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Molecular Interactions

Preferential Solvation and Hydrogen Bonding in Mixed Solvents**

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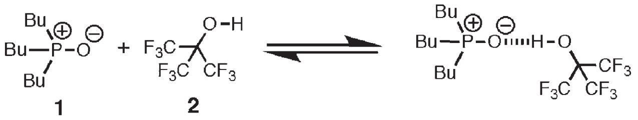
The molecular-recognition events that underpin many processes in chemistry and biology are intimately linked to accompanying changes in solvation. The subtle interplay of the different factors that contribute to these changes in solvation gives rise to phenomena that are difficult to interpret at the molecular level.[1] However, a detailed understanding of these effects is essential for the development of quantitative approaches to the analysis of non-covalent molecular interactions in solution. We recently introduced the 1:1 complex formed between tri-*n*-butylphosphine oxide (**1**) and perfluoro-*tert*-butanol (**2**; Scheme 1) as a simple probe of solvent effects on molecular interactions.[2] This complex contains a single hydrogen bond between an exceptionally strong H-bond acceptor and an exceptionally strong H-bond donor, so that complexation can be detected in even the most competitive solvent environments. This system not only provides new opportunities to investigate how solvents affect the properties of molecular interactions, but also provides a new probe for studying the nature of the solvent itself and the interactions that govern the properties of the liquid state. Herein we describe experiments on solvent mixtures of chloroform and tetrahydrofuran, a liquid mixture that shows strong deviations from ideality and does not obey regular solution theory.[3]



Scheme 1. Tri-*n*-butylphosphine oxide (**1**) is one of the strongest H-bond acceptors known ($\beta = 10.2$); perfluoro-*tert*-butanol (**2**) is a strong H-bond donor ($\alpha = 4.9$).

Solvent mixtures are used routinely in laboratory and industrial procedures and have been studied widely by using a variety of methods.[4,5] For many systems, rather complex behavior is observed as a function of liquid composition, and as a result it is difficult to make predictions based on the properties of pure solvents for all but the simplest well-behaved solvent mixtures. In practice, experiments are usually required to characterize a particular mixture for a particular purpose. One of the issues that complicates detailed analysis is the phenomenon of preferential solvation or solvent sorting:[6–13] The solvation environment of a solute is determined both by the solvent composition and by the properties of the solute. Molecular-recognition events should be particularly sensitive to this phenomenon and provide a well-defined thermodynamic probe of the solvation environment of individual functional groups.

Tri-*n*-butylphosphine oxide (**1**) and perfluoro-*tert*-butanol (**2**; Scheme 1) do not self-associate in chloroform or tetrahydrofuran, because tri-*n*-butylphosphine oxide contains only C–H H-bond donors, and the strongly electron-withdrawing CF_3 groups make both the oxygen and fluorine atoms of perfluoro-*tert*-butanol very poor H-bond acceptors. Thus, **1** and **2** form a 1:1 complex featuring a single well-defined H bond between the OH group of **2** and the oxygen atom of **1**. Complexation can be monitored readily on the basis of the large changes that are observed in the ^{31}P chemical shift of **1** on binding. The results of ^{31}P NMR titration experiments in various chloroform–tetrahydrofuran mixtures are recorded in Table 1 and illustrated in Figure 1.[14]

The stability of the **1**·**2** complex can be interpreted naively as a measurement of the effective polarity of the solvent mixture. The association constants in Table 1 span three orders of magnitude and show that the **1**·**2** complex is most stable in pure chloroform and least stable in a 2:1 mixture of chloroform and tetrahydrofuran. This intriguing result implies that the addition of a less polar solvent (chloroform) to a polar solvent (tetrahydrofuran) produces a mixture that is significantly more polar: The association constant of the complex decreased by an order of magnitude relative to that in pure tetrahydrofuran when a 1:1 mixture of chloroform and tetrahydrofuran was used. The results also indicate that very small amounts of a cosolvent can have a dramatic effect on the solvation properties of a liquid. For example, the addition of 0.3 vol% of tetrahydrofuran to chloroform decreases the stability of the **1**·**2** complex by an order of magnitude. The resulting solvent environment has the same effect as pure tetrahydrofuran on H-bonding interactions. The stability of the complex in 80 vol% tetrahydrofuran is the same as in pure acetone, which is more polar than either of the two solvents used in this study.[2] An apparent increase in the

