2-Aminothiazolinium Based Tripodal Receptors: Synthesis and Recognition of Oxoanions

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Novel 2-aminothiazolinium based tripodal receptors were designed and synthesized. The binding property of these receptors toward various anions was investigated by the isothermal titration calorimetry (ITC) method. Receptor **4** recognized the acetate anion with 1:1 stoichiometry, whereas it bound the other oxoanions such as sulfate and phosphate in complex modes. By modifying the phenyl groups at the 4-position of the thiazoline rings of the tripodal receptor **4** to induce a mutual aromatic stacking interaction among the three ligands, receptor **10** showed totally different binding behavior, which gave rise to the 1:1 binding mode for the sulfate anion. This result was confirmed by ESI MS spectrometry.

Key Words: 2-Aminothiazolinium tripodal receptors, Recognition of oxoanions

Introduction

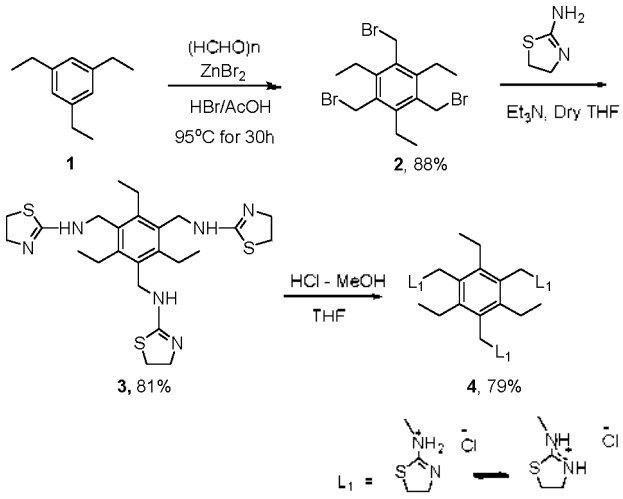
The 2-aminothiazoline ring system has been utilized in medicinal chemistry to prepare biologically active compounds, such as human nitric oxide synthase inhibitors,[1] octopaminergic agonists,[2] anthelmintics,[3] and anti-inflammatory agents.[4] Recently, cationic ligands such as ammonium,[5] isothiouronium groups,[6] and guanidinium[7] have been used as binding sites in anion recognition. However, the thiazoline ring has been explored very little in this field. Fukuyama reported the synthesis of linear and cyclic chiral oligo thiazolines for use as anticancer compounds and mandelic acid recognition.[8] In this communication, novel 2-aminothiazolinium based tripodal receptors were introduced and their binding property toward various anions is discussed.

