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Alkyl Ammonium Ion Selectivity of Hexahomotrioxacalix[3]arene Triamide Derivative having the Intramolecular Hydrogen-bonding Group

TAKEHIKO YAMATO*, FUMIKA KITAJIMA and JEONG TAE GIL
Department of Applied Chemistry, Faculty of Science and Engineering, Saga University, Honjo-machi 1, Saga-shi, Saga, 840-8502, Japan

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Abstract

The lower rim functionalized hexahomotrioxacalix[3]arene triamide **4** with cone-conformation was synthesized from triol **1** by a stepwise reaction. The different extractability for alkali metal ions, transition metal ions, and alkyl ammonium ions from water into dichloromethane is discussed. Due to the strong intramolecular hydrogen bonding between the neighboring NH and CO groups in triamide **4**, its affinity to metal cations was weakened. Triamide **4** shows a single selectivity to n-$BuNH_3^+$. The anion complexation of triamide **4** was also studied by ^1H NMR titration experiments. Triamide **4** binds halides through the intermolecular hydrogen bonding among the NH hydrogens of amide in a 1:1 fashion in $CDCl_3$. The association constants calculated from these changes in chemical shifts of the amide protons are $K_a = 223\ M^{-1}$ for Cl^- and $K_a = 71.7\ M^{-1}$ for Br^-. Triamide **4** shows a preference for Cl^- complexation than Br^- complexation.

Introduction

Calixarene and related macrocycles have received considerable attention for their host-guest chemistry as ionophoric receptors and potential enzyme mimics in biology. Chemical modification of calixarene represents a simple though effective and versatile way of producing receptors with high selective cation binding properties [1]. Shinkai and co-workers have reported the complexation of alkali metals to hexahomotrioxacalix[3]arene derivatives with alkylated phenolic oxygens [2]. Hexahomotrioxacalix[3]arene derivatives with C_3 symmetry can selectively bind ammonium ions which play important roles in both chemistry and biology [3]. Thus, Shinkai *et al.* reported the construction of C_3 symmmetry pyrene functionalized hexahomotrioxacalix[3]arenes, which selectively recognize primary ammonium ions [2b].

On the other hand, hydrogen bonding plays an important role in the self-assembly of molecular recognition and has been aroused investigation in calixarene systems. An intermolecular hydrogen-bonded duplex was formed through the interaction between a calix[4]-arene with four carboxyl groups and a calix[4]arene with stilbazole moieties was reported [4]. Arduini *et al.* also described the formation of a hydrogen-bonded dimer in $CDCl_3$ based on the self-complementarity of carboxylic acid [5]. The intramolecular hydrogen-bonding was also formed among opposing urea groups, which can bind anionic species, in calix[4]arene [6]. Thus, the design of new ditopic ligands [7] for the simultaneous complexation of anionic and cationic guest species is a new exciting area of coordination chemistry of significant relevance to the selective extraction and/or transportation of metal salts across lipophilic membranes. Rare examples of receptors containing appropriate covalently linked binding sites for anions and cations include Lewis-acidic boron [8], uranyl [9], polyammonium [10] centers combined with crown ether moieties and crown ether or urea functionalized calix[4]arene ionophores [11] which are capable of solubilizing alkali metal salts into organic media.

Incorporating these two types of recognition sites by introduction of three amide groups on the phenolic oxygens of homotrioxacalix[3]arene will create potential heteroditopic receptors capable of binding cations and anions, especially ammonium ions and halides. In the present paper, we describe the synthesis, conformations, and metal and ammonium ion complexation properties of the cone *p*-methylbenzyl amide derivative having the hydrogen-binding groups derived from hexahomotrioxacalix[3]arene tricarboxylic acid, which are supposed to have C_3 symmetric ionophoric cavities.

