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NMR Determination of Association Constants for Aqueous Calixarene Complexes and Guest Template Effects on the Conformational Freedom[1)]

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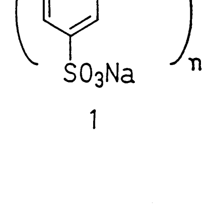
The association constants (K) for aqueous complexes with water-soluble *p*-sulfonatocalix[*n*]arene ($\mathbf{1}_n$: n=4, 6, and 8) were determined by the NMR method. It was found that $\mathbf{1}_4$ and $\mathbf{1}_6$ form 1 : 1 complexes with guest molecules (trimethylanilinium chloride and 1-adamantyltrimethylammonium chloride), whereas $\mathbf{1}_8$ forms 1 : 2 $\mathbf{1}_8$/guest complexes. The finding supports the view that calixarenes $\mathbf{1}_n$'s are capable of molecular recognition on the basis of the ring size. Examination of the thermodynamic parameters for the association process established that the complexation with $\mathbf{1}_4$ is mainly due to the electrostatic force, whereas that with $\mathbf{1}_6$ and $\mathbf{1}_8$ is mainly due to the hydrophobic force. The coalescence temperatures (T_c's) for calixarene ring inversion were subject to the template effect by these molecules. The activation parameters for the rate of ring inversion were estimated by a computer-assisted spectrum simulation: it was found that the T_c increase, observed in the presence of these guest molecules acting as templates, is caused by the increase in $\Delta H^{\neq}$. These findings provide new insights into the association characteristics of water-soluble calixarenes.

Calixarenes are cyclic oligomers which belong to the class of [1_n]cyclophanes. A variety of calixarenes may now be synthesized in good yields.[2,3)] Since they have a cavity-shaped architecture, they have been expected to be useful as a basic skeleton in the design of new functionalized host molecules.[2-5)] However, unequivocal evidence for the formation of host-guest-type complexes was not found for a long time since the discovery of calixarenes. Conceivably, the difficulty is related to the poor solubility in solvents, particularly, in water. Beginning in 1984, we synthesized and studied *p*-sulfonatocalixarenes, the first example for water-soluble calixarenes.[6)] Using these water-soluble calixarenes, we found substantial evidence that they can form host-guest-type complexes in an aqueous system.[6-8)]

The next (and probably, most urgent) approach to the design of functionalized host molecules would be to test if the calixarene cavity is capable of molecular recognition in solution. Several groups have reported on the ionophoric properties of calixarenes.[9-12)] In contrast, the study of molecular recognition of organic molecules has been very limited and the question remained unresolved. We report here the NMR method, which is more complicated but applicable to a variety of guest molecules. We have determined the association constants (K), $\Delta H°$, and $\Delta S°$ for the complexation of *p*-sulfonatocalix[*n*]arene (n=4, 6, and 8 : $\mathbf{1}_n$) with trimethylanilinium chloride (**2**) and 1-adamantyltrimethylammonium chloride (**3**). During this study we unexpectedly found unequivocal evidence for the formation of the 1 : 2 complexes with $\mathbf{1}_8$.



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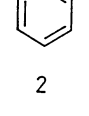

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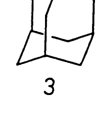


3

Experimental

The synthesis of $\mathbf{1}_n$ was reported previously.[7)] ^{1}H NMR spectra were measured with a JEOL GX-400 NMR apparatus.

The association constants were estimated from plots of δ_{obs} versus [$\mathbf{1}_n$]/[**2**]. The concentrations of $\mathbf{1}_n$'s were maintained constant while that of **2** was varied. The results were analyzed by the computer-assisted nonlinear least-squares procedure (see Results and Discussion).

The temperature-dependent ^{1}H NMR spectra of $\mathbf{1}_4$ in the absence and the presence of the guest molecules were simulated by the computer-assisted line shape analysis method. In particular, we were concerned with peaks for the ArCH$_2$Ar protons which sensitively reflected the calixarene conformation. Further details are described in Results and Discussion.

Results and Discussion

NMR Determination of Association Constants. Since the present study is related to molecular recognition, the measurements must be carried out below the critical micelle concentration (if any). As reported previously, the critical micelle concentration can be easily detected by ^{1}H NMR or conductance.[7,13)] We confirmed that none of $\mathbf{1}_4$, $\mathbf{1}_6$, and $\mathbf{1}_8$ form the micelle-like aggregate under the experimental conditions.

