

Enthalpies of solution of a series of *m*-alkoxy phenols in water, *n*-octanol and water-*n*-octanol mutually saturated: derivation of the thermodynamic parameters for solute transfer between these solvents

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Enthalpies of solution in both water and *n*-octanol have been determined for a series of phenols, in a microcalorimeter modified for titration. The thermodynamic data for solution in *n*-octanol and in water, as well as for transfer between the two, have been calculated from the free energies of transfer, based upon partition coefficients, and the free energies of solution, based upon solubility data. The results are discussed in terms of solute-solvent interactions in both phases and are used to assess, critically, the use of *n*-octanol as lipid-like solvent in QSAR studies.

The importance of thermodynamic data for the interpretation of drug action is emphasized in a recent review (Anderson et al 1981) and in several other papers (Beezer et al 1980; Riebesehl & Tomlinson 1981; James et al 1981; Dearden & Bresnen 1981). Moreover it has been pointed out (Beezer et al 1980; Anderson et al 1981) that methods based upon partition coefficient determination may be subject to errors in that such methods assume (i) that $\Delta H_{\text{trs}}^{\circ}$ is independent of temperature and (ii) that the derived values of ΔH_{trs} (assuming that ΔH_{trs} is independent of temperature) are not subject to appreciable error magnification. King (1965) has shown that even if an acid dissociation constant, pK_{a} , were measured to ± 0.02 units at 10 temperatures between 278 and 323 K then the value of the associated enthalpy change could only be known to ± 0.795 kJ mol⁻¹. The variations in derived ΔH values become progressively worse as the precision of the equilibrium constant measurement is reduced, as the temperature interval is reduced and as the number of points within the temperature interval is reduced (e.g. for 6 temperature intervals between 293 and 303 K and $\text{pK}_{\text{obs}} = \text{pK} \pm 0.02$ the error in ΔH would be ± 4.06 kJ mol⁻¹). For *n*-octanol in particular, we have shown earlier (Beezer et al 1980) that, for a series of phenols, ΔH_{trs} is significantly dependent upon temperature with little compensation between ΔH and ΔS . It therefore

becomes important to substantiate the values of $\Delta H_{\text{trs}}^{\circ}$ obtained from van't Hoff plots, by direct calorimetric measurement.

We have constructed a precision microtitration system for use with the L K B microcalorimeter (Beezer et al 1982) which, by enabling us to measure enthalpies of solution ($\Delta H_{\text{s}}^{\circ}$) directly in pure and in mutually saturated solvent systems, allows direct calculation of the enthalpies of transfer from water to anhydrous octanol or from octanol-saturated water to water-saturated octanol. By combining such enthalpy of solution data with the data for free energy of solution as determined by solubility measurements, we can calculate the entropy values for the solution and transfer processes.

MATERIALS AND METHODS

Pure deionized water (specific conductance 10⁻⁶ mho) and BDH specially pure *n*-octanol (stored over molecular sieve, size 3A) were used throughout. The preparation and purity determination of the monoalkyl ethers have been described previously (Beezer et al 1980).

To effect saturation of each phase with the opposite phase, a small volume of the saturating phase was carefully shaken with the major phase and the whole left to stand for 2 days to ensure phase separation. In practice, centrifugation of the saturated solutions (2000 rev min⁻¹ for 20 min) was not required, the solutions being totally free from suspended droplets of the opposite phase after standing. Enthalpy measurements were made in an LKB Batch microcalorimeter (Type 10700-1, LKB

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Produkter AB, Bromma, Sweden) suitably modified to permit sequential addition of titrant to titrand without disturbance of the calorimeter. In operation it was possible to make ca 15 separate additions of solute for each loading of the calorimetric system. The design and testing of the titration assembly together with detailed operating procedures have been described (Beezer et al 1982).

Enthalpies of solution at infinite dilution were calculated for each solute by extrapolation of the measured enthalpy values, for titration of the solute into each solvent system, to infinite dilution (Table 1).

Table 1. Enthalpies of solution (kJ mol⁻¹) at 303K.

