Complexation of Carbonyl Compounds with an Organic Salt Dominated by Acid-Base Interactions in Dichloromethane

Dwayne A. Bell and Eric V. Anslyn*

Department of Chemistry and Biochemistry, The University of Texas at Austin, Austin, Texas 78712

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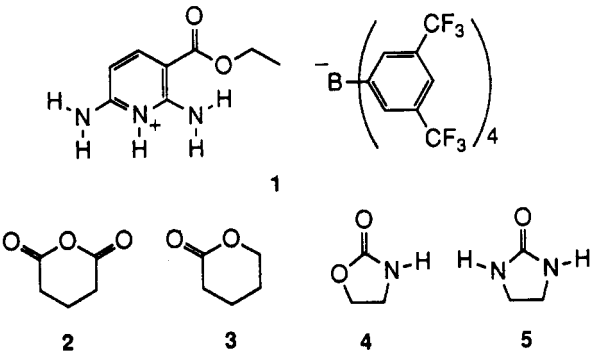
Summary: Small neutral carbonyl compounds (**2–5**) form very stable complexes (K_a's ranging from 10^3 to 10^5 M^{-1}) with ethyl 2,6-diaminonicotinium tetrakis(3,5-bis(trifluoromethyl)phenyl)borate (**1**) in dichloromethane. The dominant driving force for complexation is the strength of the acid-base interaction between the host and guest.

The study of molecular associations using synthetic host-guest systems provides insight into the forces used by nature in enzyme-substrate binding.[1] The predominant strategies used to form these complexes have included hydrogen bonding[2] and π-stacking.[3] Secondary hydrogen bonding has also proven to be important for binding between neutral compounds.[4] In addition, electrostatic interactions[5] between hosts and guests have consistently resulted in large association constants in nonpolar, noncompeting solvents and are increasingly being used to achieve binding in competitive solvents.[6] Herein, we report the use of a cationic hydrogen-bond-donating host to bind neutral carbonyl compounds in low dielectric media. The system was designed to achieve large binding constants and controllable selectivity through a combination of multiple charged hydrogen bonds, ion-dipole attractions, and constructive secondary hydrogen bonds. However, not all of these factors play important roles. Instead, the large binding constants were due almost solely to the acidic nature of the host, and selectivity was controlled by the basicity of the guests.

Chart 1



The host studied was ethyl 2,6-diaminonicotinium tetrakis (3,5-bis(trifluoromethyl)phenyl)borate (**1**),[7] and the guests were various neutral carbonyl compounds **2–5** (Chart 1). This borate anion was chosen for its solubility in organic solvents, low coordinating ability, and chemical stability.[8]

NMR spectroscopy was used to measure the binding constant of **1** with **2** but was unsuccessful for **1** with **3–5**. Initial ^{1}H-NMR titration studies[9a,10] in $CDCl_3$ of **1** (1.8×10^{-2} M) with **2** indicated the presence of multiple equlibria in solution. Dilution studies performed with **1** in $CDCl_3$ indicated a dimerization constant of 37 M^{-1}.[9a] The presence of dimers in solution increased the number of equilibria present in the system, thus making the determination of association constants difficult. Lowering the concentration of **1** to 9.3×10^{-4} M reduced the dimer concentration and made the assignment of association constants for host-guest and host-(guest)$_2$ complexes possible. The chemical shifts of the 6-amino group were plotted against the concentration of **2**, and the resulting isotherm was modeled using a nonlinear least-squares regression program.[11] Values were determined for $K_{1:1}$ and $K_{1:2}$ of 5.2×10^3 M^{-1} and 1.8×10^2 M^{-1}, respectively (Figure 1). NMR titrations of **1** with **3** and **4** were also performed. Although accurate association constants could not be assigned due to the limits of the NMR technique, we estimated $K_{1:1}$'s $> 3.0 \times 10^4$ M^{-1}. Determination of binding constants above this value required concentrations of host and/or guest that were too dilute to be practical

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(7) ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.03 (t, CH_3, J = 7.2 Hz), 4.03 (q, CH_2, J = 7.2 Hz), 5.97 (bs, NH_2), 5.47 (d, CH, J = 9 Hz), 6.95 (bs, NH_2), 7.26 (s, CH, 4H), 7.45 (s, CH, 8H), 7.92 (d, CH, J = 9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.73, 62.42, 97.45, 98.71, 117.61, 122.69, 126.31, 129.93 (q, J = 28.57), 148.30, 151.83, 152.06, 161.37 (t, J = 48.8 Hz), 164.45; mass spectra m/z (CI^+) 182 (pyridinium), (CI^-) 863 (tetraphenylborate); λ_{max} (ϵ) 334 (19 300).