*Author for correspondence. E-mail: yamatot@cc.saga-u.ac.jp

Results and discussion

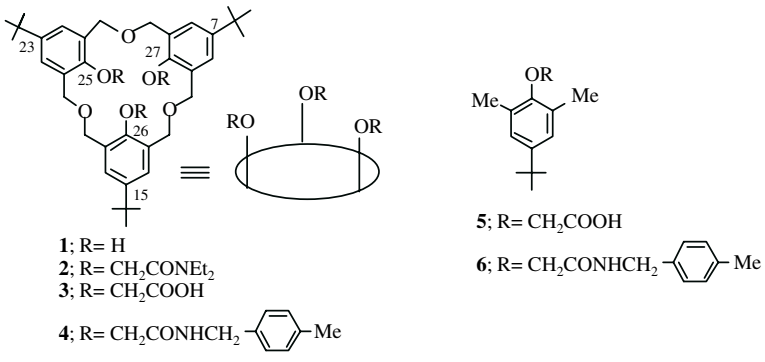
cone-Hexahomotrioxacalix[3]arene tricarboxylic acid **3** was prepared from hexahomotrioxacalix[3]arene **1** according to the reported procedures [2d,12]. Thus, cone amide derivative **2** was obtained almost quantitatively through the *O*-alkylation of triol **1** with *N,N*-diethylchloroacetamide in the presence of NaH in refluxing THF [2d]. Hydrolysis of cone amide **2** in refluxing mixture of dioxane and water afforded the desired cone triacid **3** in 51% yield in the presence of NaOH [12]. When KOH was used in the present hydrolysis reaction under the same conditions, the reaction time can be reduced from 3 days to 24 h and the yield of cone triacid **3** increased to 85%. *cone*-Hexahomotrioxacalix[3]arene triamide **4** was prepared in a yield of 75% by conversion of **3** to the corresponding acid chloride, followed by condensation reaction with *p*-methylbenzylamine in the presence of pyridine in CH_2Cl_2. From the singlet peaks for **4**, the conformation was remained in the desired compound with *cone*-conformation. In order to investigate the conformation of **4** in detail, a reference compound **6** was synthesized from 4-*tert*-butyl-2,6-dimethylphenoxyacetic acid **5** following the similar method in the preparation of **4**.

Conformation assignment for the new hexahomotrioxacalix[3]arene triamide **4** is firmly established by the presence of AB quartets for the bridging methylene protons with a $\Delta\delta$ separation between H_{ax} and H_{eq} of 0.37 ppm in its ^1H NMR spectrum ($CDCl_3$). In the calix[4]arenes, the $\Delta\delta$ values of the ArCH_2Ar protons have been correlated to the orientation of adjacent aromatic rings, i.e. $\Delta\delta > 1$ ppm with cone conformation or syn orientation, $\Delta\delta$ of about 0.5 with flattened cone or out orientation, $\Delta\delta$ of 0 ppm with 1,3-alternate or anti orientation [13]. The same findings were observed in hexahomotrioxacalix[3]arenes [2a]. Thus, we can deduce that **4** prefers a flattened cone conformation, in which hydrogen bonding can form. On comparison with the chemical shift of relative protons between **4** and the reference compound **6**, we can observe that NH proton in **4** shifted to down field ($\Delta\delta = 0.23$ ppm) so that the weak intramolecular hydrogen bonding was formed between NH and the neighboring C=O moieties.

The artificial receptors, which have carbonyl amide groups in their structure, can form intramolecular hydrogen bonding or intermolecular hydrogen bonding based on the solvent. Such as in THF, dioxane, MeCN, and DMSO these hydrogen bonding acceptor solvent, the receptor can form intermolecular hydrogen bonding with these solvents. In another kind of solvent, like $CHCl_3$, it can form intramolecular hydrogen bonding. On the other hand, when the concentration of compound **4** in $CDCl_3$ was diluted about 40 times, there is no change of the chemical shifts, which was attributed to the concentration-independent intramolecular hydrogen bonding formed in this compound. The NH proton in compound **4** was shifted to lower field to 8.42 ppm in DMSO-d_6 instead of $CDCl_3$ (7.96 ppm, $\Delta\delta = -0.46$ ppm). This phenomenon was attributed to the intermolecular hydrogen bonding formed between the NH proton and solvent DMSO-d_6. The intramolecular hydrogen bonding formed in compound **4** was broken and the new intermolecular hydrogen bonding was formed.

