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A flexible dibenzo-O_4S_2-macrocycle: *twist-and-squeeze* type metal binding via synergic action of metal–ligand and metal–π interactions

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Abstract—A 21-membered O_4S_2-donor-macrocycle (**L**) incorporating a dibenzo-subunit was synthesized. From the reaction of **L** with $AgPF_6$, an *endo*-type 1:1 complex $[AgL]PF_6$ (**1**) was obtained. On complexation, the conformation of **L** changes dramatically due to metal–ligand coordination as well as π-interactions between the metal and the dibenzo-subunit from **L**. This unique change in configuration showing a *twist-and-squeeze* type process illustrates how large flexible ligands stabilize complexes through conformational changes.

Biological receptor molecules have structures that are far from rigid, and thus, the folding or twisting of the receptor upon itself has become of increasing interest.[1] As examples, valinomycin[2] and nonactin,[3] natural selective ionophores for K^+, are able to fold in upon themselves to produce an approximately octahedral array. In the area of artificial receptor systems, the conformations of crown-type macrocyclic compounds adjust their conformations as required for optimum binding of cations of various sizes.[4]

Macrocyclic complexes fall into three categories based on the positioning of the metal cation relative to the donor atoms in the cavity of macrocycle. The first category includes the complexes in which the cation fits properly in the cavity of macrocycle. In the second category, the cation is too large to fit into the cavity, and therefore, lies above the cavity of macrocycle. In the last category, the cavity of macrocycle is larger than the cation and usually no solid complex is isolated due to the low reactivity. Very rarely, however, the large macrocycle wraps around the cation[5] or encloses two cations in the cavity.[6] In few cases in which one cation is in the center of the cavity, the host macrocycle becomes somewhat distorted to accommodate the small cation. In fact, this kind of complexation that binds guests less strongly due to the flexible nature of the host (entropy penalty) is ideal as, for example, sensors and carriers in the event that reaction sequences such as 'bind-detect' or 'transport-release' are needed.[7] Hydrogen-bonding, π–π stacking, and cation–π interaction[8,9] are important interactions that stabilize the resulting metallosupramolecules including macrocyclic complexes. These stabilizing forces also affect the transport properties of the related complexes with respect to solvent extraction and membrane transport.[7] Thus, the structure of a flexible macrocycle with such multiple contacts (or interactions) holds great potential for the development of receptors or ionophores in transport systems.

It is difficult to predict the real structure of macrocyclic complexes with multiple contacts. In fact, the larger dibenzo-30-crown-10 offers a bent conformation accommodating K^+ ion in a three dimensional configuration which is quite different from smaller macrocycle analogs.[5] Some calixarene derivatives form stable complexes with metal ions through multiple contacts.[10] Apart from the oxygen-bearing crown-type macrocycles, thia- or thiaoxa-macrocycles frequently show stable products with soft metal ions.[11] We therefore focused our attention on stabilization of the thiaoxa-macrocyclic complexes by multiple contacts. With such considerations in mind, we explored the possibility of generating soft metal coordination products with multiple contacts

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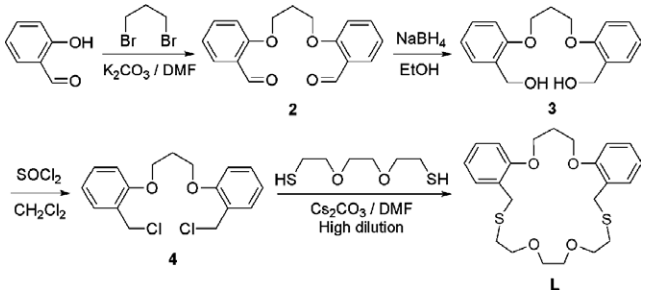
through the modification of the crown units. Our approach involved the attachment of aromatic groups and S/O mixed donors into the large macrocyclic unit. Herein, we present the synthesis and structural characterization of the flexible dibenzo-O_4S_2-macrocycle **L** and its complex, highlighting the unusual behavior of the ligand in stabilizing the complex.

L was synthesized in a four-step reaction (Scheme 1). Dialdehyde **2** was obtained by the reaction of salicylaldehyde with dibromopropane. The reduction of **2** with sodium borohydride afforded dialcohol **3**. Chlorination of **3** with thionyl chloride yielded dichloride precursor **4**.[12] **L** was obtained by coupling reaction for macrocyclization from dichloride **4** and 2,2′-(ethylenedioxy)diethanthiol in the presence of Cs_2CO_3 under high dilution condition in reasonable yield (47%).[13] The ^1H and ^{13}C NMR spectra together with elemental analysis and mass spectral data were clearly in agreement with the proposed structure.

