Side Arm Effects on Cyclen−Alkali Metal Cation Complexation: Highly Selective and Three-Dimensional Encapsulation of Na^+ Ion

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A variety of armed cyclens were prepared in which ester, amide, nitrile, and pyridine moieties were attached as cation-ligating side arms to a 12-membered ring. Ester-, amide-, and pyridine-armed cyclens nicely accommodated a Na^+ ion in a three-dimensional fashion and clearly discriminated the cation from Li^+ and K^+ ions. They extracted Na^+ ion more efficiently and selectively than common Na^+ ion-selective ligands. X-ray diffraction, FAB-MS, ^{23}Na NMR binding studies, and computer modeling experiments demonstrated that the cyclens having ester-, amide-, and pyridine-functionalized side arms formed highly selective encapsulated Na^+ complexes *via* a cooperative action of parent cyclen and side arms.

Introduction

1,4,7,10-Tetrazacyclododecane, "cyclen", is representative of the macrocyclic polyamines.[1] Many of its derivatives accommodate transition metal cations with 0.7 or 0.8 Å ionic radii in their 12-membered rings, but a few examples were reported to effectively encapsulate the larger metal ions. Although the cyclen ring is too small to include alkali and alkaline earth metal ions, the ring often adopts a well-defined "square" conformation and its arm-functionalization can offer the topology suitable for effective encapsulation of these large metal ions.[2−4] Typically, the cyclen derivatives having hydroxyethyl- and pyrazoylmethyl-functionalized side arms formed crystalline complexes with several alkali metal cations.[5]

Recently we derived a new class of three-dimensional ligands specific for Na^+ ion from the cyclen.[6] Attachment of a proper cation-ligating side arm to the cyclen ring resulted in remarkably high Na^+ ion selectivity. Such armed cyclens having four ligating side arms can use a varying number of these side arms to form different types of complexes as schematically shown in Figure 1. Since effective cation ligation of side arms can increase the coordination number of the ligand and the stability of the complex and also modify cation selectivity, several structural modifications of the cyclen can provide a new series of three-dimensional ligands for alkali metal ions.

We report below interesting side arm effects on cyclen−alkali metal cation complexation.[6] Various kinds of cation-ligating side arms are introduced into the cyclen system and their effects on the cation binding profiles are characterized using several methods. Among metal cation guests, Na^+ ion is of particular importance because of its richness in the biological system. Although the diameter of the Na^+ ion is larger than that of the 12-membered cyclen ring and the ring's nitrogen atom does not act as an effective donor for Na^+ ion in the aqueous media, we found that armed cyclens having ester-, amide-, and pyridine-functionalized side arms exhibited excellent Na^+ ion selectivity in the binding and extraction experiments. Since their Na^+ ion binding abilities are superior to those of common Na^+ ion binders, the present type of armed cyclens has promise for the rational design of new, specific ligands for alkali metal cations.

Results and Discussion

Armed Macrocycles Employed. To demonstrate side arm effects on the cation binding property of the armed cyclen we examined a series of 12-membered cyclens having an ester, amide, pyridine, or nitrile function on their side arms (Figure 2). Since armed cyclens **1b**−**e** have four side arms available for cation coordination and can have expanded cavities *via* cyclen−side arm cooperativity, they have ligand structures suitable for three-dimensional encapsulation of Na^+ ion with 1.0 Å ionic radius (see Figure 1). We present below the first systematic studies of side arm effects on cyclen−alkali metal cation complexation with liquid−liquid extraction, FAB MS,

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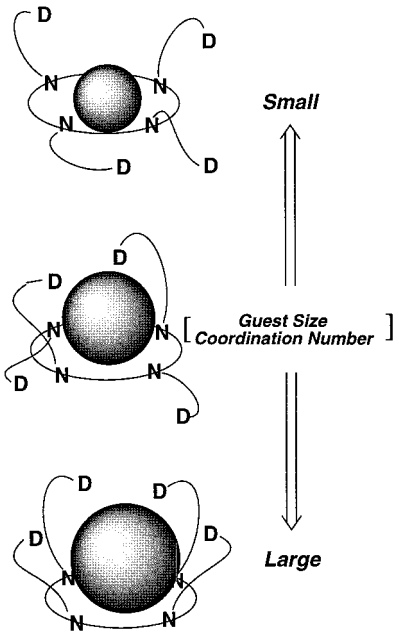

Figure 1. Schematic illustration of armed cyclen complexes.

