Ester-Armed Cyclens Having Quadruplicated Helical Geometry: Remarkably Stable and Selective Encapsulation of Na^+ Ion

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A new series of ester-armed cyclens nicely accommodated a Na^+ ion in their quadruplicated helical binding spheres and effectively discriminated the cation from Li^+ and K^+ ions. Crystallographic studies revealed that four ester-functionalized sidearms provided effective coordination with the Na^+ ion trapped in the 12-membered cyclen ring. Log *K* values for their Na^+ complexes were estimated as 9−11 in CD_3CN or C_2D_5OD, which were comparable to those of common bicyclic cryptands. FAB-MS, liquid−liquid extraction, and NMR binding experiments demonstrated that the cooperative action of the parent cyclen ring and ester-functionalized sidearms offered stable and selective encapsulation of the Na^+ ion based on unique quadruplicated helical geometry.

Introduction

Armed cyclens are characterized by 1,4,7,10-tetrazacyclododecane, cyclen, and four cation-ligating sidearms. They form a wide variety of transition metal and lanthanide complexes that have characteristic chemical, biological, or catalytic properties.[1] Since the armed cyclens can use a varying number of their sidearms to form different types of complexes for different kinds of metal cations, alkali metal cations of biological richness are potential targets for them. For example, cyclen derivatives having pyrazoylmethyl, methoxyethyl, and 2-hydroxypropyl groups on the sidearms were reported to offer hexacoordination for Li^+ ion and octacoordination for Na^+ and K^+ ions.[2] We have recently synthesized a series of cyclen derivatives having ester-, amide-, and pyridine-functionalized sidearms as receptors of alkali metal cations[3] and found that ester-armed cyclen **1a** exhibited excellent Na^+ ion selectivity. Since the diameter of the Na^+ ion is larger than that of the 12-membered cyclen ring and its nitrogen atom does not act as an effective donor for Na^+ ion,[4] the cooperative action of the cyclen ring and ester-functionalized sidearm gave the stable octadentate Na^+ complex. The resulting complex has Δ and Λ enantiomers based on helicity of the sidearm arrangements,[5] so that armed cyclens of this type can be viewed as a new class of three-dimensional receptors that have unique quadruplicated helical geometry for Na^+ ion encapsulation.[6]

In this article, we systematically prepare a variety of ester-armed cyclens, characterize them as Na^+ ion-selective receptors, and compare their receptor functions with those of common cyclen and cryptand derivatives. The stability constant determination, liquid−liquid extraction, FAB-MS, $^{13}C/^{23}Na$ NMR, and X-ray diffraction experiments revealed that all of the examined ester-armed cyclens formed stable octadentate complexes with Na^+ ion and exhibited satisfactorily high Na^+ ion selectivity. In the present type of cyclen−Na^+ complexes, four ester-functionalized sidearms pointed in the same direction and were twisted in a quadruplicated helical fashion. Their unique ligand geometry offered excellent receptor functions specific for Na^+ ion.

Results and Discussion

One-Pot Synthesis of Ester-Armed Cyclen−Na^+ Complexes. A variety of NaCl complexes with ester-armed cyclens were prepared directly by reaction of corresponding chlorides and cyclen tetrahydrochloride in the presence of Na_2CO_3 (Figure 1). The examined cyclen ligands have various ester residues with different bulkiness: **1a** (A = ethyl) < **1b** (A = cyclopentanyl) < **1c** (A =