Phenol	Solvent			
	Water	<i>n</i> -Octanol-satd water	<i>n</i> -Octanol	Water-satd <i>n</i> -octanol
<i>m</i> -Methoxy	5.77 ± 0.18	5.51 ± 0.13	-3.24 ± 0.10	-2.52 ± 0.06
<i>m</i> -Ethoxy	5.48 ± 0.08	5.25 ± 0.11	-2.67 ± 0.04	-1.70 ± 0.04
<i>m</i> -Propoxy	5.38 ± 0.10	4.99 ± 0.12	-3.05 ± 0.06	-1.97 ± 0.02
<i>m</i> -Butoxy	5.26 ± 0.01	(4.73)	-3.56 ± 0.10	-2.56 ± 0.08
<i>m</i> -Pentoxy			-4.28 ± 0.12	-2.97 ± 0.10
<i>m</i> -Hexoxy			-4.66 ± 0.14	-3.26 ± 0.12
<i>m</i> -Heptoxy			-4.02 ± 0.12	-3.42 ± 0.08
<i>m</i> -Octoxy			-3.40 ± 0.10	-2.99 ± 0.08
<i>m</i> -Nonoxy			-3.30 ± 0.16	-2.79 ± 0.20

() predicted.

The enthalpies of solution in *n*-octanol and in water-saturated *n*-octanol were determined for all the phenols, *m*-methoxy to *m*-nonyx. Enthalpies of solution in water, however, could only be determined up to the *m*-butoxy phenol and in *n*-octanol-saturated water up to the *m*-propoxy compound because of the very low aqueous solubility of the higher homologues. The low solubilities at 303 K of *m*-methoxy to *m*-pentyx phenols in water and in *n*-octanol-saturated water (Table 2) led to very slow dissolution rates and hence heat evolution was slow.

Table 2. Solubilities of *m*-alkoxyphenols in aqueous systems (mm).

Phenol	Water	<i>n</i> -Octanol-satd water
<i>m</i> -Methoxy	311.0	241.6
<i>m</i> -Ethoxy	100.3	80.78
<i>m</i> -Propoxy	25.9	18.65
<i>m</i> -Butoxy	8.24	5.42
<i>m</i> -Pentoxy	2.13	1.23

Solubilities were measured by introducing, by a 'titration' method, a very slight excess of the phenol into water and into *n*-octanol-saturated water. After about 2 days equilibration at 298 K the solute

concentrations were determined spectrophotometrically (Beezer et al 1980). Solubility limitations precluded microcalorimetric measurement of ΔH_s° for members of the series beyond *m*-propoxy in *n*-octanol-saturated water.

RESULTS AND DISCUSSION

Pure solvent systems

Abrahams (1979, 1980, 1981, 1982) has discussed the thermodynamic parameters for solution in water of rare gases, alkanes and gaseous non-polar electrolytes. The existence of a hydrophobic effect has been established and, to some extent, an interpretation of the effect given.

There remains however, a difficulty in discussion of previously published transfer thermodynamic data and of the data published here. Abrahams correctly identifies the appropriate standard for solution processes as that referring to the process.

$$\begin{aligned} & \text{solute (ideal gas, 1 atm)} \rightarrow \\ & \text{solute (ideal solution, unit mole fraction)} \end{aligned}$$

For most solutes of interest in QSAR investigations, and indeed generally, the appropriate data are not available. For the calorimetrically determined enthalpies of solution, therefore, we chose to refer to the infinitely dilute solutions as the standard state. We recognize that this choice determines the actual values of the entropy terms calculated but, like Abrahams (1979 et seq) in similar circumstances, we use these values only to make comparisons between members of the series. De Lisi et al (1980) have stressed that the partition coefficient of a non-ionic solute distributed between two immiscible phases is defined for the conditions in which the solute obeys Henry's Law in both solvents; these conditions apply, we consider, to the data presented here.

