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Synthesis and Anion-Selective Complexation of Homobenzylic Tripodal Thiourea Derivatives

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Cryptand- and tripod-type thiourea derivatives **4b** and **5a**–**d**, which have binding functionalities at the homobenzylic positions, were synthesized as possible neutral receptors toward anions with an expectation that the three binding sites work cooperatively to bind an anion selectively. ^{1}H NMR spectroscopic monitoring of the titration of cryptand **4b** with $CH_3CO_2^-$, Cl^-, and F^- in $CDCl_2CDCl_2$ at 100 °C showed that the binding constants were considerably smaller than those of tripodal thiourea **5a**, presumably owing to the presence of strong intramolecular hydrogen bonding in **4b**. Complexation constants of tripodal receptors **5a**–**d** with $H_2PO_4^-$, $CH_3CO_2^-$, Cl^-, and Br^- anions were evaluated by ^{1}H NMR and/or UV/Vis spectroscopic analysis of the titration in DMSO. Though tripodal receptors **5a**,**b** undergo complexation with phosphate anion in a 1:1 stoichiometry, their association constants were not as large as simple reference compound **14** probably because of the steric hindrance around the binding sites and the large entropy cost for cooperative binding. Receptor **5c** exhibits complexation in a 1:2 stoichiometry with $H_2PO_4^-$ and $CH_3CO_2^-$, whereas it forms 1:1 complexes with chloride and bromide anions because of the subtle balance between the steric hindrance and the binding ability. However, by increasing the acidity of the thiourea functionality, receptor **5d** exhibited remarkably enhanced binding ability and selectivity toward $H_2PO_4^-$ compared to those of reference compound **15** presumably through cooperative complexation of the three binding sites to the guest anion.

Introduction

Elucidation of basic principles for anion recognition and development of highly selective receptors toward anionic species have been attracting much interest in supramolecular chemistry during the last two decades from the view point of chemical, biological, and environmental processes.[1] A number of anion receptors have been reported so far which have various functional groups as anion binding sites. These include positively charged functional groups such as ammonium,[2] guanidinium,[3] pyridinium,[4] and imidazolium[5] ions, as well as coordinatively unsaturated metal ions.[6] For neutral hydrogen-bond donor groups, amides,[7] sulfonamides,[8] ureas,[9] thioureas,[10] and pyrroles[11] are employed. Neutral anion receptors capable of hydrogen bonding to anions have been extensively studied because counterion interferences do not have to be considered and hydrogen bonding exerts directional interactions with certain anions. On the other hand, the binding abilities of neutral receptors are weaker than the positively charged receptors and they are sensitive to the circumstances, for example polarity of solvents. One of the strategies used to design receptors which recognize a guest anion strongly and selectively is to increase dimensions of their structures in order to arrange the binding sites in an appropriate position for complexation (i.e. preorganization). Indeed, it is well-known for cation receptors that the structural dimension of host molecules plays a significant role in the recognition of guest species; receptors with higher structural dimension tend to exhibit larger binding ability and selectivity toward cations. For example, cyclic 18-crown-6 exhibits an association constant towards K^+ that is 7,000-fold larger than that of the corresponding acyclic polyether (i.e. pentaglyme), and the corresponding cryptand binds with a strength that is more than 600,000-fold stronger than 18-crown-6.[12]

According to this concept, we[13] and others[10,14] have been studying neutral receptors having thiourea moieties as binding sites to develop new selective receptors for anions. Previously, we reported that two-dimensional cyclophane-based receptors such as **1** and **2** (Scheme 1), in which binding sites are appropriately preorganized for complexation with guest anions, showed much larger association constants than those of the corresponding acyclic receptor. Especially, the association constant of lariat-type receptor **2** with a phosphate anion was more than 20 times larger than that of the acyclic one.[13b]

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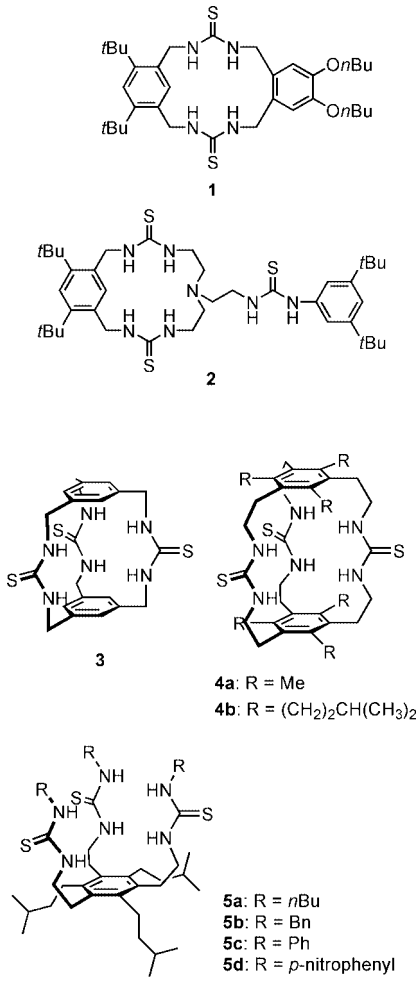
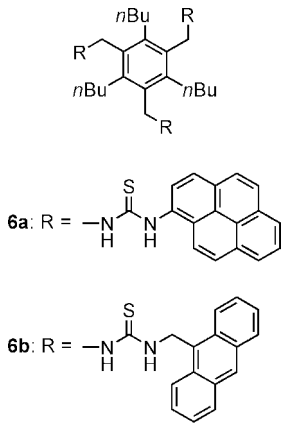


Scheme 1. Anion receptors with thiourea groups.

