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# Chirality Sensing and Size Discrimination of Anions by Macrotricyclic Cyclen–Disodium Complexes**

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Two macrotricyclic ligands composed of two face-to-face octadentate metal chelates were synthesized. These cage-shaped disodium complexes had special recognition ability for various counter anions. Specific chiral dicarboxylates bound to the complexes within the cavity and exhibited chirality induction properties. For instance, *N*-Boc-Asp dianion strongly induced circular dichroism (CD) signals, but *N*-Boc-Glu dianion, which is one carbon longer, did not.

$Na^+$ is an abundant and essential cation in biology and chemistry.[1] Pedersen's discovery of $Na^+$-selective capturing by dibenzo-18-crown-6-ether led to the dawn of supramolecular chemistry,[2] and various molecular switching systems triggered by $Na^+$ capture have since been reported.[3,4] However, there are few reports to date in which $Na^+$ serves as the active center for molecular recognition due to its weak interactions with guest species and high lability. Development of $Na^+$ complexes that can recognize the stereochemistry of anions would create novel regio- and stereoselective reactions because $Na^+$ salts are common ionic substrates in classic organic reactions.

Octadentate cyclens,[5] which are characterized by a cyclen ring and four metal-ligating side arms, are one example of potential candidate ligands for this purpose. These ligands can coordinate alkali, alkaline earth, and lanthanide metal cations to form quadruple-stranded metal helicates. In general, their metal complexes, such as $[\mathbf{1}\cdot Ln]^{3+}$, exist as a racemic mixture of two coordination isomers, $\Delta$ and $\Lambda$ forms, which are distinguished by the helical sense of the propeller structure (Figure 1 a). We previously reported various octadentate cyclen–$Na^+$, $Ca^{2+}$ and $Ln^{3+}$ complexes with chiral carboxylates, such as *N*-Boc-L-proline anion (L-**3**$^-$), coordinated to $Ca^{2+}$ and $Ln^{3+}$ centers to induce circular dichroism (CD) on the absorption bands of their side arm chromophores.[6] However, such chirality induction was not achieved with $Na^+$ complexes due to rapid interconversion of the side chains and decreased stability of the complexes.[7] Cage compounds like cryptands precisely recognize guest molecules by their rigid molecular frameworks.[8] Recently, there have been several reports on macrocyclic cyclens.[9] They and their transition metal complexes have superior molecular recognition abilities compared to non-macrocyclic cyclens.

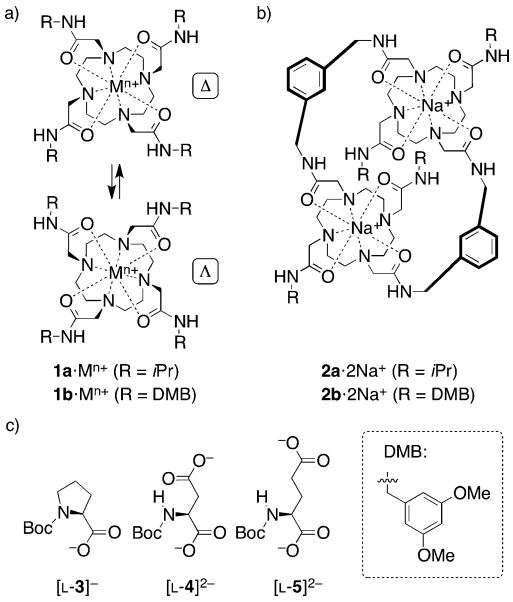


**Figure 1.** a) $\Delta$–$\Lambda$ interconversion of metal–octadentate cyclen complex. b) Macrocyclic ligand based on bis(sodium–octadentate cyclen complexes) in this study. c) Chiral mono- and dicarboxylates for external chirality source in this study.

Here we report the first macrotricyclic ligands based on two octadentate cyclens and the anion recognition properties of their $Na^+$ complexes (Figure 1 b,c). The macrotricyclic ligands **2a,b** contain two amide-type octadentate cyclens joined face-to-face by two *m*-xylyl linkers. Density functional theory (DFT) calculations (BY3LYP/6-31G*) on the $[\mathbf{2a}\cdot Na_2]^{2+}$ complex indicated that helical conformations with homochirality, ($\Delta,\Delta$)- and ($\Lambda,\Lambda$)-forms, have a large enough cavity to encapsulate small molecules (see figure S4 in the Supporting Information).

