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Ditopic Receptors based on Lower- and Upper-Rim Substituted Hexahomotrioxacalix[3]arenes: Cation-Controlled Hydrogen Bonding of Anion

Xin-Long Ni,[a, b] Jun Tahara,[a] Shofiur Rahman,[a] Xi Zeng,[b] David L. Hughes,[c] Carl Redshaw,[c] and Takehiko Yamato*[a]

Abstract: Heteroditopic hexahomotrioxacalix[3]arene receptors that are capable of binding an anion and a cation simultaneously in a cooperative fashion were synthesized. The structure of one of the triamide derivatives was confirmed by single-crystal X-ray diffraction. The binding of alkali metals at the lower rim, and the binding of anions (chloride, bromide) at the upper rim, has been investigated by using ^{1}H NMR titration experiments. Alkali metal binding at the lower rim controls the calix cavity. Li^+-ion binding to the lower rim can improve the binding ability of anions at the upper rim amide moiety by a factor of 15, thus suggesting a strong positive allosteric effect for anion recognition. However, when a Na^+ cation is bound to the ionophoric site on the lower rim, the calix cavity is changed from a "flattened cone" to a more-upright form, which is favored for intramolecular hydrogen bonding between the neighboring NH and C=O groups; this change can block the inclusion of anions onto the amide moiety at the upper rim, which strongly suggests a negative allosteric effect of Na^+-ion binding, which controls the cooperative recognition system.

Keywords: anions · calixarenes · cations · hydrogen bonds · receptors

Introduction

Calixarenes and their derivatives are attractive compounds for host–guest and supramolecular chemistry. Facile functionalization at their upper and lower rims makes them suitable as binding sites for guest encapsulation and molecular assembly.[1] The design and application of new heteroditopic receptor systems that are capable of the simultaneous coordination of both anionic and cationic guest species has recently attracted a great deal of interest, as these systems have the potential to act as agents for salt solubilization, extraction, and membrane transport.[2] However, the design of convergent heteroditopic receptors is quite a challenge because the ion-binding sites have to be incorporated into a suitably preorganized scaffold that holds them in close proximity, but not so close that the sites interact. One of the first successful examples of a ditopic salt receptor for the association of ion pairs was reported by Reetz et al.[3a] The Lewis-acidic boron atom can form a reversible dative bond with the F^- anion, which promotes simultaneous coordination of a K^+ cation by the oxygen atoms in the surrounding crown ether.

On the other hand, a growing research topic in supramolecular chemistry is controlled self-assembly;[3] for example, a number of groups have shown how salts can be used to template the dimerization of receptors in water-saturated $CDCl_3$, with water acting as a stabilizing agent.[3b] In some cases, the assembled aggregate is large enough to act as a capsule and completely encapsulate both ions of the salt.[3c] A related design is the so-called "venus fly trap" capsule, an example of which was reported by Atwood and Szumna, who showed that an extended, deep-cavity resorcinarene derivative can completely encapsulate an NMe_4^+ cation with a Cl^- anion held by hydrogen-bonding interactions at the capsule entrance.[3d] Furthermore, Beer and co-workers reported that a heteroditopic calix[4]diquinone receptor,[4a] which was capable of binding an anion and cation simultaneously in a cooperative fashion, could only recognize halide anions in the presence of a suitable co-bound cationic guest species; this receptor also displayed affinity for certain ion pairs

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when no affinity for either of the free ions was observed. By incorporating aza-crown moieties into amide-based ruthenium–bipyridyl anion receptors, chloride binding was enhanced by the presence of potassium bound in close proximity within the crowns.[4b] In a similar approach, Reinhoudt and co-workers[5] took advantage of the ease of derivatization of calix[4]arenes to build new salt-binders. By functionalizing the metacyclophane on its lower-rim with cation-binding features, and on its upper-rim with hydrogen-bond donors (ureas), they obtained several heterotropic systems (which contain binding sites for different substrates) that had cooperative binding properties. They demonstrated that prior sodium binding induces a large rearrangement in the conformations of the ligand, which preorganizes the hydrogen-bond groups for efficient anion complexation. By targeting phosphoryl–choline derivatives, which form a family of biologically relevant Zwitterions, de Mendoza and co-workers[6] prepared an efficient calix[6]arene-based receptor that binds both cationic and anionic parts of the target and offers a synthetic alternative to the very costly catalytic antibody technology. Consequently, a number of heteroditopic receptors for the recognition of ion-pairs have been recently reported by several groups.[7,8] Interest in a contact ion-pair binding approach, wherein the anion and cation are bound essentially as one moiety, is particularly noteworthy as this avoids the energetically unfavorable separation of the two ions.[9] Importantly, the geometry of the ditopic receptor must be optimized so that the anion and cation binding sites are located in an appropriate proximity to one another so as to enhance this interaction; incorrect orientation could lead to the ion pair associating outside of the receptor, or to solvent-separated ion binding. Cooperative and allosteric metal-salt-complexation behavior, whereby the binding of the charged metal-cation guest can enhance the subsequent coordination of the paired anion through electrostatic and conformational effects, has been demonstrated in a number of ditopic amide-based receptor systems.[10]

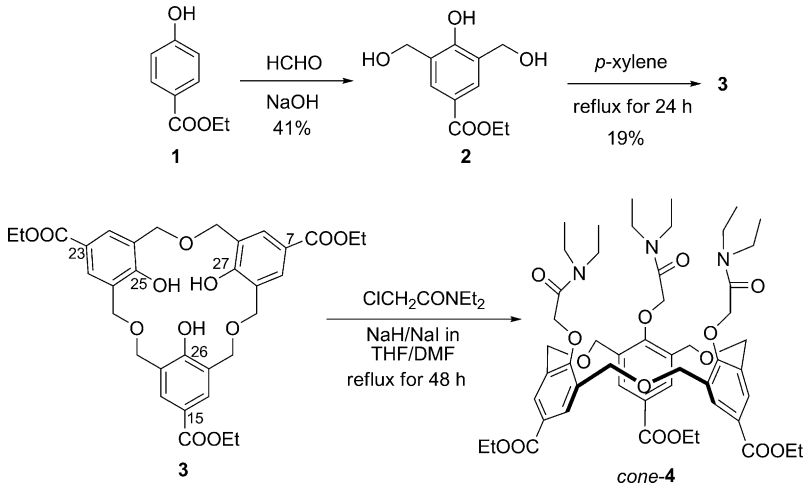
Homooxacalixarenes are hosts that have larger cavities and possess more conformational flexibility than classical calixarenes.[11,12] This flexibility is useful for inducing supramolecular responses to stimuli. For example, Shinkai and co-workers reported that hexahomotrioxacalix[3]arenes were capable of encapsulating and releasing C_{60} depending on the size of the alkali-metal cations.[11] Hexahomotrioxacalix[3]arene derivatives with C_3 symmetry can selectively bind ammonium ions, which play important roles in both chemistry and biology.[13] Recently, we reported C_3-symmetric ditopic receptors, based on functionalized hexahomotrioxacalix[3]arenes, that were capable of recognizing anions and primary ammonium ions.[14]

Moving from our interest in the synthesis of heteroditopic receptors that function not only as anion binders but also as cation binders, we introduced amide groups onto the upper rim, and diethylacetamides onto the lower rim of the hexahomotrioxacalix[3]arene. Herein, we report the synthesis and complexation studies of *cone*-hexahomotrioxacalix[3]arene-triamide derivatives that demonstrated a dramatic enhancement of anion binding at the upper rim when a Li^+ ion was bound onto the lower rim. The recognition behavior towards cations and anions was investigated by ^1H NMR experiments in $CDCl_3/CD_3CN$ solution.