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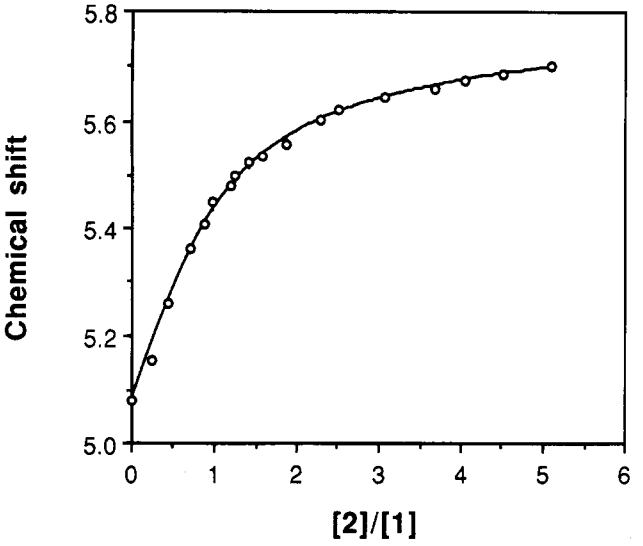

Figure 1. Observed chemical shift of the 6-amino hydrogens of 1 vs guest/host ratio. Concentration of 1 was 9.3×10^{-4} M. The curve is not hyperbolic, reflecting the presence of two equilibria in solution, both a 1:1 ($K_{1:1}$) and a 2:1 ($K_{1:2}$) guest to host complex.

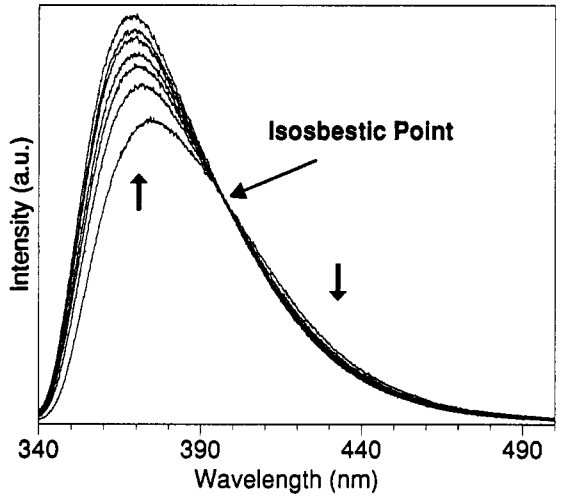

Figure 2. Increase in fluorescence of 1 with the addition of 4. A 15% increase in the integrated intensity, a 6-nm blue shift, and an isosbestic point at 398 nm are shown.

for NMR experiments. An analytical technique capable of detecting lower concentrations of host was required for **3–5**; thus, fluorescence spectroscopy was employed.

The fluorescence emission of **1** is quite sensitive to its local environment and was easily analyzed at low concentrations. Addition of **3–5** to **1** in CH_2Cl_2 resulted in 10–15% increases in fluorescence intensity, 3–6-nm blue shifts in the fluorescence emission, and an isosbestic point at 398 nm. The lifetime of the first excited state of the fluorophore also increases 9–10% upon complexation. The concentration of **1** was kept between 2.1×10^{-6} M and 4.0×10^{-6} M, and values for fluorescence intensity were measured at 368.6 nm. Guest **2** did not perturb the fluorescence spectrum of **1** in concentration ranges where dynamic effects could be ignored.[12] The fluorophore in **1** and in the host–guest complexes is ethyl 2,6-diaminonicotinium. Compound **1** had a fluorescence quantum yield[13] of 0.70 and a fluorescence lifetime[14] of 3.2 ns in CH_2Cl_2. Plots of fluorescence intensity or blue shift versus guest concentration appeared to be hyberbolic, indicative of 1:1 host–guest complexation.[9b]

Benesi–Hildebrand[15] treatment of the fluorescence isotherms (**1** with **3–5**) produced association constants (Table 1).[16] Curve fitting of the binding isotherms was also employed to determine association constants[9] (Table 1). The emission intensity yielded association constants which differed from those derived from blue shifts. In addition, the values from the Benesi–Hildebrand treatment were generally lower than those from curve fitting.[16] Despite these discrepancies, the magnitudes of the calculated association constants were consistent, and the trend in association constants **1:3** < **1:4** < **1:5** was readily apparent.

In order to test if the carbonyls of the guests were involved in complexation, changes in the IR stretching frequencies of **2–5** were followed upon addition of **1**. Both hydrogen bonding and ion–dipole interactions were expected to polarize the guest carbonyls and decrease their stretching frequencies. The addition of **1** to **4** in CH_2Cl_2 resulted in the formation of a new band at 1736 cm^{-1} which increased in intensity as the original carbonyl band at 1766 cm^{-1} disappeared. Similarly, the addition of **1** to **5** resulted in a new absorbance 29 cm^{-1} lower than the original carbonyl stretch at 1717 cm^{-1}. These shifts are similar but slightly larger than reported for **5** with a neutral hydrogen bonding host.[17] Similar shifts in the carbonyl stretching frequencies of **2** and **3** were difficult to detect due to the lower binding constant of **2** and **3** with **1** and potential overlap of the shifted resonances with the host's ester resonance. These experiments clearly demonstrate that the carbonyl oxygens of **4** and **5** (the most basic site of each guest) are involved in a hydrogen bond.

