A thermodynamic study of selective solvation in solvent mixtures†

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Changes in the ^{31}P NMR chemical shift of tri-*n*-butylphosphine oxide have been measured as function of solvent composition in a number of binary solvent mixtures. The data were analysed using a model that separates the contributions of specific H-bond interactions with the first solvation shell and the non-specific effects of the bulk solvent on the chemical shift. This allowed measurement of equilibrium constants between differently solvated states of the probe and hence thermodynamic quantification of preferential solvation in the binary mixtures. The results are analysed in the context of the electrostatic solvent competition model, which assumes that solvent effects on intermolecular interactions can be interpreted based on the exchange of specific functional group contacts, with minimal involvement of the bulk solvent. The thermodynamic measurements of preferential solvation were used to determine the H-bond donor parameter α for cyclohexane, *n*-octane, *n*-dodecane, benzene, 1,4-dioxane, carbon tetrachloride, acetone, dichloromethane, dimethyl sulfoxide and chloroform. For solvents where the H-bond donor parameters have been measured as solutes in carbon tetrachloride solution, the H-bond donor parameters measured here for the same compounds as solvents are practically identical, *i.e.* solute and solvent H-bond parameters are directly interchangable. For alkanes, the experimental H-bond donor parameter is significantly larger than expected based on calculated molecular electrostatic potential surfaces. This might suggest an increase in the relative importance of van der Waals interactions when electrostatic effects are weak.

Introduction

Solvent can have an enormous effect on reaction rates and chemical equilibria, but these effects are often difficult to rationalise and even more difficult to predict.[1–3] By studying solvent effects on spectroscopic and reactivity probes, many different empirical parameters have been developed to quantify the properties of solvents.[4–6] The influence of solvent on the properties of a system of interest can usually be explained using linear combinations of these parameters, linear solvation energy relationships.[7] This approach can also provide some insight into the molecular basis for the solvent effects. We recently introduced an alternative approach based on just two parameters, the molecular H-bond donor and H-bond acceptor parameters, α and β.[8] We assume that interactions in solution are dominated by electrostatic interactions and that the effect of solvents on molecular interactions can therefore be understood based on a simple competition between point contacts between solvents and solutes. Although the parameters α and β were originally derived from experimental measurements of H-bonded complexes, we use these parameters to treat all classes of non-covalent interaction within a single conceptual framework. Thus sites of positive electrostatic potential on the surface of a molecule are assigned an α value and sites of negative electrostatic potential are assigned a β value, regardless of whether they are able to form a conventional H-bond, electron pair donor–acceptor interaction or simple electrostatic contact. The electrostatic solvent competition model is embodied in eqn (1).

$$\Delta G = -(\alpha - \alpha_S)(\beta - \beta_S) + 6 \text{ kJ mol}^{-1} \quad (1)$$

where α and β are the H-bond donor and acceptor parameters of the solutes, α_S and β_S are the H-bond donor and acceptor parameters of the solvent and the constant of 6 kJ mol^{-1} was experimentally determined in carbon tetrachloride solution.

The values of α, β, α_S and β_S are based on Abraham's α_2^H and β_2^H scales, which were derived from experimental measurements on H-bonded complexes involving a wide range of functional groups in carbon tetrachloride and 1,1,1-trichloroethane.[9–12] In other words, the H-bond parameters for the solute, α and β, and for the solvent, α_S and β_S, are based on the properties of the individual isolated molecules, so that the same parameter can be used for a molecule regardless of whether it is a solvent or solute. The assumption is that the intermolecular interaction sites on the surface of a solvent molecule in a bulk liquid are the same as the those for an isolated molecule in a dilute solution or the gas phase. Abraham has shown that the Taft solvent β scale, which describes the H-bond acceptor properties of the bulk solvent, correlates well with corresponding solute β_2^H scale, providing some experimental support for this assumption.[13] Experimental studies of H-bonded complexes in a variety of different solvents have shown that, with exception of complexation in alcohol solvents, eqn (1) can be used to estimate the stability constants of non-covalent complexes with remarkable accuracy.[14]

The experimental solute H-bond parameters, α_2^H and β_2^H, were obtained from the stability constants of 1 : 1 complexes measured in carbon tetrachloride or 1,1,1-trichloroethane. These solvents

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have relatively positive molecular electrostatic potential surfaces and thus act as weak H-bond donors ($\alpha = 1.4$–1.5).[8] For solutes that contain functional groups that are weaker H-bond donors than these solvents, the formation of 1 : 1 complexes can not be detected, because the solute cannot compete with the solvent for H-bonding acceptor sites. Therefore experimental α values are not available for the non-polar hydrocarbon functional groups that are common to most organic solvents, and this limits the general utility of eqn (1). Values of α for these non-polar molecules can be estimated from calculation of the molecular electrostatic potential surfaces, but these calculated parameters are subject to significant error.[8,15–17] We have therefore been investigating new experimental approaches to quantifying non-covalent interactions with non-polar functional groups.[18]