^{7}Li/^{23}Na NMR, liquid membrane transport, X-ray diffraction, and computational methods.[7]

Na^+ Ion-Selective Extraction by Armed Cyclen. We first characterized cation binding properties of the new armed cyclens by liquid−liquid extraction experiments. Competitive extraction of alkali metal cations was performed in a two phase system (CH_2Cl_2/H_2O) with cyclens **1b**−**f** and related macrocycles **2**−**6** as extracting agents. Since we employed **1c**− and **1d**−Na^+ complexes in the extraction experiments (see Experimental Section), interfacial exchange processes of the Na^+ ion with Li^+ and K^+ ions was observed in these cases. Table 1 summarizes extraction percentages of Li^+, Na^+, and K^+ ions from an aqueous solution into CH_2Cl_2.

Among the examined macrocycles, ester-, amide-, and pyridine-armed cyclens **1b**−**1d** predominantly extracted Na^+ ion from the aqueous mixture of Li^+, Na^+, and K^+ ions into the CH_2Cl_2 phase (Table 1). When pyridine-armed cyclen **1d** was employed, extraction percentages were recorded as 89% for Na^+ ion and less than 4% for Li^+ and K^+ ions. Ester- and amide-armed cyclens **1b**,**c** similarly offered Na^+ ion-selective extraction: 66% and 86% of the Na^+ ion added was extracted, while the extraction of Li^+ and K^+ ions was rare (<7%). Since neither nitrile- nor benzyl-armed cyclens **1e**,**f** extracted any alkali metal ions, the nature of functionalized side arm greatly influences extraction ability of the armed cyclen. Diaza-12-crown-4 **2**[8] and 14-membered cyclam **3**[9] having ester-functionalized side arms were also examined but rarely extracted these metal ions. Thus, the cooperative action of functionalized side arm and the parent cyclen ring significantly contributes to the Na^+ ion-selective extraction function.

Although macrocycles **4**−**6** were reported to be Na^+ ion-selective ligands,[10−12] they did not exhibit efficient or selective extraction abilities under the competitive extraction conditions. For example, ester-armed calixarene **4** extracted Na^+ ion but at a percentage (35%) much lower than those of armed cyclens **1b**−**d** (66−89%). Cryptand **5** extracted Na^+ and K^+ ions nonselectively (extraction percentage: 97% and 89%),[13] and bis-crown ether **6** did not operate well (extraction percentage: <3%). Thus, armed cyclens **1b**−**d** possess extraction abilities specific for Na^+ ion which are greatly superior to those of common Na^+ ion binders.

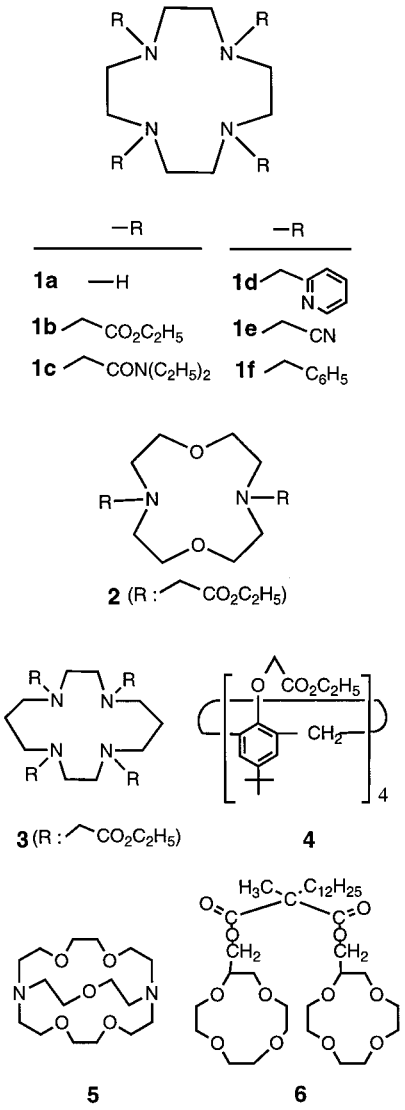

Figure 2. Armed cyclens and references.

Table 1. Competitive Extraction of Alkali Metal Cations by Armed Cyclens and References

	extraction %[a]		
macrocycle	Li^+	Na^+	K^+
1b	<3	66	<3
1c	7	86	<3
1d	4	89	<3
1e	<3	<3	<3
1f	<3	<3	<3
2	<3	<3	<3
3	<3	<3	<3
4	<3	35	<3
5	<3	97	89
6	<3	<3	<3

[a] $LiClO_4$, $NaClO_4$, and $KClO_4$ (0.015 mmol, each) in H_2O (1.5 mL)/macrocycle (0.015 mmol) in CH_2Cl_2 (1.5 mL).

