A Thermodynamic and Solvatochromic Investigation of the Effect of Water on the Phase-transfer Properties of Octan-1-ol

Andrew J. Dallas† **and Peter W. Carr***
Department of Chemistry, Smith and Kolthoff Halls, 207 Pleasant Street S. E., Minneapolis, MN 55455, USA

The octan-1-ol–water partition coefficient has played a central role in quantitative structure–activity relationships and has been applied to drug design, to model biological membranes, and to predict toxicity and transport of pollutants. The room temperature solubility of water in octan-1-ol is determined to be 2.5 mol dm^{-3}, which is equivalent to a mole fraction of 0.29. Despite this very high solubility very little is known about the effect of water on the chemical properties of the octan-1-ol phase. We have used head-space gas chromatography to measure the free energy of transfer of 14 chemically very different solutes, from neat octan-1-ol to octan-1-ol saturated with water. In addition, the infinite dilution activity coefficients of a series of 11 alcohols were measured in both phases. In general, the presence of water in octan-1-ol increases the concentration of polar and hydrogen-bonding solutes and decreases the concentration of non-polar solutes in this phase. For all solutes, the effect of water on the change in the standard free energy of transfer was less than 200 cal mol^{-1}.‡ These small changes were validated by investigating the effect of added water on the solvatochromic properties of the indicators *N,N*-diethyl-*p*-nitroaniline, *p*-nitroanisole, *p*-nitroaniline, *p*-nitrophenol, ET-30, bis[α-(2-pyridyl)benzylidene-3,4-dimethylaniline]bis(cyano)iron(II), Phenol Blue, and Nile Red in octan-1-ol. Regardless of the indicator used the addition of water had almost no effect on the wavelength of maximum adsorption. These results show that the water is almost completely associated with octan-1-ol and scarcely effects the properties of the media.

The octan-1-ol–water partition coefficient, K_{ow}, is an important property for modelling biological membranes and predicting the fate, transport, and toxicity of pollutants.[1] It has also played a central role in quantitative structure–activity relations and drug design.[2] The success of octan-1-ol as a model solvent for such systems has been attributed to its lipophilic–hydrophilic balance which results from the octyl chains, the hydrogen-bonding ability of the hydroxy group, and to the relatively high water content at saturation.[2] However, there have only been a few reports which studied the effect that water has on octan-1-ol.[3–5] In this work we studied the effect of the dissolved water on the chemical environment experienced by solutes in water-saturated octan-1-ol.

The distribution of a solute between two phases is dependent on the chemical properties of both phases and the solute. In the liquid–liquid systems typically used to determine hydrophobicity parameters it is generally assumed that mutual solubility of the two phases does not significantly perturb their bulk chemical properties or the environment experienced by a solute. In the case of octan-1-ol–water partition coefficients, where the solubility of water in the octan-1-ol phase is reported to be 2.3 mol dm^{-3},[2,4] this may not be an accurate assumption. However, for *n*-alkane–water systems such as hexadecane–water, the mutual solubility is negligible and both phases are essentially pure.[6–8] This has led to proposals that *n*-alkane–water partition coefficients may be easier to rationalize because hydrogen-bonding interactions between the solute and solvent in the alkane phase do not occur. Therefore, the partition coefficient is determined only by the desolvation of water from the solute and the free energy required to break any hydrogen-bonding and dipolar interactions between the solute and water.[7] In K_{ow} measurements the solute is transferred between mutually saturated phases and because of the strong solute–solvent interactions it has been reported that this transfer process may include the transfer of solvent along with the solute.[9] However, Watari *et al.*, examined the partitioning of chlorobenzene and bromobenzene derivatives between heptane and water and between octan-1-ol and water and observed no significant differences in the interaction energies of heptane and octan-1-ol.[10] They concluded that the partition coefficients were governed principally by the differences in cavity formation energy.

In many studies of K_{ow} it was assumed that the chemical properties of octan-1-ol, when saturated with water, are not significantly different from those of neat octan-1-ol. For example, Wasik *et al.*, reported excellent agreement between K_{ow} calculated from the ratio of activity coefficients for the solute in both phases (without presaturation) with those measured by a generator column method (where both phases were mutually saturated).[11] In that work they assumed the activity coefficient of the solute in octan-1-ol and octan-1-ol saturated with water were equal and the activity coefficient in water and water saturated with octan-1-ol were equal, but this assumption was never experimentally verified.

Using the generator column technique, Schantz *et al.*, reported excellent agreement between literature K_{ow} values and those calculated from the neat phase volume-fraction based activity coefficients.[7] This was also observed for hexadecane–water partition coefficients. Based on these data they indicated that the assumption concerning the equivalence between the activity coefficients in octan-1-ol or hexadecane-saturated water and pure water and those in water-saturated octan-1-ol or hexadecane and pure octan-1-ol or hexadecane is good. This implies that K_{ow} is equivalent to the octan-1-ol–water solubility ratio and the dissolved water in octan-1-ol has no effect on its bulk properties.

Chiou *et al.*, attempted to study the effect of mutual saturation of both phases on K_{ow} by measuring the solubility of DDT and hexachlorobenzene in octan-1-ol, octan-1-ol saturated with

---

† *Present address:* Donaldson Co. Inc., 9250 W. Bloomington Fwy, Bloomington, MN 55431, USA.

‡ 1 cal = 4.184 J.

water, water, and water saturated with octan-1-ol.[4] They concluded that the solubility of these solutes in each set of phases differed, and attributed this to the incompatibility of these solutes with the dissolved water in octan-1-ol and the dissolved octan-1-ol in water. Unfortunately, their data were presented in a manner that does not allow any further comparison of their data with respect to water solubility in octan-1-ol. Moreover, their experimental method used vigorous mixing, which probably resulted in mutual entrainment.

