Enhanced Carboxylate Binding Using Urea and Amide-Based Receptors with Internal Lewis Acid Coordination: A Cooperative Polarization Effect

Martin Patrick Hughes and Bradley D. Smith*

Department of Chemistry and Biochemistry, University of Notre Dame, Notre Dame, Indiana 46556

Received February 7, 1997[⊗]

A structural design strategy is described that greatly improves the acetate binding ability of neutral urea and amide-based receptors. The enhanced binding is due to a cooperative polarization effect which is induced by intramolecular coordination of the urea or amide carbonyl to a Lewis acidic boronate group. A series of boronate-ureas, **3**, and a related bis(boronate-amide), **23**, were prepared in two steps from 2-(aminophenyl)boronic acid and their structures elucidated using X-ray crystallography and other spectrometric methods. The abilities of the receptors to associate with tetrabutylammonium acetate in dimethyl sulfoxide solution were determined by ^{1}H NMR titration experiments. Association constants were calculated using nonlinear curve-fitting methods. The boronate-ureas **3** strongly bind to acetate in dimethyl sulfoxide solution with association constants as high as 6×10^4 M^{-1}. This is more than 150 times greater than the association constants for control urea receptors that lacked an appropriate boron substituent. Thermodynamic studies indicate that the enhanced association is due to a favorable enthalpic change. Additional NMR studies eliminated the possibility of proton transfer to the acetate during complex formation. Molecular modeling indicates that the boronate-ureas exhibit improved acetate binding because the intramolecular coordination (i) induces a larger host dipole moment which strengthens the guest/host ion−dipole interaction, and (ii) increases the positive surface potential at the urea NH residues which strengthens short range Coulombic interactions with the anionic acetate. The observed association constants correlate better with calculated host dipole moments, suggesting that for the boronate-ureas described here this is the more influential factor controlling association.

Introduction

A current research topic in supramolecular chemistry is the development of synthetic receptors for anions.[1] These compounds have a range of potential uses such as membrane transport carriers,[2] chemosensors,[3] and reaction catalysts.[4] The design of neutral anion-binders as phase transfer agents is a particularly challenging problem. Without the assistance of charge neutralization it is difficult to overcome the competing effects of a polar solvent using only hydrogen bonding and/or ion−dipole interactions. Nonetheless, an increasing number of formally neutral host compounds are being reported with impressive anion binding abilities.[5]

When designing supramolecular binding systems, it is often useful to consider the mechanisms employed by Nature. In the case of anion binding, most biotic receptors are macromolecules.[6] Nonetheless, important information can be learned by focusing on the molecular architecture that surrounds the anion binding site. A recent example is the X-ray crystallography work of Malashkevich and co-workers, who uncovered a channellike, pentameric coiled-coil structure with a cyclic array of glutamines pointing inward at the midpoint.[7] The glutamines form a ring of cooperatively hydrogen bonded amide groups that encapsulate a chloride anion. The chloride is bound by a combination of hydrogen bonds with the glutamine NH residues and ion−dipole interactions with the amide dipoles and the macrodipole produced by the α-helices in the coiled-coil.

Cooperative polarization is often observed in biological macromolecules.[8] Calculations by Guo and Karplus indicate that the hydrogen bond in the *N*-methylacetamide dimer, **1**, is strengthened 1−2 kcal/mol by the presence of hydrogen bond donor Y.[9]

To date there has been little experimental verification of the magnitude of these cooperative effects in biotic or abiotic supramolecular systems.[10] Recently, we introduced a new class of neutral urea-based receptors that exhibit high carboxylate binding affinities due to coop-

* Author to whom correspondence should be addressed. Phone: 219-631 8632, fax: 219-631 6652, email: smith.115@nd.edu.

[⊗] Abstract published in *Advance ACS Abstracts,* June 1, 1997.

(1) Recent reviews on anion complexation: (a) Scheerder, J.; Engberson, J. F. J.; Reinhoudt, D. N. *Rec. Trav. Chim. Pays-Bas* **1996**, *115*, 307−320. (b) Atwood, J. L.; Holman, K. T.; Steed, J. W. *J. Chem. Soc., Chem Commun.* **1996**, 1401−1407. (c) Beer, P. D. *J. Chem. Soc., Chem. Commun.* **1996**, 689−698.

(2) Král, V.; Sesslor, J. L. *Tetrahedron* **1995**, *51*, 539−554.

(3) (a) Teulade Fichou, M.-P.; Vigneron, J.-P.; Lehn, J.-M. *J. Chem. Soc., Perkin Trans. 2* **1996**, 2169−2175. (b) De Santis, G.; Fabbrizzi, L.; Licchelli, M.; Poggi, A.; Taglietti, A. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 202−204.

(4) (a) Anslyn, E. V.; Smith, J.; Kneeland, D. M.; Ariga, K.; Chu, F. Y. *Supramol. Chem.* **1993**, *1*, 201−208. (b) Curran, D. P.; Kuo, L. H. *Tetrahedron Lett.* **1995**, *36*, 6647−4450.

(5) (a) Berger, M.; Schmidtchen, F. P. *J. Am. Chem. Soc.* **1996**, *118*, 8947−8948. (b) Gale, P.; Sesslor, J. L. Král, V.; Lynch, V. *J. Am. Chem. Soc.* **1996**, *118*, 5140−5141. (c) Scheeder, J.; van Duynhoven, J. P. M.; Engberson, J. F. J.; Reinhoudt, D. N. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1090−1092. (d) *Molecular Design and Bioorganic Catalysis*; Wilcox, C. S, Hamilton, A. D., Eds.; Kluwer: Amsterdam, 1996.

(6) For examples of small molecular weight, biotic anion receptors, see: (a) Murphy, P. J.; Williams, H. L.; Hibbs, D. E.; Hursthouse, M. B.; Abdul Malik, K. M. *J. Chem. Soc., Chem. Commun.* **1996**, 445−447. (b) Hinzen, B.; Seiler, P.; Diederich, F. *Helv. Chim. Acta* **1996**, *79*, 942−960.

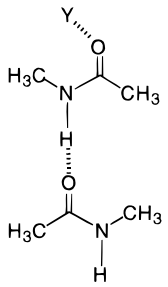
(7) Malashkevich, V.; Kammerer, R. A.; Efimov, V. P.; Schulthess, T.; Engel, J. *Science* **1996**, *274*, 761−765.

(8) Jeffrey, G. A.; Saenger, W. *Hydrogen Bonding in Biological Structures*; Springer-Verlag: Berlin, 1991.

(9) Guo, H.; Karplus, M. *J. Phys. Chem.* **1994**, *98*, 7104−7105.

(10) (a) Burrows, A. D.; Chan, C.-W.; Chowdhry, M. M.; McGrady, J. E.; Mingos, D. M. P. *Chem. Soc. Rev.* **1995**, *24*, 329−339. Burrows, A. D.; Mingos, D. M. P.; White, A. J. P.; Williams, D. J. *J. Chem. Soc., Chem. Commun.* **1996**, 97−99. (b) Gung, B.; Zhu, Z. *Tetrahedron Lett.* **1996**, *37*, 2189−2192 and references cited therein.

S0022-3263(97)00224-7 CCC: $14.00

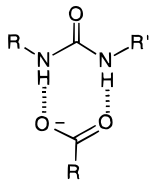


1

erative polarization of the urea group.[11,5d] This polarization effect was accomplished by intramolecular coordination of the urea carbonyl with a Lewis acidic boronate group. We now describe in detail the structures and binding properties of these boronate-ureas, as well as a related bis(boronate-amide) receptor.

Receptor Design

The anion-complexing ability of urea receptors has been studied by several research groups.[12] Ureas form chelated complexes with ditopic hydrogen bond acceptors such as phosphates, sulfonates, and carboxylates.