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Table 2. Cation Binding Selectivities of Armed Cyclens and References Assessed by FAB-MS

	relative peak intensity[a]			
macrocycle	macrocycle + 1	macrocycle + Li^+	macrocycle + Na^+	macrocycle + K^+
1b	0	7	100	4
1c	1	100	94	3
1d	2	30	100	3
1e	100	48	7	7
1f	100	2	3	0
2	1	100	55	0
3	1	4	100	1
4	1	4	100	5
5	1	1	100	3
6	0	2	100	4

[a] Conditions: LiCl, 0.0083 mol/L; NaI, 0.0083 mol/L; KI, 0.0083 mol/L; macrocycle, 0.0033 mol/L; in *m*-nitrobenzyl alcohol.

FAB MS Binding Experiments. Cation binding properties of armed cyclens and related macrocycles were also assessed on a semiquantitative level using the FAB MS competition technique.[14] Table 2 summarizes relative peak intensities of [macrocycle + metal]$^+$ ions which reflect relative cation binding affinities of the armed macrocycles, though cation binding strength could not be exactly determined by this method. When cyclens **1e**,**f** having nitrile- and benzyl-functionalized arms were employed, [macrocycle + 1]$^+$ ion peaks were observed which were much larger than [macrocycle + metal]$^+$ ion peaks. Since the former peaks were probably derived from protonated forms of the cyclens, cyclens **1e**,**f** were suggested to bind a proton more strongly than Li^+, Na^+, and K^+ ions under the FAB MS conditions. Cyclen **1e** also exhibited higher binding ability for Li^+ ion than Na^+ and K^+ ions. Since this cyclen did not extract any metal cations, its Li^+ coordination was believed to hardly compete with cation hydration in the extraction experiments. In contrast, ester-, amide-, and pyridine-armed cyclens **1b**−**d** predominantly gave the [macrocycle + metal]$^+$ ion peaks, indicating that introduction of the proper cation-ligating side arms remarkably increased cation binding ability. Ester-armed cyclen **1b** exhibited particularly high Na^+ ion selectivity: ratios of relative peak intensities were calculated as 14 for [**1b** + Na]$^+$/[**1b** + Li]$^+$ and 25 for [**1b** + Na]$^+$/[**1b** + K]$^+$. Pyridine-armed cyclen **1d** also provided Na^+ ion selectivity in the FAB MS experiment. When amide-armed cyclen **1c** was employed, we observed different guest selectivity from that in the extraction experiment. The peak intensity of the detected [**1c** + Na]$^+$ ion was similar to that of [**1c** + Li]$^+$ ion, while cyclen **1c** extracted Na^+ ion much more effectively than Li^+ ion. These observations probably indicate that the ease of cation extraction is determined by cation complex stability and also cation hydration energy. Cyclen **1c** similarly bound Li^+ and Na^+ ion, but the larger Na^+ ion with smaller hydration energy is a favorable guest for efficient extraction. Ester-armed diaza-12-crown-4 **2** and cyclam **3** exhibited characteristic cation selectivities under the FAB conditions: the former favored Li^+ ion but the latter preferred Na^+ ion. These ligands formed cation complexes in nitrobenzyl alcohol matrix but have insufficient complex stability to extract the cations from the aqueous solution into the CH_2Cl_2. Thus, the choice of side arm functionality and parent macrocycle significantly determined cation recognition behavior.

Table 2 also indicates that ester-armed calixarene **4**, cryptand **5**, and bis-crown ether **6** showed high Na^+ ion selectivity under the FAB MS conditions. Since they did not offer efficient or selective extraction of Na^+ ion (see Table 1), the Na^+ ion was suggested to be incompletely wrapped by these ligands and insufficiently shielded from the water. The FAB MS spectrum was also recorded for a mixture of equimolar armed cyclen **1c**, cryptand **5**, and Na^+ ion, in which ligands **1c** and **5** competed with each other for binding of the Na^+ ion. The relative peak intensity of [**1c** + Na]$^+$/[**5** + Na]$^+$ was observed as more than 113, indicating that armed cyclen **1c** forms a much more stable complex with Na^+ ion than cryptand **5**. Similar experiments were carried out with armed cyclens **1b**,**d**: [**1b** + Na]$^+$/[**5** + Na]$^+$ = 63; [**1d** + Na]$^+$/[**5** + Na]$^+$ = 1.5. Thus, armed cyclens **1b**−**d** form more stable Na^+ complexes than bicyclic cryptand **5** under the FAB MS conditions: the stability of Na^+ complex decreases in order **1c** > **1b** > **1d** > **5**.

Crystal Structures of Armed Cyclens. We successfully isolated Na^+ complexes with three kinds of armed cyclens **1b**−**d** and determined their crystal structures by X-ray crystallographic method. On the basis of the structural data, we calculated mean cavity radius and guest ion radius:[15] the former is an average of the difference between metal−donor distance and donor radius, 1.40 Å (oxygen) and 1.50 Å (nitrogen), for all donors; the latter can be calculated in the same manner as effective ionic radii for oxygen and nitrogen donors which increase with coordination number of the guest ion.

