Effects on Metal Binding of Circular NH- - -O═C Intramolecular Hydrogen Bonding in Hydrophilic Pseudocavities of *p-tert*-Butylcalix[4]arenes Carrying Amino Acid Moieties

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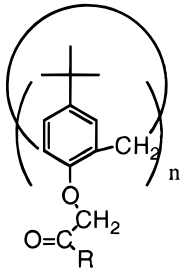
Calix[4]arenes bearing amino acid moieties were prepared by the reaction of carboxyl-protected amino acids with the acid chlorides of *O*-carboxymethylcalix[4]arenes. The binding ability toward metal ions was estimated by solvent extraction. These calixarenes showed selective extraction capability toward Na^+ and Ag^+ ions, which increased in the order **2a** < **2b** < **2d** < **2c**. The complexing ability was also affected by the nature of the solvents and was higher in ethyl acetate than dichloromethane. ^{1}H NMR studies showed that the complexation of **2c** with Na^+ ion induces a change of the orientation of the amide groups from a network-like pattern with circular N−H- - -O═C intramolecular hydrogen bonding of **2c** to a pattern in which carbonyl groups converge on the Na^+ ion. This change was also supported by a measurement of CD spectra.

Introduction

Calixarenes, which are macrocyclic oligomers that can be obtained by a base-catalyzed condensation of certain *p*-substituted phenols with formaldehyde, have been extensively studied for last two decades.[1] These compounds are of current interest as starting materials for the preparation of a wide variety of molecular receptors and ionophores.[1] We have been focusing on the binding ability of calixarenes bearing azo groups for metal ions such as Ag^+ [2] and on an octopus-type calixarene which serves as a complexing agent for alkali metal ions.[3] Many complexation studies of alkaline cations have been performed by using calixarenes with pendant esters[4] and amide groups.[5−9] Especially, several calixarene amides act not only as complexing agents toward metal cations but also as anion receptors in bifunctional calixarenes.[9−12]



Carbonyl-containing calixarenes

Carbonyl-containing calixarenes, which include calixarene esters or amides, have flexible hydrophilic pseudocavities, and their carbonyl groups converge on complexed cations.[13] It has been thought that the flexibility of the ligand is important in providing optimal surroundings of the complexed cations.[7] In calixarene chemistry, most attention has been paid to stabilizing or fixing a conformation of the calixarene skeletons by intramolecular hydrogen bonding or bulkiness of substituents.[1] Amide groups introduced into the upper[9,14] or lower[11] rim of calixarenes, which are capable of forming intramolecular hydrogen bonding, give strong conformational stability of the calixarene substructure. There are few

(1) (a) Gutsche, C. D. *Calixarenes Revisited, Monographs in Supramolecular Chemistry*; Stoddat, J. F., Ed.; The Royal Society of Chemistry: Cambridge, 1998. (b) *Calixarenes: A Versatile Class of Macrocyclic Compounds*; Vicens, J. and, Böhmer, V., Eds.; Kluwer Academic Publishers: Dordrecht, 1991.

(2) (a) Nomura, E.; Taniguchi, H.; Tamura, S. *Chem. Lett.* **1989**, 1125−1126. (b) Nomura, E.; Taniguchi, H.; Otsuji, Y. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 6, 3797−3801.

(3) Nomura, E.; Taniguchi, H.; Kawaguchi, K.; Otsuji, Y. *J. Org. Chem.* **1993**, *58*, 4709−4715.

(4) (a) Arimura, T.; Kubota, M.; Matsuda, T.; Manabe, O.; Shinkai, S. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 1674−1676. (b) Arnaud-Neu, F.; Barrett, G.; Cremin, S.; Deasy, M.; Ferguson, G.; Harris, S. J.; Lough, A. J.; Guerra, L.; McKervey, M. A.; S.-Weill, M. J.; Schwinte, P. *J. Chem. Soc., Perkin Trans. 2* **1992**, 1119−1125. (c) Barrett, G.; Corry, D.; Creaven, B. S.; Johnston, B.; McKervey, M. A.; Rooney, A. *J. Chem. Soc., Chem. Commun.* **1995**, 363−364. (d) Böhmer, V.; Vogt, W.; Goldmann, H. *J. Org. Chem.* **1990**,*55*, 2569−2570. (e) Chang, S.-K.; Jang, M. S.; Han, Y.; Lee, J. H.; Kang, M. H.; No, K. T. *Chem. Lett.* **1992**, 1937−1940. (f) McCarrick, M.; Wu, B.; Harris, S. J.; Diamond, D.; Barrett, G.; McKervey, M. A. *J. Chem. Soc. Perkin Trans. 2* **1993**, 1963−1968. (g) Perez-Jimenez, C.; Harris, S. J.; Diamond, D. *J. Chem. Soc., Chem. Commun.* **1993**, 480−481.

(5) Arduini, A.; Ghidini, E.; Pochini, A.; Ungaro, R.; Andreetti, G. D.; Calestani, G.; Ugozzoli, F. *J. Inclusion Phenom.* **1988**, *6*, 119−134.

(6) (a) Arnaud-Neu, F.; Barrett, G.; Fanni, S.; Marrs, D.; McGregor, W.; McKervey, M. A.; Schwing-Weill, M.-J.; Vetrogon, V.; Wechsler, S. *J. Chem. Soc., Perkin Trans. 2* **1995**, 453−460. (b) Arnaud-Neu, F.; Fanni, S.; Guerra, L.; McGregor, W.; Ziat, K.; Schwing-Weill, M.-J.; Barrett, G.; MaKervey, M. A.; Marrs, D.; Seward, E. M. *J. Chem. Soc., Perkin Trans. 2* **1995**, 113−118.

