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A Magnesium-Selective Ionophore Containing Four Amide Carbonyl Ligands Derived from L-Tartaric Acid and Axial Furano Oxygen Binding Sites

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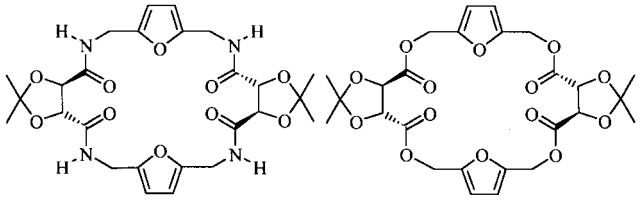
Abstract

Octahedrally converging hexadentate macrocyclic receptors **1** and **2**, based on L-tartaric acid and furan moieties, were synthesized and their complexation properties studied. In this paper, magnesium ion selectivities determined by ISE experiments, chiroptical changes observed by circular dichroism (CD) on complexation, and association constants measured by NMR titration are discussed.

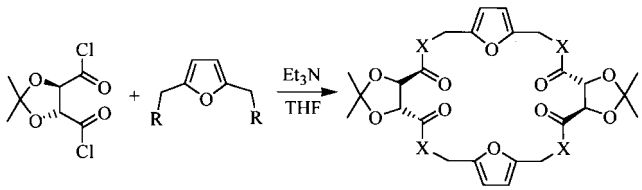
Introduction

For spherical cations, such as alkali metal and alkaline earth ions, and tetrahedral cations, such as ammonium, macrocyclic receptors with dipolar groups that are oriented to converge upon the central cavity should form complexes stabilized by ion-dipole electrostatic interactions [1]. Macrotricyclic cryptands having four bridgehead nitrogen electron pairs oriented tetrahedrally toward the center of the cavity selectively bind the tetrahedral, tetradentate ammonium cation, and when tetraprotonated bind spherical anions of appropriate size, e.g., chloride [2, 3, 4].

By the incorporation of two C_2-symmetrical L-tartaramide moieties into a macrocyclic receptor, the resulting four tetrahedrally oriented amide carbonyl dipoles can selectively bind lithium cations [5, 6, 7]. The following diagram presents a new L-tartaric acid-based tetraamide macrocycle **1** containing two furan-2,5-dimethylene spacer units providing additional axial coordination to produce a distorted octahedral 6-coordinate complex with metal cations. Anologue **2** contains four ester carbonyl ligands and two furano ligands. Furano units have often been introduced as building blocks in synthetic macrocyclic receptors that complex with cations [8, 9].



1 **2**



3 **4** R=NH_2 **5** R=OH **1** X = NH 20% **2** X = O 25%

Scheme 1.

Experimental

Key starting materials are 2,3-*O*-isopropylidene-L-tartaryl chloride, **3** [10] as a C_2-symmetrical dicarbonyl moiety, and 2,5-furandimethanamine, **4** and 2,5-furandimethanol, **5** as spacer. The compound **4** was synthesized from commercially available compound **5** by a three-step process in 40 % overall yield [11]. Chlorination of **5** with thionyl chloride in ethyl acetate at −20 °C gave 2,5-bis(chloromethyl)furan, which was unstable and was thus immediately treated with sodium azide in acetonitrile. The resulting azide was reduced by catalytic hydrogenation in ethanol in the presence of palladium and distilled to provide the diamine **4** as a colorless oil (bp 75 °C at 0.5 mm). Hexaheteromacrocycle **1** was prepared by the treatment of acid chloride **3** with diamine **4** under a high dilution condition in 20 % yield as shown in Scheme 1 [12]. The tetraester macrocycle **2** was obtained in 25% yield using a similar high dilution macrocyclization of **3** with diol **5** [13].

The [2 + 2] compositions of macrocycles **1** and **2** were demonstrated by mass spectrometry. In each of these compounds, the 2,5-furandimethylyl protons produced a pair of doublets in the proton NMR spectrum, demonstrating that these geminal protons are diastereotopic in the chiral macrocycles.

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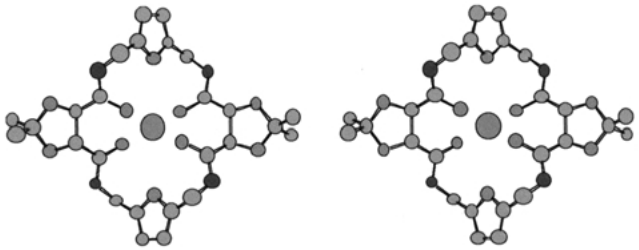

Figure 1. Stereo view of the energy-minimized pseudo-octahedral complex of Mg^{2+} with **1**. Hydrogen atoms omitted for clarity.

