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Thermodynamic Studies of Slow Metal Exchange Processes in Ionophoric Calix[n]arenes with a Capsule-like Closed Cavity

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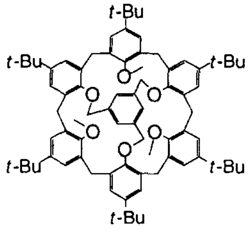
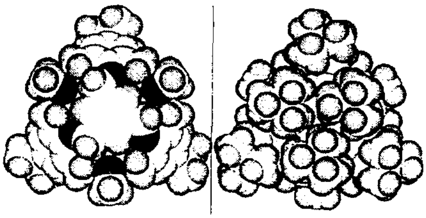
Abstract: It was found that in a triply-capped calix[6]arene (**1**) and doubly-bridged calix[8]arene (**2a** and **2b**) with a closed ionophoric cavity the Cs^+ complexation occurs *very slowly* in a human time-scale and can be followed by a conventional spectroscopic method. The unusual behavior has enabled us to determine their kinetic activation parameters for both the forward and the reverse reaction. The results established that being different from the concept believed so far, the Cs^+ complexation is heavily governed by the entropy term but not by the enthalpy term. Copyright © 1996 Elsevier Science Ltd

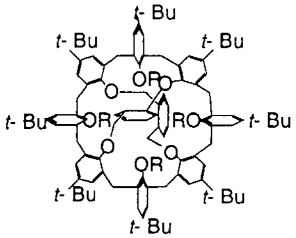
It is known that the metal exchange in conventional crown ethers and ionophoric calix[n]arenes occurs in the rate comparable with or faster than an NMR time-scale. In certain macrocycles with a closed ionophoric cavity such as spherands and cavitands, in contrast, the metal exchange occurs more slowly than a human time-scale.[1-3] Although the determination of the kinetic activation parameters which govern unit processes in these host•guest interactions has been long-awaited, neither of them is suitable to this purpose. Recently, we synthesized a mesitylene-capped calix[6]arene (**1**)[4] and a doubly-bridged calix[8]arene (**2**).[5] Both CPK molecular models and theoretical energy-minimization suggested that they have a closed inner cavity delineated by oxygen atoms and π-basic benzene rings,[4,5] the size of which is comparable with the ion size of Cs^+. As expected, they showed the high affinity and selectivity toward Cs^+.[4-6] The temperature-dependence of their ^{1}H NMR spectra showed that the signals for free calix[n]arenes and complexed calix[n]arenes appear separately even at above 100 °C.[4-6] This implies that the Cs^+ exchange rates in these calix[n]arenes are slower by far than the NMR time-scale. Then, how slow are they? Surprisingly, we have found that *the Cs^+ complexation-decomplexation rates are exactly in a human time-scale and slow enough to be followed by the conventional spectroscopic method!* Undoubtedly, this is a rare example in which the kinetic activation parameters can be determined by the conventional spectroscopic method.



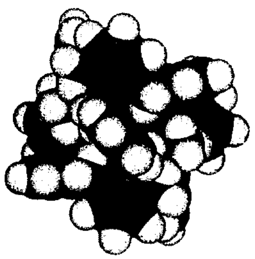
1



Energy-minimized structure of **1**



2a : R = Me
2b : R = Et



Energy-minimized structure of **2a**
(*t*-Bu groups are omitted for the simplicity)

It is known that the association constants (*K*) for alkali picrates (Pic$^-$) can be conveniently determined by a spectral change in the Pic$^-$ absorption band in THF.[7] The *K* values for Cs$^+$Pic$^-$ were estimated at 10, 15, 20, and 25 °C. As shown in Fig. 1, van't Hoff plots result in a good linear relationship for **1**, **2a**, and **2b**. The $\Delta H°$ and $\Delta S°$ values were determined from the slope ($-\Delta H° / R$) and the intercept ($\Delta S° / R$) by a least-squares procedure. The results are summarized in Table 1.

