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Articles

Synthesis and Anion-Selective Complexation of Cyclophane-Based Cyclic Thioureas

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Cyclic thiourea derivatives having three different types of cyclophane structure, ortho-meta, meta-meta, and meta-para, and a lariat-type thiourea, were synthesized, and their anion-binding ability was examined. The association constants for the complexation between the receptors and several anions in DMSO-d_6 were measured by the titration method using ^{1}H NMR spectroscopy. All receptors, except for the meta-para cyclophane, exhibit selective binding to the dihydrogenphosphate anion, which is stronger than that of the acyclic reference compound. The lariat-type receptor binds anions even more strongly than the cyclic receptors which do not possess the third binding site.

Introduction

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 of urea and thiourea groups has been used in the development of neutral receptors, because the hydrogen bond is directional in character, and correct orientation of the hydrogen bond donors can provide selective anion recognition. In general, thiourea derivatives show stronger anion-binding ability than that of the corresponding ureas[3] because of the higher acidity of the former.[4,5] For example, Umezawa et al. achieved strong complexation of the receptors with a rigid xanthene spacer toward the dihydrogenphosphate anion by using thiourea groups with acidity-enhancing substituents.[6] Other examples of spacers to fix the binding sites include benzene,[7] cyclohexane,[3b] tertiary amine,[3b] calixarene,[3a,8] calixresorcinarene,[9] porphyrine,[10] dibenzacridone,[11] and xanthene.[6,12] It has also been reported that some of these urea or

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(2) For reviews of ion-selective electrodes and optodes: Bühlmann, P.; Pretsch, E.; Bakker, E. *Chem. Rev.* **1998**, *98*, 1593−1687.

(3) In some cases, weaker anion binding ability of thiourea-based receptors than that of the corresponding urea-based receptors is observed due to the competing intramolecular hydrogen bonding of thiourea groups: (a) Scheerder, J.; Fochi, M.; Engbersen, J. F. J.; Reinhoudt, D. N. *J. Org. Chem.* **1994**, *59*, 7815−7820. (b) Raposo, C.; Almaraz, M.; Martín, M.; Weinrich, V.; Mussóns, M. L.; Alcázar, V.; Caballero, M. C.; Morán, J. R. *Chem. Lett.* **1995**, 759−760.

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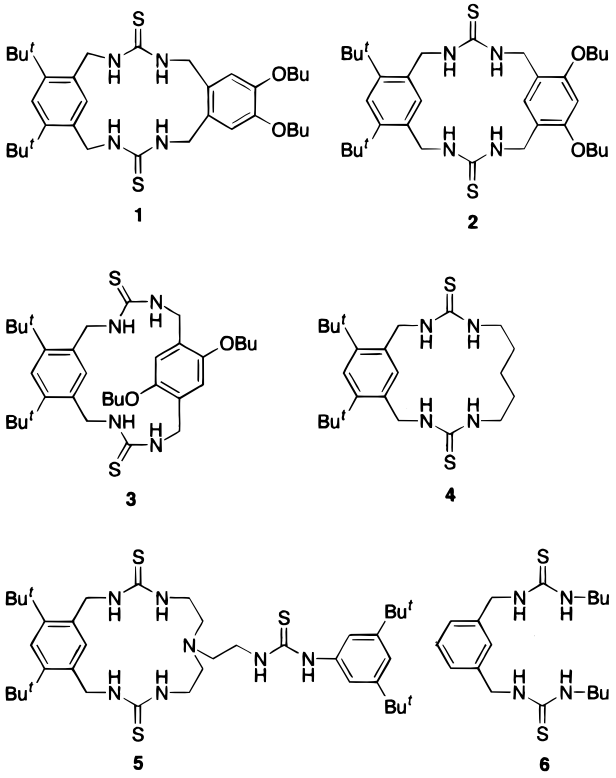
thiourea derivatives could be used in anion sensing based on absorption and fluorescence spectra[13] or ion-selective electrodes.[14] However, there seems to be no report, to our knowledge, on cyclic receptors having a urea or thiourea group as a part of the macrocyclic framework, despite the fact that preorganization of the binding sites is expected which would improve the binding ability and selectivity. In this paper, we report the synthesis of cyclophanes **1**−**4** having two thiourea groups and the lariat-type derivative **5** having the third binding site, and their binding ability and selectivity toward several guest anions.[15]



Results and Discussion

Cyclic receptors **1**−**3** having a relatively rigid ortho-meta, meta-meta, and meta-para cyclophane structure were designed in order to fix two thioureido groups in different distances and orientations. In our preliminary experiments, we found that simple cyclic receptors which do not have substituents on the benzene ring were hardly soluble in common organic solvents. Accordingly, *tert*-butyl groups were introduced in the common *m*-xylylene unit to improve the solubility. Similarly, butoxy groups were attached to other xylylene units for the same reason as well as for synthetic reasons. Besides cyclophanes **1**−**3**, pentamethylene-bridged metacyclophane **4** was prepared in order to examine the effect of flexibility of the macrocyclic ring. The lariat-type receptor **5** possesses a thiourea side chain terminated with a di-*tert*-butylbenzene unit, which would participate in the anion binding. Acyclic compound **6** was chosen as a reference, which was shown to bind selectively to the dihydrogenphosphate anion in DMSO solution[7b] and the sulfate anion in a PVC-based membrane for ion-selective electrode[14b] and at the 1,2-dichloroethane−water interface.[16]

The xylylene units having butoxy groups, *o*-, *m*-, and *p*-diisothiocyanates **9**, **13**, and **17**, were prepared from *o*-,[17] *m*-,[18] and *p*-dibutoxybenzene,[19] respectively, as shown in Scheme 1. Chloromethylation of *o*-dibutoxybenzene (**7**) with 37% formalin and HCl followed by the Gabriel reaction gave diamine **8** in 55% yield for the three steps. Diamine **8** was converted to diisothiocyanate **9** by treatment with DCC and CS_2 in 59% yield. *m*- and *p*-xylylene units **13** and **17** were prepared via the corresponding dicyanides **11** and **15**. Thus, regioselective iodination of **10** with ICl followed by replacement with CuCN gave dicyanide **11** in 62% yield. Reaction of **11** with diisobutylaluminum hydride gave diamine **12** in 34% yield, and treatment of **12** with CS_2 in the presence of NaOH followed by 30% H_2O_2 gave diisothiocyanate **13** in 33% yield. By essentially the same procedure, *p*-dibutoxybenzene (**14**) was converted to diisothiocyanate **17** in 7% overall yield through dicyanide **15** and diamine **16**.

The common *m*-xylylene unit, diamine **19**, was prepared by chloromethylation of 1,3-di-*tert*-butylbenzene (**18**).[20] With the use of $ZnCl_2$ as Lewis acid, we obtained relatively better yield of the desired product, although the reaction at the 2-position proceeded preferentially. The Gabriel reaction of the bis(chloromethyl) product gave diamine **19** in 4% yield for the three steps from **18**. Treatment of diamine **19** with DCC and CS_2 gave diisothiocyanate **20** in 93% yield. Cyclization reactions between diamine **19** and diisothiocyanates **9**, **13**, and **17** were carried out in $CHCl_3$ under dilute conditions to give cyclophane receptors **1**−**3** in 79, 70, and 31% yields, respectively (Scheme 2). In the case of the reaction between diamine **19** and diisothiocyanate **17**, 2:2 cyclization product **21** was also obtained in 17% yield besides **3**. Cyclic thiourea **4** was prepared by the reaction of diisothiocyanate **20** with 1,5-diaminopentane in 75% yield.