The stability of a H-bonded complex formed with a weak H-bond donor will be very low, even with a very strong H-bond acceptor. Consequently, very concentrated solutions of the H-bond donor are required to displace the equilibrium towards formation of the complex. In this paper, we use weak H-bond donors as solvents, so that they can compete with more polar H-bond donors for interaction with H-bond acceptor solutes. In mixtures of solvents, solutes undergo preferential or selective solvation depending on the thermodynamic properties of the solute–solvent interactions.[2,19–23] For example, a strong H-bond acceptor, A, in a mixture of two solvents, S1 and S2, will preferentially interact with the strongest H-bond donor solvent (Fig. 1). The equilibrium between the two differently solvated states depends on the relative strengths of the H-bonds (or interactions) in the A S1 and A S2 complexes and on the relative concentrations of S1 and S2.[8,20] Thus if we use a solute, A, for which the H-bond acceptor parameter is known, and a solvent, S1, for which the H-bond donor parameter is known, it will be possible to determine the H-bond donor parameter for the less polar solvent, S2.

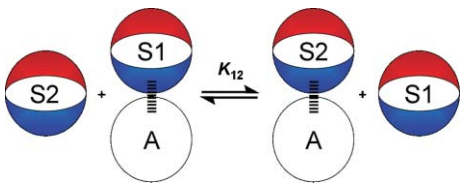

Fig. 1 Solvation equilibria in mixed solvents. A H-bond acceptor solute (A) is solvated by solvent S1 or S2.

Results

Tri-*n*-butylphosphine oxide (Bu_3PO) is one of the best H-bond acceptors, HBA ($\beta = 10.2$) and therefore offers the best opportunity to observe H-bonding interactions with non-polar solvents. This compound was therefore selected as a ^{31}P NMR probe to monitor changes in the solvation shell. ^{31}P NMR spectroscopy offers many advantages, as it is particularly sensitive to H-bonding interactions, and there is no requirement to use deuterated solvents.

Gutmann measured the ^{31}P NMR chemical shift of triethylphosphine oxide (Et_3PO) in a wide range of solvents,[24–26] and the value varies by more than 50 ppm depending on the solvent environment. Solvation of Et_3PO (or Bu_3PO) by a H-bond donor, HBD, leads to an increase in ^{31}P NMR chemical shift, due to polarisation of the phosphorous-oxygen bond. A higher chemical shift is taken to indicate a stronger solute–solvent H-bond, and so the ^{31}P NMR chemical shift of Et_3PO in different solvents was used as the basis for the acceptor number (AN) scale of solvent polarity.[24–26] The frequency of the P–O stretch in the IR spectrum of Et_3PO also correlates with the AN scale.[27–30] Although other phosphorous derivatives, *e.g.* trimethyl phosphate and hexamethyl phosphoramide, have been used to study solvation by ^{31}P NMR and IR spectroscopy, interpretation of phosphine oxide spectra is more straightforward in practice.[27,31] Et_3PO has been used to study binary mixtures of protic and non-protic solvents by IR and ^{31}P NMR spectroscopy.[25,28] The results can be interpreted in terms of complex mixtures of species with different solvation shells, but the thermodynamics of the solvation equilibria were not quantified.

Here we monitor changes in the ^{31}P NMR chemical shift of Bu_3PO as a function of the composition of a solvent mixture in order to quantify the free energy difference between the interaction of Bu_3PO with two different solvents. The viability of this approach can be evaluated using a set of HBD solvents for which the H-bond parameter α has been experimentally determined by using the compound as a solute that forms a 1 : 1 complex with a strong HBA in carbon tetrachloride solution: acetone ($\alpha = 1.5$), dichloromethane ($\alpha = 1.9$) and chloroform ($\alpha = 2.2$).[8] In addition, we make use of the α parameter for carbon tetrachloride ($\alpha = 1.4$), which is the reference point for these experiments.[8] Thus the ^{31}P NMR spectra of Bu_3PO in mixtures of the these four solvents were investigated.

Samples were prepared by mixing different volumes of two equimolar solutions of Bu_3PO dissolved in different solvents. Fig. 2 shows how the ^{31}P NMR chemical shift of Bu_3PO (δ_{obs}) varies in binary mixtures of chloroform and the other three solvents. Chloroform is the best HBD of the four solvents, and as expected, the chemical shift increases with increasing volume fraction of chloroform in all cases. However, the change in chemical shift does not vary in a linear fashion with the volume fraction of chloroform (V_{CHCl_3}). Small volume fractions of chloroform lead to very large changes in chemical shift, and this is indicative of preferential interactions between the phosphine oxide and the chloroform, because this is the best HBD present in the solution.