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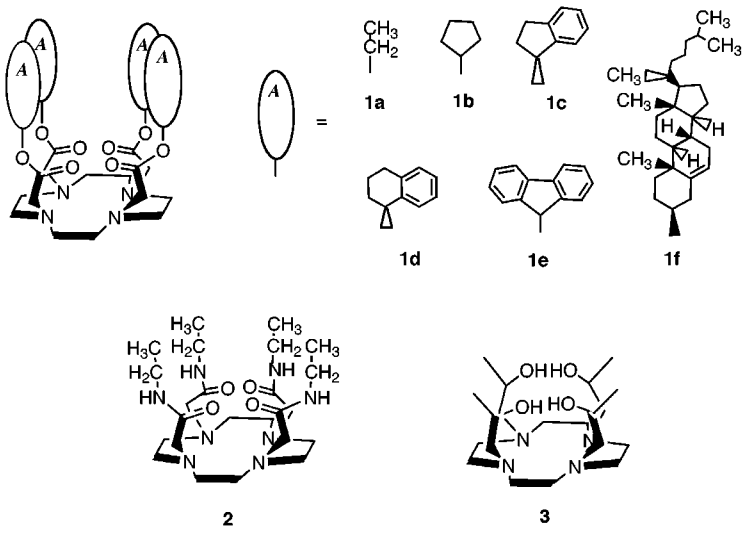

Figure 1. Ester-armed cyclens and related cyclen derivatives.

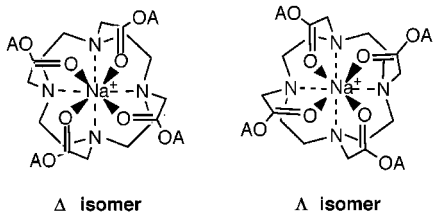

Figure 2. Stereoisomers of octadentate ester-armed cyclen−Na^+ complex. When viewed down the C_4 axis from the oxygen plane, the isomer in which that plane is twisted to the right with respect to the nitrogen plane is designated Δ. The twist is to the left for the Λ isomer.

indanyl) ≤ **1d** (A = tetrahydronaphthyl) < **1e** (A = fluorenyl) < **1f** (A = cholesteryl). These cyclen−NaCl complexes were readily isolated as white crystals that are well soluble in $CDCl_3$ and other organic solvents. Since few neutral receptors are known to solubilize the NaCl salt in the organic solvents,[7] the ester-armed cyclens were suggested to have unique coordination geometry for three-dimensional encapsulation of the Na^+ ion. Amide- and alcohol-armed cyclens **2**[8] and **3**[9] were employed for comparison, because they may have different kinds of donor groups in a similar binding geometry.

The crystal structure of the Na^+ complex with ester-armed cyclen **1e** indicated a twisted square antiprismatic structure, in which the Na^+ ion was octacoordinated by four carbonyl oxygen atoms of the sidearms and four nitrogen atoms of the cyclen ring (see Supporting Information). The averaged distances Na^+−O (ester carbonyl) and Na^+−N (cyclen) are almost the same (2.55 and 2.58 Å). Since the shorter distances Na^+−O (amide carbonyl) and longer distances Na^+−N (cyclen) were reported in the octadentate Na^+ complexes with other types of amide-armed cyclens,[10] ester-armed cyclen **1e** accommodates the Na^+ ion more deeply in the binding cavity. Four fluorenyl residues on the ester-functionalized sidearms are arranged in the helical fashion and stand as lipophilic exteriors of the Na^+ complex. When viewed from the sidearm side of the cyclen plane, four carbonyl-oxygen atoms of the sidearms are twisted by 20° or 25°. This cyclen itself has no asymmetric carbon, and both enantiomers Δ and Λ were found in the crystal state, though the ORTEP of one enantiomer is provided in Supporting Information. Since the chloride anion locates in the remote position from the coordination sphere (Na^+−Cl^-, 5.55 Å), ester-armed cyclen **1e** was confirmed to completely encapsulate the Na^+ ion in the three-dimensional fashion.

NMR Profiles and Stability Constants of Ester-Armed Cyclen−Na^+ Complexes. ^{13}C NMR spectra of the Na^+ complexes with ester-armed cyclens **1a**−**1f** indicated C_4 symmetry in solutions as well as in crystal states. When achiral armed cyclen **1e** was employed as a ligand, ^{13}C NMR signals for two cyclen ring carbons, $^{13}C_\alpha$ and $^{13}C_\beta$, of its NaCl complex separately resonated at 53.7 and 49.1 ppm at 298 K in CD_3CN solution, and one signal was observed at 56.2 ppm for N-$\underline{C}H_2$-CO-carbons of four sidearms (Table 1). Such inequivalence of the cyclen ring carbons has been reported in the octadentate complexes with other types of achiral armed cyclens and attributed to a slow process involving either a rotation of the four sidearms or an inversion of the cyclen cycle.[5] Since increasing the sample temperature to 318 K did not cause coalescence of the two cyclen carbon signals, the two stereoisomers of cyclen **1e**−Na^+ complex were confirmed to very slowly exchange with each other in the solution. The Na^+ complexes with ester-armed cyclens **1a**−**1d** and **1f** also gave the broadened, disappeared, or separated ^{13}C NMR signals for the cyclen ring carbons at 298 K. When chiral cyclen **1c**, **1d**, or **1f**