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Table 1: Association constants, *K*, determined by ^{31}P NMR titrations for the formation of the 1:1 complex between **1** and **2** in mixtures of chloroform and tetrahydrofuran at 295 K.[a]

Volume fraction of tetrahydrofuran [%][b]	*K* [M^{-1}]	log*K*
100	250	2.40
97	150	2.19
90	58	1.77
80	42	1.62
70	31	1.50
50	22	1.34
30	15	1.17
20	15	1.19
10	20	1.30
3	47	1.67
0.3	240	2.38
0	2500	3.40

[a] Average of at least three experiments; errors in *K* are ±10%.[14] [b] Chloroform and tetrahydrofuran both have a concentration of 12 M, so the volume and mole fractions are almost identical. However, large volume changes are observed on mixing, so some care is required in solvent preparation.

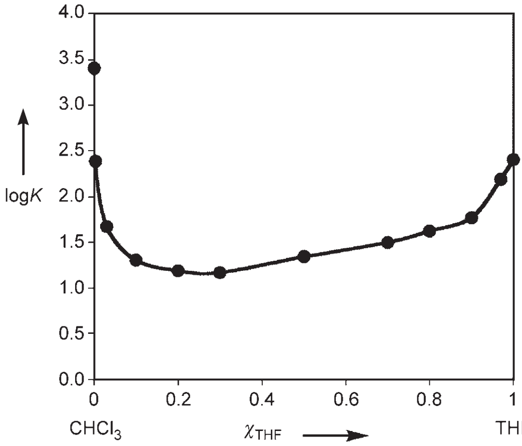


Figure 1. Stability of the **1**·**2** complex as a function of solvent composition.

polarity of solvent mixtures has also been observed with solvatochromic dyes.[15]

We showed previously that a simple solvent-competition model can be used in conjunction with H-bond donor and acceptor parameters to estimate the stability of simple H-bonded complexes in different solvents [Eq. (1); α and β, and α_S and β_S are the H-bond donor and acceptor parameters for the solute and the solvent, respectively].[15]

$$-RT\ln K = \Delta G^0 = -(\alpha-\alpha_S)(\beta-\beta_S) + 6\,\text{kJ}\,\text{mol}^{-1} \tag{1}$$

Equation (1) is based on the assumption that the relative stability of each of the four complexes involved in the equilibrium illustrated in Figure 2a can be estimated as the product of the H-bond donor and acceptor parameters. This approach provides the basis for a molecular interpretation of the properties of solvent mixtures. The equilibrium now involves more species, but the relative stabilities can again be estimated from the relevant H-bond donor and acceptor parameters. Figure 2b shows all possible interactions in a system consisting of a H-bond donor (DH), a H-bond acceptor (A), and two solvents (S1 and S2). Although the system is complicated, the subsystem equilibria highlighted in Figure 2b contain the key to decoding the behavior of the mixture. If the two solvents have similar H-bonding properties, these equilibria will be balanced, and the properties of the mixture will not differ significantly from those of the pure solvents. Any differences in the donor and/or acceptor properties of the solvents will be manifest in selectivity in the subsystem solvation equilibria in the free and bound states.

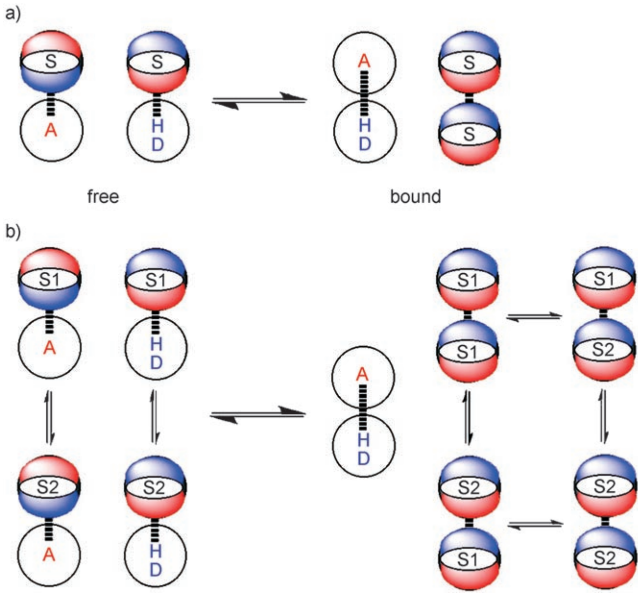
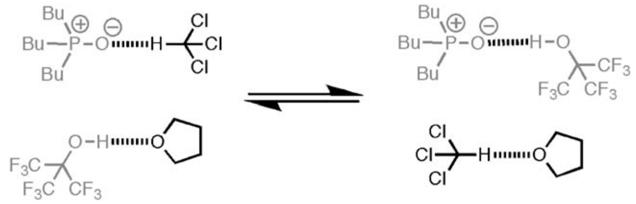