Ligands **2a,b** were synthesized as shown in Scheme 1. The macrotricyclic framework **8** was constructed by a 2:2 condensation of dichloride **7**[10a] and 1,7-di-*N*-Boc-cyclen **6**[10b] under dilute conditions. Compounds **2a,b** were obtained as free ligands by deprotection of **8** with TFA/$CH_2Cl_2$ and subsequent introduction of the respective amide side chains **11a,b**.[10c,d] Non-macrocyclic ligand **1b** was synthesized as a reference compound.

The crystal structure of $[\mathbf{2a}\cdot Na_2](ClO_4)_2$ (Figure 2, see table S1)[11,12] showed that a ($\Delta,\Lambda$)-disodium complex was formed in the solid state. Counter anions ($ClO_4^-$) were located outside the cavity. This coordination geometry is popular for

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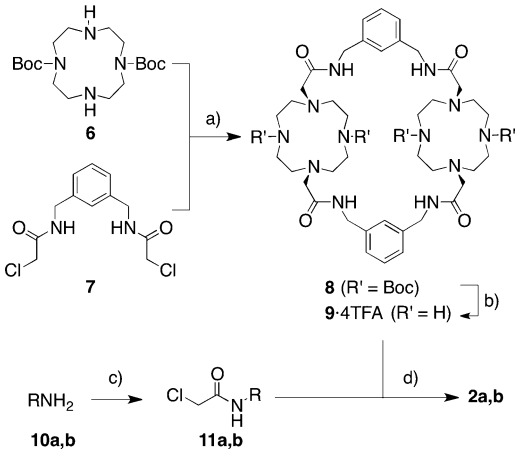


**Scheme 1.** Synthesis of macrocyclic cyclen ligands **2a**–**b**. *Reagents and conditions*: a) $K_2CO_3$, KI, molecular sieves 4 Å, xylene, reflux, 18 h, 14%; b) TFA/$CH_2Cl_2$, RT, overnight, 96%; c) chloroacetyl chloride, $Et_3N$, $CH_2Cl_2$, 0 °C→RT, overnight, 72% (**11a**); chloroacetyl chloride, aq NaOH, 0 °C→RT, overnight, 54% (**11b**); d) $Cs_2CO_3$, acetonitrile, reflux, 6 h, 68% (**2a**), 80% (**2b**).

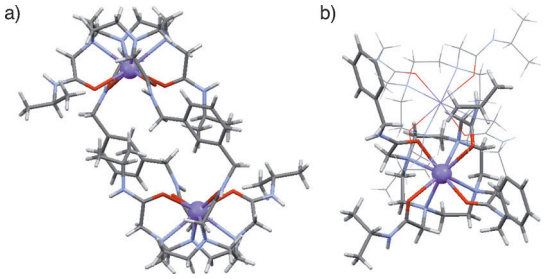


**Figure 2.** Crystal structure of [**2a**·$Na_2$]$(ClO_4)_2$. a) side view; b) the octadentate cyclen portion around a sodium cation (blue). Counter anions and solvents were omitted for clarity.

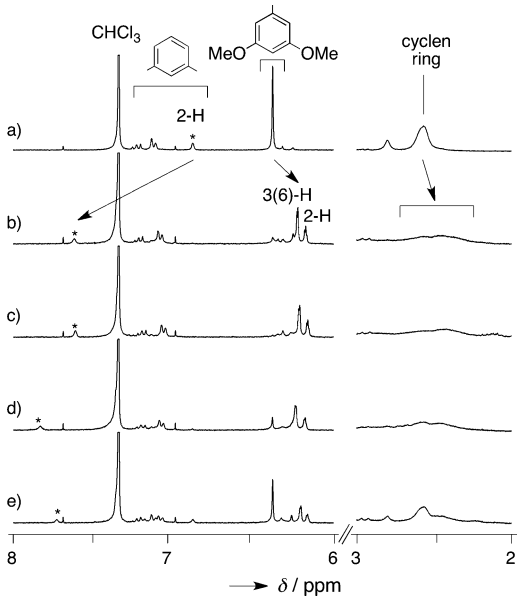


**Figure 3.** Partial $^1$H NMR spectra of **2b** with various sodium salts [300 MHz, 0.4 mM, $CDCl_3/CD_3OD$ (9:1, *v/v*), RT]. a) none; b) $NaPF_6$ (2 equiv); c) L-**3**·Na (2 equiv); d) L-**4**·2 Na (1 equiv); e) L-**5**·2 Na (1 equiv).

