An NMR Study on Complexation of Ethylammonium Ion by Alkyl p-tert-Butylcalix[6]aryl Ester Derivatives

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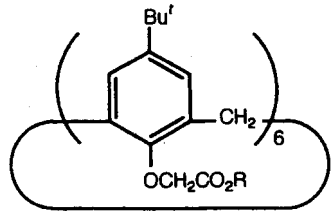
The complexation of ethylammonium ion by alkyl *p-tert*-butylcalix[6]aryl ester derivatives was studied *via* measurements of proton and carbon spin-lattice relaxation times (T_1) and chemical shift changes in solution state ($CDCl_3$). The results indicate that the *endo*-type complexes are formed and that the overall tumbling rates of these complexes are more rapid than those of the corresponding free hosts. The association constants for these complexes in THF-d_8 were determined by ^1H NMR titration at several different temperatures to estimate the relevant thermodynamic parameters. The log$K$'s for ethylammonium complexes of methyl, ethyl, and propyl esters at 313 K, for example, were found to be 1.56, 3.41, and 3.08, respectively. The complexes formed may be thought of as being kinetically stable in view of their ^1H NMR behavior in 2 : 1 host/guest solution.

Introduction

Recently, much interest has been focused on calixarenes which may be employed as molecular frameworks for the development of novel supramolecular systems.[1] Calix[6] arenes, a class of cyclic hexamers of phenol formaldehyde condensates, have larger cavities and therefore are expected to provide a more versatile platform for the formation of inclusion complexes with many interesting guest molecules compared with their tetrameric counterparts, calix[4]arenes. In fact, the former are known to be structurally much more flexible, thus being able to adopt a greater number of different conformations, than the latter. For calix[6]arenes, proper functionalization in their upper or lower rim can be envisaged as a means of modifying their conformational and complexational behaviors, thus modulating their molecular recognition properties. Unfortunately, however, relatively little is known about how such modulations of their properties are brought forth and what are the consequences of enlargement of the cavities caused by the addition of two more aryl moieties. Their complexing abilities and behaviors towards neutral molecules, various metal ions, and some organic ions have been systematically studied by several research groups[2-7] who used NMR chemical shifts, 2D NMR experiments, UV measurements, extraction experiments, *etc.* as standard tools for their investigations. Although the measurement of spin-lattice relaxation times can provide a very informative and powerful means for many areas in chemistry, its application to the study of complexation of calix[6]arenes has thus far been attempted by only a few authors.[8-10] In this paper we report some solution dynamic properties for the complexes formed between various alkyl *p-tert*-butylcalix[6]aryl esters **1-4** and an ethylammonium picrate guest which have been determined by the analysis of proton and carbon relaxation times and chemical shift data. We also report the association constants and some other relevant thermodynamic parameters for these complexes obtained by means of the ^1H NMR titration method. Finally, the kinetic stabilities of these complexes in a couple of solvents were examined by means of coalescence temperature measurements.



1 R = Me
2 R = Et
3 R = Pr
4 R = Bu^t

Experimental

The ester derivatives **1-4** were prepared following the reported standard procedures.[11] All the deuterated solvents used for the NMR experiments, $CDCl_3$, $C_2D_2Cl_4$, THF-d_8, *etc.*, were purchased from Aldrich and Sigma Chemical Co. and used without further purification. For the relaxation studies, each sample was sealed under vacuum in a 5 mm o.d. NMR tube after degassing by repeating the standard five freeze-pump-thaw cycle at least five times.

Chemical shifts. Proton and carbon NMR spectra were recorded at 200 MHz (^1H) on a Varian VXR-200S and at 125 MHz (^{13}C) on a Bruker DMX-500 spectrometer, respectively. All the proton and carbon peaks were assigned with the aid of 2D NMR experiments. Chemical shift values are expressed in parts per million (ppm) downfield from tetramethylsilane (TMS) employed as an internal reference.

Relaxation times. The spin-lattice relaxation times (T_1) for protons and carbons were measured in $CDCl_3$ by means of the conventional inversion recovery method, using at least 16 different delays between π and $\pi/2$ pulses, on a Varian VXR-200S spectrometer. The time delay for the next acquisition after one transient was set to more than 10 times the longest T_1 value. Each T_1 value was estimated with the aid of an exponential fitting program provided by the Varian NMR system. The obtained T_1's ranged from 0.2 to *ca.* 1 second for protons and 0.3 to *ca.* 7 seconds for car-

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bons. The measurement errors for T_1's were found not to exceed 5 and 10% for proton and carbon, respectively.