The water present in the octan-1-ol phase is probably strongly hydrogen-bonded to octan-1-ol. This is consistent with the fact that water is a good hydrogen-bond acid [Kamlet–Taft acidity (α) = 1.17] and octan-1-ol is a good hydrogen-bond base [Kamlet–Taft basicity (β) = 0.18]. Alcohol and water systems are known to be complex environments owing to the significant association of these compounds with themselves and each other.[12–16] Association produces small clusters for which the ratio of water molecules to alcohol molecules depends on the specific alcohol.[17] For octan-1-ol, these clusters have been reported to be water-centred tetramers.[18–21] This is consistent with the reported mole fraction of water in water-saturated octan-1-ol ($x_{H_2O} = 0.275$),[2] but is not in complete agreement with the results of ref. 17.

Taft has discussed the effect of water saturation on the chemical properties of isobutanol.[22] The large amount of water that partitions into isobutanol, 7.97 mol dm^{-3} ($x_{H_2O} = 0.46$),[23] should have a significant effect on the chemical properties of isobutanol. This is consistent with data reported for a water-saturated *sec*-butyl alcohol phase. In this system there are more water molecules than alcohol molecules.[2] Also, it has been reported that the ratio of water to butan-1-ol molecules in a water-saturated butan-1-ol phase is 1 : 1.[17] These butanol–water systems appear to be significantly different from the octan-1-ol–water system considered here. Most noticeably, the volume fraction of water present in both water-saturated phases is extremely different and probably results in significantly different contributions from the dissolved water to the phase transfer of a solute. For example, the transfer of an alcohol from the water phase to a hydrocarbon phase presumably involves complete 'dehydration' of the alcohol's hydroxy group; however, in the isobutanol–water system the alcohol is probably completely solvated by water molecules. In water-saturated octan-1-ol it seems that a solute alcohol would only be partially hydrated since most of the water is hydrogen bonded to the hydroxy group of octan-1-ol given that the ratio of octan-1-ol to water is reported to be 2.7 : 1.[17]

We expect that the effect of water on the chemical properties of octan-1-ol will be significantly different than on butanol-1-ol. It has been hypothesized that the longer hydrophobic chain of octan-1-ol should produce an environment in water-saturated octan-1-ol that is similar to a reversed micellar phase or a membrane where the hydrophobic exterior surrounds a hydrophilic interior which consists of water strongly hydrogen-bonded to the hydroxy groups of several octan-1-ol molecules. The strong association of water with the hydroxy groups is expected to produce clusters of water which are 'tied-up' so as to prevent water from having a significant effect on the bulk phase properties. However, it has not been conclusively demonstrated whether the large amount of water that partitions into octan-1-ol has any effect on a solute's interaction with octan-1-ol. In addition, if such an effect takes place will it be similar for both non-polar and polar solutes?

Many studies have shown that saturation of octan-1-ol with water had no significant effect. Tomlinson *et al.*,[18] studied the thermodynamics of liquid–liquid distribution between mutually saturated phases of water and octan-1-ol. They observed no influence of water on the measured enthalpy–entropy compensation line for solute transfer between these phases. For non-polar solutes, Berti *et al.*,[24] observed a linear relationship between the free energy of transfer between neat phases of water and octan-1-ol and the free energy of transfer between mutually saturated phases. Such non-polar solutes had a general preference for neat octan-1-ol, but this was barely significant. They studied a series of non-polar solutes and one polar solute, pentan-3-one, which had a slight preference for water-saturated octan-1-ol. This may suggest that water does have a slight effect, however, the quantitative differences between the two phases have yet to be determined.

The most conclusive results regarding the effect of the presence of water in octan-1-ol were presented by Cabani *et al.*, who measured K^*_{ow} for anhydrous octan-1-ol and using the literature K_{ow} values for mutually saturated phases were able to compute the thermodynamic standard functions of transfer from anhydrous to water-saturated octan-1-ol.[5] These data suggested that this transfer process is favourable for polar solutes and unfavourable for non-polar solutes. From their data they rationalized that the presence of water in octan-1-ol has only weak thermal effects and the entropic effects are small.

Additionally, Watari *et al.*,[10] observed no effect on the measured K_{ow} for halobenzenes upon mutual saturation. For these non-hydrogen bonding solutes, they also observed no significant difference between values for the partition coefficients between water–octan-1-ol and water–heptane systems. They concluded that as long as specific interactions with the solvent are avoided there is very little difference between these two systems. These results suggest that the primary interaction for non-polar solutes is between octan-1-ol's alkyl chain and the solute. Water was viewed as being 'tied-up' to octan-1-ol's hydroxy group. From these results and the similarity of this phase to bonded alkyl chains on a reversed-phase liquid chromatographic packing it seems that a reasonable correlation should exist between K_{ow} and reversed-phase liquid chromatographic (RPLC) capacity factors.

In order to quantify the differences between octan-1-ol and water-saturated octan-1-ol we measured the free energy of transfer of non-polar and polar solutes between neat and mutually saturated phases. The mole-fraction based infinite dilution activity coefficients, γ^∞, of a series of alcohols was also determined in each phase since this thermodynamic parameter is an excellent measure of solute–solvent interactions. In addition, we studied the solvatochromic properties of each phase. If there were no significant difference between neat and water-saturated octan-1-ol then the solvatochromic measurements for each phase should be similar and the change in free energy of transfer between phases should be small.