Molecular designs along the above line led to cage ("cryptand") structure **3**. However, molecular modeling examination revealed that the thiourea linkages of **3** are so rigid that all of the N–H groups could not orient inside the cage. In this respect, we designed "homobenzylic" cryptands **4a**,**b** in which the thiourea group can rotate freely. We also designed tripod-type host molecules **5a**–**d**. Although these do not have a three-dimensional structure, all three binding sites attached to the 1,3,5-positions on the benzene ring of **5a**–**d** are expected to orient to one of the faces of the ring because of steric repulsion between the neighboring substituents,[15] which thereby creates a three-dimensional binding site like that in cryptand-like **4**. Indeed, a number of tripodal receptors possessing binding functionalities at the benzylic positions have already been synthesized and their binding ability toward ammonium cations,[16] (spherical) anions,[10f,17] carboxylates,[18] sugar-based anions,[19] sugar derivatives,[20] and others[21] have been investigated.[22] Moreover, in regard to tripodal receptors having thiourea groups, Suzuki et al. reported that compounds **6a** and **6b**, which have benzylic thiourea groups and fluorescent chromophores bind $H_2PO_4^-$ selectively (Scheme 2).[10f] However, there is no report of the receptors having any binding functionalities at the "homobenzylic" positions. It would be interesting to see whether the cooperative effect of multiple binding sites would work even in the more flexible homobenzylic systems. In this context, we describe here the synthesis of cryptand- and tripod-type thiourea derivatives **4b** and **5a**–**d** and their anion binding abilities.

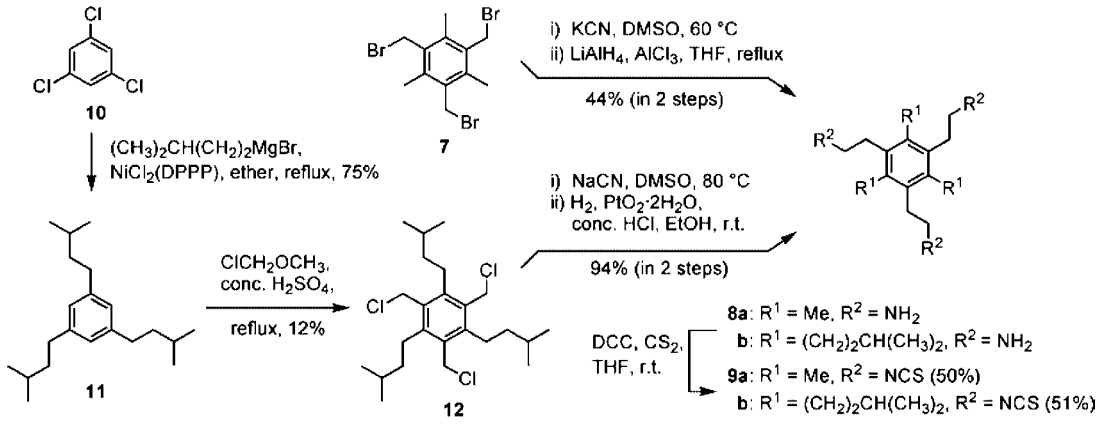


Scheme 2. Tripodal receptors having benzylic thiourea groups.

Results and Discussion

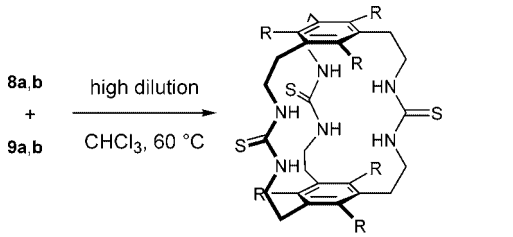
Preparation of the Receptors

First, synthesis of cryptand-type receptor **4a** having methyl groups at the 2,4,6-positions of the benzene ring was attempted as shown in Scheme 3 and Scheme 4. Substitution of tribromide **7**[23] with KCN followed by reduction with $LiAlH_4$ in the presence of $AlCl_3$ gave triamine **8a** in 44% yield over two steps. After conversion of **8a** to isothiocyanate **9a** by treatment with DCC and CS_2 (50% yield), cyclization between **8a** and **9a** was carried out in $CHCl_3$ under dilute conditions (Scheme 4). As a result, white solid precipitated from the solution, which turned out to include **4a** and higher oligomers, as judged from the FAB mass spectra of the solid. However, it was not possible to separate cyptand **4a** from the oligomers owing to their low solubilities in common organic solvents. In order to solve this solubility problem, receptor **4b** carrying isopentyl groups instead of methyl groups was prepared. Thus, the cross coupling reaction of 1,3,5-trichlorobenzene (**10**) with isopentylmagnesium bromide with $NiCl_2$(DPPP) as the catalyst[24] gave 1,3,5-tris(3-methylbutyl)benzene (**11**) in 75% yield.[25] Chloromethylation of **11** with chloromethyl methyl ether catalyzed by conc. H_2SO_4 gave trichloride **12** in 12% yield. Cyanation of **12** by NaCN in DMSO followed by reduction of the cyanide by hydrogenation with catalytic platinum oxide gave corresponding triamine **8b** in 94% yield over the two steps. Triamine **8b** was converted to isothiocyanate **9b** by treatment with DCC and CS_2 in 51% yield. Finally, cyclization of **8b** and **9b** was carried out under dilute conditions to give cryptand-type receptor **4b** in 61% yield. Tripodal receptors **5a**–**d** were prepared by the reactions of triamine **8b** with corresponding commercially available isothiocyanates **13a**–**d** (**a**: R = *n*-butyl, **b**: R = ben-

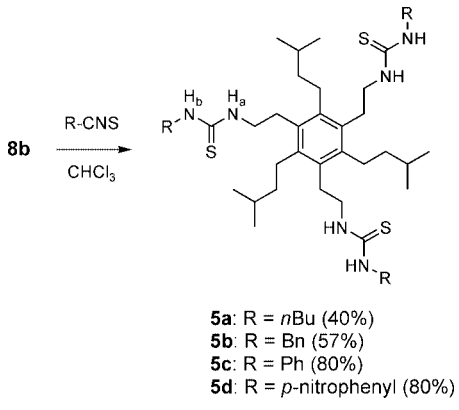


Scheme 3. Synthesis of hexasubstituted benzene derivatives **8a**,**b** and **9a**,**b**.

zyl, **c**: R = phenyl, **d**: R = *p*-nitrophenyl) in 40%, 57%, 80%, and 80% yields, respectively (Scheme 5). Model compounds **14**[26] and **15**[27] were also prepared by reaction of appropriate amines and isothiocyanates (88% and 73% yields, respectively)



Scheme 4. Synthesis of cryptands **4a**,**b**.