The structure of **L** was also characterized in the solid state by single-crystal X-ray crystallography (Fig. 1). Crystals of **L** were obtained by slow evaporation from the solution of methanol. Without exception, oxygen atoms are oriented in an *endo*-dentate fashion, while sulfur atoms are positioned *exo*-dentate.[11f–j,14] Two aromatic rings and ether linkage O1–C–C–C–O2 are unfolded forming a dihedral angle of 12.83°. Meanwhile, the other aliphatic segment S1–C–C–O3–C–C–O4–C–C–S2 is slightly bent due to its flexible nature and torsion angles between donor atoms show a *gauche–gauche–anti* arrangement [S1–C–C–O3 70.9(2), O3–C–C–O4 70.0(3), and S2–C–C–O4 179.9(2)°]. Two sulfur donors tend to be as far apart as possible (S1···S2 9.474 Å), forcing the shape of the ring cavity into an ellipsoid.



Scheme 1. Synthesis of **L**.

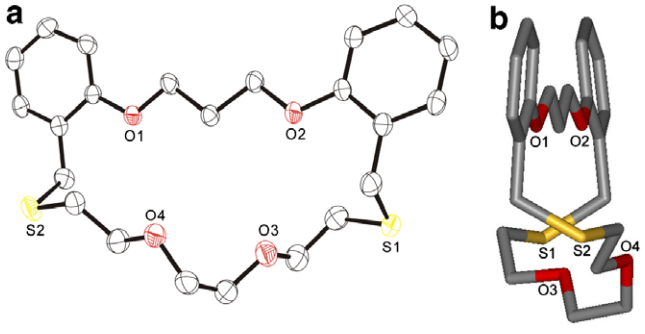


Figure 1. Crystal structure of **L**; (a) front view (ORTEP drawing) and (b) side view (stick drawing).

Complex **1** crystallized in a 1:1 complex of formula [Ag**L**]PF_6 (Fig. 2). A colorless precipitate was obtained from **L** and $AgPF_6$ in dichloromethane/methanol.[15] Single-crystals of **1** suitable for X-ray analysis were obtained by slow evaporation. Ag atom in **1** is in the cavity forming an *endo*-dentate environment. Upon silver(I) binding, **L** undergoes considerable conformational interconversional rearrangement. It is noteworthy that a conformational change in a 21-membered ring is achieved mainly by altering a single torsion angle around S2–C–C–O4, changing from *anti*- [179.9(2)°] to *gauche*-form [61.1(2)°]. In other words, the fragmental interconversion followed by twisting of the ring rendered the sulfur donors pointing inward and, consequently, all donors become a part of the complexation. The Ag atom is four-coordinated with the S_2O_2 donor set, in which each donor is located at the four corners of the least-square plane within 0.13 Å deviation. The S–Ag–S bite angle [147.2(3)°] is considerably large due to the additional interactions of Ag···O1 [3.370(2) Å] and Ag···O2 [3.389(2) Å]. Interestingly, **1** adopts a three-dimensional conformation because of the highly twisted structure that **L** adopts upon complexation. By comparing the dihedral angles between two aromatic rings in free **L** [12.8(1)°] and in its silver(I) complex **1** [73.2(1)°], we observe what resembles a *twist-and-squeeze* conformation. In fact, inspection of the folded structure of **1** reveals the additional interactions between the silver atom and the aromatic π-system [Ag···C4 3.166(3), Ag···C9 3.127(3), Ag···C18 3.251(3), and Ag···C23 3.254(3) Å]. Each silver to carbon interaction is at the short end of the range of literature values for the silver–π interaction (3.1–3.7 Å).[9] It is conceivable that a combination of silver(I) coordination with the S_2O_2 donor set and the pair η^2-type π-interactions would lead to the unique molecular folding that occurs upon complexation with the flexible ligand **L**. With respect to anion coordination ability, the preferred 3D structure of **1** is also due to the weak affinity of PF_6^- ion toward the silver(I) center, allowing the approach of the dibenzo group to form the *twist-and-squeeze* structure. The affinity of silver(I) toward **L** in 1:1 ratio was also observed by ESI-mass measurement: $[Ag\mathbf{L}]^+$ (*m*/*z* 541.9). Recently, we were able to elucidate and visualize the stabilization of the disilver(I) complex of calix[4]-bis-thiacrown by the *chopsticks-type* π-coordination process by comparing the dihedral angles of two opposite aromatic rings of 1,3-alternate calix[4] units upon complexation.[10g] To the best of our knowledge, 1:1 *endo*-type complexes of large mixed-donor macrocycles, in which the ligand is distorted in a similar manner, have not been reported.