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Table 1. NMR Profiles and Stability Constants of Armed Cyclen−Na^+ Complexes

		chemical shift[b] (ppm)			
cyclen	solvent[a]	$^{13}C_\alpha$	$^{13}C_\beta$	^{23}Na	log K
1a	A	52.4	49.5	13.7	9.9
	B	disappeared		7.2	9.5
1b	A	disappeared		13.7	9.3
1c	A	53.4	49.1	14.4	10.3
1d	A	53.6	49.2	13.7	10.1
	B	53.7	49.2	8.2	10.2
1e	A	53.7	49.1	15.9	10.1
1f	B	disappeared		17.2	11.2
2	B	broadened: 51.4		8.8	7.6
3[c]	A	51.8	50.6	15.2	6.4

[a] A: in CD_3CN; B: CD_3CD_2OD. [b] C_α and C_β mean two carbons of the cyclen ring. Conditions: armed cyclen−NaCl complex, 0.00500 mmol, in CD_3CN or CD_3CD_2OD, 0.500 mL. [c] In this case, a mixture of armed cyclen and $NaClO_4$ was employed.

was employed, the resulting Na^+ complex exhibited only one set of ^{13}C NMR signals. This suggests that each Na^+ complex predominantly exists as a single stereoisomer that undergoes exchange between two equivalent forms.[11] The chemical shifts for the two signals for cyclen ring carbons were significantly dependent on the nature of the ester residue; the difference, $\delta^{13}C_\alpha - \delta^{13}C_\beta$, was estimated as 2.9 ppm for **1a** complex, 4.4 ppm for **1d** complex, and 4.6 ppm for **1e** complex in CD_3CN (Table 1).

^{23}Na NMR experiments provided further insights of the Na^+ complexation with armed cyclens.[12] Table 1 also lists the chemical shifts of ^{23}Na NMR signals of the Na^+ complexes, with mean differences in the chemical shifts observed with and without cyclens. Their Na^+ complexes exhibited characteristic ^{23}Na signals at very low fields (δ 7.2−17.2 ppm), though the observed ^{23}Na signals were broad in all cases. When the Na^+ complexes with ester-armed cyclens **1b**, **1c**, and **1e** were compared, they offered the ^{23}Na NMR signals at similar positions in CD_3CN: 13.7 ppm for **1b** complex; 14.4 ppm for **1c** complex; and 15.9 ppm for **1e** complex. These ^{13}C and ^{23}Na NMR observations indicate that various ester-armed cyclens nicely accommodate the Na^+ ion in the quadruplicated helical binding geometry.

The stability constants for a series of ester-armed cyclen−Na^+ complexes were determined using the ^1H NMR competitive titration method. When cryptand [2.2.2] was added as a competitive ligand to a CD_3CN solution of ester-armed cyclen **1e**−NaCl complex, ^1H NMR signals for $-CO_2C\underline{H}=$ proton of cyclen **1e** were observed at 6.75 ppm for free form and 6.92 ppm for complexed form, indicating that the following competitive displacement took place slowly compared with the NMR time scale:

$$[\text{cyclen}-Na^+] + \text{cryptand} \rightleftarrows \text{cyclen} + [\text{cryptand}-Na^+]$$

The stability constant of cyclen−Na^+ complex K can be written using the equilibrium constant of the above-described equation K_{rel} and the stability constant of cryptand−Na^+ complex K_{cry}:

$$K = \frac{K_{cry}}{K_{rel}}$$

The concentrations of cyclen **1e**−Na^+ complex and free cyclen **1e** were evaluated by integration of corresponding ^1H NMR signals and used in the calculation of K_{rel}. Other Na^+ complexes with cyclens **1a**−**1d** and **1f** similarly gave the separated ^1H NMR signals upon decomplexation, indicating that ester-armed cyclens generally formed kinetically inert complexes. The ^1H NMR competitive titration experiments revealed that amide-armed cyclen **2** also formed kinetically inert Na^+ complex, though alcohol-armed cyclen **3** dynamically bound the Na^+ ion and gave only one set of ^1H NMR signals upon complexation/decomplexation.