Figure 1 shows the chemical shift of **2** in the presence of $\mathbf{1}_4$ in D$_2$O at 25 °C. Clearly, all peaks shift to higher magnetic field with increasing [$\mathbf{1}_4$]/[**2**] ratio. This indicates that **2** interacts with $\mathbf{1}_4$ and undergoes the effect of the ring current of the calixarene benzene components. The fact that the shift width of the four

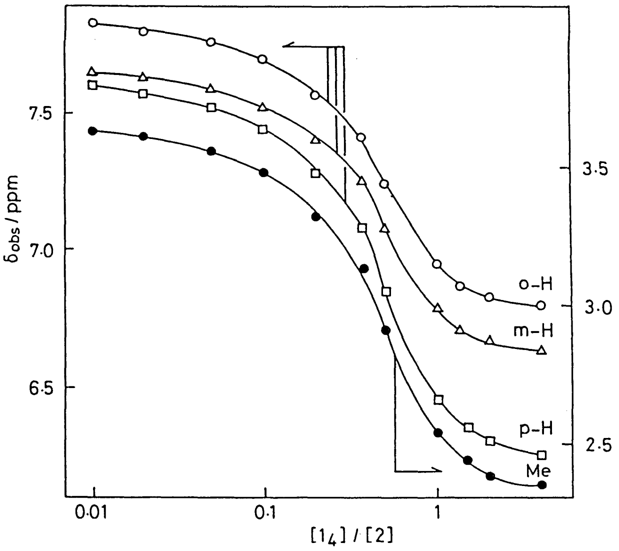


Fig. 1. Plots of δ_{obs} versus $[\mathbf{1}_4]/[\mathbf{2}]$. The concentration of $\mathbf{1}_4$ was maintained constant (1.00 mM) while that of **2** was varied (0.25—100 mM): D_2O, 25 °C, pD 7.3 with 0.1 M phosphate buffer, internal standard DSS.

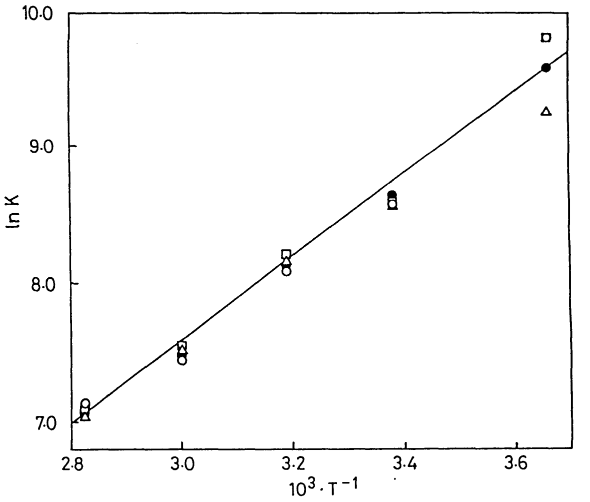


Fig. 2. Plots of ln K versus T^{-1} for the $\mathbf{1}_4$-**2** system: ○ ortho-H, △ meta-H, □ para-H, ● methyl.

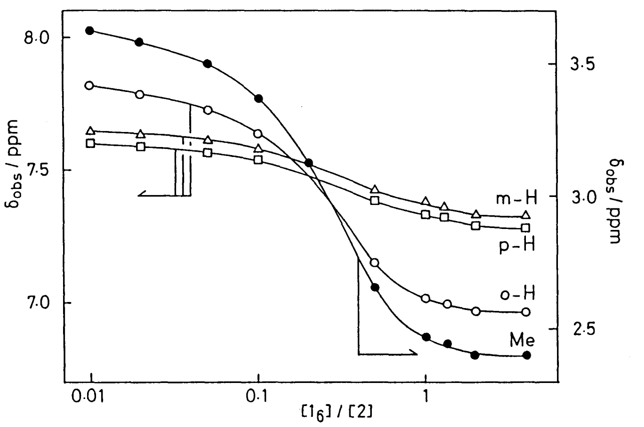


Fig. 3. Plots of δ_{obs} versus $[\mathbf{1}_6]/[\mathbf{2}]$. The measurement conditions are recorded in a caption to Fig. 1.

different protons is similar suggests that the binding of **2** to the $\mathbf{1}_4$ cavity is not specific to give a single complex structure but rather "nonspecific" to give time-averaged, various complexes. It is also seen from Fig. 1 that the change in the chemical shifts is almost saturated at $[\mathbf{1}_4]/[\mathbf{2}]=1.0$, supporting the formation of the 1 : 1 complex. The observed chemical shift (δ_{obs}) appears as an average of the free **2** (δ_{free}) and the complexed **2** ($\delta_{complex}$). Assuming the formation of a 1:1 complex ($\mathbf{1}_n+\mathbf{2} \rightleftarrows \mathbf{1}_n \cdot \mathbf{2}$), δ_{obs} is expressed by Eq. 1.