octadentate cyclen–sodium complexes with amide side chains,[13] suggesting that the macrocyclic framework does not affect $Na^+$ coordination. It was found that the [**2a**·$Na_2$]$^{2+}$ complex has a sufficient cavity size for anion recognition with two sodium cations at each end, although the isopropyl side chains filled the cavity, causing a distorted framework in the solid state.

Structures of the [**2b**·$Na_2$]$^{2+}$ complexes in solution were analyzed by $^1$H NMR spectroscopy in $CDCl_3/CD_3OD$ (9:1, *v/v*) (Figure 3). The signal for the cyclen ring (2.57 ppm) of [**2b**·$Na_2$]$(PF_6)_2$ is distinctly broadened compared to **2b**, which indicates a slow exchange between (*Δ,Δ*)-, (*Δ,Λ*)-, and (*Λ,Λ*)-isomers. The overlapped peaks of the aromatic protons of the 3,5-dimethoxybenzene moiety were distinctly upfield shifted and separated. A more significant change was observed at the 2-H of the *m*-xylyl linkers, which occurred at 6.88 ppm in the free ligand and 7.61 ppm in the disodium complex. This unusual peak shift is rationalized by the unique position of the proton. Molecular calculations indicate that the complex has enough space for the xylyl groups to freely rotate when it forms the *meso*-structure (*Δ,Λ*), while the 2-H of the xylyl linkers is forced in the direction of the center of the cavity when the complex forms a one-handed helical structure (*Δ,Δ* or *Λ,Λ*) (see figure S4). By using the 2-H proton as a probe, the conformational changes on the macrotricyclic ligand framework can be monitored. When two equivalents of *N*-Boc-L-proline (L-**3**·Na) were added to **2b**, no spectral differences with [**2b**·$Na_2$]$(PF_6)_2$ were found, suggesting that [**2b**·$Na_2$]$^{2+}$ formed similar dinuclear complex structures independent of the counter anions. On the other hand, distinct differences were found in the case of divalent chiral counter anions. Although L-**4**·2 Na and L-**5**·2 Na were hardly soluble in $CDCl_3/CD_3OD$ (9:1, *v/v*), their mixtures with **2b** were soluble in this mixed solvent. The $^1$H NMR spectrum of [**2b**·$Na_2$](L-**4**) showed that the 2-H signal was significantly downfield shifted compared to that of [**2b**·$Na_2$]$(PF_6)_2$. A smaller downfield shift was observed in [**2b**·$Na_2$](L-**5**), with some precipitation of L-**5**·2 Na.

The chiral anion bound with the disodium complex induced circular dichroism (CD) in the absorption region of the dimethoxybenzene moiety (Figure 4). The induced CD observed when L-**4**·2 Na was added to **2b** strongly implied that one of the helical structures was more stable than the other due to the interaction between the chiral counter dianion (L-**4**)$^{2-}$ and the dicationic complex [**2b**·$Na_2$]$^{2+}$. Because the mirror image spectrum was obtained by the addition of D-**4**·2 Na, the chirality of guest anion **4** could be finely transferred to the disodium complex host. As no induced CD was observed with the reference compound **1b** (2 equiv) and L-**4**·2 Na, the macrotricyclic form was effective for CD responses to the absolute configuration of an included chiral guest. Notably, the adduct of L-**5**·2 Na with **2b** showed no induced CD signals, indicating that this macrotricyclic host could precisely discriminate a one-carbon chain length difference in the guest molecular structure.