Results and Discussion

The preparation of *cone*-7,15,23-triethoxycarbonyl-25,26,27-tris(*N,N*-diethylaminocarbonylmethoxy)-2,4,10,12,18,20-hexahomo-3,11,19-trioxacalix[3]arene (*cone*-**4**) is shown in Scheme 1. Thus, bis(hydroxymethylation) of ethyl-4-hydroxybenzoate (**1**) with formaldehyde in aqueous NaOH for one week afforded ethyl-3,5-bis(hydroxymethyl)-4-hydroxybenzoate (**2**)[15] in 41% yield. Heating compound **2** to reflux in *p*-xylene for 24 hours afforded hexahomotrioxacalix[3]arene **3**.[11a] The O-alkylation of compound **3** with *N,N*-diethylchloroacetamide in the presence of NaI/NaH in refluxing tetrahydrofuran gave *cone*-tris(*N,N*-diethylaminocarbonylmethoxy)hexahomo-trioxacalix[3]arene *cone*-**4**[11a] in 52% yield. Hydrolysis of the O-alkylated compound, *cone*-**4**, was carried out with NaOH in a mixture of ethanol/water (4:1) at 50°C for 2 hours to yield the *cone*-hexahomotrioxacalix[3]arene tricarboxylic acid (*cone*-**5**[11a]; Scheme 2).

Derivatives of *cone*-Hexahomotrioxacalix[3]arene triamide (*cone*-**7a**–**7d**) were prepared by the condensation of *cone*-**5** with 4-substituted anilines **6a**–**6d** in the presence of dicyclohexylcarbodiimide (DCC) and 1-hydroxybenzotriazole (HOBt) at room temperature for 20 hours in dichloromethane. These triamides (**7a**–**7d**), which were immobilized



Scheme 1. Synthesis of calixarene *cone*-**4**.

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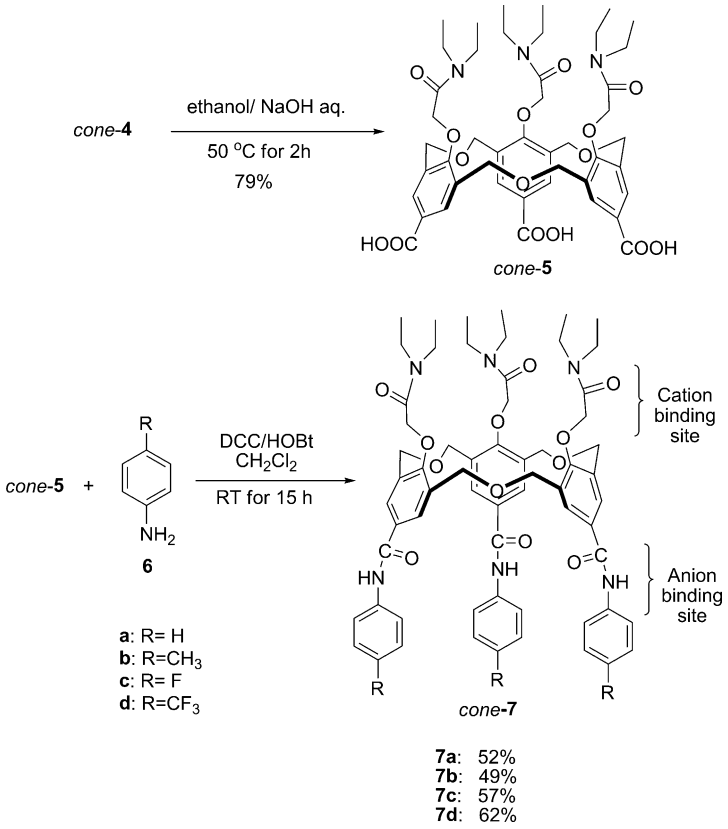


Scheme 2. Synthesis of calixarene *cone*-**7**.

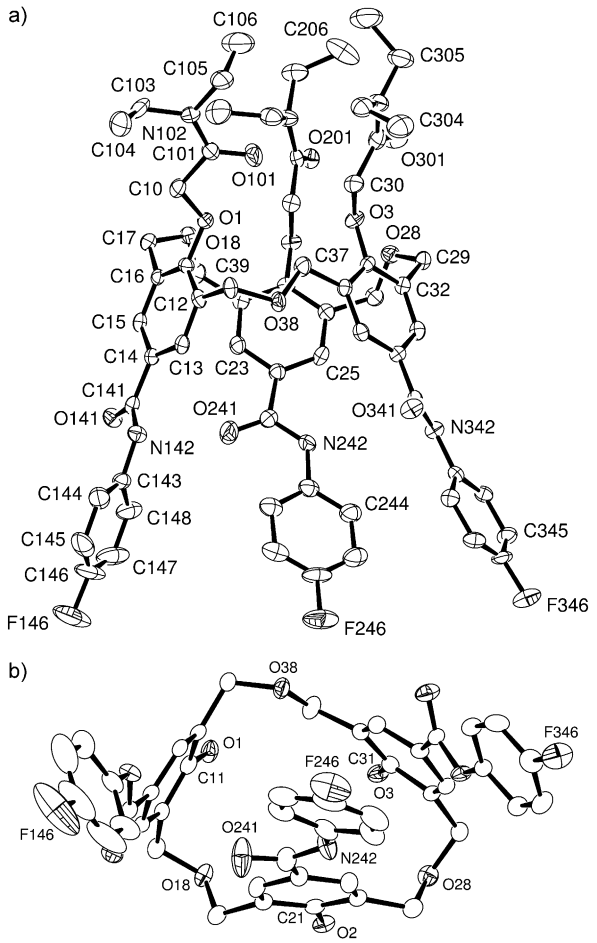


Figure 1. a) X-ray structure of *cone*-**7c**. Hydrogen atoms have been omitted for clarity. Thermal ellipsoids are drawn at the 50% probability level. b) View of the calixarene ring showing the groups on the upper rim of *cone*-**7c**, projected on to the plane of C11, C21, and C31; the orientations of the phenol rings and the distortion from C_3 symmetry are shown. Hydrogen atoms and the atoms of the lower rim groups have been omitted for clarity. Ok

in a "flattened-cone" conformation (in which the phenolic rings were tilted to open up the calixarene cavity) were obtained in moderate yields. Conformational assignments for compounds **7a–7d** were firmly established by the presence of the bridging methylene protons with $\Delta\delta_H$ separations in ^{1}H NMR spectra ($CDCl_3$) between H_{ax} and H_{eq} of 0.49, 0.51, 0.41, and 0.34 ppm, respectively. For the calix[4]arenes, the $\Delta\delta_H$ values of the ArCH_2Ar protons were correlated to the orientation of their adjacent aromatic rings.[13,16] The same findings were observed in homotrioxacalix[3]arenes.[14] In addition, singlet peaks were observed for the NH protons at $\delta = 7.96$, 7.73, 8.07, and 8.16 ppm for compounds **7a–7d,** respectively, thereby confirming the adoption of the flattened-cone conformation in these products. Because the ^{1}H NMR spectra were almost unaffected by changes in the polarity of the solvent ($CDCl_3$, $CDCl_3/CD_3CN$ (10:1), [D_6]DMSO), we concluded that possible intra-/intermolecular hydrogen bonds were either very weak or absent under the measuring conditions.

