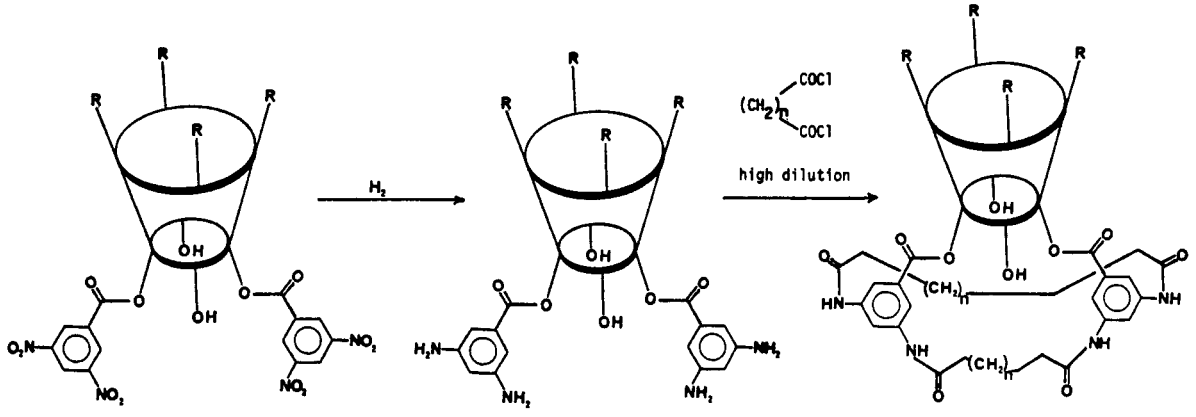
c (R = CO_2H)

6

available by reduction of the azide **5b**, and the p-quinonemethide route also provides an easy way for introducing carboxyl groups into the calixarene framework through the use of malonic ester methodology leading to **5c** and **5d**. Unfortunately, acetylides fail to react smoothly, the DMSO anion competing as a nucleophile, and the reaction appears to be limited to more weakly basic anions such as cyanide, methoxide, azide, sulfide, and malonate. Thus, hydride is not a particularly useful nucleophile, although it does yield some p-methylcalix[4]arene (**5e**) which is of historical interest in being the first calixarene to be synthesized by a stepwise, rational sequence (ref. 6).

Benzoylation route

Calix[4]arenes readily form esters and ethers, many of which have been made and studied (ref. 7). In the majority of cases all four of the hydroxyl groups react to afford the tetra-substituted compounds. However, 3,5-dinitrobenzoyl chloride reacts with only two of the hydroxyl groups to give symmetrically substituted bis 3,5-dinitrobenzoates (**7**) in high yields from which the corresponding bis-3,5-diaminobenzoates (**8**) are easily prepared by stannous chloride reduction. Treatement of **8** with the acid chlorides derived from 1,ω - alkanedioic acids produces compounds of structure **9** in which the cavity of the original calixarene is now accompanied by a second cavity on the other face of the molecule, i.e. "double cavity" calixarenes.



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COMPLEXATION PROPERTIES OF CALIXARENES

Unfunctionalized calixarenes and amines

The interaction of calix[4]arenes such as **1** and amines has been interpreted in terms of a proton transfer from the calixarene to amine followed by association of the calixarene anion (**10**) with the ammonium cation to form an endo-calix complex (**11**) (ref 8). A more detailed study of this phenomenon treats the proton transfer step (K_1) and the "complexation" step (K_2) as discrete processes, although it is recognized that these might be merged into a single step. Whereas UV spectral measurements appear to arise primarily as a result of the first step, NMR measurements assess the net result of both steps. Table 1 presents the proton chemical shift and relaxation rate values of the amine component that are observed in the ^1H NMR spectra of tert-butylamine and neopentylamine in CD_3CN solutions containing equimolar amounts of p-allylcalix[4]arene (**1c**) at 16°C. Table 2 shows similar data for the calixarene component of the complexes.

$$ArOH + R_3N \rightleftharpoons ArO^- + R_3NH^+ \rightleftharpoons ArO^-\ldots{}^+HNR_3 \qquad \text{(equation 1)}$$