Results and Discussion

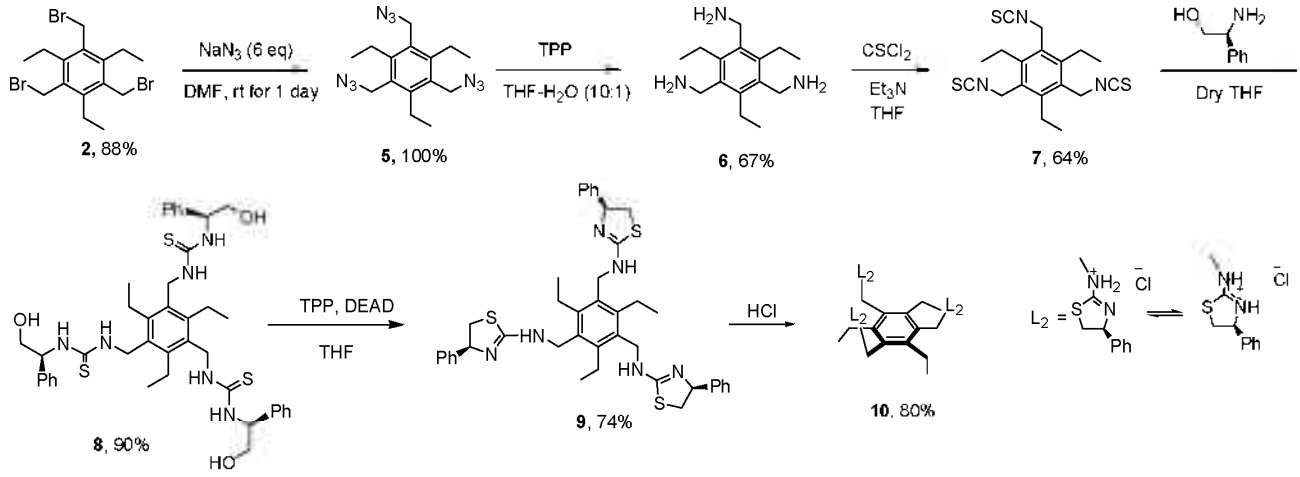
The synthesis of receptor **4** was simply accomplished by the reaction of 1,3,5-tris(bromomethyl)-2,4,6-triethylbenzene **2** and 2-aminothiazoline in the presence of triethylamine to obtain compound **3**, which was easily converted to receptor **4** after treatment with hydrochloric acid (HCl) (Scheme 1). However, the preparation of receptor **10** was more complicated and involved many steps. 1,3,5-Tris(aminomethyl)-2,4,6-triethylbenzene **6** was prepared from 1,3,5-triethylbenzene.[9] The isothiocyanate **7** was obtained by the reaction of the amine compound with thiophosgen in the presence of triethylamine and then with (*S*)-2-phenylglycinol to give the thiourea **8**. The *S*-cyclization of thiourea **8** under Mitsunobu conditions[10] afforded tris(aminothiazoline methyl)-1,3,5-triethyl benzene **9**, which was treated with HCl in methanol to obtain receptor **10** (Scheme 2).

The recognition behavior of receptor **4** toward various anions was first investigated by ^{1}H NMR spectrometry in DMSO-d_6. Upon the addition of 3 equivalents of the acetate anion (Figure 1), the NH proton peaks disappeared and the proton peaks of the three ligands containing the 2-aminothiazoline rings of the receptor shifted to the upfield region, while the other proton peaks for the ethyl groups remained almost unchanged. Although the tetramethylammonium salts of the sulfate and phosphate anions did not dissolve in DMSO-d_6, the addition of these anions to receptor **4** also had similar effects on the ^{1}H NMR spectrum, probably because the host-guest complex with sulfate and phosphate anions dissolved in the NMR solvent. In contrast, no changes in the ^{1}H NMR spectrum of receptor **4** were observed upon the addition of halide anions such as F^-, Cl^-, Br^-, and I^-.

Next, the binding characteristics of receptor **4** toward various oxoanions were evaluated by the ITC method. ITC analysis allows us to determine the host-guest stoichiometry, *n*, as well as the binding constant, by titration curve fitting using the software, Origin. The tetramethylammonium salts of sulfate, phosphate, and tetrabutylammonium salt of acetate were used for the ITC experiments in methanol solvent at 298 K.



Scheme 1. Synthesis of receptor **4**



Scheme 2. Synthesis of receptor **10**

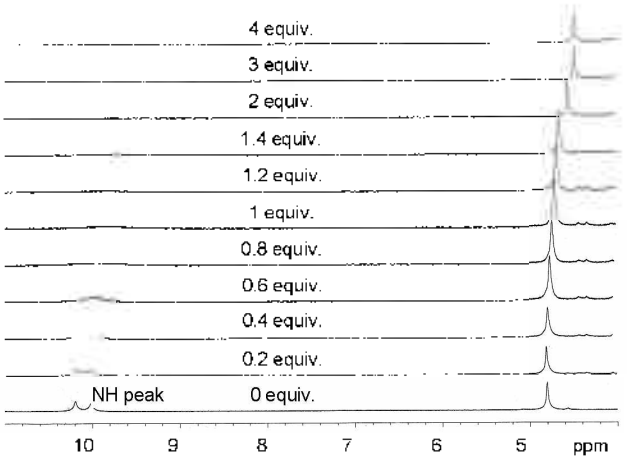


Figure 1. ^{1}H NMR titration of receptor **4** with acetate anion in DMSO-d_6.