$$\delta_{obs}=\delta_{free}(([\mathbf{1}_n]_o-[\mathbf{1}_n\cdot\mathbf{2}])/[\mathbf{1}_n]_0)+\delta_{complex}([\mathbf{1}_n\cdot\mathbf{2}]/[\mathbf{1}_n]_0) \quad (1)$$

where $[\mathbf{1}_n]_0$ is the initial concentration of $\mathbf{1}_n$. Thus, this equation is rewritten as Eq. 2.

$$\begin{aligned}\delta_{obs}=&[\mathbf{1}_n]_0+[\mathbf{2}]_0+K^{-1}\pm(([\mathbf{1}_n]_0+[\mathbf{2}]_0+K^{-1})^2\\&-4[\mathbf{1}_n]_0[\mathbf{2}]_0)^{1/2}(2[\mathbf{2}]_0)^{-1}(\delta_{complex}-\delta_{free})+\delta_{free} \quad (2)\end{aligned}$$

where $[\mathbf{2}]_0$ is the initial concentration of **2**. The K value was determined from Eq. 2 by the computer-assisted nonlinear least-squares procedure: $K=5.39\times10^3$ M^{-1}.** The similar plots of δ_{obs} vs. $[\mathbf{1}_4]/[\mathbf{2}]$ were made at 0, 40, 60, and 80 °C, and the K values were determined at each temperature. As shown in Fig. 2, plots of ln K vs. T^{-1} shows a good linear relationship with $r=0.99$. This supports the formation of the 1 : 1 complex between $\mathbf{1}_4$ and **2**. The $\Delta H°$ and $\Delta S°$ were determined from the slope ($-\Delta H°/R$) and the intercept ($\Delta S°/R$) by the least-squares procedure: $\Delta H°=-6.2$ kcal mol^{-1} and $\Delta S°=-3.6$ cal mol^{-1} deg^{-1}. From these thermodynamic parameters we calculated the most reliable association constant at 25 °C (Table 1).

The NMR peaks of **2** measured at 25 °C also shifted

Table 1. Association Constants and Thermodynamic Parameters for **2**

Parameter	$\mathbf{1}_4$	$\mathbf{1}_6$	$\mathbf{1}_8$	
			1 : 1	1 : 2
$10^{-2}\cdot K/M^{-1}$ (at 25 °C)	56.0±2.5	5.5±0.4	52.0±0.5	46.0±0.5
$\Delta G°$/kcal mol^{-1} (at 25 °C)	−5.1±0.5	−3.7±0.2	−5.1±0.2	−5.0±0.1
$\Delta H°$/kcal mol^{-1}	−6.2±0.3	−0.25±0.10	0.0±0.10	0.0±0.10
$\Delta S°$/cal mol^{-1} deg^{-1}	−3.6±0.8	11.7±0.3	17.0±0.3	16.7±0.1

** 1 M=1 mol dm^{-3}.

to higher magnetic field with increasing $[\mathbf{1}_6]/[\mathbf{2}]$ ratio and suggest the formation of a 1 : 1 complex (Fig. 3). We repeated the similar measurements at 0, 40, 60, and 80 °C in addition to 25 °C. Plots of $\ln K$ vs. T^{-1} showed a good linear relationship (r=0.99: data not shown here). Thus, we could determine the K and thermodynamic parameters for the 1 : 1 complex with $\mathbf{1}_6$ (Table 1). In contrast, plots for $\mathbf{1}_8$ showed an unusual biphasic dependence (Fig. 4): the NMR peaks of **2** shifted to higher magnetic field at $[\mathbf{1}_8]/[\mathbf{2}]<0.5$, while the slight downfield shift occurred at $[\mathbf{1}_8]/[\mathbf{2}]>0.5$. The similar biphasic dependence was also observed at 0, 40, 60, and 80 °C. The new finding that a break point appears at $[\mathbf{1}_8]/[\mathbf{2}]=0.5$ supports the formation of a 1 : 2 $\mathbf{1}_8/\mathbf{2}$ complex. We thus assumed the following two-step association scheme and estimated K_1 and K_2 independently. The results are summarized in Table 1.