The estimated log K values for cyclen−Na^+ complexes are summarized in Table 1. Ester-armed cyclens **1a**−**1f** exhibited much higher log K values (9.3−11.2) than amide- and alcohol-armed cyclens **2** and **3** (7.6 and 6.4). All of the employed cyclens had quadruplicated helical structures upon octadendate complexation,[8,9] but amide- and alcohol-armed cyclens **2** and **3** formed less stable Na^+ complexes than ester-armed cyclen **1a**. The polarity of these three sidearm functionalities should increase in the following order: $-CH_2CO_2C_2H_5 < -CH_2CHOH < -CH_2CONHC_2H_5$.[13] Therefore, the stability of the armed cyclen−Na^+ complex is significantly determined by both donor ability of sidearm functionality and cooperativity of sidearm and cyclen ring. Ester-armed cyclens containing bulky residues **1c**−**1f** exhibit enhanced stability constants for Na^+ complexation, suggesting that a bundle of four hydrophobic residues may give a favorable solvophobic effect to stabilize the Na^+ complex. Since they have log K values comparable with common cryptand [2.2.1] (log K = 10.2 in EtOH),[14] various types of substituents can be introduced into the ester-armed cyclen system without lowering the cation binding ability.

FAB-MS Binding Experiments. Cation binding selectivity of ester-armed cyclens **1a**−**1f** and related cyclens **2** and **3** were assessed on a semiquantitative level using the FAB-MS competition technique.[15] Table 2 summarizes relative peak intensities of [cyclen + metal]$^+$ ions, which reflect relative cation binding affinities of the armed cyclens, though cation binding strength cannot be exactly determined by this method. The attachment of the ester-functionalized sidearm to the cyclen ring significantly enhanced Na^+ ion binding selectivity. Typically, ester-armed cyclen **1c** gave [cyclen + Na]$^+$ ion peaks predominantly; the ratio of relative peak intensity was calculated as >50 for [**1c** + Na]$^+$/[**1c** + Li]$^+$ and >50 for

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Table 2. Cation Selectivity of Armed Cyclens Assessed by FAB-MS

	relative peak intensity[a]			
cyclen	M + 1	M + Li	M + Na	M + K
1a	<2	7	100	4
1b	<2	<2	100	4
1c	<2	<2	100	<2
1d	<2	<2	100	3
1e	<2	<2	100	4
1f	<2	12	100	15
2	<2	100	14	<2
3[b]	14	100	93	<2

[a] Conditions: cyclen−NaCl, 0.00330 mol/L; LiCl, 0.00830 mol/L; NaI, 0.00500 mol/L; KI, 0.00830 mol/L in *m*-nitrobenzyl alcohol. [b] Conditions: cyclen, 0.00330 mol/L; LiCl, 0.00830 mol/L; NaI, 0.00830 mol/L; KI, 0.00830 mol/L in *m*−nitrobenzyl alcohol.

[**1c** + Na]$^+$/[**1c** + K]$^+$. Other ester-armed cyclens **1a**, **1b**, **1e,** and **1f** similarly exhibited high Na^+ ion selectivity and acted as Na^+ ion-specific receptors. When cyclens **2** and **3** having amide- and alcohol-functionalized sidearms were employed, [cyclen + Li]$^+$ ion peaks were more strongly observed than [cyclen + Na]$^+$ and [cyclen + K]$^+$ ion peaks, indicating that these cyclens preferred Li^+ ion to Na^+ and K^+ ions under FAB-MS conditions. 1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetraacetic acid was reported to have larger stability constants for Li^+ and Na^+ complexes than K^+ complex:[16] log K = 4.32 for Li^+; 4.46 for Na^+; 1.23 for K^+ in H_2O. The electrostatic interaction plays an important role in this ligand system, but tetra-armed cyclens have suitable topology for either Li^+ or Na^+ complexation.