As seen in Figure 2, the formation of the complex is strongly driven by favorable entropy changes. The inflection point in the calorimetric isotherm occurs near a mole ratio of 1.0, indicating that receptor **4** binds the acetate anion in 1:1 binding mode with a K value of 23700 M^{-1}. In addition, the ITC titrations with sulfate and phosphate anions (Figure 3, Table 1) showed that receptor **4** binds both of these anions in complex modes. Nonlinear curve fitting in the 'one set of sites mode' of receptor **4** towards the sulfate anion provided an *n* value of 0.465. Therefore, the 2H : 1G binding mode may be suggested in this case, which fits with the partial cone conformation[11,6g] of receptor **4** (Figure 5), as proposed after the titration with acetate and sulfate anions. Since the phosphate anion has a larger size than the sulfate anion, more complicated binding behavior was observed for the phosphate anion with an *n* value of 0.249. These different binding properties towards different anions may be due to the subtle difference in the structure complementarity between host and guest and the different solvation energy. We also attempted to acquire more detailed binding information by electronspray ionization mass (ESI MS) analyses, but the 1:1 host-guest complex of receptor **4** and the acetate anion could not be obtained.

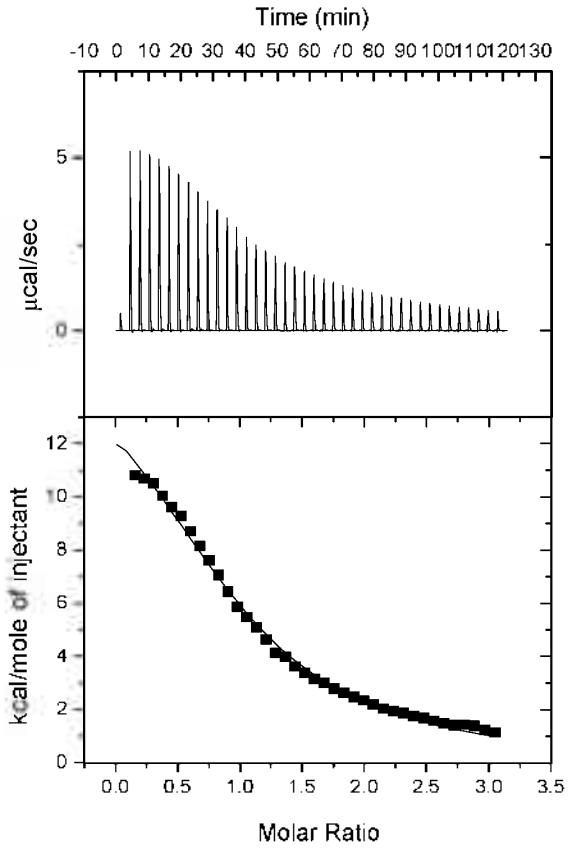


Figure 2. ITC titration data of receptor **4** with OAc^- in MeOH at 298 K.

As discussed above, receptor **4** may adopt an unusual partial cone conformation in order to form the 1:1 host-guest complex with the acetate anion and 2:1 host-guest complex with the sulfate anion (Figure 5). This partial cone conformation can also be explained by the weak interaction among the three ligands containing the simple thiazoline rings in this receptor.

To improve the mutual aromatic stacking interaction among the three ligands in order for the cone conformation to be obtained,[12] phenyl groups were introduced at the 4-position of the thiazoline rings, as seen in receptor **10**. Interestingly,