Water

The enthalpies of solution in water for this series of *m*-alkoxy phenols are all endothermic (Table 1) and analysis of these results in a stepwise solution process commences with the introduction of the solute into water which results, initially, in the breakdown of the hydrogen bonds, van der Waals' and other forces between the solute molecules. Then follows cavity formation where the hydrogen bonded framework of the solvent water is destroyed and new solute-water hydrogen bonds are formed. The size of the cavity required to accommodate the solute dictates the degree of disruption of the water structure and hence exerts a profound influence upon the sign and magnitude of the observed enthalpy of solution. To

form a large cavity within the water structure sufficient to accommodate a large alkoxy phenol molecule requires the disruption of a large number of water hydrogen bonds whose number must, apparently, exceed those that are reformed since the enthalpies of solution are positive.

The negative entropy changes shown in Table 3 suggest that, after disruption of the water structure, the water molecules rearrange in a highly ordered fashion around each solute molecule cavity and in such orientations that restrict the reformation of significant water-water hydrogen bonds. Furthermore, since any water-solute hydrogen bonds are likely to be principally of the C-H . . . O type, the strengths of which are less than those of the O-H . . . H type (Pimental & McClellan 1960), they will not contribute so greatly to the observed enthalpy of solution.

Table 3. Thermodynamic parameters from solution in water (A) or n-octanol-saturated water (B) at 303 K.

Phenol	ΔG (kJ mol ⁻¹) ^a	$\Delta(\Delta G)$ (kJ mol ⁻¹)	ΔH (kJ mol ⁻¹) ^b	ΔS (J mol ⁻¹ K ⁻¹)
A				
<i>m</i> -Methoxy	13.08	2.85	5.77	-24.11
<i>m</i> -Ethoxy	15.93	3.40	5.48	-34.47
<i>m</i> -Propoxy	19.33	2.89	5.38	-46.02
<i>m</i> -Butoxy	22.22	3.41	5.26	-55.94
<i>m</i> -Pentoxo	25.63		(5.17)	-67.49
B				
<i>m</i> -Methoxy	13.72	2.75	5.51	-27.08
<i>m</i> -Ethoxy	16.47	3.69	5.25	-37.01
<i>m</i> -Propoxy	20.16	3.12	4.99	-50.04
<i>m</i> -Butoxy	23.28	3.74	(4.73)	-61.19
<i>m</i> -Pentoxo	27.02		(4.47)	-74.38

() predicted values.

(a) Calculated from $\Delta G^\circ = -RT \ln X_s$, where X_s is the saturation solubility expressed in mole fraction units (Tanford 1980).

(b) From Table 1.

The enthalpies of solution become less endothermic (Table 1) with increase in the alkyl chain length perhaps because more possibilities for hydrogen bonding with water are presented by the increase in chain length to offset the breakdown of solvent water hydrogen bonds. Such an explanation would also require that increased solute-water hydrogen bonding would lead to greater solubility, a conclusion which is counter to observation. More probably, the order within the system is greatly increased by each additional methylene group (ΔS rapidly becomes more negative as chain length increases, Table 3) because of the increased possibility for reformation

of a large number of solvent water hydrogen bonds. It is, of course, possible that these bonds extend into the bulk water phase.

As is found for many homologous series (Krishnan & Friedman 1976) there is good linear correlation between the enthalpies of solution in water and alkyl chain length for the ethoxy to butoxy phenols, methoxy phenol having a marginally too positive value.

The calorimetrically determined enthalpies of solution in water decrease by ca 0.1 kJ mol⁻¹ per methylene group between ethoxy and butoxy phenol (Table 3). This corresponds approximately to the value of 0.3 kJ mol⁻¹ reported by Gill & Wadso (1976) for the series toluene to propylbenzene but conflicts with the results of Bohon & Claussen (1951) who found the enthalpy of solution of ethylbenzene (as calculated from the temperature dependence of solubility) to be lower than that of toluene.

