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New Tripodal Anion Receptor Based on C_{3v}-trindane Scaffold with Benzylphenylurea Motifs for Selective $H_2PO_4^-$ Sensing

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In supramolecular chemistry, the topic of anion recognition has attracted much attention because of their application in medical, environmental process, chemistry, and biology.[1] Among the various anions, the recognition of oxoanions such as phosphate, sulfate, nitrate, and carbonate and spherical halide anions is an important target due to their important role in organisms, metabolic and environmental processes.[2] In particular, the C_{3v}-symmetric anionic receptors have shown good binding affinity for such oxoanions and halide anions.[3]

Recently, we have reported that C_{3v}-symmetric anionic receptors **1a** and **1b** containing three urea or thiourea moieties on upper arms of trindane framework showed moderate binding affinities toward $H_2PO_4^-$ in DMSO-d_6; 392 and 305 M^{-1}, respectively.[5] The weakened binding affinity to anions was apparently due to hydrogen-bond breaking and unstable conformation changes in the process of anion recognition. The rigid planar arylarylurea moieties intramolecularly hydrogen bonded between adjacent urea groups in free receptors **1** need to be rotated and oriented toward the anion nested in the center of molecular cavity.[5]

To solve the matter of the rigidity of arylarylurea moieties, a much flexible anion receptor **2** was designed, which have three benzylphenylurea binding unit linked to upper arms of C_{3v}-trindane scaffold as shown in Figure 1. We expect that these benzylphenylurea units could induce a stabilization of complex with anion and consequently the binding affinity of receptor **2** could be enhanced.

The tripodal receptor **2** was synthesized according to Scheme 1. Tricarboxylic ester-scaffold **3**[3(a),4] was treated with chloro(methoxy)methane and $SnCl_4$ to afford tris(chloromethylbenzyl)-scaffold **4** that was converted into tris(azidobenzyl)-scaffold **5** by reaction with NaN_3. The azide moieties of this scaffold **5** was hydrogenated in the presence of Ni(W2) catalyst to obtain the corresponding triaminoscaffold **6**. Subsequently, reaction of scaffold **6** with commercially available phenyl isocyanate afforded the urea receptor **2** in good yield. The structure of receptor **2** was confirmed by ^{1}H NMR, ^{13}C NMR, Maldi-TOF mass, and elemental analysis.

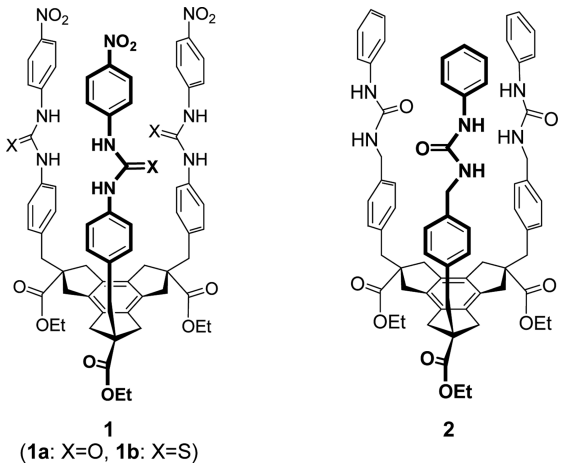
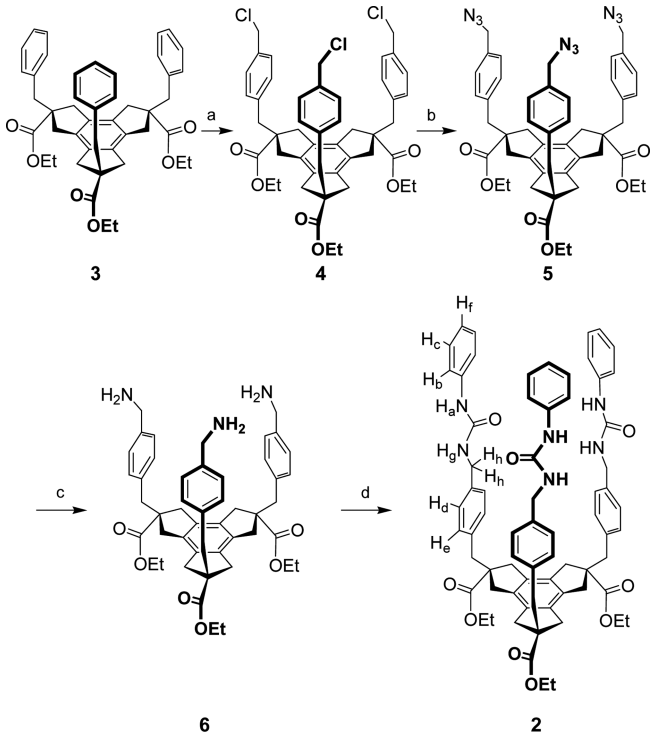


Figure 1. Tripodal urea anion receptors based on trindane framework.



