High Affinity Carboxylate Binding Using Neutral Urea-Based Receptors with Internal Lewis Acid Coordination

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Uncharged receptors for anions and cations have many potential applications ranging from membrane transport carriers for ion-selective electrodes to reaction catalysts. As a consequence, there is a need to design and synthesize neutral receptors with high binding affinity and/or high binding selectivity. Unlike cation receptors, there are essentially no examples of biotic, low molecular weight hosts for anions. Synthetic anion receptors have been designed de novo using the principles of molecular recognition. The neutral anion receptors reported to date have been shown to associate with carboxylates, phosphates, and sulfonates to produce bidentate hydrogen-bonded complexes such as 1. In this paper we describe a structural design strategy that greatly improves the anion binding ability of neutral urea-based receptors. It is likely that this strategy can be incorporated into the designs of other amide-based molecular recognition systems.

The formation of supramolecular complex 1 is driven primarily by hydrogen bonding and ion–dipole interactions. These bonding interactions can be strengthened by cooperative polarization of the urea group, which is accomplished by coordinating the urea carbonyl to a Lewis acid. A major design challenge is to ensure that the Lewis acid is held in the correct spatial orientation with a high effective molarity. One possible solution is the Lewis acid–urea conjugate 2. In line with our current interest in organoboron receptors,9 we designed boronate–urea 3 as a first-generation example of this receptor class. The valence bond structure for receptor 3 can be represented by two limiting forms, 3a or 3b. Prior to this study there was literature precedent to suggest that 3b would be the major resonance contributor.

![Scheme 1](image)

Boronate–ureas 7–10 were prepared by the sequence shown Scheme 1. (2-Aminophenyl)boronic acid, 4, was treated with the appropriate isocyanates to give heterocycles 5 and 6. Condensation of these compounds with pinacol gave 7 and 8, whereas treatment with KHF211 gave the difluoro analogues 9 and 10. The structures of compounds 5 and 9 were proven by X-ray crystallography.
Figure 1. Typical $^1$H NMR titration curves in DMSO-$d_6$ at 295 K. Change in chemical shift ($\Delta \delta$) of NH signals for hosts as a function of increasing amounts of tetrabutylammonium acetate: 10 (a); 8 (b); 11 (c); 12 (a). Initial host concentration was 1 mM, final host concentration was 0.67 mM.

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(12) The crystal structures will be described in a subsequent paper.

(13) By the end of a typical titration experiment with tetrabutylammonium acetate in “dry” DMSO, 50% of 7 and 15% of 9 had hydrolyzed to produce 5. With the acetate derivatives, <10% of 8 and <5% of 10 had hydrolyzed. In the case of 8, the products from hydrolysis, namely 6 and pinacol, were found to have no ability to bind acetate or 8 in DMSO. Thus, they were treated as minor, inert impurities. In the absence of acetate or in less polar solvents, such as chloroform, the amount of hydrolysis was considerably less.

(14) The reason for the increased stability seen with the acetate derivatives is not totally clear. One possibility is that the mechanism for hydrolysis of 7–10 involves initial attack of water at the electrophilic uronium carbon with subsequent cleavage of the uronium C–O bond. The resulting intermediate then recycles with loss of the 2X groups to generate the highly stable 5 or 6. If the initial attack by water is rate determining, then a bulky acyl could be expected to sterically hinder this step and make the compound kinetically more stable than the corresponding methyl derivative.

(15) Wilcox, C. S. In Frontiers in Supramolecular Organic Chemistry and Photochemistry; Schneider, H.-J., Durr, H., Eds.; VCH: Weinheim, 1991; pp 123–143. Although the host NH signals were the most sensitive to association, $^1$H NMR titration isotherms were generated for as many host signals as possible. A binding constant was derived by averaging the values obtained from the different isotherms, which were always within ±10% of each other. The values listed in Table 1 are the averages of three independent titration experiments. Control experiments showed no evidence for host–host association in DMSO.


(17) The curves were fitted using the simplex algorithm. Cooper, J. W. Introduction to Pascal for Scientists; Wiley: New York, 1981.


(19) To better understand the changes in host electrostatics induced by the intramolecular Lewis acid, surface electric potentials were calculated using Hartree–Fock methods (AM1 geometry optimization/6-31G* HF potentials). As expected, the ortho boron residue dramatically increases the positive electric potential surrounding the urea NH residues, as well as the magnitude of the molecular dipole. For hosts 11, 7, and 9, the positive electrostatic potentials at the NH residues were calculated to be 65.8, 81.0, and 85.7 kcal/mol; the calculated molecular dipoles were 2.4, 6.1, and 7.6 D.

(20) At present we have not determined the $pK_a$'s of the NH protons in our boronate–urea hosts; however, there is little doubt that they are more acidic than the NH protons in control urea 12 ($pK_a$ for N,N'-diphenylurea in DMSO is 19.5. Bordwell, F. G.; Algrim, D. J.; Harrelson, J. A.; J. Am. Chem. Soc. 1988, 110, 5903–5904). For example, the boronate–urea NH signals exhibited larger complex-induced shifts than the corresponding urea NH signals (see $\Delta \delta_{max}$ values in Table 1), which is indicative of stronger hydrogen bonding in the host–guest complex.

Table 1. Acetate Association Constants from $^1$H NMR Titrations in DMSO at 295 K

<table>
<thead>
<tr>
<th>host</th>
<th>$K_{assn}$ (M$^{-1}$)</th>
<th>$\Delta G_{295}$ (kcal/mol)</th>
<th>$\Delta \delta_{max}$ (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>(2.3 ± 0.2) $\times$ 10$^4$</td>
<td>2.74</td>
<td>3.56</td>
</tr>
<tr>
<td>11</td>
<td>(3.9 ± 0.4) $\times$ 10$^3$</td>
<td>3.75</td>
<td>4.36</td>
</tr>
<tr>
<td>8</td>
<td>(7.2 ± 0.1) $\times$ 10$^2$</td>
<td>5.20</td>
<td>5.80</td>
</tr>
<tr>
<td>10</td>
<td>(6.3 ± 0.2) $\times$ 10$^4$</td>
<td>6.50</td>
<td>6.90</td>
</tr>
</tbody>
</table>

$^a$ See ref 16. $^b$ Average of the $\Delta \delta_{max}$ values for both host NH signals obtained from all experiments.