(7) Guilbaud, P.; Varnek, A.; Wipff, G. *J. Am. Chem. Soc.* **1993**, *115*, 8298−8312.

(8) Kimura, K.; Matsuo, M.; Shono, T. *Chem. Lett.* **1988**, 615−616.

(9) Scheerder, J.; Duynhoven, J. P. M. v.; Engbersen, J. F. J.; Reinhoudt, D. N. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1090−1093.

(10) (a) Rudkevich, D. M.; Verboom, W.; Reinhoudt, D. N. *J. Org. Chem.* **1994**, *59*, 3683−3686. (b) Rudkevich, D. M.; Mercer-Chalmers, J. D.; Verboom, W.; Ungaro, R.; Jong, F. d.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1995**, *117*, 6124−6125.

(11) Murakami, H.; Shinkai, S. *Tetrahedron Lett.* **1993**, *34*, 4237−4240.

(12) Beer, P. D.; Chen, Z.; Goulden, A. J.; Grive, A.; Hesek, D.; Szemes, F.; Wear, T. *J. Chem. Soc., Chem. Commun.* **1994**, 1269−1271.

(13) Arduini, A.; Pochini, A.; Reverberi, S.; Ungaro, R.; Andreetti, G. D.; Ugozzoli, F. *Tetrahedron* **1986**, *42*, 2089−2100.

(14) Scheerder, J.; Vreekamp, R. H.; Engbersen, J. F. J.; Verboom, W.; Duynhoven, J. P. M. v.; Reinhoudt, D. N. *J. Org. Chem.* **1996**, *61*, 3476−3481.

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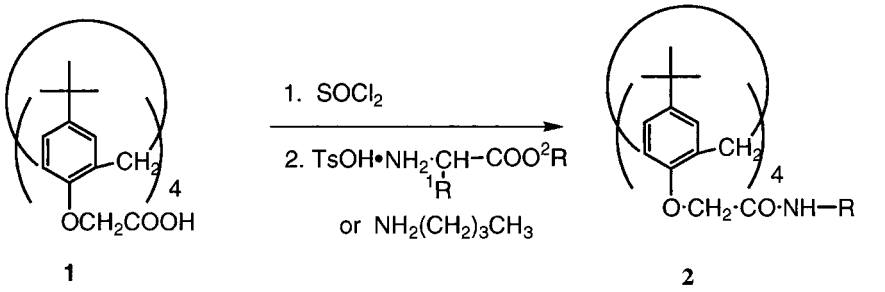
Scheme 1



1 **2**

a : R=CH_2COOBn
b : R=$CH(CH_3)COOBn$
c : R=$CH(CH(CH_3)_2)COOBn$
d : R=$CH(CH_2C_6H_5)COOBn$
e : R=$(CH_2)_3CH_3$
f : R=$CH(CH_3)COOMe$

Table 1. Extractability of Metal Picrates by the Calix[4]arenes[a]

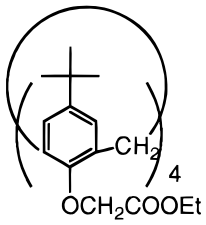
	Ex (%) of M^+Pic^-											
	Li^+			Na^+			K^+			Ag^+		
ligands	CH_2Cl_2	EtOAc	toluene	CH_2Cl_2	EtOAc	toluene	CH_2Cl_2	EtOAc	toluene	CH_2Cl_2	EtOAc	toluene
2a	0	1	0	3	9	2	0	0	<1	0	8	0
2b	0	1	0	37	64	0	2	5	1	32	60	0
2f				34			4			34		–
2c	6	1	0	73	84	0	16	20	0	72	83	0
2d	3	2	0	56	80	<1	9	7	0	58	76	0
2e	1	2	0	18	27	1	2	2	0	21	33	0
3	22	1	0	98	65	0	38	2	<1	94	27	0

[a] Extraction conditions: organic phase; 1.0×10^{-3} M of ligand, aqueous phase; 1.0×10^{-2} M of MNO_3 and 1.8×10^{-4} M of picric acid. The mixture of two solutions (5 mL each) was shaken and stored for 1 h at 20 °C. Ex (%) was determined by the absorbance of picrate ion in the aqueous phase.

papers, however, that discuss the effects on ion binding properties of the substituents forming intramolecular hydrogen bonding. We have given attention to hydrogen bonding, which is of paramount importance for the stabilization of the shapes of large biological molecules such as cellulose, proteins, and nucleic acids.[15] In this paper we describe (a) the syntheses of calixarenes carrying amino acids on the lower rim to stabilize binding sites of calixarenes and (b) the effects on the binding ability of intramolecular hydrogen bonding in the hydrophilic pseudocavities of these calixarenes toward metal ions by means of solvent extractions, ^{1}H NMR, and CD titrations.

Results and Discussion

Synthesis of Calix[4]arenes Bearing Amino Acids. Amino acids that were chosen as hydrogen-bonding forming moieties were glycine, L-alanine, L-valine, and L-phenylalanine and were introduced on the lower rim of *p-tert*-butylcalix[4]arene. We also used butylamine to obtain a simple amide calix[4]arene which can form intramolecular hydrogen bonding. The *O*-carboxymethylcalix[4]arene **1** was prepared from alkaline hydrolysis of the calix[4]arene tetraethyl ester **3**.[16] The acid chloride of **1** was prepared and then reacted with *p*-toluenesulfonates of suitable amino acid benzyl esters (Scheme 1). The yields are moderate (48−60%). All of these derivatives had the cone conformation, which was determined by ^{1}H NMR. The ^{1}H NMR spectra showed singlets for *tert*-butyl groups and AB quartets for bridging methylenes of the calixarene skeleton. The calix[4]arenes **2b**, **2d**, and **2c** are optically active molecules.