Scheme 1. Tripodal urea anion receptors based on trindane framework.

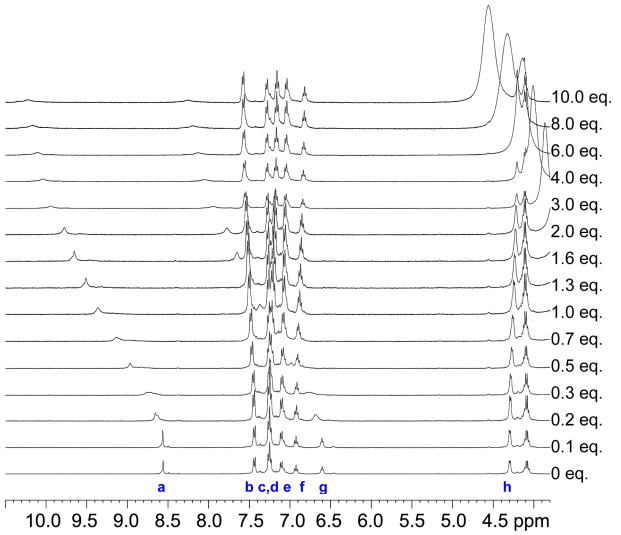


Figure 2. Partial ^{1}H NMR spectra showing the chemical shift changes of tripodal urea receptor **2** upon the addition of Bu_4N^+ $H_2PO_4^-$ in DMSO-d_6 at 25 °C.

The ^{1}H NMR spectrum of receptor **2** at room temperature in DMSO-d_6 showed well resolved sharp signals of an expected C_{3v}-symmetry with -NH protons appearing at 8.55 ppm as a singlet and 6.58 ppm as a triplet.

The anion recognition abilities of tripodal receptor **2** with F^-, Cl^-, Br^-, I^-, NO_3^-, HSO_4^-, and $H_2PO_4^-$ were investigated by the ^{1}H NMR titrations studies in DMSO-d_6 with the *n*-Bu_4N^+ as a cation. In ^{1}H NMR, the -NH peaks become broad and are all downfield shifted, which indicated the participation of urea -NH protons in binding anions by hydrogen bonding interactions. Although general tripodal anion receptors were known to have good affinity for tetrahedral oxoanions,[3] for receptor **2** the largest urea -NH chemical shift change was found on addition of F^- anion. However, titration isotherm with F^- anion is not well fitted to reasonable binding model. A complex binding equilibrium was suspected.

In case of $H_2PO_4^-$, the urea -NH signal was also shifted downfield significantly and the peak was broaden, but with less than did fluoride ion. Upon addition of 10.0 equiv of $H_2PO_4^-$ anion, urea receptor **2** showed the large downfield shifts of the urea -NH_a peak from 8.55 to 10.20 ppm ($\Delta\delta$ = +1.65 ppm) and -NH_g from 6.60 to 8.21 ppm ($\Delta\delta$ = +1.61 ppm). Also, the aromatic *ortho*-protons (H_b) of the urea binding site are gradually shifted to downfield ($\Delta\delta$ = +0.13), but benzylic protons (H_h) moved to upfield ($\Delta\delta$ = –0.10 ppm) relative to those of receptor **2**, which is ascribed to the effect of through space electrostatic interaction by the anion binding. Interestingly, obvious upfield shifts of the aromatic *meta*- and *para*-protons (H_c and H_f) of the urea binding site were also observed (Figure 2).

The energy-minimized structure of receptor-anion complex **2**·$H_2PO_4^-$ shows that it has a pseudo C_3-symmetry of a well-defined 1:1 complex and its three benzylphenylurea moieties are arranged perpendicularly each other (Figure 3).