Recrystallization from methanol and chloroform produced X-ray-quality colorless crystals of *cone*-**7c**. An ORTEP of *cone*-**7c** is shown in Figure 1a. In the solid state, *cone*-**7c** adopts quite a different, deformed-cone conformation; two of the phenol rings are tilted outwards (as in a normal cone), but the third, C21–C26, tilts inwards so that the fluorophenyl group (of F246) lies between the other two fluorophenyl groups (Figure 1b). The whole molecule is distorted considerably from a C_3-symmetric cone shape. There were no intramolecular hydrogen bonding interactions observed, but two of the amide N*H* groups formed intermolecular hydrogen bonds.

The anion-coordination properties of *cone*-**7a–7d** were investigated by ^{1}H NMR titration experiments with various tetrabutylammonium (TBA) anions, such as chloride, bromide, acetate, and benzoate in $CDCl_3/CD_3CN = 10:1$ (v/v). All of the titration experiments were performed at a constant concentration of receptor (ca. 3×10^{-3} M), with an increasing number of equivalents of the anion solution (0–9 equiv TBA salts). Substantial downfield shifts of the amide N*H* signal were observed when tetrabutylammonium chloride and -bromide salts were added, thereby indicating that anion binding was taking place in the vicinity of the amide N*H* group (Figure 2 and Figure 3). Figure 2 shows the ^{1}H NMR spectra of *cone*-**7c** in the presence of lithium and chloride ions.

When 1 equivalent of $LiClO_4$ was added to solutions of *cone*-**7**, the $\Delta\delta_H$ values for H_{ax} and H_{eq} for the ArCH_2O

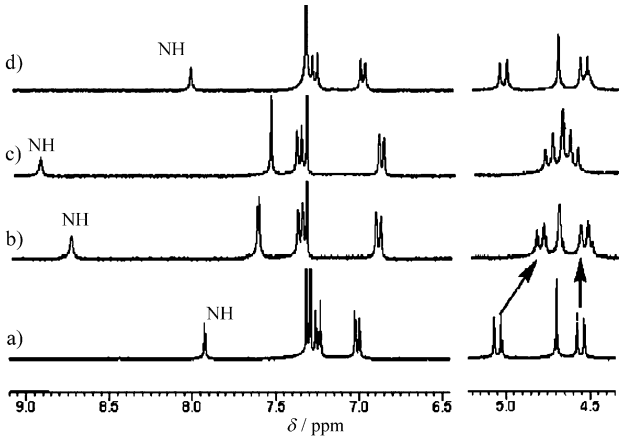


Figure 2. Partial ^{1}H NMR titration of *cone*-**7c**/guest complex (H/G = 1:1); a) free *cone*-**7c**; b) *cone*-**7c**⊃$LiClO_4$; c) Bu_4NCl⊂[*cone*-**7c**⊃Li^+]; d) *cone*-**7c**⊃Bu_4NCl. Solvent: $CDCl_3/CD_3CN$ (10:1, v/v).ok

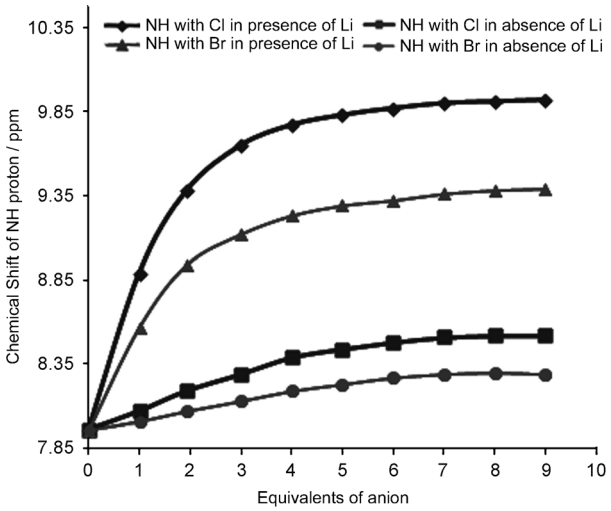


Figure 3. Changes in the ^{1}H NMR spectra of *cone*-**7c**/Bu_4NX (X = Cl and Br) in the presence and absence of $LiClO_4$. Solvent: $CDCl_3/CD_3CN$ (10:1, v/v).ok

methylene protons changed and the signals for the *N,N*-diethylmethoxycarbonylmethoxy protons ($ArOCH_2CONEt_2$) were shifted downfield ($\delta = 3.49$ and 3.51 ppm for *cone*-**7b** and *cone*-**7c**, respectively). It is known that the introduction of bulky substituents onto the OH groups forces the phenol units to stand upright from the calixarene ring plane.[1] This inclination is reflected by the chemical-shift difference ($\Delta\delta_H$) between the axial and equatorial $ArCH_2$ protons. Shinkai and co-workers demonstrated that metal cations that appropriately preorganize the hexahomotrioxacalix[3]-calixarene ester derivatives into their cone conformation can make these calixarenes excellent [60]fullerene receptors in solution through an allosteric effect.[11a,d] Interestingly, the $\Delta\delta_H$ value (from peaks around 4.5–5.1 ppm) for the *cone*-**7c**⊃Li^+ complex (0.26 ppm) was smaller than that of the free *cone*-**7c** (0.49 ppm; Figure 2). This result implies that lithium ions form complexes with the *N,N*-diethylmethoxycarbonylmethoxy groups, and that the phenol groups in the *cone*-**7c**⊃Li^+ complex adopt the more-upright C_3-symmetric form. Similar findings were observed for the *cone*-**7b**⊃Li^+ complex ($\Delta\delta_H = 0.25$ ppm) compared to the free *cone*-**7b** ($\Delta\delta_H = 0.51$ ppm). Therefore, the conformations of the hosts *cone*-**7b** and *cone*-**7c** have been rearranged by the Li^+-ion binding to afford conformations that are more appealing for anion inclusion. Further addition of lithium ions did not change the spectra, thereby indicating that 1:1 complexes of Li^+-ions/*cone*-**7** were formed.