The FAB-MS spectra of an equimolar mixture of three NaCl complexes with cyclens **1b**, **2**, and **3** were recorded by adding free cryptand [2.2.1]. When 1 equiv of cryptand [2.2.1] competed with three armed cyclens, the [**3** + Na]$^+$ ion peak almost disappeared, and an intense [cryptand + Na]$^+$ ion peak was observed. Addition of 3 equiv of cryptand [2.2.1] significantly decreased the [**2** + Na]$^+$ ion peak, but the [**1b** + Na]$^+$ ion peak still remained. These observations support that the stability of the Na^+ complex decreases in the order **1c**−Na^+ complex ≫ **2**−Na^+ complex > **3**−Na^+ complex.

Competitive Extraction Experiments. Cation binding properties of the ester-armed cyclens were further examined by liquid−liquid extraction experiments of alkali metal cations. We shook a $CHCl_3$ solution of ester-armed cyclen−NaCl complex with an aqueous solution of $LiClO_4$ and $KClO_4$, and the distribution percentages of the three metal cations were estimated as $([M^+]_{org}/[M^+]_{total}) \times 100$ (M^+ = Li^+, Na^+, or K^+). Table 3 summarizes distribution percentages of Li^+, Na^+, and K^+ ions with armed cyclens **1** and **3**. When free cyclen **3** was examined, competitive extraction was performed with an aqueous solution containing equimolar Li^+, Na^+, and K^+ ions. Amide-armed cyclen **2** was not employed here because of its low solubility into the organic phase.

Among the examined cyclens, ester-armed cyclens **1a**−**1f** selectively and efficiently bound Na^+ ion in the presence of equimolar Li^+ and K^+ ions. When ester-armed cyclen **1c** was typically employed, 66% of the Na^+ ion was distributed as the cyclen complex in the $CHCl_3$ phase, though the distribution percentages of Li^+ and K^+ ions were recorded as less than 3%. Other ester-armed cyclens

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Table 3. Liquid-Liquid Extraction of Alkali Metal Cations with Armed Cyclens

	distribution %[a]		
cyclen	Li^+	Na^+	K^+
1a	<3	73	<3
1b	<3	38	<3
1c	<3	66	<3
1d	<3	71	<3
1e	<3	91	<3
1f	<3	94	<3
3[b]	10	17	<3

[a] $LiClO_4$, 0.0100 mmol; $KClO_4$, 0.0100 mmol in H_2O 1.50 mL; armed cyclen−NaCl complex, 0.0100 mmol in $CHCl_3$ 1.50 mL. [b] $LiClO_4$, $NaClO_4$, and $KClO_4$, 0.0100 mmol each in H_2O 1.50 mL; armed cyclen, 0.0100 mmol in $CHCl_3$ 1.50 mL.

1a, **1b**, and **1d**−**1f** similarly exhibited Na^+ ion selectivity: 38−94% of the Na^+ ion added was complexed and solubilized in the $CHCl_3$ phases, while most Li^+ and K^+ ions remained in the aqueous phases. The sidearm effects on the lipophilicity of cyclen and its complexes were assessed by considering the sidearm as a whole molecule, e.g., $-CH_2CO_2C_2H_5$ was considered to be $CH_3CO_2C_2H_5$. We estimated log D values for CH_3CO_2−A derivatives using the PALLAS program[17] (A, see Figure 1): log D = 0.54 for ethyl acetate, 2.33 for cyclopentanyl acetate, 2.97 for indanyl acetate, 3.48 for tetrahydronaphthyl acetate, 4.14 for fluorenyl acetate, and 8.98 for cholesteryl acetate. These log D values suggest that the lipophilicity increases in the order **1a**−Na^+ complex ≪ **1b**−Na^+ complex < **1c**−Na^+ complex < **1d**−Na^+ complex < **1e**−Na^+ complex ≪ **1f**−Na^+ complex. Since the stability of the Na^+ complex obtained above showed a different order of **1a** > **1b** < **1c** ≈ **1d** ≈ **1e** < **1f**, both stability constant and lipophilic property of the cyclen−Na^+ complex should reflect the cation extraction profile.

