Molecular Recognition

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Solvent Effects on Hydrogen Bonding**

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Changes in solvation are an integral part of almost all chemical processes that take place in solution, and in the field of molecular recognition, desolvation can be the dominant factor that determines the behavior of a system.[1] Although there are many methods for classifying the properties of solvents and rationalizing their effects, solvation is a complex phenomenon, and predictive quantitative models remain at a rudimentary level.[2] At the most simplistic level, polar interactions such as hydrogen bonding are favored in nonpolar organic solvents, while polar solvents lead to attractive interactions between nonpolar groups. As an integral part of the system, it is often difficult to vary the solvent in a systematic way. Quantitative studies of intermolecular interactions, such as hydrogen bonding, have traditionally focused on nonpolar solvents such as carbon tetrachloride, where there is limited solvent competition, so it is possible to characterize interactions between a wide range of different functional groups.[3] There have been some systematic studies on the effects of the solvent on interactions between relatively nonpolar aromatic groups: interactions were shown to be stronger in polar solvents, where solvophobic effects dominate, and weaker in nonpolar solvents that compete for the binding sites.[4] There has been some progress in the development of hydrogen-bonded complexes that function in more competitive solvent environments, but the range of solvent systems is limited, and ionic interactions are often required to drive complexation.[5] Here, we describe a study of the effects of solvent competition on intermolecular hydrogen-bonding interactions between neutral molecules in a range of competitive solvents.

Experimental measurement of the association constants for the formation of 1:1 complexes in nonpolar solvents allows the identification of functional groups with exceptional hydrogen-bonding properties. One of the most polar hydrogen-bond donors is perfluoro-*tert*-butyl alcohol (**1**)[3b] and one of the best hydrogen-bond acceptors is tri-*n*-butylphosphine oxide (**2**).[3c] Experiments on the complexation of these compounds with standard reference hydrogen-bond acceptors and donors in carbon tetrachloride suggest that the **1**·**2** complex should exhibit extraordinary stability, thereby allowing quantification of the hydrogen-bonding interactions in competitive polar solvents. The compounds have additional features that make them attractive for use in this experiment:

1) both **1** and **2** have good solubility in most solvents, thus facilitating accurate experimental measurement of weak binding interactions;
2) self-association of both compounds is negligible, even in concentrated solutions in nonpolar solvents, because tri-*n*-butylphosphine oxide contains only C–H donors, and the strongly electron-withdrawing CF_3 groups render both the oxygen and fluorine atoms of perfluoro-*tert*-butyl alcohol very poor hydrogen-bond acceptors;
3) the ^{31}P and ^{19}F NMR signals of **1** and **2**, respectively, provide convenient spectroscopic probes of complex formation, thus allowing NMR titrations to be performed in a range of solvents that is not limited by the availability of deuterated analogues.

The ^{31}P NMR signal of **2** is particularly sensitive to hydrogen-bonding interactions, and triethylphosphine oxide was previously used as a spectroscopic probe of the hydrogen-bonding properties of solvents, because the chemical shift varies by more than 10 ppm in different solvent environments.[6] Association constants were measured by ^{31}P NMR spectroscopy by titrating the alcohol into the phosphine oxide. Although Job plots for the titrations are consistent with the formation of a 1:1 complex, the binding isotherms show clear evidence of a second weaker complexation event, and the data fit significantly better to a 2:1 model than a 1:1 model (Figure 1).

Association constants were measured in 13 different solvents that cover a range of solvent properties, including strong hydrogen-bond donors and acceptors. The results are shown in Table 1. The **1**·**2** association constant spans a range of five orders of magnitude for the different solvents studied. Relatively stable complexes are formed in competitive hydrogen-bonding solvents such as acetone and tetrahydrofuran, but the stability of the complex drops to barely detectable levels in the most polar solvents, *N*-methylformamide and dimethyl sulfoxide. In noncompetitive solvents such as carbon tetrachloride, complexation is detectable down to micromolar concentrations, and in cyclohexane, the association constant is too large to measure by NMR titration experiments.[7] In solvents containing hydroxy groups, the changes in the ^{31}P NMR chemical shift are very small, which could be due to a relatively small change in the environment of the phosphine oxide on exchanging one OH group for