Free energies of transfer were calculated from measurements of the partition coefficients between the vapour phase and the various liquids by head-space gas chromatography (HSGC). The pertinent experimental methods have been outlined in ref. 25. The free energy of transfer between octan-1-ol and water-saturated octan-1-ol, $\Delta G_{o/ow}$, can be calculated as follows assuming the free energy of transfer between the vapour phases above each solution is negligible. Where $\Delta G_{g/ow}$ is the free energy

$$\Delta G_{o/ow} = \Delta G_{g/ow} - \Delta G_{g/o} \qquad (1)$$

of transfer from the vapour phase to water-saturated and $\Delta G_{o/o}$ is the free energy of transfer from the vapour phase to octan-1-ol. Eqn. (1) can be expressed as follows:

$$\Delta G_{o/ow} = -RT\ln\left(\frac{K_{g/o}}{K_{g/ow}}\right) \qquad (2)$$

where $K_{g/o}$ is the partition coefficient between the vapour phase above pure octan-1-ol and pure octan-1-ol and $K_{g/ow}$ is the partition coefficient between the vapour phase above water-

Table 1 Physical and solvatochromic properties of solutes[a]

Solute	V_1	π_2^*	β_2
Nonane	0.939	0.02	0.00
Toluene	0.592	0.55	0.11
Bromobenzene	0.624	0.79	0.06
Nitroethane	0.445	0.80	0.25
1-Nitropropane	0.543	0.78	0.25
2,2,2-Trifluoroethanol	0.376	0.78	0.18
Methanol	0.205	0.40	0.42
Ethanol	0.305	0.40	0.45
Propan-1-ol	0.402	0.40	0.45
Butan-1-ol	0.499	0.40	0.45
Pentan-1-ol	0.593	0.40	0.45
Triethylamine	0.704	0.14	0.71
Pentan-2-one	0.574	0.65	0.48
Propionitrile	0.369	0.70	0.31

[a] Parameters are taken from ref. 35.

saturated octan-1-ol and water-saturated octan-1-ol. The gas–liquid partition coefficients are directly measured in the head-space experiment. The partition coefficients and free energies of transfer referred to above are all based on a unit molarity standard state to be consistent with the well researched recommendations of Ben-Naim.[26]

The solvatochromic measures of solvent π^* (dipolarity/polarizability), β (hydrogen-bond basicity), and α (hydrogen-bond acidity), have been used to understand the chemistry of phase transfer processes.[27–38] We measured these parameters for octan-1-ol and water-saturated octan-1-ol in order to determine whether water had any effect on octan-1-ol's bulk chemical properties. These measurements were also performed in order to rationalize the free energy data.

Experimental

The concentration of water in water-saturated octan-1-ol and the concentration of octan-1-ol in octan-1-ol-saturated water were measured to ensure complete saturation and as a comparison with previous measurements. The water concentration in octan-1-ol was determined using a modification of a method recently developed by Dix *et al.*[39] This method uses the acid-catalysed hydrolysis reaction of 2,2-dimethoxypropane to acetone and methanol. The acid catalyst used in this work is hydrochloric acid.[40] A stock reaction mixture which contained a solution of 50% ethyl acetate and 50% 2,2-dimethoxypropane was prepared. Hydrochloric acid was added to this mixture at a concentration of approximately 1 mmol dm^{-3}. This mixture was gently heated under vacuum to remove completely acetone and methanol, the reaction products. This stock mixture is termed the 'blanked' reagent. A 2 cm^3 aliquot of the octan-1-ol phase was added to 1 cm^3 of the 'blanked' reaction solution. A known amount of the internal standard, 2-methylpentane, was then added to this mixture. Quantitation of acetone was performed using on-column injection/FID gas chromatography on a 15m × 0.53 DB-1 megabore column (J&W Scientific, Folsom, CA). The amount of octan-1-ol present in the water phase was quantitated using on-column injection and hexadecane as the internal standard.

HSGC Measurements.—The free energy of transfer from neat octan-1-ol to water-saturated octan-1-ol, $\Delta G_{o/ow}$, was determined from an individual solute's infinite dilution partition coefficient which was measured by HSGC. The HSGC system design is similar to that described in ref. 41. The solutes studied are given in Table 1 (parameters discussed below). They were judiciously chosen so as to span a large range of chemical properties as is evident from their solvatochromic parameters. A homologous series of *n*-alcohols were included in order to determine the effect that water has on the methylene group increment to the free energy of transfer. Anhydrous octan-1-ol (Aldrich; 99 + %, <0.005% water) was used for all measurements. A 40 cm^3 sample of the neat octan-1-ol was equilibrated at 25 °C (±0.05 °C). A known amount of a solute mixture was added, solute concentrations were maintained at mole fractions less than 10^{-4}, well within the range of Henry's law.

Water-saturated octan-1-ol was generated by slowly equilibrating octan-1-ol against HPLC-grade water (J. T. Baker) for more than 1 week. These phases were gently mixed at 25 °C (±0.5 °C) to minimize mutual entrainment. A 40 cm^3 sample of the octan-1-ol phase was removed and placed in the thermostatted cell. The same procedure and concentrations as stated above were used. The ratio of the area counts, for each solute, above neat octan-1-ol and water-saturated octan-1-ol was taken as a measure of $\Delta G_{o/ow}$.

The γ^∞, at 25 °C, for a series of 11 alcohols, given in Table 4, were measured in all four phases, using the HSGC apparatus and techniques described in ref. 25. Vapour pressures of the pure solutes were either taken from ref. 42 or calculated from the Antoine equation. The neat phases were HPLC-grade water (J. T. Baker) and anhydrous octan-1-ol (Aldrich; 99 + %, <0.005% water).

Solvatochromic Measurements.—All measurements were made on a Varian DMS-200 spectrophotometer using a 0.2 nm slit width, 20 nm min^{-1} scan rate, 1 cm pathlength cells, and a smoothing constant of 5 s. All samples were thermostatted at 25 °C (±0.2 °C) during the analysis using a thermostatted cell holder controlled by a constant temperature bath (Haake, Type FE). Peak maxima were obtained using the '9/10' method prescribed by Kamlet and Taft in order to minimize the effect of changes in bandshape with solvent.[43]

The same phases, used in the head-space experiment, were analysed for changes in π^* (dipolarity/polarizability), β (hydrogen-bond basicity), and α (hydrogen-bond acidity). A 10 cm^3 alliquot of the equilibrated phase was removed and probe dye was added so as to give an absorbance between 0.80 and 1.00. These samples sat overnight at room temperature. Two replicate measurements were made on each phase and an additional measurement was made using another aliquot from the equilibrated phases two weeks later to ensure that the phases had achieved complete equilibrium. The following indicators and methods were used to measure the bulk solvatochromic parameters.