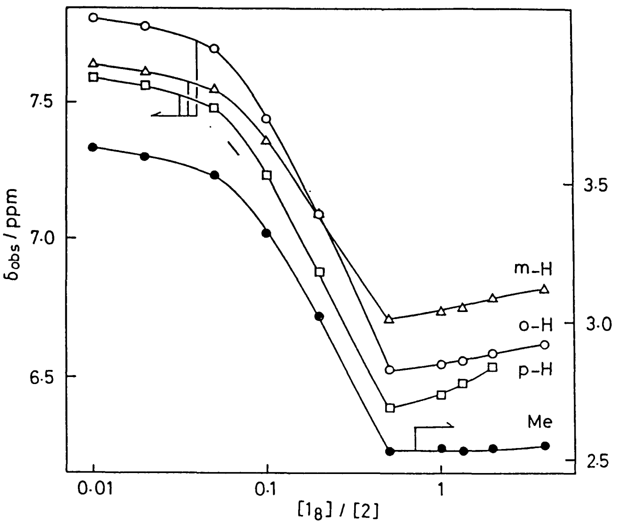


Fig. 4. Plots of δ_{obs} versus $[\mathbf{1}_8]/[\mathbf{2}]$. The measurement conditions are recorded in a caption to Fig. 1.

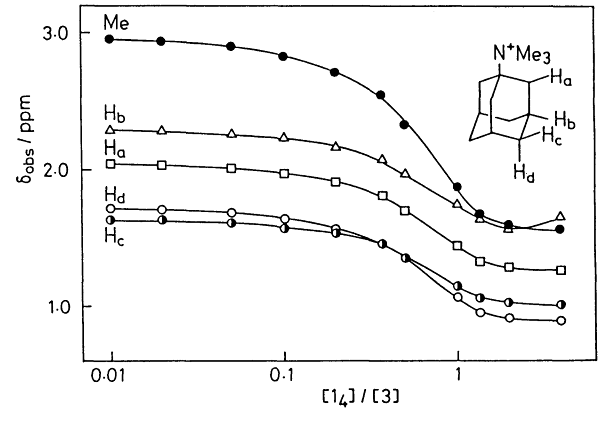


Fig. 5. Plots of δ_{obs} versus $[\mathbf{1}_4]/[\mathbf{3}]$. The concentration of $\mathbf{1}_4$ was maintained constant (1.00 mM) while that of **3** was varied (0.25—100 mM): D_2O, 25 °C, pD 7.3 with 0.1 M phosphate buffer, internal standard DSS.

$$\mathbf{1}_8+\mathbf{2} \overset{K_1}{\rightleftarrows} \mathbf{1}_8\cdot\mathbf{2} \tag{3}$$

$$\mathbf{1}_8\cdot\mathbf{2}+\mathbf{2} \overset{K_2}{\rightleftarrows} \mathbf{1}_8\cdot(\mathbf{2})_2 \tag{4}$$

We carried out the ^{1}H NMR measurements about **3**, the larger guest molecule at 0, 25, 40, 60, and 80 °C.

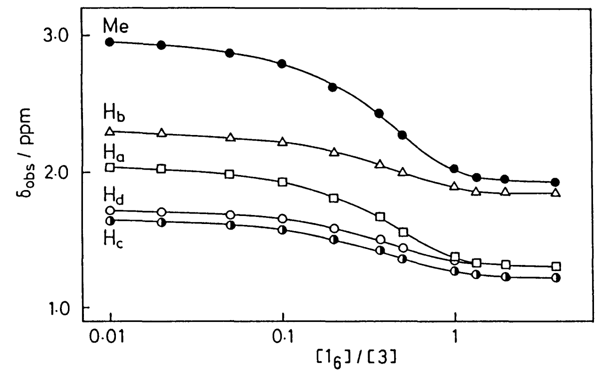


Fig. 6. Plots of δ_{obs} versus $[\mathbf{1}_6]/[\mathbf{3}]$. The measurement conditions are recorded in a caption to Fig. 5.

