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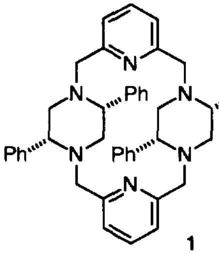
Polyaza Macrocycles Containing the Piperazine Ring as a Semi-Flexible Moiety

Kaoru Fuji,* Kiyosei Takasu, Hisashi Miyamoto, and Kiyoshi Tanaka
Institute for Chemical Research, Kyoto University, Uji 611, Japan.

Tooru Taga
Faculty of Pharmaceutical Sciences, Kyoto University, Sakyo-ku, Kyoto 606-01, Japan

Abstract: Azamacrocycles **1**-**4** were synthesized from **9** in 20-30% overall yields. Compounds **1** and **2** extracted some metal ions into organic solvents, but **3** and **4** did not. The crystal structure of the Ag(I) complex of **1** has been determined.

Polyaza macrocycles have received much attention as receptors of both organic anions[1] and metal cations.[2] It is widely accepted that the size of the macrocyclic ring is an important factor in controlling metal ion selectivity.[3] It is also reported that metal ion selectivity is regulated more by the chelate ring size than by the ring size of polyaza macrocycles.[4] In 1982, Ramasubbu and Wainwright described the incorporation of the piperazine unit in 1,4,7,10-tetra-azacyclododecane to circumscribe Ni(II) rigidly.[5] Since that time, several azamacrocycles structurally reinforced by the piperazine unit have been synthesized for metal selective ligands.[6] Here, we report the syntheses of new polyaza macrocycles **1**-**4** containing (2*R*,5*R*)-diphenylpiperazine as a structural unit, where 2,5-*cis*-diphenyl groups provide a hydrophobic nature as well as additional structural reinforcement of the macrocyclic ring, and extraction of metal ions by **1** and **2** into chloroform. The 18-membered ligand **5** binds to Pb(II).[6a] Lithium cation is selectively extracted by a cyclophane-type macrocycle **6**.[6c] However, none of the polyaza macrocycles structurally reinforced by piperazine rings are reported to coordinate to Ag(I).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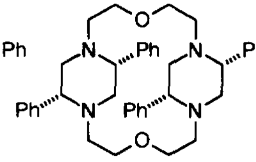
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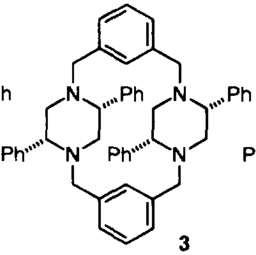
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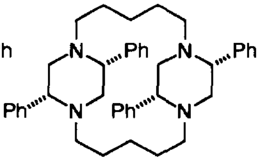
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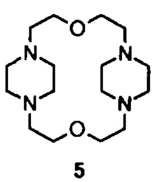
Synthesis of **1**[7] starts from acylation of (2*R*,5*R*)-1-*tert*-butoxycarbonyl-2,5-diphenylpiperazine (**9**)[8] with 2,6-pyridinedicarbonyl dichloride to give **10** in 84% yield after acid hydrolysis. Acylation of **10** with 2,6-

pyridinedicarbonyl dichloride was performed under high dilution conditions with Cs_2CO_3 as a base to give **11** in 52% yield. Reduction of **11** with aluminum hydride gave **1** in 63% yield. Other macrocycles **2** - **4** were synthesized in a similar manner to that for **1** in 20 -30% overall yield from **9**.

Preliminary results of metal 2,4-dinitrophenolate extraction into chloroform showed that **1** could extract Ag(I) , Hg(I) and (II), Cu(I), Tl(I) and **2** extracted Ag(I) and Hg(I), while the other two macrocycles **3** and **4** did not extract any of metal cations tested.[9] It was suggested that the presence of a hetero atom in the chain connecting two piperazine rings was indispensable for metal binding. The Ag(I) complex of **1** was isolated from a mixture of **1** and $AgClO_4$ in CH_2Cl_2, and the crystal structure of the complex was determined (Figure 1a).[10]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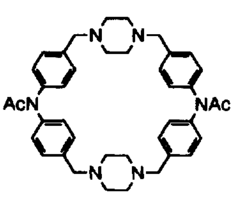
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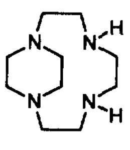
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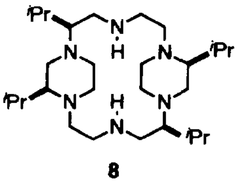
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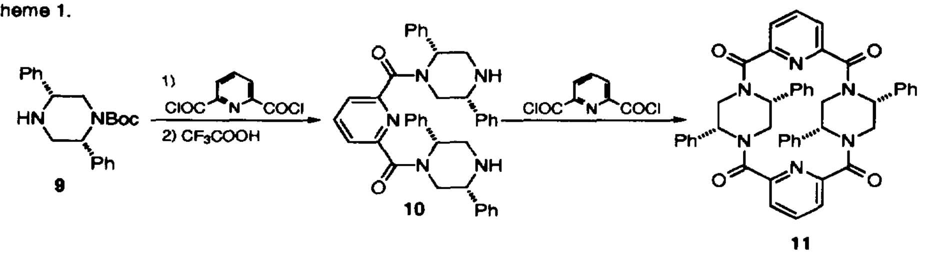
Scheme 1.