Examination of Table 1 reveals the factors that control the selectivity of binding with **1**. As the basicity of the guests increases[18] the association constant with **1** increases, while no such correlation exists with the dipole moments[19] or with the potential number of hydrogen bonds. For example, the dipole of **5** is the smallest, yet it has the largest binding constant. Also, **2** can form three linear hydrogen bonds with **1**, yet **2** has the weakest interaction. Furthermore, although **4** can form two linear hydrogen bonds with **1**, and compound **5** can form only two bent bonds, the binding constant with **4** is smaller than with **5**. This selectivity trend suggests that the complexation

(12) Using the Stern–Volmer equation gives a lifetime of the first excited state of 3.2 ns and a rate of quenching of 10^9 mol/s. The concentration necessary to achieve 2% quenching by a dynamic process was 6×10^{-4} M. Even though quenching was not observed, a concentration of 6×10^{-4} M was used to estimate the limits for dynamic effects. All concentrations were kept below this value.

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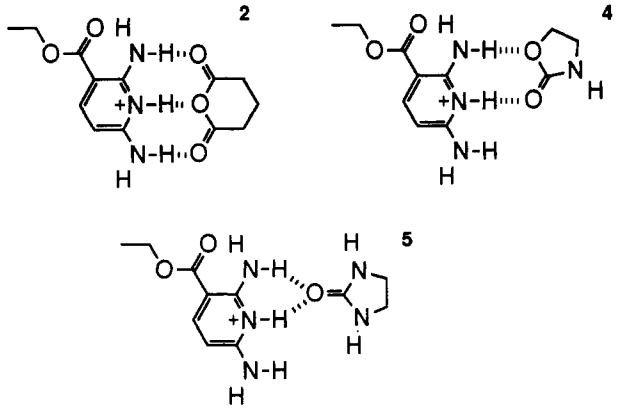
Table 1. Association Constants of Carbonyl Compounds 2–5 with an Organic Salt (1)[a]

	blue shift curve fitting (M^{-1})	blue shift Benesi–Hildebrand (M^{-1})	emission int curve fitting (M^{-1})	emission int Benesi–Hildebrand (M^{-1})	dipole moment in benzene[19]	pK_a of functional grp[18]
2[b]	$(5.20 \pm 0.60) \times 10^3$				4.14	anhydrides, −12 to −8
3	$(4.30 \pm 1.4) \times 10^4$	$(5.20 \pm 2.20) \times 10^4$	$(7.30 \pm 1.30) \times 10^4$	$(6.40 \pm 1.20) \times 10^4$	4.30	esters, −7 to −4
4	$(1.94 \pm 0.64) \times 10^5$	$(1.19 \pm 0.50) \times 10^5$	$(1.19 \pm 0.22) \times 10^5$	$(9.00 \pm 1.70) \times 10^4$	3.58	urethanes, −3 to −2
5	$(5.00 \pm 0.165) \times 10^5$	$(2.80 \pm 1.20) \times 10^5$	$(5.30 \pm 0.95) \times 10^5$	$(2.60 \pm 0.50) \times 10^5$	2.94	ureas, −2 to 1

[a] Association constants of 1 with 3–5 are derived from curve fitting the fluorescence intensity or blue-shift isotherms and Benesi–Hildebrand treatments.[15] [b] Determined by ^1H NMR (see text). The errors reported are based upon the standard deviations of five independent association constants determined for 1 with 4. Only a rough estimate of the pK_a for the anhydride can be provided because of rapid hydrolysis under the conditions necessary to measure the pK_a.[22]

geometry of all the guests is similar to that shown for 5 and that the basicity of the carbonyls dominates the binding, not the potential number of hydrogen bonds.[20] Currently, however, the structures shown for 2 and 4 cannot be definitively ruled out.



The binding constant of 1 with 5 is larger than any reported value for binding of compounds similar to 5 with receptors which use four uncharged hydrogen bonds.[2d-f] In fact, the binding of 5, with at most two bent hydrogen bonds, has a binding constant of the same magnitude for barbiturate binding using six linear hydrogen bonds.[21] Clearly, the combination of a cationic hydrogen bond donor, a noncoordinating counter ion as with 1, and a low dielectric media such as dichloromethane can result in exceptionally strong complexation of neutral compounds.

In summary, using a cationic hydrogen bond donor in dichloromethane yields large association constants. In the system under study, the pairing of the most acidic donor with the most basic acceptor determined the strength of complexation and not the number of potential hydrogen bonds. It will be interesting to discover if such complexation of carbonyl groups can be used for electrophilic activation in catalytic processes.

Acknowledgment. We would like to thank Dr. Sarah Green and Jack Chan for helpful discussions with regard to fluorescence and lifetime measurements. We also gratefully acknowledge financial support for this project from both the Welch Foundation and an NSF–PYI award to E.V.A.

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