The inspiration for our design can be traced to earlier reports from the research groups of Etter[13] and Wilcox.[14] Initially, Etter showed that 1,3-bis(*m*-nitrophenyl)urea acts as a good hydrogen bond acceptor in the solid-state. Etter attributed this observation to a urea polarization effect caused by weak intramolecular C−H···O hydrogen bonding interactions between the urea carbonyl and the acidified *ortho* hydrogens (Figure 1). Subsequent work by Wilcox found that this *meta* effect disappeared in the solution-state and that observed binding affinities were well correlated with calculated surface electric potentials.

Inspection of the supramolecular complex shown in Figure 1 provided us with an idea. We reasoned that the urea polarization effect invoked by Etter would be dramatically enhanced if the CH group was substituted with a stronger Lewis acid. Thus, we designed the general urea derivative **2**, where L is a Lewis acid (Scheme 1). This report describes the organoboron analogue, **3**, which can be represented by two limiting forms, **3a** or **3b**. At the beginning of the project there was literature precedence suggesting that **3b** would be the more likely structure. In particular, Groziak and co-

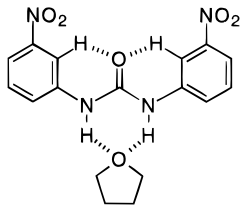
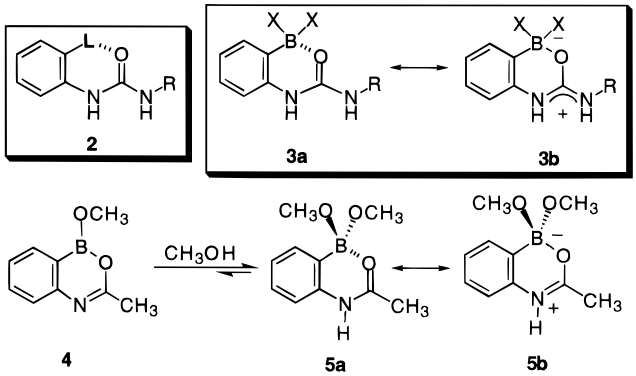


Figure 1. Typical 1:1 crystalline complex observed for 1,3-bis(*m*-nitrophenyl)urea.[13]

Scheme 1



workers showed that the product obtained by dissolving compound **4** in methanol was the zwitterion **5b**.[15]

Synthesis

Boronate-ureas **11**−**16** were prepared by the reactions shown in Scheme 2. (2-Aminophenyl)boronic acid, **6**,[15] was treated with the appropriate isocyanates to give heterocycles **7**−**9**. Condensation of these compounds with pinacol gave **11**−**13**, whereas treatment with KHF_2 gave the difluoro analogues **15** and **16**. In the case of the *tert*-butyl analogue, **14**, the intermediate **10** could not be formed. Therefore, the two-step sequence was reversed: **6** was condensed with pinacol and the resulting trigonal boronate ester treated with *tert*-butyl isocyanate which gave **14**. Control compounds **17**−**22** were prepared by standard methods. Attempts to prepare bis(boronate-amide) **23** by first treating **6** with isophthaloyl dichloride were unsuccessful. A better method was to condense **6** with pinacol and react the resulting boronate ester with isophthaloyl dichloride using sodium hydride activation.

Receptor Stability

Preliminary NMR studies showed that **11** was very susceptible to hydrolysis in highly polar, hygroscopic solvents. By the end of a typical NMR titration experiment with tetrabutylammonium acetate in "dry" DMSO-d_6 (freshly opened ampule purchased from Aldrich), 50% of **11** had cleanly hydrolyzed to produce pinacol and **7**. The related control compound **17**, however, was stable under these conditions. A likely mechanism for the hydrolysis of **11** involves initial attack of adventitious water at the electrophilic uronium carbon with subsequent cleavage of the uronium C−O bond. The resulting intermediate, **24**, then recyclizes with loss of pinacol to generate the highly stable **7**.

If the initial attack by water is rate determining, then a bulkier urea side chain would sterically hinder this step

(11) Hughes, M. P.; Shang, M.; Smith, B. D. *J. Org. Chem.* **1996**, *61*, 4510−4511.

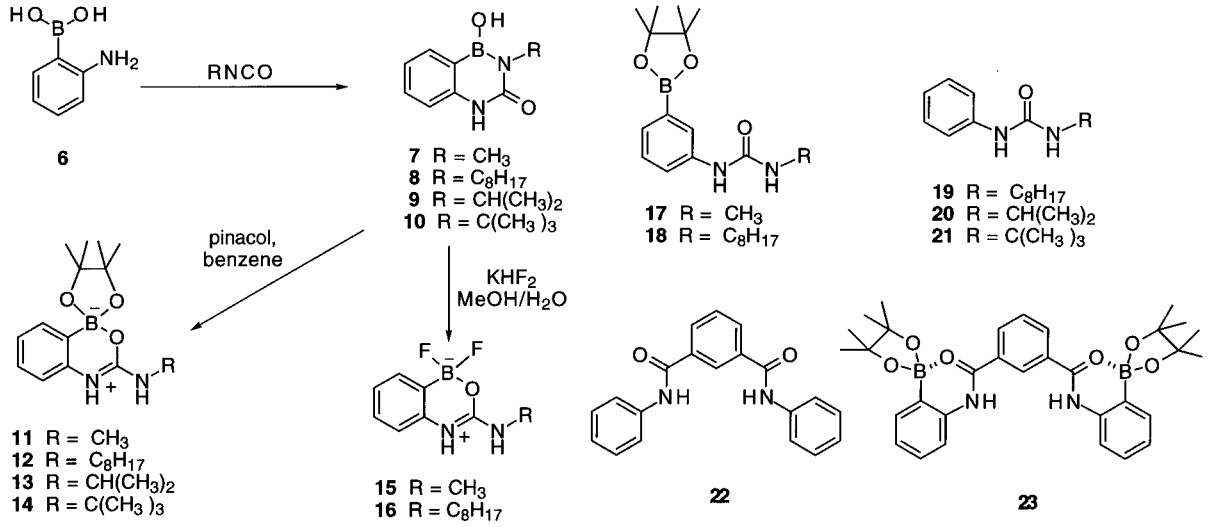
(12) (a) Jeong, K.-S.; Park, J. W.; Cho, Y. L. *Tetrahedron Lett.* **1996**, *37*, 2795−2798. (b) Nishizawa, S.; Bühlmann, P.; Iwao, M.; Umezawa, Y. *Tetrahedron Lett.* **1995**, *36*, 6483−6486. (c) Scheerder, J.; Fochi, M.; Engbersen, J. F. J.; Reinhoudt, D. N. *J. Org. Chem.* **1994**, *59*, 7815−7820. (d) Kelly, T. R.; Kim, M. H. *J. Am. Chem. Soc.* **1994**, *116*, 7072−7080. (e) Hamann, B. C.; Branda, N. R.; Rebek, J., Jr. *Tetrahedron Lett.* **1993**, *34*, 6837−6840. (f) Smith, P. J.; Reddington, M. V.; Wilcox, C. S. *Tetrahedron Lett.* **1992**, *33*, 6085−6088. (g) Garcia-Tellado, F.; Goswami, S.; Chang, S. K.; Geib, S. J.; Hamilton, A. D. *J. Am. Chem. Soc.* **1990**, *112*, 7393−7394. (h) Nolte, R. J. M.; Cram, D. J. *J. Am. Chem. Soc.* **1984**, *106*, 1416−1420.

(13) Etter, M. C., Urbanczyk-Lipkowska, Z., Zia-Ebrahimi, M., Panunto, T. W. *J. Am. Chem. Soc.* **1990**, *112*, 8415−8426.