Figure 3 illustrates crystal structures of the Na^+ complexes with armed cyclens **1b**−**d**. There are marked differences in the coordination structures, though the Na^+ ion was cooperatively coordinated both by cyclen nitrogens and side arm donors in each complex. When amide-armed cyclen **1c** was employed, the Na^+ ion was octacoordinated by four carbonyl oxygen atoms of the amide-functionalized side arms and four nitrogen atoms of the cyclen ring. As summarized in Table 3, the mean lengths between Na^+−O(amide) and Na^+−N(cyclen) are almost the same (2.57 and 2.56 Å), showing that the guest Na^+ ion is located at the center of the three-dimensional cavity. The mean cavity radius and the guest ion radius of the Na^+ ion were calculated as 1.12 and 1.09 Å, respectively. This Na^+ complex was believed to have a highly lipophilic exterior and to be easily extracted into CH_2Cl_2 phase. Ester-armed cyclen **1b** also formed an octacoordinated complex with the Na^+ ion. Although four ester-functionalized side arms coordinated the Na^+ ion together with cyclen nitrogen atoms, one of the side arms used not carbonyl but an ether oxygen atom. The mean lengths between Na^+−N and Na^+−O were calculated as 2.54 and 2.53 Å, respectively, and the calculated mean cavity radius (1.09 Å) and the guest ion radius (1.06 Å) were slightly smaller than those obtained in the **1c**−Na^+ complex. Pyridine-armed cyclen **1d** offered a different coordination sphere around the Na^+ ion. In this complex, three pyridine rings strongly interacted with the Na^+ ion as well as with four nitrogen atoms of the cyclen ring, but one pyridine-functionalized side arm stood apart from the Na^+ ion. Bulkiness of the pyridine-functionalized side arm

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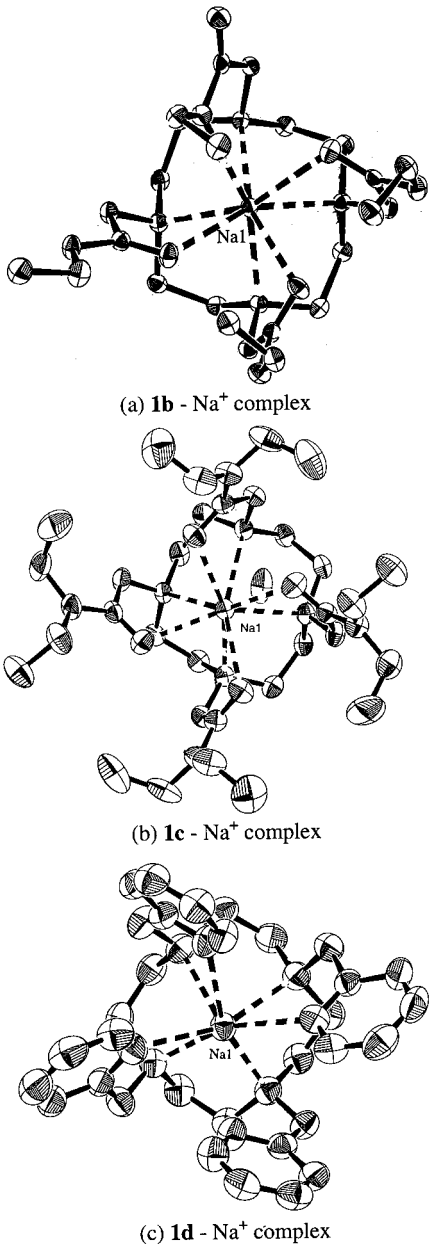

(a) **1b** - Na^+ complex

(b) **1c** - Na^+ complex

(c) **1d** - Na^+ complex

Figure 3. Crystal structures of armed cyclen−Na^+ complexes

Table 3. Coordination Bond Lengths in Armed Cyclen − Na^+ Complexes

	bond length (Å)	
complex	Na^+-N_{cyclen}	Na^+-D_{arm}
1b−Na^+	2.557(2)	2.470(2)
	2.523(2)	2.522(2)
	2.524(2)	2.562(2)
	2.551(2)	2.582(2)
1c−Na^+	2.549(3)	2.595(3)
	2.573(3)	2.556(3)
	2.543(3)	2.583(3)
	2.581(3)	2.557(3)
1d−Na^+	2.584(2)	2.644(2)
	2.575(2)	2.621(2)
	2.573(2)	2.623(3)
	2.573(2)	2.820(3)

might hinder bundling up of four side arms upon complexation and offer somewhat lower complex stability than those with ester- and amide-armed cyclens **1b**,**c** as observed in the FAB MS experiment. The parent cyclen is a tetradentate ligand