Table 3 shows that the Gibbs Energies of solution are positive and increase with increase in the alkyl chain length, reflecting the decrease in solubility as molecular weight increases. An admittedly empirical relationship between the Gibbs Energy of solution, at 298 K (ΔG_{298}°), the hydrophobic Gibbs Energy change and the number of hydrogen atoms in the molecule (nH) has been derived by Gill & Wadso (1976) for normal alkanes and alkenes, viz:

$$\Delta G_{298}^\circ = 6.4 + 1.85nH$$

At 303 K the data reported here for the *m*-alkoxy phenols yield a similar relationship.

$$\Delta G_{303}^\circ = 0.4 + 1.57 nH$$

The lower intercept value arises here because of the greater solubility of the *m*-alkoxy phenols than that of the *n*-alkanes and *n*-alkenes; the higher temperature probably also contributes to the difference. Similar values were obtained for the gradient in the series toluene to propylbenzene (1.59) and for the simple primary alcohols (1.64) (Gill & Wadso 1976). For these homologous series of compounds therefore the changes in the Gibbs Energies of solution in water on ascending each series are approximately equally dependent on the number of hydrogen atoms in the molecule. Interpreting this in terms of a methylene group contribution to the Gibbs Energy of solution (the two hydrogen atoms constituting a methylene group and assuming $\Delta(\Delta G)$ to be constant over the temperature range 298–303 K) yields a value of 3.33 ± 0.38 kJ mol⁻¹ per methylene group. In the light of Abrahams results this empirical dependence upon nH is perhaps too simple.

The data on the Gibbs Energy of solution in water

of the *n*-alkanes and primary alcohols (Gill & Wadso 1976) yield a value of -14.55 ± 0.91 kJ mol⁻¹ for the contribution of a hydroxyl group whilst the Gibbs Energy of solution of benzene in water is 19.33 ± 0.05 kJ mol⁻¹ as calculated from solubility data.

These group contributions, therefore, allow for example the Gibbs Energy of solution of xylene in water to be calculated, i.e. $(19.33 \pm 0.06) + 2(3.33 \pm 0.38)$ as 25.99 ± 0.82 kJ mol⁻¹. Solubility data (McAuliffe 1963) show that *m*- and *p*-xylene have Gibbs Energies of solution of 25.56 and 25.61 kJ mol⁻¹ respectively, in good agreement with the calculated value. That for *o*-xylene is determined to be 27.44 ± 1.15 kJ mol⁻¹ from solubility data and thus suggests that steric interactions between the two methyl groups occur in this compound. Similarly for 1,2,4-trimethylbenzene the calculated value from solubility data (McAuliffe 1963) is 30.39 ± 1.6 kJ mol⁻¹ whilst that based on the present work is 29.32 ± 1.14 kJ mol⁻¹.

From the experimental data reported here a group contribution value for the *m*-methoxy group may be found by considering the Gibbs Energies of solution of phenol and *m*-methoxy phenol, 4.78 kJ mol⁻¹ (from group contribution values) and 13.08 kJ mol⁻¹ (from solubility data, Table 3) respectively, the contribution for a *m*-methoxy group is, therefore, 8.3 kJ mol⁻¹. This value has not however been 'tested' in any calculations of Gibbs Energies and subsequent comparison with experimental values. The derived group contribution terms are shown in Table 4.

Table 4. Group contribution parameters to Gibbs Energy of solution in water.

Group	Contribution (kJ mol ⁻¹)
-CH ₂	3.33 ± 0.38
-OH	-14.55 ± 0.9
C ₆ H ₅	19.33 ± 0.06
<i>m</i> -OCH ₃	8.3

For most sparingly water-soluble solutes the entropy term is the main determinant of the value of the Gibbs Energy of solution (Table 3). Furthermore, it has been noted previously (Franks & Reid 1973) that enthalpies of solution change only marginally upon ascending an homologues series whereas the entropies of solution change quite markedly and therefore compensate for any small irregularities in the enthalpy term. McAuliffe (1963) has calculated that the entropy of solution should decrease by about

5.8 kJ mol⁻¹ for each incremental H-atom (adopting the tetrahedral structure model for water, Tanford 1980). At 298 K this would account for a contribution of 3.45 kJ mol⁻¹ per methylene group to the Gibbs Energy of solution, a value close to the derived contribution (3.33) per methylene group. These results support Gill & Wadso's (1976) model for the interaction of water with hydrocarbon solutes, namely that the hydrogen atoms are primarily responsible for the decrease in entropy of solution as chain length increases.