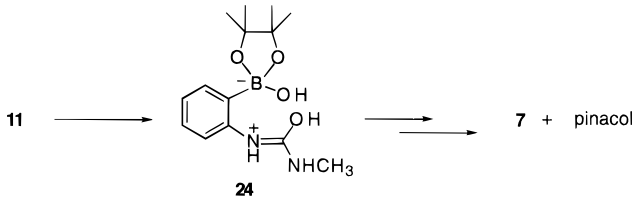
(14) Wilcox, C. S., Kim, E. K., Romano, D., Kuo, L. H., Burt, A. L.; Curran, D. P. *Tetrahedron* **1995**, *51*, 621−634.

(15) Groziak, M. P., Ganguly, A. D.; Robinson, P. D. *J. Am. Chem. Soc.* **1994**, *116*, 7597−7605.

Scheme 2



and make the compound kinetically more stable. Thus, the octyl, isopropyl, and *tert*-butyl analogues, **12**−**14**,



respectively, were prepared and found to exhibit greatly enhanced stabilities. By the end of a typical titration with **12** the amount of hydrolysis was observed to be <10%, with **13** it was <5%, and with compound **14** it was <1%. The hydrolysis products, namely pinacol and **8**−**10**, respectively, were found to have no ability to bind acetate or the parent boronate-urea in DMSO-d_6. Thus they were treated in the titration experiment as minor, inert impurities.

The difluoroboronates **15** and **16** were prepared by modification of the procedure reported by Vedejs and coworkers.[16] These compounds displayed improved hydrolytic stability compared to their oxygen analogues, **11** and **12**. At the end of a typical titration about 15% of **15** had hydrolyzed, and with **16** the amount of hydrolysis was <5%. This improvement in hydrolytic stability matches the observations reported by Vedejs.[16]

The bis(boronate-amide) **23** displayed the same good stability as the trigonal boronates, **17** and **18**, *i.e.*, it remained intact during a typical NMR titration experiment with tetrabutylammonium acetate in DMSO-d_6.

Receptor Structure

The structures of all heterocyclic receptors were characterized by NMR spectroscopy and mass spectrometry. In addition, the structures of **7** (see Supporting Information) and **15** (Figure 2) were solved by X-ray crystallography. A summary of the important bond lengths and bond angles for both structures is provided in the Supporting Information. An inspection of these structural details provides strong evidence that isomer **3b** is the correct representation for this class of compounds.

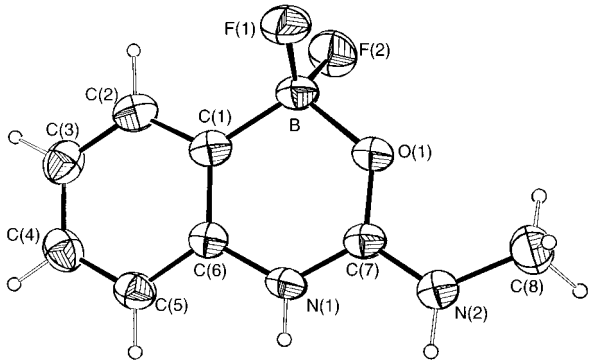
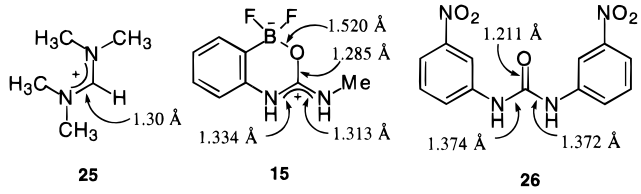


Figure 2. ORTEP drawing and atomic numbering scheme for **15**.

Scheme 3



Scheme 3 compares some important bond lengths in **15** with those observed for a related guanidinium cation **25**[17] and the *N,N′*-diarylurea **26**.[13] The C−N bonds in **15** are significantly shorter than the urea C−N bonds in **26** and are close to the C−N bond lengths in **25**. On the other hand, the corresponding C−O bond in **15** is more than 0.05 Å longer than a typical urea C−O bond.

Are the solid-state structures for **7** and **15** retained during the titration experiments? The NMR data suggests they are. For example, the ^{1}H NMR spectrum of **7** in DMSO-d_6 shows no coupling between the NH group and the methyl protons, which is inconsistent with isomer **27** (Scheme 4). In the case of the tetrahedral boronate-urea **3b**, there are potentially three isomeric structures. However, the presence of coupling between the NH and side-chain C_1 protons in **12**−**16** is strong evidence against **28**, and isomer **29** is ruled out because the very strong association with acetate, described below, implies that both NH residues are in a syn orientation. Only structure **3b** provides this syn relationship.

(16) Vedejs, E.; Chapman, R. W.; Fields, S. C.; Lin, S.; Schrimpf, M. R. *J. Org. Chem.* **1995**, *60*, 3020−3027.

(17) Prick, P. A. J.; Beurskens, P. T. *Cryst. Struct. Commun.* **1979**, *8*, 293−298.

Scheme 4

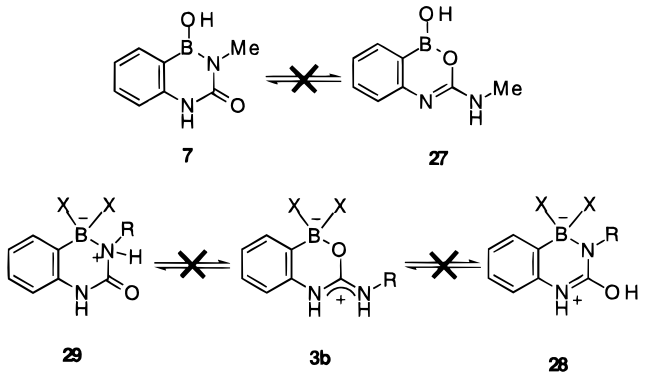


Table 1. ^{11}B NMR Chemical Shifts

compound	^{11}B NMR[a] (ppm)	compound	^{11}B NMR[a] (ppm)
7	11.0	**14**	−9.3
8	13.7	**15**	−15.2
9	11.5	**16**	−14.8
11	−9.3	**17**	12.3
12	−10.9	**18**	12.0
13	−10.1		

[a] Referenced to external trimethyl borate.

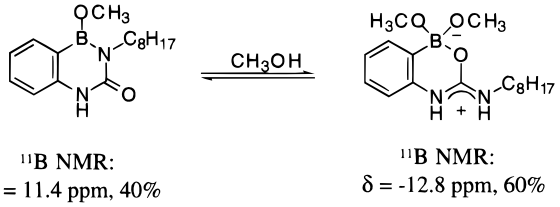


Figure 3. Likely structures for **8** in methanol solution.

The structures of the other compounds were assigned on the basis of their closely analogous NMR and mass spectra. The ^{11}B NMR spectra were particularly useful. For example, **8** has a ^{11}B chemical shift of 13.7 ppm in DMSO (referenced to trimethyl borate), which is very close to that observed for trigonal boronate **18** (12.0 ppm). In contrast, the chemical shifts for compounds **11**−**16** were 20 to 27 ppm upfield and clearly indicate tetrahedral boron hybridization (Table 1).[15,18] The ^{1}H and ^{13}C NMR spectra were also very indicative of the change in boron hybridization from trigonal to tetrahedral.

When compound **8** was dissolved in methanol two resonances were observed in the ^{11}B NMR spectrum. These peaks are attributed to a slow exchanging mixture of trigonal and tetrahedral forms (Figure 3). This is in slight contrast to the behavior of **4** which is completely converted to the bis-methanol adduct **5**.[15]

The structure of the bis(boronate-amide) **23** was dependent on the experimental conditions. A combination of ^{1}H COSY and NOE difference experiments indicated that in DMSO-d_6 the compound adopts the convergent cleft-shaped conformation **30** (Figure 4). The NOE difference spectrum was particularly revealing: saturating the NH resonance resulted in a strong enhancement of the signal for H-2, but no signal enhancement was observed for H-4 or H-5. The ^{11}B spectrum of **30** in DMSO exhibited a broad peak at δ 1.3 ppm (ΔJ = 820 Hz), indicating that the boron is only weakly coordinated by the amide carbonyl. Titration with tetrabutylammonium acetate shifted the ^{11}B signal upfield (δ −11.3 ppm, ΔJ = 250 Hz in the presence of ∼20 equiv of acetate). Since control experiments showed that acetate has no affinity for the trigonal boron in **18**, we conclude that the acetate forms hydrogen bonds with the amide NH residues, resulting in cooperative polarization of the amide carbonyl and a stronger carbonyl−boron dative bond. The result is structure **31** with a tetrahedral boron (Figure 4).