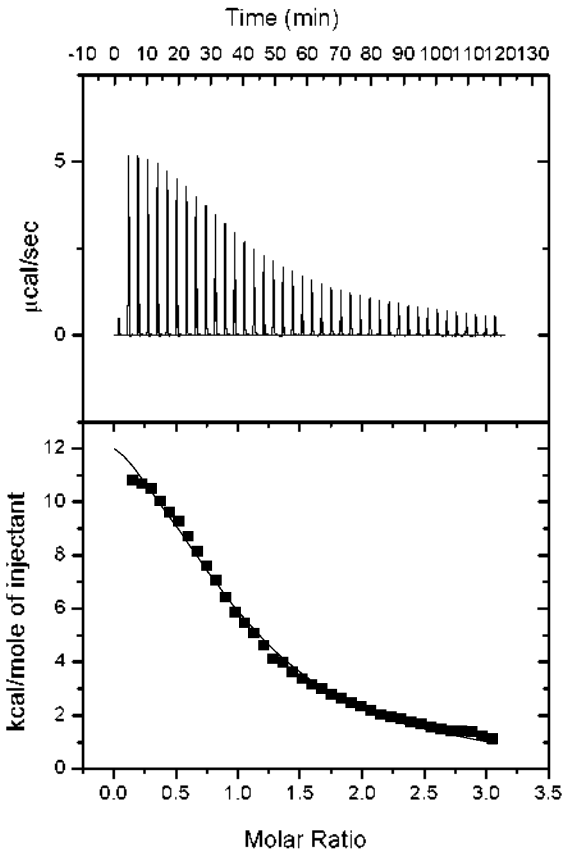


Figure 3. ITC titration data of receptor **4** with SO_4^{2-} in MeOH at 298 K.

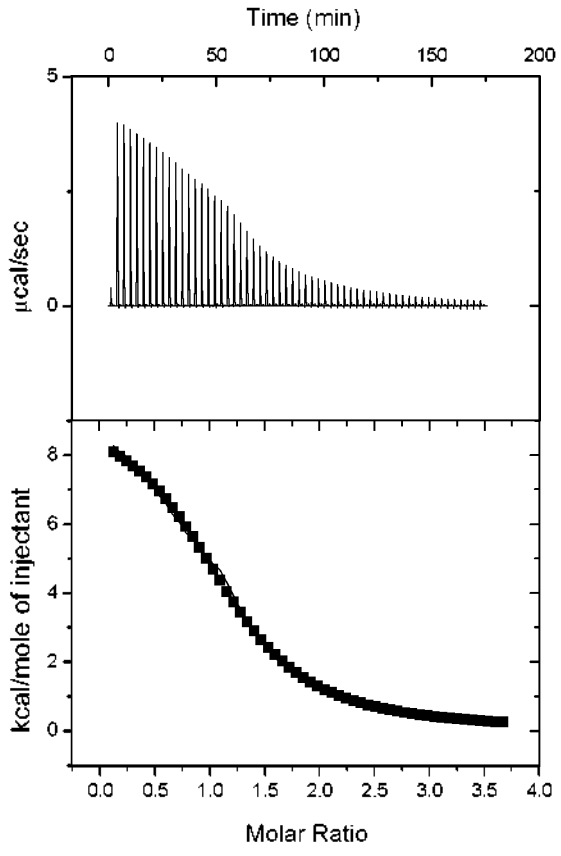


Figure 4. ITC titration data of receptor **10** with SO_4^{2-} in MeOH at 298 K.

according to the ITC experiments, the binding characteristic of receptor **10** is totally different from that of receptor **4**. Receptor **10** binds the sulfate anion in 1:1 stoichiometry with a K value of 51300 M^{-1} (Figure 4). The recognition behavior of receptor **10** in the ^1H NMR spectrum was similar to that of receptor **4**. Due to their subtle structural complementarity, receptor **10** does not fit the phosphate and acetate anions very well and, consequently, *n* values of 0.561 and 2.38, respectively, were observed (Table 1). According to these results, the formation of a 2:1 host-guest complex with the phosphate anion and 1:2 host-guest complex with the acetate anion are suggested. The binding property of receptor **10** towards various anions is quite similar to that of the tripodal receptor based on isothiouronium, as reported by Ahn and coworkers.[6g] The cone conformation of receptor **10** is suitable for binding the sulfate anion. This means that the phenyl groups on the thiazoline rings play an important role in the cone conformation of receptor **10** (Figure 5) in polar methanol solvent.