The time-course of the Cs$^+$ complexation process was followed by the absorption maximum of the Cs$^+$ complexes (390 nm) in THF. Firstly, a Cs$^+$Pic$^-$ solution (3 ml) in a quartz cuvette was equilibrated to the desired temperature and then a calix[n]arene solution (30 µl) was quickly injected from a microsyringe. After shaking for a few seconds, the absorbance change was monitored spectrophotometrically. This operation

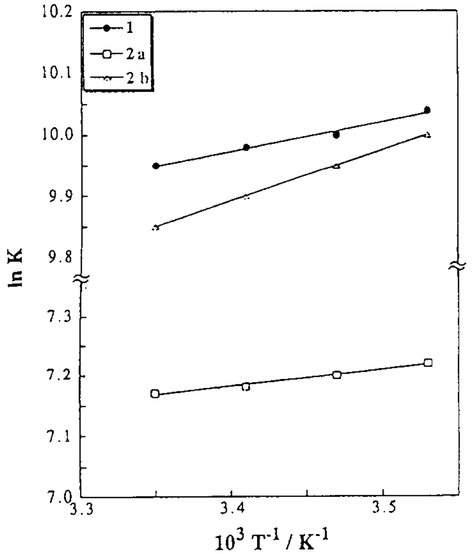


Fig. 1. Plots of ln *K* versus T^{-1} for the Cs$^+$ complexation: ● **1**, ■ **2a**, ▲ **2b**. The conditions used for the *K* determination at each temperature are [Cs$^+$Pic$^-$] = 1.00 X 10^{-5} M, [calixarene] = 0 ~ 5.00 X 10^{-4} M (6 different concentration), THF.

Table 1. Thermodynamic parameters for the equilibrium and the reaction between Cs$^+$Pic$^-$ and **1**, **2a**, and **2b**

	1	2a	2b
K(M^{-1})	2.1 X 10^4	1.3 X 10^3	1.9 X 10^4
ΔG^0(kJ / mol)	-25	-18	-24
ΔH^0(kJ / mol)	-1.3	-0.11	-4.8
ΔS^0(J / K · mol)	78	62	70
k_f (M^{-1} s^{-1})	1100	520	410
$\Delta G_f^‡$(kJ / mol)	54	57	58
$\Delta H_f^‡$ (kJ / mol)	25	41	16
$\Delta S_f^‡$(J / K · mol)	-110	-52	-140
k_r (s^{-1})	0.047	0.38	0.021
$\Delta G_r^‡$ (kJ / mol)	79	75	83
$\Delta H_r^‡$(kJ / mol)	27	41	21
$\Delta S_r^‡$ (J / K · mol)	-200	-110	-200

[a] K, k_f, and k_r are those at 298 K.

required the dead-time of *ca.* 5 s. The typical time-dependences are shown in Fig. 2. In contrast , a hexakis(ethoxycarbonylmethoxy) derivative of *p*-*t*-butylcalix[6]arene and an octakis(ethoxycarbonylmethoxy) derivative of *p*-*t*-butylcalix[8]arene, used as reference compounds, gave a time-independent, constant absorbance after 5 s: that is, the reaction with Cs^+Pic^- has been completed in 5 s in these compounds. The kinetic analysis of the absorbance versus time plots established that they obey the first-order-kinetics in the presence of excess calix[n]arenes. For the complexation equilibrium, calix[n]arene + $Cs^+ \rightleftharpoons$ calix[n]arene•Cs^+, the pseudo-first-order rate constant (k_{obs}) is given by $k_{obs} = k_f\,[C] + k_r$, where [C] is the calix[n]arene concentration and k_f and k_r are the forward and the reverse rate constant, respectively.[8] We thus repeated the measurements to make plots of k_{obs} versus [C] at 10, 15, 20, and 25 °C. The plots for **2b** are shown in Fig. 3.