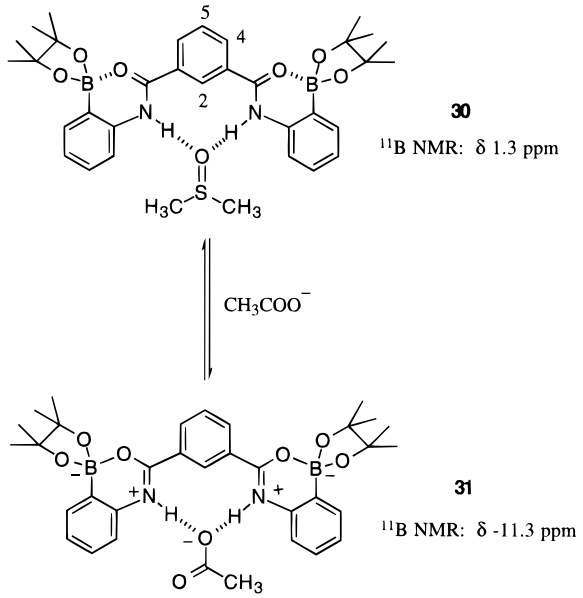
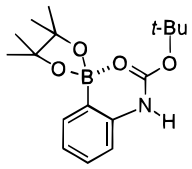


Figure 4. Likely supramolecular structures for **23**.

It is interesting to note that the related carbamate **32** was recently prepared by Lamba and Tour.[19] While the ^{11}B NMR spectrum was not reported, a comparison of the other spectroscopic data (*i.e.*, IR, ^{1}H NMR, ^{13}C NMR) with our data for **11**−**14** suggests that there is only a weak dative interaction between the boron and the carbamate carbonyl.



32

Binding Studies

Solutions of the host in DMSO-d_6 were titrated with increasing amounts of tetrabutylammonium acetate. In all cases, the observed titration isotherms nicely matched a 1:1 binding model. Control experiments showed no evidence for host dimerization. Association constants and complex-induced shifts, ($\Delta\delta_{max}$), were extracted by iterative curve-fitting methods and are listed in Table 2. Inspection of the association constants for the pinacol-derived boronate-ureas reveals that the ortho-substituted derivatives **12**−**14** bind acetate about 20 times better than the meta-substituted controls **17** and **18** and non-boron controls **19**−**21**. Even more impressive is the difluoroboronate **16** which binds acetate 150 times better

(18) Kidd, R. G. In *NMR of Newly Accessible Nuclei*; Laslo, P., Ed.; Academic Press: New York, 1983; Vol. 2, pp 49−77.

(19) Lamba, J. J. S.; Tour, J. M. *J. Am. Chem. Soc.*, **1994**, *116*, 11723−11736.

Table 2. Acetate Association Constants from ^{1}H NMR Titrations in DMSO-d_6 at 295 K

host	K_{assn} (M^{-1})[a]	ΔG_{295} (kcal/mol)	$\Delta\delta$[b] (ppm)
12	$(7 \pm 1) \times 10^3$	−5.2	4.03
13	$(6.9 \pm 0.9) \times 10^3$	−5.2	4.13
14	$(7.1 \pm 0.3) \times 10^3$	−5.2	3.89
16	$(6 \pm 3) \times 10^4$	−6.4	3.94
17	$(4.1 \pm 0.5) \times 10^2$	−3.5	2.95
18	$(3.9 \pm 0.4) \times 10^2$	−3.5	3.13
19	$(3.7 \pm 0.4) \times 10^2$	−3.5	3.08
20	$(3.1 \pm 0.5) \times 10^2$	−3.4	3.16
21	$(2.6 \pm 0.6) \times 10^2$	−3.3	2.50
22	$(1.1 \pm 0.1) \times 10^2$	−2.7	1.92
23	$(2.1 \pm 0.2) \times 10^3$	−4.5	*c*

[a] Average of at least three independent trials. Association constants are average of all host protons which exhibited complexation-induced titration isotherms. [b] Average of the $\Delta\delta$ values for both NH residues obtained from computer fitting. [c] NH peak broadens during titration and becomes indistinguishable from baseline. Association constant was determined from titration isotherms of other host protons.

than its control version **18**. The 1:1 binding stoichiometry was verified by a Job plot.[20]

In the case of host **13** and its control **20**, the acetate association constants were measured as a function of temperature (295−333 K) which allowed the thermodynamics of association to be extracted from van't Hoff plots ($R \ln K$ vs $1/T$ which gave straight lines of $r^2 > 0.99$). The results (**13**, $\Delta H = -5.6$ kcal/mol, $\Delta S = -1.2$ cal/mol K; **20**, $\Delta H = -3.9$ kcal/mol, $\Delta S = -1.5$ cal/mol K) indicate that the difference in binding ability is due primarily to enthalpic effects.

Discussion

As summarized in Table 2, Lewis acid induced polarization of a urea or amide group increases its acetate binding ability in DMSO by up to 3 kcal/mol. This is due to a favorable change in the enthalpy of association, which is assigned qualitatively to an enhancement in receptor hydrogen bonding ability and/or stronger ion−dipole interactions (see below). The increase in urea hydrogen bond donation raises the possibility of proton transfer to the acetate during complex formation. As summarized by Wilcox, treatment of an acidic host with a basic guest may result in either (i) association due to hydrogen bonding, (ii) proton exchange from acid to base, or (iii) proton exchange followed by hydrogen bonded association.[21] All three processes are known to give hyperbolic curves using the titration method described in Table 2. Control experiments using a dilution method also exhibited hyberbolic curves, which eliminated simple acid−base exchange.[21] However, proton exchange followed by association remained a possibility.

There is little doubt that the boronate-ureas **11**−**16** are more acidic than the control ureas **17**−**21** (pK_a for *N*,*N*′-diphenylurea in DMSO is 19.6[22]). But are the boronate-ureas sufficiently acidic to transfer a proton to acetate (pK_a for acetic acid in DMSO is 12.3[22])? Attempts to directly measure boronate-urea p*K*a's in DMSO using the methods of Bordwell were unsuccessful due to sample

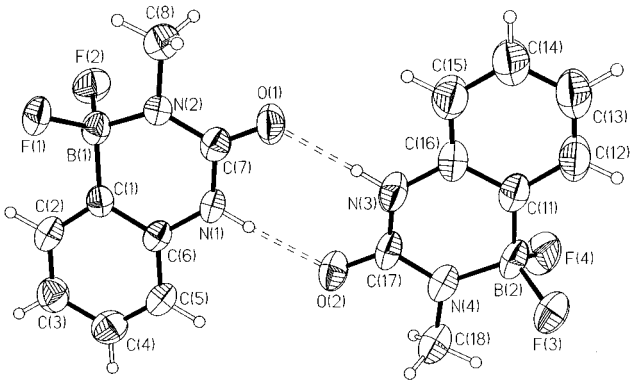
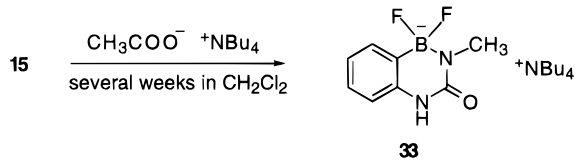


Figure 5. ORTEP drawing and atomic numbering scheme for the solid-state dimer of **33**. The tetrabutylammonium counterions have been omitted for clarity.