Controlled titration experiment of *cone*-**3** and *cone*-**4** with Li^+ and Na^+ ions suggested that both alkali-metal cations could not be complexed by the lower rim functionalization moiety (*N,N*-diethylmethoxycarbonylmethoxy) rather than the upper rim moiety of the series of hexahomotrioxacalix[3]arene derivatives[11a,d] (see the Supporting Information, Figures S1 and S2). In addition, an investigation of the downfield shift observed for the amide protons of receptor *cone*-**7c** upon complexation with alkali metals demonstrated that this shift is caused by the formation of intramolecular hydrogen bonds following a conformational change in the receptor (*cone*-**7c**) and not by the effect of the counterions (see the Supporting Information, Figures S3 and S4).

To investigate the enhanced anion binding in the presence of alkali metals, Bu_4NCl (1 equiv) was added to solutions of compounds **7a**–**7d** (3×10^{-3} M) in the presence of $LiClO_4$ in $CDCl_3/CD_3CN$ (10:1, v/v). This addition resulted in, for example, a further downfield shift of the N*H* protons ($\delta = 8.74$ to 8.93 ppm) when chloride ions were added to the solution of [*cone*-**7c**⊃$LiClO_4$] (Figure 2c). On the other hand, when only chloride ions were added (in the absence of $LiClO_4$), the large downfield shift of the N*H* protons was not observed (Figure 2d). The other receptors exhibited similar trends to *cone*-**7c** in their affinity towards spherical anions, such as Cl^- and Br^-. With increasing size/decreasing basicity of the halides, the association constants (calculated from the changes in chemical shifts of the amide protons; summarized in Table 1) were generally diminished for hosts *cone*-**7**; in the presence of Li^+ ions, the corresponding association constants were greatly increased.

Table 1. Association constants[a] of hosts *cone*-**7a**–**7d** with chloride and bromide ions.[b]

		Association constant K_a [M^{-1}]			
Host	R	Cl^-	Cl^-+Li^+	Br^-	Br^-+Li^+
cone-**7a**	H	31(±6)	1557(±140)	50(±6)	1241(±130)
cone-**7b**	Me	50(±7)	1082(±110)	24(±5)	134(±12)
cone-**7c**	F	150(±20)	2234(±200)	95(±10)	1449(±135)
cone-**7d**	CF_3	396(±36)	5123(±420)	168(±23)	3289(±330)

[a] Measured in $CDCl_3/CD_3CN$ (10:1, v/v) at 27 °C by the ^{1}H NMR titration method using the chemical-shift change of the N*H* proton; host concentration was 3×10^{-3} M. [b] Guests used: $LiClO_4$, tetrabutylammonium chloride, and bromide.ok

Thus, a significant increase, more than 15-fold, in the strength of the anion binding was observed when lithium ions were complexed. This positive cooperative binding of

the halide in the presence of lithium ion could be attributed to the allosteric and electrostatic effects of the complexed lithium ions.

Figure 3 shows that further addition of Bu_4NX (X = Cl, Br) to the solution of *cone*-**7c** in $CDCl_3/CD_3CN$ (10:1, v/v), in the presence and absence of $LiClO_4$ resulted in clear downfield shifts of the ^1H NMR signals of the N*H* proton, thus indicating that complexation of the halide guests is through hydrogen-bonding interactions (also see the Supporting Information, Figures S5 and S6).

We note that the complexation constants also depended on the substituents on the upper rim. In the presence of more-electronegative atoms, such as F and CF_3 (*cone*-**7c** and *cone*-**7d**, respectively), the association constants were greater than for the unsubstituted receptor (*cone*-**7a**). By contrast, in the case of *cone*-**7b**, with the electron-donating Me group, there was a general decrease in the K_a value for the complexation with halides. Therefore, the introduction of electron-withdrawing groups onto the upper rim appears to increase the acidity of the amide protons, and hence enhance the anion-binding ability through hydrogen-bonding interactions.

Receptors *cone*-**7a–d** showed a preference for complexation of Cl^- over Br^- (Table 1). This preference suggests that the cavity formed by the three amide moieties might be more complementary to the size of the Cl^- ions than to that of the Br^- ions, as well as the higher electronegativity of the Cl^- anion versus the Br^- anion. In the case of tris(urea)-functionalized calix[6]arene, the preferred anion complexation is of Br^- ions because the calix cavity is large and the three functionalized moieties at the 1, 3, and 5 positions of the calix[6]arene[17] are more complementary for the size of the Br^- ions than for the Cl^- ions. Calix[5]arene derivatives have been reported to form complexes with alkylammonium ions and are known to display an enzyme-like selectivity[18] towards biologically important ammonium substrates. Because hexahomotrioxacalix[3]arenes and their derivatives also have a potentially C_3-symmetric conformation, they might also bind to primary ammonium ions, thereby having a potential application not only in chemical but also in biological systems.

Interestingly, no complexation of halide anions by the receptors *cone*-**7** was observed in the presence of $NaClO_4$. The $\Delta\delta_H$ value for the *cone*-**7c**$\supset Na^+$ complex (0.11 ppm, Figure 4b) was smaller than that of *cone*-**7c**$\supset Li^+$ (0.28 ppm, Figure 2b). This result indicates that the phenol groups in *cone*-**7**$\supset Na^+$ are positioned in a more-upright orientation[11d] from the interaction of the *N,N*-diethylmethoxycarbonylmethoxy groups with Na^+ ions. Presumably, the much closer

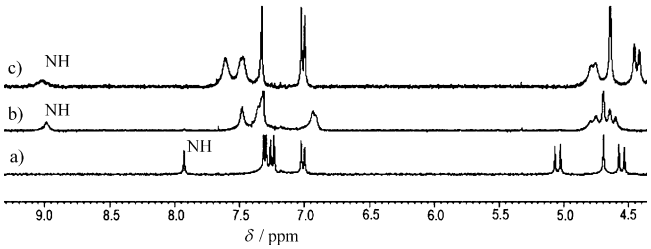
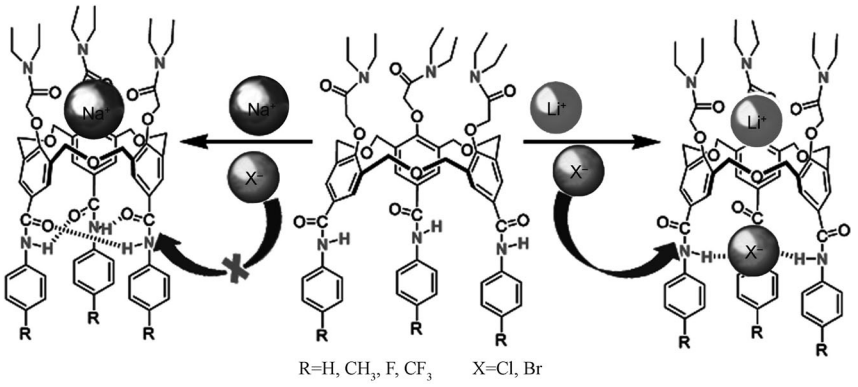


Figure 4. Partial ^1H NMR spectra of *cone*-**7c**/guest (H/G = 1:1); a) free *cone*-**7c**; b) *cone*-**7c**$\supset NaClO_4$; c) $Bu_4NCl\subset$[*cone*-**7c**$\supset Na^+$]. Solvent: $CDCl_3/CD_3CN$ (10:1, v/v).ok

proximity of the amide moieties around the cavity means that the anion binding site would be blocked and controlled by intramolecular hydrogen-bonding interactions and conformational allosteric effects. Similar findings were also observed for *cone*-**7a**, *cone*-**7b**, and *cone*-**7d** in the absence and in the presence of Na^+ ions. Thus, a plausible halide anion binding mode of the ditopic receptors *cone*-**7**, controlled by Li^+ and Na^+ cations (see the Supporting Information, Figures S7–S10) is shown in Scheme 3.