Scheme 5. Synthesis of tripods **5a**–**d** and the structures of model compounds **14** and **15**.

Complexation with Guest Anions

To investigate complexation of cryptand-type receptor **4b** with anionic species, ^{1}H NMR spectroscopic monitoring of the titration experiment of **4b** was carried out in [D_6]-DMSO. However, the observed ^{1}H NMR signals of **4b** in [D_6]DMSO were very broad even at high temperatures, probably because of its slow conformational change on the NMR timescale owing to the relatively rigid three-dimensional cyclophane structure and intramolecular hydrogen bonds between the thiourea functionalities. In less polar solvents such as $CDCl_3$ and $CDCl_2CDCl_2$, the signals of **4b** were barely sharp enough to determine exact chemical shifts. Moreover, because the thiourea binding site of **4b** is not electronically conjugated with an aromatic chromophore, spectral changes in the UV spectrum of **4b** were not expected to be sufficient to determine complexation constants with the anions. For these reasons, titration experiments of **4b** toward anionic species were carried out at 100 °C in $CDCl_2CDCl_2$ by using NMR spectroscopy and the binding constants were compared with those of tripodal thiourea **5a** (vide infra). Prior to the titration, the absence of concentration dependence on the chemical shifts of **4b** and **5a** was checked, and the possibility of *intermolecular* hydrogen bonding between their thiourea groups was thus excluded. Because the NH proton signal became significantly broad upon addition of a guest anion, the titration was carried out following the chemical shift change of the methylene protons adjacent to the NH group. Though the chemical shift change with bromide, nitrate, hydrogensulfate, and perchlorate anions was too small to determine the binding constants, reliable results were obtained with acetate, chloride, and fluoride.[28] The association constants that were determined assuming a 1:1 binding stoichiometry are listed in Table 1.[29] In spite of our expectation, the binding constants of **4b** were much smaller than those of **5a**, which suggests the absence of cooperative anion binding. Moreover, neither **4b** nor **5a** exhibits binding selectivity toward the anions, except for the small selectivity of **5a** toward chloride anion. The lower binding ability of **4b** than that of acyclic **5a** is attributed to the presence of strong *intramolecular* hydrogen bonding in the nonpolar solvent which hinders the competitive anion binding.

On the other hand, tripodal thiourea derivatives **5a**–**d** are readily soluble and gave unambiguous ^{1}H NMR signals in [D_6]DMSO solution, which allowed for the determination of the complexation constants by ^{1}H NMR spectroscopy. For host **5d**, UV/Vis spectra can also be used because the thiourea group is directly linked to the *p*-nitrophenyl chro-

Table 1. Association constants (M^{-1}) of cryptand-type receptor **4b** and tripodal receptor **5a**.[a]

Anion[b]	**4b**	**5a**
$CH_3CO_2^-$	116 ± 9	3030 ± 330
Cl^-	112 ± 3	3700 ± 430
F^-	93 ± 10	1770 ± 89

[a] Determined by ^1H NMR spectroscopy in $CDCl_2CDCl_2$ at 373 K. [b] Used as a tetrabutylammonium salt.

mophore. First, the stoichiometry of the complexations of **5a**,**b** with $Bu_4N^+H_2PO_4^-$ was investigated by the Job's plot by using ^1H NMR spectra as shown in Figure 1 for **5b**. It is revealed that both **5a** and **5b** bind $H_2PO_4^-$ with a 1:1 stoichiometry, which indicates that three thiourea moieties in these host molecules cooperatively bind one guest anion. To determine the association constants of hosts **5a** and **5b** with anions, titration experiments by ^1H NMR spectroscopy were undertaken with the use of $H_2PO_4^-$, $CH_3CO_2^-$, Cl^-, and Br^- as the corresponding Bu_4N^+ salts.[30] The chemical shift change of the NH proton in the thiourea group was used for determination of the binding constants. The results are shown in Table 2. Receptors **5a** and **5b** bind $H_2PO_4^-$ most strongly, followed by $CH_3CO_2^-$, Cl^-, and Br^-. The binding constants of receptor **5b** are almost identical to those of **5a**, which indicates little effect of the terminal benzyl group upon complexation. Moreover, the binding constants of **5a** and **5b** toward $H_2PO_4^-$ and $CH_3CO_2^-$ are obviously smaller than those of reference receptor **14** which has only one binding site. These facts indicate that even though the three thiourea moieties that are bonded to the 1,3,5-positions of the benzene ring participate in the complexation to a guest anion cooperatively, the binding ability was not enhanced unlike benzylic thiourea **6b**. This is probably due to the steric hindrance around the binding site and the large entropy cost for cooperative binding.

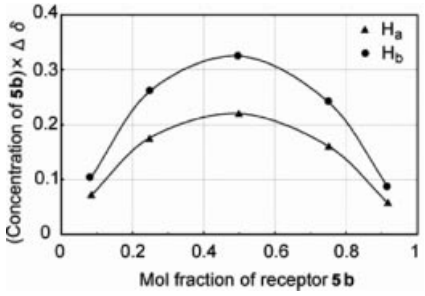


Figure 1. Job's plot for complexation of receptor **5b** with phosphate anion.

To investigate if the cooperative effect due to the homobenzylic tripod structure would elicit large and/or selective binding ability toward a specific anion when the interaction between a host and a guest is strengthened, the acidity of NH in the thiourea group was increased by introducing phenyl groups. Contrary to our expectation, however, receptor **5c** formed complexes with $H_2PO_4^-$ and $CH_3CO_2^-$ in a 1:2 stoichiometry, as indicated by the Job's plot using ^1H NMR spectra as shown in Figure 2 for $CH_3CO_2^-$. On the other hand, the Job's plot revealed that receptor **5c** binds spherical anions, Cl^- and Br^-, in a 1:1 stoichiometry. These results indicate that the bulky phenyl groups directly attached to the binding sites interfere with the cooperative complexation of a nonspherical anion for steric reasons; accordingly the binding sites interact with the anions independently. Such a subtle balance between steric hindrance and binding ability of the host, and the geometry of the guests is not fully understood. The association constants toward $H_2PO_4^-$ and $CH_3CO_2^-$ were estimated assuming a 1:2 complexation [K_a = (56000 ± 23000) M^{-2}, and (52000 ± 5000) M^{-2}, respectively], while those toward Cl^- and Br^- with a 1:1 complexation [K_a = (9.5 ± 0.7) M^{-1}, (1.80 ± 0.07) M^{-1}, respectively].