decomposition.[23] Indirect evidence against a proton transfer to acetate include the following points: (i) UV titration experiments produced weak, 10 nm bathochromic shifts in boronate-urea absorption upon acetate complexation.[14] (ii) A recent, high level *ab initio* study of the association of formate and guanidinium ions found that in polar solvents like DMSO there is no proton transfer to the carboxylate.[24]

Ironically the case against proton transfer was made more definite after we isolated a deprotonated boronate-urea. Upon standing for several weeks, an equimolar solution of **15** and tetrabutylammonium acetate in methylene chloride produced a crystalline material that was shown by X-ray crystallography to be **33**, the deprotonated (and isomerized) version of **15** (Figure 5, see Supporting Information for bond lengths and bond angles). Although this was clearly an example of proton exchange to acetate, subsequent experiments proved that this process was not occurring during the titration experiments in DMSO. For example, the ^{1}H NMR spectrum of **33** is quite distinct from **15**, and addition of **33** to a DMSO-d_6 solution of **15** and tetrabutylammonium acetate showed that **15** and **33** do not undergo fast exchange. Since **33** is not observed during the ^{1}H NMR titration experiments, we deduce that it is not present to any significant amount. In any case, **33** is incapable of producing the titration isotherms described in Table 2 as it has an extremely weak affinity for acetic acid in DMSO-d_6 solution. We conclude that the deprotonated boronate-urea **33** is not present to any measurable extent during the acetate titration experiments in DMSO-d_6. It is produced in methylene chloride because its extreme insolubility in that solvent allows it to accumulate over an extended period of time.



33

To better understand how the binding enthalpy is affected by intramolecular coordination, we attempted to correlate calculated molecular properties for our boronate-ureas with the observed acetate association con-

(20) Conners, K. A. *Binding Constants, The Measurement of Molecular Complex Stability*; Wiley: New York, 1987.
(21) Wilcox, C. S. In *Frontiers in Supramolecular Organic Chemistry and Photochemistry*; Schneider, H.-J., Dürr, H., Eds.; VCH: Weinham, 1991.
(22) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456−463.
(23) Matthews, W. S. *et al. J. Am. Chem. Soc.* **1975**, *97*, 7006−7014.
(24) Zheng, Y.-J.; Ornstein, R. L. *J. Am. Chem. Soc.* **1996**, *118*, 11237−11243.

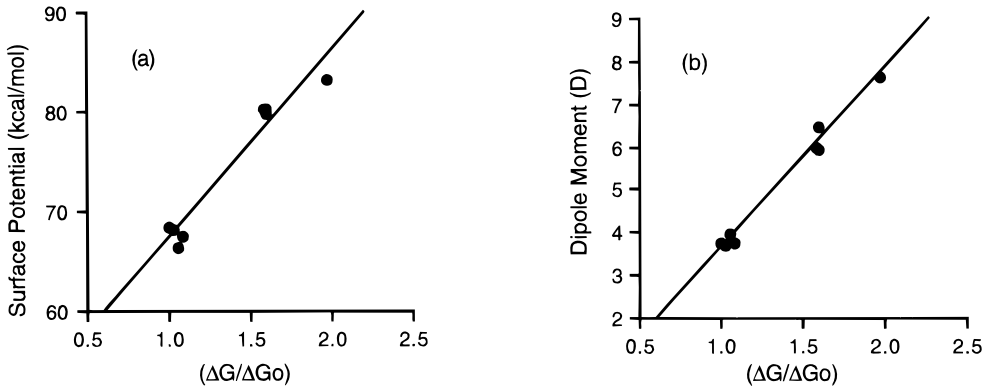


Figure 6. Correlation of association energies (ΔG) relative to **21** (ΔG_o) with (a) calculated electrostatic surface potentials (r^2 = 0.939); (b) calculated molecular dipole moments (r^2 = 0.987).

stants. We followed the approach of Wilcox and calculated host dipole moments and surface electric potentials using Hartree−Fock methods (AM1 to optimize geometry followed by HF methods to calculate dipole moments and surface potentials using a 6-31G* basis set).[14] Wilcox found that the sulfonate binding ability of substituted arylureas and arylthioureas correlated very well with the maximum electrostatic surface potential in the vicinity of the NH residues (r^2 = 0.980) and less well with host dipole moments (r^2 = 0.946).[14] In our case (Figure 6), we found that the correlation with dipole moment (r^2 = 0.987) was better than with electrostatic surface potential (r^2 = 0.939).

Conclusion

Polarization of a urea or amide group by intramolecular coordination with a Lewis acidic boronate increases acetate association constants by up to 3 kcal/mol. Boronate-ureas exhibit improved acetate binding ability because the intramolecular coordination (i) induces a larger host dipole moment which strengthens the guest/host ion−dipole interaction, and (ii) increases the positive surface potential at the urea NH residues which strengthens short range Coulombic interactions with the anionic acetate. The observed association constants correlate better with calculated host dipole moments suggesting that for the boronate-ureas described here this is the more influential factor controlling association.

Experimental Section

(2-Nitrophenyl)boronic Acid. This material was prepared according to the method of Groziak.[15] The crude product was purified by flash column chromatography on alumina, using a mobile phase of 1:10 CH_3OH/CH_2Cl_2. The desired product was recrystallized twice from hot water (yield: 41%).

(2-Aminophenyl)boronic Acid (6). This material was obtained by hydrogenation of (2-nitrophenyl)boronic acid according to the method of Groziak.[15]

1-Hydroxy-2-methyl-1*H*-2,4,1-benzodiazaborin-3-one (7). A solution of (2-aminophenyl)boronic acid (350 mg, 2.6 mmol) dissolved in 20 mL of acetonitrile was stirred at room temperature. Methyl isocyanate (2.5 equiv, 380 μL) dissolved in 1 mL of acetonitrile was added to the reaction flask, after which the solution turned cloudy. The reaction was stopped after a total of 4 h. The precipitated product was filtered, washed with cold acetonitrile, and dried *in vacuo* (yield: 90%): mp > 250 °C; TLC R_f = 0.40 (hexane/ethyl acetate/methanol 4:4:1); ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.23 (1H, s, exchanges with D_2O), 9.18 (1H, s, exchanges with D_2O), 7.93 (1H, d, J = 7.2 Hz), 7.40 (1H, t, J = 7.2 Hz), 7.02−6.95 (2H, m), 2.98 (3H, s) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 155.0, 145.3, 132.2, 132.1, 120.4, 114.0, 27.2 ppm; ^{11}B NMR (96 MHz, DMSO-d_6) δ 11.0 (ΔJ = 900 Hz) ppm; MS (EI) m/z 176 (M^+).

1-Hydroxy-2-octyl-1*H*-2,4,1-benzodiazaborin-3-one (8). This compound was prepared using the method described for **7** (yield: 75%): mp = 115−116 °C; TLC: R_f = 0.35 (2:1 hexanes/ethyl acetate); ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.15 (1H, s), 9.08 (1H, s), 7.91 (1H, d, J = 7.5 Hz), 7.39 (1H, t, J = 7.5 Hz), 7.01−6.94 (2H, m), 3.53 (2H, t, J = 6.9 Hz), 1.48 (2H, bs), 1.24 (10H, bs), 0.83 (3H, t, J = 7.2 Hz) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) δ 153.4, 144.2, 131.2, 131.0, 119.2, 112.8, 29.8, 29.2, 28.4, 27.7, 27.5, 25.4, 20.9, 13.1 ppm; ^{11}B NMR (96 MHz, DMSO-d_6) δ 13.7 (ΔJ = 1630 Hz) ppm; ^{11}B NMR (96 MHz, CD_3OD) δ 11.4 (40%, ΔJ = 377 Hz), −12.8 (60%, ΔJ = 241 Hz) ppm; MS (FAB in 2-nitrobenzyl alcohol) m/z 275 $(MH)^+$; HRMS (FAB) calcd for ($C_{15}H_{23}BN_2O_2$ + H) 275.1934, found 275.1949.