An entropy-enthalpy plot for the series ethoxy to pentoxyphenol yields a straight line with a compensation temperature of 105 K, unusually low for a small molecule solute (Lumry & Rajender 1970). The value is, however, much closer to the value determined for *transfer* of the same phenols from water to *n*-octanol (Beezer et al 1980) and suggests that partitioning of these compounds from water to *n*-octanol is controlled mainly by interactions occurring in the aqueous phase.

n-Octanol

The enthalpies of solution for the alkoxy phenols in *n*-octanol are all exothermic (Table 1). As in the case of water as solvent, introduction of solute molecules into *n*-octanol initially results in cavity formation and subsequent favourable solute-solvent bonding occurs which more than compensates for the enthalpy required to break solute-solute bonding forces. For the heptyl and higher derivatives the enthalpy of solution becomes progressively less exothermic. It would appear, therefore, that once the molecular dimensions of the solute exceed some critical size then there is greater disruption of the *n*-octanol structure i.e. that a discontinuity exists. A butoxyphenol molecule should occupy a similar volume to an *n*-octanol molecule ($\sim 190 \times 10^{-30}$ m³ for butoxyphenol calculated from: benzene ring, 80×10^{-30} m³; hydroxyl group, 22×10^{-30} m³; methylene group 20.9×10^{-30} m³; ether oxygen, 15×10^{-30} m³; methyl group 22.5×10^{-30} m³, Cramer 1977). Table 1 shows that the enthalpy of solution in *n*-octanol of the hexoxy derivative is slightly lower than that anticipated by reference to enthalpy changes for the lower members of the series. This suggests a slight increase in the degree of disruption of the *n*-octanol structure as the solute molecular size increases beyond that of *n*-octanol.

Unfortunately there are no data available which allow calculation of the Gibbs Energies of solution for this series of compounds in *n*-octanol. However if the abrupt change in enthalpy of solution noted here

were reflected in the Gibbs Energies then discontinuities may be manifest in other physical and chemical properties. The antibacterial potencies (Beezer et al 1981) of these compounds increase in a linear fashion up to the hexyl derivative, the heptyl and octyl derivatives have a somewhat lower potency than would be projected from the behaviour of the lower homologues. There are no experimentally determined partition coefficients for these higher members (Beezer et al 1980), only calculated values (Lien et al 1968) which have been calculated assuming no discontinuity.

The partition coefficients for *m*-methoxy to *m*-pentoxy phenols (partitioned between the mutually saturated solvents) have been shown (Beezer et al 1980) to alternate in increments of 0.42 and 0.61 log units corresponding to increments in the Gibbs Energy of transfer of 2.5 and 3.4 kJ mol⁻¹ per methylene group. The Gibbs Energies for solution in water and in *n*-octanol-saturated water also exhibit a similar alternation through the series (Table 3). The main determinant of the partition coefficients for these compounds therefore is their solubility in water (and in *n*-octanol-saturated water). We conclude, therefore, that any lipid-like solvent which displays, as apparently does *n*-octanol, 'invariant' interactions with a series of solute molecules may be used as the lipid-like phase for partitioning. Krishnan & Friedman (1969) for this reason have recommended the use of propylene carbonate as the non-aqueous phase to investigate solvent structuring and group contributions in the thermodynamics of transfer of simple primary alcohols.

The enthalpies for the true thermodynamic transfer process (pure water to pure *n*-octanol, referred to the infinitely dilute solutions) do not vary linearly with alkyl chain length (Table 5) but remain approximately constant for the ethyl to butyl derivatives. However, as there are no ΔG data available for solution in *n*-octanol it is not possible to develop any group contribution concept that refers to transfer processes between the pure solvent systems. Such a transfer process involves binary systems whereas the real, i.e. observable, process is described by ternary systems of mutually saturated solvents and solute. Thus transfer between the mutually saturated solvent systems may, in addition to solute transfer, involve solvent transfer. The extent of solute desolvation upon transfer will clearly affect the derived Gibbs Energies for the transfer process. This superimposed complexity is a major objection to the continued use of *n*-octanol-water systems in partitioning studies. The use of a solvent totally immisc-

ible with water to represent the 'oily' phase is preferable but such solvents have not been so widely used as has *n*-octanol, in QSAR studies; there are therefore few data for comparison. The matter is still open to investigation but no definite choice of an appropriate solvent can be made until the solution thermodynamics of such systems are known in much greater detail than they are at present (James et al 1981).