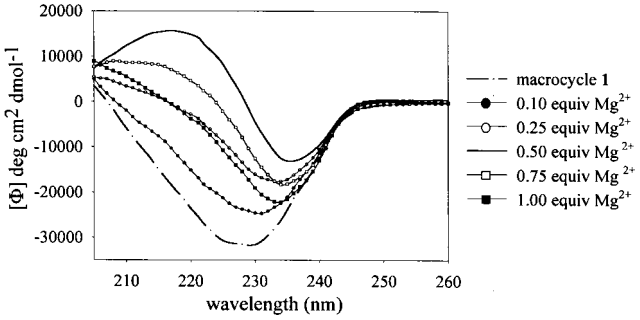

Figure 2. CD spectra of macrocycle **1** (0.125 mM) in acetonitrile at 298 K with various amounts of magnesium perchlorate.

Results and discussion

It has been reported that the magnesium ion exhibits octahedral coordination with four oxygen atoms from the amide functional groups and two nitrogen atoms from the amino groups of *N*,*N*′-diheptyl-*N*,*N*′-dimethylaspartamide in a 1 : 2 Mg^{2+} : receptor complex [14]. It can be assumed that macrocycles **1** and **2** should form 1 : 1 Mg^{2+} : receptor complexes with distorted octahedral coordination of Mg^{2+} by the four oxygen atoms from the amide group and the two oxygen atoms from the furano units. Molecular mechanics calculations indicate that in the most stable conformation of the 1 : 1 Mg^{2+} : receptor complex of **1** all four amide carbonyl oxygens and two furano oxygens pseudo-octahedrally converge towards the Mg^{2+} cation in the molecular cavity, as shown in Figure 1 [15]. The NMR spectral data of **1** with 1 equivalent Mg^{2+} is consistent with a D_2-symmetrical structure (*vide infra*).

The macrocycles **1** and **2** have been tested as magnesium ionophores in PVC membranes containing the plasticizer *o*-nitrophenyloctyl ether (*o*-NPOE) [16]. The magnesium ion selectivities of the resulting electrodes were determined by the separate solution method [17]. Lipophilic solvent PVC membranes containing **1** or **2** gave good potentiometric responses, yet exhibited poor magnesium selectivity over alkali metal ions. The membrane containing **1** gave weaker potentiometric responses to alkali metal ions than the membrane containing ester analogue **2** [18]. Although the lipophilic PVC membrane containing **1** in *o*-NPOE plasticizer could not exclude alkali metal ions, it does discriminate against other alkaline earth metal ions, showing Mg^{2+} ion selectivities over Ba^{2+} and Ca^{2+} by factors of 40 and 3200, respectively [18]. The observed high magnesium ion selectivity over calcium ion is unusual. It is superior to the known magnesium ionophore, 4,13-[bis(*N*-adamantylcarbamoyl)acetyl]-1,7,10,16-tetraoxa-4,13-diazacyclooctadecane which previously showed the highest magnesium ion selectivity over calcium ion, by a factor of 320 [19]. The properties of macrocycle **1** expected from its novel structure were further investigated.

Chiroptical changes caused by complexation of **1** with magnesium ion were measured by circular dichroism. The CD spectrum of **1** shows a negative Cotton effect (CE); CD (C, 0.125 mM; CH_3CN, deg cm^2 dmol^{-1}, 25 °C); $[\theta]_{207}$ 0; $[\theta]_{229}$ −31700; $[\theta]_{253}$ 0. When magnesium perchlorate was added, the magnitude of the CE decreased, and the CD curve became a distinctive bisignate shape at 0.5 equivalents of the added magnesium. The magnitude of CE eventually converged on a spectrum at one equivalent magnesium ion, as shown in Figure 2 [20].