2D-NMR experiments. The 2D experiments were performed on a Varian Unity-500 and Bruker AMX-500 (500 MHz) NMR spectrometers. The 2D-NOESY spectra were measured on Varian Unity-500 in the phase-sensitive mode using the States-Haberkorn-Ruben method[12] (2×256 slices of 1 K points) with mixing time and relaxation delay, respectively, of 800 ms and 2.0 sec. All other data were collected on Bruker AMX-500 spectrometer in TPPI mode.

Association constants and kinetic stability. The experiments were performed on a Varian VXR-200S spectrometer equipped with variable temperature controller over the temperature range of 303-333 K. The chemical shifts of protons in host molecules were observed as a function of ρ, the ratio of [guest] *vs.* [host]. With the concentration of host being fixed at 0.04 M in THF-d_8 that of guest (ethylammonium picrate) was varied from 0 to 0.20 M, thus varying ρ over the range of 0 to 5. For the determination of kinetic stability ^{1}H NMR spectra were recorded for the solutions of ρ=0.5 in THF-d_8 and $C_2D_2Cl_4$ over the temperature range of 253-373 K.

Results and Discussion

Chemical shifts. Observed ^{1}H NMR chemical shifts for the free ester derivatives **1-4** and their complexes in $CDCl_3$ are summarized in Table 1. The ^{1}H NMR spectrum of **3** is not sufficiently resolved to allow precise assignments of all the resonance lines, while that of **4** shows relatively well resolved multiplet peaks originating from the 1,2,3-alternate conformation at room temperature.[3(b),13] Upon complexation, bridging methylene resonances ($ArCH_2Ar$) in all the investigated hosts are split into two doublets (J~15 Hz), indicating that the complexes formed have the well established cone conformation in solution. Furthermore, the δ values for methylene resonances in these complexes are all but identical, which means that they have similar structures in solution. However, it could readily be seen that the ^{1}H nmr chemical shift behaviors for methyl ester are substantially different from those for ethyl and propyl esters . In particular, for those protons in *p-tert*-butyl (*a*) at the upper rim and ester group (*f*, *g*, and *h*) at the lower rim these differences are conspicuous. The conformational difference between methyl ester and other higher homologues may be one of the factors responsible for this.[14] Also noteworthy is the dramatic complexation-induced upfield shift of proton resonances of the ethyl group in the guest. Upon complexation, the methyl and methylene protons in the ethylammonium guest undergo upfield shifts by 2.6 and 2.9 ppm, respectively, which indicates that the guest is held tightly in the aromatic cavity of calixarene, thus forming *endo*-type complex.

The interaction of calixarene derivatives with primary alkylammonium ion may be assumed to arise from the hydrogen bonds arising from a tripodal arrangement of N^+-H···O=C (host) and charge-dipole interactions R-NH_3^+···O=C (host).[3(a)] Due to this type of primary interaction in the complex, the ethylammonium guest can have two possible orientations to assume, either head-up or head-down with respect to the cone cavity. The large upfield shifts observed indicate that the ethyl group moiety of the guest is embedded inside the cavity and subject to the ring current of phenyl groups so that the so-called CH-π interaction[15] comes into play in forming the endo type complex in this case (Figure 1). This can also be confirmed by the 2D-NOESY spectrum of **2**-ethylammonium complex (Figure 2) which shows the presence of two cross peaks between the methyl protons (δ_H~−1.2 ppm) of the guest and the aromatic (δ_H~7.0 ppm) and *p-tert*-butyl (δ_H~1.0 ppm) protons of the host. The intensities of these cross peaks, which arise from the intermolecular interactions, appear to be much weaker than those of other cross peaks originating from the intramolecular interactions such as that between two protons in $ArCH_2Ar$.

The ^{13}C chemical shifts in the free ester derivatives and their complexed forms in $CDCl_3$ at 298 K are summarized in Table 2. With the aid of a 2D-hetero COSY spectrum of

Table 1. ^{1}H NMR chemical shifts of free hosts and their complexes in $CDCl_3$ at 298 K[a]