3

To compare with the calixarene in which the intramolecular hydrogen bonding is impossible, the calix[4]arene **3** was used. The selective binding property of this compound toward sodium ion has been established.[16,17] The calixarene **2f** in which the terminal benzyl groups of **2b** are exchanged for methyl groups was also used to investigate the effect of the terminal group on the metal binding ability.

Solvent Extraction of Metal Picrates. The intramolecular hydrogen bonding in the calix[4]arenes

(15) Stryer, L. *Biochemistry*, 3rd ed.; W. H. Freeman and Co.: New York, 1988.
(16) Chang, S.-K.; Cho, I. *J. Chem. Soc., Perkin Trans. 1* **1986**, 211−214.
(17) Arnaud-Neu, F.; Collins, E. M.; Deasy, M.; Ferguson, G.; Harris, S. J.; Kaitner, B.; Lough, A. J.; Mckervey, M. A.; Marques, E.; Ruhl, B. L.; Schwing-Weill, M. J.; Seward, E. M. *J. Am. Chem. Soc.* **1989**, *111*, 8681−8691.

bearing amino acids has been assumed to affect the extractability of the calixarenes toward metal ions. The extractability of the calix[4]arenes toward alkali metal cations and Ag^+ was evaluated by means of solvent extraction of their metal picrates from aqueous phase to organic phase. The results are summarized in Table 1. The calix[4]arenes **2b**, **2c**, **2d**, and **2e** showed extractability toward Na^+ and Ag^+ ions using dichloromethane as the organic phase. The calix[4]arene **2a** showed very low extractability toward Na^+ ion and no extractability toward Li^+, K^+, and Ag^+ ions under the same conditions. The extraction capability of **2f** was similar to that of **2b**, showing that the terminal group of the calixarene exerts no effect. The extractability in dichloromethane increases in the order **2a** < **2e** < **2b** < **2d** < **2c**. The extractability of **2b**, **2c**, and **2d**, which have bulky substituents in the amino acid moieties, is relatively larger than that of **2a** and **2e**.

The solvent effect on the extraction was examined, and the results are also listed in Table 1. The extractability of **2a**, **2b**, **2c**, **2d**, and **2e** toward Na^+ and Ag^+ ions is higher in ethyl acetate than in dichloromethane. When toluene was used as the organic phase, **2a**, **2b**, **2c**, **2d**, and **2e** exhibited very little extraction capability toward all the metal ions which we examined. Similar results were obtained by the use of chloroform as the organic phase. On the other hand, **3** exhibited extractability toward all of the ions which we used, but the ability was unexpectedly lower in ethyl acetate than in dichloromethane.

The equilibrium constants (K_e) for the extraction of alkali metal picrates (M^+Pic^-) with the calixarene from aqueous solution into organic solvents were estimated.[13] The stoichiometry for the complex formation of the calix[4]arene with sodium picrate in dichloromethane-d_2 was estimated by NMR titration as shown in Figure 1. Upon adding an excess of sodium picrate, the spectra did not change further, and insoluble sodium picrate remained. This suggests that **2c** forms a 1:1 complex with Na^+ ion. The alkali metal extraction equilibria with the calixarenes from aqueous solution to organic solvents can be expressed by

$$M^+_{aq} + Pic^-_{aq} + L_{org} \rightleftharpoons \{L\cdot M^+, Pic^-\}_{org}$$

where L and L_{org} are a ligand and a ligand in the organic phase, respectively, M^+_{aq} and Pic^-_{aq} represent an alkali metal cation and the picrate anion in the aqueous phase, respectively, and $\{L\cdot M^+, Pic^-\}_{org}$ is a complex that is formed between the calixarene and a metal picrate in an organic solvent. The extraction equilibrium constants (K_e) are given by the following equation:

$$K_e = [\{L\cdot M^+, Pic^-\}_{org}]/\gamma^2[M^+_{aq}][Pic^-_{aq}]([L_{org}]_0 - [\{L\cdot M^+, Pic^-\}_{org}])$$

where γ is the mean activity coefficient of the picrate salt in water. The complex concentrations of L/alkali metal picrate in organic solvents, [{L·M^+, Pic^-}$_{org}$], were determined spectroscopically. The evaluated K_e values for **2a**, **2b**, **2d**, **2c**, and **3** with sodium picrate are 1.9×10^4, 9.9×10^4, 1.6×10^5, 2.8×10^5, and 9.9×10^6 M^{-2}, respectively, in dichloromethane and are 1.3×10^4, 1.6×10^5, 4.3×10^5, 5.3×10^5, and 1.5×10^5 M^{-2}, respectively, in ethyl acetate. From these results, chiral