π^*. The dipolarity/polarizability of a solvent can be calculated from the shift in the adsorption maximum of a probe dye where the wavelength maximum is insensitive to hydrogen-bond interactions with the solvent.[43] This bulk property was measured for neat octan-1-ol and octan-1-ol saturated with water using *N*,*N*-diethyl-*p*-nitroaniline (DENA) and *p*-nitroanisole (PNAS).

β. The hydrogen-bond basicity of a solvent is usually measured using a two-probe dye system. One of these is termed the reference dye, which is generally just a π^* indicator. This probe does not respond to hydrogen bonding interactions with the solvent.[44] In addition, one must use a probe dye that is able to donate a hydrogen bond to the solvent. However, it is now known that OH and NH donors give inconsistent results.[45–47] Therefore, both types of donors were studied. For the NH donor system, *N*,*N*-diethyl-*p*-nitroaniline and *p*-nitroaniline were used as the reference and donor probes, respectively; and for the OH donor system, *p*-nitroanisole and *p*-nitrophenol were used as the reference and donor probes.[45]

α. We suspected that the hydrogen-bond acidity would be very sensitive to the presence of water. Therefore, four probes sensitive to this property were studied: Reichardt's

Table 2 $\Delta G_{o/ow}$ of all 14 solutes

Solutes	$\Delta G_{o/ow}$/cal mol$^{-1\,a}$
Nonane	52.1
Toluene	−23.8
Bromobenzene	−25.9
Nitroethane	−137.8
1-Nitropropane	−97.2
2,2,2-Trifluoroethanol	−141.3
Methanol	−175.2
Ethanol	−159.5
Propan-1-ol	−134.1
Butan-1-ol	−104.0
Pentan-1-ol	−93.2
Triethylamine	−146.5
Pentan-2-one	−109.1
Propionitrile	−111.3

[a] Standard deviations for three replicate measurements did not exceed 15 cal mol^{-1}.

Betaine (ET-30), bis[α-(2-pyridyl)benzylidene-3,4-dimethylaniline]bis(cyano)iron(II) (abbreviated Fe complex), Phenol Blue, and Nile Red. All of these probes are sensitive to both solvent hydrogen-bond donor acidity and dipolarity/polarizability, therefore a two-indicator set is required. In order to back calculate a solvent α, we used the reported regression equations [eqns. (3)–(6)] for each probe's absorbance maximum

$$E_T(\text{ET-30})/\text{kcal mol}^{-1} = 31.00 + 13.43\pi^* + 15.06\alpha \quad (3)$$

$$n = 40 \quad \text{s.d.} = 1.65 \quad r = 0.984$$

$$\nu_{max}(\text{Fe Complex})/\text{kK} = 14.02 + 0.98\pi^* + 1.56\alpha \quad (4)$$

$$n = 13 \quad \text{s.d.} = 0.04 \quad r = 0.999$$

$$E_T(\text{PB})/\text{kcal mol}^{-1} = 51.82 + 4.26\pi^* + 2.46\alpha \quad (5)$$

$$n = 49 \quad \text{s.d.} = 0.10 \quad r = 0.992$$

$$E_T(\text{NR})/\text{kcal mol}^{-1} = 58.41 + 6.16\pi^* + 3.43\alpha \quad (6)$$

$$n = 47 \quad \text{s.d.} = 0.53 \quad r = 0.980$$

against α and π*. In all cases, α was calculated using an average π* obtained from the two probes used to measure this property. The regression equations for the energy of transitions were taken from refs. 48, 38, 49 and 50, respectively.

Results and Discussion

The concentration of water in octan-1-ol at equilibrium at 25 °C was measured as 2.46 mol dm^{-3} (±0.05 mol dm^{-3}), x_{H_2O} = 0.289, and that of octan-1-ol in water at 3.29 × 10^{-3} mol dm^{-3} (±5 × 10^{-5} mol dm^{-3}), x_{OCT} = 9.32 × 10^{-4}. Previously reported data, which are in good agreement with these measurements, gave results of 2.3 mol dm^{-3}, x_{H_2O} = 0.275,[2,17,51] for the concentration of water in octan-1-ol and 4.5 × 10^{-3} mol dm^{-3} for the concentration of octan-1-ol in water.[2,52,53] The concentration of water in octan-1-ol has been reported to be as low as 1.7 mol dm^{-3},[7] and x_{H_2O} = 0.11.[22] We believe, owing to such good agreement between our data and that of Leo *et al.*,[2] Backlund *et al.*[17] and Smith *et al.*,[51] that these data are significantly low. Our agreement with refs. 2, 17 and 51 leads us to believe that our saturated phases are at equilibrium and do not contain significant amounts of entrained water or octan-1-ol. The concentration of water in the original neat octan-1-ol phase was determined to be less than 2.5 mmol dm^{-3}, approximately the detection limit for this approach and sample.

The HSGC measurements of $\Delta G_{o/ow}$ for all 14 solutes studied are given in Table 2. Nonane, which is the only completely nonpolar solute studied, has an unfavourable or positive value indicating a preference for the neat octan-1-ol phase. This is in good agreement with the studies of Berti *et al.*,[24] and Cabani *et al.*,[5] discussed above and is consistent with chemical intuition and the hydrophobic effect. For all polar solutes, the transfer from neat octan-1-ol to water-saturated octan-1-ol is favourable; these solutes prefer the water-saturated phase. This is consonant with the large amount of water present in the saturated phase and is in good agreement with the observations of Berti *et al.*[24] and Cabani *et al.*[5] We expect these polar solutes to prefer this environment owing to strong hydrogen-bonding and dipolar interactions with water. However, these free energy changes are very small and at first glance are not consistent with the change expected for the large amounts of water present in the octan-1-ol phase. To emphasize further how small these differences are we refer the reader to the work of Hildebrand *et al.*,[54] who have eloquently argued that free energy differences of a magnitude similar to a small fraction of the thermal energies (60–120 cal mol^{-1} at 25 °C) can easily arise from minor perturbations of the system and should be considered insignificant. We suspect that very little 'free' water exists in this phase owing to complexation of water with octan-1-ol. Clusters of octan-1-ol and water must exist, as has been previously hypothesized.[2] Therefore, water-saturated octan-1-ol is significantly different from the water-saturated butan-1-ol case described above and these differences are due to differences in the ratio of alcohol to water.[17]