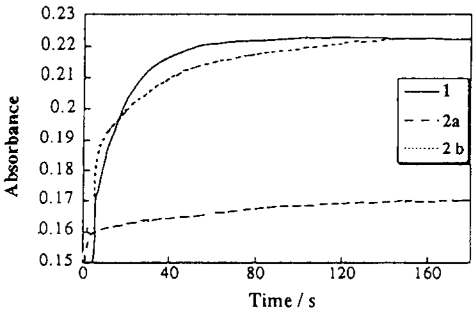


Fig. 2. Time-dependence of the 390 nm band: $[Cs^+Pic^-] = 1.00 \times 10^{-5}$ M, [calixarene] = 1.00×10^{-4} M, THF 10 ℃.

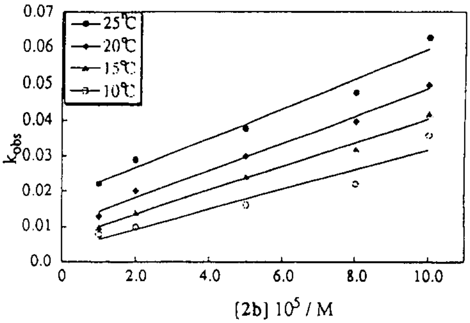


Fig. 3. Plots of k_{obs} versus [**2b**]. The conditions are recorded in a caption to Fig. 2.

The k_f values could be determined from the slopes (within the 10% relative error range). As shown in Fig. 3, on the other hand, the intercepts (*i.e.*, k_r) were so small that the precise analysis applicable to the activation parameters determination was impossible. To avoid the erroneous estimation of the k_r values we did not use the intercepts but computed them from a relation, $K = k_f / k_r$. By using the k_f and k_r values thus obtained at each temperature we eventually obtained $\Delta H^\ddagger$ and $\Delta S^\ddagger$ for the forward and the reverse reaction. The results are summarized in Table 1.

One can raise a number of important and novel features of the Cs^+ complexation process disclosed for the first time by the kinetic studies of the capsule-like calix[n]arenes. Firstly, the k_f values are different to a smaller extent (only 2.7-fold between fastest **1** and slowest **2b**) whereas the k_r values are largely different (18-fold between fastest **2a** and slowest **2b**). The result implies that the K is governed mainly by the decrease in the k_r. The conclusion is in line with that of the metal complexation behavior in crown ethers and cryptands which can be obtained only by the use of a stopped-flow method or a *T*-jump method.[9,10] Secondly and most intriguingly, the $\Delta S°$ values are all positive and the order of the K is consistent with that of $\Delta S°$ (*i.e.*, **1** > **2b** > **2a**) but not with that of $-\Delta H°$(**2b** > **1** > **2**). In general, the metal complexation process is driven by the negative (favorable) enthalpy change and accompanies the negative (unfavorable) entropy change.[11] In contrast, the present results indicate that the major driving-force for metal inclusion is not the $\Delta H°$term (*e.g.*, not the

M$^+$····oxygen interactions) but the $\Delta S°$ term and the final complexation state is more entropically-favorable than the initial state. The careful survey of the past literatures teaches us that such an unusual positive $\Delta S°$ change results when the ionophore is sterically rigid and the metal complexation accompanies the considerable desolvation effect.[12,13] As demonstrated by ^{1}H NMR spectroscopy and theoretical calculations, [4-6] these compounds are sterically very rigid and exactly classified into this class of ionophores. Thirdly, the structural difference between **2a** and **2b** is the O-substituent (methyl or ethyl). Examination of the activation parameters reveals that **2b** possesses the more favorable $\Delta H^‡$ term and the more unfavorable $\Delta S^‡$ term both for the forward and the reverse reaction than **2a**. This indicates that the steric crowding increases the $-\Delta S^‡$ term, which eventually enables us to determine the reaction rates with a conventional spectroscopic method.

In conclusion, the present calix[n]arene system is a very rare example in which the metal complexation process can be followed by a conventional spectroscopic method. By taking this advantage, one can readily determine the activation parameters. The results established that the metal complexation equilibrium in rigid calix[n]arenes is crucially governed by the entropy term but not by the enthalpy term, being different from the concept believed so far. This is a new thermodynamic insight into the metal inclusion chemistry. Further thermodynamic studies are currently continued in this laboratory.

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