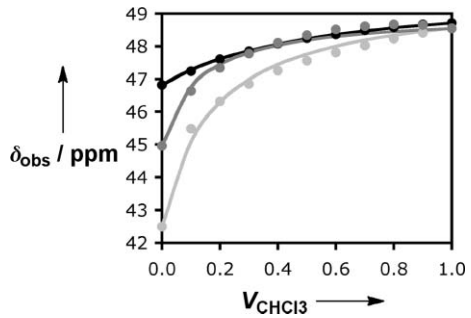

Fig. 2 ^{31}P NMR chemical shift of tri-*n*-butylphosphine oxide (δ_{obs}) as a function of volume fraction of chloroform (V_{CHCl_3}) in binary mixtures of chloroform with carbon tetrachloride (pale grey), acetone (dark grey) or dichloromethane (black). The solid lines represent the best fit to Eqn. 6.

For a quantitative analysis of these experimental data, we use the picture in Fig. 1 to make some simplifying assumptions: the number of solvent–solute H-bond interactions in the first

solvent shell of the Bu_3PO oxygen is independent of the solvent; if the solvent makes more than one H-bond with the Bu_3PO oxygen, the interactions at different sites are non-cooperative and identical; and K_{12} is independent of solvent composition. The latter assumption will be valid if the H-bond interactions between the solvent HBD sites and the Bu_3PO probe are significantly larger than the interactions between solvent HBA and HBD sites, *i.e.* $\beta \gg \beta_{S1}$ and $\beta \gg \beta_{S2}$, so that the equilibrium in Fig. 1 is not strongly perturbed by changes in solvent–solvent interactions with solvent composition. This is the reason for choosing a spectroscopic probe that has a very large β, but the implications for systems where these criteria are not satisfied are addressed below in the discussion section. The assumptions about the nature of the solvation shell allow the equilibrium to be treated as a straightforward competition between two different H-bond interactions. Thus the equilibrium constant for solvation of A, Bu_3PO in this case, by two different solvents, S1 and S2, is given by eqn (2).

$$K_{12} = \frac{N_{S1}[\mathrm{S1}][\mathrm{A}\cdot\mathrm{S2}]}{N_{S2}[\mathrm{S2}][\mathrm{A}\cdot\mathrm{S1}]} \quad (2)$$

where [S1] and [S2] are the concentrations of the solvents present in the mixture, and N_{S1} and N_{S2} are the number of HBD sites on each solvent molecule. We note that K_{12} is dimensionless and therefore independent of any definition of standard states.

If we assume that A is fully bound to the solvent and that it does not exist in a free gas phase-like state, the mole fractions of A bound to S1 and S2, $\chi_{A\,S1}$ and $\chi_{A\,S2}$, are defined by eqn (3–4).

$$\chi_{A\cdot S1} = \frac{[\mathrm{A}\cdot\mathrm{S1}]}{[\mathrm{A}\cdot\mathrm{S1}]+[\mathrm{A}\cdot\mathrm{S2}]} \quad (3)$$

$$\chi_{A\cdot S2} = \frac{[\mathrm{A}\cdot\mathrm{S2}]}{[\mathrm{A}\cdot\mathrm{S1}]+[\mathrm{A}\cdot\mathrm{S2}]} \quad (4)$$

The observed chemical shift in a mixture of solvents S1 and S2, δ_{obs}, depends on the chemical shifts of the two different solvated states and their populations (eqn (5)).

$$\delta_{obs} = \chi_{A\cdot S1}\delta_1 + \chi_{A\cdot S2}\delta_2 \quad (5)$$

where δ_1 and δ_2 are the chemical shifts of A observed in the pure solvents, S1 and S2 respectively.

Combining eqn (2–5) gives an expression for the observed chemical shift as a function of the solvent composition and the equilibrium constant, K_{12} (eqn (6)).

$$\delta_{obs} = \delta_1 + (\delta_2 - \delta_1)\frac{K_{12}N_{S2}[S2]}{N_{S1}[S1] + K_{12}N_{S2}[S2]} \quad (6)$$

The value of K_{12} can be determined by minimising the differences between the experimental data and the values calculated using eqn (6) with the Excel Solver routine. The results for mixtures of chloroform, carbon tetrachloride, acetone and dichloromethane are illustrated in Fig. 2. Although the theoretical curves calculated using eqn (6) provide a qualitative description of the experiments, they do not fit the experimental data points well (Fig. 2). This suggests that either the simplifying assumptions made above are wrong or that there are additional factors that affect the experiment. Experimental data that we have collected for other solvents mixtures indicate that the latter is true. Fig. 3 shows how the ^{31}P NMR chemical shift of Bu_3PO (δ_{obs}) varies in binary mixtures of benzene and carbon tetrachloride. Eqn (6) requires that the chemical shift of the probe in a binary mixture lies between the chemical shifts in the two pure solvents. Although the changes in chemical shift are small, this is clearly not the case for benzene-carbon tetrachloride mixtures.