It is interesting to examine the $\Delta G_{o/ow}$ values for the homologous series of alcohols given in Table 2. As the alkyl chain length approaches that of octan-1-ol, the free energy of transfer from neat octan-1-ol to octan-1-ol saturated with water should become exactly zero for octan-1-ol. Of the solutes studied, methanol has properties most similar to that of water and least like those of octan-1-ol. This is revealed in our results as methanol has the most negative value of $\Delta G_{o/ow}$ showing that methanol has a preference for the water-saturated phase. Moreover, as the alkyl chain length approaches that of octan-1-ol (*i.e.* the properties are less like those of water), the free energy of transfer of an octan-1-ol molecule between 'wet' and 'dry' octan-1-ol approaches zero. A value that is consistent with an octan-1-ol molecule being unable to detect any difference between the 'wet' or 'dry' phase. This suggests that the chemical properties of the octan-1-ol phase when it is either 'wet' or 'dry' must be very similar and the differences can only be observed by small very strong hydrogen-bond acids and bases. However, to account for the methylene group selectivity observed for the alcohols some differences must exist between the two phases. A least-squares analysis of the $\Delta G_{o/ow}$ of the alcohols *versus* carbon number, N_c, gives eqn. (7). From this equation, the calculated

$$\Delta G_{o/ow}(\text{cal mol}^{-1}) = -199.1(\pm 5.8) + 22.0(\pm 1.7)N_c \quad (7)$$

$$n = 5 \quad \text{s.d.} = 5.5 \quad r = 0.991$$

$\Delta G_{o/ow}$ for octan-1-ol would be −23.1 cal mol^{-1} which suggests the presence of water produces a slightly favourable situation for the clustering of octan-1-ol and water. This is consistent with water being an excellent hydrogen-bond acid (significantly stronger than octan-1-ol) and octan-1-ol being an excellent hydrogen-bond base (significantly stronger than water). The change in $\Delta G_{o/ow}$ for the *n*-alcohols is 22.0 cal mol^{-1} per CH_2 group, however, the change is 40.0 cal mol^{-1} between nitroethane and 1-nitropropane. Nitro compounds have two acceptor sites and can interact more strongly with a donor molecule than can an alcohol.[55] It has been reported that multiple acceptor sites are additive in systems incorporating nitro compounds.[55] The decrease in $\Delta G_{o/ow}$ for the nitroalkanes

Table 3 Solvatochromic measurements of both neat and water-saturated octan-1-ol

Parameter (probe)	Octan-1-ol	Octan-1-ol–H_2O[a]	Difference
π^* (DENA)	0.53	0.58	0.05
π^* (PNAS)	0.47	0.48	0.01
β (NH donor)	0.86	0.79	−0.07
β (OH donor)	0.96	0.95	−0.01
α (ET-30)	0.70	0.71	0.01
α (Fe complex)	0.73	0.78	0.05
α (Phenol Blue)	0.78	0.82	0.04
α (Nile Red)	0.82	0.82	0.00

[a] Water-saturated octan-1-ol.

is approximately twice that of the alcohols, therefore the increase in carbon number probably influences each nitro acceptor site. However, the cummulative change in accepting ability is probably larger for a nitroalkane relative to an alcohol.

To obtain a better understanding of the specific solute–solvent interactions that control the transfer process, a linear free energy relationship using the solute solvatochromic parameters in Table 1 was attempted. The regression eqn. of $\Delta G_{o/ow}$ for all 14 solutes against their $V_1/100$ (intrinsic volume), π_2^*, and β_2 (where subscript 2 refers to a solute property) is:

$$\Delta G_{o/ow}(\text{cal mol}^{-1}) = -120.2(\pm 39.5) + 192.5(\pm 39.7)V_1/100 - 33.7(\pm 30.0)\pi_2^* - 189.1(\pm 35.7)\beta_2 \quad (8)$$

$$n = 14 \quad \text{s.d.} = 21.1 \quad r = 0.955$$

The transfer free energy is primarily dependent on the difference in energy required to create a cavity in both phases, modelled by the solute size parameter V_1, and the hydrogen-bond donating ability of the solvent, probed through the solute β_2. Eqn. (8) shows that more energy is required to form a cavity in water-saturated octan-1-ol than in neat octan-1-ol. Also, the strong hydrogen-bond donating ability of water must 'pull' polar and hydrogen bond acceptor solutes into the water-saturated octan-1-ol phase. LSERs of K_{ow} have revealed that β_2 is a major factor which determines the magnitude of K_{ow} and opposes the transfer of polar and hydrogen bond acceptor solutes from water to octan-1-ol. This suggests that the water-saturated octan-1-ol phase should possesses a significantly higher hydrogen bond donor acidity (α) than the neat phase which is consistent with the relative properties of the individual neat phases and chemical intuition. It is interesting to note that dipolar interactions are only barely statistically significant in affecting the transfer process, implying that dipolar interactions are very similar in the two phases. The relatively large dependence on V_1, the cavity formation parameter, is the primary reason for the unfavourable transfer of non-polar solutes into the water-saturated octan-1-ol and probably gives rise to the CH_2 group selectivity increment since all of the normal alcohols have the same β_2 value. Increased ordering in water-saturated octan-1-ol is expected to occur through the formation of clusters with water and is probably the reason for the positive contribution to $\Delta G_{o/ow}$. While all of the coefficients given in eqn. (8) are statistically significant it must be remembered that they are really very small. For example, in the correlation of the free energy of transfer from octan-1-ol to water against the same parameters Kamlet *et al.*[35] found that the coefficients of $V_1/100$ and β_2 were −7299 (±68) and 5239 (±68), respectively.