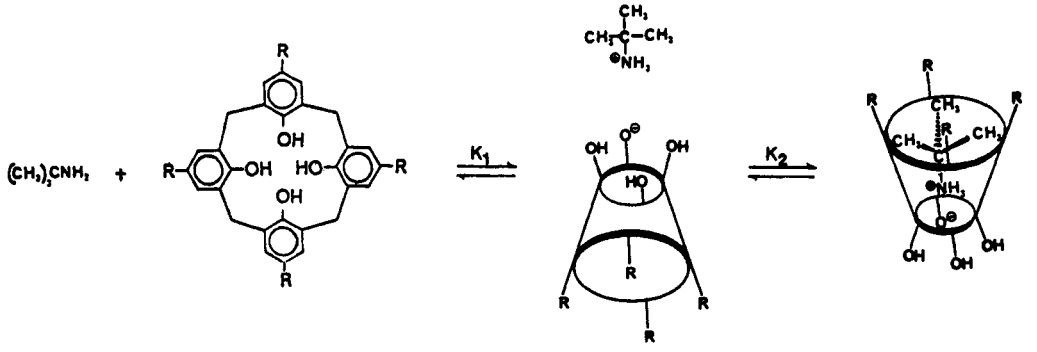

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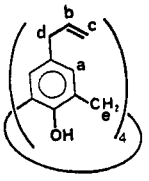
Table 1. Chemical shift and T_1 values for the protons in tert-butylamine and neopentylamine in the presence of an equimolar amount of p-allylcalix[4]arene or CF_3CO_2H in 0.007 M concentration in CD_3CN.

Acid	tert-Butylamine			Neopentylamine		
	δ (CH_3)	$T_1(CH_3)$	δ (CH_2)	δ (CH_3)	$T_1(CH_2)$	$T_1(CH_3)$
None	1.062	5.507	2.318	0.826	5.548	5.170
p-Allylcalix[4]arene	1.302	0.706	2.569	0.920	2.566	2.332
CF_3CO_2H	1.337	2.115	2.766	0.982	2.035	2.332

Table 2. Chemical shift and T_1 values for the protons in p-allylcalix[4]arene in the tert-butylamine and neopentylamine complexes at 0.007 M concentration in CD_3CN



	δ, Base				T_1 Values			
Position	None	tert-Butylamine	Neopentylamine	NaOH	None	tert-Butylamine	Neopentylamine	NaOH
a					1.945	1.197	1.720	1.835
b	5.837	5.854	5.850	5.857	4.758	3.772	4.190	4.526
c	4.927	4.974	4.976	4.974	2.994	2.055	2.677	2.939
d	3.160	3.126	3.132	3.124	1.234	0.657	1.073	1.093

Inspection of Table 1 shows that both p-allylcalix[4]arene (**1c**) and trifluoroacetic acid exert a downfield shift on the methyl resonances of tert-butylamine and the methyl and methylene resonances of neopentylamine. These values are interpretable as a measure of the extent of proton transfer from the phenol to the amine (assuming 100% proton transfer for trifluoroacetic acid). However, factors other than inherent basicities must come into play in determining the chemical shift values, and this is supported by the fact that the pattern noted for the chemical shifts is not observed for the relaxation times. Thus, calixarene is more effective than trifluoroacetic acid in reducing the relaxation time of tert-butylamine but less effective in the case of neopentylamine. The ^1H NMR data for the calixarene

component, shown in Table 2, display trends similar to those in Table 1 for the amine components; the relaxation times for the protons at positions a, b, c, and d are significantly shorter in the presence of tert-butylamine and somewhat shorter in the presence of neopentylamine than in the presence of NaOH, again emphasizing the fact that the interaction with the amines is more than a simple proton transfer process. Additional support is provided by the data in Table 3 for various other amines.

To gain further insight into the structure of the amine-calixarene complexes a 2D NOE experiment was carried out on an equimolar mixture of tert-butylamine and p-allylcalix[4]-arene in CD_3CN. The spectrum shows a moderately strong pair of off-diagonal signals with the coordinates δ = 1.2 (methyl groups of tert-butylamine) and δ = 5 (terminal protons of the allyl groups of the calixarene), indicating an interaction between these groups. Since the NOE effect is a through-space phenomenon that arises only if groups are proximate, one is forced to the conclusion that in the tert-butylamine/p-allylcalixarene complex the amine is close to the allyl groups. Although the ^{1}H NMR data in Tables 1-3 are commensurate with either an exo-calix or an endo-calix complex, the NOE data provide strong evidence for the latter. Thus, a possible sequence of events involves the initial proton transfer followed by formation of an exo-calix complex which, through partial or complete conformational inversion of the calixarene, transforms into an endo-calix complex.

As a measure of the magnitude of the proton transfer step alone, UV measurements were made on dilute solutions containing several different calixarenes and amines in various ratios, resulting in a change from an absorption pattern showing a major peak at 280 nm and a flat shoulder at 290 nm to one possessing a single, more intense, peak at 292 nm and a new, less intense peak, at ca 310 nm. Dissociation constants for the calixarenes in the presence of amines were obtained by measuring absorptivities at various ratios of calixarene to amine and analyzing the data by the Benesi-Hildebrand expression (ref 9) as well as by a computer program using a similar expression (ref 10). The results are shown in Table 4.