Lariat-type receptor **5** was prepared as shown in Scheme 3. Isothiocyanate **23** was prepared from 3,5-di-*tert*-butylaniline (**22**) in 89% yield. The reaction of

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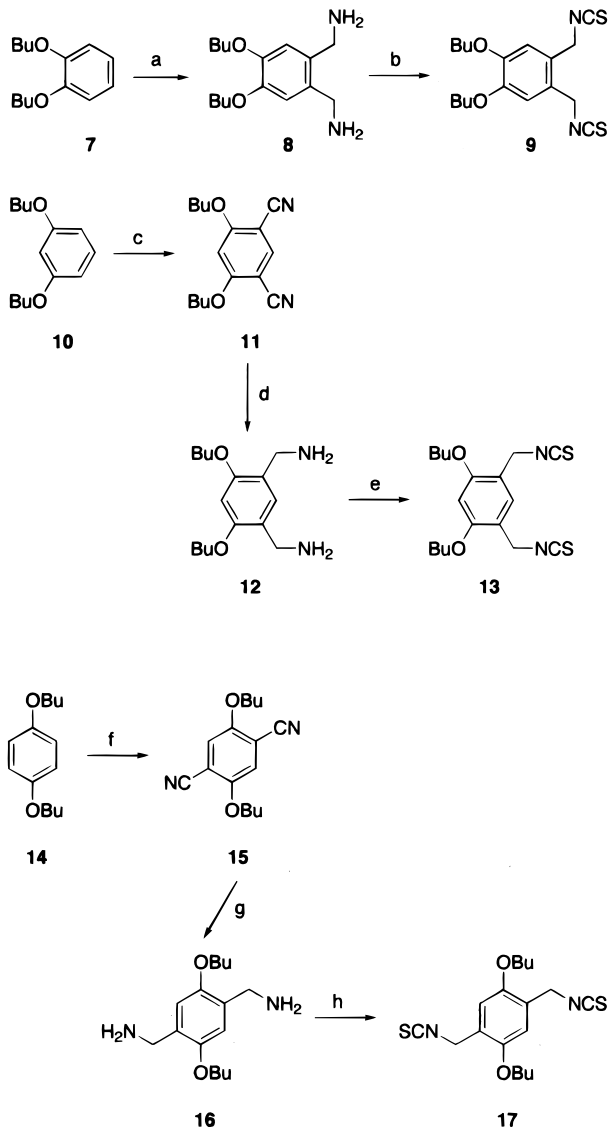
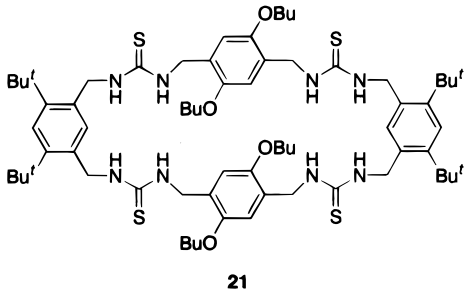
Scheme 1. Synthesis of Receptor Building Blocks[a]

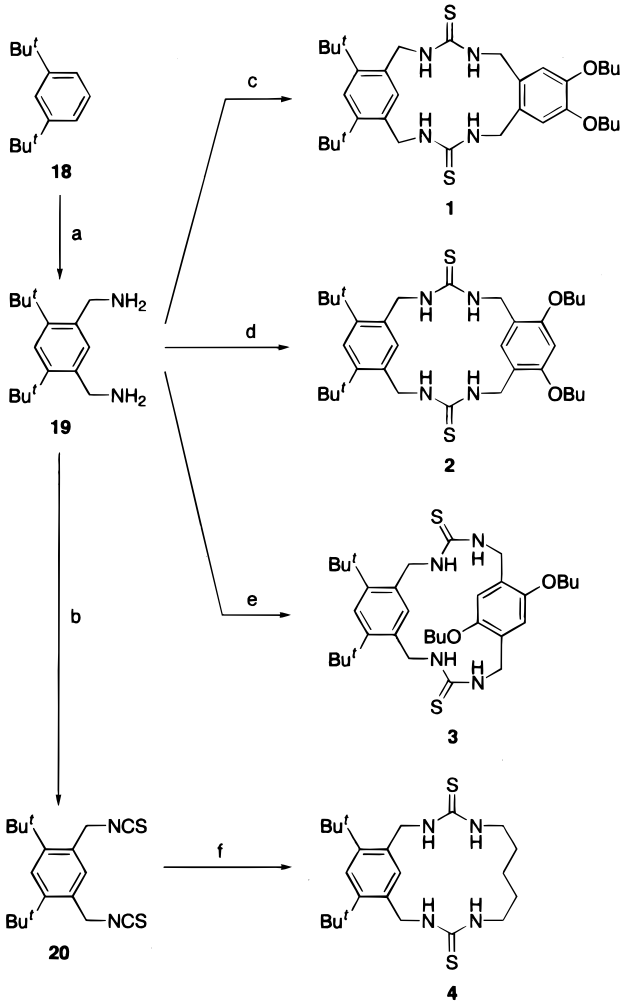


[a] Reagents and conditions: (a) (i) 37% formalin, HCl (g), concentrated HCl, dioxane, 0 °C, (ii) potassium phthalimide, DMF, 60 °C, (iii) $H_2NNH_2 \cdot H_2O$, EtOH, reflux, 55%; (b) DCC, CS_2, THF, room temperature, 59%; (c) (i) ICl, AcOH, room temperature, (ii) CuCN, HMPA, 150 °C, 62%; (d) (*i*-Bu) $_2$AlH, toluene, room temperature, 34%; (e) NaOH, CS_2, H_2O/THF then 30% H_2O_2, 33%; (f) (i) ICl, AcOH, 60 °C, (ii) CuCN, HMPA, 150 °C, 34%; (g) $LiAlH_4$, ether, reflux, 51%; (h) NaOH, CS_2, H_2O/THF then 30% H_2O_2, 42%.



isothiocyanate **23** with 1 equiv of tris(2-aminoethyl)amine was carried out in THF, and, without isolation, the product was treated with DCC and CS_2 to give diisothiocyanate **24** in 24% yield. Cyclization reaction between

Scheme 2. Synthesis of Cyclic Receptors[a]

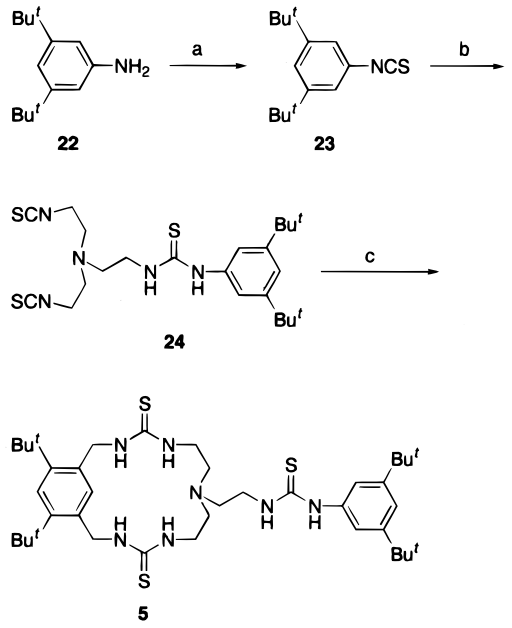


[a] Reagents and conditions: (a) (i) $ClCH_2OCH_3$, $ZnCl_2$, 60 °C, (ii) potassium phthalimide, DMF, 100 °C, (iii) $H_2NNH_2 \cdot H_2O$, EtOH, reflux, 4%; (b) DCC, CS_2, THF, room temperature, 93%; (c) **9**, $CHCl_3$, high dilution, 60 °C, 79%; (d) **13**, $CHCl_3$, high dilution, 60 °C, 70%; (e) **17**, $CHCl_3$, high dilution, 60 °C, 31%; (f) 1,5-diaminopentane, $CHCl_3$, high dilution, 60 °C, 75%.

diamine **19** and diisothiocyanate **24** under dilute conditions gave the lariat-type receptor **5** in 55% yield.