These $\Delta G_{o/ow}$ data should be consistent with the specific chemical properties of the phases as measured solvatochromically, hence we expect that very little difference should be observed between the two phases. Table 3 lists the measured solvatochromic properties for both phases using several indicators along with literature values for the neat octan-1-ol phase. Water is a very dipolar solvent, $\pi^* = 1.09$, and it is also a very good hydrogen-bond acid, $\alpha = 1.17$, but is a relatively weak hydrogen-bond base, $\beta = 0.18$. From the large mole fraction of water present in octan-1-ol we expected that a significant change should be observed in all of these parameters since the values for octan-1-ol are $\pi^* = 0.50$, $\alpha = 0.76$ and $\beta = 0.86$. Previous studies of mixtures of water with methanol, ethanol and isopropyl alcohol led us to expect, by comparisons on a mole fraction scale, a significant effect especially on the hydrogen bond acidity of the mixtures.[37,38] However, it must be realised that the volume fraction of water present in octan-1-ol is less than 0.05. Based on the results of refs. 37 and 38 this small volume of water has only a minimal effect on the solvatochromically measured properties of the mixtures, which is in agreement with our observations. The average change in π^*, for octan-1-ol, upon saturation is only 0.03, the change in α does not exceed 0.03, and β (NH donor) decreases by 0.07 and β (OH donor) decreases by 0.01 units. The sorption of water into octan-1-ol does slightly alter the bulk properties in a direction that is consistent with the properties of both phases and chemical intuition. But these changes are not what would be calculated based on the mole fraction of water present. From the changes in these parameters, upon sorption of water, it would be predicted that polar and hydrogen bond accepting solutes would have a slight preference for the water-saturated octan-1-ol phase over the neat octan-1-ol phase as is observed in eqn. (8).

The above data are consistent with sorbed water forming hydrogen-bonded clusters with octan-1-ol and its association with the hydroxy group preventing any significant changes in the measured properties. It has been suggested that a linear aggregation structure is probably the case for long chain alcohols and the addition of water breaks this structure.[17] Reports of octan-1-ol and water forming a complex in the ratio of one water molecule to four octan-1-ol molecules have been proposed and may be correct. However, it cannot be fulfulled for every water molecule since the number of alcohol molecules per water molecule is only 2.7 at saturation for alcohol homologues with carbon chains longer than seven carbons.[17] This can be rationalized from the favourable free energy of transfer of octan-1-ol to water-saturated octan-1-ol. Based on the ratio of 2.7:1, all of the water is expected to be tied up with octan-1-ol and the probe dyes are 'seeing' the properties of this cluster, clusters of octan-1-ol, and free octan-1-ol. The average value of which must not be significantly different from that of neat octan-1-ol where the dye is probably 'seeing' clusters of octan-1-ol, and free octan-1-ol. The complex of water and octan-1-ol must either have properties that are not significantly different from those of octan-1-ol or the complex is present in such small proportions that it cannot significantly alter the properties of the bulk phase.

In order to gain a different perspective on the effect of water on the phase transfer properties of octan-1-ol we measured the infinite dilution activity of a series of alcohols (see Table 4) in neat octan-1-ol, octan-1-ol saturated with water, water and water saturated with octan-1-ol. These are very closely related to the solute partition coefficients used above. The subscript 2

$$\gamma_2^\infty = \frac{RT}{K_2 p_2^\circ \bar{V}_1} \quad (9)$$

refers to the solute and 1 to the solvent, T(K) is the temperature, p_2° is the solute vapour pressure, and $\bar{V}_1$ is the solvent molar volume. In fact the use of γ^∞ as the basis for the free energy of transfer implies a change in standard state from unit molarity to unit mole fraction and this change is not without complication in terms of the chemical interpretation.[26] In order to perform the necessary calculations to obtain γ^∞ as discussed in ref. 25,

Table 4 γ^∞ of a series of alcohols in neat and mutually saturated phases

Solute	p_2°/torr	Octan-1-ol	Octan-1-ol–H_2O[a]	Water	H_2O–Octan-1-ol[b]
Methanol	127.04	1.337	1.245	1.580	1.582
Ethanol	59.03	1.256	1.192	3.744	3.757
Propan-1-ol	20.99	1.161	1.143	13.36	13.36
Butan-1-ol	6.83	1.110	1.125	50.19	49.47
Pentan-1-ol	2.22	1.080	1.106	198.0	192.4
Hexan-1-ol	0.72	1.094	1.098	798.8	783.8
Propan-2-ol	43.32	1.119	1.100	7.595	7.610
2-Methylpropan-2-ol	42.28	0.876	0.895	11.91	11.87
2-Methylpropan-1-ol	11.45	1.206	1.285	48.86	48.55
3-Methylbutan-1-ol	2.37	1.519	1.602	208.0	206.6
Cyclohexanol	0.56	1.380	1.375	157.0	157.3

[a] Water-saturated octan-1-ol. [b] Octan-1-ol-saturated water.

the molar volume of the water-saturated octan-1-ol phase had to be determined. This was calculated as the mole-fraction weighted average of the molecular weights and a measurement of the density as described in ref. 25. The values are 97.801 g mol^{-1} and 0.837 74 g cm^{-3}, respectively. The effect of water on the density of octan-1-ol (0.8270 g cm^{-3}) is minimal.

