Molecular Recognition: Hydrogen-Bonding Receptors That Function in Highly Competitive Solvents

Erkang Fan, Scott A. Van Arman, Scott Kincaid, and Andrew D. Hamilton*

Materials Research Center and Department of Chemistry, University of Pittsburgh Pittsburgh, Pennsylvania 15260

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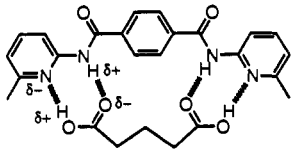
In recent years, many synthetic receptors have been constructed based on the incorporation of several hydrogen-bonding groups into a cleft or cavity.[1,2] In general, these hosts are only effective in nonpolar organic solvents,[3] and they are characterized by large unfavorable entropies of binding.[2] For example, a receptor formed by spanning two 2-amino-6-methylpyridine groups across a terephthaloyl spacer forms complexes with glutaric acid (at 295 K, $K_a = (6.4 \pm 1.4) \times 10^2$ M^{-1}, $\Delta G_{295} = -3.8$ kcal mol^{-1}) in 5% THF/$CDCl_3$, as seen in **1**.[4] The weak solvation of the hydrogen-bonding sites leads to a strongly enthalpic driving force for binding ($\Delta H = -7.9$ kcal mol^{-1}, $\Delta S = -14$ cal mol^{-1} K^{-1}) with a substantial negative entropy term due to the loss of translational and rotational motion inherent in bimolecular association and also the freezing of bond rotations in the complex.[5] Addition of dimethyl sulfoxide to **1** leads to strong solvation of the hydrogen-bond donor sites and an almost complete disruption of the binding. Our interest in extending these receptors to more polar and protic solvents prompted us to search for alternatives to 2-(acylamino)pyridines as the carboxylic acid binding elements.[3]



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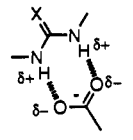
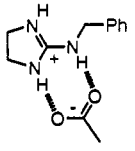


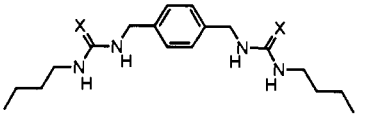
2a. X=O. 2b. X=S.



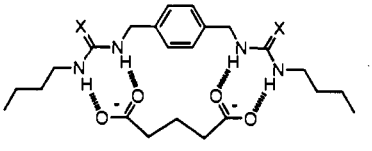
3

A simple modification involves placing both hydrogen-bond donors on the host, as in the urea carboxylate complex **2a**. This has the advantages of creating four favorable secondary hydrogen-bonding interactions[6] (as opposed to four unfavorable interactions in **1**) and of increasing the strength of the primary interaction through the use of charged hydrogen-bond acceptors.[7] Addition of tetramethylammonium acetate to a DMSO-d_6 solution of 1,3-dimethylurea (1.0×10^{-2} M) gave large downfield shifts of the urea NH resonance (>1 ppm), consistent with the formation of a bidentate hydrogen-bonded complex, as in **2a**. The resultant binding curve was analyzed by nonlinear regression methods[8] and gave an association constant of 45 ± 3 M^{-1}. Further gains in binding energy can be achieved by increasing the acidity of the H-bond donor sites in the receptor.[9] Thiourea ($pK_a = 21.0$) is more acidic than urea ($pK_a = 26.9$),[10] and the 1,3-dimethylthiourea complex, **2b** ($K_a = (3.4 \pm 0.7) \times 10^2$ M^{-1}), shows a nearly 10-fold increase in stability over **2a**. Similarly, the increased acidity of alkylguanidiniums ($pK_a \approx 14$) coupled with the additional stabilization of complementary charges leads to exceptionally strong binding between 2-(benzylamino)imidazoline hydriodide and acetate ($K_a = (1.2 \pm 0.3) \times 10^4$ M^{-1}) in DMSO-d_6, as in **3**.