Table 4. Macrocycle-Induced Changes in ^7Li and ^{23}Na NMR Chemical Shifts

	induced chem shift (ppm)[a]	
macrocycle	Li^+	Na^+
1b	3.2[b]	13.9
1c	*d*	11.7[b]
1d	*d*	16.1
1e	2.3	7.7
1f	2.6[c]	0.2[c]
2	2.7	9.2
4	2.3[b]	2.8
5	1.3	12.5
6	1.1	3.3

[a] Conditions: macrocycle, 0.025 mmol; $LiClO_4$ or $NaClO_4$, 0.025 mmol in CD_3CN-CH_3CN (2/3), 0.5 mL. Positive values indicate downfield shifts. [b] A slight amount of precipitate was observed. [c] A considerable amount of precipitate was observed. [d] Because **1c**,**d** were isolated only as Na^+ complexes, ^7Li NMR spectra were not measured.

effective for two-dimensional incorporation of small transition metal cations, but armed cyclens **1b**−**d** have expanded three-dimensional cavities which can completely encapsulate large Na^+ ion. This can well explain why these armed cyclens extract the Na^+ ion effectively and selectively.

NMR Binding Studies. ^{23}Na NMR binding experiments were carried out in CD_3CN/CH_3CN solutions. Since the employed acetonitrile has weaker solvation ability than nitrobenzyl alcohol and water, the results obtained below emphasize side arm participation in the binding of Na^+ ion more strongly than those with FAB MS and extraction techniques.[16] When armed cyclen **1b**, **1c**, **1d**, **1e**, or **1f** is added to a solution of Na^+ salt, the changes in ^{23}Na NMR chemical shifts ($\Delta\delta$) induced by the cyclen derivative should relate to the coordination ability of its functionalized side arm. As summarized in Table 4, armed cyclens **1b**−**d** having ester, amide, and pyridine moieties offered larger shift values ($\Delta\delta$ = 13.9, 11.7, and 16.1) for the Na signal than nitrile- and benzyl-armed cyclens **1e**,**f** ($\Delta\delta$ = 7.7 and 0.2 ppm). These observations indicate that ester, amide, and pyridine donor groups on the side arms work as more effective binding sites for the Na^+ ion than nitrile donor groups. We also took ^{23}Na NMR spectra in the presence of macrocycles **4**−**6** and observed characteristic shift changes: $\Delta\delta$ = 2.8 ppm for **4**, 12.5 ppm for **5**, and 3.3 ppm for **6**. Although direct comparison was difficult, armed cyclens **1b**−**d** could very nicely wrap the Na^+ ion in the three-dimensional fashion as observed with bicyclic cryptand **5**. On the other hand, the cyclens **1b**,**e**,**f** brought about similar changes in ^7Li NMR spectra: $\Delta\delta$ = 3.2 ppm for **1b**, 2.3 ppm for **1e**, and 2.6 ppm for **1f**. These ^7Li NMR binding results suggested that the nature of the side arm only slightly influenced the Li^+ ion binding.

Liquid Membrane Transport. Since cation binding studies support that the employed armed cyclens have potential as a new type of ion carrier, their cation transport abilities were characterized using CH_2Cl_2 liquid membrane.[17] Table 5 summarizes initial transport rates obtained under the competitive transport conditions, in which an aqueous source phase included equimolar Li^+, Na^+, and K^+ ions.

Compared with common carriers **4**−**6**, amide-, pyridine-, and nitrile-armed cyclens **1c**−**e** showed lower transport efficiencies for Li^+, Na^+, and K^+ ions. In contrast, ester-armed cyclen **1b**

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Table 5. Competitive Transport of Alkali Metal Cations by Armed Cyclens and References

	transport rate × 10^7 mol/h[a]		
macrocycle	Li^+	Na^+	K^+
1b	3.4	0.7	9.2
1c	0.5	1.9	<0.1
1d	<0.2	0.8	<0.1
1e	<0.2	0.5	<0.1
1f	<0.2	0.2	<0.1
4	0.6	2.5	8.3
5	4.2	0.7	7.1
6	<0.2	70.8	2.6

[a] Conditions: $LiClO_4$, $NaClO_4$, and $KClO_4$ (0.50 mmol, each) in H_2O (5 mL)/macrocycle, 0.0372 mmol in CH_2Cl_2 (12 mL)/H_2O (5 mL).

offered comparable transport rates with calixarene **4** and cryptand **5**. This cyclen exhibited 5 and 13 times lower transport rates of the Na^+ ion than Li^+ and K^+ ions. It is noted that ester-armed cyclen **1b** exhibited excellent Na^+ ion selectivity in FAB MS and liquid−liquid extraction experiments. As frequently reported,[18] **1b** probably binds the Na^+ ion too strongly to release the cation from membrane phase into the receiving aqueous phase. Similar transport profiles were observed with calixarene **4** and cryptand **5**; they bound the Na^+ ion more strongly than Li^+ and K^+ ions but transported the K^+ ion with greater efficiency.