1-Hydroxy-2-(1-methylethyl)-1*H*-2,4,1-benzodiazaborin-3-one (9). This compound was prepared using the method described for **7** except the reaction was stirred for 12 h at 50 °C (yield: 41%): mp > 260 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.04 (1H, s), 9.09 (1H, s), 7.92 (1H, d, J = 7.5 Hz), 7.38 (1H, t, J = 7.5 Hz), 6.98−6.93 (2H, m), 4.68 (1H, septet, J = 6.9 Hz), 1.36 (6H, d, J = 6.9 Hz) ppm; ^{11}B NMR (96 MHz, DMSO-d_6) δ 11.5 (ΔJ = 1100 Hz) ppm; MS (FAB in 2-nitrobenzyl alcohol) m/z 205 $(M + H)^+$.

1-(2′,2′,3′,3′-Tetramethylethylenedioxy)-3-(methylamino)-1*H*-2,4,1-benzoxazaborine (11). A mixture of **7** (180 mg, 1.0 mmol) and pinacol (130 mg, 1.1 mmol) in 30 mL of benzene was stirred under reflux in a Dean−Stark apparatus. After 6 h the reaction was stopped and the remaining solution evaporated to leave the desired compound as a yellow-white powder (283 mg, 100%): mp = 206−208 °C; TLC R_f = 0.31 (hexane/ethyl acetate/methanol 4:4:1); ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.90 (1H, s), 7.30 (1H, dd, J_1 = 7.2 Hz, J_2 = 1.7 Hz), 7.09 (1H, td, J_1 = 7.6 Hz, J_2 = 1.7 Hz), 6.91 (1H, td, J_1 = 7.3 Hz, J_2 = 0.9 Hz), 6.79 (1H, bs), 2.76 (3H, d, J = 4.4 Hz), 1.13 (12H, s) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 157.0, 139.7, 132.1, 127.0, 122.4, 113.9, 79.0, 26.0, 24.9 ppm; ^{11}B NMR (96 MHz, DMSO-d_6) δ −9.3 (ΔJ = 600 Hz) ppm; MS (FAB) m/z 277 $(MH)^+$; HRMS (FAB) calcd for ($C_{14}H_{21}BN_2O_3$ + H) 277.1494, found 277.1726.

1-(2′,2′,3′,3′-Tetramethylethylenedioxy)-3-(octylamino)-1*H*-2,4,1-benzoxazaborine (12). This compound was prepared using the method described for **11** (yield: 100%): mp = 75−80 °C; TLC: R_f = 0.58 (2:1 hexane/ethyl acetate); ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.74 (1H, s), 7.29 (1H, d, J = 6.9 Hz), 7.21 (1H, bs), 7.08 (1H, t, J = 7.5 Hz), 6.91 (1H, t, J = 7.2 Hz), 6.77 (1H, bs), 3.16 (2H, q, J = 6.6 Hz), 1.49 (2H, bs), 1.26 (10H, bs), 1.12 (12H, bs), 0.84 (3H, t, J = 6.6 Hz) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 156.5, 139.5, 132.0, 126.9, 122.4, 113.8, 78.9, 31.2, 29.3, 28.6, 26.1, 26.0, 24.9, 22.0, 13.9 ppm; ^{11}B NMR (96 MHz, $CDCl_3$) δ −10.9 (ΔJ = 700 Hz) ppm; MS (FAB in 2-nitrobenzyl alcohol) m/z 375 $(MH)^+$.

1-(2′,2′,3′,3′-Tetramethylethylenedioxy)-3-[(1-methylethyl)amino]-1*H*-2,4,1-benzoxazaborine (13). This compound was prepared using the method described for **11** (yield:

82%): mp = 214 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.53 (1H, s), 7.30 (1H, d, J = 6.6 Hz), 7.18 (1H, bs), 7.09 (1H, t, J = 7.5 Hz), 6.91 (1H, t, J = 7.2 Hz), 6.77 (1H, d, J = 7.2 Hz), 3.85 (1H, m, J = 6.9 Hz), 1.16 (6H, d, J = 6.6 Hz), 1.13 (12H, s) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.2, 139.4, 132.8, 127.9, 123.4, 113.5, 77.2, 42.6, 26.0, 22.4 ppm; ^{11}B NMR (96 MHz, $CDCl_3$) δ −10.1 (ΔJ = 850 Hz) ppm; MS (FAB in 2-nitrobenzyl alcohol) m/z 305 $(MH)^+$.

1-(2′,2′,3′,3′-Tetramethylethylenedioxy)-3-[(1,1-dimethylethyl)amino]-1*H*-2,4,1-benzoxazaborine (14). (2-Aminophenyl)boronic acid (3.0 mmol) and pinacol (3.3 mmol) were taken up in benzene (30 mL) and stirred at 110 °C for 2 h under Dean−Stark conditions. Evaporation of the solvent left 2-(3′,3′,4′,4′-tetramethyl-2′,5′-dioxaborolanyl)benzenamine (608 mg, 92%): mp = 59−61 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.34 (1H, d, J = 6.3 Hz), 7.11 (1H, t, J = 6.9 Hz), 6.55 (1H, d, J = 8.1 Hz), 6.45 (1H, t, J = 7.2 Hz), 5.47 (2H, s), 1.27 (12H, s) ppm. 2-(3′,3′,4′,4′-Tetramethyl-2′,5′-dioxaborolanyl)-benzenamine (306 mg, 1.4 mmol) was dissolved in 10 mL of dry acetonitrile and stirred under N_2. Excess *tert*-butyl isocyanate (700 μL, 6.1 mmol) was added directly to the reaction vessel, and the solution was heated at 70 °C for 24 h. After cooling, the precipitated material was collected by filtration, then triturated in acetone to give pure, **10** (191 mg, 43%). mp = 195−198 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.31 (1H, s), 7.31 (1H, d, J = 6.0 Hz), 7.08 (1H, t, J = 7.5 Hz), 6.93 (1H, s), 6.91 (1H, t, J = 7.5 Hz), 6.65 (1H, d, J = 7.8 Hz), 1.35 (9H, s), 1.14 (12H, s) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 156.3, 139.2, 132.2, 127.0, 122.3, 113.5, 78.9, 51.0, 28.8, 26.3 ppm; ^{11}B NMR (96 MHz, DMSO-d_6) δ −9.3 (ΔJ = 700 Hz) ppm; MS (FAB in 2-nitrobenzyl alcohol) m/z 319 $(MH)^+$.

1,1-Difluoro-3-(methylamino)-1*H*-2,4,1-benzoxazaborine (15). An aqueous solution of KHF_2 (4.2 M, 0.5 mL) was added dropwise to a solution of **7** (93 mg, 0.52 mmol) in methanol (1 mL). The solution was heated for 1 h at 50 °C and cooled. Upon addition of cold water (1 mL), a white precipitate formed which was filtered and dried *in vacuo* to give **15** (72 mg, 70%): mp = 175 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.28 (1H, d, J = 6.9 Hz), 7.17 (1H, t, J = 6.6 Hz), 6.97 (1H, t, J = 7.2 Hz), 6.92 (1H, bs), 2.82 (3H, s) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 156.2, 130.7, 130.5, 127.9, 118.5, 114.0, 111.6, 26.6 ppm; ^{11}B NMR (96 MHz, DMSO-d_6) δ −15.1 (ΔJ = 248 Hz) ppm; ^{19}F NMR (470 MHz, $CDCl_3$) δ −54.5 (s) ppm.