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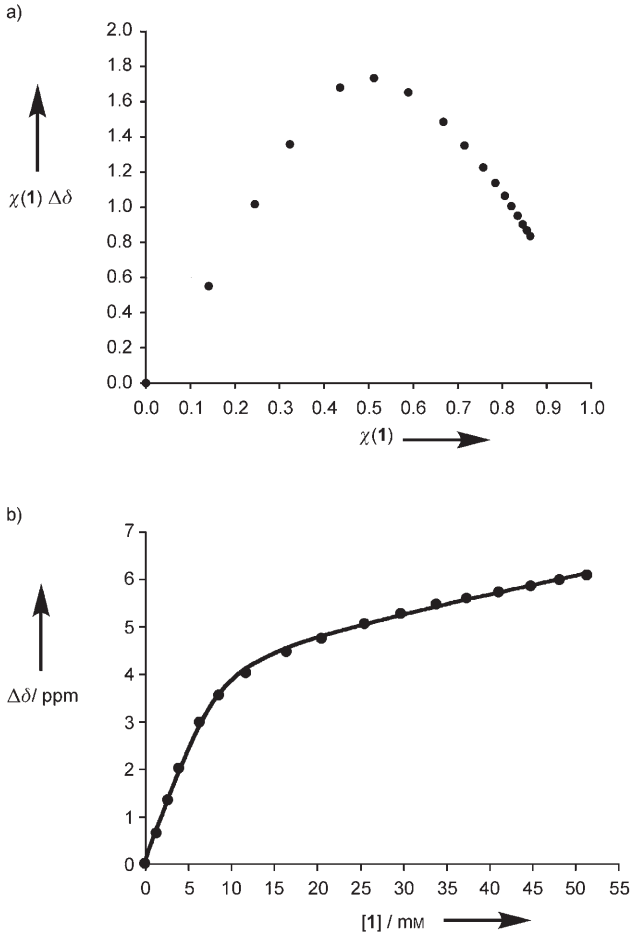

Figure 1. ^{31}P NMR titration data for the addition of **1** to **2** in chloroform, recorded in the tight binding limit (K[**2**]$\approx$10) to allow accurate determination of the stoichiometry. a) The Job plot shows a maximum for a 1:1 ratio of **1**:**2**, thus indicating the predominance of a 1:1 complexation mode. b) The titration curve shows clear evidence of a second binding event that leads to an almost linear second phase in the titration after the 1:1 stiochiometry is reached ([**1**] = 8 mM).

another or to very weak binding interactions. However, titration data could be obtained in *n*-decanol, which gave an association constant at the lower limit of detection.

These data provide us with an opportunity to investigate how the solvent environment perturbs hydrogen-bonding interactions and to evaluate the relative importance of properties such as hydrogen-bond donor/acceptor ability, internal cohesive energy, and effective dielectric constant. Figure 2a shows the correlation between the solvent polarity parameter $E_T(30)$ and the stability of the complex (log K_{expt}).[2] While there is some relationship, solvent polarity alone is clearly insufficient to account for the variations observed in this system. Similar results were obtained with a range of other solvent descriptors (α, β, π^*, δ, donor number (DN), acceptor number (AN), μ).[2] It might be possible to construct some kind of linear free energy relationship by using combinations of these parameters, but we recently proposed a simple solvent competition model that makes remarkably accurate predictions for the system described here (Table 1, Figure 2b).[8] The one outlier is *n*-decanol. The experimental association constant in this solvent is not very accurate, because the interaction is very weak, but it is clear that the alcohol behaves as a significantly more polar solvent than the solute-based H-bond parameters used in Table 1 would suggest. This finding may be due to the high degree of self-association in this solvent or may be due to polarization of the hydroxy groups in the bulk liquid, thus rendering the alcohol a stronger H-bond donor and/or acceptor than the isolated molecule.[9]

The model used to calculate the values of log K_{pred} in Table 1 makes some gross simplifying assumptions about the nature of intermolecular interactions and the role played by the solvent:

1) in solution, changes in the van der Waals interactions approximately cancel out, provided the molecules fit together properly and there are no steric restrictions on solvation of the solutes, such as a tightly enclosed cavity with a bulky solvent;[10]
2) the dominant intermolecular interactions are electrostatic interactions between the maxima and minima on the molecular electrostatic potential surfaces, so that all interactions of functional groups (hydrogen bonding, aromatic interactions, halogen bonding, etc) can be treated by using a single conceptual framework;
3) the cost of bringing two molecules together in a bimolecular complex in solution is an approximately constant value of 6 kJ mol^{-1};
4) the properties of solvent molecules do not change significantly as a bulk solvent relative to their behavior as solutes in dilute solution;[11]