To provide a continuum from the UV measurements in very dilute solutions to the NMR measurements in considerably more concentrated solutions, NMR determinations were made on equimolar mixtures of p-allylcalix[4]arene and tert-butylamine over a concentration range from .03 M to 0.28 M. Plots of the data allowed reasonably reliable extrapolations to very high and very low concentrations, providing limiting values of δ = 1.51 and 1.26, respectively. With these values, the magnitude of K_2 was calculated to be 50 ± 5. In similar fashion the T_1 values for a 1:1 mixture of calixarene and amine were measured over a concentration range of .03 M to 0.28 M, and from the extrapolated values a K_2 of 65 ± 5 was calculated, in reasonably good agreement with the values calculated from the chemical shifts.

Table 3. Chemical shift and relaxation time values for the protons in various amines in the presence of an equimolar amount of p-allylcalix[4]arene or an excess of trifluoroacetic acid

		δ, T_1 Values							
Amine	**pKa**	**Neat**	**p-Allylcalixarene**			CF_3CO_2H		**Reduction Factor**	
		δ	$(T_1)_a$	δ	$(T_1)_b$	δ	$(T_1)_c$	T_{1a}/T_{1b}	T_{1a}/T_{1c}
tert-Butylamine	10.83	1.062	5.676	1.302	0.706	1.337	2.45	8.04	2.31
Adamantylamine (H-2)		1.986	5.445			salt insoluble			
(H-3)		1.624	4.143	1.686	0.881			4.70	
(H-4)		1.519	4.538	1.801	0.954				
Dodecylamine (H-1)	10.63	2.552	3.131	2.871	0.835	2.898	1.400		
(H-2)		1.265	2.349	1.266	1.361	1.267	1.733		
(H-3)		0.874	3.167	0.883	2.814	0.873	2.994		
Triethylamine (H-1)	11.01	2.432	4.422	3.002	1.322	3.103	2.780	3.34	1.59
(H-2)		0.950	4.365	1.177	1.761	1.224	2.869	2.47	1.52
Morpholine	8.33	3.531	5.731	3.684	1.781	3.839	2.258	3.22	2.53
		2.716	5.634	2.936	1.609	3.072	1.963	4.89	2.76
Piperidine (H-1)	11.12	2.685	5.430	3.014	1.090	3.072	1.963	4.98	2.76
(H-2)		1.421	5.525	1.721		1.743	2.176		
Neopentylamine (CH_2)	10.15	2.318	5.548	2.569	2.566	2.766	2.035	2.16	2.72
(CH_3)		0.826	5.170	0.920	2.586	0.982	2.332	1.99	2.21

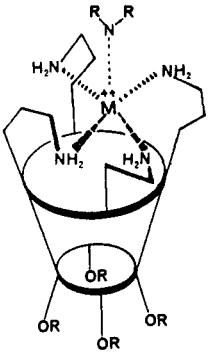
Table 4. Association constants and molar absorptivities (parenthetical values) for calixarene-amine interactions

	tert-Butylamine	Neopentylamine	tert-Amylamine	n-Butylamine
p-Allylcalix[4]arene	4.7×10^4 (4310)	3.0×10^4 (3530)	5.0×10^4 (3440)	9.6×10^4(3470)
p-tert-Butyl-calix[4]arene	4.8×10^4 (2550)	6.0×10^4 (1850)		
p-Morphilino-calix[4]arene	4.0×10^4 (4490)			

These data show that the association constants for the interaction of calix[4]arenes and amines, as expressed in equation 1, are approximately 10^6. On the basis of the UV and ^{1}H NMR data, these constants are viewed as the product of a proton transfer step, which accounts for the larger fraction of the overall constant, and an endo-calix-forming step, which accounts for the smaller fraction.

Aminocalixarenes and metal ions

Molecular models of p-(2-aminoethyl)calix[4]arene (**6b**) suggest that the compound might coordinate with a metal ion in a square planar fashion, leaving a fifth coordination site readily accessible to another amine, e.g. imidazole, and a sixth site accessible only through the cavity of the calixarene and, therefore, restricted to small molecules such as oxygen (**12**). Studies of the interaction of the p-bromobenzenesulfonate of **6b** with Pd^{+2}, Ni^{+2}, Cu^{+2}, Fe^{+2}, and Co^{+2} have been carried, and the copper complex appears to be the one most likely to assume a square pyramidal 5-coordinate configuration. The p-bromobenzenesulfonate of the Schiff base of **6b**, prepared from **6b** and benzaldehyde, shows similar metal ion complexation behavior.