In the calix[n]arene series, the $\Delta\delta$ values of the Ar CH_2Ar protons have been correlated to the orientation of adjacent aromatic rings and it is applicable to homooxacalix[3]arene [2a]. We have deduced that compound **4** prefers to the flatten-cone conformation for the intramolecular hydrogen bonding in $CDCl_3$. The difference of chemical shift between the proton H_{ax} and H_{eq} in the bridge methylene in compound **4** was smaller in DMSO-d_6 (0.25 ppm) than that in $CDCl_3$ (0.37 ppm). The ethereal linkage in homooxacalix[3]arene is more flexible than the methylene group in calix[4]arene, when the NH proton was solvated by solvent in DMSO-d_6, the wobbling intensity of the calix benzene ring becomes stronger than that in $CDCl_3$, and make the conformation more flatten.

The alkyloxy calixarene can bind cations, neutral molecules or anions to form complexes, which had been investigated by several groups through different types of calixarenes [1]. The two phase solvent extraction is an efficient and available method to investigate the host molecules bind metal cations [14]. Extraction studies were conducted by the standard two phase procedure whereby dilute solutions of each calixarene derivatives in dichloromethane were shaken with neutral aqueous metal



Scheme 1.

picrate solutions, following which the equilibrium distribution of the picrate was measured spectrophotometrically.

Interestingly, triamide **4** shows low efficiency for metal cations compared to *N, N*-diethylamide **2** [2d,12]. The ionophoric activity of compound **4** was almost absent. Tri-amide **4** shows a single affinity only to *n*-butyl ammonium ion because of the C_3-symmetry as discussed later. However, no extractability for *i*-butyl or *t*-butyl ammonium ion was observed under the conditions used. The ionophores usually form a loose ion pairs with metal picrates, which produced the maximum absorption peak at 377 nm [15]. Interestingly, the triamide **4** also forms a contact ion pairs with *n*-$BuNH_3^+$ and shows the maximum absorption peak at 365 nm. In comparison with **4**, *N,N*-diethylamide **2** has higher affinity to alkali metal ions, Na^+ (93.0%), K^+ (71.6%), transition metal ions, Ag^+ (90.4%) and Cu (27.5%) and typical metal ion Al^{3+} (19.1%). And the higher extractabilities of *N,N*-diethylamide **2** for *n*-butyl (97.8%), *i*-butyl (48.1%) and *t*-butyl ammonium ion (35.4%) were observed attributable to the higher electron density of oxygen of carbonyl group by electron-donation ability of the amide group through conjugation N—C=O ↔N^+=C—O^- [2d,12]. These findings clearly indicate that due to the strong hydrogen bonding formation between NH and neighboring CO groups in triamide **4**, it shows no affinity to either hard or soft metal cations.

The present binding mode can be demonstrated more clearly by using ^{1}H NMR spectroscopy. There are two modes for **4** to bind with *n*-butyl ammonium ion, i.e. from the lower rim through substituents moieties or from the upper rim through the π-cavity formed by three aromatic rings. As shown in Figure 1, the chemical shifts of **4** are different in the absence and presence of *n*-butyl ammonium ion. After adding an equivalent of *n*-$BuNH_3Cl$ to solution of **4** (5×10^{-3} M^{-1}) in $CDCl_3$ at 27 °C, protons on aromatic rings, ArCH_2O, Ar'OCH_2 were dramatically shifted to lower magnetic field, which indicate that the binding mode is occurred through the π-cavity formed by three aromatic rings. This binding is attributed to the π-effect of aromatic rings because both the host and the guest molecules have a C_3-symmetric conformation. With excess of *n*-$BuNH_3Cl$, the free guest molecule and the encapsulated guest molecule were clearly observed by the ^{1}H NMR spectroscopy, in which the encapsulated one was shifted to upfield, CH_3 (0.95–0.26, $\Delta\delta = -0.69$ ppm), CH_3 CH_2 (1.45–0.30, $\Delta\delta = -1.05$ ppm), CH_3CH_2 CH_2 (1.77 to −0.25, $\Delta\ \delta = -2.02$ ppm) and CH_2N (3.00–0.30, $\Delta\delta = -2.70$ ppm). The chemical shift of *NH* proton in **4** was shifted to lower magnetic field (δ 7.96–9.30; $\Delta\delta = 1.34$ ppm) while NH in *n*-$BuNH_3Cl$ was shifted to upper field (δ 8.30–5.80; $\Delta\delta = -2.50$ ppm). Intramolecular hydrogen bonding in **4** weakens the affinity of **4** to metal ions which were encapsulated through the lower rim of homotrioxacalix[3]arene derivative. When **4** was complexed with n-$BuNH_3^+$ through π-cavity, the conformation was changed and intramolecular hydrogen bonding was impossible in this conformation, the NH proton in **4** was shifted to lower magnetic field to indicate complexation of the anionic guest Cl^- through hydrogen bonding (Figure 2)[16]. Addition of *n*-Bu_4NI and $PhMe_3NCl$ to a solution of **4** in $CDCl_3$ (5×10^{-3} M^{-1}), no complexation of halide anions was observed. Due to the strong intramolecular hydrogen bonding, the anion binding site is blocked.