Table 2. Association constants (M^{-1}) of tripodal receptors **5a**–**c** and model compound **14**.[a]

Anion[b]	**5a**	**5b**	**5c**	**14**
$H_2PO_4^-$	87 ± 4	90 ± 5	56000 ± 23000[c]	128 ± 14
$CH_3CO_2^-$	44 ± 3	52 ± 4	52000 ± 5000[c]	351 ± 28
Cl^-	6.8 ± 0.4	11 ± 1	9.5 ± 0.7	ND[d]
Br^-	2.2 ± 0.1	1.4 ± 0.1	1.80 ± 0.07	ND[d]

[a] Determined by ^1H NMR spectroscopy in [D_6]DMSO at 303 K. [b] Used as a tetrabutylammonium salt. [c] Assuming the complexation of the host and guest in a 1:2 stoichiometry. The unit is given in M^{-2}. [d] Not determined.

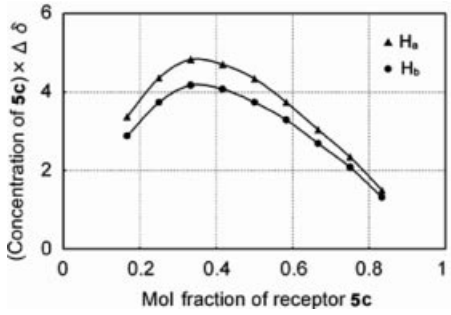


Figure 2. Job's plot for complexation of receptor **5c** with acetate anion.

In order for further investigation on the cooperative effect due to the homobenzylic tripod structure, the acidity of NH in the thiourea group[31] was increased further by introducing *p*-nitrophenyl groups.[14j,14f,32] In contrast to the structurally similar tripodal receptor **5c**, the Job's plot (not shown) using UV/Vis spectroscopy showed that **5d** bound $H_2PO_4^-$ and $CH_3CO_2^-$ with a 1:1 stoichiometry, which indicates cooperative anion binding. The association constants of **5d** as well as model compound **15** were determined by UV/Vis spectra[33] for $H_2PO_4^-$ and $CH_3CO_2^-$ in DMSO and by ^1H NMR spectra for Cl^- and Br^- in [D_6]DMSO. The results are summarized in Table 3. As we expected, the association constants of **5d** became significantly larger than those of **5a** and **5b**, particularly so for $H_2PO_4^-$ and $CH_3CO_2^-$. The increase in the binding constants for Cl^- and Br^- was not as remarkable. As a result, **5d** exhibits highly selective anion binding in the order $CH_3CO_2^-$ ≈

$H_2PO_4^- >> Cl^- > Br^-$. It should be pointed out, however, that model compound **15** also exhibits larger binding constants for $H_2PO_4^-$ and $CH_3CO_2^-$ compared with corresponding model compound **14**.

Table 3. Association constants (M^{-1}) of tripodal receptor **5d** and model compound **15**.

Anion[a]	**5d**	**15**
$H_2PO_4^-$	41000 ± 8000[b]	3100 ± 400[b]
$CH_3CO_2^-$	51000 ± 4000[b]	40000 ± 8000[b]
Cl^-	23.5 ± 0.6[c]	41.9 ± 0.5[c]
Br^-	4.2 ± 0.2[c]	4.5 ± 0.1[c]

[a] Used as a tetrabutylammonium salt. [b] Determined by UV/Vis spectroscopy in DMSO at 303 K. [c] Determined by ^1H NMR spectroscopy in $[D_6]$DMSO at 303 K.

It should be pointed out that benzylic thioureas **6a** and **6b** are reported to a show slight preference for $H_2PO_4^-$ compared with $CH_3CO_2^-$, whereas their acyclic reference compounds exhibit selectivity toward the latter anion,[10f] as observed for **14** and **15**. Even though **5d** binds $CH_3CO_2^-$ more strongly in contrast to **6a** and **6b**, the difference is negligible when the experimental errors are taken into account. These results suggest that the three thiourea groups of **5d** bind an anion cooperatively like **6a** and **6b** in spite of the larger conformational flexibility of **5d**.

In Figure 3 and Figure 4, the UV/Vis spectral changes of **5d** and **15** upon complexation with $H_2PO_4^-$ and $CH_3CO_2^-$ are shown. When $H_2PO_4^-$ was used, the intensity of the absorption band of **5d** at 361 nm decreased, while the band at around 382 nm increased with an increase in the concentration of the guest anion (Figure 3a). On the other hand, when $CH_3CO_2^-$ was used, the growth of a new band at 488 nm, much more redshifted than the new band observed in the case of $H_2PO_4^-$, was observed together with the decay of the band at 361 nm (Figure 3b). The same behavior was observed in the case of complexation of model compound **15** with both $H_2PO_4^-$ (Figure 4a) and $CH_3CO_2^-$ (Figure 4b). These remarkably redshifted bands indicate the formation of a thioureido anion arising from proton transfer from the relatively acidic NH group in **5d** and **15** to $H_2PO_4^-$ or $CH_3CO_2^-$as shown in Figure 5.[32a,34] To confirm this possibility, we examined the UV/Vis spectral change of **5d** and **15** in the presence of a strong base such as NaOH. As a result, upon addition of an equimolar amount of NaOH, **5d** and **15** exhibited absorptions at 490 and 483 nm (Figures S28 and S29 in Supporting Information), respectively, which indicates that the complexation between **5d** and $CH_3CO_2^-$ and between **15** and both $H_2PO_4^-$ and $CH_3CO_2^-$ take place between the corresponding thioureido anion and the neutral acids in a manner shown in Figure 5. The remarkable larger binding constant of **5d** with $H_2PO_4^-$ than that of **15** is therefore ascribed to the cooperative hydrogen bonding of the three binding sites of **5d**. In contrast, the binding constant of **5d** with more basic $CH_3CO_2^-$ is in the same order of magnitude as that of **15**, presumably because cooperative hydrogen bonding of the thiourea groups is not possible owing to the formation of the thioureido anion. Further design of suitable thiourea-based, anion-binding host molecules with high structural dimension is currently undertaken in our laboratories.