1,1-Difluoro-3-(octylamino)-1*H*-2,4,1-benzoxazaborine (16). This compound was prepared using the method described for **15** (yield: 86%): mp = 135−138; °C ^{1}H NMR (300 MHz, DMSO-d_6) ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.61 (1H, bs), 7.58 (1H, d, J = 4.2 Hz), 7.20 (1H, t, J = 4.2 Hz), 7.17 (1H, t, J = 4.2 Hz), 6.66 (1H, bs), 6.32 (1H, bs), 3.20 (2H, q, J = 4.2 Hz), 1.45 (2H, bs), 1.23 (10H, s), 0.86 (3H, t, J = 4.2 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.8, 137.5, 131.1, 128.7, 124.6, 114.1, 41.0, 31.7, 29.1, 26.6, 22.6, 14.1 ppm; ^{11}B NMR (96 MHz, $CDCl_3$) δ −14.8 (ΔJ = 211 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ −54.5 (s) ppm; MS (FAB in 2-nitrobenzyl alcohol) m/z 335 $(M + K^+)$.

***N*-Methyl-*N*′-[3-(3′,3′,4′,4′-Tetramethyl-2′,5′-dioxaborolanyl)phenyl]urea (17).** A solution of (3-aminophenyl)-boronic acid (155 mg, 1.1 mmol) in acetonitrile was treated with methyl isocyanate (162 μL, 2.75 mmol) and the reaction stirred at room temperature for 2 h. The precipitate was filtered and dried *in vacuo* to yield *N*-(3-boronophenyl)-*N*′-methylurea (118 mg, 55%): mp = 206−210 °C; TLC R_f = 0.36 (hexane/ethyl acetate/methanol 4:4:1); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.35 (1H, s), 7.93 (2H, s), 7.57 (1H, d, J = 8.1 Hz), 7.54 (1H, s), 7.30 (1H, d, J = 7.2 Hz), 7.16 (1H, t, J = 7.8 Hz), 5.94 (1H, q, J = 4.8 Hz), 2.62 (3H, d, J = 4.8 Hz) ppm. A solution of *N*-(3-boronophenyl)-*N*′-methylurea (194 mg, 1.0 mmol) and pinacol (1.1 mmol) in benzene (30 mL) was refluxed in a Dean−Stark apparatus for 2.5 h. After periodic removal of the benzene−water azeotrope had reduced the volume to 15 mL, the solution was cooled. The resulting precipitate was filtered and dried (yield: 63%): mp = 181−183 °C; TLC R_f = 0.46 (hexane/ethyl acetate 1:3); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.51 (1H, s), 7.73 (1H, d, J = 2.4 Hz), 7.49 (1H, dt, J_1 = 7.5 Hz, J_2 = 2.1 Hz), 7.23−7.16 (2H, m), 5.93 (1H, d, J = 4.5 Hz), 2.62 (3H, d, J = 4.5 Hz), 1.27 (12H, s) ppm; MS (EI) m/z 276 $(M)^+$.

***N*-[3-(3′,3′,4′,4′-Tetramethyl-2′,5′-dioxaborolanyl)phenyl]-*N*′-octylurea (18).** This compound was prepared using the method described for **17**. mp = 137−138 °C; TLC: R_f = 0.68 (1:1 hexane/ethyl acetate); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.40 (1H, s), 7.76 (1H, s), 7.43 (1H, dt, J_1 = 7.5 Hz, J_2 = 2.1 Hz), 7.23−7.16 (2H, m) 6.03 (1H, t, J = 5.4 Hz), 3.04 (2H, q, J = 6.6 Hz), 1.40 (2H, p, J = 6.6 Hz), 1.27 (12H, s), 1.25 (10H, bs), 0.85 (3H, t, J = 6.9 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.2, 138.3, 129.8, 128.6, 126.9, 123.9, 83.8, 40.3, 31.8, 30.1, 29.3, 29.2, 26.9, 24.8, 22.6, 14.0 ppm; ^{11}B NMR (96 MHz, $CDCl_3$) δ 12.0 (ΔJ = 550 Hz) ppm; MS (FAB in 2-nitrobenzyl alcohol) m/z 375 (MH^+).

***N*-Phenyl-*N*′-octylurea (19).** A solution of freshly distilled aniline (456 μL, 5.0 mmol) and octyl isocyanate (1.06 mL, 6.0 mmol) in 25 mL of acetonitrile was then stirred under N_2 for 2 h at 40 °C, 1 h at 85 °C, and finally 12 h at room temperature. The resulting precipitate was filtered and a second crop collected (693 mg, 56%): mp = 67−70 °C; TLC: R_f = 0.45 (1:1 hexane/ethyl acetate); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.34 (1H, s), 7.35 (2H, d, J = 5.1 Hz), 7.19 (2H, t, J = 5.1 Hz), 6.86 (1H, t, J = 4.5 Hz), 6.07 (1H, t, J = 3.3 Hz), 3.04 (2H, q, J = 3.9 Hz), 1.40 (2H, bs), 1.26 (10H, bs), 0.85 (3H, t, J = 3.9 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.4, 138.9, 129.1, 123.3, 120.6, 40.3, 31.8, 30.1, 29.3, 29.2, 26.9, 22.6, 14.1 ppm; MS (FAB) m/z 249 $(MH)^+$.

***N*-Phenyl-*N*′-(1-methylethyl)urea (20).** This compound was prepared using the method described for **19** (yield: 66%): mp = 153 °C; TLC R_f = 0.22 (hexane/ethyl acetate 3:1); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.24 (1H, s), 7.34 (2H, d, J = 8.0 Hz), 7.19 (2H, t, J = 8.0 Hz), 6.86 (1H, t, J = 7.0 Hz), 5.96 (1H, d, J = 8.0 Hz), 3.73 (1H, m, J = 7.0 Hz), 1.07 (6H, d, J = 7.0 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.9, 139.2, 129.0, 122.9, 120.1, 41.9, 23.1 ppm; MS (FAB) m/z 179 (MH).

***N*-Phenyl-*N*′-(1,1-dimethylethyl)urea (21).** This compound was prepared using the method described for **19** (yield: 59%): mp = 165 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.19 (1H, s), 7.32 (2H, d, J = 8.1 Hz), 7.18 (2H, t, J = 8.1 Hz), 6.85 (1H, t, J = 8.1 Hz), 5.96 (1H, s), 1.27 (9H, s) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 154.4, 140.6, 128.6, 120.7, 117.3, 49.3, 29.0 ppm; MS (FAB) m/z 193 $(MH)^+$.

1,3-Bis(phenylcarbamoyl)benzene (22). A mixture of isophthaloyl dichloride (812 mg, 4 mmol), triethylamine (1.12 mL, 8 mmol), and aniline (730 μL, 8 mmol) in 25 mL of acetonitrile was heated at 55 °C for 3 h. The resulting precipitate was collected and triturated in 15 mL of warm methanol. The solid remaining was dried *in vacuo* (yield: 72%): mp > 250 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.42 (2H, s), 8.52 (1H, t, J = 1.5 Hz), 8.13 (2H, dd, J_1 = 7.8 Hz, J_2 = 1.5 Hz), 7.79 (4H, d, J = 7.5 Hz), 7.69 (1H, t, J = 7.8 Hz), 7.37 (4H, t, J = 7.5 Hz), 7.11 (2H, t, J = 7.5 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.0, 139.0, 135.1, 130.5, 128.6, 126.9, 123.7, 120.3 ppm.