Table 5. Enthalpies of transfer (kJ mol⁻¹) at 303 K.

Phenol	From water to <i>n</i> -octanol	From <i>n</i> -octanol-satd water to water-satd <i>n</i> -octanol	From variation of K_D with T^a
<i>m</i> -Methoxy	-9.01 ± 0.28	-8.03 ± 0.19	-7.9 ± 0.6
<i>m</i> -Ethoxy	-8.15 ± 0.12	-6.95 ± 0.15	-7.2 ± 0.8
<i>m</i> -Propoxy	-8.43 ± 0.16	-6.96 ± 0.14	-5.9 ± 1.4
<i>m</i> -Butoxy	-8.82 ± 0.14	(-7.18 ± 0.08)	-5.2 ± 1.0
<i>m</i> -Pentoxy	—	—	-5.1 ± 0.8

() predicted value.

(a) From Beezer et al (1980).

The mutually saturated solvent systems

Upon saturation of water with *n*-octanol, cavities are formed in the water structure to accommodate the *n*-octanol molecules. The Gibbs Energy of solution of *n*-octanol is calculated as 23.75 kJ mol⁻¹ at 303 K from solubility data (4.5 mM is the saturating concentration of *n*-octanol in water at this temperature, Hertz 1968). It is reasonable to assume that the enthalpy of solution of *n*-octanol in water is rather similar to that of *m*-butoxyphenol (Table 1) since (i) the Gibbs Energies of solution are similar, (ii) the molecular features are comparable, each has a large hydrophobic moiety attached to a small hydroxyl hydrophilic moiety, (iii) the molecular dimensions are comparable. Thus, we suggest, the large positive Gibbs Energy of solution of *n*-octanol in water is primarily the result of a large unfavourable entropy term. As argued for the *m*-alkoxy phenols in water this results from the disruption of solvent water structures and the formation of weaker solute-solvent hydrogen bonds and the possible re-formation of solvent hydrogen bonds due to the orientations of the water molecules around the solute molecule in a cavity. The water-*n*-octanol system is therefore fairly complex and is pictured as being composed of 'icebergs' of structured water surrounding cavities containing the *n*-octanol molecules. Interpretation of the thermodynamic consequences of introducing a further solute into this already complex system is, not surprisingly, difficult.

The enthalpies of solution of the *m*-alkoxy phenols in *n*-octanol-saturated water are all endothermic but

smaller than the values recorded for solution in pure water (Table 1). Two possible explanations are (i) that fewer water-water hydrogen bonds are disrupted in cavity formation and (ii) that more hydrogen bonds are re-formed following cavity formation. The larger entropies of solution in *n*-octanol-saturated water compared with solution in water indicate greater ordering of water molecules (Table 3) and therefore lend some weight to the latter explanation (we include here, as introduced earlier, hydrogen bond extension beyond 'nearest neighbour' water molecules).

There exists a linear relationship between the enthalpies of solution in *n*-octanol-saturated water and alkyl chain length for those compounds whose solubilities permitted microcalorimetric measurements.

As with pure water as solvent the Gibbs Energies of solution in *n*-octanol-saturated water are positive and increase with increase in alkyl chain length.