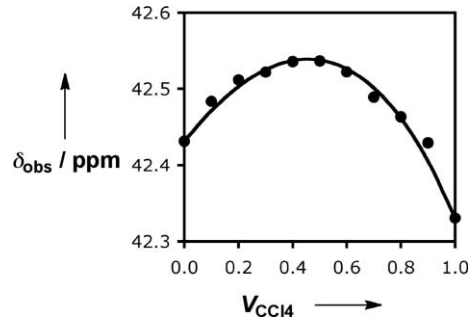

Fig. 3 ^{31}P NMR chemical shift of tri-*n*-butylphosphine oxide (δ_{obs}) as a function of volume fraction of carbon tetrachloride (V_{CCl_4}) in binary mixtures of carbon tetrachloride and benzene. The solid line represents the best fit to Eqn. 10.

Variables that are not considered in eqn (6) include differences in the water content of the solvents, differences in bulk susceptibility, and differences in long range through space effects, like ring currents of aromatic solvents.[32–36] We used spectroscopic grade solvents without any additional purification. The water contents were determined by the Karl-Fisher titration method and are recorded in Table 1 (dry solvent entries). There is a substantial variation with solvent, and in order to quantify the effect on the ^{31}P chemical shift of Bu_3PO, we carried out experiments on binary mixtures of dry and wet solvents. Wet solvents were obtained by saturating samples of the dry solvent with water overnight, and the water content was again determined by the Karl-Fisher titration method (wet entries in Table 1). The literature values for the maximum solubility of water in these solvents indicate that a reasonable degree of saturation was achieved (Table 1).

Fig. 4 shows how the ^{31}P chemical shift of Bu_3PO varies as a function of water content in benzene and in chloroform solution. There is an increase in chemical shift with increasing concentration of water in the solvent, due to H-bonding interactions between the water and the phosphine oxide. However, the changes in

Table 1 Water content (mM) of solvents used in this study

Solvent	Maximum[a]	Dry	Wet
Cyclohexane	2.4	0.9 ± 0.2	2.1 ± 0.2
Carbon tetrachloride	11.9	0.8 ± 0.1	4.5 ± 0.2
Benzene	30.7	10.4 ± 0.4	28 ± 9
Chloroform	76.0	4.1 ± 0.4	46 ± 5
Acetone	miscible	—	—
Dimethyl sulfoxide	miscible	140 ± 15	—
1,4-Dioxane	miscible	35 ± 3	—
n-Dodecane	2.7	0.8 ± 0.4	—
n-Octane	3.7	1.4 ± 0.3	—
Dichloromethane	144.7	1.9 ± 0.3	89 ± 21

[a] Values from reference 7.

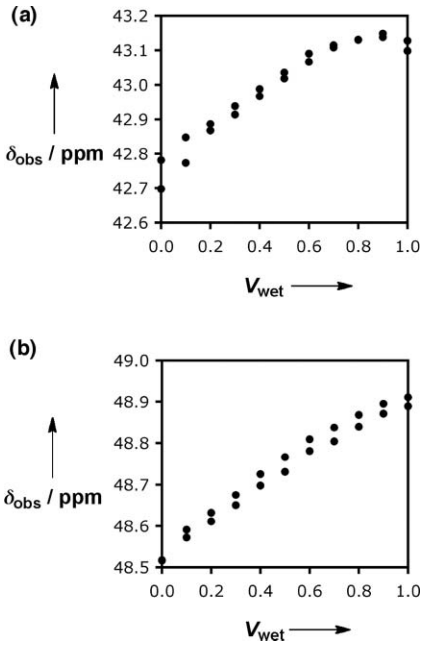

Fig. 4 ^{31}P NMR chemical shift of tri-*n*-butylphosphine oxide (δ_{obs}) as a function of volume fraction of wet solvent (V_{wet}) in binary mixtures of dry and water-saturated (a) benzene and (b) chloroform. Data from two different experiments are shown for each solvent.

chemical shift are relatively small (< 0.5 ppm), and the variation is approximately linear with the volume fraction of wet solvent (V_{wet}). For V_{wet} greater than 90%, there is some deviation from linearity (Fig. 4a), and we suspect that this is caused by microdroplets of water that are not fully dissolved in the water-saturated wet solvent. In general, the absolute concentration of water is difficult to control, because Bu_3PO is hygroscopic. However, the results in Fig. 4 suggest that the effects of differences in water content on the ^{31}P chemical shift of Bu_3PO will be a linear function of the volume fraction of binary mixtures.

Any non-specific contributions to solvent effects on the chemical shift, such as differences in bulk susceptibility or long range through space effects, are also likely to be linear functions of the volume fraction of binary mixtures.[2,19,35,36] We therefore introduce an additional variable in order to separate the effects of specific solvation of the probe through H-bonding interactions with the solvent and non-specific effects due to changes in the properties of the bulk solvent, which will also account for the effects of residual water.