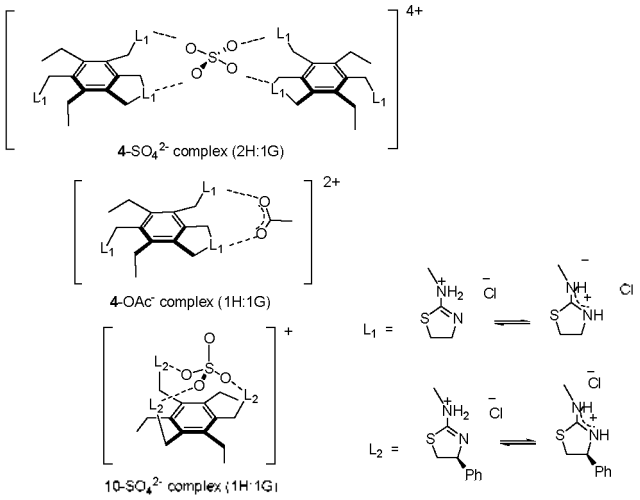


Figure 5. The proposed binding modes of receptors **4** and **10** with SO_4^{2-} and OAc^-.

Table 1. Binding data for the host-guest complexation determined by ITC

Entry	Host	Guest	*n*	ΔG^0 (kcal·mol^{-1})	ΔH^0 (kcal·mol^{-1})	-TΔS (kcal·mol^{-1})	K (M^{-1})
1	**4**	OAc^-	1.00	-5.95	+17.29	-23.24	23700
2	**4**	SO_4^{2-}	0.47	-5.73	+17.90	-23.63	16100
3	**4**	PO_4^{3-}	0.25	-5.61	+19.57	-25.18	13400
4	**10**	OAc^-	2.38	-5.97	+6.72	-12.69	24300
5	**10**	SO_4^{2-}	1.13	-6.42	+9.99	-16.41	51300
6	**10**	PO_4^{3-}	0.54	-5.80	+14.70	-20.50	18100