Addition of a tetrabutylammonium salt of a guest anion to a DMSO-d_6 solution of the receptors **1**, **2**, and **4**−**6** resulted in large downfield shifts of the NH resonances at room temperature, which is consistent with the formation of hydrogen-bonded complexes. On the other hand, meta-para type receptor **3** did not show any binding ability toward the anions examined, because no chemical shift change of **3** was observed even on addition of a large excess amount of the guest anions. In the case of meta-meta cyclophane **2**, the ^{1}H NMR spectrum exhibited signals due to both the free host and the complex at 30 °C (spectrum (b) in Figure 1), indicating that the equilibrium of the complexation is slow on the NMR time-scale. Namely, in the presence of tetrabutylammonium dihydrogenphosphate, the two NH proton signals of the complex (δ 8.9, 9.3) appeared at low fields in addition to those of the free host (δ 7.7, 7.9). The other signals for aromatic and benzylic protons also appeared as a pair of signals due to the complex and the free host. However, at 60 °C most of the NMR signals were averaged owing to the rapid equilibrium (spectrum (c) in Figure 1).

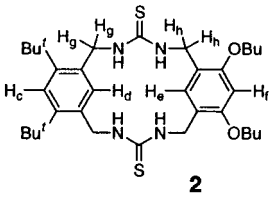
Scheme 3. Synthesis of Lariat Type Receptor[a]



[a] Reagents and conditions: (a) DCC, CS_2, THF, room temperature, 89%; (b) (i) $N(CH_2CH_2NH_2)_3$, THF, room temperature, (ii) DCC, CS_2, THF, room temperature, 24%; (c) **19**, $CHCl_3$, high dilution, 60 °C, 55%.

The association constants (K_a) of these hosts with several guest anions were determined by the titration method using ^{1}H NMR spectroscopy in DMSO-d_6 at 60 °C following the chemical shift change of the inner aromatic proton and the NH protons. The possibility of self-association[21] of the hosts was ruled out on the basis of the absence of concentration dependence of the chemical shifts of the hosts under the same temperature and concentration as those of the titration experiments. The 1:1 stoichiometry of the complexes was checked by Job's plot[22] for complexation between meta-meta type receptor **2** and dihydrogenphosphate and acetate anions as shown in Figure 2, which exhibits maxima at 0.5 mol fraction of **2**. Job's plot for complexation between lariat-type receptor **5** and the dihydrogenphosphate anion was also checked, which clearly showed the 1:1 stoichiometry.

The binding constants of the receptors **1**, **2**, and **4**−**6** with dihydrogenphosphate, acetate, hydrogensulfate, chloride, and bromide anions are summarized in Table 1. The data shows that the selectivities of cyclic hosts **1**, **2**, **4**, and **5** toward the guest anions are similar to that of acyclic host **6**. Thus, all receptors bind $H_2PO_4^-$ most strongly, followed by CH_3COO^-, Cl^-, HSO_4^-, and Br^-. As to the strength of anion binding, cyclic thioureas bind anions more strongly than acyclic compound **6** does. The large association constants of the cyclic hosts compared to those of acyclic thiourea is ascribed to the preorganization effect of these receptors. Moreover, it should be pointed out that the association constants of lariat-type receptor **5** are about 10−30 times larger than those of receptor **4** with related structure. The binding constant of the receptor **5** with the dihydrogenphosphate anion



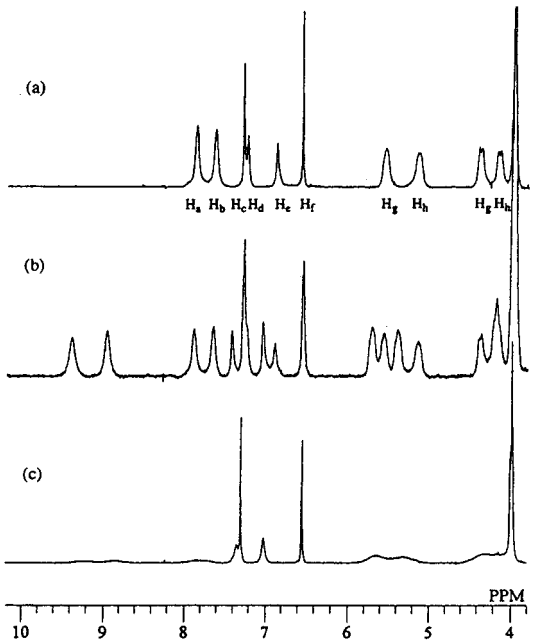


Figure 1. ^{1}H NMR spectra (400 MHz, DMSO-d_6) of (a) meta-meta type receptor **2** at 30 °C, (b) **2** with 0.5 equiv of dihydrogenphosphate anion at 30 °C, and (c) **2** with 0.5 equiv of dihydrogenphosphate anion at 60 °C. The assignment of H_a−H_h was done on the basis of the NOE and the spin−spin decoupling experiments.

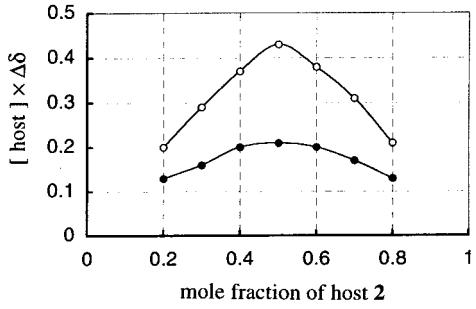


Figure 2. Job's plot of meta-meta type receptor **2** with the dihydrogenphosphate anion (open circles) and acetate anion (filled circles). The analysis was carried out in DMSO-d_6 at 60 °C with the total concentration of 5 mM.

was too large to be determined precisely by the ^{1}H NMR titration method. Namely, addition of aliquots of the dihydrogenphosphate anion to a solution of receptor **5** caused a linear chemical shift change of the receptor until 1 equiv of the anion was added, and after that essentially no change of the chemical shift was observed. These results suggest that the association constant is considerably large ($>10^4$) and, in addition, that a 1:1 complex is formed between the receptor and the guest anion. As shown in Figure 3, all the NH protons of receptor **5** (H_a−H_d) showed significant downfield shift upon addition of guest anions, indicating that all six NH protons partici-

(21) *m*-Xylylene type thiourea **6** forms aggregate in nonpolar solvents: (a) Tobe, Y.; Sasaki, S.; Hirose, K.; Naemura, K. *Tetrahedron Lett.* **1997**, *38*, 4791−4794. (b) Tobe, Y.; Sasaki, S.; Mizuno, M.; Hirose, K.; Naemura, K. *J. Org. Chem.* **1998**, *63*, 7481−7489.

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Table 1. Association Constants with Guest Anions[a]

	receptor				
anion[b]	**1**	**2**	**4**	**5**	**6**
$H_2PO_4^-$	12000	2500	4800	*c*	520
CH_3COO^-	2200	390	560	8300	110
Cl^-	120	14	54	1500	7
HSO_4^-	19	2	4	120	1
Br^-	12	<1	3	40	<1

[a] Measured in DMSO-d_6 at 60 °C by the ^{1}H NMR titration method. [b] Anions were used as their tetrabutylammonium salts. [c] The association constant was too large (>10^4) to be determined precisely.