Table 1: Results of ^{31}P NMR titration experiments showing the association constant for formation of a 1:1 complex at 295 K as a function of solvent properties.[a]

solvent	α_S	β_S	$E_T(30)$	K/M^{-1}	Log K expt	Log K pred
n-decanol	2.7	5.8	47.7	1.6×10^{-1}	−0.8	0.7
DMSO	0.8[b]	8.9	45.1	6.8×10^{-1}	−0.2	−0.1
NMF	2.9	8.3	54.1	8.9×10^{-1}	−0.1	−0.1
pyridine	1.4[b]	7.0	40.5	6.5×10^{0}	0.8	0.9
pyrrole	3.0	4.1	51.0	1.3×10^{1}	1.1	1.0
acetone	1.5	5.8	42.2	6.5×10^{1}	1.8	1.6
acetonitrile	1.7	4.7	45.6	1.6×10^{2}	2.2	2.1
tetrahydrofuran	0.9[b]	5.3	37.4	2.4×10^{2}	2.4	2.4
nitromethane	1.8	3.7	46.3	1.5×10^{3}	3.2	2.8
$CHCl_3$	2.2	0.8	39.1	2.7×10^{3}	3.4	3.5
benzene	1.0[b]	2.2	34.3	1.9×10^{4}	4.3	4.5
CCl_4	1.4	0.6	32.4	7.6×10^{4}	4.9	4.9
cyclohexane	0.4[b]	0.3[b]	30.9	$>10^{5}$	>5	6.9

[a] All experiments were repeated at least three times and average values of K are quoted. Errors in K are ±20%, except for the values in *N*-methylformamide (NMF), dimethyl sulfoxide (DMSO), and *n*-decanol, where only 30–40% of the binding isotherm was accessible and the values are accurate to within an order of magnitude. [b] Estimated from the AM1 molecular electrostatic potential surface.

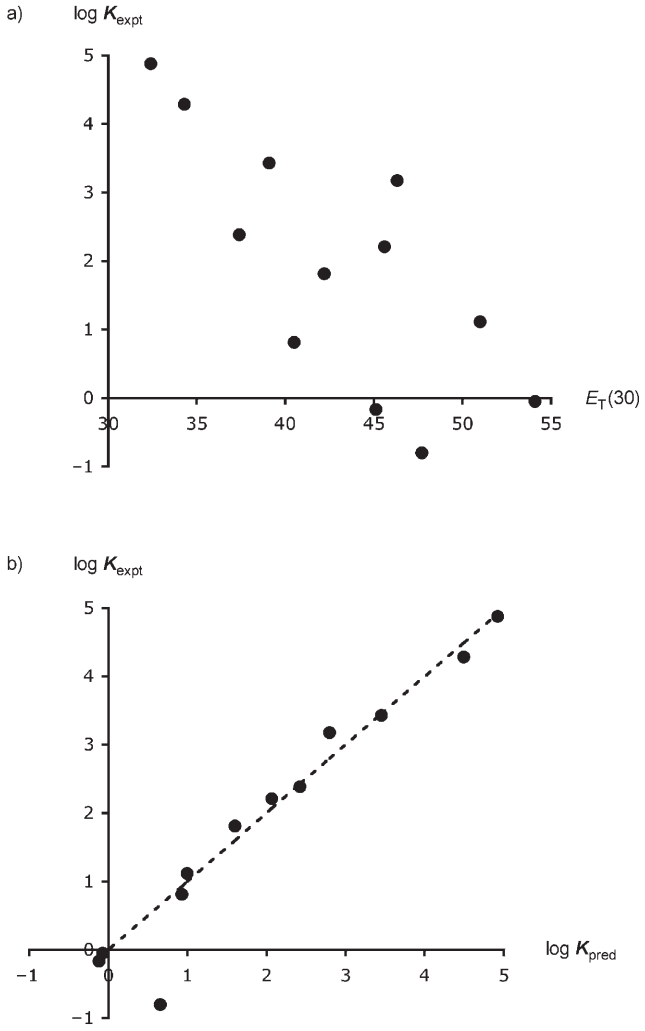

Figure 2. Correlation of $\log K_{expt}$ for the **1**·**2** complex in various solvents with a) $E_T(30)$ in kcal mol^{-1} and b) $\log K_{pred}$. These latter valuea were calculated using Equation (2), the values of α_S and β_S in Table 1, $\alpha = 4.9$ for **1**, and $\beta = 10.2$ for **2**. The dotted line corresponds to a perfect correlation ($y = x$).