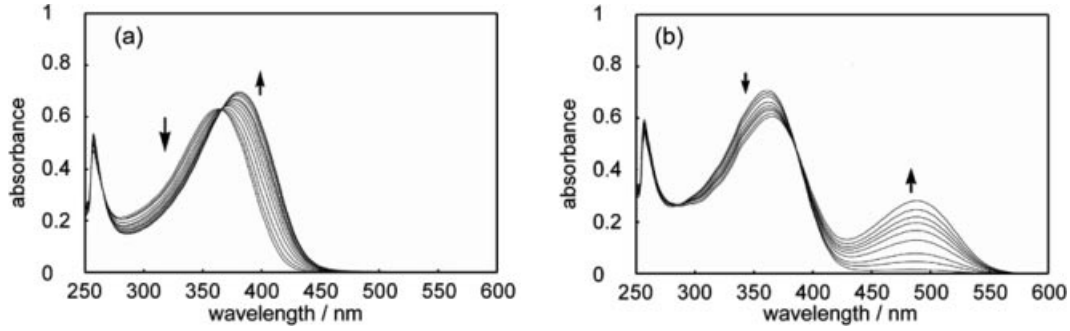


Figure 3. UV/Vis spectral change of receptor **5d** upon complexation with (a) tetrabutylammonium phosphate ([host] = 1.43×10^{-5} M, $0 \leq$ [guest] $\leq 8.74 \times 10^{-5}$ M) and (b) tetrabutylammonium acetate ([host] = 1.55×10^{-5} M, $0 \leq$ [guest] $\leq 4.16 \times 10^{-5}$ M).

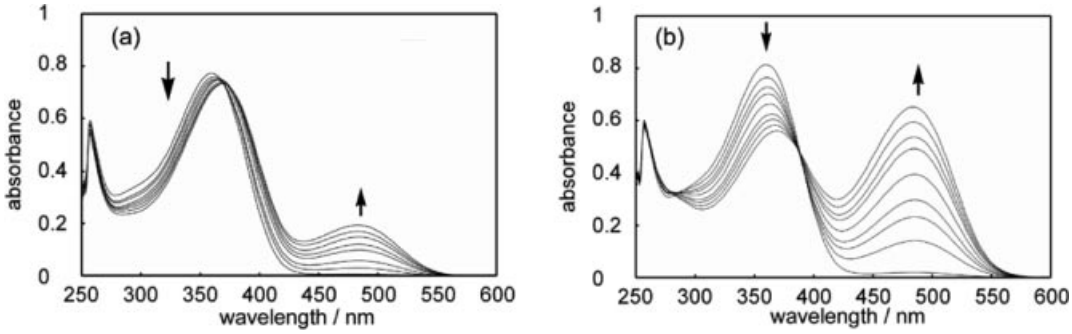


Figure 4. UV/Vis spectral change of receptor **15** upon complexation with (a) tetrabutylammonium phosphate ([host] = 5.19×10^{-5} M, $0 \leq$ [guest] $\leq 8.99 \times 10^{-4}$ M) and (b) tetrabutylammonium acetate ([host] = 5.40×10^{-5} M, $0 \leq$ [guest] $\leq 1.44 \times 10^{-4}$ M).

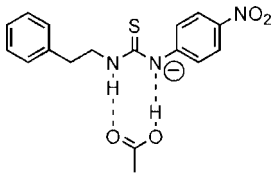


Figure 5. A complex of the thioureido anion of **15** with acetic acid.

Conclusions

In summary, we have prepared cryptand- and tripod-shaped neutral receptors having thiourea groups as anion-binding sites and examined their binding ability toward guest anions. The binding constants of **4b** with $CH_3CO_2^-$, Cl^-, and F^- were considerably smaller than those of tripodal thiourea **5a**, presumably owing to the presence of strong *intramolecular* hydrogen bonds in **4b**. Although the three binding sites of tripodal receptors **5a** and **5b** bind an anion cooperatively, they showed unexpectedly small association constants toward the anions, presumably owing to the steric hindrance and the entropy cost for cooperative binding. On the other hand, **5c** exhibits complexation in a 1:2 stoichiometry with $H_2PO_4^-$ and $CH_3CO_2^-$, whereas it binds in a 1:1 stoichiometry with chloride and bromide because of the subtle balance between the steric hindrance and the binding ability. Finally, as a result of enhanced acidity of the binding moieties, tripodal receptor **5d** exhibits a 10-fold increase in the association constant in the complexation with $H_2PO_4^-$ than that of model compound **15** through cooperative binding.

Experimental Section

General: ^{1}H NMR spectra were recorded with a JEOL JNM-AL-400 or a JEOL JNM-GSX-270 spectrometer in $CDCl_3$, [D_6]-DMSO, or $CDCl_2CDCl_2$ with Me_4Si as an internal standard. IR spectra were recorded as a KBr disk or a neat film with a JASCO FTIR-410 instrument. Mass spectral analysis was preformed with a JEOL JMS-DX303HF instrument. Elemental analyses were performed with a Perkin–Elmer 2400 II analyzer. Column chromatography and TLC were performed using Merck silica gel 60 (70–230 mesh ASTM) and Merck silica gel 60 F_{254}, respectively. Preparative HPLC separation was undertaken with a JAI LC-908 chromatograph by using 600-mm × 20-mm JAIGEL-1H and 2H GPC columns with $CHCl_3$ as the eluent.