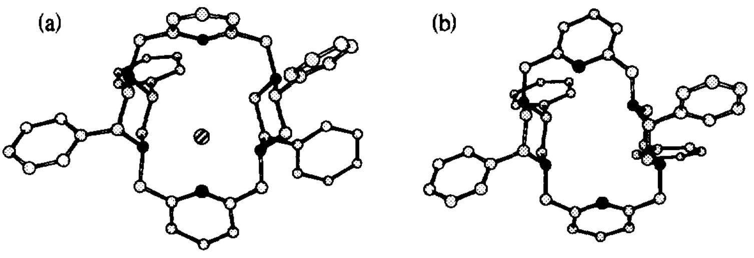


Figure 1. (a) Crystal structure of the complex $(1{\bullet}Ag)^+ClO_4^-{\bullet}CH_2Cl_2$. Hydrogen atoms, ClO_4^-, and CH_2Cl_2 are omitted for clarity. (b) The lowest energy conformation of **1** calculated by MacroModel (ver 4.5). Hydrogen atoms are omitted for clarity.

Both piperazine rings exist in chair form. The piperazine ring of the Ni(II) complex of 7 and those of the dinuclear Cu(II) complex of 8 are reported to assume the boat conformation.[6b,d] As clearly seen from the crystal structure, three lone pairs in the southern hemisphere of the macrocyclic ring are located and pointing suitably to coordinate to Ag(I) and those in the northern hemisphere are exposed outside of the ring. Molecular mechanics (MM) calculations[11] on the free host 1, however, gave another structure as shown in Figure 1b as the lowest energy conformation, where one of the piperazine rings flips to an alternative chair conformation. Thus, it is assumed that the reorganization of the macrocycle 1 operates to bind to specific metal cations (induced fit). The most stable conformation of the macrocycle 4 calculated by MM[11] is almost identical with that of the solid state determined by X-ray analysis (Figure 2),[12] which supports the validity of the calculation for 1.

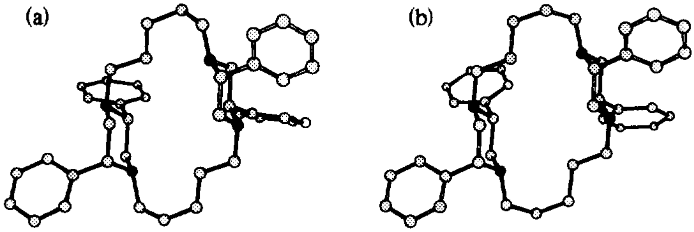


Figure 2. (a) Crystal structure of 4. (b) The lowest energy conformation of 4 calculated by MacroModel (ver 4.5). Hydrogen atoms are omitted for clarity.

Complexation of 1 with Ag(I) caused downfield shifts for all of the protons but one in the aromatic region in ^1H NMR spectrum, a part of which is shown in Figure 3. Two distinct triplets (δ 7.19 and 7.59, 1H each, J = 7.7 Hz) appeared in the complex. These observations also indicate the incorporation of the metal ion into the host 1 in solution, in such a way as observed for the solid state, where the complexed and the uncomplexed pyridine rings both exist. This means that the rapid equilibrium between the complexed and the uncomplexed macrocycle 1 is not established on the NMR time scale.

In conclusion, we have synthesized polyaza macrocycles containing piperazine units as a partially flexible moiety, which extracted several metal cations including Ag(I) into organic solvents, and showed that one of the piperazine rings in 1 was flipped to an alternative chair conformation to bind with Ag(I).

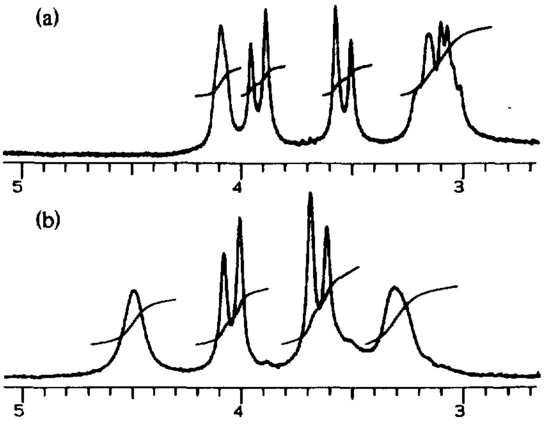


Figure 3. ^1H NMR spectra of the δ 3 to 5 ppm region in $CDCl_3$ at 25 °C. (a) Free host 1 and (b) the 1 : 1 mixture of $AgClO_4$ and 1.

References and Notes

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9. The following metal ions were tested: Li(I), Na(I), K(I), Ba(II), Al(III), Tl(I), Pd(II), Cu(I) and (II), Ag(I), Au(I), Au(III), Zn(II), Cd(II), Hg(I) and (II), Cr(II), Mn(II), Fe(II) and (III), Co(II), Ni(II), Pb(II).
10. Crystal data: Orthorhombic, space group $P2_12_12_1$, a = 18.608(14), b = 19.456(12), c = 12.438(23) Å, V = 4503.0 $Å^3$, Z = 4, Dcalc = 1.438 g cm^{-3}. The structure was refined to R = 0.099, Rw = 0.093, and S = 9.61. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.
11. The MacroModel / MM2* (version 4.5) force field was used. See: Mohamdi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Canfield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440.
12. Crystal data: Orthorhombic, space group $P2_12_12_1$, a = 19.028(3), b = 18.943(3), c = 10.026(2) Å, V = 3613.8 $Å^3$, Z = 4, Dcalc = 1.126 g cm^{-3}. The structure was refined to R = 0.074, Rw = 0.082, and S = 3.05. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.

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