H	Chemical shifts, δ (ppm), of hosts and complexes and downfield shifts, Δ (ppm)[b], on complexation											
	1	**1+G**	Δ_1	**2**	**2+G**	Δ_2	**3**[c]	**3+G**	Δ_3	**4**[d]	**4+G**	Δ_4
a	1.15	1.08	−0.07	0.97	1.09	0.12	0.94	1.09	0.15	0.97	1.08	0.11
b	7.11	6.91	−0.20	6.95	6.90	−0.05	6.93	6.90	−0.03	7.07	6.89	−0.18
c	4.00	3.46	−0.54	4.06	3.46	−0.60	4.10	3.47	−0.63		3.43	
d	4.00	4.43	0.43	4.06	4.45	0.39	4.10	4.46	0.36		4.49	
e	4.23	4.59	0.36	4.53	4.57	0.04	4.59	4.59	0.00	4.56	4.48	−0.08
f	3.38	3.80	0.42	4.18	4.24	0.06	4.14	4.12	0.02	1.14	1.50	0.36
g				1.24	1.31	0.07	1.68	1.71	0.03			
h							0.94	0.97	0.03			
NH_3^+	7.92[a]	5.78	−2.14		5.81	−2.11		5.85	−2.07		6.42	−1.50
CH_2	3.12[a]	0.13	−2.99		0.14	−2.98		0.15	−2.97		0.33	−2.79
CH_3	1.35[a]	−1.28	−2.63		−1.29	−2.64		−1.27	−2.67		−1.36	−2.71
Picrate	8.77[a]	8.79	0.02		8.79	0.02		8.83	0.06		8.78	0.01

[a]Host and guest (G) concentrations are 50 mM and 60 mM, respectively. The chemical shifts of free guest are measured in THF-d_8 at 298 K due to their insolubility in $CDCl_3$, [b]Negative values represent upfield shifts, [c]Chemical shifts at 323 K (Signals are too broad to allow precise assignments at 298 K), [d]Chemical shifts measured for coalesced lines in $C_2D_2Cl_4$ solutions at an elevated temperature (368 K). At room temperature line splittings due to the presence of 1,2,3-alternate conformations makes these measurements difficult.

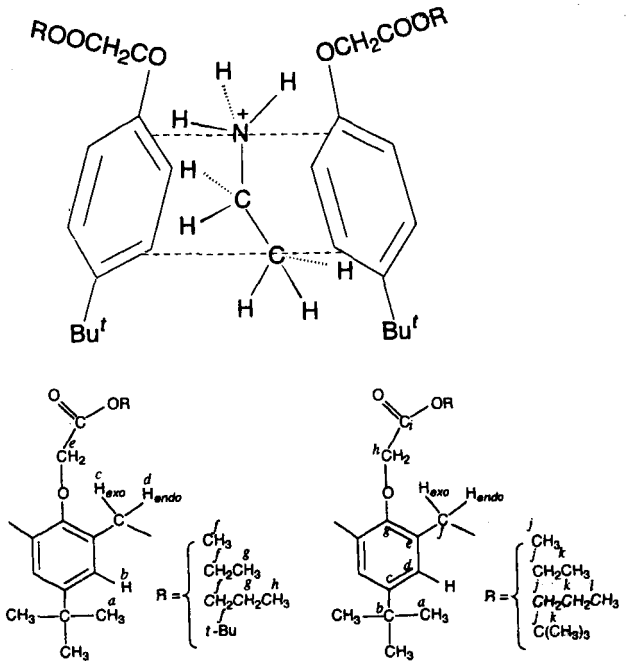

Figure 1. Structure of *endo* type complex resulting from complexation of ethylammonium ion by calixarene ester derivatives and alphabetic numbering of C and H atoms in the compounds.

2-ethylammonium picrate complex, carbon lines could readily be assigned. The chemical shifts for carbons in hosts did not change significantly upon complexation unlike those for the protons. However, two carbons in the guest (ethylammonium ion) were found to undergo upfield shifts ($\Delta\delta_C > 2$ ppm) as in the case of the protons, which may be regarded as an additional evidence for the *endo* type complexation in this host-guest system.

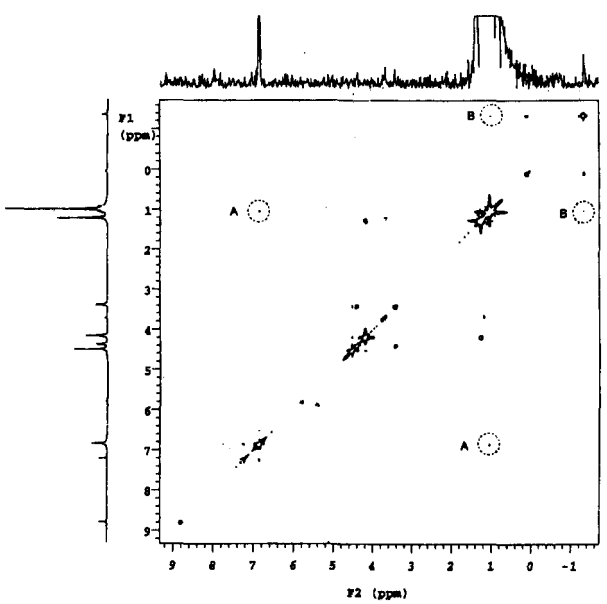

Figure 2. 2D-NOESY spectrum of the complex formed between calix[6]arene ethyl ester **2** and ethylammonium picrate in $CDCl_3$ at 288 K (recorded on Varian Unity 500 NMR spectrometer with 2× 512 slices of 2 K points, mixing time of 500 ms, and relaxation delay of 4 sec). Cross peaks A circumscribed by dotted circles are due to the interactions between *p-tert*-butyl protons and aromatic protons while cross peaks B arise from the interactions between *p-tert*-butyl protons and methyl protons in ethylammonium ion.