1,3,5-Tris(chloromethyl)-2,4,6-tris(3-methylbutyl)benzene (12): To a solution of 1,3,5-tris(3-methylbutyl)benzene (**11**)[25] (6.40 g, 22.0 mmol) in chloromethyl methyl ether (50 mL) was added concentrated sulfuric acid (4 mL), and the reaction mixture was heated at reflux for 10 h. Water was added with cooling in an ice bath, and the mixture was extracted with diethyl ether. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried with anhydrous $MgSO_4$, filtered, and concentrated. The product was purified by column chromatography (silica gel, hexane) to afford 1.16 g (12%) of **12** as a white solid. M.p. 98–100 °C. IR (KBr): $\tilde{\nu}$ = 722, 663 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.03 (d, J = 6.6 Hz, 18 H), 1.45–1.53 (m, 6 H), 1.71–1.84 (m, 3 H), 2.83–2.88 (m, 6 H), 4.64 (s, 6 H) ppm. MS (EI): m/z = 432 [M]$^+$. $C_{24}H_{39}Cl_3$ (432.21): calcd. C 66.43, H 9.06; found C 66.59, H 9.28.

1,3,5-Tris(2-aminoethyl)-2,4,6-trimethylbenzene (8a): A mixture of tribromide **7**[22] (21.5 g, 54.0 mmol) and potassium cyanide (17.6 g, 270 mmol) in DMSO (150 mL) was warmed to 60 °C and stirred for 20 h at this temperature. The mixture was then poured into water to give a precipitate, which was filtered, washed with water, and dried. The product was purified by column chromatography (silica gel, 50% AcOEt in benzene) to afford 10.4 g (81%) of 1,3,5-tris(cyanomethyl)-2,4,6-trimethylbenzene as a white solid. M.p. 212–214 °C. IR (KBr): $\tilde{\nu}$ = 2249, 803 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.46 (s, 9 H), 3.73 (s, 6 H) ppm. To a suspension of $LiAlH_4$ (3.80 g, 100 mmol) in THF (250 mL) was added dropwise a solution of $AlCl_3$ (13.3 g, 100 mmol) in THF (200 mL), and the mixture was stirred for 5 min at room temperature. A solution of 1,3,5-tris(cyanomethyl)-2,4,6-trimethylbenzene (2.37 g, 9.99 mmol) in THF (150 mL) was added dropwise, and the mixture was heated at reflux for 12 h. Water was added dropwise with cooling in an ice bath and then 10% aqueous HCl was added. The mixture was washed with diethyl ether, and the aqueous layer was made alkaline with 2 N aqueous NaOH. To this solution was added $CHCl_3$, and the mixture was shaken vigorously. The resulting emulsion was passed through a pad of Celite and the organic phase was separated, washed with brine, dried with anhydrous $MgSO_4$, filtered, and concentrated to leave 1.35 g (54%) of **8a** as a white solid, which was used for the subsequent reaction without further purification. M.p. 109–111 °C. IR (KBr): $\tilde{\nu}$ = 3354, 878, 748 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26 (br. s, 6 H), 2.32 (s, 9 H), 2.83 (m, 12 H) ppm.

1,3,5-Tris(2-aminoethyl)-2,4,6-tris(3-methylbutyl)benzene (8b): A mixture of trichloride **12** (670 mg, 1.5 mmol) and sodium cyanide (0.74 g, 15 mmol) in DMSO (10 mL) was warmed to 80 °C and stirred for 1 h at this temperature. Water was added, and the reaction mixture was extracted with ethyl acetate. The organic layer was washed with water and brine, dried with anhydrous $MgSO_4$, filtered, and concentrated. The product was purified by column chromatography (silica gel, benzene) to afford 615 mg (98%) of 1,3,5-tris(cyanomethyl)-2,4,6-tris(3-methylbutyl)benzene as a white solid. M.p. 193–194 °C. IR (KBr): $\tilde{\nu}$ = 2275, 920, 758 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.05 (d, J = 6.6 Hz, 18 H), 1.40–1.48 (m, 6 H), 1.73–1.83 (m, 3 H), 2.72–2.78 (m, 6 H), 3.68 (s, 6 H) ppm. MS (CI): m/z = 406 [M]$^+$. $C_{27}H_{39}N_3$ (405.62): calcd. C 79.95, H 9.69, N 10.36; found C 79.76, H 9.82, N 10.17. To a suspension of 1,3,5-tris(cyanomethyl)-2,4,6-tris(3-methylbutyl)benzene (100 mg, 0.25 mmol) in ethanol (30 mL) was added platinum(IV) oxide dehydrate (30 mg, 0.11 mmol) and concentrated aqueous HCl (1 mL), and the reaction mixture was stirred for 60 h at room temperature under an atmosphere of hydrogen. The mixture was passed through a pad of Celite and the filtrate was concentrated. To the residue was added 10% aqueous HCl, and the solution was washed with diethyl ether. The aqueous phase was made alkaline with 2 N aqueous NaOH and extracted with $CHCl_3$. The extract was washed with water and brine, dried with anhydrous $MgSO_4$, filtered and concentrated to leave 100 mg (96%) of **8b** as a white solid, which was used for the subsequent reaction without further purification. M.p. 78–80 °C. IR (KBr): $\tilde{\nu}$ = 3371, 818, 745 cm^{-1}. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 0.99 (d, J = 6.6 Hz, 18 H), 1.31 (br. s, 6 H), 1.35–1.44 (m, 6 H), 1.62–1.77 (m, 3 H), 2.52–2.58 (m, 6 H), 2.67–2.75 (m, 6 H), 2.79–2.87 (m, 6 H) ppm. HRMS (EI): calcd. for $C_{27}H_{51}N_3$ [M]$^+$ 417.4083; found 417.4106.

