CHEMISTRY LETTERS, pp. 205-208, 1993.

Cation-π Interactions in Calix[4]arene-based Host Molecules. What Kind of Cavity-shape Is Favored for the Cation-binding?

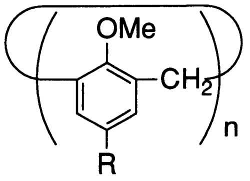
Koji ARAKI, Hiroyasu SHIMIZU, and Seiji SHINKAI *
Department of Organic Synthesis, Faculty of Engineering,
Kyushu University, Fukuoka 812

The cation-π interaction was studied using 9 calix[n]arenes with the different cavity size and the different cavity shape: the efficient binding of N-methylpyridinium iodide was observed for calix[6]arenes among calix[n]arenes and for cone isomers among calix[4]arene conformers, indicating the importance of the host-guest-type cation inclusion in the π-base cavities.

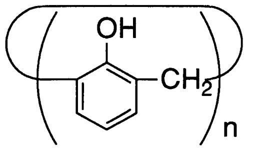
Among secondary valence forces, the cation-π interaction has been classified as a less important force. Recent investigations reveal, however, that the cation-π interaction frequently plays a crucial role in various molecular interactions.[1-5] The strongest impact has been brought forth by X-ray crystallographic evidence that the binding site for Me_3N^+ in acetylcholine esterase consists of π-bases but not of anionic charges as generally believed so far.[6] Several complementary findings have been obtained in artificial systems.[1-5] Dougherty *et al.*[1,2] demonstrated, for example, that certain cyclophanes are capable of binding ammonium cations into their cavities. We also found that ammonium cations are included in the cavity of water-soluble calix[4]arenes.[4] It is not yet understood, however, what kind of cavity-shape is favored for the binding of cations. Is the "hole-size selectivity" operative also in the cation-π interaction? We noticed that calix[n]arenes serve as convenient hosts to answer the question because one can systematically change the size of the π-base cavity[7] and the structure of the π-base cavity can be systematically changed by the conformational isomerism.[8,9] In this paper we employed 9 calix[n]arene derivatives ($\mathbf{1}_n$R, $\mathbf{2}_n$, and $\mathbf{3}_n$) and one noncyclic reference compound (**4**) in which the ring size and the cavity shape are systematically changed and estimated their host ability in inclusion of cationic guest molecules (**5** and **6**).

Preparations of $\mathbf{1}_n$R, $\mathbf{2}_n$, and $\mathbf{3}_n$ were described previously.[8,9] The ^{1}H NMR spectra were measured with a 400 MHz NMR apparatus (JEOL GSX-400).

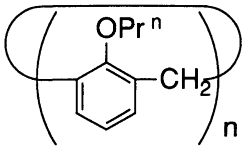
First, we qualitatively estimated the inclusion ability of each calix[n]arene in $CDCl_3$ through the chemical shift change in ^{1}H NMR spectroscopy. The results are



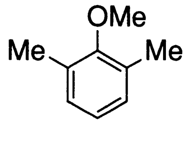
1_nR



2_n



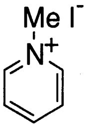
3_n



4

$CH_3(CH_2)_7N^+(CH_3)_3\ Br^-$

5



6

summarized in Tables 1 and 2. A number of interesting points that disclose the characteristics of cation-π interactions can be raised about the data. When **5** was used as a guest molecule (Table 1), the significant up-field shift was observed only for the CH_3N^+ and CH_2N^+ protons. This reveals that the trimethylammonium head group is predominantly included in the cavity. Among **1_n**H, the magnitude of the up-field shift appeared in the order of **1_6**H>**1_8**H>**1_4**H. The large up-field shift was also observed for **2_6**. On the other hand, the presence of the *t*-Bu group at the *p*-position drastically decreased the inclusion ability. The *t*-Bu groups on the upper rim sterically interfere with guest inclusion. In contrast, noncyclic **4** could not induce the significant up-field shift. The difference suggests the importance of the ring structure in inclusion of cationic guest molecules.

The similar results were obtained from the ^{1}H NMR measurements about **6** ($CDCl_3$:CD_3CN=10:1 v/v; Table 2). In this case, the largest up-field shift for the pyridine protons was observed for **1_4**H whereas the largest up-field shift for the CH_3N^+ protons was observed for **1_6**H. It is known that **1_4**H bearing four methoxy groups on the lower rim is conformationally mobile because the methoxy-through-the-annulus rotation is still allowed.[8] The conformer distribution can be conveniently determined from the ^{1}H NMR spectrum (below 0 °C; at room temperature it can not be determined because of the line-broadening). In $CDCl_3$:CD_3CN=10:1 v/v at -50 °C, **1_4**H exists as a mixture of cone (31%) and partial cone (69 %). Addition of **6** (1.0 equiv.) increased the fraction of cone-**1_4**H up to 67%. The chemical shifts for cone-**1_4**H were significantly influenced by added **6** whereas those for partial-cone-**1_4**H were not. The results clearly indicate that the cation is favorably included in the cone cavity. The conclusion is further corroborated from the chemical shift change in conformationally-immobile **3_n** (Table 2). In **3_n** the propoxy-through-the-annulus rotation is inhibited, so that one can isolate four conformational isomers.[8,9] Among four conformational isomers the significant up-field shift was observed only for cone-**3_4** and the magnitude of the up-field shift was greater than that for conformationally-mobile **1_4**H.