Thus, the binding of alkali-metal cations at the lower rim appears to control the conformation of the calix cavity. Li^+-ion binding at the lower rim can improve the binding ability of anions to the amide moiety on the upper rim and the anion-complexation ability increases 15-fold, thus suggesting a strong positive allosteric effect. However, when a Na^+ cation is bound to the ionophoric lower rim, a more-upright mode may be adopted; this narrow cavity might be smaller and favor intramolecular hydrogen bonding between neighboring NH and C=O groups and would thus block the inclusion of halide anions binding onto the amide moiety on the upper rim; this result strongly suggests that a negative allosteric effect exists in the case of Na^+-ion binding and controls the cooperative-recognition system.

Receptor *cone*-**7** was able to bind all of the anions tested, irrespective of their shape. The association constants for the complexation of the *cone*-**7a–7d** receptors with other tetrabutylammonium (TBA) anions, such as fluoride, acetate, and benzoate (see the Supporting Information, Figures S11



Scheme 3. Plausible binding mode of *cone*-**7** complex with Bu_4NX (X = Cl and Br) in the presence of $LiClO_4$ and $NaClO_4$ in $CDCl_3/CD_3CN$ (10:1, v/v).

and S12), were also calculated from chemical-shift changes for the amide protons (Table 2); these results shows that the complexation constants were strongly affected by the size

Table 2. Association constants[a] of hosts *cone*-**7a**–**7d** with various anions.[b]

			Association constant K_a [M^{-1}]			
Host	R	F^-	Cl^-	Br^-	$MeCOO^-$	$PhCOO^-$
cone-**7a**	H	–[c]	31(±6)	50(±6)	57(±8)	83(±8)
cone-**7b**	Me	–	50(±7)	24(±5)	56(±7)	60(±7)
cone-**7c**	F	–	150(±20)	95(±10)	553(±58)	1107(±110)
cone-**7d**	CF_3	–	396(±36)	168(±23)	1085(±105)	3307(±310)

[a] Measured in $CDCl_3/CD_3CN$ (10:1, v/v) at 27 °C by the ^1H NMR titration method using the chemical-shift change of the NH proton; host concentration was 3×10^{-3} M. [b] Guest used: tetrabutyammonium anions. [c] No change in the chemical shift of NH proton was observed under the conditions used.ok

and/or shape of the guest anions. Interestingly, the association constants (K_a) for acetate and benzoate were much larger than those for Cl^- and Br^- ions. These findings might be attributable to the trigonal shapes of acetate and benzoate which could lead to favorable intermolecular hydrogen-bonding interactions with the amide protons; C–H···π interactions or stacking interactions between the planar acetate group or the benzoate arene ring and the phenyl rings of the amide groups may also be contributing factors, and may be responsible for the disappearance of the ^1H NMR signal of the N*H* proton in the presence of alkali metals (see the Supporting Information, Figures S13 and S14).

Conclusions

Heteroditopic hexahomotrioxacalix[3]arene receptors are capable of binding an anion and cation simultaneously in a cooperative fashion. *cone*-Hexahomotrioxacalix[3]arenes bearing *N,N*-diethylacetamide and substituted-triamide chains on their lower and upper rims, respectively, were synthesized in a stepwise fashion from triol **3**. The binding of the alkali metals and anions (chloride, bromide) at the lower and upper rims, respectively, was investigated by using ^1H NMR titration experiments. Cation binding of the alkali metals at the lower rim controls the cavity size and shape of the calixarene; for example, Li^+-ion binding to the lower rim can improve the binding ability of anions to the amide moiety on the upper rim by a factor of 15. However, when a Na^+ cation was bound to the ionophoric lower rim, the calix cavity changed from a flattened cone shape to a more-upright form that may favor intramolecular hydrogen bonding between neighboring NH and C=O groups and thus block the binding site for anions at the upper rim.

Further studies on the synthesis of ion-controlled ditopic receptors based on hexahomotrioxacalix[3]arenes are underway in our laboratory.

Experimental Section

General

All melting points (Yanagimoto MP-S_1) are uncorrected. ^1H NMR spectra (300 MHz) were recorded on a Nippon Denshi JEOL FT-300 NMR spectrometer with $SiMe_4$ as an internal reference: *J*-values are given in Hz. IR spectra were measured for samples as KBr pellets in a Nippon Denshi JIR-AQ2OM spectrophotometer. Elemental analyses were performed on a Yanaco MT-5.

*Synthesis of Ethyl-3,5-bis(hydroxymethyl)-4-hydroxybenzoate (**2**)[15]*

Ethyl-4-hydroxybenzoate (**1**; 20 g, 0.12 mol) was dissolved in cold aqueous NaOH (6 g in 50 mL H_2O) and condensed with aqueous formaldehyde (30 mL, 37% solution). After 2 days, additional aqueous formaldehyde solution (2×30 mL) was added and the solution was heated to reflux for 1 week. After cooling to RT, the solution was stirred vigorously and neutralized with HCl solution (4 M, 25 mL), thereby resulting in the formation of a yellow oil. The oil was extracted with $CHCl_3$ (3×50 mL) and the organic layer was dried with $MgSO_4$. The solution was filtered and the volatile compounds were removed under reduced pressure to yield a pale-yellow tar. The tar was dissolved in ($CHCl_3/CH_3OH$, 1:5), cooled to 0 °C for 12 h, and filtered to give a pale-yellow solid (11.2 g, yield 41%). Recrystallization from ($CHCl_3/CH_3OH$, 3:1) gave ethyl-3,5-bis(hydroxymethyl)-4-hydroxybenzoate (**2**) as a white solid. M.p. 122–123 °C; ^1H NMR (300 MHz, [D_6]DMSO): $\delta_H=1.28$ (t, 3H; CH_3), 4.25 (q, 2H; OCH_2), 4.55 (s, 4H; ArCH_2O), 7.82 (s, 2H; Ar*H*), 9.36 ppm (s, 1H; Ar*OH*).