1,3,5-Tris(2-isothiocyanatoethyl)-2,4,6-trimethylbenzene (9a): To a solution of DCC (1.24 g, 6.01 mmol) in THF (20 mL) and CS_2 (1.52 g, 20.0 mmol), **8a** (500 mg, 2.00 mmol) was added. The reaction mixture was stirred for 3 h, and the solvent was removed in vacuo. The product was purified by column chromatography (silica

gel, 50% benzene in hexane) to afford 373 mg (50%) of **9a** as a white solid. M.p. 107–108 °C. IR (KBr): $\tilde{\nu}$ = 2191, 2108 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ = 2.34 (s, 9 H), 3.15 (t, J = 7.6 Hz, 6 H), 3.61 (t, J = 7.6 Hz, 6 H) ppm.

1,3,5-Tris(2-isothiocyanatoethyl)-2,4,6-tris(3-methylbutyl)benzene (9b): Isothiocyanate **9b** was prepared by the same procedure as described for the preparation of **9a** in 51% yield. M.p. 124–126 °C. IR (KBr): $\tilde{\nu}$ = 2188, 2110, 704 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.02 (d, J = 6.6 Hz, 18 H), 1.29–1.37 (m, 6 H), 1.68–1.77 (m, 3 H), 2.51–2.57 (m, 6 H), 3.01 (t, J = 7.6 Hz, 6 H), 3.63 (t, J = 7.6 Hz, 6 H) ppm. MS (FAB): m/z = 544 $[M + 1]^+$. $C_{30}H_{45}N_3S_3$ (543.90): calcd. C 66.25, H 8.34, N 7.73; found C 66.55, H 8.61, N 7.65.

Cryptand-Type Receptor 4b: A solution of amine **8b** (75 mg, 0.18 mmol) in $CHCl_3$ (50 mL) and a solution of isothiocyanate **9b** (98 mg, 0.18 mmol) in $CHCl_3$ (50 mL) were added dropwise simultaneously to $CHCl_3$ (50 mL) at 60 °C over 1 h. The reaction mixture was heated at reflux for 0.5 h and cooled to room temperature. The crude product was purified by column chromatography (silica gel, $CHCl_3$) to afford 105 mg (61%) of **4b** as a white solid. M.p. 270 °C (dec). IR (KBr): $\tilde{\nu}$ = 3425, 3385, 1545, 886 cm^{-1}. ^1H NMR (400 MHz, $CDCl_2CDCl_2$, 100 °C): δ = 0.94 (d, J = 6.6 Hz, 36 H), 1.20–1.26 (m, 12 H), 1.60–1.66 (m, 6 H), 1.60–1.66 (m, 12 H), 2.46 (t, J = 7.1 Hz, 12 H), 3.35 (br. s, 12 H), 5.36 (br. s, 6 H) ppm. MS (FAB): m/z = 961 $[M]^+$. $C_{57}H_{96}N_6S_3$ (961.61): calcd. C 71.20, H 10.06, N 8.74; found C 71.34, H 10.01, N 8.48.

Tripod-Type Receptor 5a: A solution of butyl isothiocyanate (**13a**) (346 mg, 3.00 mmol) in $CHCl_3$ (5 mL) was added to a solution of triamine **8b** (418 mg, 1.00 mmol) in $CHCl_3$ (5 mL). The reaction mixture was heated at reflux for 0.5 h, and the solvent was removed in vacuo. The product was purified by column chromatography (silica gel, AcOEt and $CHCl_3$) followed by preparative HPLC to afford 305 mg (40%) of **5a** as a white solid. M.p. 100 °C (dec). IR (KBr): $\tilde{\nu}$ = 3268, 1553, 753 cm^{-1}. ^1H NMR (270 MHz, $CDCl_2CDCl_2$, 100 °C): δ = 0.90 (t, J = 7.3 Hz, 9 H), 0.97 (d, J = 6.6 Hz, 18 H), 1.27–1.73 (m, 27 H), 2.10–2.64 (m, 6 H), 2.92 (br. s, 6 H), 3.36 (t, J = 6.9 Hz, 6 H), 3.64 (br. s, 6 H), 5.92 (br. s, 6 H) ppm. MS (FAB): m/z = 764 $[M + 1]^+$. $C_{42}H_{78}N_6S_3$ (763.31): calcd. C 66.09, H 10.30, N 11.01; found C 66.06, H 10.55, N 10.79.

Tripod-Type Receptor 5b: The coupling reaction of benzyl isothiocyanate (**13b**) (131 mg, 0.878 mmol) and triamine **8b** (107 mg, 0.256 mmol) was carried out as described for the preparation of **5a**. The product was purified by column chromatography (silica gel, 20% AcOEt in hexane) followed by recrystallization from ethanol to afford 127 mg (57%) of **5b** as a white solid. M.p. 166–169 °C. IR (KBr): $\tilde{\nu}$ = 3428, 3226, 1557, 753 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.93 (d, J = 6.6 Hz, 18 H), 1.19–1.23 (m, 6 H), 1.56–1.69 (m, 3 H), 2.50–2.55 (m, 6 H), 2.82 (t, J = 6.3 Hz, 6 H), 3.57 (br. s, 6 H), 4.58 (d, J = 4.4 Hz, 6 H), 6.17 (br. s, 3 H), 6.46 (br. s, 3 H), 7.23–7.33 (m, 15 H) ppm. MS (FAB): m/z = 865 $[M + 1]^+$. $C_{51}H_{72}N_6S_3$ (865.36): calcd. C 70.79, H 8.38, N 9.71; found C 70.49, H 8.46, N 9.66.

Tripod-Type Receptor 5c: The coupling reaction of phenyl isothiocyanate (**13c**) (988 mg, 7.31 mmol) and triamine **8b** (781 mg, 1.87 mmol) was carried out as described for the preparation of **5a**. The product was purified by column chromatography (silica gel, 20% AcOEt in hexane) followed by recrystallization from ethanol to afford 1.23 g (80%) of **5c** as a white solid. M.p. 102–105 °C. IR (KBr): $\tilde{\nu}$ = 3398, 3243, 1536, 747 cm^{-1}. ^1H NMR (270 MHz, $[D_6]$-DMSO): δ = 0.98 (d, J = 6.4 Hz, 18 H), 1.24 (br. s, 6 H), 1.72–1.79 (m, 3 H), 2.81 (br. s, 12 H), 3.53 (br. s, 6 H), 7.11 (t, J = 7.3 Hz, 3 H), 7.32 (dd, J = 8.1, 7.3 Hz, 6 H), 7.40 (d, J = 8.1 Hz, 6 H), 8.02 (br. s, 3 H), 9.47 (br. s, 3 H) ppm. MS (FAB): m/z = 823 $[M + 1]^+$. $C_{48}H_{66}N_6S_3$ (822.45): calcd. C 70.03, H 8.08, N 10.21; found C 69.79, H 8.26, N 10.10.