As expected from the low solubility of octan-1-ol in water, the γ^∞ for linear, branched, and cyclic alcohols are essentially the same in both the neat water and the octan-1-ol-saturated water. This indicates that the small amount of dissolved octan-1-ol does not perturb the bulk phase properties of water. This is consistent with the solvatochromic studies above. If the water phase contained entrained octan-1-ol it is expected that a significant change in the bulk phase properties would result and would be observed in all the measurements made. This was clearly observed in some of our early work where the two phases were mixed by completely inverting the vials in the equilibration step. This resulted in entrained octan-1-ol as was observed by the following. The aqueous phase was removed and ET-30 was added. This dye is usually insoluble in water, however the dye dissolved quickly producing a pink hue to the phase (this dye is red in the linear alcohols). Centrifugation of this phase resulted in small red droplets at the bottom and these also adhered to the sides of the tube. When entrainment is avoided, the dissolved octan-1-ol probably acts like another solute at infinite dilution in water. We believe that the effect of octan-1-ol in the water phase is nil and the differences seen in the two columns of Table 4 is a measure of the random experimental error. The measured γ^∞ in neat octan-1-ol and water-saturated octan-1-ol confirm the $\Delta G_{o/ow}$ and solvatochromic measurements. The largest effect produced by the dissolved water is on the lower alcohols as was observed in the $\Delta G_{o/ow}$ measurements. The effect is also enhanced for the branched alcohols relative to their linear homologues, probably owing to the increased ordering induced by the dissolved water. However, the effect is very small, having no effect on the higher alcohols. These data confirm the assumptions that the environment experienced by a solute in neat or mutually saturated phases of water and octan-1-ol is very similar.

K_{ow} has met with considerable success in modelling drug interactions with membranes. Membranes are known to accumulate large amounts of water at their surface which provides a hydrophilic region at the surface and a hydrophobic interior. This is essentially what we have observed in this work, the hydrophilic site being the water complexed to octan-1-ol's hydroxy group and the alkyl chain of octan-1-ol being the hydrophobic region. Therefore, a solute probably observes a similar environment in aqueous octan-1-ol systems and aqueous membrane systems. Apparently, this similarity allows aqueous octan-1-ol systems to be excellent models for understanding drug interactions with membranes.

It seems reasonable to expect good correlations between K_{ow} and measured capacity factors in RPLC since water saturation of the octan-1-ol phase produces a structured phase. This phase can be viewed as being clusters of water 'tied-up' with octan-1-ol which may be similar to the structured environment of a reversed micellar system or a reversed-phase liquid chromatographic bonded phase. However, there is no conclusive evidence for large aqueous or alkane-like domains in these systems. In support of this, ref. 18 revealed better fits between $\log k'$ and K_{ow} as the mobile phase water concentration increased. In addition, K_{ow} values calculated from RPLC data are often determined from extrapolations to pure water. These observations are in concordance with the spectroscopic measurements of the polarity of a bonded C18 phase in equilibrium with pure water.[56,57] It was reported that under these conditions the polarity of the bonded phase was very similar to that of octan-1-ol. Therefore, some of the success attributed to K_{ow} being a predictor of RPLC capacity factors may be due to a similarity in the environment experienced by a solute.

Conclusions

The saturation of octan-1-ol with water does have a real but small effect on the bulk properties of neat octan-1-ol. The presence of water in octan-1-ol produces a favourable contribution to the free energy of transfer of polar solutes and an unfavourable contribution to the free energy of transfer of non-polar solutes from neat octan-1-ol to water-saturated octan-1-ol. Quantitative measures of these contributions have been presented and are shown to be due to differences in the energy required to create a cavity for the solute in both phases, modelled by the intrinsic volume (V_I), and an increase in the hydrogen bond donating ability of the water-saturated phase. However, these changes are very small and are not consistent with the large amount of water present in octan-1-ol upon saturation. From the thermodynamic and spectroscopic data, we have shown that water saturation of octan-1-ol has very little effect on the chemical properties of bulk octan-1-ol presumably due to the strong hydrogen-bonding interaction between water and the hydroxy group. The water is essentially 'tied-up' with octan-1-ol in a cluster and is unable to exert a significant effect on the environment experienced by a solute in water-saturated octan-1-ol, relative to that in neat octan-1-ol. This environment must possess properties that are very similar to those observed in membrane, lipid, and soil systems, and consequently is the basis for the success of using octan-1-ol–water partition coefficients to model these systems. Therefore, we conclude that the success of K_{ow} is due primarily to the intrinsic properties of neat octan-1-ol and not due to the presence of a large amount of dissolved water. Reports citing the large solubility of water in octan-1-ol as the major reason to prefer the use of K_{HW} as a model system are not consistent with the results of this work.

Acknowledgements

This work was supported by grants from the National Science Foundation and the Petroleum Research Foundation of the American Chemical Society. The authors would like to recognise the efforts of David Eikens and thank him for many helpful discussions.