Based on this observation, we investigate the complexation of **4** with *n*-butyl ammonium halide counterions. With addition of ammonium halide counterions the proton peaks in **4** were separated into complex and uncomplex. The integral intensity of proton peaks of complex was increased with increasing amount of ammonium halide counterions, and changed to complex completely. Furthermore, the methylene proton of the ArCH_2NH at the amide group shows a downfield (+0.21 ppm) while the benzene protons slightly shift to upper field (−0.05 to −0.07 ppm) in the complex. The

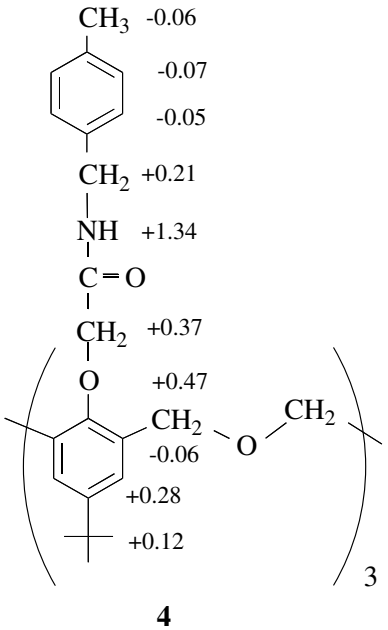


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Figure 1. Chemical shift changes of **4** induced in the presence of *n*-$BuNH_3Cl$; (+) denotes the down-field and (−) denotes the up-field shift.

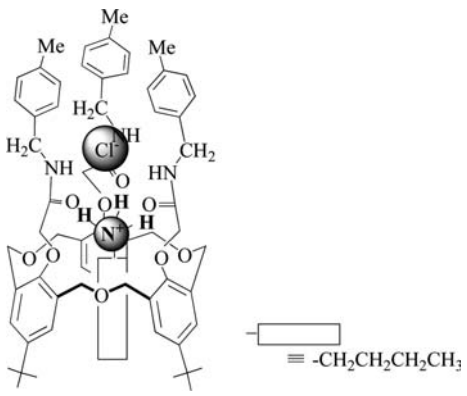

Figure 2. Binding mode of tris[(4-methylbenzyl)aminocarbonyl]methoxy]hexahomotrioxacalix[3] arene **4** and *n*-$BuNH_3Cl$.

former observation might be attributed to the presence of the anionic guest close to the NH group by the intramolecular hydrogen bonding. Chloride anion induces a larger downfield shift for amide hydrogen of **4** than bromide anion does. For example, significant downfield shifts of $\Delta\delta$ 1.34 ppm for the NH proton in the case of Cl^- and $\Delta\delta$ 0.71 ppm in the case of Br^-, respectively, were observed. As the electron negativity of halogen atom decreased with the series of Cl, Br to I atom, the intensity of hydrogen bonding formed between their anions and NH protons should be decreased following the same order. In fact, in the proton NMR spectrum of a mixture of **4** and n-$BuNH_3^+X^-$, the larger down field of chemical shift in the complex of NH with Cl^- than that with Br^- and I^- was observed. The association constants calculated from these changes in chemical shifts of the amide protons are $K_a = 223\ M^{-1}$ ($-\Delta G^\circ = 13.5$ kJ mol^{-1}) for Cl^- and $K_a = 71.7\ M^{-1}$ ($-\Delta G^\circ = 10.7$ kJ mol^{-1}) for Br^-. Amide **4** shows a preference for Cl^- complexation than Br^- complexation.

