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Synthesis and dual binding character of novel macrocyclic thiourea derivatives

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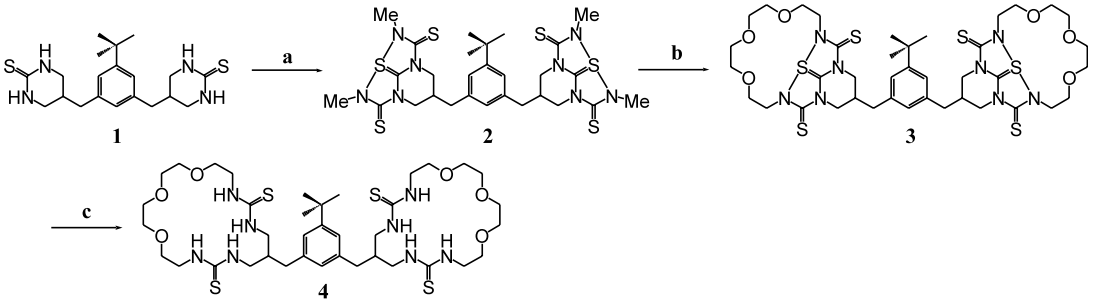
Abstract—Novel macrocyclic thiourea derivative was synthesized, and their ambident binding ability toward dihydrogenphosphate anion and several cations was evaluated by NMR titration and Meisenheimer test.

The design and synthesis of neutral anion receptors is of current interest due to their possible application to ion sensors such as ion-selective electrodes and optodes.[1,2] The relatively strong hydrogen bonding formed from urea and thiourea groups has been used in the development of neutral receptors. Because the hydrogen bond has a directional character, correct orientation of the hydrogen bond makes the selective anion recognition possible. In general, thiourea derivatives have stronger anion-binding ability than that of the corresponding ureas[3] due to the higher acidity of thiourea derivatives.[4,5] For example, Umezawa et al. achieved strong complexation of the receptors tethered by a rigid xanthene spacer toward the dihydrogenphosphate anion by using thiourea groups having acidity-enhancing substituents.[6] Tobe et al. reported that several anions were selectively captured by cyclic thiourea.[7] Recently, we have reported the effective synthesis of cyclic thiourea derivatives by using bond-character of hypervalent sulfur included to 10-*S*-3 tetraazathiapentalene derivatives.[8,9] In this paper, we report the synthesis of novel cyclic compounds having two rings containing oligoethyleneglycol chain and thiourea moieties utilizing bond character of hypervalent sulfur and their binding ability toward dihydrogenphosphate anion and several cations.

The synthesis of **3** and **4** are shown in Scheme 1. Tetraazathiapentalene derivative **2** was prepared by the procedure reported by us previously.[8] Dithiourea **1** was treated with 4 equiv. of *n*-butyllithium, 2 equiv. of phenacyl chloride, and 6 equiv. of methyl isothiocyanate to give **2** in 45% yield. Reaction of **2** with 3,6,9-trioxaundecane-1,11-diisothiocyanate afforded **3**



Scheme 1. *Reagents and conditions*: (a) i. *n*-BuLi, THF, 0°C, 3 h, ii. $PhCOCH_2Cl$, THF, reflux, 5 h, iii. MeNCS, THF, rt, 15 h, 45%; (b) 3,6,9-trioxaundecane-1,11-diisothiocyanate, benzene, reflux, 56%; (c) aq KOH, EtOH, reflux, 15 h, 69%.

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in 56% yield. Then, **4** was obtained by alkaline hydrolysis of **3**.

The binding ability of **4** for anion was investigated by ^{1}H NMR spectroscopy. Addition of tetrabutylammonium dihydrogenphosphate as a guest anion to a DMSO-d_6 solution of the receptor **4** resulted in downfield shifts of the NH resonances at room temperature, which is consistent with the formation of hydrogen-bonded complex. The resulting binding curve (Fig. 1) and Job's plot[10] (Fig. 2) clearly demonstrated the 1:2 stoichiometry of the complex. The association constant was 3.94×10^5, which was calculated by nonlinear least-squares analysis.[11]

Then we turned our attention to the cation binding ability of **3**, **4**, and **5** by the technique reported by Htay.[12] MOH (M = Li, Na, K, NH_4) were added as guest cations into the solutions of trinitrobenzene and receptors **3** and **4**, the color of the solutions immediately changed (Table 1). The color changes indicated the formation of deep-red Meisenheimer complexes by the nucleophilic addition of free hydroxide ion to trinitrobenzene (Scheme 2).[13] These results suggested the complexation of receptors **3** and **4** with these cations.