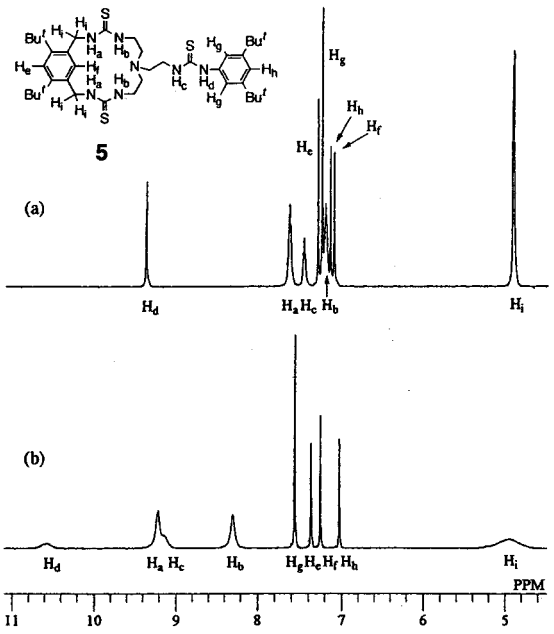

Figure 3. ^{1}H NMR spectra (400 MHz) of (a) lariate type receptor **5** and (b) **5** with 1 equiv of tetrabutylammonium dihydrogenphosphate in DMSO-d_6 at 60 °C. The assignment of H_a−H_i was done on the basis of the NOE and the ^{1}H−^{1}H COSY experiments.

pate in the formation of hydrogen-bonded complexes. Therefore, the larger association constants of receptor **5** is ascribed to the enthalpy gain due to additional hydrogen-bonding by the third binding site.

Since these receptors and their complexes did not give crystals suitable for X-ray structure analysis, no structural information is available for the host−guest complexes. Therefore, the hydrogen bonded geometries of the complexes were assessed by molecular modeling study. Geometry optimization was done by the semiempirical AM1[23] method for the complexes of the model compounds having no substituents on the benzene ring and acyclic compound **6** with dihydrogenphosphate and acetate anions.[24] Figure 4 illustrates the optimized structure of a complex of model compound **25** with the dihydrogenphosphate anion. Similar geometries were also obtained for the calculated structures of the other complexes. The

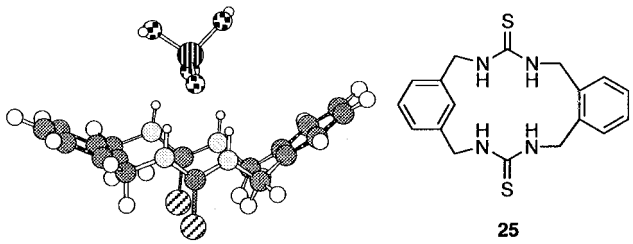

Figure 4. AM1-calculated structure of a complex of model compound **25** with the dihydrogenphosphate anion.

common features are (i) two thioureido groups adopt a trans−trans conformation, (ii) the anion perches on the four NH groups oriented to the same direction, and (iii) the anion bridges the two thiourea groups. As shown in Table 1, among the simple cyclic hosts **1**, **2**, and **4**, the association constants of ortho-meta isomer **1** are larger than those of meta-meta isomer **2** and metacyclophane **4**. Accordingly, the stronger binding ability may be ascribed to the shorter distance between the two thiourea groups than those of **2** and **4**.

The selectivity of the thiourea hosts toward anions merits comment. In view of the basicity of the anions, the selectivity should be in the order of $CH_3COO^- > H_2PO_4^- > HSO_4^- > Cl^- > Br^-$. However, all the cyclophane hosts bind $H_2PO_4^-$ most strongly. This tendency is also observed for simple acyclic thioureas.[6,7] Accordingly, the observed selectivity toward $H_2PO_4^-$ must be due to the difference between the solvation of DMSO to the anions, and it is unlikely that the difference is due to the geometry of the complexes.[7b] It has been well documented that polar aprotic solvents such as DMSO are capable of electron-pair donation (Lewis basic) but are not very effective on the Lewis acidity scale. Thus, for acetate, dihydrogenphosphate, and sulfate anions, the solvation of DMSO stabilizes the positively polarized atoms of the anions, i.e., carbon, phosphorus, and sulfur, respectively, rather than the negatively charged oxygen atoms. However, because the positively polarized phosphorus atom of $H_2PO_4^-$ is surrounded by the four negative oxygen atoms, it is not effectively solvated by DMSO. On the contrary, the corresponding carbon atom of the acetate anion must be more susceptible to the solvation of DMSO. Accordingly, the lower binding constants observed for CH_3COO^- than those of $H_2PO_4^-$ can be attributed to the stronger interaction of the former with the solvent than that of the latter. A similar explanation, but which is different in some aspects, based on the solvation of DMSO is given in ref 6.

As described above, meta-para isomer **3** did not exhibit binding ability toward the anions. To understand this observation, an X-ray crystallographic structure analysis of **3** was undertaken. Single crystals of **3** suitable for X-ray diffraction were obtained from a DMSO solution. Figure 5 shows the crystal structure of **3**, wherein the hydrogen atoms except for NH and the solvent molecules (DMSO) are omitted. It is revealed that, in the solid state, two thiourea groups of **3** adopt a trans−cis geometry and one of the thioureido hydrogens (H_b) is oriented toward the outside of the cyclophane ring, a geometry that is not suitable for anion binding. In addition, the ^{1}H NMR spectrum of **3** measured in DMSO-d_6 (Figure 6) provided further information regarding the conformation of **3** in solution. First, as shown in Figure 6, the pairs of benzylic protons H_f and H_g appear as unisochronous pairs of

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(24) The AM1 calculations were performed using SPARTAN ver. 5.0 program package; Wavefunction, Inc., Irvine, CA 92612. The initial input conformations for the AM1 calculations were selected from the Monte Carlo conformation search performed using MacroModel ver. 5.5: Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440−467.

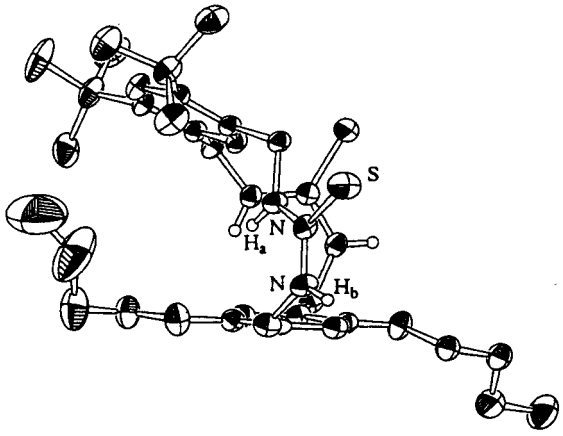

Figure 5. Crystal structure of meta-para type receptor **3**. Hydrogen atoms except for those of the NH groups and the solvent molecules (DMSO) are omitted for clarity.

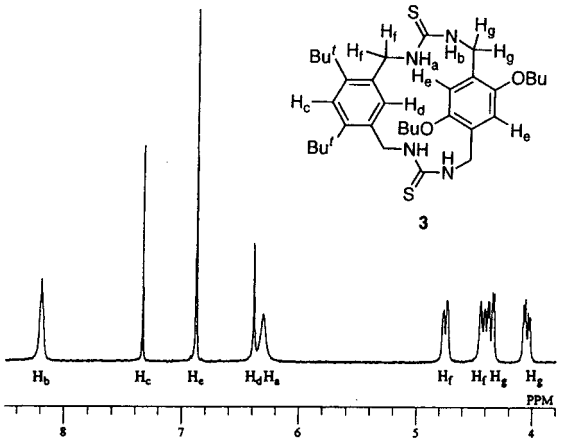

Figure 6. ^{1}H NMR spectrum (400 MHz) of meta-para type receptor **3** in DMSO-d_6 at 30 °C. The assignment of H_a−H_g was done on the basis of the NOE and the ^{1}H−^{1}H COSY experiments.

doublet of doublet (an ABX pattern), indicating that the conformational flipping of the cyclophane ring is slow on the NMR time scale. This behavior is quite different from those of other cyclic receptors **1** and **4**, which show time-averaged signals for the benzylic protons. The conformational mobility of meta-meta isomer **2** is also small, since its benzylic protons appear as nonisochronous pairs (spectrum (a) in Figure 1). More importantly, the inner aromatic proton H_d (δ 6.39) on the meta-bridged benzene ring and the NH_a protons (δ 6.31) which are located closer to this aromatic ring display a remarkable upfield shift compared to the corresponding protons of the other receptors as shown in Figure 6. Since this 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 that found in the solid state. Consequently, the lack of binding ability of **3** is ascribed to the conformation of the thioureido groups that is not suited for binding an anion.