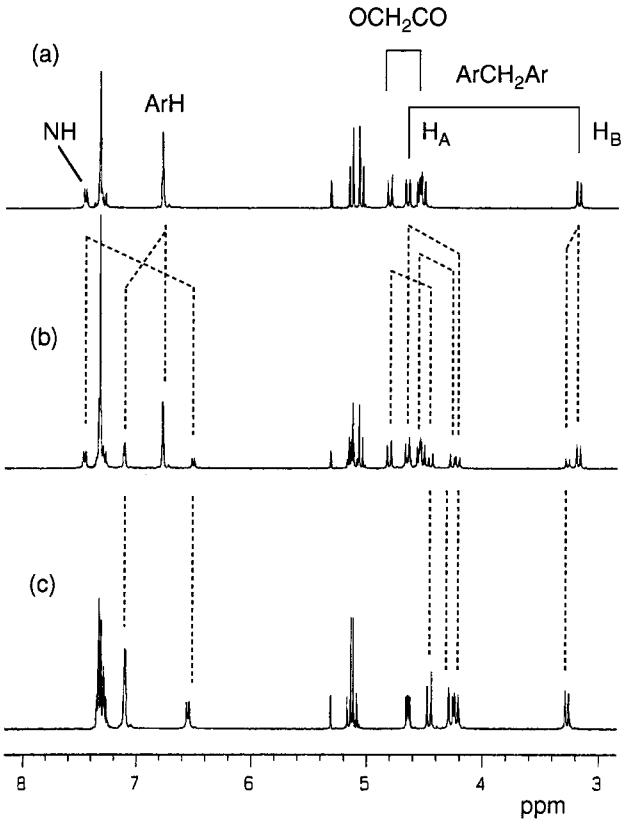


Figure 1. ^{1}H NMR spectra (400 MHz) of **2c** in the presence of sodium picrate in CD_2Cl_2 at 20 °C. The molar ratio [NaPic]/[**2c**] = (a) 0, (b) 0.35, and (c) 1.0.

calixarenes **2b**, **2d**, and **2c** have 2−3 times larger K_e values in ethyl acetate than in dichloromethane. On the other hand, **3** has a much smaller K_e value in ethyl acetate than in dichloromethane. It is thought that bulky substituents included in amino acid moieties might serve a suitable binding site geometry of the hydrophilic pseudocavities in the calixarenes to capture metal cations.

NMR Studies. The complexation of **2c** with Na^+ ion was observed by ^{1}H NMR spectroscopy. Figure 1 shows the ^{1}H NMR spectra of **2c** and of its sodium picrate complex in CD_2Cl_2. Upon adding variable amounts of sodium picrate to the $CDCl_2$ solution of **2c**, new shifted signals for the complex appeared at all of the original signals, and then the original signals of **2c** disappeared after the [sodium picrate]/[ligand] ratio reached unity. The NH protons move 0.90 ppm upfield, and the aromatic protons of the calixarene skeleton move 0.34 ppm downfield. The methylene protons of the OCH_2CO groups move 0.30 ppm upfield. These signals show a pair of doublets because their methylene protons are diastereotopic. The axial (H_A) and equatorial (H_B) protons of the bridging methylene in the calixarene move 0.42 ppm upfield and 0.09 ppm downfield, respectively. It is assumed that these variations are induced by the complexation of **2c** with Na^+ ion, resulting in a change of the orientation of the amide groups as shown in Figure 2. In the absence of Na^+ ion, it is assumed that amide groups of binding sites of the calixarenes cooperate to form a network-like pattern with a circular N−H- - -O═C hydrogen bond, existing in equilibrium between A and B in Scheme 2. The upfield shift of the NH protons upon complexation suggests that intramolecular hydrogen bonding among

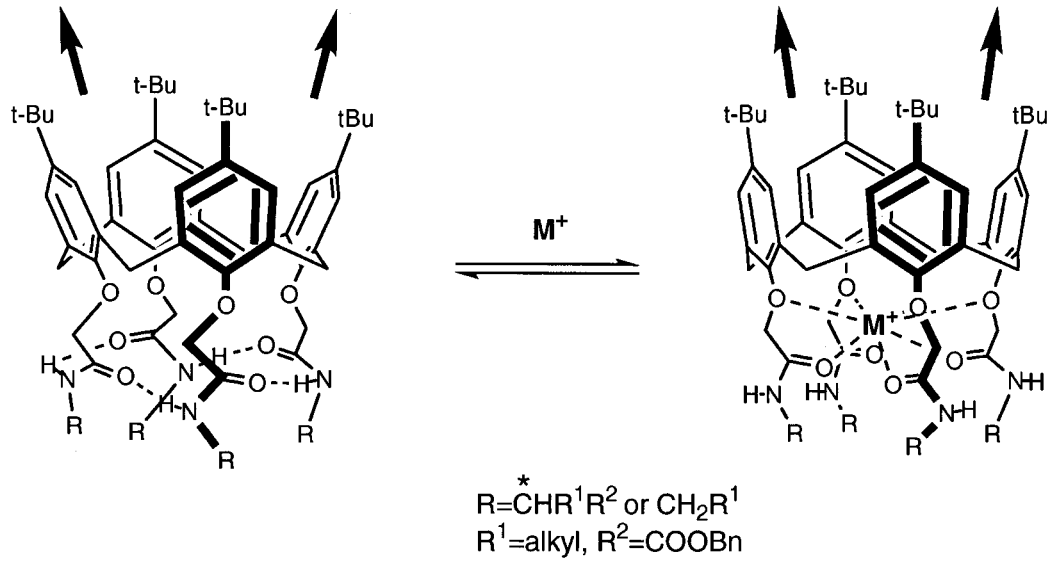
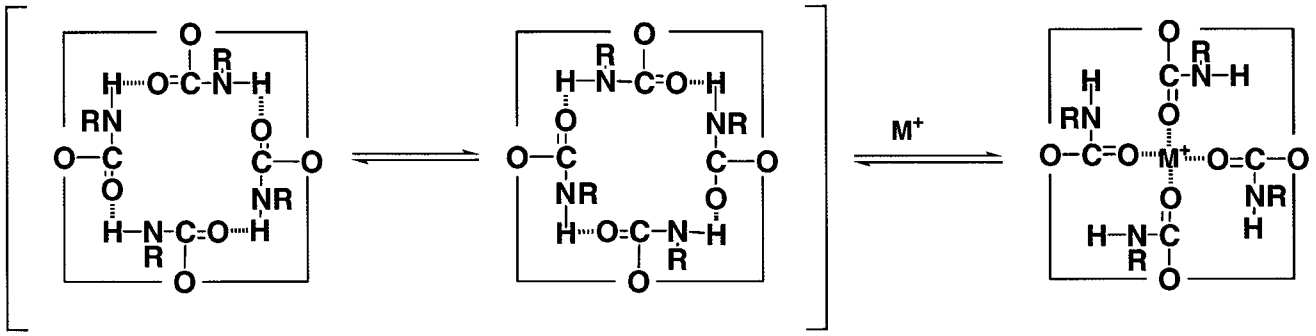


Figure 2. Schematic representation of binding mechanism of the calix[4]arenes.