Table 2 shows that the solubilities of the *m*-alkoxy phenols in *n*-octanol-saturated water are lower than those in pure water hence it is the entropy terms which are largely responsible for the large, positive Gibbs Energies of solution. As noted previously the low solubility of all phenols beyond *m*-propoxy phenol in *n*-octanol-saturated water prevented microcalorimetric determination of $\Delta H_{\text{sol}}^{\circ}$ for these compounds; in pure water however the greater solubility permitted $\Delta H_{\text{sol}}^{\circ}$ measurements up to *m*-butoxy phenol. The lowered solubility in *n*-octanol-saturated water (0.005 M octanol) appears consistent throughout the series and consistent, too, with the solution behaviour expected of mixtures of sparingly soluble solutes; in this respect *n*-octanol at a concentration of 0.0045 M is perhaps not acting as a co-solvent but is more properly regarded as an additional solute. As argued above, *n*-octanol molecules in water result in high degrees of order in the system and the introduction of a further solute species presumably requires even greater order to be imposed to achieve cavity formation and solute accommodation. An enthalpy-entropy plot for solution in *n*-octanol-saturated water is linear for *m*-methoxy to *m*-pentoxy and permits the calculation of a compensation temperature of 44K. This value is considerably lower than that found from solution data for pure water as solvent and results from the more rapid decline in the enthalpy of solution in the *n*-octanol-saturated water system.

The enthalpies of solution in water-saturated *n*-octanol are exothermic (Table 1) increase in exothermicity with increase in alkyl chain length but

are, overall, marginally less exothermic than those in pure *n*-octanol (Table 1). The trend changes here at the octyl derivative and not with the heptyl derivative as was found for solution in pure *n*-octanol. It has been proposed (Smith et al 1975) that in the water-*n*-octanol system (mole fraction of water at saturation, 0.268) there exist tetrahedra composed of both types of molecule and that introduction of another solute species displaces *n*-octanol from these tetrahedra. When the solute molecular dimensions exceed those of *n*-octanol we should therefore expect greater disruption of the hydrogen bonded network. The presence of water in *n*-octanol may also permit the cavity size itself to increase; an increase by one water molecule would be enough to accommodate the heptyl rather than the hexyl compound without a serious increase in disruption. The entropies of solution in water-saturated *n*-octanol (Table 6) are negative, do not vary greatly with alkyl chain length and, except for *m*-methoxyphenol, are all lower than the corresponding values for solution in aqueous systems (Table 3). Thus, relative to the aqueous systems, there appears to be an increase in the extent of hydrogen bonding, a conclusion reflected in the small but negative enthalpies of solution. Unquestionably H-bonding is not the only factor contributing to the thermodynamics of the transfer process. Other forces, more difficult to evaluate (e.g. dispersion), will no doubt contribute to the effects discussed.

Table 6. Thermodynamic parameters for solution in water-saturated *n*-octanol at 303 K.

Phenol	$\Delta G_{\text{tr}}^{\circ}$ (kJ mol ⁻¹) ^a	$\Delta G_{\text{sw}}^{\circ}$ (kJ mol ⁻¹) ^b	$\Delta H_{\text{sol}}^{\circ}$ (kJ mol ⁻¹) ^c	$\Delta S_{\text{sol}}^{\circ}$ (J mol ⁻¹ K ⁻¹)
<i>m</i> -Methoxy	-9.43	+4.23	-2.52	-22.27
<i>m</i> -Ethoxy	-11.83	+4.64	-1.70	-20.91
<i>m</i> -Propoxy	-15.40	+4.76	-1.97	-22.20
<i>m</i> -Butoxy	-17.98	+5.30	-2.45	-25.56
<i>m</i> -Pentoxy	-21.46	+5.56	-2.97	-28.14

(a) Gibbs Energy of transfer from water to *n*-octanol derived from partition coefficient values (Beezer et al 1980).

(b) Gibbs Energy of solution in water-saturated *n*-octanol calculated from

$\Delta G_{\text{tr}}^{\circ} = \Delta G_{\text{sw}}^{\circ} - \Delta G_{\text{w}}^{\circ}$
where $\Delta G_{\text{sw}}^{\circ}$ is the Gibbs Energy of solution in *n*-octanol-saturated water as calculated from the solubility data in Table 2.

(c) From Table 1.

The Gibbs Energies of solution in water-saturated *n*-octanol do not vary greatly with alkyl chain length (Table 6) but are smaller than those recorded for solution in aqueous systems.