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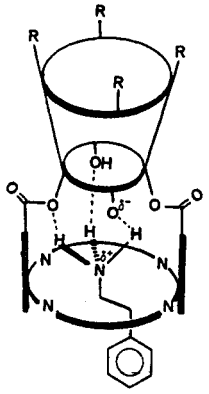
'Double cavity calixarenes' and guest molecules



The "double cavity" calixarenes (**9**), prepared by the benzoylation route as described above, share with unfunctionalized calixarenes the property of forming complexes with various amines. In this case, however, the selectivities are considerably more dependent on the structure of the amine, as illustrated by the data in Table 5. Thus, p-methoxyphenylethylamine forms a tighter complex than either its lower or higher homolog, and n-butylamine forms a considerably tighter complex than its isomer tert-butylamine. It is postulated that the complex-forming cavity is the one provided by the tetraamino face of the calixarene, the mechanism of the complexation possibly depending on a proton transfer from calixarene to amine in the manner discussed above and as pictured at the left.

Table 5. Downfield ^{1}H NMR shifts of 1:1 mixtures of **9** (n = 4) and various amines

	^{1}H NMR Downfield Shifts in ppm					
	a	b	c	ArH-1	ArH-2	OMe
CH_3O-Ar-CH_2NH_2 (a)	0.07			0.08	0.04	0.01
CH_3O-Ar-$CH_2CH_2NH_2$ (b a)	0.11	0.14		0.11	0.04	0.02
CH_3O-Ar-$CH_2CH_2CH_2NH_2$ (c b a)	0.07	0.09	0.04	0.03	0.02	0.01
$CH_2CH_2CH_2CH_2NH_2$ (c b a)	0.17	0.21	0.10			
$(CH_3)_3CNH_2$	0.01					

CONFORMATIONS OF ANIONS OF CALIX[4]ARENES

The formation of ethers and esters of calix[4]arenes is often carried out in the presence of very strong bases such as NaH, and the conformation of the product has been shown to be strongly dependent on the reaction conditions as well as the reagents (ref. 11). It was of interest, therefore, to study the ionization behavior of the calix[4]arenes under such conditions. Solutions of the calixarene in DMSO to which one, two, three, and four equivalents of n-butyllithium were added were studied by means of UV, ^{1}H NMR and ^{7}Li NMR spectra, with the results shown in Figs 1 & 2. All of these data are consistent with the

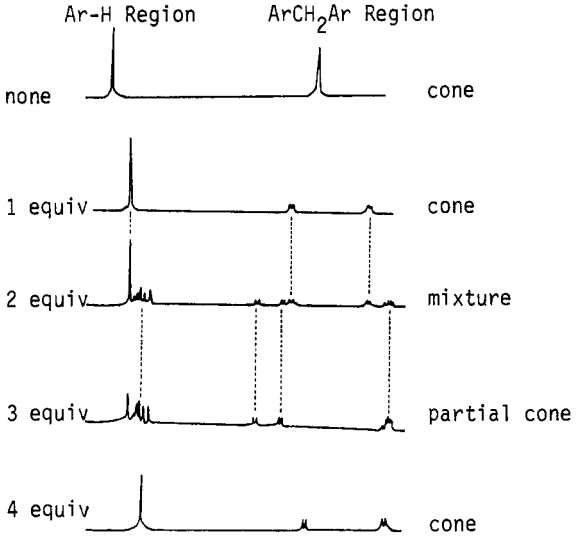


Fig 1. ^{1}H NMR spectra of calixarene anions

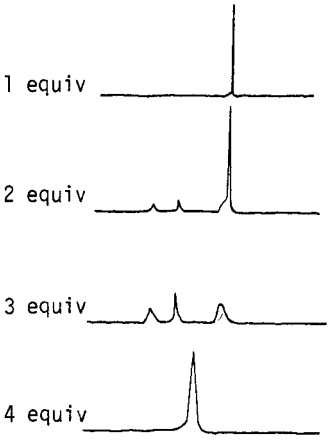


Fig. 2. ^{7}Li NMR spectra of calixarene anions

postulate that the mono-anion exists in a cone conformation, that the dianion partitions between the mono- and tri-anions, that the tri-anion exists in a partial cone conformation, and that the tetra-anion exists in a cone conformation. Temperature-dependent NMR studies reveal that all of these conformations are stable at least to 160°C when lithium is the counter ion. However, when sodium is the counter ion the tetra-anion shows incipient coalescence of the methylene resonances at 160°C, and when potassium is the counter ion the tetra-anion is already at the coalescence point close to room temperature. The extraordinary stability of the cone conformation when lithium is the counter ion may be due to a crown ether-like structure in which a lithium ion occupies the center of the circular array of oxygen atoms; sodium and potassium ions are too large to be able to occupy a similar position. If this is true, however, it requires the postulate that there is sufficiently rapid exchange between "inside" and "outside" lithium to account for the single resonance in the ^{7}Li NMR spectrum of the tetra-anion.

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