Computational Studies. We attempted to optimize the geometry of the armed cyclen complexes with Li^+ and Na^+ ions using AMBER[19] and *ab initio* calculations,[20] though the effects of counteranion and solvation were neglected. Since the armed cyclens have four flexible side arms, they can vary the side arm number to coordinate with the guest cation. Thus, we employed the X-ray coordinates of the Na^+ complexes (see Figure 3) as an initial geometry of the theoretical calculation.

The optimized structure of the Na^+ complex with armed cyclen **1c** is closely similar to that observed in the crystal. The Na^+ ion locates at the center of the armed cyclen cavity and is octacoordinated by four cyclen nitrogen and carbonyl oxygen atoms. The Na^+−N(cyclen) and the Na^+−O(amide) distances were calculated as 2.65 and 2.53 Å. The former is somewhat longer than that determined in the crystal, while the latter is slightly shorter. Interestingly, cyclen **1c** was suggested to form a hexacoordinated complex with Li^+ ion. The Li^+−N(cyclen) distances in the complex were estimated to be 2.41 and 2.58 Å, while the Li^+−O(amide) lengths were calculated as 2.01 Å for the coordinated oxygens and 3.28 Å for the noncoordinated oxygens. We did not obtain the crystal of cyclen **1c**−Li^+ complex experimentally, but the Li^+ ion is too small to form an octacoordination complex and must therefore be incompletely wrapped by cyclen **1c**. This may be the main reason cyclen **1c** favors Na^+ ion over Li^+ ion. Ester- and pyridine-armed cyclens **1b**,**d** were also examined. Although they offered different coordination modes in the crystals from that with amide-armed cyclen **1c**, the *ab initio* MO calculations suggested that they offer hexacoordination for Li^+ ion and octacoordination for Na^+ ion as predicted for cyclen **1c**.[21] Probably, the effects of counteranion, solvation, and packing should be considered in order to obtain theoretical results which can be directly compared with experimental ones.

We successfully demonstrated above that arm-functionalization of the cyclen ligand provided a practical strategy for development of Na^+ ion-specific receptors. In particular, introduction of ester, amide, and pyridine donor groups to the side arms of the cyclen system enhanced both selectivity and efficiency in the binding of Na^+ ion. We further showed that the *ab initio* calculation provided an interesting possibility for the design of a cation-specific armed macrocycle.

Experimental Section

Materials. Cyclen **1a** and related macrocycles **4**−**6** were commercially available and used without additional purification. Cyclen **1f**, diaza-12-crown-4 **2**, cyclam **3** were synthesized by methods described in the literature.[8,9]

Preparation of Armed Cyclens. Armed cyclens **1b**−**e** were derived from unsubstituted cyclen **1a** in a fashion similar to that reported for diaza-crown ethers:[8] Ester- and nitrile-armed cyclens **1b**,**e** were isolated as free ligands, while cyclens **1c**,**d** were isolated as Na^+ complexes. They had correct elemental compositions as determined by microanalysis and high-resolution mass spectroscopy. Selected data of the newly obtained ligands and complexes are summarized below.

1,4,7,10-Tetrakis[(ethoxycarbonyl)methyl]-1,4,7,10-tetraazacyclododecane (1b). A solution of **1a** (0.69 g, 4 mmol), ethyl chloroacetate (2.94 g, 24 mmol), and Cs_2CO_3 (20.0 g, 60 mmol) in CH_3CN (60 mL) was refluxed for 10 h and then filtered. The solvent was evaporated, and the residue was washed with hexane and diethyl ether and chromatographed (hexane/ethyl acetate, activated alumina ca. 200 mesh) (oil, 26%): IR (neat) ν 1736 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.26 (t, 12H), 2.83 (s, 16H), 3.40 (s, 8H), 4.14 (q, 8H); ^{13}C NMR ($CDCl_3$) δ 14.38, 52.10, 55.80, 60.23, 171.80; HRMS (*m*/*e*) calcd for $C_{24}H_{44}N_4O_8$ 516.3159, found 516.3190.

The **1b**−NaI complex was similarly obtained in the presence of NaI using Na_2CO_3 as a base. Recrystallization from CH_2Cl_2/diethyl ether gave white crystals of NaI complex (57%): mp 195−196 °C; IR (neat) ν 1732 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (t, 12H), 2.36 (br s, 16H), 3.21 (br s, 8H), 4.14 (br q, 8H); ^{13}C NMR ($CDCl_3$) δ 14.21, 51.26, 51.23, 61.23, 173.69. Anal. Calcd for $C_{24}H_{44}O_8N_4$·NaI: C, 43.25; H, 6.55; N, 8.41. Found: C, 43.35; H, 6.65; N, 8.31.