The microcalorimetrically determined enthalpies for solute transfer from *n*-octanol-saturated water to water-saturated *n*-octanol, shown in Table 5, show

modest agreement with enthalpy data derived from the dependence of the partition coefficient upon temperature only for the methyl and ethyl derivatives (Beezer et al 1980). Moreover they appear to approach a constant value from the butyl derivative onwards. These calorimetric results emphasize the caution expressed earlier (Beezer et al 1980) about overmuch reliance upon van't Hoff enthalpy data. Transfer from n-octanol-saturated water to water-saturated n-octanol is favoured both enthalpically (Table 5) and entropically (Table 7) and, since the enthalpies of transfer remain fairly constant, the process is increasingly entropically controlled as the homologous series is ascended. Examination of the data for solution in each of the mutually saturated systems shows that (i) solution in n-octanol-saturated water is unfavourable on both enthalpic and entropic criteria—but principally entropic, (ii) solution in water-saturated n-octanol is slightly favoured by the enthalpy term but the resultant positive Gibbs Energy is determined by the large unfavourable entropy terms. Transfer thus is driven largely by the unfavourable interactions occurring in the aqueous phase. The theories described by Frank & Evans (1945), Nemethy & Scheraga (1962a,b), Kozak et al (1968), Tenne & Ben-Naim (1976), Tanford (1980), account for the transfer to the lipid-like phase in terms of the energetics of the disruption of highly ordered water structures around non-polar solutes. Attention is thereby focussed primarily on the role of water in the transfer process. There has been criticism of these theories by Hildebrand (1968) and Holtzer & Emerson (1969). The data reported here do however seem to support a dominant role for water in the transfer process.

Table 7. Entropies of transfer ($\text{J mol}^{-1} \text{K}^{-1}$) at 303 K.^a

Phenol	From n-octanol-satd	From varn. of
	water to water-satd n-octanol	
<i>m</i> -Methoxy	+4.62	+5.05
<i>m</i> -Ethoxy	+16.10	+15.27
<i>m</i> -Propoxy	+27.84	+31.34
<i>m</i> -Butoxy	—	+42.16
<i>m</i> -Pentoxy	—	+53.97

(a) Calculated from $\Delta G_{\text{tr}}^{\circ} = \Delta H_{\text{tr}}^{\circ} - T\Delta S_{\text{tr}}^{\circ}$. Gibbs Energy of transfer values ($\Delta G_{\text{tr}}^{\circ}$) derived from partition coefficient values at 303 K (Beezer et al 1980) and enthalpy of transfer values shown in Table 5.

'Hydrophobic' theories have also gained support from, for example, correlations between the Gibbs Energy of partitioning and molecular volume or area as described by Leo et al (1976), Tanford (1980) and others (Hermann 1972; Moriguchi 1975; Amidon &

Anick 1976). It is interesting to note that the Gibbs Energy of transfer $\sim 3 \pm 0.5 \text{ kJ mol}^{-1}$ for each incremental methylene group, is very close to the value (3.3 kJ mol^{-1}) for the Gibbs Energy of solution of a methylene group in n-octanol-saturated water.

In conformity with the expectations of a hydrophobic theory which ascribes the dominant role to bulk dependent repulsions between water and solute the data shown in Tables 3 and 6 when plotted against molecular bulk do yield the appropriate straight lines.

As is apparent from the approximately constant values for the enthalpies of transfer in the mutually saturated solvents there is no useful linear relationship between this parameter and biological activity. Insufficient data are available to examine the relationship for the pure solvent transfer process. The results reported here do, however, underline the need to examine carefully the thermodynamic reasons for the existence of apparent linear Gibbs Energy relationships particularly under the appropriate environmental control (temperature, solvent system etc). There is, seemingly, increasing support for these views (James et al 1981; Riebesehl & Tomlinson 1981; Dearden & Bresnen 1981). Indeed preliminary thermodynamic results on partitioning in model biological membranes will, it is claimed (James et al 1981) reveal more about lipoidal biological phases. The data reported here also suggest that, on thermodynamic grounds, n-octanol is not a satisfactory solvent to mimic a biological lipoidal phase.

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