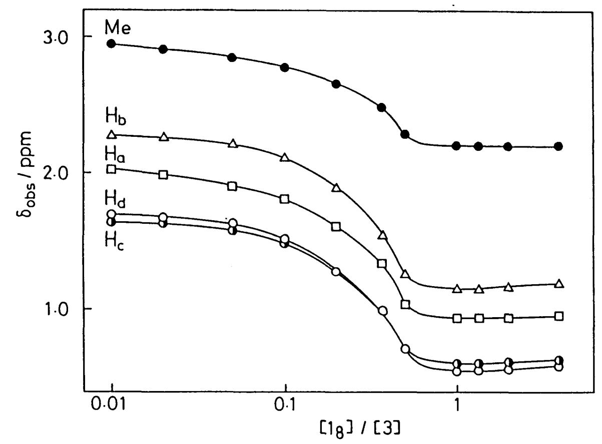


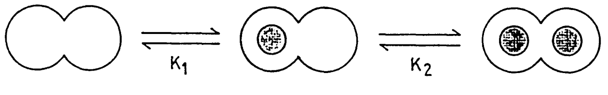
Fig. 7. Plots of δ_{obs} versus $[\mathbf{1}_8]/[\mathbf{3}]$. The measurement conditions are recorded in a caption to Fig. 5.

Table 2. Association Constants and Thermodynamic Parameters for **3**

Parameter	$\mathbf{1}_4$	$\mathbf{1}_6$	$\mathbf{1}_8$	
			1 : 1	1 : 2
$10^{-3}\cdot K/\mathrm{M}^{-1}$ (at 25 °C)	21.0±1.5	1.0±0.3	19.0±0.5	17.0±0.5
$\Delta G°/\mathrm{kcal\,mol^{-1}}$ (at 25 °C)	−5.9±0.4	−4.1±0.2	−5.8±0.2	−5.8±0.1
$\Delta H°/\mathrm{kcal\,mol^{-1}}$	−5.7±0.3	−0.15±0.10	0.0±0.10	0.0±0.10
$\Delta S°/\mathrm{cal\,mol^{-1}\,deg^{-1}}$	0.65±0.6	13.3±0.3	19.6±0.3	19.3±0.2

The results are illustrated in Figs. 5—7. It is seen from these figures that **1**$_4$ and **1**$_6$ form the 1 : 1 complexes with **3**, whereas **1**$_8$ form the 1 : 2 complex indicating that the cavity of **1**$_8$ is still big enough to accept two **3** molecules. From the plots of $\ln K$ vs. T^{-1} we determined ΔH° and ΔS°. The results are summarized in Table 2.

The formation of the 1 : 2 complex with **1**$_8$ is primarily attributed to the large ring size. This means that in principle, the "hole-size" selectivity is operative in molecular recognition by water-soluble calixarenes. In this connection, it is interesting to note that among *p*-alkylcalix[*n*]arenes (n=4, 6, and 8) only *p*-alkylcalix[8]arene is capable of extracting alkali metal cations in a 1 : 2 calixarene/M^+ ratio.[14] We consider that in addition to the ring size, the ring flexibility plays an important role in the binding of the second guest molecule. It is known that β- and γ-cyclodextrins can include two guest molecules in the cavity.[15—17] In these 1 : 2 complexes K_2 is usually greater than K_1. This situation is observed because the molecular size of the first guest is smaller than the cyclodextrin cavity and the cavity is just filled up by the binding of the second guest. In other words, the cyclodextrin cavity is relatively rigid. In the binding of **2** and **3** to **1**$_8$, on the other hand, we observed the relation $K_1 \approx K_2$. The fact that the thermodynamic parameters for K_1 are similar to those for K_2 supports the view that the binding mechanism for K_1 and K_2 is also similar. The results can be reasonably rationalized in terms of the flexibility of **1**$_8$ called a "pinched conformation":[2,3] flexible calix[8]arene can "pinch" transannularly to provide two half-cavities. Hence, the first guest is included in the cavity in an induced-fit manner and the circumstance is similar to the remaining half-cavity for the binding of the second guest (Eq. 5). Comparison of Fig. 4 with Fig. 7 manifests, however, that in the **1**$_8$·**2** complex the highest chemical shifts are attained for the 1 : 2 complex (i.e., at [**1**$_8$]/[**2**]=0.5), whereas in the **1**$_8$·**3** complex the chemical shifts are similar between the 1 : 1 and 1 : 2 complexes (i.e., constant δ_{obs} at [**1**$_8$]/[**3**]$\geqq$0.5). This suggests that two **2** molecules can adopt, although in some probability, a face-to-face orientation, undergoing the anisotropic effect of each benzene π-system.