Figure 2. a) Solvent-competition model for H-bonding interactions in solution. The H-bond donor (DH) is solvated by the most negative site on the electrostatic potential surface of the solvent (red), and the H-bond acceptor (A) is solvated by the most positive site on the electrostatic potential surface of the solvent (blue). b) In a mixture of two solvents, S1 and S2, there are competing solvation equilibria.

In the simplest analysis, the equilibria in the solvent mixture will be dominated by the most stable complexes. Chloroform has good H-bond-donor but relatively weak H-bond-acceptor properties ($\alpha = 2.2$, $\beta = 0.8$). In contrast, tetrahydrofuran is a good H-bond acceptor but a very weak H-bond donor ($\alpha = 0.9, \beta = 5.3$).[2] Thus, in the free state, **1** will be solvated preferentially by chloroform, and **2** will be solvated preferentially by tetrahydrofuran (Scheme 2). If we assume that these solvated forms of **1** and **2** are the only important species, we can estimate the stability of the **1**·**2** complex in the mixed solvent by using Equation (2).

$$-RT\ln K = -(\alpha-\alpha_{\text{CHCl}_3})(\beta-\beta_{\text{THF}}) + 6\,\text{kJ}\,\text{mol}^{-1} \tag{2}$$

Equation (2) gives $\log K = 1.3$, a value that is remarkably close to the minimum experimental value observed in chloroform–tetrahydrofuran mixtures, accounting for the unusually high polarity of the mixed solvent. In pure chloroform, the H-bond donor **2** is poorly solvated, and in pure tetrahydro-



Scheme 2. Preferential solvation in chloroform–tetrahydrofuran mixtures.

furan, the H-bond acceptor **1** is poorly solvated; however, in the mixed solvent, **1** and **2** each interact strongly with the solvent which they select from the mixture. The shape of the curve in Figure 1 provides information about competition between the solvent–solvent and solvent–solute interactions and should be related to the Boltzmann distribution of all possible complexes shown in Figure 2b. However, the solvent–solvent term in the bound state, in particular, is nontrivial, and a more elaborate treatment is required to treat the system quantitatively.

The special feature of the solvent combination described herein is that one component has strong H-bond-donor and very poor H-bond-acceptor properties, whereas the other has strong H-bond-acceptor and poor H-bond-donor properties. The resulting significant increase in the solvation power of the mixture is predicted to be associated with highly selective solvation of the solutes. This feature is the reason for the deviation of the properties of the mixture from regular solution theory, which is based on a single polarity parameter, δ_H, rather than decomposition into the positive (H-bond-donor, α) and negative (H-bond-acceptor, β) polarity parameters used herein. Similar increases in the apparent polarity of solvent mixtures are therefore expected to be associated with any mixtures that show deviations from regular solution theory.

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[13] The NMR titration data fit best to a 2:1 binding isotherm.[2] The second binding constant is much lower than the first, so in some solvent systems, the second phase of the titration was almost linear and did not reach saturation. All data were therefore fitted to an isotherm, whereby the second association constant was fixed at $0.1\,\text{M}^{-1}$, which describes the second linear phase well. The reported values of K are the first association constant. For solvent systems in which binding is stronger, so that both K_1 and K_2 could be determined reliably, the K_1 value is not very sensitive to the K_2 value, and so the reported results are not perturbed significantly by fixing K_2.

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