We successfully demonstrated that various ester-armed cyclens **1a**−**1f** acted as three-dimensional ligands specific for Na^+ ion. They had unique quadruplicated helical geometry and formed more inert and stable Na^+ complexes than corresponding amide- and alcohol-armed cyclens **2** and **3**. Since the ester-armed cyclens having fluorenyl, cholesteryl, and other bulky groups gave highly selective and stable encapsulation of the Na^+ ion, the ester-armed cyclen skeleton can provide a useful scaffold in the development of Na^+ ion-responsive functional materials.

Experimental Section

Materials. NaCl complexes with ester-armed cyclens **1a** and **1f** and alcohol-armed cyclen **3** were synthesized by methods described in the literature.[3,18,9] Cryptands [2.2.2] and [2.2.1] and 15-crown-5 were commercially available and were used without additional purification in the determination of stability constants.

Preparation of Ester-Armed Cyclen−NaCl Complexes. All of the employed NaCl complexes with ester-armed cyclens were directly prepared from cyclen tetrahydrochloride and corresponding chlorides in a fashion similar to that reported earlier.[3] They were isolated as NaCl complexes and fully characterized by ^1H, ^{13}C, and ^{23}Na NMR, IR, microanalysis, and mass spectroscopy. Selected data of the newly obtained complexes are summarized below.

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1,4,7,10-Tetrakis[(cyclopentoxycarbonyl)methyl]-1,4,7,-10-tetraazacyclododecane (1b)−NaCl Complex. A solution of cyclen tetrahydrochlorid**e** (0.20 g, 0.62 mmol), cyclopentanyl chloroacetate (0.50 g, 3.1 mmol), and Na_2CO_3 (0.98 g, 9.2 mmol) in CH_3CN (25 mL) was refluxed for 4 h and then filtered. The solvent was evaporated, the residue was washed with hexane, and recrystallization from CH_2Cl_2/hexane gave white crystals of NaCl complex (20%): mp 79−81 °C (decomp); IR (neat) υ 1727 cm^{-1}; FAB-MS (*m*-nitrobenzyl alcohol) *m*/*z* 699 (**1b** + Na^+); ^1H NMR ($CDCl_3$) δ 1.25−1.79 (br m, 32H), 2.37 (br s, 12H), 3.15 (br s, 12H), 5.11−5.15 (br m, 4H); ^{13}C NMR ($CDCl_3$) δ 23.63, 32.37, 48.67, 52.63, 55.22, 78.35, 173.59. Anal. Calcd for $C_{36}H_{60}N_4O_8 \cdot NaCl \cdot 4.5H_2O$: C, 52.96; H, 8.52; N, 6.86. Found: C, 52.99; H, 8.14; N, 6.93.

1,4,7,10-Tetrakis{[(*R*)-1-indanoxycarbamoyl]methyl}-1,4,7,10-teraazacyclododecane (1c)−NaCl complex: yield, 24%; mp 104−106 °C; $[\alpha]_D = 215$ (*c* = 0.985 g/100 mL, $CHCl_3$); IR (KBr) υ 1726 cm^{-1}; FAB-MS (*m*-nitrobenzyl alcohol) *m*/*z* 891 (**1c** + Na^+); ^1H NMR ($CDCl_3$) δ 2.17−2.53 (br m, 20H), 2.80−2.89 (m, 4H), 3.06−3.17 (m, 8H), 3.54 (br s, 8H), 6.26−6.30 (m, 4H), 6.67 (br s, 4H), 7.11 (br s, 4H), 7.26 (s, 4H), 7.68 (br s, 4H); ^{13}C NMR ($CDCl_3$) δ 30.05, 31.70, 48.58, 52.77, 55.48, 79.07, 124.89, 125.49, 126.61, 129.16, 140.64, 144.35, 174.06. Anal. Calcd for $C_{52}H_{60}N_4O_8 \cdot NaCl \cdot 3.5H_2O$: C, 63.05; H, 6.82; N, 5.66. Found: C, 63.13; H, 6.64; N, 5.63.