Tripod-Type Receptor 5d: The coupling reaction of *p*-nitrophenyl isothiocyanate (**13d**) (1.86 g, 10.3 mmol) and triamine **8b** (1.12 g, 2.68 mmol) was carried out as described for the preparation of **5a**. The resulting precipitate was washed with $CHCl_3$ to afford 2.07 g (80%) of pure **5d** as a yellow solid. M.p. 132 °C (dec). IR (KBr): $\tilde{\nu}$ = 3110, 1532, 1330 cm^{-1}. ^1H NMR (400 MHz, $[D_6]$DMSO, 30 °C): δ = 0.98 (d, J = 6.4 Hz, 18 H), 8.19 (d, J = 8.8 Hz, 6 H), 8.62 (br. s, 3 H), 10.20 (br. s, 3 H) ppm. HRMS (FAB): calcd. for $C_{48}H_{64}N_9O_6S_3$ $[M + H]^+$ 958.4142; found 958.4129.

Model compound 14: The coupling reaction of benzyl isothiocyanate (**13b**) (801 mg, 5.37 mmol) and benzylamine (1.06 g, 9.95 mmol) was carried out as described for the preparation of **5a**. The resulting precipitate was washed with diethyl ether to afford 1.22 g (88%) of pure **14** as a white solid. M.p. 145.5–146.0 °C. IR (KBr): $\tilde{\nu}$ = 3324, 3290, 1556 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$, 30 °C): δ = 4.63 (d, J = 5.4 Hz, 4 H), 6.00 (br. s, 2 H), 7.36–7.22 (m, 10 H) ppm. MS (FAB): m/z = 257 $[M + 1]^+$. $C_{13}H_{12}N_2S$ (256.10): calcd. C 70.27, H 6.29, N 10.93; found C 69.98, H 6.28, N 10.89.

Model Compound 15: The coupling reaction of *p*-nitrophenyl isothiocyanate (**13d**) (311 mg, 1.73 mmol) and 2-(phenylethyl)amine (560 mg, 4.62 mmol) was carried out as described for the preparation of **5a**. The reaction mixture was extracted with $CHCl_3$, washed with 10% HCl, saturated aqueous $NaHCO_3$, and brine, dried with anhydrous $MgSO_4$, filtered, and concentrated. The product was purified by recrystallization from $CHCl_3$ to give 380 mg (73%) of pure **15** as a pale yellow solid. M.p. 145.0–145.5 °C. IR (KBr): $\tilde{\nu}$ = 3169, 1520, 1347 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$, 30 °C): δ = 3.00 (t, J = 6.7 Hz, 2 H), 4.00–3.93 (m, 2 H), 6.15 (br. s, 2 H), 7.06–7.03 (m, 2 H), 7.66–7.21 (m, 5 H), 8.14–8.10 (m, 2 H) ppm. MS (FAB): m/z = 302 $[M + 1]^+$. $C_{15}H_{15}N_3O_2S$ (301.09): calcd. C 59.78, H 5.02, N 13.84; found C 59.67, H 4.70, N 13.84.

General Procedure for Determination of Association Constants (K_a): $[D_6]$DMSO and DMSO were dried with molecular sieves (4 Å). $CDCl_2CDCl_2$ was passed through a column of activated alumina prior to use. All guest anions are commercially available as tetrabutylammonium salts and were recrystallized from the following solvents: for $Bu_4N^+H_2PO_4^-$ and $Bu_4N^+HSO_4^-$ from EtOAc/acetone, for $Bu_4N^+Cl^-$ and $Bu_4N^+Br^-$ from EtOAc/hexane, and for $Bu_4N^+CH_3CO_2^-$ from EtOAc. $Bu_4N^+F^-$ was obtained as a trihydrate and used without purification.

Titration Experiments Using NMR Spectroscopy: As an example, titration experiment of tripodal receptor **5a** with a $Bu_4N^+H_2PO_4^-$ using ^1H NMR spectroscopy is described here. A 6.18 mM solution of **5a** in $[D_6]$DMSO was prepared in a volumetric flask, and the initial NMR spectrum was recorded. Alternatively, a 103 mM solution of the guest anion in $[D_6]$DMSO was prepared in a volumetric flask. Into a 600 μL solution of the host compound, 40, 55, 5, 10, 20, 20, 30, 30, 40, 40, 40, and 50 μL aliquots of the above solution of the guest was added in this order (a total of 380 μL), and the chemical shifts of the NH and the aromatic protons were recorded each time. Relatively broad peaks were treated by a curve-fitting program implemented in the NMR spectroscopic data system (EXcalibur for Windows 95 ver. 2.02). The association constants were calculated by the nonlinear least-squares technique. The curve fitting data are given in the Supporting Information.

Titration Experiments Using UV/Vis Spectroscopy: As an example, titration experiment of tripodal receptor **5d** with $Bu_4N^+H_2PO_4^-$

using UV/Vis spectroscopy is described here. A 7.14×10^{-5} M solution of **5d** in [D_6]DMSO was prepared in a volumetric flask. Alternatively, a 1.09×10^{-4} M solution of the guest anion in [D_6]DMSO was prepared in a volumetric flask. By using the stock solutions, 14 different solutions containing **5d** (1.43×10^{-5} M) and the guest (ranging from 0 to 8.74×10^{-5} M^{-1}) were prepared. The absorbance at 382 nm was used for calculation of the association constant.

Supporting Information (see footnote on the first page of this article): Titration plots of **4b** with anions, titration plots of **5a**–**d**, titration plots of **14** and **15**, UV spectral changes of **5d** and **15** upon addition of NaOH.

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