Conclusions

In summary, we have synthesized cyclic neutral receptors having thiourea groups as anion-binding sites and examined their binding ability toward guest anions in DMSO-d_6. Selective binding to the dihydrogenphosphate anion was observed for all these cyclophane-based cyclic thioureas. The cyclic receptors showed larger association constants than those of the acyclic reference compound. Moreover, a lariat-type receptor exhibited even stronger anion-binding ability than those of the simple cyclic compounds.

Experimental Section

Materials. THF was dried and distilled under nitrogen from sodium benzophenone ketyl immediately before use. Diethyl ether was dried with $LiAlH_4$ and distilled. 1,2-Dibutoxybenzene (**7**),[17] 1,3-dibutoxybenzene (**10**),[18] 1,4-dibutoxybenzene (**14**),[19] and 1,3-di-*tert*-butylbenzene (**18**)[20] were prepared according to literature procedures. Other solvents and reagents used were of reagent grade and were employed as purchased without further purification.

1,2-Bis(aminomethyl)-4,5-dibutoxybenzene (8). To an ice-cooled solution of 22.3 g (0.10 mol) of 1,2-dibutoxybenzene (**7**) in 150 mL of dioxane was added 30 mL of concentrated aqueous HCl, and then 20 mL of 37% formalin was added dropwise while gaseous HCl was bubbled into the solution. The same amount of formalin was added after 30 min. The mixture was allowed to warm to room temperature and stirred for 5 h. Water was added while cooling with an ice bath and the mixture was extracted three times with ether. The extract was washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to leave a white solid (31.9 g, 100%), which was used for the following reaction without further purification. An analytical sample of 1,2-dibutoxy-4,5-bis(chloromethyl)benzene was obtained by preparative HPLC: mp 69−71 °C; IR (KBr) 872, 762, 740, 680 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.98 (t, J = 7.3 Hz, 6H), 1.44−1.56 (m, 4H), 1.75−1.85 (m, 4H), 4.01 (t, J = 6.5 Hz, 4H), 4.68 (s, 4H), 6.87 (s, 2H); MS (CI) m/z (rel intensity) 318 (M^+, 25), 283 (100). Anal. Calcd for $C_{16}H_{24}Cl_2O_2$: C, 60.19; H, 7.58. Found: C, 60.47; H, 7.80.

Potassium phthalimide (46.3 g, 0.25 mol) was added to a solution of the above dichloride (31.9 g, 0.10 mol) in 200 mL of DMF. The reaction mixture was stirred at 60 °C for 40 min and then cooled to room temperature. Aqueous NaOH (0.5 N) was added, and the mixture was extracted with $CHCl_3$. The extract was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. The solid residue was washed with ether to afford 32.1 g (59% for the two steps) of 1,2-dibutoxy-4,5-bis(imidomethyl)benzene as a white solid: mp 160−161 °C; IR (KBr) 1704, 715 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.92 (t, J = 7.4 Hz, 6H), 1.40−1.48 (m, 4H), 1.67−1.77 (m, 4H), 3.49 (t, J = 6.5 Hz, 4H), 5.19 (s, 4H), 7.02 (s, 2H), 7.68−7.85 (m, 8H); MS (FAB) m/z 541 (M^+ + 1). Anal. Calcd for $C_{32}H_{32}N_2O_6$: C, 71.10; H, 5.97; N, 5.18. Found: C, 71.00; H, 6.00; N, 5.29.

To a refluxing suspension of the above imide (2.16 g, 4.0 mmol) in 30 mL of EtOH was added 2.0 mL (40 mmol) of hydrazine monohydrate (80%), and the mixture was refluxed for 30 min. After cooling, 6 N aqueous HCl was added to acidify the mixture and it was refluxed for 30 min. After cooling to 0 °C by an ice−water bath, aqueous NaOH was added to make the solution alkaline and it was extracted three times with $CHCl_3$. The organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to give 1.05 g (94%) of **8** as a white solid: IR (KBr) 3342, 3282, 870, 742 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.97 (t, J = 7.3 Hz, 6H), 1.44−1.56 (m, 4H), 1.68 (br s, 4H), 1.74−1.84 (m, 4H), 3.83 (s, 4H), 4.00 (t, J = 6.6 Hz, 4H), 6.86 (s, 2H).

1,2-Dibutoxy-4,5-bis(isothiocyanatomethyl)benzene (9). To a solution of 840 mg (3.0 mmol) of **8** and 1.24 g (6.0 mmol) of DCC in 20 mL of THF was added 1.8 mL (30 mmol) of CS_2. The mixture was stirred for 30 min, and then the solvent was removed to dryness. The product was purified by column chromatography (silica gel, hexane−benzene 1:1) to afford 646 mg (59%) of **9** as a white solid: mp 82−84 °C; IR (KBr) 2144, 2076, 876, 774, 700, 679 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.99 (t, J = 7.4 Hz, 6H), 1.45−1.58 (m, 4H), 1.77−1.86 (m, 4H),

4.03 (t, $J = 6.6$ Hz, 4H), 4.66 (s, 4H), 6.86 (s, 2H); MS (EI) *m/z* (rel intensity) 364 (M^+, 73), 194 (100). Anal. Calcd for $C_{18}H_{24}N_2O_2S_2$: C, 59.31; H, 6.64; N, 7.68. Found: C, 59.52; H, 6.80; N, 7.72.

1,3-Dibutoxy-4,6-dicyanobenzene (11). To a solution of 10.0 g (0.045 mol) of 1,3-dibutoxybenzene (**10**) in 300 mL of acetic acid was added dropwise ICl (15.3 g, 0.095 mol), and the mixture was stirred for 3 h at room temperature. 500 mL water was added, and the mixture was extracted three times with hexane. The combined extract was washed with aqueous $NaHSO_3$, dried over anhydrous $MgSO_4$, filtered, and concentrated to leave 1,3-dibutoxy-4,6-diiodobenzene as a slightly colored solid (20.0 g, 94%), which was used for the following reaction without further purification. An analytical sample was obtained by recrystallization from hexane as colorless needles: mp 90−91 °C (dec); IR (KBr) 873, 805, 672 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.99 (t, $J = 7.4$ Hz, 6H), 1.48−1.62 (m, 4H), 1.77−1.87 (m, 4H), 3.99 (t, $J = 6.3$ Hz, 4H), 6.32 (s, 1H), 8.02 (s, 1H); MS (EI) *m/z* (rel intensity) 474 (M^+, 75), 362 (100). Anal. Calcd for $C_{14}H_{20}I_2O_2$: C, 35.47; H, 4.25. Found: C, 35.84; H, 4.26.

A mixture of the above iodide (19.4 g, 0.041 mol) and CuCN (11.0 g, 0.12 mol) in 30 mL of HMPA was stirred at 150 °C for 3 h. The mixture was poured into a solution of $FeCl_3$ (67 g, 0.41 mol) in 300 mL of water and stirred vigorously for 10 min. The aqueous solution was removed by decantation, and the remaining gum was washed with water. To this gum was added 300 mL of $CHCl_3$, and the mixture was stirred for 10 min. The insoluble material was removed by filtration through a pad of Celite, and the filtrate was washed with aqueous $NaHSO_3$ and water, dried over anhydrous $MgSO_4$, filtered, and concentrated. The product was purified by column chromatography (silica gel, hexanes−EtOAc 8:2) to afford 7.29 g (66%) of **11** as a white solid: mp 78−80 °C; IR (KBr) 2227, 906, 848 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.00 (t, $J = 7.4$ Hz, 6H), 1.48−1.62 (m, 4H), 1.82−1.92 (m, 4H), 4.12 (t, $J = 6.4$ Hz, 4H), 6.44 (s, 1H), 7.72 (s, 1H); MS (EI) *m/z* (rel intensity) 272 (M^+, 45), 160 (100). Anal. Calcd for $C_{16}H_{20}N_2O_2$: C, 70.56; H, 7.40; N, 10.29. Found: C, 70.58; H, 7.59; N, 10.24.