We define the chemical shift of A in pure S1 as the sum of a specific contribution due to interactions in the first solvation shell of the probe, $\delta_{A\,S1}$, and a non-specific contribution due to the presence of the bulk solvent, δ_{S1}, (eqn (7)).

$$\delta_1 = \delta_{A\cdot S1} + \delta_{S1} \quad (7)$$

Similarly for S2,

$$\delta_2 = \delta_{A\cdot S2} + \delta_{S2} \quad (8)$$

In a binary solvent mixture, the specific contributions to the observed chemical shift will vary as a function of the mole fractions of A bound to S1 and S2, $\chi_{A\,S1}$ and $\chi_{A\,S2}$ (eqn (3–4)), and the non-specific contributions will vary as a function of the volume fractions of S1 and S2, V_{S1} and V_{S2} (eqn (9)).

$$\delta_{obs} = \chi_{A\cdot S1}\delta_{A\cdot S1} + \chi_{A\cdot S2}\delta_{A\cdot S2} + V_{S1}\delta_{S1} + V_{S2}\delta_{S2} \quad (9)$$

Using that fact that the volume fractions total unity, we can combine, eqn (2–4) with eqn (9) to obtain an expression for the observed chemical shift as a function of the solvent composition, the equilibrium constant, K_{12}, and an additional parameter $\Delta\delta$ that corrects for differences in the non-specific contribution to the observed chemical shift in the pure solvents (eqn (10)).

$$\delta_{obs} = \delta_1 + \left(\delta_2 - \delta_1 - \Delta\delta\right)\frac{K_{12}N_{S2}[S2]}{N_{S1}[S1] + K_{12}N_{S2}[S2]} + V_{S2}\Delta\delta \quad (10)$$

where

$$\Delta\delta = \delta_{S2} - \delta_{S1} \quad (11)$$

The chemical shift data for the binary mixtures of chloroform, carbon tetrachloride, acetone and dichloromethane shown in Fig. 2 were reanalysed using eqn (10). The difference between the experimental data and the values calculated using eqn (10) were minimised with the Excel Solver routine to obtain best fit values for K_{12} and $\Delta\delta$. The results in Fig. 5 show that eqn (10) provides a statistically significant improvement in the fit to the experimental data. The best fit line for the benzene–carbon tetrachloride data, which is shown in Fig. 3, demonstrates that eqn (10) also provides an excellent description of this more unusual case.

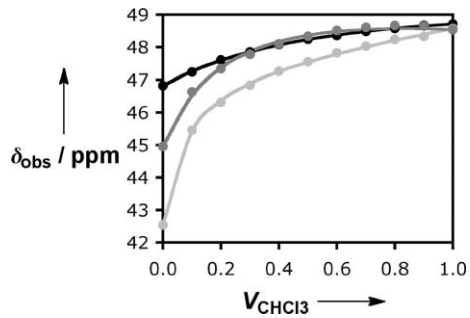

Fig. 5 ^{31}P NMR chemical shift of tri-*n*-butylphosphine oxide (δ_{obs}) as a function of volume fraction of chloroform (V_{CHCl_3}) in binary mixtures of chloroform with carbon tetrachloride (pale grey), acetone (dark grey) or dichloromethane (black). The solid lines represent the best fit to Eqn. 10.

The values of K_{12} obtained from the fits in Fig. 5 now allow us to test the validity of the basic approach. If we assume that the equilibrium shown in Fig. 1 is governed solely by specific H-bond interactions between the phosphine oxide oxygen of probe and the solvent HBD sites, we can relate the experimentally determined equilibrium constant to the H-bond parameters of the solvents (eqn (12)).

$$-RTLnK_{12} = \Delta G_{12} = \alpha_{S1}\beta_A - \alpha_{S2}\beta_A = \beta_A\Delta\alpha_S \quad (12)$$

where β is the H-bond acceptor parameter of A (Bu_3PO), and $\Delta\alpha_S$ is the difference between H-bond donor parameters of the two solvents, α_{S1} and α_{S2}.

Fig. 6 shows the relationship between the values of ΔG_{12} obtained from the fits in Fig. 5 and the values of $\Delta\alpha_S$ for the solvent mixtures. Although there are only three data points, the

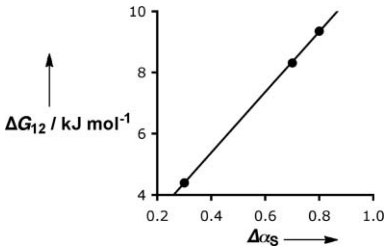

Fig. 6 The thermodynamic properties of the preferential solvation equilibria in binary solvent mixtures of chloroform with carbon tetrachloride, acetone or dichloromethane (ΔG_{12}) correlate with the difference between the H-bond parameters of the two solvents (Equ. 12). The best fit straight line is shown.

correlation is excellent, which suggests that the thermodynamics of selective solvation provides a useful new tool for the determination of H-bond parameters for non-polar functional groups that are not accessible *via* conventional experiments. We therefore applied this method to a range of organic solvents for which solute α H-bond parameters are not available: *n*-octane, *n*-dodecane, cyclohexane, benzene, 1,4-dioxane, and dimethyl sulfoxide. In all cases, excellent fits to eqn (10) were obtained, and the results are summarised in Table 2. The equilibrium constants vary from close to one, for benzene–carbon tetrachloride mixtures, where there is almost no selectivity in solvation of the probe, to over 200, for chloroform–alkane mixtures where there is a very strong preference for solvation by chloroform.