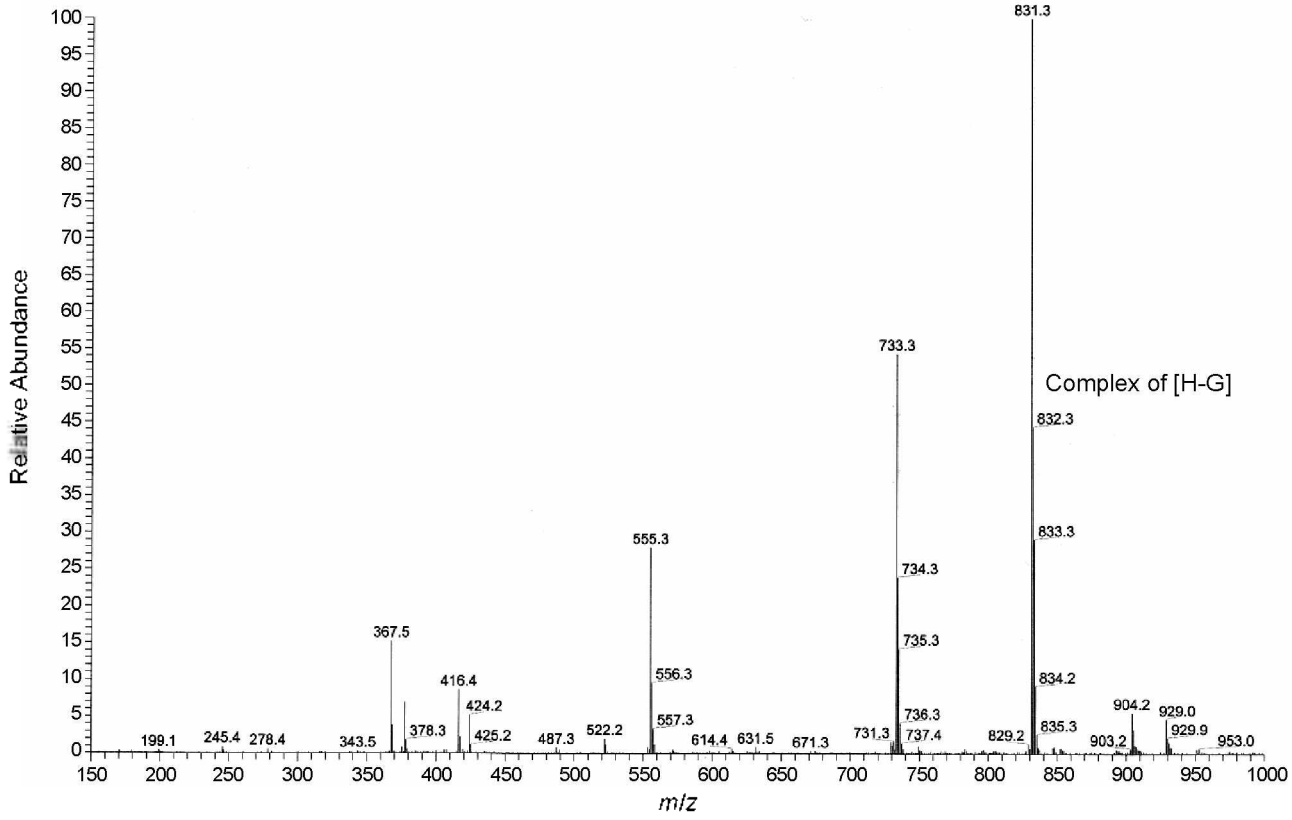


Figure 6. ESI-Mass spectrum (positive mode) of the complex of receptor **10** and SO_4^{2-}.