As a result, these aromatic protons (H_c and H_f) are located inside the magnetic shielding zone of adjacent benzylphenylurea unit and was shifted upfield (H_c: $\Delta\delta$ = –0.11 ppm and H_f: $\Delta\delta$ = –0.10 ppm).

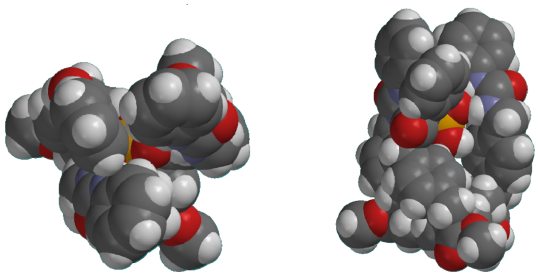


Figure 3. Side and top views of energy-minimized structure of receptor-anion complex **2**·$H_2PO_4^-$ as obtained with Hatree-Fock/6-31G. The distances between NH···O=P were measured to be 1.972 Å, 2.086 Å, and 1.930 Å; 1.838 Å for chelated H-bonds.

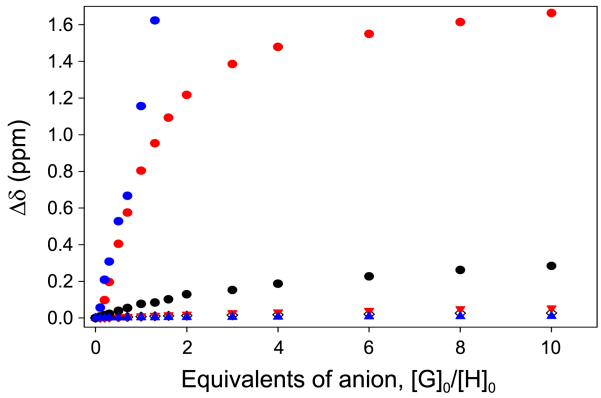


Figure 4. ^{1}H NMR titration curve of urea receptor **2** with tetrabutylammonium salts of anionic guests in DMSO-d_6 at 25 °C. (axis: complexation-induced chemical shifts of the urea -NH_a protons, $[H]_0$ = 4.0 mM, $[G]_0$ = 40.0 mM.). (●, F^-; ●, $H_2PO_4^-$; ●, Cl^-; ▼, Br^-; ◇, HSO_4^-; ▲, NO_3^-).

In contrast, addition of HSO_4^-, Cl^-, Br^-, and NO_3^- anions caused only a small downfield shift of the -NH peaks.

The ^{1}H NMR titration curves of receptor **2** with various anionic guests are shown in Figure 4.

In all cases, only one set of signals were observed for free receptor and complex, showing fast exchanges on the NMR time scale. The data obtained was fitted using the computer program WinEQNMR,[6] which calculates binding constants based on NMR shift data. All binding constants were monitored by the complexation induced shifts of the -NH_a resonance upon addition of anions. Tripodal receptor **2** showed the highest anion binding affinity to $H_2PO_4^-$ anion (K_a = 463 M^{-1}), followed by $Cl^- > HSO_4^- > Br^- > NO_3^-$ anions. When titrated with I^- anion, the chemical shift changes of receptor **2** were too small to be measured. The binding constants of tripodal receptor **2** for various anions are shown in Table 1.

The binding affinity (K_a = 463 M^{-1}) toward $H_2PO_4^-$ of receptor **2** was found to be relatively higher than those of receptor **1a** and **1b**. It may be attributed to the presence of benzylphenylurea moieties on upper arms of C_{3v}-trindan

Table 1. Binding constants (K_a, M^{-1}) of receptor **2** determined by ^{1}H NMR titrations with tetrabutylammonium salts in DMSO-d_6 at 25 °C ^{1}H NMR titration curve of urea receptor **2** with tetrabutylammonium salts[a]

anions	$H_2PO_4^-$	Cl^-	HSO_4^-	Br^-	NO_3^-
K_a (M^{-1})	463	30	25	16	12

[a]Determined by titrating a receptor solution in DMSO-d_6, $[H]_0$ = 4.0 mM with anion salt solution, $[G]_0$ = 40 mM. Estimated errors are within ± 5%. Water content in DMSO-d_6 is 0.01-1.04%.

scaffold which can lead to better flexibility and preorganization in complexation with anions.