*Synthesis of 7,15,23-Triethoxycarbonyl-25,26,27-trihydroxy-2,4,10,12,18,20-hexahomo-3,11,19-trioxacalix[3]arene (**3**)[11a]*

Ethyl-3,5-bis(hydroxymethyl)-4-hydroxybenzoate (**2**; 2.5 g, 0.011 mol) was heated to reflux at 145–150 °C for 24 h in *p*-xylene (100 mL); the water produced was removed at intervals. The solvent was removed under reduced pressure. The residue was extracted with $CHCl_3$ and the solvent was again removed under reduced pressure. The residue was dissolved in a minimum amount of CH_2Cl_2 and then MeOH was added until the solution became cloudy. On cooling the solution to 0 °C for 12 h, product **3** precipitated as a white solid (435 mg; yield 19%). M.p. 225–226 °C; ^1H NMR (300 MHz, $CDCl_3$): $\delta_H=1.37$ (t, 9H; OCH_2CH_3), 4.34 (q, 6H; OCH_2), 4.76 (s, 12H; ArCH_2O), 7.87 (s, 6H; Ar*H*), 9.19 ppm (s, 3H; Ar*OH*).

*Synthesis of 7,15,23-Triethoxycarbonyl-25,26,27-tris(N,N-diethylaminocarbonylmethoxy)-3,11,19-trioxacalix[3]arene (cone-**4**)[11a]*

NaH (172 mg) and NaI (719 mg) were added to a solution of hexahomotrioxacalix[3]arene **3** (300 mg, 0.48 mmol) in dry THF/DMF (25 mL, 5:1, v/v), and stirring was continued at RT for 1 h. *N,N*-diethylchloroacetamide (719 mg, 4.8 mmol) was added to the stirring solution and the mixture was heated to reflux at 60 °C for 48 h under an Ar atmosphere. After cooling to RT, the mixture was poured onto ice and acidified with 1 M HCl. The solution was extracted with EtOAc (2×50 mL), and washed with water (2×50 mL) and brine (50 mL). After drying with $MgSO_4$, the solvent was removed under reduced pressure. The residue was recrystallized from MeOH to afford *cone*-**4** (240 mg, yield 52%). M.p. 190–191 °C; ^1H NMR (300 MHz, $CDCl_3$): $\delta_H=1.19$–1.26 (m, 18H; NCH_2CH_3), 1.32–1.36 (t, $J=7.8$ Hz, 9H; OCH_2CH_3), 3.25 (q, $J=6.5$ Hz, 6H; NCH_2CH_3), 3.47 (q, $J=6.5$ Hz, 6H; NCH_2CH_3), 4.27–4.35(m, 6H; OCH_2CH_3), 4.78(s, 12H; ArCH_2O), 4.81 (s, 6H; ArOCH_2), 7.92 ppm (s, 6H; Ar*H*).

*Synthesis of 7,15,23-Trihydroxycarbonyl-25,26,27-tris(N,N-diethylaminocarbonylmethoxy)-3,11,19-trioxacalix[3]arene triacid (cone-**5**)[11a]*

Hexahomotrioxacalix[3]arene *cone*-**4** (200 mg, 0.20 mmol) was added to a solution of 300 mg NaOH (EtOH/water, 4:1, 25 mL) and heated under refluxing conditions at 50 °C for 2 h. After being cooled to RT, the reaction mixture was neutralized with 1 M HCl solution and extracted with CH_2Cl_2 (2×50 mL), and washed with water (2×50 mL) and brine (50 mL). After drying with $MgSO_4$, the solvent was removed under re-

duced pressure. The residue was recrystallized from CH_2Cl_2/*n*-hexane (1:3, v/v) to afford *cone*-**5** (139 mg, yield 79%). M.p. 126–127 °C, ^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 1.16–1.24 (m, 18H; NCH_2CH_3), 3.32 (q, J = 6.0 Hz, 6H; NCH_2CH_3), 3.43 (q, J = 6.0 Hz, 6H; NCH_2CH_3), 4.55 (s, 6H; ArOCH_2), 4.70 (d, J = 13.8 Hz; Ar$CH_{2(eq)}$O), 4.82 (d, J = 13.8 Hz; Ar$CH_{2(ax)}$O), 7.95 ppm (s, 6H; Ar*H*).

*Synthesis of 7,15,23–Tris(4-methylphenylaminocarbonyl)-25,26,27-tris-(N,N-diethylaminocarbonylmethoxy)-2,4,10,12,18,20-hexahomo-3,11,19-trioxacalix[3]arene (cone-**7b**)*

A solution of dicyclohexylcarbodiimide (DCC; 190 mg, 0.92 mmol) in CH_2Cl_2 (5 mL) was added dropwise at 0 °C to a solution of *cone*-**5** (100 mg, 0.11 mmol), *p*-toluidine (**6b**; 130 mg, 1.17 mmol) and 1-hydroxybenzotriazole (HOBt; 26 mg, 0.17 mmol) in CH_2Cl_2 (12 mL). The reaction mixture was stirred for 15 h at RT, then condensed under reduced pressure. The residue was extracted with EtOAc (2×30 mL); the combined extracts were washed with 10% citric acid (2×20 mL), 5% sodium bicarbonate (20 mL), water (20 mL), and saturated brine (20 mL); the solution was dried (Na_2SO_4) and condensed under reduced pressure. The residue was recrystallized from MeOH to give *cone*-**7b** (64 mg, 49%) as colorless prisms. M.p. 186–188 °C; IR (KBr): $\tilde{\nu}$ = 2977, 2929, 1644, 1519, 1477, 1456, 1323, 1190, 1093, 1072, 1054, 904, 823, 667, 513 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 1.12–1.23 (m, 18H; NCH_2CH_3), 2.25 (9H, s; PhCH_3), 3.31 (q, J = 7.14 Hz, 6H; NCH_2CH_3), 3.38 (q, J = 7.14 Hz, 6H; NCH_2CH_3), 4.55 (d, J = 12.6 Hz; Ar$CH_{2(eq)}$O), 4.67 (s, 6H; ArOCH_2), 5.06 (d, J = 12.6 Hz; Ar$CH_{2(ax)}$O), 7.03 (d, J = 8.25 Hz, 6H; PhH_a), 7.25 (d, J = 11.9 Hz, 6H; PhH_b), 7.27 (s, 6H; Ar*H*), 7.73 ppm (3H, s, N*H*). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.73, 14.00, 20.65, 40.06, 40.08, 68.98, 72.03, 120.99, 129.04, 129.12, 131.04, 132.20, 133.84, 135.12, 158.58, 166.04, 167.05 ppm. FAB-MS: m/z 1147.53 $[M]^+$; elemental analysis calcd. (%) for $C_{66}H_{78}O_{12}N_6$ (1147.36): C 69.09, H 6.85, N 7.32; found: C 68.79, H 7.00, N 7.45.

Similarly, compounds *cone*-**7a**, *cone*-**7c**, and *cone*-**7d** were synthesized as described above in 52, 57, and 62% yields, respectively.