1,4,7,10-Tetrakis{[(*R*)-tetrahydro-1-naphthoxycarbamoyl]methyl}-1,4,7,10-tetraazacyclododecane (1d)−NaCl complex: yield, 23%; mp 114−115 °C; $[\alpha]_D = 129$ (*c* = 0.850 g/100 mL, $CHCl_3$); IR (neat) υ 1724 cm^{-1}; FAB-MS (*m*-nitrobenzyl alcohol) *m*/*z* 947 (**1d** + Na^+); ^1H NMR ($CDCl_3$) δ 1.78−3.57 (br m, 48H), 6.14 (br s, 4H), 6.86−7.66 (br m, 16H); ^{13}C NMR ($CDCl_3$) δ 18.62, 28.79, 29.09, 48.58, 52.77, 55.61, 70.95, 126.03, 128.48, 129.29, 129.37. 133.74, 138.04, 173.73. Anal. Calcd for $C_{56}H_{68}N_4O_8 \cdot NaCl \cdot 2.5H_2O$: C, 65.39; H, 7.15; N, 5.45. Found: C, 65.28; H, 7.02; N, 5.39.

1,4,7,10-Tetrakis[(fluorenoxycarbonyl)methyl]-1,4,7,-10-tetraazacyclododecane (1e)−NaCl complex: yield, 70%; mp 164−166 °C; IR (neat) υ 1727 cm^{-1}; FAB-MS (*m*-nitrobenzyl alcohol) *m*/*z* 1083 (**1e** + Na^+); ^1H NMR ($CDCl_3$) δ 2.38 (br s, 4H), 2.73 (br s, 8H), 3.31 (br s, 4H), 3.88 (br s, 8H), 6.54 (br s, 4H), 6.85 (s, 4H), 7.03−7.89 (br m, 28H); ^{13}C NMR ($CDCl_3$) δ 48.75, 53.18, 55.63, 76.21, 120.04, 125.64, 127.71, 129.75, 140.83, 141.07, 175.55. Anal. Calcd for $C_{68}H_{60}N_4O_8 \cdot NaCl \cdot 2H_2O \cdot 0.25CH_2Cl_2 \cdot 0.75C_4H_{10}O$: C, 69.43; H, 5.89; N, 4.55. Found: C, 69.70; H, 5.76; N, 4.55.

1,4,7,10-Tetrakis[(ethylcarbamoyl)methyl]-1,4,7,10-tetraazacyclododecane (2)−NaCl Complex. This was similarly prepared from cyclen tetrahydrochloride and *N*-ethylchloroacetamide in the presence of Na_2CO_3 (53%):[8] mp 200−201 °C; IR (KBr) υ 1658, 1556 cm^{-1}; ^1H NMR (CD_3OD) δ 1.12 (t, 12H), 2.37 (br s, 8H), 2.65 (br s, 8H), 3.04 (br s, 8H), 3.22 (q, 8H); ^{13}C NMR (CD_3OD) δ 15.0, 35.2, 49.0 (overlapped with CD_3OD), 51.8, 58.2, 173.0. Anal. Calcd for $C_{44}H_{56}N_8O_4 \cdot NaCl \cdot 2H_2O$: C, 47.48; H, 8.63; N, 18.45. Found: C, 47.54; H, 8.55; N, 18.36.