Table 2. ^{13}C NMR chemical shifts of free hosts and their complexes in $CDCl_3$ at 298 K[a]

Carbon	Chemical shifts, δ (ppm)						
	1	**1+G**	**2**	**2+G**	**3**	**3+G**	**4+G**
a	31.27	31.18	31.20	31.23	31.22	31.25	31.30
b	34.13	34.09	33.90	34.12	33.89	34.14	34.09
c	146.43	147.20	146.44	147.11	146.57	147.08	146.72
d	126.63	126.53	126.31	126.58	126.15	126.08	126.03
e	132.49	132.11	132.75	132.17	132.88	132.16	132.06
f	30.83	29.62	[b]	29.72	[c]	29.82	29.58
g	152.77	151.63	152.62	151.87	152.72	151.94	152.37
h	70.21	69.87	70.63	70.07	70.64	70.03	71.17
i	169.49	169.69	169.43	169.28	169.55	169.31	168.82
j	51.38	51.93	60.69	61.04	66.29	66.87	82.00
k			14.16	14.09	21.98	21.87	28.14
l					10.32	10.29	
CH_2	36.23	33.21		33.18		33.14	32.94
CH_3	13.10	11.17		11.21		11.35	10.12

[a]Measured at the same concentrations as specified in Table 1. The chemical shifts of free host **4** could not be measured with accuracy. [b]Unable to be distinguished from *p-tert*-butyl carbon *a*.

Spin-lattice relaxation times (T_1). To gain further insight into the solution structure of the present host-guest system, the spin-lattice relaxation times for protons in the ethylammonium guest, free hosts, and their complexes were measured by the inversion recovery method and the results are summarized in Table 3. That the observed relaxation times for various complexes are close to one another is also consistent with the ^1H NMR chemical shift data, which strongly suggests that the ethylammonium complexes formed have mutually very similar structural and dynamical properties. Temperature dependence of relaxation times indicate that the extreme narrowing condition is satisfied for the present system. As was expected, the T_1's for the protons in the ethylammonium guest were found to decrease markedly upon complexation by calixarene-based ester hosts. In general one may expect that mobility of the guest will decrease upon complexation, thus decreasing T_1 for its protons. In contrast to this, the relaxation times for protons in the hosts were found to increase by *ca.* 10 to 20% upon complexation, which conflicts with the observation made by Shinkai *et al.*[9] who observed that the relaxation times of most protons in **2** decreased upon complexation with Na^+ ion as guest (in THF). They also observed that the $ArCH_2$-Ar methylene protons, *c* and *d*, of **2** remained as a singlet, which could be attributed to the fact that in THF solution the conformational interconversions are still taking place very fast on the NMR time scale since the guest Na^+ is only loosely bound to the host. Observations for our host-guest system, however, are completely contrary to these reports. As was previously mentioned, the $ArCH_2Ar$ methylene protons were well resolved into a pair of doublets in our case, indicating that the complex 2-ethylammonium picrate formed in $CDCl_3$ is more stable than the **2**-Na^+ com-

Tabel 3. ^{1}H NMR spin-lattice relaxation times in free hosts and their complexes[a]

H	Relaxation times T_1 in unit of second														
	1			**1+G**			**2**			**2+G**			**3**	**3+G**	**4+G**[#]
	298 K	308 K	318 K	298 K	308 K	318 K	298 K	308 K	318 K	298 K	308 K	318 K	298 K	298 K	298 K
a	0.58	0.65	0.70	0.63	0.68	0.78	0.53	0.59	0.67	0.60	0.69	0.76	[b]	0.55	0.60
b	0.50	0.53	0.56	0.56	0.58	0.62	0.47	0.51	0.57	0.55	0.57	0.61	[b]	0.52	0.52
c	0.15	0.15	0.16	0.16	0.16	0.17	0.14	0.15	0.15	0.15	0.16	0.16	[b]	0.14	0.15
d	0.15	0.15	0.16	0.15	0.16	0.17	0.14	0.15	0.15	0.15	0.16	0.17	[b]	0.14	0.17
e	0.22	0.24	0.27	0.27	0.29	0.32	0.23	0.24	0.26	0.27	0.30	0.33	0.21	0.25	0.28
f	0.53	0.57	0.65	0.66	0.67	0.73	0.63	0.80	0.96	0.80	0.94	1.03	0.76	0.75	0.47
g							1.11	1.20	1.26	1.23	1.49	1.67	1.05	1.03	
h													[b]	1.36	
NH_3^+	1.16	1.26	1.39	0.24	0.28	0.31				0.29	0.30	0.34		0.28	0.27
CH_2	2.76	2.88	3.10	0.55	0.58	0.66				0.60	0.66	0.73		0.57	0.49
CH_3	3.45	3.54	3.74	0.85	0.99	1.18				0.89	1.05	1.17		0.74	0.79