1,3-Bis(aminomethyl)-4,6-dibutoxybenzene (12). To a solution of **11** (817 mg, 3.0 mmol) in 5 mL of toluene was added dropwise a 1.5 M toluene solution of DIBAL-H (20 mL, 30 mmol). The mixture was stirred for 10 h at room temperature under nitrogen, and then it was poured into water. Aqueous solution of NaOH was added, and the mixture was extracted three times with ether. The extract was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to leave a slightly colored oil (290 mg, 34%). The crude product was used for the following reaction without further purification: IR (neat) 3313, 821, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.99 (t, $J = 7.4$ Hz, 6H), 1.47−1.56 (m, 4H), 1.76−1.83 (m, 4H), 3.74 (s, 4H), 3.98 (t, $J = 6.3$ Hz, 4H), 6.43 (s, 1H), 7.02 (s, 1H); MS (EI) *m/z* (rel intensity) 280 (M^+, 72), 250 (100). HRMS calcd for $C_{16}H_{28}N_2O_2$ 280.2151, found 280.2141.

1,3-Dibutoxy-4,6-bis(isothiocyanatomethyl)benzene (13). To a solution of diamine **12** (140 mg, 0.5 mmol) in 2 mL of THF was added a solution of NaOH (50 mg, 1.3 mmol) in 0.5 mL of water. CS_2 (5.0 mmol, 0.3 mL) was added, and the mixture was stirred for 1 h at room temperature. H_2O_2 (30%) was added dropwise with cooling in an ice bath, and then 10% aqueous HCl was added. The mixture was extracted three times with ether, and the extract was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to leave 180 mg of a brown oil. In the same procedure, 85 mg of **12** gave 108 mg of a crude product. The combined products were purified by column chromatography (silica gel, hexanes−EtOAc 9:1) to afford 95 mg (33%) of **13** as a colorless oil: IR (neat) 2158, 2082, 885, 824, 752 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.00 (t, $J = 7.4$ Hz, 6H), 1.46−1.60 (m, 4H), 1.78−1.88 (m, 4H), 4.02 (t, $J = 6.4$ Hz, 4H), 4.60 (s, 4H), 6.44 (s, 1H), 7.14 (s, 1H); MS (EI) *m/z* (rel intensity) 364 (M^+, 22), 306 (100). HRMS calcd for $C_{18}H_{24}N_2O_2S_2$ 364.1279, found 364.1227.

1,4-Dibutoxy-2,5-dicyanobenzene (15). To a solution of 8.00 g (0.036 mol) of 1,4-dibutoxybenzene (**14**) in 150 mL of acetic acid was added 12.4 g (0.076 mol) of ICl, and the mixture was stirred for 6 h at 60 °C. Water (500 mL) was added, and the mixture was extracted three times with ether. The combined extract was washed successively with 1 N aqueous NaOH, aqueous $Na_2S_2O_3$, water, and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to leave 15.7 g of crude product as a brown solid. Recrystallization from hexane gave 7.87 g of colorless plates, which contained ca. 15% (by ^1H NMR) of 1,4-dibutoxy-2-chloro-5-iodobenzene as a byproduct. The product was used for the following reaction without further purification. For 1,4-dibutoxy-2,5-diiodobenzene:[19c,25] ^1H NMR (400 MHz, $CDCl_3$) δ 0.98 (t, $J = 7.4$ Hz, 6H), 1.49−1.58 (m, 4H), 1.75−1.82 (m, 4H), 3.93 (t, $J = 6.3$ Hz, 4H), 7.17 (s, 2H).

Reaction of the above iodide (6.20 g, 0.013 mol) and CuCN (3.49 g, 0.039 mol) was carried out as described for the preparation of **11**. The crude product was washed with hexane to give 2.58 g (34% for the two steps) of pure **15** as a white solid: mp 150 °C (dec); IR (KBr) 2226, 891, 821, 687 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.99 (t, $J = 7.4$ Hz, 6H), 1.48−1.57 (m, 4H), 1.79−1.86 (m, 4H), 4.04 (t, $J = 6.5$ Hz, 4H), 7.12 (s, 2H); MS (EI) *m/z* (rel intensity) 272 (M^+, 13), 160 (100). Anal. Calcd for $C_{16}H_{20}N_2O_2$: C, 70.56; H, 7.40; N, 10.29. Found: C, 70.48; H, 7.28; N, 10.29.

1,4-Dibutoxy-2-chloro-5-cyanobenzene derived from 1,4-dibutoxy-2-chloro-5-iodobenzene was isolated from the filtrate: mp 72−74 °C; IR (KBr) 2228, 885, 861, 811 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.98 (t, $J = 7.3$ Hz, 6H), 1.49−1.56 (m, 4H), 1.76−1.84 (m, 4H), 3.97 (t, $J = 6.5$ Hz, 2H), 4.01 (t, $J = 6.4$ Hz, 2H), 7.00 (s, 1H), 7.05 (s, 1H); MS (EI) *m/z* (rel intensity) 281 (M^+, 15), 169 (100).

1,4-Bis(aminomethyl)-2,5-dibutoxybenzene (16). To a suspension of $LiAlH_4$ (767 mg, 20.2 mmol) in 100 mL of ether was added 1.83 g (6.72 mmol) of **15** in small portions. After refluxing the mixture for 1 h, 10% aqueous HCl was added dropwise with cooling in an ice bath. The organic phase was separated, and the aqueous phase was washed with ether, made alkaline with aqueous NaOH, and extracted three times with ether. The extract was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to give 960 mg (51%) of **16** as a yellow oil. The product was used for the following reaction without further purification: IR (neat) 3372, 3297, 872, 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.98 (t, $J = 7.3$ Hz, 6H), 1.46−1.55 (m, 8H), 1.73−1.80 (m, 4H), 3.79 (s, 4H), 3.96 (t, $J = 6.4$ Hz, 4H), 6.78 (s, 2H); MS (EI) *m/z* (rel intensity) 280 (M^+, 100). HRMS calcd for $C_{16}H_{28}N_2O_2$ 280.2151, found 280.2164.

1,4-Dibutoxy-2,5-bis(isothiocyanatomethyl)benzene (17). Diisothiocyanate **17** was prepared by the same procedure as described for the preparation of **13** in 42% yield from diamine **16**: mp 76−77 °C; IR (KBr) 2178, 2103, 879, 764, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.99 (t, $J = 7.4$ Hz, 6H), 1.46−1.55 (m, 4H), 1.75−1.82 (m, 4H), 3.99 (t, $J = 6.4$ Hz, 4H), 4.70 (s, 4H), 6.87 (s, 2H); MS (EI) *m/z* (rel intensity) 364 (M^+, 100). Anal. Calcd for $C_{18}H_{24}N_2O_2S_2$: C, 59.31; H, 6.64; N, 7.68. Found: C, 59.09; H, 6.87; N, 7.40.

