Synthesis and Anion Binding Ability of Metacyclophane-Based Cyclic Thioureas

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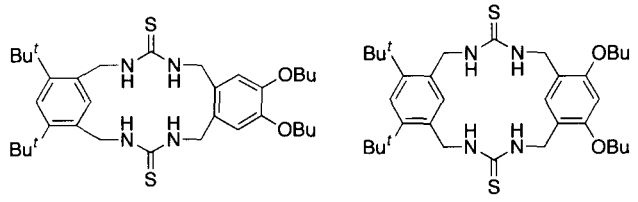
Cyclophanes having two thiourea groups were synthesized and their anion binding ability was examined by titration method using ^{1}H-NMR spectroscopy. Strong and selective anion binding of the preorganized cyclic receptors was observed in the general order of $H_2PO_4^- > CH_3COO^- > Cl^- > HSO_4^- > Br^-$.

The disign of neutral anion receptors is of current interest due to their possible applications to selective ion detective sensors in biological systems.[1] It is well known that urea and thiourea groups bind various anions through hydrogen bonding,[2] and several receptors possessing these functional groups and suitable spacers such as benzene,[3] cyclohexane,[4] tertiary amine,[4] calixarene,[5] porphyrin,[6] dibenzacridone,[7] and xanthene[8] have been developed. However, there seems to be no report, to our knowledge, on cyclic receptors having urea or thiourea groups as a part of the macrocyclic frameworks, despite the fact that the binding groups would be preorganized to bind a guest anion. Here we report the synthesis of metacyclophane-based thioureas **1**-**4** having two thioureido groups as the bridging unit and their binding ability and selectivity toward several anions.



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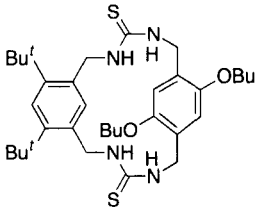

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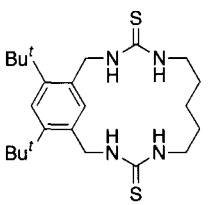

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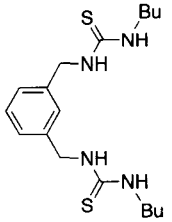

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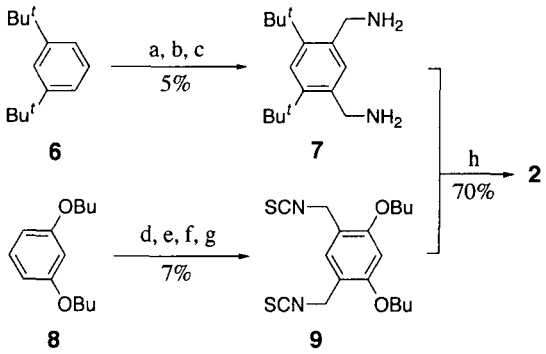
Cyclic receptors **1**-**3** were designed to fix two thiourea groups with relatively rigid orthometa, metameta, and metaparacyclophane structure, respectively. *tert*-Butyl and butoxy groups were introduced to increase their solubility in organic solvents. Methylene bridged metacyclophane **4** was prepared in order to examine the effect of flexibility of the macrocyclic ring. Acyclic compound **5** was chosen as a reference, which was shown to bind selectively to dihydrogenphosphate anion in solution[3b] and sulfate anion in PVC-based membrane for ion-selective electrode.[3c]

Host **2** was prepared as shown in Scheme 1. Namely, diamine **7** was obtained by chloromethylation of di-*tert*-butylbenzene (**6**) followed by the Gabriel synthesis. 1,3-Dibutoxybenzene was transformed into diisothiocyanate **9** through a dinitrile in four steps. Cyclization reaction between **7** and **9** was carried out in



a) CH_3OCH_2Cl, dioxane, HCl (g); b) potassium phthalimido, DMF; c) $H_2NNH_2 \cdot H_2O$, EtOH; d) ICl, AcOH; e) CuCN, HMPA; f) $(i\text{-Bu})_2AlH$, toluene; g) NaOH, CS_2, H_2O/THF then 30% H_2O_2; h) $CHCl_3$, high dilution.

Scheme 1.

$CHCl_3$ at 60 °C under high dilution condition to give cyclophane **2** in 70% yield. Other hosts **1**, **3**, and **4** were prepared in a similar way by the reaction of appropriate diamine and diisothiocyanate.[9]

The association constants (K_a) of these hosts with several guest anions were determined by titration method using ^{1}H-NMR spectroscopy in DMSO-d_6. Addition of a guest anion to a DMSO-d_6 solution of the receptor **1**, **4**, and **5** resulted in large downfield shifts of the NH resonances at room temperature, which is consistant with the formation of hydrogen-bonded complexes. On the contrary, the ^{1}H-NMR spectrum of metametacyclophane **2** exhibited signals both due to the free host and complex at 30 °C, indicating that the equilibrium of complexation is slow on the NMR time-scale. For example, in the presence of tetrabutylammonium dihydrogenphosphate the two NH proton signals of the complex (δ 9.2, 9.6) appeared downfield relative to those of the host (δ 7.7, 7.9) by 1.5-1.7 ppm. However, at 60 °C the NMR signals were averaged owing to the rapid equilibrium. Therefore, all titration experiments were carried out at this temperature following the chemical shift change of the inner aromatic proton and NH protons. The possibility of self-association[3b, 8b, 10] of the hosts was excluded by the absence of concentration dependence of the chemical shifts of the hosts. 1:1 stoichiometry of the complexes was checked by the Job's plot for complexation between **2** and dihydrogenphosphate and acetate anions. The association constants thus obtained are summarized in Table 1.