For comparison with this in solution, NMR titration was carried out for the parallel system in CD_3CN (Fig. 3). The signals of the six methylene (H_{1-6}) and the aromatic (H_{a-d}) protons in **L** were well resolved and identified. The titration curves [plotting $\Delta\delta$ (ppm) vs added equivalents of silver(I)] for each proton clearly

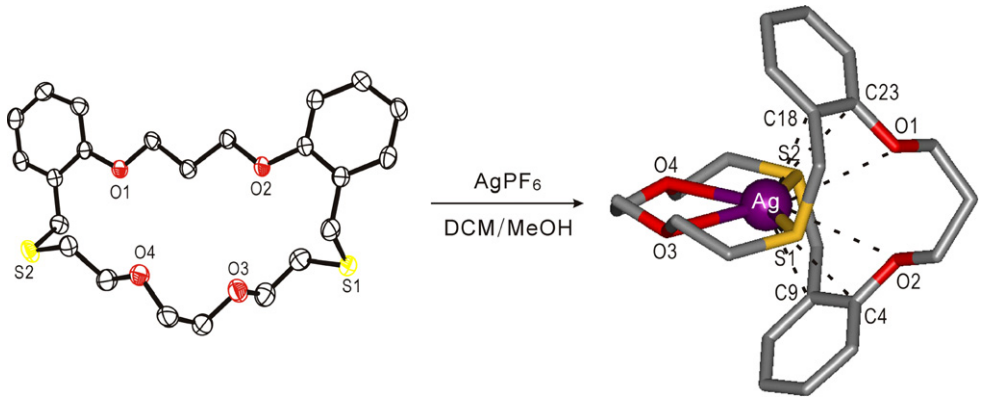


Figure 2. Crystal structures of **L** (left, ORTEP drawing) and its silver(I) complex 1, $[AgL]PF_6$ (right, ball-stick drawing); noncoordinating anions are omitted for clarity. Selected bond lengths [Å] and angles [°]: Ag–S1 2.478(1), Ag–S2 2.468(1), S2–Ag–S1 147.2(3), Ag–O3 2.606(2), Ag–O4 2.661(2), O1–Ag–O2 58.7(1), S1–Ag–O3 75.1(1), S2–Ag–O4 74.4(1).

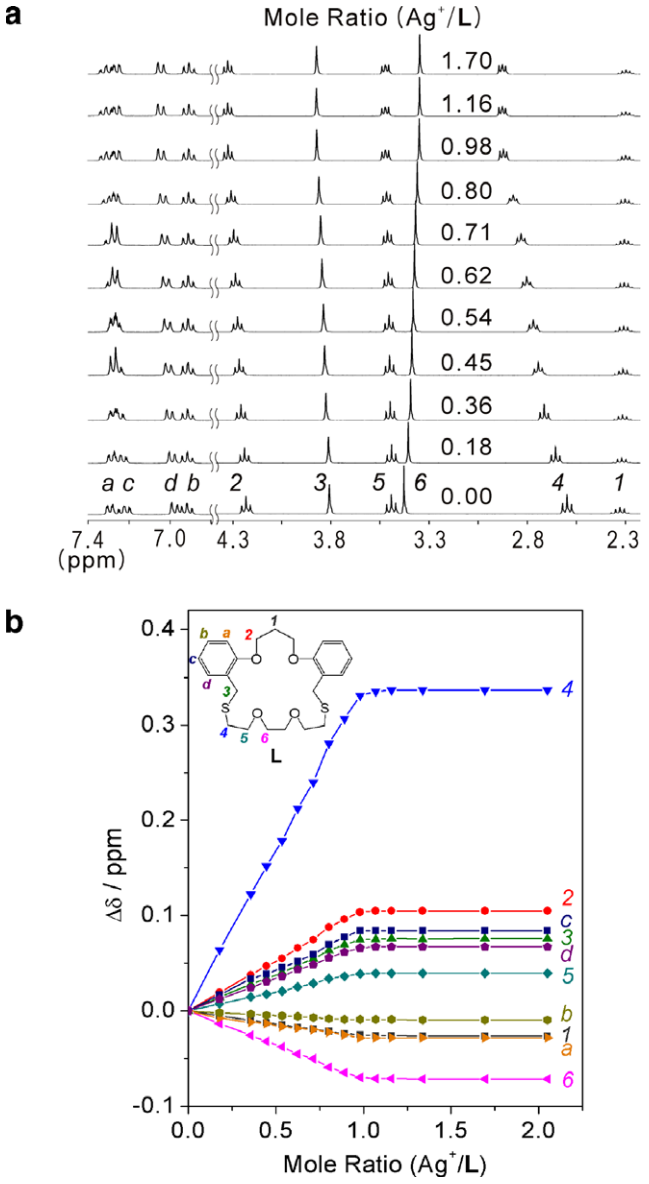


Figure 3. (a) Aliphatic region of ^1H NMR spectra of **L** by stepwise addition of $AgPF_6$ and (b) the ^1H NMR titration curves for **L** with $AgPF_6$ in CD_3CN.