1,3-Bis(aminomethyl)-4,6-di-*tert*-butylbenzene (19). To a solution of 9.52 g (0.050 mol) of 1,3-di-*tert*-butylbenzene (**18**) in 100 mL of chloromethyl methyl ether was added $ZnCl_2$ (13.6 g, 0.10 mol), and the resulting mixture was stirred for 3 h at 60 °C. The mixture was poured into water and extracted three times with ether. The extract was washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to leave a brown oil (17.2 g). In a similar procedure, 19.0 and 37.5 g of **18** gave 34.0 and 66.4 g of crude products, respectively. The combined crude products were purified by column chromatography (silica gel, hexane) to afford 12.7 g (13%) of 1,3-di-*tert*-butyl-4,6-bis(chloromethyl)-benzene as a white solid: mp 55−57 °C; IR (KBr) 890, 746, 676 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.44 (s, 18H), 4.84 (s, 4H), 7.41 (s, 1H), 7.49 (s, 1H); MS (EI) *m/z* (rel intensity) 286 (M^+, 38), 271 (100). Anal. Calcd for $C_{16}H_{24}Cl_2$: C, 66.90; H, 8.42. Found: C, 67.08; H, 8.36.

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Diamine **19** was prepared by the same procedure as described for the preparation of **8** in 31% yield (for the two steps) from the above chloride. 1,3-Di-*tert*-butyl-4,6-bis(phthalimidomethyl)benzene: mp 260−262 °C; IR (KBr) 1715, 872, 753, 714 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.50 (s, 18H), 4.98 (s, 4H), 6.64 (s, 1H), 7.44 (s, 1H), 7.59−7.68 (m, 8H); MS (EI) *m/z* (rel intensity) 508 (M^+, 12), 451 (100). Anal. Calcd for $C_{32}H_{32}N_2O_4$: C, 75.57; H, 6.34; N, 5.51. Found: C, 75.35; H, 6.44; N, 5.62. Diamine **19**: mp 78−79 °C; IR (KBr) 3257, 3189, 925 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.42 (s, 18H), 1.45 (s, 4H), 4.05 (s, 4H), 7.38 (s, 1H), 7.42 (s, 1H); MS (EI) *m/z* (rel intensity) 248 (M^+, 7), 57 (100). Hydrochloride salt of **19**: mp 250 °C (dec); IR (KBr) 3435, 912 cm^{-1}. Anal. Calcd for $C_{16}H_{28}N_2 \cdot 2HCl$: C, 59.81; H, 9.41; N, 8.72. Found: C, 59.66; H, 9.62; N, 8.71.

1,3-Di-*tert*-butyl-4,6-bis(isothiocyanatomethyl)benzene (20). Diisothiocyanate **20** was prepared by the same procedure as described for the preparation of **9** in 93% yield from diamine **19**: mp 118−120 °C; IR (KBr) 2179, 2091, 893, 773, 668 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.41 (s, 18H), 4.93 (s, 4H), 7.38 (s, 1H), 7.47 (s, 1H); MS (EI) *m/z* (rel intensity) 332 (M^+, 20), 274 (100). Anal. Calcd for $C_{18}H_{24}N_2S_2$: C, 65.02; H, 7.27; N, 8.42. Found: C, 64.89; H, 7.34; N, 8.50.

Ortho-Meta Type Receptor 1. A solution of **19** (248 mg, 1.0 mmol) in 200 mL of $CHCl_3$ and a solution of **9** (365 mg, 1.0 mmol) in 200 mL of $CHCl_3$ were added dropwise simultaneously to 100 mL of $CHCl_3$ at 60 °C. The mixture was refluxed for 30 min and then the solvent was removed to dryness. The crude product was dissolved in 100 mL of $CHCl_3$ and passed through a column of silica gel ($CHCl_3$-EtOAc 9:1), and concentrated to leave a white solid. To this solid was added 10 mL of $CHCl_3$ and the mixture was stirred at room temperature. The insoluble material was filtered off and washed with a 3 mL portion of $CHCl_3$, and the solvent was removed in vacuo to give pure **1** (485 mg, 79%) as a white solid: mp 268−270 °C (dec); IR (KBr) 3318, 1557, 884, 720 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6, 60 °C) δ 0.94 (t, J = 7.4 Hz, 6H), 1.38 (s, 18H), 1.41−1.49 (m, 4H), 1.66−1.73 (m, 4H), 4.00 (t, J = 6.5 Hz, 4H), 4.48 (br s, 4H), 4.93 (br s, 4H), 7.04 (s+s, 3H), 7.23 (br s, 2H), 7.30 (s, 1H), 7.39 (br s, 2H); MS (FAB) *m/z* 613 (M^+). Anal. Calcd for $C_{34}H_{52}N_4O_2S_2$: C, 66.63; H, 8.55; N, 9.14. Found: C, 66.69; H, 8.61; N, 9.17.

Meta-Meta Type Receptor 2. Cyclization reaction between diamine **19** (50 mg, 0.20 mmol) and diisothiocyanate **13** (73 mg, 0.20 mmol) was carried out as described for the preparation of **1**. The crude product was passed through a column of silica gel ($CHCl_3$−MeOH 98:2) to afford 102 mg of a white solid. The sample (72 mg) was purified by preparative HPLC to give 61 mg (70%) of **2** as a white solid: mp 194−196 °C; IR (KBr) 3302, 1559, 887 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6, 120 °C) δ 0.96 (t, J = 7.4 Hz, 6H), 1.41 (s, 18H), 1.44−1.51 (m, 4H), 1.70−1.76 (m, 4H), 4.01 (t, J = 6.3 Hz, 4H), 4.69 (br s, 4H), 4.99 (br s, 4H), 6.56 (s, 1H), 7.02 (s, 1H), 7.32 (s, 1H), 7.35 (s, 1H), 7.49 (t, J = 6.0 Hz, 2H), 7.57 (t, J = 5.2 Hz, 2H); MS (FAB) *m/z* 613 (M^+ + 1). Anal. Calcd for $C_{34}H_{52}N_4O_2S_2$: C, 66.63; H, 8.55; N, 9.14. Found: C, 66.33; H, 8.51; N, 9.17.

Meta−Para Type Receptor 3. Cyclization reaction between diamine **19** (450 mg, 1.23 mmol) and diisothiocyanate **13** (306 mg, 1.23 mmol) was carried out as described for the preparation of **1**. The product was purified by column chromatography (silica gel, $CHCl_3$−AcOEt 9:1) followed by preparative HPLC to afford 230 mg (31%) of **3** and 130 mg (17%) of **21** both as white solids. **3**: mp 243−245 °C; IR (KBr) 3384, 3237, 1548, 890, 749 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6, 30 °C) δ 0.88 (t, J = 7.3 Hz, 6H), 1.2−1.3 (m, 4H), 1.37 (s, 18H), 1.4−1.6 (m, 4H), 3.2−3.4 (−OCH_2− signals overlap with the H_2O signal), 3.71 (dt, J = 8.7, 6.8 Hz, 2H), 4.05 (dd, J = 15.6, 6.6 Hz, 2H), 4.36 (dd, J = 15.6, 5.2 Hz, 2H), 4.43 (d, J = 13.2 Hz, 2H), 4.75 (dd, J = 13.2, 4.4 Hz, 2H), 6.31 (br s, 2H), 6.39 (s, 1H), 6.88 (s, 2H), 7.34 (s, 1H), 8.20 (br s, 2H); MS (FAB) *m/z* 612 (M^+). Anal. Calcd for $C_{34}H_{52}N_4O_2S_2$: C, 66.63; H, 8.55; N, 9.14. Found: C, 66.53; H, 8.65; N, 8.78. **21**: mp 210 °C (dec); IR (KBr) 3332, 3234, 1578, 884, 755, 729 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6, 30 °C) δ 0.89 (t, J = 7.3 Hz, 12H), 1.38 (s, 36H), 1.4−1.5 (m, 8H), 1.6−1.7 (m, 8H), 3.86 (t, J = 6.3 Hz, 8H), 4.54 (br s, 8H), 4.72 (br s, 8H), 6.93 (s, 4H), 7.20 (s, 2H), 7.40 (s, 2H), 7.47 (br s, 4H), 7.57 (br s, 4H); MS (FAB) *m/z* 1225 (M^+). Anal. Calcd for $C_{68}H_{104}N_8O_4S_4$: C, 66.63; H, 8.55; N, 9.14. Found: C, 66.33; H, 8.60; N, 8.86.