Crystal Structure Determination of Cyclen 1e−NaCl Complex. Data collection was carried out at 23 °C on a Rigaku RAXIS-RAPID Imaging Plate diffractometer equipped with graphite monochromated Mo Kα radiation ($\mu = 1.27$ cm^{-1}). The structure was solved by the automated direct method (SIR92).[19] Atomic coordinates and anisotropic thermal parameters of the non-hydrogen atoms were refined on F by full-matrix least-squares calculations. The remaining hydrogen atom coordinates were calculated at optimum positions. All computer programs used were from teXsan software (Molecular Structure Corporation). Crystal and structure refinement data for this complex are the following: empirical formula, $C_{72}H_{72}O_{10}N_4ClNa$; formula weight, 1211.82; crystal size (mm), 0.30 × 0.30 × 0.20; crystal system, monoclinic; space group, $P2_1/n$; *a* 18.4124(7), *b* 15.4028(5), *c* 23.3264(9) Å; β (deg), 99.167(1); *V* 6531.0(4) $Å^3$; *Z*, 4; ρ_{calcd} (g cm^{-3}) 1.232; *F*(000) 2560.00; scan mode ω; 2θ max (deg) 55.0; total measured reflections 56752; unique measured reflections 14335; observed reflections 4634 ($I > 3.00\sigma(I)$) ($R_{int} = 0.053$); refined parameters, 769; residue electron density (e$Å^{-3}$), 0.58/−0.28; *R* 0.057; *Rw* 0.077; GOF 0.53.

FAB-MS Experiments. Competitive complexation of cyclen derivative with Li^+, Na^+, and K^+ ions in *m*-nitrobenzyl alcohol was studied by measuring the relative peak intensities of $[cyclen + M]^+$ ions. Since the NaCl complexes with ester-armed cyclens **1a**−**1f** (0.00330 mol/L) were employed, total Na^+ concentration was adjusted by addition of NaCl as 0.00830 mol/L, while the initial concentrations of LiCl and KI were 0.00830 mol/L, respectively. To complete the exchange of Na^+ ion with Li^+ and K^+ ions, *m*-nitrobenzyl alcohol solutions were stirred for 12 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 intensities were averaged over at least 20 scans.

Liquid−Liquid Extraction Experiments. Determination of distribution percentage for each cation was made by adding a $CHCl_3$ solution of the cyclen−NaCl complex (0.0100 mmol in 1.50 mL) to an aqueous mixture of Li^+ and K^+ perchlorates (0.0100 mmol, each in 1.50 mL). After the mixture had been stirred for 2 h, the concentrations of these metal ions in the aqueous phase were determined by atomic absorption or flame spectroscopic method (Exlan Technical Center, Okayama, Japan). We confirmed that negligible amounts of metal perchlorates were distributed into the $CHCl_3$ in the absence of cyclen ligands (<3%).

NMR Binding Experiments. ^{23}Na NMR spectra were recorded with a JEOL LA-300. The chemical shifts indicated in Table 1 mean differences in the chemical shifts of ^{23}Na nuclei observed with and without cyclens, though the observed ^{23}Na signals were broad in all cases. Each complex was dissolved in CD_3CN or C_2D_5OD at a concentration of 0.0100 mol/L.

Determination of Stability Constants. The competitive method was applied to determine stability constants of cyclen−Na^+ complexes. When cryptand [2.2.2] or 15-crown-5 was added to the cyclen−NaCl complex solution, competitive displacement took place slowly and reached equilibrium after a few days. The reported log *K* values[14] were employed in calculation: log *K* = 9.63 in CH_3CN and 8.57 in C_2H_5OH for cryptand [2.2.2] and 4.92 in CH_3CN for 15-crown-5. The displacement process was successfully followed by monitoring ^1H NMR signals for sidearm protons of free and Na^+ ion-bound cyclens. Exceptionally, alcohol-armed cyclen **3** gave the averaged ^1H NMR signals for sidearm protons of free and Na^+ ion-bound cyclens. Since the observed signals shifted upon competitive complexation with 15-crown-5, the shifted values were employed in the calculation of log *K* value. We usually added three different amounts of cryptand or crown ether and averaged the three estimated log *K* values. The reproducibility was confirmed to be 0.04 or better in log scale for cyclens **1a** and **1c**−**1e**, 0.09 or better for cyclen **1f**, and 0.30 or better for cyclens **1b**, **2**, and **3**.

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Supporting Information Available: X-ray crystallographic data for NaCl complex with **1e** and ^1H NMR spectra of NaCl complexes with **1b**−**1e** and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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