This finding suggests that the cavity formed by the three-fold amide moieties is more complementary to the size of the Cl^- than to that of Br^- as well as the higher electronegativity of Cl^- than that of Br^-. In the case of tri(urea)-functionalized calix[6]arene, the anion complexation is preference for Br^- because it has a large calix cavity and the three functionalized moieties in 1,3,5-position of calix[6]arene are more complementary to the size of the Br^- than to that of Cl^- [16b]. Calix[5]arene derivatives were reported to complex with alkylammonium ions and display an enzymelike selectivity [17] towards biologically important ammonium substrates. Since hexahomotrioxacalix[3]arenes and their derivatives have the C_3-symmetrical conformation, they can bind with primary ammonium ions having potential function not only in chemical but also in biological system [2,3]. The ammonium ions form complexes with **4** entering the cavity formed by calix benzene rings from the upper rim. Thus the n-butyl substituent remains the cavity and is shielded under the resonance of calix benzene rings, the CH_3 CH_2 CH_2 CH_2 on ammonium ion will be shifted to the upper rim correspondingly compared to their free protons.

As mentioned above, $\Delta\delta$ between H_{ax} and H_{eq} of the Ar CH_2Ar methylene protons in calix[4]arene serves as a measure of the 'flattening'. $\Delta\delta$ value increases from 0.37 to 0.92 ppm in **4** upon the binding of n-$BuNH_3^+$. These findings imply that **4** stands up when the guest is included because n-$BuNH_3^+$ enters into the π-cavity formed by three aromatic rings and Cl^- complexes with NH by hydrogen-bonding interaction.

Conclusion

For the first time, the relationship between properties of ionophore hosts and their intramolecular hydrogen bonding was taken into account in C_3-symmetric conformation. Due to the intramolecular hydrogen bonding, the affinities of ionophore **4** to metal ions were weakened, it does not bind alkali metal ions because the binding site was blocked. However, triamide **4** can bind n-butyl ammonium ion through the π-cavity formed by three aryl rings, which can provide functional moieties in biologic systems with good affinity and high selectivity. Interestingly, triamide **4** binds halide through the intermolecular hydrogen bonding among the NH hydrogens of amide in a 1:1 fashion in $CDCl_3$. Thus, triamide **4** serves as a heteroditopic receptor which can complex with Cl^- and n-$BuNH_3^+$ at the same time. To the best of our knowledge the present result is the first example of heterogeneous dinuclear complex in the hexahomooxacalix[3]arene family. These results give some insight into the molecular design of new synthetic receptors for use in anion controlled of biomimetic systems.

Experimental

All mps (Yanagimoto MP-S1) are uncorrected. – NMR spectra were determined at 270 MHz with a Nippon Denshi JEOL FT-270 NMR spectrometer with $SiMe_4$ as an internal reference: J-values are given in Hz. – IR spectra were measured for samples as KBr pellets or a liquid film on NaCl plates in a Nipon Denshi JIR-AQ2OM spectrophotometer. UV spectra were measured by Shimadzu 240 spectrophotometer. Mass spectra were obtained on a Nippon Denshi JMS-01SA-2 spectrometer at 75 eV using a direct-inlet system through GLC. – Elemental analysis: Yanaco MT-5.

Materials. *cone*-Hexahomotrioxacalix[3]arene triacetic acid **3** was prepared according to the literature [2a,12].

