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

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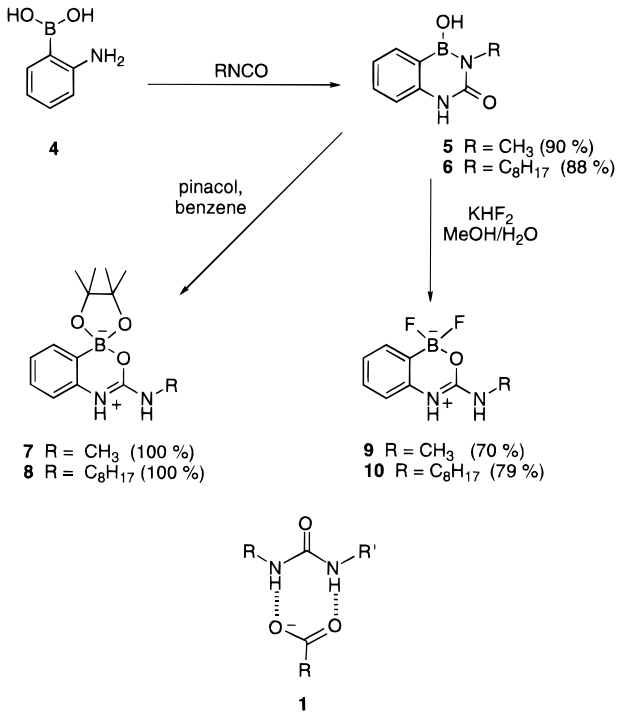
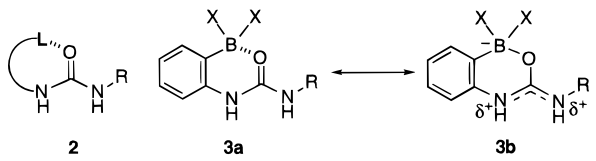
Uncharged receptors for anions and cations have many potential applications ranging from membrane transport carriers for ion-selective electrodes to reaction catalysts.[1] As a consequence, there is a need to design and synthesize neutral receptors with high binding affinities and/or high binding selectivities. Unlike cation receptors, there are essentially no examples of biotic, low molecular weight hosts for anions.[2] Synthetic anion receptors have to be designed *de novo* using the principles of molecular recognition. The neutral anion-receptors reported to date have employed either Lewis acid−base,[3] hydrogen bonding,[4] and/or ion−dipole interactions.[5] Most of the hydrogen bonding systems have used urea groups as the recognition motif. Urea-based hosts have been shown to associate with carboxylates, phosphates, and sulfonates to produce bidentate hydrogen-bonded complexes such as **1**.[4] 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.[6,7] 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.[8] 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.[10]

Scheme 1





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**.[10] Condensation of these compounds with pinacol gave **7** and **8**, whereas treatment with KHF_2[11] gave the difluoro analogues **9** and **10**. The structures of compounds **5** and **9** were proven by X-ray crystal-

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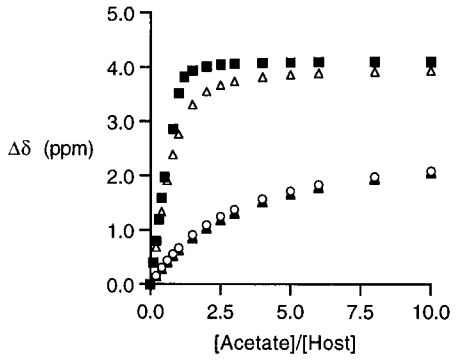


Figure 1. Typical ^{1}H NMR titration curves in DMSO-d_6 at 295 K. Change in chemical shift ($\Delta\delta$) of NH signals for hosts as a function of increasing amounts of tetrabutylammonium acetate: **10** (■); **8** (△); **11** (○); **12** (▲). Initial host concentration was 1 mM, final host concentration was 0.67 mM.

lography.[12] This allowed the other structures to be assigned on the basis of their closely analogous NMR spectra.

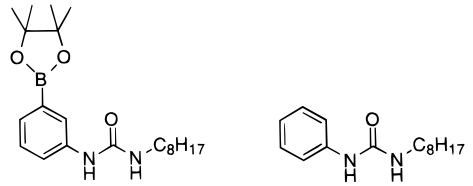
Binding studies were initially conducted with tetrabutylammonium acetate and host compounds **7** and **9**. These studies were complicated by the propensity of the hosts to hydrolyze and regenerate precursor **5**.[13] Because of this, the octyl derivatives **8** and **10** were prepared and found to be significantly more stable.[13,14] This allowed the acetate binding ability of **8** and **10** to be determined and compared to the binding ability of control compounds **11** and **12**. Association constants were measured by ^{1}H NMR titration experiments in the highly competitive solvent DMSO-d_6.[15] In each case 1:1 binding was verified by a Job plot.[16] Control experiments using ^{11}B NMR showed that acetate has no affinity for the trigonal boron in **11**.

An appreciation of the differences in acetate binding abilities can be gained by comparing the binding isotherms shown in Figure 1. The association constants obtained by iterative curve-fitting methods are listed in Table 1.[15,17] There is essentially no difference in binding ability between the *meta* borolane derivative **11** and urea control **12**. This was expected because the electronegativity of boron is similar to hydrogen.[18] Boronate−ureas **8** and **10**, however, showed improvements in binding affinities of 1.7 and 3.0 kcal/mol, respectively. These large increases are attributed primarily to two effects, improved host hydrogen bond donation ability and the generation of a strong host molecular dipole that is oriented in a favorable direction for anion binding. The greater binding ability of **10** over **8** reflects the structural change to a more withdrawing boron difluoride, which further strengthens these two effects.[19]

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

host	K_{assn}[a] (M^{-1})	ΔG_{295} (kcal/mol)	$\Delta\delta_{max}$[b] (ppm)
12	$(3.7 \pm 0.4) \times 10^2$	−3.5	2.14
11	$(3.9 \pm 0.4) \times 10^2$	−3.5	2.16
8	$(7 \pm 2) \times 10^3$	−5.2	3.75
10	$(6 \pm 3) \times 10^4$	−6.5	3.96

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



Thus, a strategically placed Lewis acid is able to polarize the urea carbonyl and greatly increase acetate binding by acidifying the urea NH residues and enhancing the ion−dipole interaction between host and acetate.[19,20] The fact that **10** is a better acetate binder than guanidinium cation ($K_{assn} = 1.2 \times 10^4$ M^{-1} in DMSO)[4g] is quite remarkable and demonstrates that formally neutral receptors for anions (and cations) can be designed to have very high binding affinities if the host structure incorporates a judicious distribution of partial charge.

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Supporting Information Available: Preparative and analytical procedures, as well as characterization data (9 pages).

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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 octyl 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 octyl 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 recyclizes 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 octyl could be expected to sterically hinder this step and make the compound kinetically more stable than the corresponding methyl derivative.

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(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).[6] 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.