The binding constant of [**2b**·$Na_2$]$^{2+}$ and (L-**4**)$^{2-}$ in $CDCl_3/CD_3OD$ (9:1, *v/v*) at room temperature was estimated to be 2×

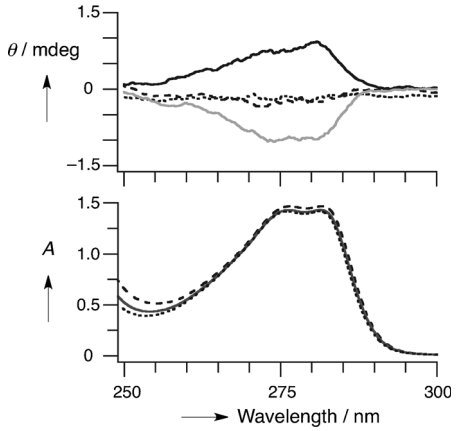


**Figure 4.** Absorption (bottom) and CD (top) spectra of **2b** with various sodium salts [0.4 mM in $CDCl_3/CD_3OD$ (9:1, *v/v*), 0.5 mm quartz cell, RT]. None (– – –), L-**4**·2Na (1 equiv, ——), D-**4**·2Na (1 equiv, ——), L-**5**·2Na (1 equiv, -----).

$10^5\ M^{-1}$ by the integrated peak ratio of the Boc signals in the $^1H$ NMR spectrum at $1.0\times10^{-5}$ M (see figure S5), because complexation equilibrium is slow on the NMR timescale. The complex was stable enough to show the mass peak at *m/z* 1884 for $[(\mathbf{2b}\cdot Na_2)\cdot(L\text{-}\mathbf{4})\cdot H]^+$ by ESI-MS (see figure S6). In the NOESY spectrum, interactions between dimethoxybenzene groups of $[\mathbf{2b}\cdot Na_2]^{2+}$ and the Boc group of $(L\text{-}\mathbf{4})^{2-}$ indicated strong binding of $(L\text{-}\mathbf{4})^{2-}$ to $[\mathbf{2b}\cdot Na_2]^{2+}$, probably by the coordination of the carboxylates to both sodium cations (Figure 5).

In conclusion, we successfully synthesized macrotricyclic octadentate cyclen dimer ligands. These ligands afforded cage-

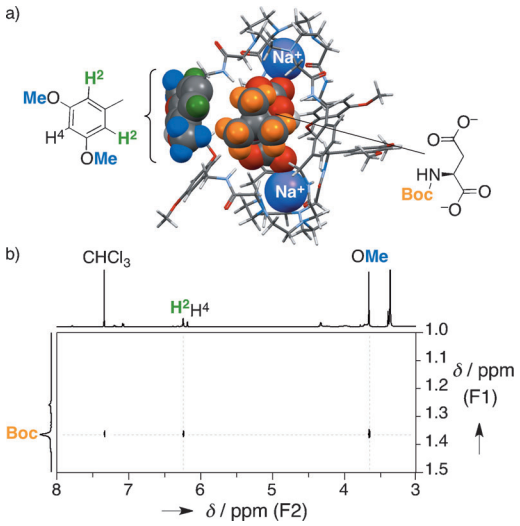


**Figure 5.** a) Results of DFT calculations (B3LYP/6-31G*) and b) partial NOESY spectrum of $[\mathbf{2b}\cdot Na_2](L\text{-}\mathbf{4})$ [600 MHz, $CDCl_3/CD_3OD$ (9:1, *v/v*), RT].

shaped dinuclear $Na^+$ complexes. X-ray crystallographic analysis revealed that the complex formed helical structures around the $Na^+$ ion and adopted the *meso*-($\Delta,\Lambda$) form in the solid state, while DFT calculations indicated that homochiral ($\Delta,\Delta$ or $\Lambda,\Lambda$) forms with an inner cavity were also stable. $^1H$ NMR spectral analyses showed that the disodium complexes changed their conformations dynamically in solution. CD, absorption, and $^1H$ NMR spectral analyses showed the chirality transfer from the bound anions to the complex framework. Dicarboxylates were strongly bound to the sodium complexes within the cavity. Moreover, $(N\text{-Boc-L-Asp})^{2-}$ strongly induced CD, but $(N\text{-Boc-L-Glu})^{2-}$, which is one carbon longer than $(N\text{-Boc-L-Asp})^{2-}$, did not. This superior selectivity was derived from the restricted distance between the two $Na^+$ cations and the directions of the binding sites. This is the first example of chirality sensing by a sodium complex host, and we are now examining a more precise mechanism of anion recognition by the metal complexes using this ligand system.

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[12] CCDC 1017270 ([**2a**·$Na_2$]($ClO_4$)$_2$) 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.

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