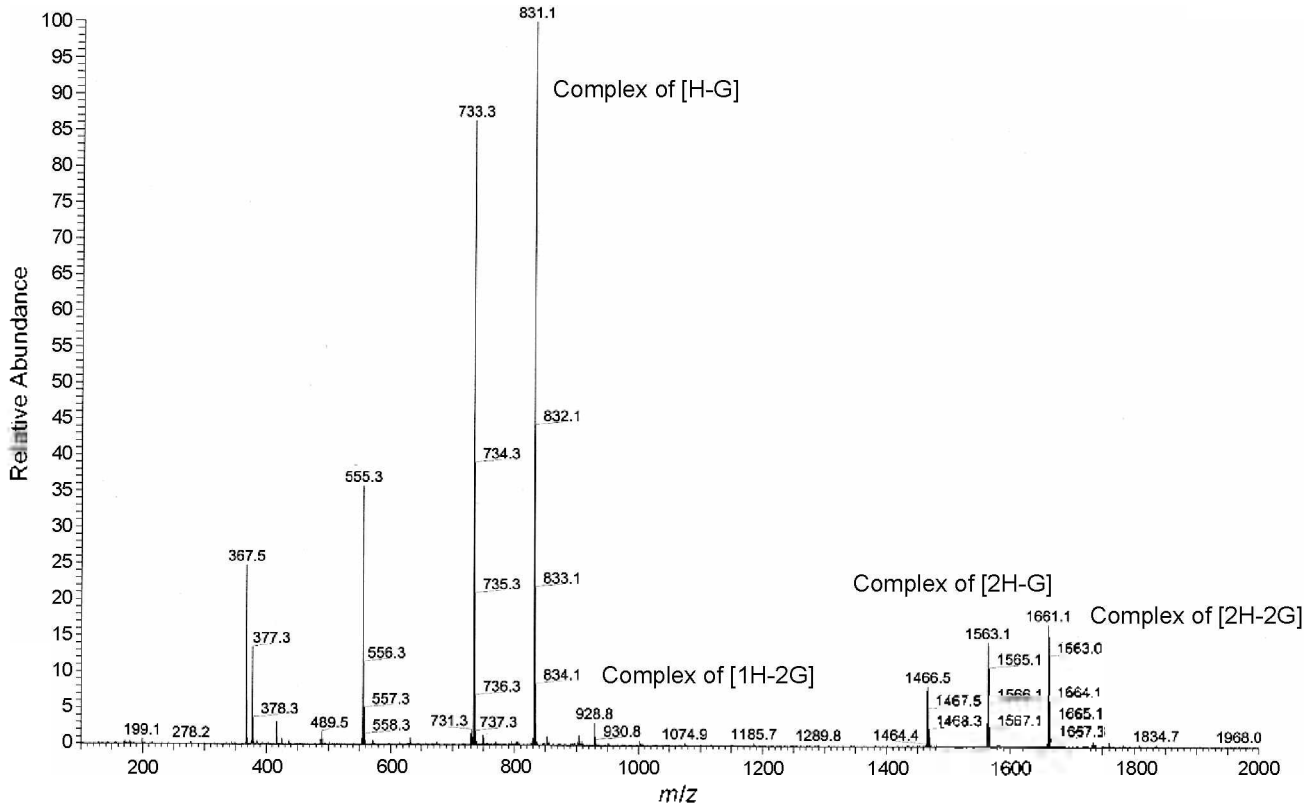


Figure 7. ESI-Mass spectrum (positive mode) of the complex of receptor **10** and PO_4^{3-}

To acquire additional information on the binding modes with various anions, ESI MS analyses were carried out. From the ESI MS spectra, we were able to readily observe the mass of the 1:1 host-guest complex of receptor **10** with the sulfate anion (Figure 6). In addition, host-guest complexes of receptor **10** with the phosphate anion in various complex modes with different ratios of 1:1, 1:2, 2:1, and 2:2 (Figure 7) were also observed.

In conclusion, 2-aminothiazolinium based tripodal receptors were designed and synthesized for the first time. Receptor **4** showed totally different binding modes toward anions compared to receptor **10**, probably due to the low mutual interaction of the three ligands in receptor **4**, causing it to adopt an unusual partial cone conformation. The phenyl groups on the thiazoline rings play an important role in the cone conformation of receptor **10**. The different binding modes of these receptors toward various anions seem to be related to the cavity of the receptors, which arises from the subtle structure constraints of the benzene-based tripodal system, as well as the solvation energy. The use of receptor **10** for chiral anion recognition is under study.

Experimental Section

Preparation of *N,N',N''*-(2,4,6-triethylbenzene-1,3,5-triyl) tris(methylene)tris(4,5-dihydrothiazol-2-amine) (3). A reaction mixture consisting of 1,3,5-tris(bromomethyl)-2,4,6-triethylbenzene (1.1 g, 2.5 mmol), triethylamine (808 mg, 8 mmol) and 2-aminothiazoline (820 mg, 8 mmol) in dry THF was stirred overnight. Water was added to the mixture, and the aqueous layer was extracted with methylene chloride and dried over $MgSO_4$. After concentration, a white solid was obtained (1.03 g, 81%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.14 (t, 9H, J = 7.4 Hz), 2.76 (q, 6H, J = 7.4 Hz), 3.00 (t, 6H, J = 6.8 Hz), 3.29 (t, 6H, J = 6.8 Hz), 4.47 (s, 6H), 7.31 (s, 3H).

Preparation of *N,N',N''*-(2,4,6-triethylbenzene-1,3,5-triyl) tris(methylene)tris(4,5-dihydrothiazol-2-amine) hydrochloride (4). Compound **3** was dissolved in dry THF and 1.25 N HCl in methanol was added dropwise. During the addition of HCl, a precipitate separated out, which was isolated by filtration, washed with THF and dried *in vacuo* to provide the HCl salt **4** as a white solid (79%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.06 (t, 9H, J = 7.4 Hz), 2.64 (q, 6H, J = 7.4 Hz), 3.32 (t, 6H, J = 6.8 Hz), 3.52 (t, 6H, J = 6.8 Hz), 4.82 (s, 6H), 10.12 (s, 3H), 10.27 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 15.26, 22.39, 27.61, 44.78, 52.02, 128.72, 146.02, 169.23; ESI-MS (positive mode) [M^+] 505.2; ESI-MS (negative mode) [M-Cl$^-$] 539.3.