These simple binding units can be readily incorporated into receptors for dicarboxylates, in analogy to **1**. Reaction of 1,4-bis(aminomethyl)benzene with butyl isocyanate or butyl isothiocyanate, followed by treatment with aqueous HCl, leads to bis-urea **4** and bis-thiourea **5** in 77 and 75% yields, respectively. In contrast to the corresponding bis-(acylamino)pyridine complex **1**, bis-urea receptor **4** binds effectively ($K_a = (6.4 \pm 0.4) \times 10^2$ M^{-1}, $\Delta G_{295} = -3.8$ kcal mol^{-1}) to the bis-tetrabutylammonium salts (TBA) of glutaric acid in DMSO-d_6. The proposed tetrahydrogen-bonding structure of the complex **6** was supported by the large downfield shifts of both the inner and outer urea NH resonances (>1 ppm), the observation of intramolecular ^{1}H NOEs between the receptor aryl and the substrate CH_2 resonances, and a Job's plot which gave a maximum at mole ratio 0.5.[11]



4. X = O 5. X = S.



6. X = O 7. X = S.

Variable-temperature measurements of K_a[12] for **6** in DMSO-d_6 gave $\Delta H = -3.9$ kcal mol^{-1} and $\Delta S = -0.1$ cal mol^{-1} K^{-1}. The binding enthalpy is reduced (compared to **1** in 5% THF/$CDCl_3$) due to increased solvation, but is still significant enough to drive association (unlike **1** in DMSO). This underlines the advantage of positioning H-bond donor sites close together in the host[13] where, for steric reasons, they are less effectively solvated than when widely spaced. This effect is clearly seen in the shift of the NH

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(12) Titrations (4-5) were performed over a temperature range of 293-323 K. Plots of $R \ln K$ vs $1/T$ gave straight lines ($R > 0.99$) from which ΔH and ΔS values of association were derived.

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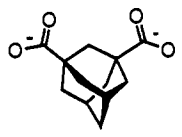
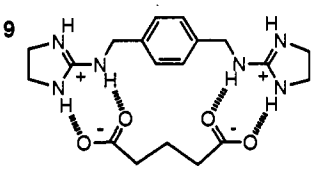
resonances on going from $CDCl_3$ to DMSO-d_6, which is smaller for the dialkylureas (1.65 ppm) than for the 2-(acylamino)-pyridines (2.33 ppm). Nonetheless, the increase in binding strength in **6** is modest compared to **2a** (ΔG_{295} = -2.2 kcal mol^{-1}, ΔH = -2.7 kcal mol^{-1}, and ΔS = -1.7 cal mol^{-1} K^{-1}), possibly reflecting that glutarate is binding in a higher energy conformation.[14] This interpretation is supported by the very strong interaction between **4** and adamantane-1,3-dicarboxylate **8**, a rigid analog of glutarate (ΔG_{295} = -4.5 kcal mol^{-1}, ΔH = -5.6 kcal mol^{-1}, and ΔS = -2.6 cal mol^{-1} K^{-1}). The entropies of association for **2a**, **6**, and **4**:**8** in DMSO-d_6 are all small despite the inherent entropic cost of bimolecular association and the greater flexibility of the xylylene spacer, compared to the terephthaloyl group in **1**. Binding must therefore involve an entropically favorable component to counterbalance these unfavorable factors. This may derive from displacement of DMSO molecules solvating the urea NH sites or ion-paired tetrabutylammonium cations on substrate binding. The resultant randomization of solvent or ions would lead to an increase in entropy, and similar effects have been seen with other synthetic receptors.[5,15]



8



10

The complex **7** formed between bis-thiourea receptor **5** and glutarate-TBA in DMSO-d_6 shows a 15-fold increase in stability (K_a = (1.0 ± 0.2) × 10^4 M^{-1}) over **6**.[16] The corresponding bis-alkylguanidinium receptor **9**[17] is formed by reaction of 1,4-bis(aminomethyl)benzene with 2-(methylthio)imidazoline hydriodide. The association constant for the complex between **9** (as its bis-iodide salt) and glutarate-TBA in DMSO-d_6 was too large (K_a > 5 × 10^4 M^{-1}) to be measured by ^{1}H NMR. Addition of D_2O to the DMSO solution led to the expected decrease in K_a, due to increased solvation of the carboxylate groups. However, binding was still clearly observable at 12% D_2O/DMSO (K_a = (8.5 ± 1.5) × 10^3 M^{-1}) and even 25% D_2O/DMSO (K_a = (4.8 ± 2.5) × 10^2 M^{-1}).[18]

In summary, we have shown that manipulation of both the location and charge of hydrogen-bonding sites can convert synthetic receptors that function only in nonpolar solvents into ones that bind strongly in highly competitive solvents. We are currently applying these designs to new catalytic systems.