show an inflection point at mole ratio (Ag^+/**L**) of 1.0, indicating the stoichiometry for the formation of the complex is 1:1 in solution, which is the same as that of the solid state. However, the titration curves were very sharp, and consequently, the stability constant was too high to be calculated using the EQNMR[16] least-square nonlinear fitting procedure. The order of magnitude of the chemical shift variation for the aliphatic region is H_4 ($\Delta\delta$: 0.337 ppm) $\gg H_2$ (0.105 ppm) $> H_3$, H_6 (0.072–0.076 ppm) $> H_5$ (0.040 ppm) $> H_1$ (0.026 ppm). Upon complexation, silver(I) causes a much larger downfield shift for the H_4 peak than for those of H_1, H_2, H_5, and H_6. Thus, silver(I) appears to be more strongly coordinated by S donors, while the O donors interact with the silver(I) relatively weakly, once again as in the solid state. For almost all of the aromatic proton signals, the silver(I)-induced shifts ($\Delta\delta$: 0.009–0.084 ppm) and 1:1 break point were also observed due to the Ag–π interactions. Notably, all the NMR data in Figure 3 agree with the binding mode in the solid state, suggesting that structure **1** is also retained in solution.

In summary, we have described the synthesis of a 21-membered dibenzo-O_4S_2 macrocycle with a flexible nature. We have determined the structural characteristics of its silver(I) complexation in both the solid and solution states. These results clearly indicate that a synergic cooperation of multiple contacts results in a flexible macrocycle with the highly organized structure. Thus, the conformational flexibility and aromatic subunits of larger macrocyles offer another potential design tool for engineering new receptors with preprogrammed properties.

Supplementary crystallographic data associated to **L** and **1** have been deposited at the Cambridge Crystallographic Data Centre, CCDC Nos. 645648 and 645645. Copies of the data can be obtained free of charge on application to CCDC, 12 Union road, Cambridge CB2 1EZ, UK (fax: +44 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk), or electronically via www.ccdc.cam.ac.uk/data_request/cif.

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13. *Synthesis of* **L**: Cesium carbonate (6.01 g, 18.45 mmol) were dissolved in DMF (1000 mL) in a 3-L round-bottom flask. 2,2′-(Ethylenedioxy)diethanthiol (2.23 g, 12.3 mmol) and 2,2′-(propyleneoxy)bis(benzyl chloride) (4.0 g, 12.3 mmol) were dissolved in DMF (30 mL) and this solution was added to a 50-mL glass syringe. Under a nitrogen atmosphere, the contents of the syringe was added dropwise (a rate of 0.6 mL h^{-1}) into a DMF solution of Cs_2CO_3 at 45–50 °C for 50 h. The reaction mixture was kept for a further 10 h with rapid stirring, allowed to cool to room temperature, then filtered. The filtrate was evaporated and the residue was partitioned between water and dichloromethane. The aqueous phase was separated and extracted with two further portions of dichloromethane. The combined organic phases were dried with anhydrous sodium sulfate and then evaporated to dryness. Flash column chromatography on silica gel using 10% ethyl acetate/*n*-hexane as the eluent led to the isolation of **L** as a colorless crystalline product in 47% yield. Mp 67–70 °C. $C_{23}H_{30}O_4S_2$ (434.61): Anal. Calcd: C, 63.56; H, 6.96; S, 14.76. Found: C, 63.72; H, 7.10; S, 14.64. IR (KBr) 2861, 1607, 1496, 1460, 1243, 1123, 1104, 1047, 1014, 755 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.34$–6.87 (m, 8H, Ar), 4.23 (t, 4H, OCH_2), 3.83 (s, 4H, $ArCH_2$), 3.53 (t, 4H, SCH_2CH_2O), 3.48 (s, 4H, OCH_2CH_2O), 2.64 (t, 4H, SCH_2CH_2O), 2.39 (m, 2H, $OCH_2CH_2CH_2O$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) 156.46, 130.65, 128.27, 127.54, 120.95, 111.35, 71.08, 70.37, 64.99, 30.99, 30.30, 29.37 ppm. ESI-MS *m*/*z* 435.7 (MH^+).
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15. Complex **1**: Mp (decomp.) >225 °C. [Ag**L**]PF_6: Anal. Calcd: C, 40.18; H, 4.40; S, 9.33. Found: C, 40.27; H, 4.67; S, 9.40. IR (KBr) 2877, 1597, 1496, 1471, 1455, 1294, 1243, 1112, 992, 842 (PF_6^-), 755, 559 cm^{-1}. ESI-MS *m*/*z* 541.9 $[Ag\mathbf{L}]^+$.
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