In conclusion, new tripodal anion receptor **2** with three benzylphenylurea moieties on the upper arms of a C_{3v}-symmetric trindane framework was synthesized and its anion binding property was studied by ^{1}H NMR titration in DMSO-d_6. This new receptor has a good binding affinity for $H_2PO_4^-$ anion with 1:1 binding complex. From these results, C_{3v}-symmetric trindane framework could be utilized as a useful organic scaffold for the development of new anion receptors.[3(a),5]

Experimental

Synthesis of Triethyl *cis,cis,cis*-2,5,8-tris(*p*-(3-phenylureidomethyl)benzyl)trindane-2,5,8-tricarboxylate (2): To a solution of *cis,cis,cis*-2,5,8-tris(aminomethyl)-2,5,8-tribenzyltrindane (100 mg, 0.13 mmol) in dry THF (7 mL) at room temperature under nitrogen atmosphere was added phenyl isocyanate (100 μL, 0.8 mmol) *via* a syringe and the mixture was stirred overnight. The reaction mixture was concentrated to dryness. The residue was purified by a flash column chromatography on silica gel using CH_2Cl_2 and then EtOAc/CH_2Cl_2 (1:9) and finally MeOH/CH_2Cl_2 (5:95) as eluent to give a product as a white glassy solid (123 mg, 84%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (br m, 3H, -NH), 7.25-7.05 (m, 18H, Ar-*H*), 7.00-6.85 (m, 9H, Ar-*H*), 6.27 (br m, 3H, -N*H*), 4.13, (m, 12H, -COCH_2CH$_3$ and Ar-CH_2-NH-), 3.11 (br d, J = 15.6 Hz, 6H, ArCH_aH$_b$-), 2.86 (br s, 6H, ArCH_2), 2.76 (br d, J = 15.6 Hz, 6H, ArCH$_a$$H_b$-), 1.26 (t, J = 7.2 Hz, 3H, -COCH$_2$CH_3), 1.22 (t, J = 7.2 Hz, 6H, -COCH$_2$CH_3); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.55 (br s, 3H, -NH), 7.40 (d, J = 7.6 Hz, 6H, Ar-*H*), 7.22 (t, J = 7.6 Hz, 6H, Ar-*H*), 7.20 (d, J = 8.4 Hz, 6H, Ar-*H*), 7.06 (d, J = 8.4 Hz, 6H, Ar-*H*), 6.89 (t, J = 7.2 Hz, 3H, Ar-*H*), 6.58 (br t, J = 7.2 Hz, 3H, -N*H*), 4.26 (br d, J = 5.6 Hz, 6H, -HN-CH_2Ar), 4.05 (q, J = 7.1 Hz, 6H, -O-CH_2CH$_3$), 3.07 (d, J = 15.6 Hz, 6H, ArCH_aH$_b$-), 2.96 (s, 6H, ArCH_2), 2.83 (d, J = 15.6 Hz, 6H, ArCH$_a$$H_b$-), 1.15 (t, J = 7.2 Hz, 3H, -COCH$_2$CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.9, 157.1, 139.4, 138.1, 136.9, 135.6, 130.4, 129.3, 127.3, 123.2, 120.2, 61.3, 55.8, 43.6, 43.3, 39.8, 14.6; ^{13}C NMR (100 MHz, DMSO-d_6) δ 175.4, 155.3, 140.5, 138.6, 136.2, 134.8, 129.5, 128.7, 127.0, 121.1, 117.7, 60.4, 55.5, 42.9, 42.5, 40.0 (overlapping with solvent signals), 14.4; MALDI-TOF-MS (CHCA), *m/z* (rel intensity) 1151.9600 (100), 1152.9527 (93), 1153.9436 (51), 1154.9430 (15), 1155.9534 (3), Calcd for $C_{69}H_{72}N_6O_9Na^+$: *m/z* 1151.5258 (M+Na$^+$, 100), 1152.5292 (M+1+Na$^+$, 76.8), 1153.5326 (M+2+Na$^+$, 30.9), 1154.5359 (M+3+Na$^+$, 8.0), 1155.5393 (M+4+Na$^+$, 1.2); Anal. Cald for $C_{69}H_{72}N_6O_9$: C, 73.47; H, 6.61: N, 7.34. Found: C, 73.13; H, 6.25: N, 7.56.

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Supporting Information. Experimental details, spectroscopic data, and additional molecular modeling.

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