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

Yeon Sil Park, Won Kim,† and Heung-Jin Choi†,*

Department of Chemistry, Soongsil University, Seoul 156-743, Korea
†Department of Applied Chemistry, Kyungpook National University, Daegu 702-701, Korea. *E-mail: choihj@knu.ac.kr

Received July 2, 2014, Accepted July 15, 2014

Key Words: Anion molecular sensor, $C_{3v}$-symmetric tripodal anion receptor, Urea anion recognition motif, Trindane

In supramolecular chemistry, the topic of anion recognition has attracted much attention because of their application in medical, environmental process, chemistry, and biology. 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.

Recently, we have reported that $C_{3v}$-symmetric anionic receptors 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. 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 need to be rotated and oriented toward the anion nested in the center of molecular cavity.

To solve the matter of the rigidity of arylarylurea moieties, a much flexible anion receptor 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 could be enhanced.

The tripod receptor was synthesized according to Scheme 1. Tricarboxylic ester-scaffold was treated with chloro(methoxy)methane and SnCl$_4$ to afford tris(chloromethylbenzyl)-scaffold that was converted into tris(azidobenzyl)-scaffold by reaction with NaN$_3$. The azide moieties of this scaffold was hydrogenated in the presence of Ni(W2) catalyst to obtain the corresponding triamino-scaffold. Subsequently, reaction of scaffold with commercially available phenyl isocyanate afforded the urea receptor in good yield. The structure of receptor 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.](image1)

![Scheme 1. Tripodal urea anion receptors based on trindane framework.](image2)
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$,\text{Cl},\text{Br},\text{I},\text{NO}_3^-,\text{HSO}_4^-$, and H$_2$PO$_4^-$ were investigated by the $^1$H NMR titration studies in DMSO-$d_6$ with the n-Bu$_4$N$^+$ 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$_2$PO$_4^-$, 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$_2$PO$_4^-$ anion, urea receptor 2 showed the large downfield shifts of the urea -NH peak from 8.55 to 10.20 ppm ($\Delta\delta = +1.65$ ppm) and -NH$_2$ from 6.60 to 8.21 ppm ($\Delta\delta = +1.61$ ppm). Also, the aromatic ortho-protons (H$_6$) of the urea binding site are gradually shifted to downfield ($\Delta\delta = +0.13$), but benzylic protons (H$_4$) moved to upfield ($\Delta\delta = -0.10$ ppm) relative to those of receptor 2, which is ascerted to the effect of through space electrostatic interaction by the anion binding. Interestingly, obvious upfield shifts of the aromatic meta- and para-protons (H$_2$ and H$_3$) of the urea binding site were also observed (Figure 2).

The energy-minimized structure of receptor-anion complex 2H$_2$PO$_4^-$ 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$_2$ and H$_3$) are located inside the magnetic shielding zone of adjacent benzylphenylurea unit and was shifted upfield (H$_2$: $\Delta\delta = -0.11$ ppm and H$_3$: $\Delta\delta = -0.10$ ppm).

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$_2$ resonance upon addition of anions. Tripodal receptor 2 showed the highest anion binding affinity to H$_2$PO$_4^-$ 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$_2$PO$_4^-$ 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 $C_{3v}$-tridan...
scaffold which can lead to better flexibility and preorganization in complexation with anions.

In conclusion, new tripod anion receptor 2 with three benzylpyrenylurea moieties on the upper arms of a C3a-symmetric trindane framework was synthesized and its anion binding property was studied by 1H NMR titration in DMSO-d6. This new receptor has a good binding affinity for H2PO4− anion with 1:1 binding complex. From these results, C3a-symmetric trindane framework could be utilized as a useful organic scaffold for the development of new anion receptors.2,3,5

Experimental

Synthesis of Triethyl cis,cis,cis-2,5,8-tris(3-phenylureidomethyl)benzyltrindane-2,5,8-tricarboxylic acid (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 CH2Cl2 and then EtOAc/CH2Cl2 (1:9) and finally MeOH/CH2Cl2 (5:95) as eluent to produce a product as a white glassy solid (123 mg, 84%). 1H NMR (400 MHz, DMSO-d6) 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, -OH), 4.13 (m, 12H, -COCH3 and Ar-C=CH2-NH+), 3.11 (br d, J = 15.6 Hz, 6H, ArCH2H+), 2.86 (br s, 6H, ArCH2), 2.76 (br d, J = 15.6 Hz, 6H, ArCH2H+), 1.26 (t, J = 7.2 Hz, 3H, -COCH3), 1.22 (t, J = 7.2 Hz, 6H, -COCH3), 1.14 (m, 18H, ArCH2H+), 0.90 (q, J = 7.1 Hz, 6H, -OH-C(=CH2)3), 0.95 (s, 6H, ArCH2H+), 0.78 (s, 6H, ArCH2H+), 0.70 (d, J = 7.2 Hz, 3H, -OH-C(=CH2)3), 0.25 (br d, J = 7.2 Hz, 6H, -OH-C(=CH2)3).

<table>
<thead>
<tr>
<th>anions</th>
<th>H2PO4−</th>
<th>Cl−</th>
<th>HSO4−</th>
<th>Br−</th>
<th>NO3−</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kd (M−1)</td>
<td>463</td>
<td>30</td>
<td>25</td>
<td>16</td>
<td>12</td>
</tr>
</tbody>
</table>

* Determined by titrating a receptor solution in DMSO-d6, [H2PO4−] = 4.0 mM with anion salt solution, [G]0 = 40 mM. Estimated errors are within ±5%. Water content in DMSO-d6 is 0.01-0.04%.

Acknowledgments. This research was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (NRF-2010-0008583), and by Kyungpook National University Research Fund, 2012.

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

References