Discussion

As explained above, we started by making the simplifying assumption that solvation of the HBD sites on the free solvent molecules by the bulk does not affect the equilibirum in Fig. 1. This allowed experimental determination of K_{12} in a straightforward manner, but in general, we should consider a more complicated scenario where the solvent HBD sites can be solvated by S1 or by S2 (Fig. 7). These additional solvent–solvent complexes could have a significant impact on the observed equilibrium constant. Thus eqn (12) should be rewritten to account for differences in the solvent–solvent interactions on the two sides of the equilibrium in Fig. 7.

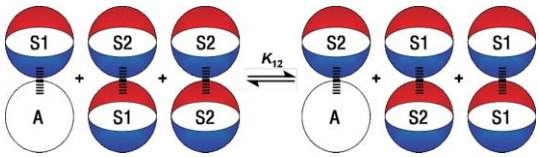

Fig. 7 The solvent competition model in mixed solvents, taking solvation of the solvent into account.

This requires the Boltzmann-weighted sum of all possible pairwise interactions (eqn (13)).

$$\Delta G_{12} = -(\alpha_{S2}\beta + \chi_{11}\alpha_{S1}\beta_{S1} + \chi_{12}\alpha_{S1}\beta_{S2}) + (\alpha_{S1}\beta + \chi_{22}\alpha_{S1}\beta_{S2} + \chi_{21}\alpha_{S2}\beta_{S1}) = \Delta\alpha_S\beta - \alpha_{S1}(\chi_{11}\beta_{S1} + \chi_{12}\beta_{S2}) + \alpha_{S2}(\chi_{22}\beta_{S2} + \chi_{21}\beta_{S1}) \quad (13)$$

where β_{S1} and β_{S2} are the H-bond acceptor parameters of the two solvents, and χ_{11}, χ_{12}, χ_{21} and χ_{22} are the populations of the four solvent–solvent complexes illustrated in Fig. 7.

Preferential solvation in the solvation shell of both the solute and solvents makes this a complicated problem, as there is no simple experimental approach that would allow us to determine the populations of all of the species involved.[28] However, if we rewrite eqn (13) as eqn (14), where β_S is an approximation that describes the average H-bond acceptor properties of the binary mixture of S1 and S2, it is clear that β_S must take a value that lies between β_{S1} and β_{S2} for all solvent compositions.

$$\Delta G_{12} \approx \Delta\alpha_S(\beta - \beta_S) \quad (14)$$

Thus by solving eqn (14) using $\beta_S = \beta_{S1}$ and then using $\beta_S = \beta_{S2}$, we can place upper and lower limits on the value of $\Delta\alpha_S$ for each binary solvent mixture. The results of this analysis are collected in Table 3. In most cases, the limiting $\Delta\alpha_S$ values are not strongly dependent on which β_S parameter is used. However, there are some exceptions: for mixtures of chloroform–1,4-dioxane and chloroform–acetone, the two limiting values of $\Delta\alpha_S$ differ by about one unit. The reason is that 1,4-dioxane and acetone both have much stronger HBA groups than chloroform, and chloroform has a much stronger HBD than 1,4-dioxane and acetone, so the solvent–solvent equilibria are strongly biased by preferential solvation in these systems. In general, the determination of $\Delta\alpha_S$ is likely to be less accurate when the values of β_{S1} and β_{S2} for the

Table 2 Solvent competition equilibrium constant, K_{12}, obtained from fitting experimental ^{31}P NMR chemical shift data for Bu_3PO in binary solvent mixtures at 295 K to eqn (10)[a]

S1	S2	N_{S1}	N_{S2}	$\Delta\delta$ (ppm)	K_{12}
Chloroform	Benzene	1	6	1.41 ± 0.03	0.018 ± 0.001
Chloroform	1,4-Dioxane	1	8	1.07 ± 0.06	0.020 ± 0.001
Chloroform	Carbon tetrachloride	1	4	1.39 ± 0.07	0.023 ± 0.001
Chloroform	Acetone	1	6	1.55 ± 0.39	0.035 ± 0.007
Chloroform	Dichloromethane	1	2	0.35 ± 0.55	0.17 ± 0.03
Chloroform	Dimethyl sulfoxide	1	6	3.15 ± 0.03	0.87 ± 0.10
Benzene	Carbon tetrachloride	6	4	1.80 ± 0.39	1.1 ± 0.2
Cyclohexane	Benzene	12	6	0.64 ±0.04	4.6 ± 0.8
Cyclohexane	Carbon tetrachloride	12	4	0.92 ± 0.66	9.6 ± 1.5
Benzene	Dichloromethane	6	2	0.95 ± 0.43	8.5 ± 1.1
n-Octane	Chloroform	18	1	0.93 ± 0.02	240 ± 13
Cyclohexane	Chloroform	12	1	1.22 ± 0.06	250 ± 1
n-Dodecane	Chloroform	26	1	0.96 ± 0.05	260 ± 1

[a] All experiments were repeated at least twice and average values are reported with errors at the 95% confidence limit. The other parameter that is obtained from the fitting procedure, $\Delta\delta$, is defined in Equ. 11.