7,15,23-Tris(phenylaminocarbonyl)-25,26,27-tris(*N,N*-diethylaminocarbonylmethoxy)-2,4,10,12,18,20-hexahomo-3,11,19-trioxacalix[3]arene (*cone*-**7a**) was obtained as colorless prisms. M.p. 204–205 °C; IR (KBr): $\tilde{\nu}$ = 2931, 1650, 1560, 1540, 1504, 1452, 1052, 809, 667 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 1.13–1.23 (m, 18H; NCH_2CH_3), 3.31–3.44 (m, 12H; NCH_2), 4.54 (d, J = 12.6 Hz, 6H; Ar$CH_{2(eq)}$O), 4.68 (s, 6H; ArOCH_2), 5.03 (d, J = 13.2 Hz, 6H; Ar$CH_{2(ax)}$O), 7.04–7.40 (m, 15H; Ar*H*), 7.32 (s, 6H; Ar*H*), 7.96 ppm (3H, s; *NH*); ^{13}C NMR(75 MHz, $CDCl_3$): δ = 12.97, 14.30, 40.16, 41.00, 69.28, 72.11, 120.92, 124.43, 128.78, 129.16, 131.19, 132.57, 137.86, 158.84, 166.09, 166.89 ppm; FAB-MS: m/z 1105.53 $[M]^+$; elemental analysis calcd. (%) for $C_{63}H_{72}O_{12}N_6$ (1105.28): C 68.46, H 6.57, N 7.60; found: C 68.18, H 6.28, N 7.66.

7,15,23-Tris(4-fluorophenylaminocarbonyl)-25,26,27-tris-(*N,N*-diethylaminocarbonylmethoxy)-2,4,10,12,18,20-hexahomo-3,11,19-trioxacalix[3]arene (*cone*-**7c**) was obtained as colorless prisms. M.p. 237–238 °C; IR (KBr): $\tilde{\nu}$ = 2959, 2863, 1689, 1602, 1537, 1483, 1445, 1363, 1311, 1198, 1068, 879, 754, 693, 503 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 1.17–1.22 (m, 18H; NCH_3), 3.29 (q, J = 7.14 Hz, 6H; NCH_2), 3.40 (q, J = 7.14 Hz, 6H; NCH_2), 4.58 (d, J = 13.0 Hz; Ar$CH_{2(eq)}$O), 4.67 (s, 6H; ArOCH_2), 4.99 (d, J = 13.0 Hz; Ar$CH_{2(ax)}$O), 6.88 (t, J = 8.82 Hz, 6H; PhH_a), 7.33 (t, J = 6.9 Hz, 6H; PhH_b), 7.35 (s, 6H; Ar*H*), 8.07 ppm (3H, s; N*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.94, 14.28, 40.16, 41.00, 69.42, 72.19, 108.25, 114.10, 119.87, 124.50, 128.49, 132.66, 133.44, 143.14, 161.53, 161.83, 166.45 ppm. FAB-MS: m/z 1159.45 $[M]^+$; elemental analysis calcd. (%) for $C_{63}H_{69}O_{12}N_6F_3$ (1159.25): C 65.27, H 6.00, N 7.25; found: C 65.55, H 6.28, N 7.28.

7,15,23-Tris(4-trifluoromethylphenylaminocarbonyl)-25,26,27-tris-(*N,N*-diethylaminocarbonylmethoxy)-2,4,10,12,18,20-hexahomo-3,11,19-trioxacalix[3]arene (*cone*-**7d**) was obtained as colorless prisms. M.p. 273–274 °C; IR (KBr): $\tilde{\nu}$ = 2974, 2931, 1789, 1652, 1477, 1458, 1439, 1309, 1161, 1092, 1074, 742 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 1.14–1.25 (m, 18H; NCH_2CH_3), 3.37 (q, 12H, J = 7.8 Hz; NCH_2), 4.63 (d, J = 13.2 Hz, 6H; Ar$CH_{2(eq)}$O), 4.67 (s, 6H; ArOCH_2), 4.97 (d, J = 13.2 Hz; Ar$CH_{2(ax)}$O), 7.38 (d, J = 8.4 Hz, 6H; PhH_a), 7.43 (s, 6H; Ar*H*), 7.49 (d, J = 8.4 Hz, 6H; PhH_b), 8.16 ppm (3H, s, N*H*); ^{13}C NMR(75 MHz, $CDCl_3$): δ = 12.94, 14.05, 40.08, 40.88, 68.82, 72.17, 115.01, 115.30, 122.69, 122.79, 129.03, 130.90, 132.41, 134.07, 158.60, 166.05, 166.88 ppm; FAB-MS: m/z 1309.46 $[M]^+$; elemental analysis calcd. (%) for $C_{66}H_{69}O_{12}N_6F_9$ (1309.27): C 60.55, H 5.31, N 6.42; found: C 60.25, H 5.36, N 6.28.

Determination of the Association Constants

The association constants were determined by using ^{1}H NMR titration experiments in a constant concentration of host receptor (3×10^{-3} M) and varying the guest concentration ($0–10\times10^{-3}$ M). The ^{1}H NMR chemical shift of the amide protons (N*H*) signal was used as a probe. The association constant (K_a) for the complexes of *cone*-**7** were calculated by nonlinear curve-fitting analysis of the observed chemical shifts of the N*H* protons according to the literature procedure.[19]

^{1}H NMR Titration Experiments

A solution of Bu_4NX (X = Cl, Br) in $CDCl_3/CD_3CN$ (10:1, v/v, $0–9\times10^{-3}$ M) in the presence or absence of $LiClO_4$ and $NaClO_4$ was added to a $CDCl_3/CD_3CN$ (10:1, v/v, 3×10^{-3} M) solution of *cone*-**7** in an NMR tube. ^{1}H NMR spectra were recorded after addition of the reactants and the temperature of the NMR probe was kept constant at 27 °C. The ^{1}H NMR data of the most-representative complexes are given below:

cone-**7b**⊃Li^+: ($CDCl_3/CD_3CN$, 10:1, v/v): δ_H = 1.15–1.24 (m, 18H; NCH_3), 2.26 (9H, s; PhCH_3), 3.17 (q, 6H; NCH_2), 3.49 (q, 6H; NCH_2), 4.55 (d, 6H; Ar$CH_{2(eq)}$O), 4.69 (s, 6H; ArOCH_2), 4.80 (d, 6H; Ar$CH_{2(ax)}$O), 6.89(d, 6H; PhH_a), 7.36 (d, 6H; PhH_b), 7.61(s, 6H; Ar*H*), 8.74 ppm (3H, s, N*H*).

$Cl^-\subset$[*cone*-**7b**⊃Li^+]: ($CDCl_3/CD_3CN$, 10:1, v/v): δ_H = 1.12–1.23 (m, 18H; NCH_3), 2.25 (9H, s; PhCH_3), 3.18 (q, 6H; NCH_2), 3.49 (q, 6H; NCH_2), 4.57 (d, 6H; Ar$CH_{2(eq)}$O), 4.68 (s, 6H; ArOCH_2), 4.79 (d, 6H; Ar$CH_{2(ax)}$O), 6.87 (d, 6H; PhH_a), 7.37 (d, 6H; PhH_b), 7.62 (s, 6H; Ar*H*), 8.97 ppm (3H, s; *NH*).