Cyclic Receptor 4. A solution of 1,5-diaminopentane (123 mg, 1.2 mmol) in 200 mL of $CHCl_3$ and a solution of diisothiocyanate **20** (400 mg, 1.2 mmol) in 200 mL of $CHCl_3$ were added dropwise simultaneously to 20 mL of $CHCl_3$ at 60 °C. The mixture was refluxed for 4.5 h and cooled to room temperature. The resulting solid was filtered and washed with $CHCl_3$ to give 257 mg of pure **4** as a white solid. The filtrate was concentrated and purified by column chromatography (silica gel, $CHCl_3$−MeOH 97:3) to afford 133 mg of **4** (total 390 mg, 75%): mp 268−270 °C; IR (KBr) 3247, 1559, 887, 850, 668 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6, 60 °C) δ 1.39 (s, 18H), 1.48−1.57 (m, 6H), 3.46 (br s, 4H), 4.91 (d, J = 5.2 Hz, 4H), 7.20 (s, 1H), 7.27 (br s, 2H), 7.31 (s, 1H), 7.54 (br s, 2H); MS (FAB) *m/z* 435 (M^+ + 1). Anal. Calcd for $C_{23}H_{38}N_4S_2$: C, 63.55; H, 8.81; N, 12.89. Found: C, 63.28; H, 8.81; N, 12.77.

3,5-Di-*tert*-butylphenyl Isothiocyanate (23). Isothiocyanate **23** was prepared by the same procedure as described for the preparation of **9** in 89% yield from 3,5-di-*tert*-butylaniline (**22**): mp 78−80 °C; IR (KBr) 2151, 867, 737, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.30 (s, 18H), 7.05 (d, J = 1.6 Hz, 2H), 7.32 (t, J = 1.6 Hz, 1H); MS (EI) *m/z* (rel intensity) 247 (M^+, 52), 232 (100).

2-(*N*′-(3,5-Di-*tert*-butylphenyl)thioureido)ethyl-bis(2-isothiocyanatoethyl)amine (24). To a solution of tris(2-aminoethyl)amine (517 mg, 3.5 mmol) in 10 mL of THF was added dropwise a solution of isothiocyanate **23** (874 mg, 3.5 mmol) in 25 mL of THF. After stirring for 2 h, 1.82 g (8.8 mmol) of DCC and 0.56 mL (0.35 mol) of CS_2 were added, the mixture was stirred for 26 h at room temperature, and then the solvent was removed to dryness. The product was purified by column chromatography (silica gel, 8:2 hexanes−EtOAc) to afford 409 mg (24%) of **24** as a white solid: mp 109−110 °C; IR (KBr) 3356, 3165, 2079, 1545, 871, 709 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.32 (s, 18H), 2.87 (t, J = 6.0 Hz, 6H), 3.49 (t, J = 6.0 Hz, 4H), 3.69 (dt, J = 6.0, 6.0 Hz, 2H), 6.38 (t, J = 6.0 Hz, 1H), 7.06 (d, J = 1.6 Hz, 2H), 7.38 (t, J = 1.6 Hz, 1H), 7.58 (br s, 1H); MS (CI) *m/z* 478 (M^+ + 1). Anal. Calcd for $C_{23}H_{35}N_5S_3$: C, 57.82; H, 7.38; N, 14.66. Found: C, 57.60; H, 7.30; N, 14.53.

The Lariat-Type Receptor 5. Cyclization reaction between diamine **19** (213 mg, 0.86 mmol) and diisothiocyanate **24** (409 mg, 0.86 mmol) was carried out as described for the preparation of **1**. The crude product was purified by column chromatography (silica gel, $CHCl_3$) followed by recrystallization from hexane−CH_2Cl_2 to afford 340 mg (55%) of **5** as a white solid: mp 228−230 °C; IR (KBr) 3275, 1560, 872, 709 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 50 °C) δ 1.15 (s, 18H), 1.37 (s, 18H), 2.69 (br s, 4H), 2.78 (br s, 2H), 3.66 (br s, 4H), 3.94 (br s, 2H), 4.90 (br s, 4H), 6.76 (br s, 5H), 7.06 (s, 1H), 7.15 (s, 1H), 7.31 (s, 2H), 7.33 (s, 1H), 8.57 (br s, 1H); MS (FAB) *m/z* 726 (M^++1). Anal. Calcd for $C_{39}H_{63}N_7S_3$: C, 64.51; H, 8.74; N, 13.50. Found: C, 64.21; H, 8.81; N, 13.41.

X-ray Crystallography. Data collection was carried out at 20 °C on a Rigaku AFC7R diffractometer with graphite-monochromated Mo Kα radiation (λ = 0.71069 Å). The structure was solved by direct method (SHELXS-97[26]) and refined by full-matrix least-squares techniques. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined.

Crystal Data for 3. Single crystals were obtained from a DMSO solution. A colorless crystal with dimensions of 0.45 × 0.30 × 0.30 mm was used for data collection. $C_{34}H_{52}N_4O_2S_2 \cdot 3DMSO$, f_w = 847.30, triclinic, space group $P\bar{1}$, a = 14.408(1), b = 17.467(1), 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}, μ(Mo Kα) = 2.84 cm^{-1}. Unique reflections (11005) were obtained, and 5546 observed reflections ($I > 2\sigma(I)$) were used for refinement to give R = 0.073 and Rw = 0.210.

(26) Sheldrick, G. M. SHELXS-97, Program for the Refinement of Crystal Structures, University of Göttingen, Germany, 1997.

Determination of Association Constants (K_a). DMSO-d_6 was dried over molecular sieves (3 Å). All guest anions were commercially available as tetrabutylammonium (TBA) salts. Recrystallization was performed using the following solvents: for dihydrogenphosphate and hydrogensulfate from EtOAc/acetone, for chloride and bromide from EtOAc/hexane, and for acetate from EtOAc. The curve-fitting analysis was performed on a Macintosh personal computer using Microsoft Excel 5.0 software.[27]

As an example, titration experiment of ortho-meta type receptor **1** with an acetate anion is described here. A 5.21 mM solution of **1** in DMSO-d_6 was prepared in a volumetric flask, and the initial NMR spectrum was recorded. Alternatively, a 20.1 mM solution of the guest anion in DMSO-d_6 was prepared in a volumetric flask. The solution of the guest anion was then added, initially in 20-μL portions, and the chemical shifts of the NH and the aromatic protons were recorded after each addition. After 1 equiv of the guest anion had been added, the aliquot size was increased to 30 μL until a total of 360 μL (2.2 equiv) was added. Relatively broad peaks were treated by a curve-fitting program implemented in the NMR data system (EXcalibur for Windows 95 ver. 2.02). However, in some cases, the NH peaks were too broad to determine the chemical shift exactly, and only the aromatic protons which showed a chemical shift change of larger than 0.1 ppm were adopted for the caluculation. The association constants were calculated by nonlinear least-squares technique using the Excel program. The reported K_a values in Table 1 are calculated by averaging the K_a values obtained from a few different protons. In most cases, the deviations are within 10%.

General Procedure for Determination of Binding Stoichiometry. Solutions (5 mM) of host and the guest anion in DMSO-d_6 were prepared in volumetric flasks, respectively. The host and guest solutions were added to NMR tubes to make the same amount of total volume with different ratios. ^{1}H NMR spectra were recorded, and a plot of [host] $\times$ $\Delta\delta$ versus the mole fraction of the host was obtained, where $\Delta\delta = \delta_{host} - \delta_{obs}$, [host]: the total concentration of the host in the sample solution, δ_{host}: the initial chemical shift (host only), and δ_{obs}: the observed chemical shift for each sample, as shown in Figure 2.

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Supporting Information Available: X-ray crystallographic data for **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(27) Excel version 5.0; Microsoft Corp., Tokyo.