Further evidence for the inclusion of **6** in cone-**3_4** was obtained from the NOE study. The NOE peak intensities with respect to the meta-ArH protons are shown in

Table 1. Chemical shift changes (Δδ, ppm) in **5** induced by added calix[n]arenes$^{a)}$

Calix[n]arene	Me-N$^+$ protons		CH$_2$-N$^+$ protons	
	δ	Δδ^b	δ	Δδ$^{b)}$
None	3.481	-	3.585	-
1$_4$H	3.474	-0.007	3.584	-0.001
1$_6$H	3.425	-0.056	3.523	-0.062
1$_8$H	3.463	-0.018	3.554	-0.031
1$_6$Bu^t	3.479	-0.002	3.582	-0.003
2$_6$	3.386	-0.095	3.527	-0.058
Cone-**3**$_4$	3.477	-0.004	3.578	-0.007
4	3.476	-0.005	3.581	-0.004

a) 30 °C, CDCl$_3$, [calix[n]arene]=[**5**]=1.00x10^{-2} M.
b) - denotes the shift to higher magnetic field.

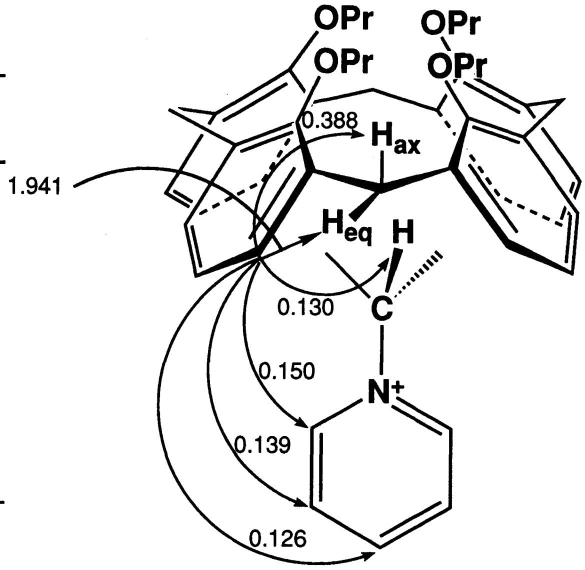


Fig. 1. NOE peak intensites with respect to the meta-ArH protons in cone-**3**$_4$: 30 °C, CDCl$_3$: CD$_3$CN =10:1 v/v, [cone-**3**]=[**6**]=0.10 M.

Table 2. Chemical shift changes (Δδ, ppm) in **6** induced by added calix[n]arenes$^{a)}$

Calix[n]arene	Me protons		α-H		β-H		γ-H	
	δ	Δδ$^{b)}$	δ	Δδ$^{b)}$	δ	Δδ$^{b)}$	δ	Δδ$^{b)}$
None	4.619	-	9.159	-	8.127	-	8.553	-
1$_4$H	4.380	-0.239	8.667	-0.492	7.676	-0.451	8.008	-0.545
1$_6$H	4.369	-0.250	8.868	-0.291	7.993	-0.134	8.447	-0.106
1$_8$H	4.430	-0.189	8.921	-0.238	7.929	-0.198	8.342	-0.211
Cone-**3**$_4$	4.560	-0.059	9.035	-0.124	8.027	-0.100	8.409	-0.144
4	4.612	-0.007	9.157	-0.002	8.125	-0.002	8.552	-0.001
None$^{c)}$	4.645	-	9.171	-	8.164	-	8.596	-
Cone-**3**$_4$$^{c)}$	4.335	-0.310	8.464	-0.707	7.534	-0.630	7.792	-0.804
Partial-cone-**3**$_4$$^{c)}$	4.634	-0.011	9.122	-0.049	8.109	-0.055	8.523	-0.073
1,2-Alternate-**3**$_4$$^{c)}$	4.648	+0.003	9.152	-0.019	8.143	-0.021	8.561	-0.035
1,3-Alternate-**3**$_4$$^{c)}$	4.648	+0.003	9.153	-0.018	8.143	-0.021	8.561	-0.035

a) 30 °C, CDCl$_3$:CD$_3$CN=10:1 v/v, [calix[n]arene]=[**6**]=1.00x10^{-2} M.
b) - denotes the shift to higher magnetic field.
c) -50 °C.

Fig. 1. The peak intensities are strong enough to support the inclusion of **6.** In contrast to the foregoing findings, neither the up-field shift of the proton signals nor the significant NOE peak was observed for *N,N*-dimethyloctylamine (noncationic reference for **5**) and pyridine (noncationic reference for **6**). One can thus conclude that these cationic guest molecules are included in the π-base cavities of calix[n]arenes owing to the cation-π interaction.

We estimated the stoichiometry and the association constants (K_{ass}) from plots of $\Delta\delta$ against [$\mathbf{1}_n$H] / [guest]. This method was applied to several systems in which the large change in the chemical shift was induced. All peaks in **6** shifted to higher magnetic field with increasing [$\mathbf{1}_8$H] / [**6**] ratio and the stoichiometry was 1:1. The similar results were obtained from other systems: for the formation of the 1:1 complex, log K_{ass}=1.72±0.04 for $\mathbf{1}_4$H + **6**, 2.28±0.09 for $\mathbf{1}_6$H + **6**, and 2.12±0.06 for $\mathbf{1}_8$H + **6**. The results show that the cation-π interaction in the calix[n]arene cavity brings forth the stabilization energy of 1.03-1.37 kcal mol^{-1}.

In conclusion, the present paper established that the cation-π interaction is observable only for such host molecules that can include the cation by the π-base cavity but not for such molecules that form a 1:1 face-to-face-type complex (*i.e.*, as in a charge-transfer complex). Calix[n]arenes with a cone conformation exactly provide such π-base cavities.

This work was partially supported by a Grant-in-Aid from the Kurata Foundation.

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(Received September 24, 1992)