(5)

The K value for **1**$_4$ is apparently comparable with K_1 and K_2 for **1**$_8$. Careful examination of Tables 1 and 2 indicates, however, that the thermodynamic parameters are quite different: the binding to **1**$_4$ occurs owing to negative ΔH°, whereas that to **1**$_8$ occurs owing to positive ΔS°. The results suggest that the association of **1**$_8$ with **2** and **3** is primarily based on hydrophobic interactions, whereas that of **1**$_4$ with **2** and **3** is rather supported by electrostatic interactions. What is the origin of this difference? The first difference is that the cavity of calix[4]arene is very rigid and open like a bowl.[2,3] Since hydrophobic interactions are based on stacks between host and guest,[18] it seems fairly difficult for rigid, open **1**$_4$ to adopt such an association mode favorable for hydrophobic interactions. The second difference is related to the strong, anionic electrostatic field provided by **1**$_4$. We have found that *p*-sulfonatocalixarenes, having anionic sulfonato groups on one side of the calixarene cavity, provide a strong anionic field.[7,19] In particular, *p*-sulfonatocalix[4]arene, having four sulfonato groups on the small cavity showed the strongest electrostatic effect.[19,20] These characteristics of **1**$_4$ would lead to the negative ΔH°.

Another interesting point seen from Tables 1 and 2 is that the K values for **1**$_6$ are generally smaller than those for **1**$_4$ and **1**$_8$. Examination of the thermodynamic parameters for **1**$_6$ reveals that the ΔH° values are not so negative as those for **1**$_4$ while the ΔS° values are not so positive as those for **1**$_8$. Probably, the association with **1**$_6$ is an intermediary case between **1**$_4$ and **1**$_8$ where neither the electrostatic force nor the hydrophobic force operates efficiently.

The K values for **3** are greater by a factor of about 5 than those for **2**. When the thermodynamic parameters for **3** are compared with those for **2**, we notice that the K values are enhanced owing to the increase in ΔS°. This is well-accounted for by the hydrophobic effect of the adamantyl group.

The complexation geometry of **2** and **3** can be

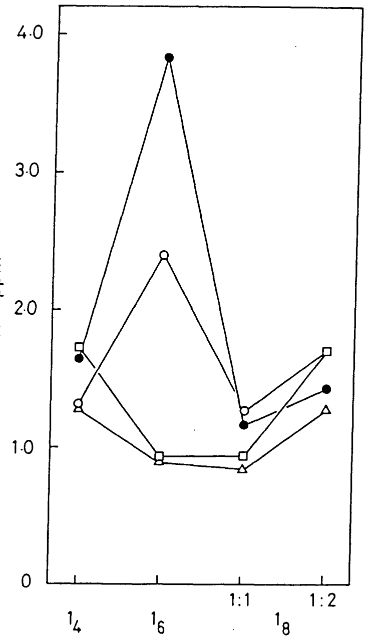


Fig. 8. Shifts of the ^{1}H NMR peaks of **2** to higher magnetic field. The shift width was calculated for 100%-complexed **2** from the parameters obtained by the nonlinear least-squares procedure (Eq. 2) used for the determination of K in Figs. 1, 3, and 4.

presumed from the magnitude of the higher magnetic-field shifts. As shown in Fig. 8, the shift width observed for the **1**$_4$ and **1**$_8$ complexes is rather similar among all protons, suggesting that **2** is bound in a nonselective manner. In contrast, the *N*-methyl and ortho protons particularly shift to higher magnetic field on the addition of **1**$_6$. This suggests that the ammonium moiety, rather than the phenyl moiety, is incorporated into the aromatic cavity of **1**$_6$. A similar trend is observed for **3** (Fig. 9). The unusual chemical shifts were also observed by Stauffer and Dougherty$^{21)}$ for **3** bound to water-soluble cyclophanes. They proposed an ion-dipole interaction between guest N^+ and host π-system. At present, we are not sure if this is the case in our system. Probably, the ion-dipole interaction is hidden in an aqueous system but becomes operative when the hydrophobic interaction between the guest and the host cavity is mismatched. This may be related to the small *K* values for **1**$_6$.

Guest Template Effects. What influence does included **2** (or **3**) have on the calixarene conformation? It is known that the temperature-dependent ^{1}H NMR spectrum displays a singlet resonance for the $ArCH_2Ar$ methylene protons at high temperature and a pair of doublets at low temperature. Thus, the coalescence temperature (T_c) appears at intermediary temperature. This behavior has been interpreted in terms of a conformational change from "alternate" to "cone" (Fig. 10).$^{2,3,22,23)}$ We estimated the influence of added **2** (or **3**) on T_c of **1**$_4$ in D_2O. The T_c in the absence of a guest molecule appeared at 9 °C (Table 3). Very interestingly, we found that the T_c values are significantly enhanced in the presence of **2** or **3**. This indicates that these organic guest molecules act as template cations. The Corey-Pauling-Koltun molecular model buildings and the recent X-ray crystallographic studies show that the "cone" conformation provides a cavity-shaped stoma more suitable to guest-binding than the "alternate" conformation.$^{24-26)}$ The circular dichroism studies also support the view that the conformation of water-soluble calixarenes is fixed to "cone" upon inclusion of guest molecules.$^{27)}$ Probably, **2** and **3** act as efficient templates not only because of electrostatic interactions between NMe_3^+ and oxide anions but also because of inclusion of a phenyl or adamantyl group into the "cone"-shape hydrophobic cavity of **1**$_4$.