The receptor **4** having two thiourea rings showed excellent cation binding ability, and the cation binding ability decreased in the order of **4**>**3**>**5**.[14] As for the cation

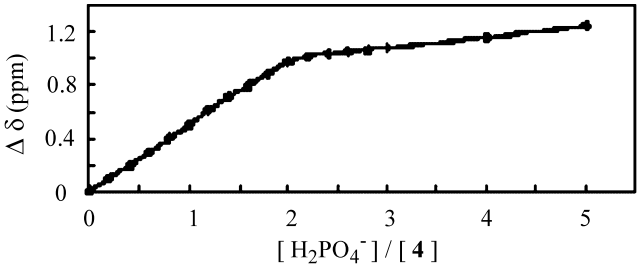


Figure 1. Change of ^{1}H NMR chemical shift of a NH proton in the thiourea moieties of **4** by the addition of $H_2PO_4^-$ in DMSO-d_6.

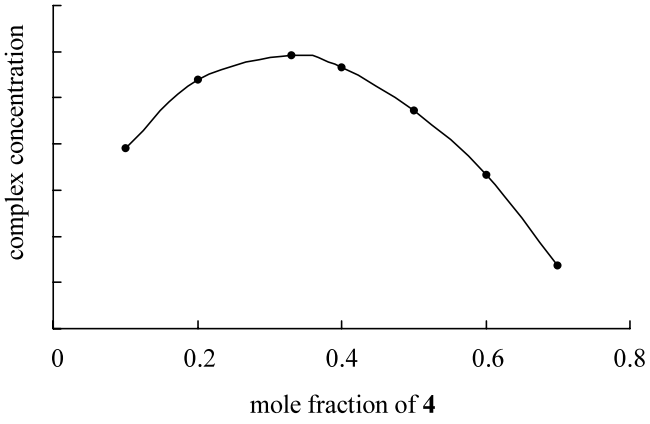
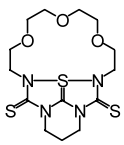


Figure 2. Job's plot of receptor **4** with the dihydrogenphosphate anion. The analysis was carried out in DMSO-d_6 with the total concentration of 4 mM.

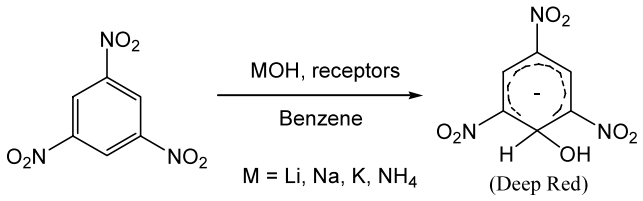
Table 1. The color changes on Meisenheimer test of **3**–**5**[a]

	Li^+	Na^+	K^+	NH_4^+
3	++	+	+	+
4	++	++	++	+
5	+	–	–	–

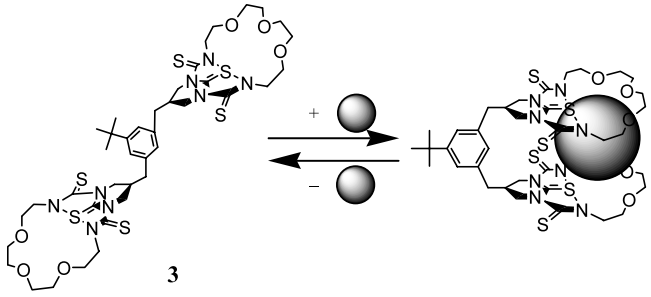


5

[a] The double plus (++) indicates immediate strong color change; the plus (+) indicates weak color change; the minus (-) indicates a negative result.



Scheme 2.



Scheme 3.

species, lithium cation is the most favorable for binding, and ease of complexation depended on the size of cation (Li^+>Na^+, K^+>NH_4^+). The difference of the cation binding ability between **3** and **5** is explained by schematic representation shown in Scheme 3, where receptor **3** connecting two cyclic rings intramolecularly can bind relatively large size cations through the formation of sandwich complex.

In summary, neutral receptors having ambident binding character was designed and synthesized by virtue of hypervalent sulfur. The scope and mechanistic details are now under investigation.

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