[a]Measured at the same concentrations as specified in Table 1. T_1 of free guests were obtained in THF-d_8 due to their insolubility in $CDCl_3$, [b]Too broad to determine the relaxation times. [c]Not precise enough to give reliable estimation of relaxation times for free host.

plex in THF and that the former assumes a relatively rigid cone conformation upon complexation. Furthermore, the ArCH_2Ar methylene protons in our complexes were also found well resolved into a pair of doublets in THF solvent. The fact that these proton doublet lines were found not to coalesce even beyond 400 K (in $C_2D_2Cl_4$) suggests relatively deep and tight binding of ethylammonium guest into the calixarene cavity in our case. One may expect that the molecular size of such tightly bound complexes will be in general smaller than that of the corresponding free host molecules.

The difference in the behavior of T_1 upon complexation for the above two cases may be explained in terms of overall molecular rotations of the resulting complex. That is, a longer T_1 means a shorter correlation time for overall tumbling motions (and thus a faster tumbling rate) of the complex. With all other conditions remaining invariant, faster tumbling may be attributed to the smaller effective radius of the complex according to the Debye theory.[16] This means that the loosely bound **2**-Na^+ complex will have a larger effective radius than the free host while for tightly bound calixarene-ethylammonium picrate complexes the opposite is true. This inference is consistent with our previous conclusion that complexation with ethylammonium guest will produce the complex with a cone conformation, which has a relatively smaller effective radius compared to the original host molecule. Relative reduction in effective molecular radii could be calculated from the observed increases in relaxation times on the basis of the Debye relation assuming isotropic overall molecular tumbling. It turned out that the effective radii shrank by about 2-2.5% upon complex formation in our case. Of course, the conformational interconversions are expected to be nearly quenched upon complex formation but this can hardly affect the observed spin-lattice relaxation times because these motions ($\tau > 10^{-5}$ sec) are expected to be too slow to make any significant contributions to T_1 which is in general affected only by much faster molecular motions ($\tau \sim 10^{-7}$–^{12} sec).[16]

The observed ^{13}C spin-lattice relaxation times for free hosts and their complexes with ethylammonium ion are summarized in Table 4. From these data, we can see that the relaxation times for carbon resonances due to the *p-tert*-butyl and aryl ester groups increase as in the case of the protons but those for the aromatic carbons (*c*, *d*, and *e* carbons which can interact with guest protons) decrease upon complexation. This fact is also in accordance with the results from previous experiments which suggest endo type complexation and tight binding of the guest.[7,10]

Association constants and kinetic stability of complexes. The association constants for complexation of ethylammonium picrate salt by esters **1**, **2**, and **3** in THF-d_8 were determined by ^{1}H NMR titration methods. Varying the concentration ratios of [Guest]/[Host] ($\equiv\rho$) with host concentration held fixed at 0.04 M, the ^{1}H chemical shifts (δ_{obs}) for esters **1**, **2**, and **3** were observed. One can estimate the association constant (K) for a given calixarene complex, as shown in Figs. 3 and 4, by fitting the observed δ_{obs} *vs.* ρ data numerically with the following expression:[17]

$$\delta_{obs} = \frac{1}{2}\left[\left(1 - \frac{1}{\rho} - \frac{1}{K[\text{host}]}\right) + \left\{\left(1 - \frac{1}{\rho} - \frac{1}{K[\text{host}]}\right)^2\right.\right.$$

Table 4. ^{13}C NMR spin-lattice relaxation times in free hosts and their complexes in $CDCl_3$ at 298 K[a]

Carbon	Relaxation times, T_1 (sec)					
	1	**1+G**	**2**	**2+G**	**3**	**3+G**
a	0.47	0.56	0.45	0.54	0.47	0.54
b	6.86	7.18	6.88	7.21	6.97	7.67
c	2.71	2.80	2.68	2.41	2.63	2.45
d	0.19	0.19	0.20	0.19	0.22	0.17
e	2.20	2.09	2.04	1.99	2.05	1.98
f	[b]	[b]	[b]	0.10	[b]	0.11
g	4.25	4.32	4.12	4.06		4.39
h	0.17	0.21	0.17	0.22	0.18	0.21
i	4.50	5.00	5.54	4.67	4.71	4.57
j	1.15	1.21	0.73	0.98	0.86	0.75
k			2.06	2.06	1.28	1.23
l					3.04	3.21

[a]Measured at the same concentrations as specified in Table 1. [b]Difficult to determine the relexation time due to the presence of large peak *a*.