The data in Table 1 show that cyclic thioureas **1**, **2**, and **4** bind anions stronger than acyclic compound **5** does. On the contrary, metaparacyclophane **3** does not show any binding ability toward the anions examined. Among the cyclic hosts, the association constants of orthometa isomer **1** are larger than those of metameta

Table 1. Association constants (K_a)[a] of hosts **1**, **2**, **4**, and **5** with anions[b]

anion[b]	1	2	4	5
$H_2PO_4^-$	12000	2500	4800	520
CH_3COO^-	2200	390	560	110
Cl^-	120	14	54	7
HSO_4^-	19	2	4	1
Br^-	12	<1	3	<1

[a] $mol^{-1}dm^3$, [b] in DMSO-d_6 at 60 °C, [c] Counter-ion: Bu_4N^+.

isomer **2** and metacyclophane **4**. Figure 1 illustrates the structure of a complex of model compound **10** of orthometa isomer **1** with dihydrogenphosphate anion optimized by AM1[11] calculations. As shown in Figure 1, the thioureido groups adopt a trans-trans conformation. Moreover, the anion perches on the four NH groups oriented to the same direction and bridges the two thiourea groups. Therefore, the strong binding ability of orthometa isomer **1** can be ascribed to the shorter distance between the two thiourea groups than those of **2** and **4**. Although the K_a values of cyclic hosts **1**, **2**, and **4** are larger than those of acyclic **5** first reported by Umezawa et al.,[3b] their selectivities are similar to that of **5**. Thus **1**, **2**, and **4** bind $H_2PO_4^-$ most strongly followed by CH_3COO^-, Cl^-, HSO_4^-, and Br^-.

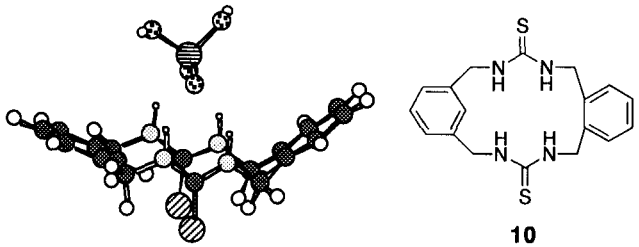


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Figure 1. AM1-calculated structure of a complex of model compound **10** with dihydrogenphosphate anion.

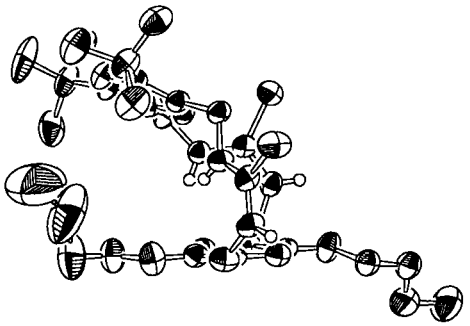

Figure 2. Crystal structure of metaparacyclophane **3**. Hydrogen atoms except for those of NH and the solvent molecules (DMSO) are omitted for clarity.

In order to understand the absence of anion binding ability of metapara isomer **3**, an X-ray crystallographic structure analysis of **3** was undertaken.[12] Figure 2 shows the crystal structure of **3**. In solid state, two thiourea groups of **3** adopt a trans-cis geometry which is not suitable for anion-binding. In addition, in the ^{1}H-NMR spectrum of **3** (DMSO-d_6) the inner aromatic proton (δ 6.39) on the meta-bridged benzene ring and the NH protons (δ 6.31) closer to this aromatic ring displayed a remarkable upfield shift compared to the corresponding protons of other receptors. Since these upfield shift is attributed to the shielding effect of the para-bridged benzene ring, it is deduced that the predominant conformation of **3** in solution is similar to the one found in solid state. Consequently, the absence of binding ability of **3** is ascribed to the unfavorable conformation of the thioureido groups for binding an anion.

In summary, we have synthesized several cyclic thiourea receptors and demonstrated their strong binding ability and high selectivity to $H_2PO_4^-$ anion.

References and Notes

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9 **1**: mp 268-270 °C (dec.), **2**: mp 194-196 °C, **3**: mp 243-245 °C, **4**: mp 268-270 °C. Detail of the preparation of **1**-**4** will be reported in a full paper.

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11 Calculations were done using SPARTAN ver. 5.0 program package; Wavefunction Inc., Irvine, CA.

12 Crystal data for **3**: $C_{34}H_{52}N_4O_2S_2 \cdot 3DMSO$, 0.45 × 0.30 × 0.30 mm, f_w = 847.30, triclinic, space group $P\bar{1}$, a = 14.408(1) Å, b = 17.467(1) Å, c = 10.089(7) Å, α = 93.08(6)°, β = 108.44(5)°, γ = 92.71(6)°, V = 2400(3) Å^3, Z = 2, D_c = 1.173 g/cm^3, temperature 296 K, R = 0.073, R_w = 0.210, and GOF = 1.05; number of unique reflections = 11005.