The bisignate CE couplets; CD; $[\theta]_{200}$ +3300; $[\theta]_{217}$ +15660; $[\theta]_{229}$ 0; $[\theta]_{236}$ −13020; $[\theta]_{251}$ 0, apparently arise from exciton coupling. This is caused by the dynamic coupling between the individual furanyl chromophores when they are in close spatial proximity and form a chiral array. This observed negative exciton CD spectrum matches well with the exciton chirality rule expected from *R*,*R*-tartaric acid derivatives having chromophores [21]. It is interesting that free receptor **1** and its 1 : 1 Mg^{2+} : receptor complex only show a negative Cotton effect, whereas negative exciton coupling is clearly observed from the 1 : 2 Mg^{2+} : receptor complex. This was probably formed with 0.5 equivalent magnesium ion, suggesting that the complex is conformationally quite stable and strong. This unusual complexation phenomenon was investigated by means of the NMR titration technique.

Proton NMR spectra of **1** in deuterated acetonitrile taken at temperatures ranging from −40 °C to 50 °C show the number of resonances expected from the symmetry of **1** in a D_2 point group, implying that compound **1** is conformationally mobile. The resonances of geminal dimethyl and methine protons were barely temperature dependent. However, the chemical shift of the amide protons shifted from 7.79 ppm at −40 °C to 7.42 at 50 °C. Furthermore, the signals for 2,5-furandimethylyl diastereotopic protons monotonically changed from a weakly coupled AB spin system ($\Delta\delta v/J_{ab}$ = 3.5, δ_a = 4.43 ppm, δ_b = 4.30 ppm; J_{ab} = 15.0 Hz) at −40 °C to a strongly coupled AB spin system ($\Delta\delta v/J_{ab} < 1$, δ_a = 4.36 ppm, δ_b = 4.35 ppm; J_{ab} = 15.0 Hz) at 50 °C. However, as magnesium perchlorate was added to **1**, the signals became complex and broadened below room temperature, suggesting that the rates of complexation and decomplexation are somewhat slow on the NMR time scale on a 400 MHz spectrometer. Above 30 °C, the amide protons and furanyl protons were observed to be singlets, as expected from the symmetry of the complex. This allowed the association constant for complexation of **1** with Mg^{2+} ion to be determined using standard ^{1}H NMR titration methods [22, 23]. The addition of magnesium perchlorate to **1** in deuterated acetonitrile caused substantial downfield shifts of the amide and furanyl proton resonances, indicating the formation of a complex. Chemical shift changes during the titration of a 5 mM solution of **1** in CD_3CN with a 25 mM

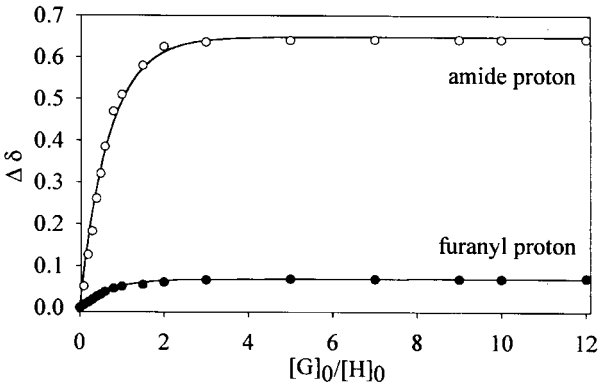

Figure 3. Titration data and calculated curves for amide proton and furanyl proton chemical shifts for **1** ($[H]_0 = 5$ mM) in CD_3CN at 30 °C as a function of increasing amounts of magnesium perchlorate ($[G]_0 = 25$ mM).

solution of magnesium perchlorate changed almost linearly to $\Delta\delta_{max}$ (0.6 ppm for NH, 0.06 ppm for furanyl) up to the 1 equivalent titration point, as shown in Figure 3. The resulting titration isotherms fitted well to a 1 : 1 binding model using established iterative curve-fitting methods [23]. Both titration curves resulted in a reliable association constant (K_a) 13000 ± 2200 M^{-1} at 30 °C. Although such a strong association constant is over the limit of accurate measurement by NMR titration, it clearly indicates that macrocycle **1** with four amide and two axial furanyl ligands can form a very strong complex with Mg^{2+}, as designed. It is reasonable for an amide carbonyl ligand to bind very tightly with magnesium ion by ion-dipole interactions.