Scheme 2



the amide groups in the calixarene is disrupted. The downfield shift for the aromatic protons of the calixarene ring can be explained by assuming that the deshielding effect by neighboring aromatic rings in the calixarene is strengthened by changing the molecular arrangement (Figure 2). The variation of the methylene proton signals for the OCH_2CO groups is more difficult to explain. It seems to be affected by the change of both shielding and deshielding effects of aromatic rings and neighboring carbonyl groups. The large upfield shift for the axial protons of the bridging methylene in the calixarene ring can be explained by assuming that the deshielding effect of the carbonyl groups in the OCH_2CO moieties diminished by changing the direction of the amide groups. In the region of lower values of the [sodium picrate]/[ligand] ratio, signals of both the complexed and uncomplexed ligands appeared. This shows that the exchange rate between the two species is slow on the NMR time scale.[18] A similar NMR spectrum was also observed for the complex of **2c** with Ag^+ ion.

The ^1H NMR data of uncomplexed and complexed **2a**, **2b**, **2c**, **2d**, and **2e** with sodium picrate in CD_2Cl_2 are summarized in Table 2. The signals for the NH, ArH, and axial proton H_A of complexed **2a**, **2b**, and **2e** became broad when the [sodium picrate]/[ligand] ratio reached unity. On the other hand, all signals for complexed **2c** and **2d** became sharp under the same conditions. These data indicate that the exchange rate of **2c** and **2d** as shown in Figure 2 are relatively slower than those of **2a**, **2b**, and **2e** on the NMR time scale. Compounds **2c** and **2d** are considered to form tight and stable complexes with Na^+ ion. The NH signals for complexed **2a**, **2b**, **2c**, **2d**, and **2e** were observed at 7.29, 6.90, 6.55, 6.59, and 6.97 ppm, respectively. These results show that the strength of the intramolecular hydrogen bonding among the amide groups in the complexed calixarenes is increased in the order **2c** < **2d** ≪ **2b** < **2e** < **2a**. Judging from the strength of intramolecular hydrogen bonding in complexed calixarenes, the extractability toward Na^+ ion increases with decreasing strength of the intramolecular hydrogen bonding.

It is also thought that the solvent effects on the binding ability are relevant to the intramolecular hydrogen bonding. The NH signals for **2c** and its complex with sodium picrate in various solvents are listed in Table 3. The amide groups can form either inter- or intramolecular hydrogen bonds depending on the nature of the solvents.[18] The formation of intramolecular hydrogen bonds is favored in non- or weak-hydrogen-bonding solvents such as toluene and chloroform. A sharp doublet

(18) Reichardt, C. *Solvent and Solvent Effects in Organic Chemistry*, 2nd ed.; VCH: Weinheim, 1988; pp 13−17.

Table 2. ^{1}H NMR Spectral Data of the Calix[4]arenes and Their Complexes with Na−Picrate[a]

	chemical shift, δ (ppm)			
calixarenes	NH	ArH	OCH_2CO	$ArCH_2Ar$
2a	7.87 (t)	6.86 (s)	4.54 (s)	4.54 (d), 3.28 (d)
2a + Na^+	7.29 (s)	7.08 (br s)	4.54 (s)	4.41 (bd s), 3.35 (br d)
2b	7.74 (d)	6.78 (s)	4.65 (d), 4.53 (d)	4.58 (d), 3.20 (d)
2b + Na^+	6.90 (br s)	7.11 (br s)	4.55 (d), 4.20 (br d)	4.31 (br d), 3.31 (d)
2c	7.45 (d)	6.77 (s)	4.81 (d), 4.52 (d)	4.65 (d), 3.18 (d)
2c + Na^+	6.55 (d)	7.11 (s)	4.46 (d), 4.26 (d)	4.23 (d), 3.27 (d)
2d	7.75 (d)	6.78 (s)	4.66 (d), 4.47 (d)	4.57 (d), 3.12 (d)
2d + Na^+	6.59 (d)	7.30 (s)	4.40 (d), 3.92 (d)	4.09 (d), 3.92 (d)
2e	7.55 (t)	6.81 (s)	4.46 (s)	4.48 (d), 3.24 (d)
2e + Na^+	6.97 (br s)	7.12 (br s)	4.48 (s)	4.39 (br d), 3.34 (d)

[a] ^{1}H NMR spectra were measured in CD_2Cl_2 at 20 °C.

Table 3. Chemical Shifts of the NH Protons of Uncomplexed and Complexed 2c in Various Solvents

	NH chemical shift, δ (ppm)			DN[a]
solvents	uncomplexed	complexed	$\Delta\delta$	(kcal/mol)
CD_2Cl_2	7.45 (d)	6.55 (d)	−0.90	
$CDCl_3$	7.48 (br d)	6.88 (br s)	−0.60	
$C_6D_5CD_3$	7.96 (br d)	7.63 (br d)	−0.33	
$C_6D_5NO_2$	7.90 (d)	6.95 (br d)	−0.95	8.1
dioxane-d_8	7.91 (d)	7.43 (d)	−0.48	14.8
aceton-d_6	8.05 (d)	7.45 (d)	−0.60	17.0
DMSO-d_6	8.45 (d)	8.33 (br s)	−0.12	29.8
C_5D_5N	9.35 (d)	9.47 (d)	0.12	33.1