5) the effects of desolvation can be treated using the simple pairwise molecular interactions illustrated by the equilibrium in Equation (1).

$$A \cdot S + D \cdot S \rightleftharpoons A \cdot D + S \cdot S \quad (1)$$

A and D are the hydrogen-bond acceptor and donor, respectively, and S is the solvent.

The solvent competition model provides a simple conceptual framework for thinking about intermolecular interactions in solution, but the remarkable finding reported here is that, with the exception of alcohols, the approach also provides quantitatively accurate predictions of solvent effects on intermolecular association constants. Equation (2) was used to estimate the association constants for the formation of the **1**·**2** complex in the solvents listed in Table 1 by using values of α and β reported previously (α and β, and α_S and β_S are the hydrogen-bond donor and acceptor parameters for the solute and solvent, respectively).[8] The hydrogen-bond parameters come from experimental measurements of 1:1 association constants in carbon tetrachloride or AM1 molecular electrostatic potential surfaces, but they are clearly applicable to equilibria in a wide range of solvents. The application of Equation (2) assumes that the solvent contains one type of hydrogen-bond donor and one type of acceptor, so that the values of α_S and β_S are uniquely defined. In principle, a more elaborate treatment of solvents with multiple donors and acceptors is possible, but for the purposes of this study, we have either used solvents where this is not the case or where one interaction site dominates the solvation of the solute; for example, the amide NH group in formamide is much more important than the CH group in the solvation of the phosphine oxide, as reflected in the chemical shift of the free phosphine oxide.

$$-R\,T\,\mathrm{Ln}\,K_{pred} = \Delta G = -(\alpha - \alpha_S)\,(\beta - \beta_S) + 6\ \mathrm{kJ\,mol^{-1}} \quad (2)$$

The results in Figure 2b imply that the role played by the solvent in this system is simply to compete for binding sites, and that other solvent properties are of secondary importance. Thus, solvent effects on molecular recognition can be understood in terms of the pairwise intermolecular interactions between the solvent and solute molecules according to Equation (1).

This study shows that the simple solvent competition model embodied by Equation (2) in conjunction with the new scale of hydrogen-bond parameters α and β can provide an accurate quantitative description of intermolecular interactions in solution.[8] The case of alcohols requires further investigation, as the H-bond parameters used here significantly underestimate the solvent polarity. More complicated complexes containing more than one interaction introduce factors that are not considered here and will certainly require further refinement of the model, but the potential Gibbs energy contributions of individual functional group interactions can at least be estimated with some confidence. The success in treating simple interactions in simple solvents indicates that this approach has the potential to yield new quantitative insight into molecular recognition and the role of the solvent in general.

Experimental Section

Association constants were determined by using standard NMR titration protocols.[12] All solvents were dried to minimize the effects of adventitious water. The host solution was prepared at a concentration between 0.1 and 10 mM depending on the stability of the complex ($[\mathbf{2}] \approx 1/K$). The guest solution was prepared by dissolving the guest in a sample of the host stock solution, so that there was no dilution of the host during the titration. On addition of aliquots of the guest solution, the NMR tube was thoroughly shaken to mix the two solutions, and a ^{31}P NMR spectrum was recorded by using an external capillary containing a 5 mM solution of methylene diphosphonic acid in D_2O to provide a ^{31}P reference signal ($\delta = 17.98$ ppm) and a deuterium lock signal. The observed changes in chemical shift (1 to 10 ppm depending on the solvent) were analyzed using purpose-written software on an Apple Macintosh microcomputer. In some

solvents, there was a second almost linear phase in the titration (see Figure 1b), indicative of a second weaker binding event. These data fit well to a 2:1 binding isotherm, thus allowing determination of both K_1 and K_2. However, for weaker binding complexes, the second phase of the titration did not reach saturation. All of the data were therefore fit to an isotherm where the second association constant was fixed at $0.1\,\text{M}^{-1}$, which describes the second linear phase well, and the values of K reported are the first association constants. For titrations with a well-defined second phase, the values of K_1 are not very sensitive to the values of K_2, and so the values of K reported are not significantly perturbed by this assumption.

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