Synthesis

*Preparation of cone-hexahomotrioxacalix[3]arene triacetic acid (**3**)*

To a mixture of **2** (1.0 g, 1.14 mmol) in dioxane (35 ml) was added 1 N KOH aqueous solution (40 ml). After the mixture was refluxed for 24 h, it was condensed under reduced pressure, then acidified by hydrochloric acid to pH 1–2. The dispersion was extracted with ethyl acetate (2×20 ml). The combined extracts were washed with water (2×20 ml), saturated brine (20 ml), dried (Na_2SO_4) and condensed under reduce pressure. The residue was washed with small amount of diethyl ether to give the crude **3** as a colorless solid. Recrystallization from methanol gave **3** (730 mg, 85%) as colorless powder; m.p. 227–229 °C (lit. [12] m.p. 227–229 °C).

*Preparation of cone-7,15,23-tri-tert-butyl-25,26,27-tris [(p-methylbenzyl)amino] carbonylmethoxy]-2,3,10, 11,18,19-hexahomo-3,11,19-trioxacalix[3]arene (**4**)*

cone-Hexahomotrioxacalix[3]arene triacetic acid **3** (200 mg, 0.266 mmol) was dissolved in dry benzene

(25 ml) under nitrogen and oxalyl dichloride (0.8 ml, 9.1 mmol) and pyridine (three drops) were added. The soltuion was stirred at room temperature for 8 h, following which all volatiles were removed at reduced pressure to afford acid chloride homooxacalixarene as white solid, which was used without further purification. Pyridine (4 ml) was added to a solution of *p*-methyl benzylamine in CH_2Cl_2 (40 ml) over 10 min at 0°C and the mixture was stirred for half an hour. A solution of cone triacid chloride homooxacalix[3]arene in CH_2Cl_2 (10 ml) was added and the reaction mixture was stirred at room temperature of 12 h. The reaction mixture was diluted with CH_2Cl_2 (60 ml) and washed with 2 M hydrochloric acid. The combined extracts were washed with 10% citric acid (2 × 20 ml), 5% sodium bicarbonate (20 ml), water (20 ml), saturated brine (20 ml), dried (Na_2SO_4) and condensed under reduce pressure. The residue was chromatographed over silica gel (Wako, C-300; 100 g) with hexane-EtOAc (1:1, v/v) as eluent to give a colorless solid. The solid was recrystallized from methanol to give **4** (212 mg, 75%) as colorless powder; m.p. 151–153 °C; ν_{max} (KBr)/cm^{-1} 3307, 2953, 2869, 1664, 1535, 1483, 1458, 1198, 1096, 1046; ^{1}H NMR ($CDCl_3$) δ 1.09 (27H, s, *t*Bu), 2.31 (9H, s, Ar'- *CH*$_3$), 4.11 (6H, s, ArO *CH*$_2$), 4.26 (6H, d, *J* 12.7, Ar *CH*$_2$O), 4.29 (6H, d, N- *CH*$_2$, *J* 6.84), 4.63 (6H, d, *J* 12.7, Ar *CH*$_2$O), 6.91 (6 H, s, Ar- *H*), 7.10 (6H, d, *J* 7.81, Ar'- H$_b$), 7.17 (each 6H, d, *J* 7.81, Ar'- *H*$_a$) and 7.96 (3 H, t, NH$_)$; ^{1}H NMR (DMSO-d$_6$) δ 1.09 (27H, s, *t*Bu), 2.31 (9H, s, Ar'- *CH*$_3$), 4.15 (6H, s, ArO *CH*$_2$), 4.24 (6H, d, N- *CH*$_2$, *J* 6.84), 4.41 (6H, d, *J* 12.7, Ar *CH*$_2$O), 4.66 (6H, d, *J* 12.7, Ar *CH*$_2$O), 6.91 (6H, s, Ar- *H*), 7.09 (6H, d, *J* 7.8, Ar'- *H*$_b$), 7.15 (6H, d, *J* 7.8, Ar'- *H*$_a$), 8.42 (3H, t, *NH*). Anal. calcd. for $C_{66}H_{81}O_9N_3$(1060.4): C, 74.76; H, 7.70; N, 3.96. Found: 74.45; H, 7.65; N, 3.97.