[a] The Gutmann's donor numbers of EPD solvents.[19]

for the NH protons of **2c** was observed at 7.45 ppm in CD_2Cl_2. In this solvent, relatively stable complexes with Na^+ ion are formed. On the other hand, the broad NH signals for **2c** in $CDCl_3$ and toluene-d_8 were observed at 7.48 and 7.90 ppm, respectively. The downfield shift for the NH proton in toluene-d_8 can be explained by assuming that the intramolecular hydrogen bonding among the amide groups in the calixarene is strengthened. The binding ability is related to the stability of the complex in the solvents.[6] The broadening of the signals in $CDCl_3$ and toluene-d_8 can be explained by a fast exchange rate between complexed (C) and uncomplexed ligands (A or B) as shown in Scheme 2. Therefore, the complexes with Na^+ ion are not expected to be stable in these solvents because strong intramolecular hydrogen bonding is favored.

The intramolecular hydrogen bonding among amide groups in the calixarene is broken in electron pair donor (EPD) solvents such as acetone and pyridine.[18] The downfield shift for the NH signals of **2c** is ordered according to increasing the donicitis (Gutmann's donor numbers[19]) of EPD solvents as shown in Table 3. The NH signals in various EPD solvents are thought to reflect the strength of intermolecular hydrogen bonding between the amide groups and solvents. In these solvents, the intramolecular hydrogen bonding is disrupted or weakened. Therefore, the orientation of amide groups in the calixarene is suitable for coordination of metal ions, resulting in the formation of a stable complex. On the other hand, **3** has no amino groups with which to stabilize the orientation of the carbonyl groups in binding the Na^+ ion, resulting in the low binding ability in an EPD solvent such as ethyl acetate.

(19) Reference 18, pp 19−21.

(20) (a) Shinkai, S.; Arimura, T.; Satoh, H.; Manabe, O. *J. Chem. Soc., Chem. Commun.* **1987**, 1495−1496. (b) Arimura, T.; Kawabata, H.; Matsuda, T.; Muramatsu, T.; Satoh, H.; Fujio, K.; Manabe, O.; Shinkai, S. *J. Org. Chem.* **1991**, *56*, 301−306.

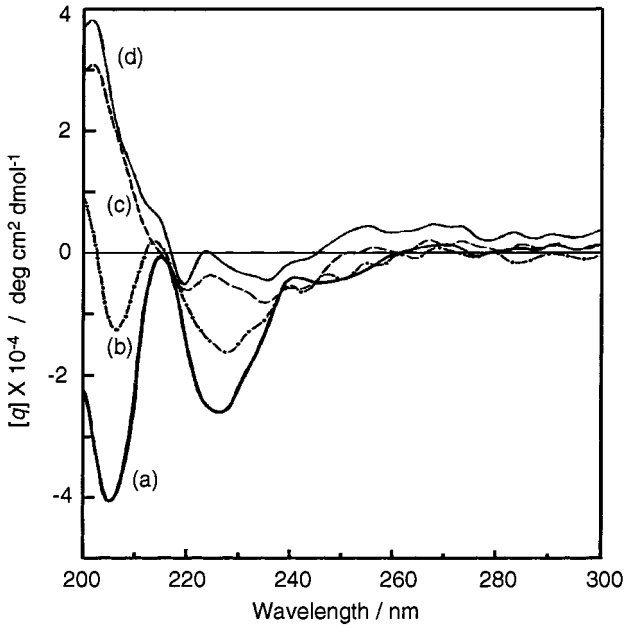


Figure 3. CD spectra of **2c** in the absence and the presence of sodium picrate in CH_3CN at 20 °C. [NaPic]/[**2c**] = (a) 0, (b) 0.3, (c) 0.6, and (d)1.0.

CD Spectra Measurement. A CD technique is useful for evaluating chiral host−guest interactions in calixarene chemistry.[20] The chiral calixarenes **2b**, **2c**, and **2d** gave Cotton effects in the region of around 200−250 nm in acetonitrile. The complexation of **2c** with Na^+ ion was observed by CD titration and is shown in Figure 3. Uncomplexed **2c** gave two strong negative Cotton effects. The CD spectrum of **2c** was remarkably affected by the addition of sodium picrate. The CD band was weakened with increasing concentration of sodium picrate and finally gave a strong positive Cotton effect after the [sodium picrate]/[ligand] ratio reached 0.5. Similar spectral changes of **2c** were observed by using $NaClO_4$ which has no absorption band. These variations, together with the NMR data, are induced by the change of orientation of the amide groups in the calixarene and also by the change of molecular arrangement of the calixarene substructure as shown in Figure 2.

Experimental Section

General Methods. Melting points were uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz spectrometer using TMS as an internal standard. FAB mass spectra were recorded using 3-nitrobenzyl alcohol as a matrix. Electronic spectra were measured at 20 °C. CD spectra were measured at 20 °C in a 2 mm cell.

Compounds **1** and **3** were prepared according to the literature procedures.[16] Carboxyl-protected amino acid *p*-toluenesulfonates were prepared by the literature method.[21]

Alkali metal picrates were prepared by the following manner. An aqueous solution of 1.0 g of picric acid was neutralized with alkali metal hydroxide and was dissolved in water, and solvent was evaporated. The resulting residue was recrystallized twice from methanol.