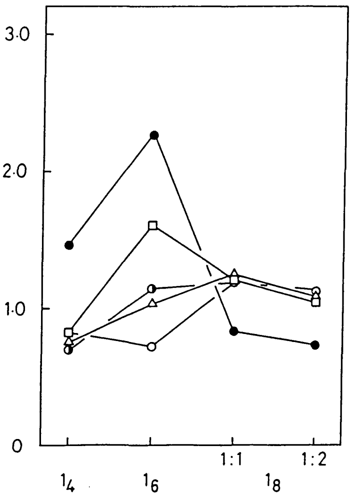


Fig. 9. Shifts of the ^{1}H NMR peaks of **3** to higher magnetic field. The shift width was calculated for 100-complexed **3** from the parameters obtained by the nonlinear least-squares proceduce (Eq. 2) used for the determination of *K* in Figs. 5—7.

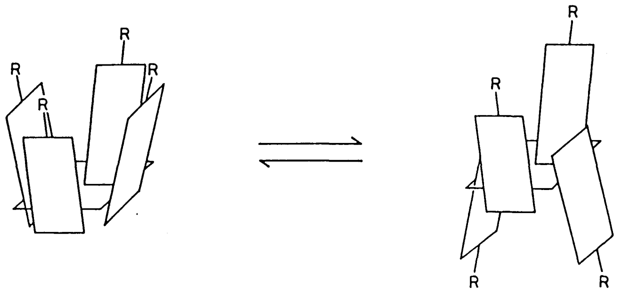


Fig. 10. Schematic illustration of "cone" and "alternate" calix[4]arene.

Table 3. Influence of Guest Molecules on T_c of **1**$_4$$^{a)}$

Guest (concn/M)	T_c/°C
None	9
2 (0.005)	20
2 (0.010)	43
2 (0.020)	50
2 (2.00)	65
3 (0.005)	25
3 (0.010)	50
3 (0.020)	57

a) pD 8.9 with 0.5 M borate buffer, [**1**$_4$]=1.10×10^{-2} M.

In order to obtain a further insight into the template effect we applied computer-assisted spectrum simulation (complete line shape analysis)$^{28)}$ to the temperature-dependent ^{1}H NMR spectra of **1**$_4$ in the absence and the presence of these guest molecules. The typical example is shown in Fig. 11: the observed spectral change (*A*) was simulated assuming the lifetime (τ) at each temperature (*B*). Excellent agreement is seen between the observed and the simulated spectra. Plots of $\log k$ (rate constant for the spin exchange τ^{-1}) vs. T^{-1} afforded excellent linear relationships ($r>0.99$), as shown in Fig. 12, from which we obtained $\log A$ and E_a. From these values we calculated $\Delta G^{\ddagger}_{298}$, $\Delta H^{\ddagger}$, and $\Delta S^{\ddagger}$ (Table 4).

As mentioned above, the spectral change has been interpreted in terms of a conformational change from "cone" to "alternate".$^{2,3,22,23)}$ However, the continuity in the Arrhenius plots indicates that such a conformational transition does not exist. This means that the spectral change is best understood as a consequence of the temperature-dependent rate