Acknowledgment. We thank the National Institutes of Health (GM 35208) for financial support of this research, Prof. Steven Weber for many helpful discussions, and Prof. Craig Wilcox for his generous provision of the Hostest-II program.

(13) A similar proximity of H-bond donor sites is seen in the carboxylate-binding pocket of the antibiotic vancomycin. See: Kannan, R.; Harris, C. M.; Harris, T. M.; Waltho, J. P.; Skelton, N. N.; Williams, D. H. *J. Am. Chem. Soc.* **1988**, *110*, 2946.

(14) Adipic acid binds to the bis-(acylamino)pyridine receptor **1** in a less stable conformation.[4]

(15) For a discussion of related effects in cyclophane receptors, see: Stauffer, D. A.; Barrans, R. E., Jr.; Dougherty, D. A. *J. Org. Chem.* **1990**, *55*, 9412.

(16) The stronger binding of anions by thioureas compared to ureas has also been observed by C. S. Wilcox and his group. A detailed analysis of this effect will be the subject of a future paper.

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(18) Binding was monitored by following the upfield shifts of the benzylic proton resonances and was further supported by the observation of an NOE between the aromatic and glutarate protons.

Multidentate Lewis Acids. Simultaneous Coordination of a Carbonyl Oxygen Atom by Four Lewis Acids

Michel Simard, Jean Vaugeois,[1] and James D. Wuest*[,2]

Département de Chimie, Université de Montréal Montréal, Québec, H3C 3J7 Canada

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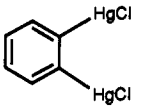
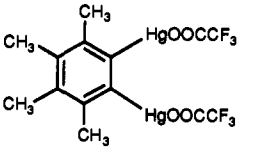
Basic oxygen atoms in neutral organic molecules are able to accept multiple hydrogen bonds at the same time.[3] These multiple interactions play a chemically important role by helping determine structure and reactivity. In contrast, the simultaneous interaction of basic oxygen atoms with multiple sites of Lewis acidity is a more elusive phenomenon. Complexes in which the oxygen atom of an ether or a carbonyl compound is bound by two Lewis acids are rare,[5-8] and higher degrees of association are unknown. In this communication, we describe the unprecedented structure of a complex in which the oxygen atom of a simple amide interacts simultaneously with four Lewis acidic atoms of mercury.

Phenylenedimercury dichloride **1**, a bidentate Lewis acid,[9] is known to form a 1:1 complex with dimethylformamide in which the carbonyl oxygen atom is bonded to both atoms of mercury at once.[5c] A partial structure is shown in Figure 1a, along with selected geometric parameters. We have now found that crystallization of the more strongly Lewis acidic bis(trifluoroacetate) **2**[5b] from dimethylformamide or diethylformamide produces complexes in which the bidentate Lewis acid and the amide are present in a 2:3 molar ratio.[10] The structures of these two complexes were determined by X-ray crystallography and proved to be very similar;[11] the structure of the diethylformamide adduct is illustrated in Figures 1 and 2, along with selected interatomic distances and angles.



1



2

Two of the three bound amides are complexed in the expected manner. Each carbonyl oxygen atom interacts with two Lewis

(1) Fellow of the Natural Sciences and Engineering Research Council of Canada, 1988-1992.

(2) Killam Research Fellow, 1992-1994.

(3) A dramatic example is provided by the carbonyl oxygen atom of crystalline urea, which accepts four hydrogen bonds.[4]

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