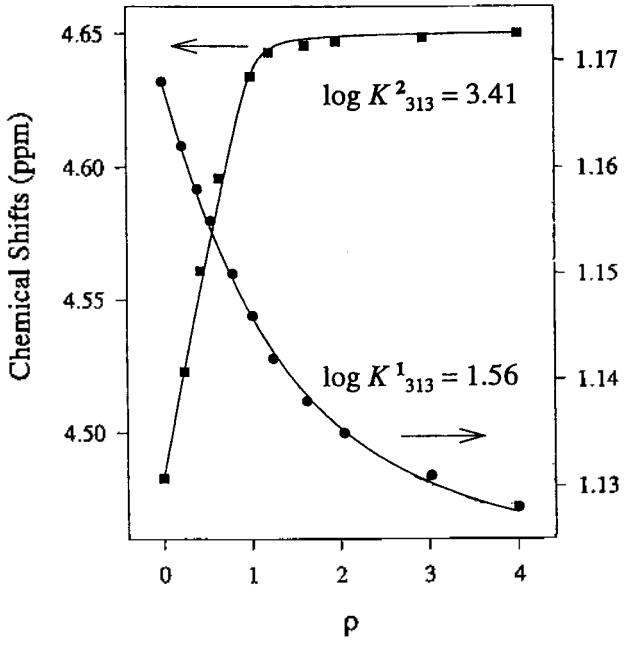

Figure 3. Plots of the chemical shifts for *p-tert*-butyl protons (filled circles) and OCH_2CO protons (filled squares) in ester **1** and **2**, respectively, versus ρ in THF-d_8 at 313 K. The concentrations of **1** and **2** were maintained constant (0.04 M) while that of guest was varied.

$$+\frac{4}{K[\text{host}]}\Bigg\}^{\frac{1}{2}}\Bigg]\times(\delta_{\text{free}}-\delta_{\text{complex}})+\delta_{\text{complex}} \qquad (1)$$

where δ_{free} and δ_{complex} denote, respectively, the ^{1}H chemical shifts in the free and complexed host, and [host] is the total concentration of the host. The resulting association constants indicate that the methyl ester **1** has relatively poor binding ability toward ethylammonium ion in comparison with its higher homologues, ethyl and propyl esters **2** and **3**. This observation is consistent with the reports by other investigators[1(b),3(b)] who estimated the binding abilities of esters **1-3** toward butylammonium and alkali metal ions by extraction experiments. The logarithms of the association constant K for ethyl and propyl ester were found to increase linearly with inverse temperature, T^{-1}, as can be seen from Figure 5. From the slope of these linear plots we could estimate thermodynamic parameters, ΔH, ΔS and ΔG, for the corresponding complexation process. As we see from the tabulated results (Table 5), for ethyl and propyl esters the contributions to ΔG from entropy change are comparable to those from enthalpy change. For methyl ester, however, we could not precisely estimate these parameters because of poor linearity in the ln K *vs.* $1/T$ plot. Such poor linearity probably arises from the fact that for methyl ester the association constant is small and does not vary very much with temperature, and, therefore, may be seriously affected by experimental errors. Nonetheless, they are obviously much smaller than those for its higher homologues. This is presumably due to the fact that smaller methyl groups quench ring mobility far less effectively than ethyl and propyl groups, thus making the formed complex less stable and less organized. Accordingly, the behaviors of methyl ester (in conformation,[14] complexational ability,[1] *etc.*) are found to be quite different from those of its higher homologues as previously mentioned.

To look into the kinetic stabilities of these complexes, we have examined the coalescence temperatures of nmr signals for *p-tert*-butyl protons and OCH_2CO_2 protons in prepared solutions (ρ=0.5). When the temperature was lowered, broadening and splitting of the resonance lines were ob-