References

1 C. Hansch and A. Leo, *Substituent Constants for Correlation Analysis in Chemistry and Biology*, Wiley, New York, 1979.
2 A. Leo, C. Hansch and D. Elkins, *Chem. Rev.*, 1971, **71**, 525.
3 S. H. Yalkowsky, S. C. Valvani and T. L. Roseman, *J. Pharm. Sci.*, 1983, **72**, 866.
4 C. T. Chiou, D. W. Schmedding and M. Manes, *Env. Sci. Tech.*, 1982, **16**, 4.
5 S. Cabani, G. Conti, V. Mollica and L. Bernazzani, *J. Chem. Soc., Faraday Trans.*, 1991, **87**, 2433.
6 M. H. Abraham, G. S. Whiting, R. Fuchs and E. J. Chambers, *J. Chem. Soc., Perkin Trans. 2*, 1990, 291.
7 M. M. Schantz and D. E. Martire, *J. Chromatog.*, 1987, **391**, 35.
8 W. A. P. Luck, *Pure Appl. Chem.*, 1987, **59**, 1215.
9 A. E. Beezer, W. H. Hunter and D. E. Storey, *J. Pharm. Pharmacol.*, 1983, **35**, 350.
10 H. Watari, M. Tanaka and N. Suzuki, *Anal. Chem.*, 1982, **54**, 702.
11 S. P. Wasik, Y. B. Tewari, M. M. Miller and J. H. Purnell, *J. Res. Nat. Bur. Stand. (US)*, 1982, **87**, 311.
12 C. D. Visser, G. Perron and J. E. Desnoyers, *Can. J. Chem.*, 1977, **55**, 856.
13 L. Nord, E. E. Tucker and S. D. Christian, *J. Solution Chem.*, 1984, **13**, 849.
14 F. Franks and J. E. Desnoyers, *Water Science Reviews*, 1985, **1**, 171.
15 G. Roux, D. Roberts, G. Perron and J. E. Desnoyers, *J. Solution Chem.*, 1980, **9**, 629.
16 G. C. Benson and O. Kiyohara, *J. Solution Chem.*, 1980, **9**, 791.
17 S. Backlund, H. Hoiland and I. Vikholm, *J. Solution Chem.*, 1984, **13**, 749.
18 E. Tomlinson, W. Riebesehl and H. J. M. Grunbauer, *Pure Appl. Chem.*, 1986, **58**, 1573.
19 B. C. Lippold and M. S. Adel, *Arch. Pharm.*, 1972, **305**, 417.
20 G. M. Bresnen, Ph.D. Thesis, Liverpool Polytechnic, 1984.
21 R. N. Smith, C. Hansch and M. M. Ames, *J. Pharm. Sci.*, 1975, **64**, 599.
22 R. W. Taft, unpublished results.
23 J. L. M. Abboud, unpublished results.
24 P. Berti, S. Cabini, G. Conti and V. Mollica, *J. Chem. Soc., Faraday Trans. 1*, 1986, **82**, 2547.
25 A. J. Dallas, Ph.D. Thesis, University of Minnesota, Minneapolis, 1992.
26 A. Ben-Naim, *J. Phys. Chem.*, 1978, **82**, 792.
27 P. W. Carr, *J. Chromatogr.*, 1980, **194**, 105.
28 M. J. Kamlet, R. W. Taft, P. W. Carr and M. H. Abraham, *J. Chem. Soc., Faraday Trans. 1*, 1982, **78**, 1689.
29 M. J. Kamlet, M. H. Abraham, R. M. Doherty and R. W. Taft, *J. Am. Chem. Soc.*, 1984, **106**, 464.
30 R. W. Taft, M. H. Abraham, G. R. Famini, R. M. Doherty, J. M. Abboud and M. J. Kamlet, *J. Pharm. Sci.*, 1985, **74**, 807.
31 R. W. Taft, J. M. Abboud, M. J. Kamlet and M. H. Abraham, *J. Solution Chem.*, 1985, **14**, 153.
32 M. J. Kamlet, R. M. Doherty, J. M. Abboud, M. H. Abraham and R. W. Taft, *J. Pharm. Sci.*, 1986, **75**, 338.
33 M. J. Kamlet, M. H. Abraham, P. W. Carr, R. M. Doherty and R. W. Taft, *J. Chem. Soc., Perkin Trans. 2*, 1988, 2087.
34 M. J. Kamlet, R. M. Doherty, P. W. Carr, D. Mackay, M. H. Abraham and R. W. Taft, *Environ. Sci. Tech.*, 1988, **22**, 503.
35 M. J. Kamlet, R. M. Doherty, M. H. Abraham, Y. Marcus and R. W. Taft, *J. Phys. Chem.*, 1988, **92**, 5244.
36 P. C. Sadek, P. W. Carr, R. M. Doherty, M. J. Kamlet, R. W. Taft and M. H. Abraham, *Anal. Chem.*, 1985, **57**, 2971.
37 W. J. Cheong and P. W. Carr, *Anal. Chem.*, 1988, **60**, 820.
38 J. H. Park, M. D. Jang, D. S. Kim and P. W. Carr, *J. Chromatogr.*, 1990, **513**, 107.
39 K. D. Dix, P. A. Sakkinen and J. S. Fritz, *Anal. Chem.*, 1989, **61**, 1325.
40 J. S. Fritz, personal communication.
41 J. H. Park, Ph.D. Thesis, University of Minnesota, Minneapolis, 1988.
42 J. A. Riddick, W. B. Bunger and T. K. Sakano, *Techniques in Chemistry Volume II, Organic Solvents: Physical Properties and Methods of Purification*, 4th ed., Wiley, New York, 1986.
43 M. J. Kamlet, J. L. M. Abboud and R. W. Taft, *J. Am. Chem. Soc.*, 1977, **99**, 6027.
44 M. J. Kamlet and R. W. Taft, *J. Am. Chem. Soc.*, 1976, **98**, 377.
45 P. Nicolet and C. Laurence, *J. Chem. Soc., Perkin Trans. 2*, 1986, 1071.
46 C. Laurence, P. Nicolet and M. Helbert, *J. Chem. Soc., Perkin Trans. 2*, 1986, 1081.
47 P.-C. Maria, J.-F. Gal, J. Franceschi and E. Fargin, *J. Am. Chem. Soc.*, 1987, **109**, 483.
48 M. J. Kamlet, personal communication.
49 O. W. Kolling, *Anal. Chem.*, 1981, **53**, 54.
50 A. J. Dallas and P. W. Carr, unpublished work.
51 R. N. Smith, C. Hansch and M. M. Ames, *J. Pharm. Sci.*, 1975, **64**, 599.
52 J. A. V. Butler, D. W. Thompson and W. H. Maclennan, *J. Chem. Soc.*, 1933, 674.
53 R. Collander, *Acta Chem. Scand.*, 1951, **5**, 774.
54 J. H. Hildebrand, J. M. Prausnitz and R. L. Scott, *Regular and Related Solutions*, Van Norstrand Reinhold Co., New York, 1970.
55 R. W. Taft, M. H. Abraham, G. R. Famini, R. M. Doherty, J. M. Abboud and M. J. Kamlet, *J. Pharm. Sci.*, 1985, **74**, 807.
56 J. Stahlberg and M. Almgren, *Anal. Chem.*, 1985, **57**, 817.
57 S. C. Rutan and J. L. Jones, *Anal. Chem.*, 1991, **63**, 1318.

Paper 2/04025E
Received 27*th July* 1992
Accepted 28*th July* 1992