Table 3 Difference in H-bond donor parameters for binary solvent mixtures determined using eqn (14)

				$\Delta\alpha_S$	
S1	S2	β_{S1}	β_{S2}	$\beta_S = \beta_{S1}$	$\beta_S = \beta_{S2}$
Chloroform	Benzene	0.8	2.2	1.0	1.2
Chloroform	1,4-Dioxane	0.8	5.3	1.0	2.0
Chloroform	Carbon tetrachloride	0.8	0.6	1.0	1.0
Chloroform	Acetone	0.8	5.3	0.9	1.8
Chloroform	Dichloromethane	0.8	1.1	0.5	0.5
Chloroform	Dimethyl sulfoxide	0.8	8.9	0.0	0.3
Benzene	Carbon tetrachloride	2.2	0.6	0.0	0.0
Cyclohexane	Benzene	0.3[a]	2.2	−0.4	−0.5
Cyclohexane	Carbon tetrachloride	0.3[a]	0.6	−0.6	−0.6
Benzene	Dichloromethane	2.2	1.1	0.7	0.6
n-Octane	Chloroform	0.3[a]	0.8	1.4	1.4
Cyclohexane	Chloroform	0.3[a]	0.8	1.4	1.4
n-Dodecane	Chloroform	0.3[a]	0.8	1.4	1.4

[a] No experimental parameters are available for alkanes, and this value is estimated based on calculations of the AM1 electrostatic potential surface. However, errors in this parameter have little effect on the values of $\Delta\alpha_S$.

solvents in the binary mixture differ significantly. The exception in Table 3 is the chloroform–dimethyl sulfoxide mixture, where there is a very large difference between the β parameters, yet the two limiting values of $\Delta\alpha_S$ are very similar. The reason is that when $\Delta\alpha_S$ is close to zero, there is no preferential solvation of the probe, and the value of ΔG_{12} is close to zero, independent of the β parameters of the probe and the solvents (eqn (14)).

The values of $\Delta\alpha_S$ in Table 3 were used to determine a self-consistent set of absolute values for the H-bond donor parameter for each solvent, using the carbon tetrachloride parameter ($\alpha = 1.4$) as a fixed reference point.[8] The results are presented in Table 4. Experimental values of α based on studies of the same compounds as solutes that form 1 : 1 complexes in carbon tetrachloride,[15] as well as values estimated from gas phase AM1 calculations of the molecular electrostatic potential surfaces are included in Table 4 for comparison (eqn (15)).

$$\alpha = \frac{E_{max}}{52\ \text{kJ mol}^{-1}} \quad (15)$$

The H-bond donor parameters obtained from the solvent competition experiments in Table 4 agree very well with the experimental values previously reported for the solvents that have been characterised as solutes in carbon tetrachloride, verifying the validity of the approach. The new experimental parameters that we have determined for benzene, 1,4-dioxane and dimethyl sulfoxide are consistent with the values calculated from the molecular electrostatic potential surfaces, but for alkanes there is a significant discrepancy between calculation and experiment. Alkanes are much better solvents than the calculated electrostatic parameters suggest. The new experimental parameters are consistent with experimental measurements of the stability of 1 : 1 H-bonded complexes in alkane solvents, which suggest that $\alpha \approx 1.2$ for alkanes.[18] The discrepancy between the calculations and the experiments could be associated with the densely-packed array of HBD sites that hydrocarbons present on their surface, which might be capable of establishing multiple cooperative contacts with a HBA site. Alternatively, the relative importance of van der Waals interactions might become more significant, as the electrostatic nature of the interaction is reduced in these solvents.

Table 4 H-Bond donor parameters for the solvents used in this study

Solvent	Experiment as solvent	Experiment as solute[a]	Calculated from MEP
Cyclohexane	0.9 ± 0.1	—	0.4
n-Octane	1.0 ± 0.1	—	0.5
n-Dodecane	1.0 ± 0.1	—	0.5
Benzene	1.3 ± 0.1	—	1.0
1,4-Dioxane	0.9 ± 0.5	—	1.2
Carbon tetrachloride	1.4 (fixed)	1.4	1.6
Acetone	1.1 ± 0.5	1.5	1.4
Dichloromethane	1.9 ± 0.1	1.9	1.9
Dimethyl sulfoxide	2.2 ± 0.1	—	2.5
Chloroform	2.4 ± 0.1	2.2	2.3

[a] Based on literature α_2^H values reported.[15]

The relationship between the H-bond donor parameter of the solvent α and the corresponding ^{31}P NMR chemical shift of the probe (Bu_3PO) in the pure solvent is illustrated in Fig. 8. This plot highlights the discrepancy between the calculated and experimental α values for alkanes and the large error associated with the measurement of α for acetone and 1,4-dioxane. Despite the uncertainty in some of the α parameters, it is clear that the observed ^{31}P NMR chemical shift is related to the H-bond donor properties of the solvent. The ^{31}P NMR chemical shift of Bu_3PO is very similar to that of Et_3PO in these solvents, and so the correlation shown in Fig. 8 is equivalent to a correlation between the Gutmann AN solvent parameter and the H-bond parameter α. In other words, the thermodynamic H-bond parameters measured in this work could be related to the spectroscopic solvent polarity scales.