5,11,17,23-Tetra-*tert*-butyl-25,26,27,28-tetrakis[(*N*-benzyloxycarbonylmethylamino)carbonylmethoxy]calix[4]arene (2a). A mixture of 1.0 g (1.13 mmol) of 5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetrakis(caboxymethoxy)calix[4]arene **1** and 5 mL (68 mmol) of thionyl chloride was refluxed for 2 h. The residue after evaporation of the unreacted thionyl chloride under reduced pressure was dissolved in 10 mL of anhydrous dichloromethane, and to the solution was added dropwise a solution of 2.7 g (8 mmol) of *N*-benzyloxycarbonylmethylamine *p*-toluenesulfonate and 0.63 g (8 mmol) of pyridine in 10 mL of dichloromethane. The mixture was stirred at 0 °C for 1 h and then stirred at room temperature for an additional 30 h. After the reaction was complete, the mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was dissolved in 30 mL of dichloromethane, followed by washing with water (50 mL × 3), 10% citric acid (50 mL × 3), and water (50 mL × 3), and then dried over anhydrous $MgSO_4$. The solution was concentrated, and ether/petroether (1/1) was added to produce precipitates. Recrystallyzation from dichloromethane/ether afforded 1.13 g of crystals in 77% yield: mp 187−189 °C; IR (KBr) 3354, 1751, and 1682 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.09 (s, 36H), 3.28 (d, 4H), 4.13 (d, 8H), 4.54 (d, 4H), 4.58 (s, 8H), 5.06 (s, 8H,), 6.82 (s, 8H), 7.26 (s, 20H) 7.91 (t, 4H); ^{13}C NMR ($CDCl_3$) δ 170.4, 170.1, 152.5, 146.2, 135.3, 132.7, 128.6, 128.3, 128.2, 126.0, 74.2, 67.1, 41.0, 34.0, 31.3, 31.1; HRMS (FAB) calcd for $C_{88}H_{101}N_4O_{16}^+$ $(M + H)^+$, 1470.783, found 1470.772; Anal. Calcd for $C_{88}H_{100}N_4O_{16}$: C, 71.94; H, 6.81; N, 3.82. Found: C, 71.79; H, 6.98; N, 3.79.

5,11,17,23-Tetra-*tert*-butyl-(*S*,*S*,*S*,*S*)-25,26,27,28-tetrakis-[[*N*-(1-benzyloxycarbonylethyl)amino]carbonylmethoxy]-calix[4]arene (2b). Using procedures similar to those described for the preparation of **2a**, a 59% yield of the product was obtained as needles: mp 183−185 °C; $[\alpha]^{20}_D$ −21.9 (*c* 2.00, $CHCl_3$); IR (KBr) 3304, 1746, and 1674 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.08 (s, 36H), 1.46 (d, 8H), 3.19 (d, 4H), 4.56 (d, 4H), 4.60 (d, 4H), 4.69 (d, 4H), 4.70 (t, 4H), 5.05 (d, 4H), 5.12 (d, 4H), 6.74 (s, 8H), 7.25−7.32 (m, 5H) 7.74 (d, 4H); ^{13}C NMR ($CDCl_3$) δ 172.9, 169.8, 153.0, 145.5, 135.5, 133.1, 132.5, 128.5, 128.3, 128.0, 125.8, 125.5, 74.3, 67.0, 48.0, 33.9, 31.8, 31.4, 17.6; HRMS (FAB) calcd for $C_{92}H_{109}N_4O_{16}^+$ $(M + H)^+$ 1526.804, found 1526.461. Anal. Calcd for $C_{92}H_{108}N_4O_{16}$: C, 72.44; H, 7.09; N, 3.68. Found: C, 72.40; H, 7.28; N, 3.63.

5,11,17,23-Tetra-*tert*-butyl-(*S*,*S*,*S*,*S*)-25,26,27,28-tetrakis-[[*N*-(1-benzyloxycarbonyl-2-methylpropyl)amino]carbonylmethoxy]calix[4]arene (2c). Using procedures similar to those described for the preparation of **2a**, a 72% yield of the product was obtained as needles: mp 260−263 °C; $[\alpha]^{20}_D$ −27.4 (*c* 2.00, $CHCl_3$); IR (KBr) 3302, 1742, and 1676 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.77−0.82 (m, 24H), 1.07 (s, 36H), 2.11 (q, 4H), 3.18 (d, 4H), 4.53 (d, 4H), 4.60 (dd, 4H), 4.69 (d, 4H), 4.85 (d, 4H), 5.02 (d, 4H), 5.14 (d, 4H), 6.73 (s, 8H), 7.30−7.35 (m, 5H), 7.48 (d, 4H); ^{13}C NMR ($CDCl_3$) δ 172.0, 169.9, 152.7, 145.3, 135.6, 133.5, 132.9, 128.5, 128.3, 125.7, 125.4, 74.2, 66.8, 57.4, 33.8, 31.9, 31.4, 31.0, 18.9, 18.2; HRMS (FAB) calcd for $C_{100}H_{125}N_4O_{16}^+$ $(M + H)^+$ 1639.105, found 1639.245. Anal. Calcd for $C_{100}H_{124}N_4O_{16}$: C, 73.35; H, 7.58; N, 3.42. Found: C, 73.36; H, 7.79; N, 3.46.

5,11,17,23-Tetra-*tert*-butyl-(*S*,*S*,*S*,*S*)-25,26,27,28-tetrakis[[*N*-(1-benzyloxycarbonyl-2-phenylethyl)amino]carbonylmethoxy]calix[4]arene (2d). Using procedures similar to those described for the preparation of **2a**, a 67% yield of the product was obtained as crystals: mp 162−163 °C; $[\alpha]^{20}_D$ +15.8 (*c* 2.00, $CHCl_3$); IR (KBr) 3312, 1744, and 1676 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.08 (s, 36H), 3.10 (d, 4H), 3.11 (d, 8H), 4.51 (d, 4H), 4.60 (d, 4H), 4.69 (d, 8H), 4.82 (d, 4H), 4.96 (d, 4H), 5.01 (dd, 4H), 6.74 (s, 8H), 6.99−7.26 (m, 40H) 7.80 (d, 4H); ^{13}C NMR ($CDCl_3$) δ 171.8, 169.9, 153.0, 145.3, 136.4, 135.2, 133.3, 132.6, 129.3, 128.4, 128.2, 128.1, 126.7, 125.8, 125.5, 74.0, 67.0, 53.5, 37.7, 33.9, 31.8, 31.4; HRMS (FAB) calcd for $C_{116}H_{125}N_4O_{16}^+$ $(M + H)^+$ 1831.281, found 1831.172. Anal. Calcd for $C_{116}H_{124}N_4O_{16}$: C, 76.15; H, 6.78; N, 3.06. Found: C, 76.21; H, 6.94; N, 2.98.