Preparation of 1,3,5-tris(isothiocynatomethyl)-2,4,6-triethylbenzene (7). To a solution of 1,3,5-tris(aminomethyl)-2,4,6-triethylbenzene **6** (1.25 g, 5 mmol) and triethylamine (3 g, 300 mmol) in dry THF was added dropwise thiophosgene (2.3 g, 20 mmol) in dry THF at 0 °C. The reaction mixture was stirred at rt for 2h. After the removal of the solvent, the residue was purified by column chromatography to afford the isothiocyanate **7** as a yellow solid (960 mg, 51%). ^{1}H NMR ($CDCl_3$) δ 1.27 (t, 9H, J = 7.6 Hz), 2.85 (q, 6H, J = 7.6 Hz), 4.75 (s, 6H).

Preparation of 1,3,5-tris-1-methyl-3-(2-hydroxy-1-phenylethyl)-thiourea thiazol-2-yl)-2,4,6,-triethylbenzene (8). To a stirred solution of (S)-(+)2-phenylglycinol (247 mg, 1.8 mmol) in THF (10 mL) under nitrogen at rt was added a solution of isothiocyanate **7** (230 mg, 0.6 mmol) in THF (5 mL) dropwise for 5 min with a syringe. The reaction mixture was stirred for 30 min and evaporated. The crude product was purified by column chromatography to give the thiourea **8** (423 mg, 90%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (t, 9H, J = 7.6 Hz), 2.76 (q, 6H, J = 7.6 Hz), 3.28 (s, 3H), 3.74 (s, 6H), 4.67-4.74 (dd, 6H), 7.21-7.30 (m, 15H).

Preparation of (4*S*)-*N*-(3,5-bis(((*S*)-4,5-dihydro-4-phenylthiazol-2-ylamino)methyl)-2,4,6-triethylbenzyl)-4,5-dihydro-4-phenylthiazol-2-amine (9). To a stirred solution of thiourea **8** (540 mg, 0.69 mmol) and triphenylphosphine (810 mg, 3.09 mmol) in THF (15 mL) under nitrogen at room temperature was added a solution of diethyl azodicarboxylate (538 mg, 3.09 mmol) in THF (5 mL) dropwise for 5 min with a syringe. The reaction mixture was stirred for 30 min and evaporated. The crude product was purified by column chromatography with ethyl acetate to give compound **9** as a white solid (354 mg, 70%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (t, 9H, J = 6.9 Hz), 2.83 (q, 6H, J = 6.9 Hz), 3.27 (dd, 3H), 3.75 (dd, 3H), 3.74 (s, 6H), 4.56 (d, 3H, J = 13 Hz), 4.66 (d, 3H, J = 13 Hz), 5.38 (t, 3H, J = 7.7 Hz), 7.32-7.43 (m, 15H).

Preparation of (4*S*)-*N*-(3,5-bis(((*S*)-4,5-dihydro-4-phenylthiazol-2-ylamino)methyl)-2,4,6-triethylbenzyl)-4,5-dihydro-4-phenylthiazol-2-amine hydrochloride (10). Compound **9** was dissolved in dry THF and 1.25 N HCl in methanol was added dropwise. During the addition of HCl, a precipitate separated out, which was isolated by filtration, washed with THF and dried *in vacuo* to provide the HCl salt **10** as a yellow solid (80%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.12 (t, 9H, J = 7.1 Hz), 2.73 (m, 6H), 3.49 (m, 3H), 4.00 (m, 3H), 4.72 (s, 6H), 5.56 (t, 3H, J = 9 Hz), 7.32-7.63 (m, 15H), 10.31 (s, 3H), 10.85 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 16.10, 23.29, 50.21, 55.17, 63.89, 126.55, 127.30, 128.80, 129.39, 138.40, 145.04, 169.14; ESI MS (positive mode) [M^+] 733.

A typical ITC experiment. A methanol solution of the examined anion (2 mM) was introduced into a methanol solution of receptor **4** or **10** (0.1 mM) in a calorimetry cell (Microcal Inc.). The solution was kept at an operating temperature of 298 K. Analysis and curve fitting using the software Origin™ afforded the thermodynamic data.

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