$Br^-\subset$[*cone*-**7b**⊃Li^+]: ($CDCl_3/CD_3CN$, 10:1, v/v): δ_H = 1.12–1.23 (m, 18H; NCH_3), 2.25 (9H, s; PhCH_3), 3.18 (q, J = 7.1 Hz; NCH_2), 3.48 (q, 6H; NCH_2), 4.56 (d, 6H; Ar$CH_{2(eq)}$O), 4.68 (s, 6H; ArOCH_2), 4.77 (d, 6H; Ar$CH_{2(ax)}$O), 6.88 (d, 6H; PhH_a), 7.41 (d, 6H; PhH_b), 7.73 (s, 6H; Ar*H*), 8.87 ppm (3H, s; *NH*).

cone-**7c**⊃Li^+: ($CDCl_3/CD_3CN$, 10:1, v/v): δ_H = 1.17–1.24 (m, 18H; NCH_3), 3.20 (q, 6H; NCH_2), 3.51 (q, 6H; NCH_2), 4.52 (d, 6H, Ar$CH_{2(eq)}$O), 4.69 (s, 6H, ArOCH_2), 4.80 (d, 6H; Ar$CH_{2(ax)}$O), 6.88 (t, 6H; PhH_a), 7.37(d, 6H; PhH_b), 7.62(s, 6H; Ar*H*), 8.74 ppm (3H, s; *NH*).

cone-**7c**⊃Na^+: ($CDCl_3/CD_3CN$, 10:1, v/v): δ_H = 1.17–1.24 (m, 18H; NCH_3), 3.23 (q, 6H; NCH_2), 3.54 (q, 6H; NCH_2), 4.64 (d, 6H; Ar$CH_{2(eq)}$O), 4.69 (s, 6H; ArOCH_2), 4.75 (d, 6H; Ar$CH_{2(ax)}$O), 6.93 (t, 6H; PhH_a), 7.31 (d, 6H; PhH_b), 7.47 (s, 6H; Ar*H*), 8.98 ppm (3H, s; N*H*).

$Cl^-\subset$[*cone*-**7c**⊃Li^+]: ($CDCl_3/CD_3CN$, 10:1, v/v): δ_H = 1.17–1.25 (m, 18H; NCH_3), 3.20 (q, 6H; NCH_2), 3.51 (q, 6H; NCH_2), 4.58 (d, 6H; Ar$CH_{2(eq)}$O), 4.67 (s, 6H; ArOCH_2), 4.74 (d, 6H; Ar$CH_{2(ax)}$O), 6.70 (t, 6H; PhH_a), 7.41 (d, 6H; PhH_b), 7.57 (s, 6H; Ar*H*), 8.93 ppm (3H, s; *NH*).

cone-**7c**⊃Cl^-: ($CDCl_3/CD_3CN$, 10:1, v/v): δ_H = 1.17–1.23 (m, 18H; NCH_3), 3.27 (q, 6H; NCH_2), 3.40 (q, 6H; NCH_2), 4.57 (d, 6H; Ar$CH_{2(eq)}$O), 4.70 (s, 6H; ArOCH_2), 5.04 (d, 6H; Ar$CH_{2(ax)}$O), 6.83 (t, 6H; PhH_a), 7.44 (d, 6H; PhH_b), 7.43 (s, 6H; Ar*H*), 8.01 ppm (3H, s; *NH*).

$Br^-\subset$[*cone*-**7c**⊃Li^+]: ($CDCl_3/CD_3CN$, 10:1, v/v): δ_H = 1.17–1.23 (m, 18H; NCH_3), 3.19 (q, 6H; NCH_2), 3.50 (q, 6H; NCH_2), 4.61 (d, 6H; Ar$CH_{2(eq)}$O), 4.69 (s, 6H; ArOCH_2), 4.76 (d, 6H; Ar$CH_{2(ax)}$O), 6.75 (t, 6H; PhH_a), 7.58 (d, 6H; PhH_b), 7.80 (s, 6H; Ar*H*), 8.57 ppm (3H, s; N*H*).

cone-**7c**⊃Br^-: ($CDCl_3/CD_3CN$, 10:1, v/v): δ_H = 1.17–1.24 (m, 18H; NCH_3), 3.29 (q, 6H; NCH_2), 3.42 (q, 6H; NCH_2), 4.57 (d, 6H; Ar$CH_{2(eq)}$O), 4.70 (s, 6H; ArOCH_2), 5.06 (d, 6H; Ar$CH_{2(ax)}$O), 6.95 (t, 6H; PhH_a), 7.24 (d, 6H; PhH_b), 7.32 (s, 6H; Ar*H*) and 7.96 ppm (3H, s; N*H*).

*Crystallographic Analysis of cone-**7c***

Crystal data: $C_{63}H_{69}F_3N_6O_{12}$; M_r = 1159.2; monoclinic; space group: $P2_1/n$ (equiv to no. 14); a = 20.9753(3), b = 12.9216(2), c = 22.2116(3) Å; β =

91.4868(14)°; V=6018.08(15) Å^3; Z=4; ρ_{cald}=1.279 g cm^{-3}; $F(000)$=2448; T=140(1) K; $\mu(Mo_{K\alpha})$=1.0 cm^{-1}; $\lambda(Mo_{K\alpha})$=0.71069 Å.

Crystals were colorless blocks. One, crystal size 0.35×0.27×0.12 mm, was mounted in oil on a glass fiber and fixed in a stream of cold nitrogen on an Oxford Diffraction Xcalibur-3 CCD diffractometer equipped with $Mo_{K\alpha}$ radiation and a graphite monochromator. Intensity data were measured by thin-slice ω- and ϕ-scans. 81209 reflections measured, 7854 unique reflections (R_{int}=0.100) to θ_{max}=22.5°; 5904 observed with $I>2\sigma(I)$.

The data were processed using the CrysAlisPro-CCD and -RED[20] programs. The structure was determined by direct methods using the SHELXS program[21] and refined by the full-matrix least-squares method, on F^2s, in SHELXL.[21] The non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were included in idealized positions and their Uiso values were set to ride on the Ueq values of the parent carbon or nitrogen atoms. At the conclusion of the refinement, wR_2=0.109 and R_1=0.110[21] for all 7854 reflections weighted $w=[\sigma^2(F_o^2)+(0.0463P)^2]^{-1}$ with $P=(F_o^2+2F_c^2)/3$; for the "observed" data only, R_1=0.064. In the final difference map, the highest peak (ca. 0.25 e Å^{-3}) was 2.5 Å from H(30 J).

Scattering factors for neutral atoms were taken from reference [22]. Computer programs used in this analysis have been noted above, and were run through WinGX[23] on a Dell Precision 370 PC at the University of East Anglia. CCDC 826164 (*cone*-**7c**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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