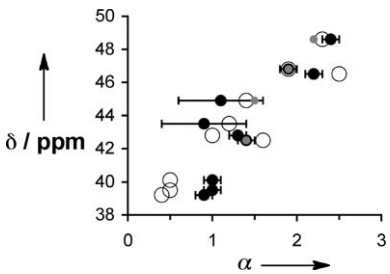

Fig. 8 Relationship between the ^{31}P NMR chemical shift of tri-*n*-butylphosphine oxide (δ) and the H-bond parameter for the solvent, α measured in this work (black circles), α measured as a solute in carbon tetrachloride (grey circles) and α calculated from the MEP (open circles).

3. Conclusions

These experiments show that it is possible to interpret preferential solvation phenomena in terms of polar interactions between specific H-bonding sites on the solute and H-bonding sites in the first solvation shell. Spectroscopic monitoring of changes in the populations of differently solvated states of a specific probe solute as a function of solvent composition can in turn be used to probe the H-bonding properties of the solvent. In this paper, we show how tri-*n*-butylphosphine oxide can be exploited as a ^{31}P NMR probe of selective solvation in solvent mixtures.

The thermodynamics of the preferential solvation equilibria have been used to determine H-bond donor parameters for non-polar functional groups that are difficult to study by conventional methods but are common in organic solvents. The method can in principle be applied to any probe solute in any binary solvent mixture, but the error can be minimised by using a very polar probe and by using matched pairs of solvents that have similar β parameters to determine α, or matched pairs of solvents that have similar α parameters to determine β. This minimises the impact of preferential solvation of the solvents on solvation of the probe.

For compounds where the solute H-bond properties have been measured in carbon tetrachloride solution, we find that the solvent H-bond parameters measured here are practically identical. This demonstrates that H-bonding interactions involving solvents and solutes can be treated within the same conceptual framework, confirming the validity of eqn (1) for the treatment of solvent effects on intermolecular interactions. Complexation equilibria simply involve exchange of functional group interactions between the molecules with minimal effect of the surrounding bulk solvent.

The new experimental H-bond donor parameters measured here generally compare well with the values estimated from calculated MEP surfaces. However, alkanes appear to be better solvents than expected based on the calculated electrostatic properties, because the experimental α parameter is significantly larger than predicted by calculation. The electrostatic solvent competition model ignores contributions due to changes in van der Waals interactions, and the discrepancy between the calculated and experimental results for alkanes might reflect an increase in the relative significance of van der Waals interactions for complexation equilibria involving very non-polar functional groups. We recently made a similar observation based on the properties of 1 : 1 H-bonded complexes in alkane solvents.

Phosphine oxides have been used as probes of solvation phenomena for decades. These approaches are simply based on measurement of the ^{31}P NMR chemical shift as a function of solvent and were used to establish empirical scales of relative solvent polarity.[1,24–26,37–39] The experiment that we have developed uses the same spectroscopic probe to measure the thermodynamics of selective solvation in solvent mixtures and so provides quantitative information on the free energy differences between differently solvated states. These free energy differences are absolute rather than relative measurements. The relationship that we have demonstrated between free energy and the α/β H-bond parameters implies that it will be possible to make accurate quantitative predictions of the speciation associated with preferential solvation for any solute in any solvent mixture for which α and β parameters are available.

4. Experimental

NMR experiments

Equimolar stock solutions of tri-*n*-butylphosphine oxide were prepared at a concentration of 10 mM in two different solvents. NMR tubes with different solvent compositions were prepared manually by mixing different volumes of the stock solutions, so that the concentration of tri-*n*-butylphosphine oxide is constant. An external capillary containing a 50 mM solution of methylene diphosphonic acid in D_2O was used to provide a ^{31}P NMR chemical shift reference (δ = 17.98 ppm) and a deuterium lock signal. ^{31}P NMR spectra were recorded on a Bruker AMX-400 MHz spectrometer using a graphical interface for automated acquisition and processing (*ICON-NMR*). The observed changes in ^{31}P NMR chemical shift of tri-*n*-butylphosphine oxide as a function of solvent composition were analysed using Excel as described in the main text.

Semi-empirical calculations

The Spartan software package was used to build molecular structures, which were then optimised using AM1, and the maxima and minima in the electrostatic potential calculated on the 0.002 Bohr/Å^3 isodensity surface were used to estimate H-bond parameters using eqn (15).[40]

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