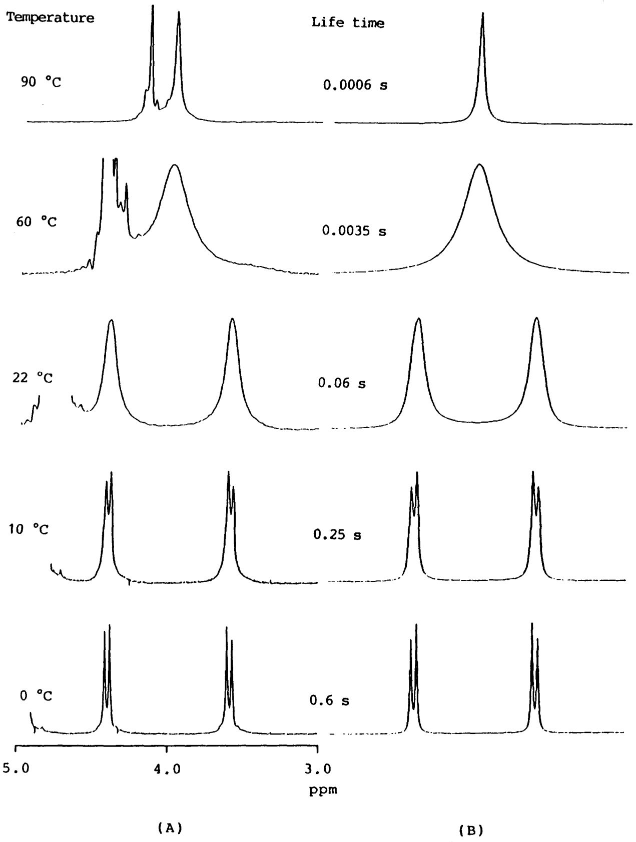


Fig. 11. Observed (A) and simulated spectra (B) of the $ArCH_2Ar$ protons in $\mathbf{1}_4$ (1.00×10^{-2} M) in the presence of **2** (2.00×10^{-2} M).

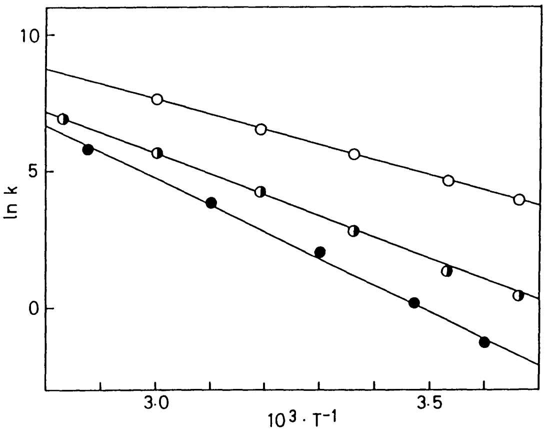


Fig. 12. Arrhenius plots for the rate of $\mathbf{1}_4$ (1.00×10^{-2} M) ring inversion: ○ no guest, ◑ [**2**]=2.00×10^{-2} M, ● [**3**]=2.00×10^{-2} M.

change for ring inversion between "cone" conformations.[29)]

Examination of Table 4 represents an interesting view: $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ compensates each other and the $\Delta G^{\ddagger}_{298}$ increase, observed in the presence of **2** or **3**, is caused by the $\Delta H^{\ddagger}$ increase. On the contrary, the $\Delta S^{\ddagger}$ value increases in the presence of these guest molecules, indicating that from a steric viewpoint, guest inclusion makes the ring inversion easier. In order to attain the ring inversion, the $\mathbf{1}_4$-guest complex should be dissociated once at a transition state. This dissociation process would be reflected by the $\Delta H^{\ddagger}$ increase. On the other hand, it is not easy to elucidate the $\Delta S^{\ddagger}$ increase reasonably. We believe that complexed $\mathbf{1}_4$ is sterically more hindred than vacant $\mathbf{1}_4$, leading to entropic destabilization of the initial state.

Table 4. Activation Parameters for the Spin Exchange in $\mathbf{1}_4$ (0.010 M)[a)]

Guest (concn/M)	$\Delta G^{\ddagger}_{298}$	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$
	kcal mol^{-1}	kcal mol^{-1}	cal mol^{-1} deg^{-1}
None	14.1±0.3	10.4±0.1	−12±1.3
2 (0.020 M)[b)]	15.7±0.6	14.6±0.3	−1.8±3.0
3 (0.020 M)[c)]	16.7±1.4	18.7±0.7	6.7±4.0

a) pD 7.3 with 0.1 M phophate buffer, [$\mathbf{1}_4$]=1.00×10^{-2} M. b) Under the measurement conditions (25 °C) 98.3% of $\mathbf{1}_4$ include **2**. c) Under the measurement conditions (25 °C) 99.5% of $\mathbf{1}_4$ include **3**.

Conclusion

The present study demonstrated that the association properties of water-soluble calixarenes are conveniently estimated by the NMR methods. Of particular significance are the unexpected findings that only $\mathbf{1}_8$ can form the 1:2 complexes with organic guest molecules and that these guests serve as efficient templates to fix the calixarene conformation. This suggests that in principle, calixarene cavities are capable of molecular recognition. We believe that in near future calixarenes would become a useful building block to design enzyme mimics in totally synthetic systems.

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