1,4,7,10-Tetrakis[(diethylcarbamoyl)methyl]-1,4,7,10-tetraazacyclododecane (1c)−NaCl Complex. This was similarly prepared from cyclen **1a** and *N*,*N*-diethylchloroacetamide in the presence of Na_2CO_3 (70%): mp 178−179 °C; IR (Nujol) ν 1637 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.05 (t, 12H), 1.16 (t, 12H), 2.43 (br s, 16H), 3.20 (br s + q, 24H), 5.32(s, 2H); ^{13}C NMR ($CDCl_3$) δ 12.44, 14.01, 40.38, 40.85, 49.57, 52.62, 53.35, 54.83, 169.78. Anal. Calcd for $C_{32}H_{64}O_4N_8$·NaCl·CH_2Cl_2: C, 51.59; H, 8.66; N, 14.58. Found: C, 51.55; H, 8.82; N, 14.43.

1,4,7,10-Tetrakis(2′-pyridylmethyl)-1,4,7,10-tetraazacyclododecane (1d)−NaI Complex. This was obtained from cyclen **1a** and (chloromethyl)pyridine hydrochloride in the presence of NaI and Na_2CO_3 (70%): mp 242−244 °C; IR (Nujol) ν 1593 and 1568 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.47 + 3.47(br s + br s, 24H), 6.99 (dd, 4H), 7.13 (d, 4H), 7.42 (d, 4H), 7.64 (dt, 4H); ^{13}C NMR ($CDCl_3$) δ 50.52, 59.19, 122.52, 123.93, 137.02, 148.91, 158.74. Anal. Calcd for $C_{32}H_{40}N_8$·NaI: C, 55.98; H, 5.87; N, 16.32. Found: C, 56.19; H, 5.92; N, 16.40.

1,4,7,10-Tetrakis(cyanomethyl)-1,4,7,10-tetraazacyclododecane (1e). This was obtained from cyclen **1a** and chloroacetonitrile in the presence

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(21) We also estimated stabilization energies due to the Na^+ complexation: −21.8 kcal/mol for **1c** and −18.1 kcal/mol for **1d** at the RHF/6-31G*//RHF/6-31G level of theory. This trend is parallel to that observed in the FAB MS experiment.

Table 6. Crystal and Structure Refinement Data for Na^+ Complexes with **1b**−**d**

	1b−NaI	**1c**−NaCl·CH_2Cl_2	**1d**−NaI
empirical formula	$C_{24}H_{44}O_8N_4NaI$	$C_{33}H_{66}O_4N_8NaCl_3$	$C_{32}H_{40}N_8NaI$
formula mass	666.5	768.3	686.6
cryst size (mm)	0.20 × 0.20 × 0.40	0.63 × 0.68 × 0.60	0.70 × 0.60 × 0.40
cryst system	monoclinic	triclinic	monoclinic
space group	$P2_1/n$	$P\bar{1}$	$P2_1/c$
a (Å)	13.486(7)	12.021(3)	8.997(3)
b (Å)	13.637(4)	14.668(4)	14.117(4)
c (Å)	17.274(4)	12.023(3)	25.162(4)
α (deg)		91.94(2)	
β (deg)	112.50(2)	90.61(2)	95.52(2)
γ (deg)		91.96(2)	
V (Å^3)	2934(1)	2117.3(10)	3181(1)
Z	4	2	4
ρ_{calcd} (g cm^{-1})	1.508	1.205	1.434
F(000) (e)	1376	828	1408
T (°C)	−123.0	23.0	23.0
μ(Mo Kα) (cm^{-1})	11.57	2.70	10.56
scan mode	$\omega-2\theta$	$\omega-2\theta$	$\omega-2\theta$
2θ range (deg)	6.0−50.0	6.0−50.0	6.0−50.0
measd reflcns	5412	7438	5738
obsd reflcns	4236 ($I > 3.00\sigma(I)$)	4448 ($I > 3.00\sigma(I)$)	5035 ($I > 3.00\sigma(I)$)
refined params	520	443	540
resid electron dens (e Å^{-3})	0.68/−0.95	0.38/−0.38	0.43/−0.72
R^a	0.024	0.054	0.032
$R_w{}^b$	0.033	0.076	0.059
GOF	1.40	1.81	1.67

[a] $R = \sum(||F_o| - |F_c||)/\sum|F_o|$. [b] $R_w = [\sum w(|F_o| - |F_c|)^2/\sum wF_o^2]^{1/2}$.

of Cs_2CO_3 (70%): mp 158−160 °C; IR (Nujol) ν 2229 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.76 (s, 16H), 3.58 (s, 8H); ^{13}C NMR ($CDCl_3$) δ 43.58, 51.50, 114.88. Anal. Calcd for $C_{16}H_{24}N_8$: C, 58.52; H, 7.37; N, 34.12. Found: C, 58.14; H, 7.41; N, 34.20.