In summary, novel macrocycle **1** containing four amide oxygens from two L-tartaric acid moieties and two furanyl oxygens as axial ligand sites has been synthesized, as well as ester analogue **2**. Macrocycle **1** shows unusually high magnesium ion selectivity over calcium ion ($K^{pot}_{Mg,Ca}$ = 3,200) when measured by an ISE experiment. Its strong association constant, K_a 13000 ± 2200 M^{-1} with Mg^{2+} ion was measured by ^{1}H NMR titration in CD_3CN. The L-tartaric acid moiety is a useful building block for dipolar amide carbonyl groups in tetraamide macrocyclic receptors containing two additional axial ligands that converge toward a guest ion in the molecular cavity.

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12. Macrocycle **1** was prepared by simultaneous slow addition of a solution of **3** in THF and a solution of **4** in THF to a stirred solution of triethylamine in THF at rt. The crude product was purified by column chromatography (silica gel, dichloromethane/methanol (95 : 5)), and then was recrystallized from hexane/dichloromethane to give pure **1** as a solid (mp 133.5–136.0 °C) in 20% yield: ^{1}H NMR ($CDCl_3$) δ 7.36 (br t, J = 6 Hz, 4H, N*H*), 6.16 (s, 4H, Ar*H*), 4.60 (dd, J = 15.6, 7.0 Hz, 4H, CH_aH$_b$), 4.43 (s, 4H, C*H*), 4.30 (dd, J = 15.6, 5.3 Hz, 4H, CH$_a$$H_b$), 1.45 (s, 12H, C(C$H_3$)$_2$); ^{1}H NMR ($CD_3CN$, 30 °C) δ 7.52 (br t, 4H), 6.15 (s, 4H), 4.37–4.36 (m, 4H), 4.32 (s, 4H), 1.38 (s, 12H); ^{13}C NMR ($CDCl_3$) δ 169.5, 150.5, 112.6, 108.4, 77.4, 36.0, 25.9; ^{13}C NMR (CD_3CN, 30 °C) δ 170.4, 152.7, 113.6, 109.1, 79.4, 36.6, 26.7; IR (KBr) 3308, 2994, 1667, 1530, 1251, 1215, 1089, 756 cm^{-1}; mass spectrum, m/z (rel intensity) 561 (9), 560 (M^+, 30), 282 (10), 281 (64), 110 (37), 109 (100), 95 (9), 94 (56); Anal. Calcd for $C_{26}H_{32}N_4O_{10}$: C, 55.71; H, 5.75; N, 9.99. Found: C, 55.52; H, 6.01; N, 9.65.
13. As mentioned in the synthesis of **1**, a similar high dilution macrocyclization of **3** with diol **5** resulted in **2** (mp 118.5–121.0 °C) in 25% yield after column chromatography (silica gel, dichloromethane/ethyl acetate (97 : 3)) and then recrystallization from hexane/dichloromethane: ^{1}H NMR ($CDCl_3$) δ 6.42 (s, 4H, Ar*H*), 5.18 (d, J = 13 Hz, 4H, CH_aH$_b$), 5.11 (dd, J = 13 Hz, 4H, CH$_a$$H_b$), 4.73 (s, 4H, C*H*), 1.51 (s, 12H, C(CH_3)$_2$); ^{13}C NMR ($CDCl_3$) δ 168.9, 149.5, 114.3, 112.4, 76.9, 58.8, 26.5; IR (KBr) 3134, 2996, 1760, 1205 cm^{-1}; mass spectrum, m/z (rel intensity) 565 (M^+, 9), 94 (100); Anal. Calcd for $C_{26}H_{28}O_{14}$: C, 55.32; H, 4.99. Found: C, 55.08; H, 5.08.
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18. Membrane compositions: 1 wt% macrocycle **1**, 66 wt% *o*-NPOE and 33 wt% PVC. Electrochemical cell system: Ag; AgCl, 3 M KCl | 0.3 M NH_4NO_3 | test solution | membrane | 0.1 M $MgCl_2$, AgCl; Ag. Mg^{2+} ion selectivities of **1** over metal ions (log $K^{pot}_{Mg,M}$): Cs^+, 1.3; Rb^+, 1.2; K^+, 1.0; NH_4^+, 0.4; Na^+, 0.2; Li^+, −1.3; Ba^{2+}, −1.6; Ca^{2+}, −3.5. Mg^{2+} ion selectivities of **2** over metal ions (log $K^{pot}_{Mg,M}$): Cs^+, 1.9; Rb^+, 1.9; K^+, 1.9; NH_4^+, 1.1; Na^+, 0.6; Li^+, 1.6; Ba^{2+}, −1.3; Ca^{2+}, −2.6.

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