5,11,17,23-Tetra-*tert*-butyl-25,26,27,28-tetrakis[(*N*-butylamino)carbonylmethoxy]calix[4]arene (2e). Using procedures similar to those described for the preparation of **2a**, a 56% yield of the product was obtained as crystals: mp 249−251 °C; IR (KBr) 3300 and 1659 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (t, 3H), 1.07 (s, 9H), 1.34 (m, 2H), 1.55 (m, 2H), 3.23 (d, 1H), 3.36 (q, 2H), 4.47 (d, 1H), 4.48 (s, 2H), 6.78 (s, 2H), 7.49 (t, 1H); ^{13}C NMR ($CDCl_3$) δ 169.5, 152.9, 145.8, 132.7, 125.8, 74.6, 39.3, 33.9, 31.8, 31.5, 31.3, 20.2, 13.8. Anal. Calcd for $C_{68}H_{100}N_4O_8$: C, 74.18; H, 9.09; N, 5.09. Found: C, 73.93; H, 9.02; N, 5.03.

5,11,17,23-Tetra-*tert*-butyl-(*S*,*S*,*S*,*S*)-25,26,27,28-tetrakis-[[*N*-(1-methyloxycarbonylethyl)amino]carbonylmethoxy]-calix[4]arene (2f). Using procedures similar to those described for the preparation of **2a**, a 60% yield of the product was obtained as crystals: mp 261−262 °C; $[\alpha]^{20}_D$ −26.9 (*c* 2.00, $CHCl_3$); IR (KBr) 3320, 1747, and 1676 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.74 (d, 4H), 6.76 (s, 8H), 4.70 (d, 4H), 4.64 (q, 8H), 4.63 (d, 4H), 4.57 (d, 4H), 3.71 (s, 12H), 3.23 (d, 4H), 1.43 (d, 12H), 1.08 (s, 36H); ^{13}C NMR ($CDCl_3$) δ 173.5, 169.8, 152.9, 145.5, 133.2, 132.5, 125.8, 125.5, 74.2, 52.3, 47.8, 33.9, 31.8, 31.3, 17.6; HRMS (FAB) calcd for $C_{68}H_{93}N_4O_{16}^+$ $(M + H)^+$ 1222.414, found 1222.597. Anal. Calcd for $C_{68}H_{92}N_4O_{16}$: C, 66.89; H, 7.54; N, 4.59. Found: C, 66.84; H, 7.64; N, 4.50.

Solvent Extraction and Determination of Extraction Equilibrium Constants. A 5 mL of dichloromethane solution of calixarene (1.0×10^{-3} M) and a 5 mL of aqueous solution containing a metal nitrate (1.0×10^{-2} M) and picric acid (1.8×10^{-5} M) was shaken for 3 min and stored for 1 h at 20 °C. The control experiment was carried out by extraction using pure dichloromethane as extraction solvent without adding calixarene. The extractability was determined from the difference in absorbance due to the metal picrate in two aqueous phases which were obtained by the above two methods.

Extraction equilibrium constants (K_e) for the extraction of alkaline metal picrates with calixarenes from aqueous phase to organic solvents were determined by a method similar to that in the literature.[13] A solution of an alkali metal picrate in deionized water and a solution of the calixarene in an organic solvent were made. Equal volumes (5 mL) of the organic solution of calixarene (1.0×10^{-3} M) and the aqueous alkali metal picrate solution ($1.0-10.0 \times 10^{-3}$ M) were repeatedly shaken in a stoppered flask at 20 °C for 3 min. After phase separation, the concentration of the complexed picrate salt in the organic layer was determined spectrophotometrically, using $\epsilon = 18000$ M^{-1} cm^{-1} at 377 nm for dichloromethane and $\epsilon = 15000$ M^{-1} cm^{-1} at 348 nm for ethyl acetate. As an initial check, the decrease in concentration of the picrate salts in water (λ_{max} 354 nm, $\epsilon = 14500$ M^{-1} cm^{-1}) was measured and it was found to be in agreement with those of organic layers. The activity coefficients, γ^2, that were used to calculate K_e values were 0.79 for 10^{-2} M, 0.88 for 5×10^{-3} M, and 0.95 for 10^{-3} M picrate solutions, respectively.[13]

NMR Titrations. A suspension of sodium picrate in 0.7 mL of a $CDCl_3$ solution containing 20 mg (1.25×10^{-5} mol) of **2c** was exposed to ultrasonification for 1 h. ^1H NMR spectra were recorded from the obtained solution of the complex at 20 °C. The amounts of sodium picrate were chosen in the range of 0−3.15 mg (0−1.25×10^{-5} mol).

CD Titrations. The concentration of **2c** was kept constant (3.0×10^{-5} M), and the concentration of sodium picrate was varied (0−3×10^{-5} M). All the spectra were measured in CH_3CN at 20 °C.

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(21) Greenstein, J. P.; Winitz, M. *Chemistry of the Amino Acids*, Vol. 2; John Wiley & Sons: New York, 1961; p 940.