*Preparation of 4-tert-butyl-2,6-dimethyl[(4-methylbenzyl)aminocarbonyl]methoxy]benzene (***6***)*

To a solution of (4- *tert*-butyl-2,6-dimethyl)phenoxyacetic acid **5** (100 mg, 0.43 mmol) was dissolved in dry benzene (10 ml) under nitrogen and oxalyl dichloride (9.1 mmol) and pyridine (three drops) were added. The soltuion was stirred at room temperature for 8 h, following which all volatiles were removed at reduced pressure to afford acid chloride as white solid, which was used without further purification. Pyridine (2 ml) was added to a solution of *p*-methylbenzylamine in CH_2Cl_2 (20 ml over 10 min at 0 °C and the mixture was stirred for half an hour. A solution of acid chloride in CH_2Cl_2 (6 ml) was added and the reaction mixture was stirred at room temperature of 12 h. The reaction mixture was diluted with CH_2Cl_2 (30 ml) and washed with 2 M hydrochloric acid. The combined extracts were washed with 10% citric acid (2 × 10 ml), 5% sodium bicarbonate (10 ml), water (10 ml), saturated brine (10 ml), dried (Na_2SO_4) and condensed under reduce pressure. The residue was chromatographed over silica gel (Wako, C-300; 100 g) with hexane-EtOAc (1:1, v/v) as eluent to give 212 mg (75%) of **6** as a colorless oil; ν_{max} (KBr)/cm^{-1} 3277, 2950, 2928, 2865, 1667, 1533, 1515, 1484, 1458, 1443, 1408, 1360, 1322, 1310, 1195, 1124, 1050, 870, 819, 753; ^{1} H NMR ($CDCl_3$) δ 1.30 (9H, s, *t*Bu), 2.31 (3H, s, Ar'-*CH*$_3$), 2.34 (6H, s, Ar-*CH*$_3$), 4.44 (2H, s, ArO*CH*$_2$), 4.46 (2H, s, Ar'*CH*$_2$), 7.12 (2H, d, *J* 8.8, Ar'-*H*$_a$), 7.16 (2H, s, Ar-*H*), 7.34 (2H, d, *J* 8.8, Ar'-*H*$_b$), 7.73 (1H, s, NH); *m*/*z*: 339 (M$^+$). Anal. calcd. for $C_{22}H_{29}O_2N$ (339.22): C, 77.84; H, 8.61; N, 4.13. Found: 77.58; H, 8.53; N, 4.17.

Picrate extraction measurements

Alkali metal picrates (1.25×10^{-4} M) were prepared in situ by dissolving 0.1 M of alkali metal hydroxide in 1.25×10^{-4} M of picric acid; triply distilled water was used for all aqueous solutions. Similarly, silver picrate was prepared in situ by dissolving 0.1 M of $AgNO_3$ in 1.25×10^{-4} M of picric acid. Alkyl ammonium picrates were prepared by mixing an equimolar of alkylamine and picric acid in methanol.

Two-phase solvent extraction was carried out between water (5 ml, [alkali picrate] = 1.25×10^{-4} M) and CH_2Cl_2 (5 ml, [ionophore] = 1.25×10^{-4} M). The two-phase mixture was shaken in a stoppered flask for 24 h at 25 °C. We confirmed that this period is sufficient to attain the distribution equilibrium. This was repeated 3 times, and the solutions were left standing until phase separation was complete. The extractability was determined spectrophotochemically from the decrease in the absorbance of the picrate ion in the aqueous phase as described by Pedersen [18].

^{1}H NMR Complexation experiment

To a $CDCl_3$ solution (5×10^{-3} M) of **4** in the NMR tube was added an equivalent of *n*-BuNH$_3$X. The spectrum was registered after addition and the temperature of NMR probe kept constant at 27 °C.

Determination of association constants

The measurements were performed by ^{1}H NMR titration experiments in a varying guest concentration of 0–50 mM and a constant concentration of host receptors with 5 mM. As a probe the chemical shift of the amide protons [C(O)N*H*] signal was used. The assiciation constant values were calculated by the integral intensity of NH protons in the complex and free host molecules according to the literature [19].

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