FAB MS Experiments. Complexation of macrocycle (0.0033 mol/L) with LiCl, NaI, and KI (0.0083 mol/L, each) in *m*-nitrobenzyl alcohol was studied by measuring the relative peak heights of [macrocycle + M]$^+$ ions. When the Na^+ complexes with **1c**,**d** were employed, total Na^+ concentration was adjusted as 0.0083 mol/L. To complete the exchange of Na^+ ion with Li^+ and K^+ ions, *m*-nitrobenzyl alcohol solutions were stirred for 3 h prior to measurements. FAB MS spectra were recorded with a JEOL AX 500 instrument (a beam energy of Xe, 6 keV), and the peak heights were averaged over at least 20 scans.

Extraction Experiments. Extraction experiments were performed by adding a CH_2Cl_2 solution of the macrocycle (0.015 mmol in 1.5 mL) to an aqueous mixture of Li^+, Na^+, and K^+ perchlorates (0.015 mmol, each in 1.5 mL). After the mixture had been stirred for 2 h, the remaining concentrations of these metal ions in the aqueous phase were determined by atomic absorption or flame spectroscopic method (carried out at Exlan Technical Center, Okayama, Japan). When the Na^+ complexes with **1c**,**d** were examined, Na^+ salt was not added to the aqueous phases. We confirmed that negligible amounts of metal perchlorates were extracted into the CH_2Cl_2 in the absence of macrocycle (<3%).

Crystal Structure Determinations of Na^+ Complexes. Specific information is provided in Table 6. Data collection was carried out at −123 °C (**1b**) and 23 °C (**1c**,**1d**) on a Rigaku AFC7R four-circle, computer-controlled diffractometer equipped with graphite-monochromated Mo Kα radiation. The final orientation matrix and unit cell parameters were determined from 20 machine-centered reflections. Monitoring of the three standard reflections every 150 measurements indicated no decay of crystals over the period of data collection. The raw data were reduced to net intensities, estimated standard deviations were calculated by counting statistics, and equivalent reflections were averaged. The structures of Na^+ complexes with **1b**,**d** were solved by the automated Patterson method (DRDIF92 PATTY),[22] and the structure of complex with **1c** was solved by direct methods (SIR92).[23] Atomic coordinates and anisotropic thermal parameters of the non-hydrogen atoms of all crystals were refined on F by full-matrix least-squares calculations. An absorption correction (ψ scan) was applied to all crystal data. Hydrogen atoms of complexes with **1b**,**c** were placed in the positions observed in the difference Fourier map and refined isotropically, and those of complex with **1c** were included at the positions calculated but not refined. All computer programs used were from teXsan software (Molecular Structure Corp.).

NMR Binding Experiments. ^{7}Li and ^{23}Na NMR spectra were recorded with a JEOL LA-300. Induced shift values indicated in Table 4 mean differences in the chemical shifts of ^{7}Li and ^{23}Na nuclei observed with and without macrocycle. Each macrocycle was dissolved in CD_3CN/CH_3CN (2/3) at a concentration of 0.05 mol/L. Reproducibility: <0.2 ppm.

Transport Experiments. Transport experiments were performed at room temperature (ca. 18 °C) in a U-tube glass cell (2.0 cm i.d.).[17] The macrocycle, dissolved in CH_2Cl_2, was placed in the base of the U-tube, and two aqueous phases were placed in the tube arms, floating on the CH_2Cl_2 membrane phase. The membrane phase was constantly stirred with a magnetic stirrer. The transport rates indicated in Table 5 were calculated from the initial rates of appearance of guest metal cations in the receiving aqueous phase, which were determined by the atomic absorption or flame spectroscopic method (carried out at Exlan Technical Center). We confirmed that all guest salts were rarely transported in the absence of macrocycle (<0.1 × 10^{-7} mol/h).

Method of Calculation. The structures of armed cyclen−cation complexes were optimized using the AMBER method[19] and then the *ab initio* method (RHF/6-31G).[20] *Ab initio* MO calculations were performed using the GAUSSIAN 94 program to optimize structures of armed cyclens and their cation complexes at the RHF/6-31G level of theory. The initial geometries for optimization were based on their X-ray crystallographic results.

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Supporting Information Available: X-ray crystallographic files, in CIF format, and tables of X-ray data for the structures of complexes **1b**−NaI, **1c**−NaCl, and **1d**−NaI and schematic illustrations of the optimized structures of the Li^+ and Na^+ complexes with cyclen **1c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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