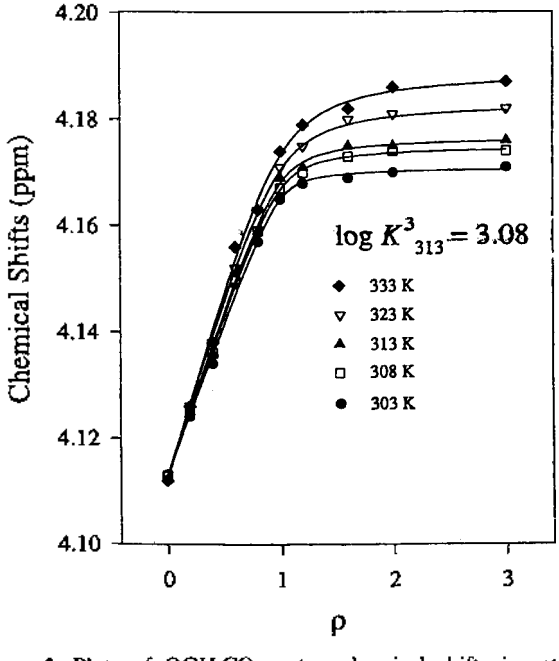

Figure 4. Plots of OCH_2CO proton chemical shifts in ester **3** versus in THF-d_8 at several different temperatures. The concentration of **3** was maintained constant (0.04 M) while that of guest was varied.

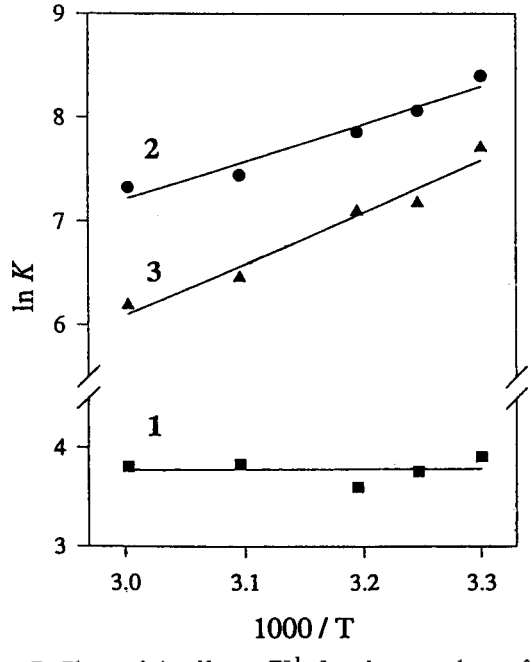

Figure 5. Plots of ln K *vs.* T^{-1} for the complexes formed between calix[6]arene ester derivatives and ethylammonium picrate.

Table 5. Association constants and thermodynamic parameters for complexation in THF-d_8[a]

	Association constants, log K					ΔH (kJ/mol)	ΔS (J/mol K)	ΔG_{298} (kJ/mol)
	303 K	308 K	313 K	323 K	333 K			
1+G	1.70	1.63	1.56	1.67	1.65	−0.37(?)[b]	30.30(?)[b]	−8.66[b]
2+G	3.65	3.50	3.41	3.23	3.18	−29.90	29.89	−20.99
3+G	3.35	3.11	3.08	2.81	2.69	−41.34	−73.30	−19.50

[a]Measured with the host concentrations held fixed at 0.04 M. [b]The log K *vs.* $1/T$ plot shows poor linearity for methyl ester **1**.

served for both free hosts and complexes. The coalescence of the proton lines in this system may be assumed to arise from the following exchange process:

$$\text{Calix[6]arene} - CH_3CH_2NH_3^+ \cdot Pic^- + \text{Calix[6]arene}^* \rightleftharpoons \text{Calix[6]arene} + \text{Calix[6]arene}^* - CH_3CH_2NH_3^+ \cdot Pic^- \quad (2)$$

The spectra utilized for estimating the coalescence temperatures (T_c) and the free energy of activation ($\Delta G^{\neq}$) for the exchange process are shown in Figure 6. The coalescence temperatures for this host-guest system (**1**-ethylammonium picrate) were found to be about 311 K and 369 K in THF-d_8 and $C_2D_2Cl_4$, respectively. The free energies of activation for the exchange process described by Eq. (2) were calculated at the coalescence temperatures by making use of the relation[18]

$$\Delta G^{\neq} = RT_c\,[22.96 + \ln(T_c/\delta\nu)]\ (\text{J mol}^{-1}), \quad (3)$$

where $\delta\nu$ represents the chemical shift difference between two coalescing lines expressed in unit of Hz and T_c the coalescence temperature in unit of K, to give 66.0 kJ/mol and 77.9 kJ/mol in THF-d_8 and $C_2D_2Cl_4$, respectively. These values are much higher than those for the crown ether-*t*-butylammonium ion system,[19] which indicates that the complex formed in the **1**-ethylammonium picrate system is kinetically much more stable than those formed in the crown ether-*t*-butylammonium ion system. This, we believe, can mainly be attributed to the fact that in the former case stable *endo* type complex is formed. This is understandable considering that in *endo* type complexes the guest can be tightly bound to the cavity of the host, thus inhibiting the conformational interconversions. Coalescence temperatures were found to depend on the solvent used as well. For example, in $C_2D_2Cl_4$, a viscous and nonpolar solvent in which the guest ethylammonium picrate is not easily solvated, the coalescence temperatures were found to be relatively higher than in THF-d_8, a relatively nonviscous and polar solvent (The difference in coalescence temperature was found to be as much as 50 °C).