1,3-Bis[2′-(3″,3″,4″,4″-tetramethyl-2″,5″-dioxaborolanyl)-phenylcarbomoyl]benzene (23). A solution of 2-(3′,3′,4′,4′-Tetramethyl-2′,5′-dioxaborolanyl)benzenamine (1.5 mmol, see procedure for **14**), isophthaloyl dichloride (1.5 mmol), and triethylamine (7 mmol) in dry THF (20 mL) was stirred at 60 °C for 5 h. The precipitate was removed and the filtrate evaporated to leave a solid material which was taken up in 30 mL of ethyl acetate and washed with 10 mL of brine solution. As soon as the two phases were mixed, a precipitate formed which was collected and dried (526 mg, 31% for two steps): mp = 190 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.60 (2H, s), 8.70 (1H, s), 8.33 (2H, d, J = 7.8 Hz), 7.90 (1H, t, J = 7.8 Hz), 7.70 (2H, d, J = 7.2 Hz), 7.56 (2H, d, J = 7.2 Hz), 7.41 (2H, t, J = 7.2 Hz), 7.20 (2H, t, J = 7.2 Hz), 1.26 (24H, s) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 164.3, 140.2, 133.6, 132.8, 131.6, 129.5, 129.4, 127.3, 125.1, 118.2, 81.5, 25.6 ppm; ^{11}B NMR (96 MHz, DMSO-d_6) δ 1.3 (ΔJ = 836 Hz) ppm; ^{11}B NMR (96 MHz, DMSO-d_6 with excess tetrabutylammonium acetate) δ −11.3 (ΔJ = 250 Hz) ppm; MS (FAB in 2-nitrobenzyl alcohol): m/z 569 (MH^+), m/z 591 $(M + Na)^+$.

1,1-Difluoro-2-methyl-2,4,1-benzodiazaborin-3-one1-(Tetrabutylammonium Salt) (33). A solution of **15** and tetrabutylammonium hydroxide (both 1 mM) in methylene chloride was allowed to stand for several weeks. Crystals formed which were shown by X-ray crystallography to be **33**. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.19 (1H, s), 7.19 (1H, d, J = 7.2 Hz), 6.84 (1H, t, J = 7.8 Hz), 6.60 (1H, t, J = 7.2 Hz), 6.58 (1H, d, J = 7.4 Hz), 3.18 (8H, m), 1.58 (8H, m), 1.24 (8H, m), 0.96 (12H, t) ppm.

X-ray Crystallography.[25] Crystal data for **7** (see Supporting Information for ORTEP diagram): $C_8H_9BN_2O_2$, M = 175.98, monoclinic $P2_1/n$ (no. 14), a = 10.038(2), b = 7.093(9), c = 11.813(2) Å, β = 104.64(1)°, V = 813.8(2) Å^3, Z = 4, D_c = 1.44 g/cm^3 (293 K), μ(Mo Kα) = 0.958 cm^{-1}, $R_{merge}(I)$ = 0.012, 1561 unique reflections, 1113 with $F_o^2 > 3.0\sigma(F_o^2)$, coordinates of all hydrogen atoms refined R_1 = 0.041, R_2 = 0.057, gof = 1.45.

Crystal data for **15** (monohydrate): $C_8H_{11}BF_2N_2O_2$, M = 216.00, triclinic $P\bar{1}$ (no. 2), a = 6.752(1), b = 8.761(1), c = 9.097(2) Å, β = 68.65(2)°, V = 466.5(2) Å^3, Z = 2, D_c = 1.54 g/cm^3 (293 K), μ(Mo Kα) = 1.269 cm^{-1}, $R_{merge}(I)$ = 0.023, 1460 unique reflections, 1183 with $F_o^2 > 1.5\sigma(F_o^2)$, coordinates of all hydrogen atoms refined R_1 = 0.037, R_2 = 0.043, gof = 1.37.

Crystal data for **33** (tetrabutylammonium salt): $C_{24}H_{44}BF_2N_3O$, M = 439.43, monoclinic Pc (no.7), a = 15.702(4), b = 8.7968(13), c = 19.135(4) Å, β = 90.663(9)°, V = 2642.9(9) Å^3, Z = 4, D_c = 1.104g/cm^3 (293 K), μ(Mo Kα) = 0.076 mm^{-1}, all reflections unique, 5369 with $F^2 > 2\sigma(F^2)$, coordinates of all hydrogen atoms refined R_1 = 0.052, R_2 = 0.106, gof = 1.114.

Binding Titrations. A stock solution of host compound (15 mL, 1 mM) was divided into 15 NMR tubes (1 mL solutions). Aliquots of guest stock solution (2.5 mL, 20 mM) were then added to each NMR tube in increasing increments as follows (in μL): 0, 10, 20, 30, 40, 50, 75, 100, 125, 150, 200, 250, 300, 400, 500. This provided a range of guest:host ratios from 0 to 10 equiv and covered generally >95% of the chemical shift migration range. (A lower concentration guest stock solution was used for tighter-binding systems to cover a range of guest:host ratios out to 5 or even 3 equiv. The concentrations and equivalents were chosen to give the optimum range, 0.2−0.8, of Weber p-values.) Care was taken to avoid water absorption from the atmosphere. Diagnostic host peak shifts were followed by NMR (600 or 500 MHz) and the titration curves were fit to the 1:1 binding model

$$\delta_{obs} = \delta_o + (\delta_{max} - \delta_o)([C]/[H]_o) \quad (1)$$

where δ_{obs} is the observed chemical shift, δ_o is the chemical shift of the free (unbound) host, δ_{max} is the chemical shift of the completely bound host, $[H]_o$ is the preequilibrium concentration of host, and [C] is determined from the binding quadratic:

$$[C]^2 + (-[H]_o - [G]_o - 1/K)[C] + [H]_o[G]_o = 0 \quad (2)$$

where $[H]_o$ and $[G]_o$ are the preequilibrium host and guest concentrations, respectively. Equation 1 was then treated with a nonlinear least squares regression analysis program (using the Simplex algorithm). Our program was designed to determine the best fit for eq 1 by iterative minimization of the standard deviation:

$$X = (\delta_{calc} - \delta_{obs})^2 \quad (3)$$

where δ_{calc} is the calculated chemical shift value for a given titration point (from eq 1), and δ_{obs} is the actual (observed) chemical shift value for that titration point. The minimization was performed by simultaneously varying δ_o, δ_{max}, and K, thus providing a best fit value for the binding constant.

In cases where the diagnostic peak shift migrates upfield, the fitting equation is modified to:

$$\delta_{obs} = \delta_o - (\delta_o - \delta_{max})([C]/[H]_o) \quad (4)$$

During the titration of **12**, the pinacol−boronate group was hydrolyzed in small amounts (<10%) resulting in a decrease in host concentration. The true host concentration was determined by comparing the integration of the methyl peaks for **12** and free pinacol.

Job's Plot. Stock solutions of host and guest were prepared (5 mM each) and separated into vials to give the following host:guest volume ratios: 10:0, 9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8, 1:9. ^{1}H NMR spectra of all samples were obtained and the concentration of complex ([C]) for each solution was determined from the equation

$$[C] = [H]_o(\delta_{obs} - \delta_o)/(\delta_{max} - \delta_o) \quad (5)$$

where $[H]_o$ is the preequilibrium host concentration, δ_{obs} is the observed chemical shift, δ_o is the chemical shift of the free host, and δ_{max} is the chemical shift of the complex. The conventional Job's plot ($[C]_{eq}$ vs $[H]_o/[G]_o$) was then determined.

Molecular Modeling. The computer application Spartan was employed. Trigonal nitrogen was used for all urea comopunds, and tetrahedral boron was used for the boronate-ureas. In addition, a bond order of 1.5 was used for the urea carbon−nitrogen bonds in the boronate−ureas. Semiempirical geometry optimizations were performed using the AM1 basis set. This was followed by an *ab-initio* single point energy calculation using Hartree−Fock (HF) methods and the 6-31G* basis set. The electrostatic surface potential was then determined from this calculation, along with the molecular dipole moment.

Acknowledgment. The X-ray crystal structures were solved by Dr. M. Shang, University of Notre Dame. This work was supported by a grant from the US National Science Foundation (CHE96-27099). M.P.H. thanks the University of Notre Dame for a Schmidt Fellowship.

Supporting Information Available: ^{1}H NMR spectra of all new compounds, ORTEP diagrams and tables of bond angles and bond lengths for **7**, **15**, and **33**, and typical titration curves (27 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO9702249

(25) The authors have deposited atomic coordinates for compounds **7**, **15**, and **33** with the Cambridge Crystallograhic Data Center. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CD2 1EZ, UK.