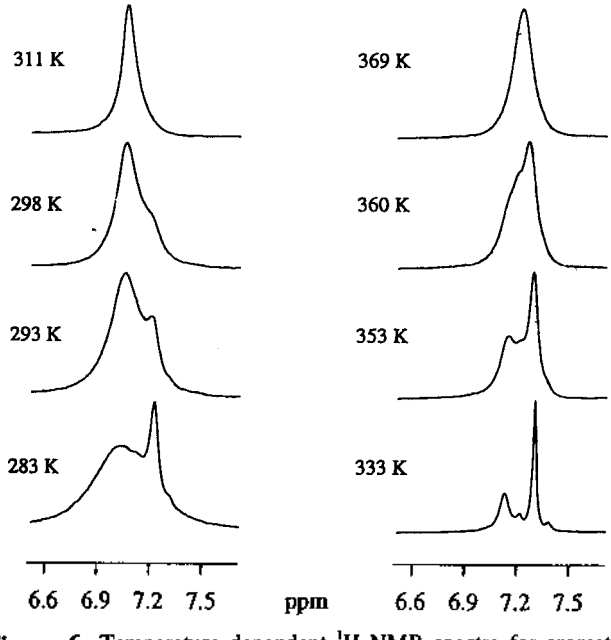

Figure 6. Temperature dependent ^{1}H NMR spectra for aromatic region of calix[6]arene methyl ester **1** and ethylammonium picrate in THF-d_8 (left) and $C_2D_2Cl_4$ (right) with ρ=0.5.

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Synthesis of Novel 9-Fluoroanthracycline Derivatives

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Synthesis of novel 9-fluoroanthracyclines carrying L-fucose as a sugar component is described. Compound **3** containing a fluorine at the C-9 position was synthesized from an epoxide **2** and HF/Pyr (7 : 3). Bromination and hydrolysis of compound **3** resulted in synthesis of an aglycone, 9-fluoroanthracyclinone **6**. The α-(**1b**) and β-anomers (**1a**) of the final product were obtained in high yields by a coupling reaction with the L-fucose.

Introduction

A numerous anthracycline derivatives have been synthesized and tested for anticancer activity.[1] Nevertheless, the clinical use of anthracyclines requires further development of a more potent derivative with less cardiotoxicity.[2] Recently, it was reported[3] that introduction of fluorine to anthracycline increases anticancer activity. Derivatives of anthracycline showed either improved antitumor activity or reduced toxicity when fluorine was introduced at the C-1 and/or C-4 positions[4] of the D ring, the C-8[5] or C-14[6] positions of the A-ring, and the C-2' position of the glycone.[7]

We have synthesized a novel anthracycline derivative in which fluorine was introduced at the C-9 position on the aglycone A-ring. A sugar moiety, L-fucose, was subsequently coupled.[8] It was anticipated that the introduction of fluorine would result in higher affinity and increased binding to DNA.[9] Thus, we here describe the synthesis of anthracycline derivatives where fluorine and L-fucose were introduced.

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Results and Discussion

We have been using 3-phenylsulfonyl-1(3*H*)-isobenzofuranone derivatives[10] as Michael donors in constructing tetracyclic ring systems. However, we recently found[11] that the same results could be obtained by using newly synthesized 3-carbomethoxy-1(3*H*)-isobenzofuranone instead of these phthalide sulfones. Initially, a 95% yield of an epoxide (±)-**2**, (Scheme 1; yellow powder, mp 207-209 °C; lit.[10c] 208-211 °C) was obtained using methods previously described in the literature.[11] Hydrofluorination of epoxide **2** was then carried out with Olah's reagent[12] under various reaction conditions (Table 1) to obtain compound **3**, where a fluorine atom was introduced at the C-9 position. When Arcamone's method[5] was used (run 1), the yield was only 15% and the major reaction product was a ketone compound **4**. By optimizing the reaction time and the solvents (runs 2-5), the yield was raised to 50%: shorter reaction time and the use of methylene chloride as a solvent improved the yield. To improve the yield further, **2** was dissolved in chloroform and was added into HF/Pyr (7 : 3) in an ice-bath. The mixture was then kept at room temperature for 5 minutes to complete the reaction (run 6). Using this method, a yield