

Thermodynamics of liquid/liquid distribution

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Abstract - The thermodynamics of aliphatic and aromatic solute distribution between various polar and nonpolar liquid phases have been determined using a novel flow microcalorimetry approach for the enthalpy term, and conventional shake-flask procedures for the free-energy term. Data have been examined using enthalpy/entropy compensation analysis, and the origin of the thermodynamics found has been studied by examination of the corresponding enthalpies and free energies of solute solvation.

INTRODUCTION

The distribution of solutes between water and organic solvents has been the subject of numerous studies in many scientific disciplines. Since the finding of a simple relation between relative narcotic activities of drugs and their oil/water liquid/liquid distribution coefficients (refs. 1,2), extensive work has been carried out on similar correlations between drug activity and lipophilicity properties (refs. 3,4). In environmental chemistry it has been recognized that the liposolubility of (mostly) nondegradable pollutants correlates well with their biological accumulation (refs. 5,6). Also, general extraction chemistry relies to a large extent on knowledge of the distribution coefficient of solutes. These interests in liquid/liquid distribution have given considerable impetus to studies on the extent and nature of solute distribution between water and immiscible organic phases (ref. 7). In addition, the observation that the solution properties of compounds are comprised of functional group contributions (refs. 8,9) has led to various group-contribution models being developed for the free energy term of distribution processes (refs. 7,10). In contrast, there exist no systematic studies of the complete thermodynamics of solute distribution which would permit group-contribution models for the enthalpic and/or entropic terms. However, the importance of the enthalpy of liquid/liquid distribution is evident (ref. 11). Since the suggestion that the thermodynamics of liquid/liquid distribution could be determined from (literature) heats of solution and heats of vaporization (ref. 12), few published studies have examined this possibility (refs. 13-16). However, a number of workers have reported heats of solute-transfer values estimated by the van't Hoff equation using activity data obtained from the temperature dependency of, for example, solubility (ref. 17), distribution equilibria (ref. 18), and vapor/liquid equilibria (ref. 19). Unfortunately, these approaches give rise to large discrepancies between calculated enthalpies of transfer. (For example, for phenol, values in the range -15 to +21 kJ.mol⁻¹ have been reported). In addition, there exist a few cases where calorimetric measurements have been performed using either a dissolution step (refs. 13,15,20,21) or an extraction step (refs. 22-25). Recently, it has been shown that caution must be exercised in interpretation of these calorimetric heats of transfer (ref. 26).

Since 1979 we have been attempting to systematically study the thermodynamics and extrathermodynamics of small organic molecule distribution between aqueous solution and a variety of organic solvents affording different extents and types of solute solvation, with the aim of gaining insight into the driving forces for the distribution process (refs. 11, 26-33). This paper describes the thermodynamics of liquid/liquid distribution of both aliphatic and aromatic solutes between variously: water and 2,2,4-trimethylpentane, *n*-octane, chloroform and octan-1-ol, and examines also derived values for transfer between various non-aqueous solvents.

THEORY

The transfer of solute *i* from phase *a* to phase *b* may be expressed by Eqn. 1 (developed using the convention proposed by Krishnan and Friedman (ref. 34)).

$$X_{i(B+A)} = A_{i,B}^O - X_{i,A}^O \quad (1)$$

where $X_{i,A}^{\circ}$ and $X_{i,B}^{\circ}$ are the partial molar quantities (H, G, S,) of solute *i* in its standard state in phase A and B, respectively. In the present work standard states refer to one mole per litre both in the hypothetical ideal gas phase and in the hypothetical ideal solution. Thus the process of solution of *i* is considered as the transfer from its gaseous state into solution, which is identical with the solvation process.

Similarly, the heat of transfer of solute *i* between two solvents A and B may be given as:

$$\text{or } \Delta_t H_{i,(B+A)} = \Delta_{\text{sol}} H_{i,B} - \Delta_{\text{sol}} H_{i,A} \quad (2)$$

$$\Delta_t H_{i,(B+A)} = \Delta_{\text{solv}} H_{i,B} - \Delta_{\text{solv}} H_{i,A} \quad (3)$$

Conversely, the thermodynamics of solvation in one phase may be calculated from a knowledge of the thermodynamics of transfer and of solvation in the second phase.

EXPERIMENTAL

Enthalpy changes for the distribution of small aliphatic alcohols and ketones and mono- and disubstituted benzenes between two immiscible solvents are generally obtained from determination of the temperature dependence of the liquid-liquid distribution coefficient. For solvent pairs with high mutual solubilities such studies can be criticised (ref. 27) on the basis of changes in standard state with temperature. Some recent attention has been given to calorimetric methods for the determination of enthalpies of transfer. There appear to be three approaches given in the literature. First, Breslauer *et al.* (ref. 22) have reported on the determination of enthalpies of transfer of ionisable solutes from oil to water using simultaneous extraction and ionisation to ensure complete extraction within a flow microcalorimeter. This method requires (a) complete reaction, (b) corrections for heats of formation of water and (c) that solutes possess a site for facile protonation or deprotonation. A second approach is due to Goffredi and coworkers (refs. 24,25) who have proposed a batch-calorimetric method based on measurement of the heat change obtained following prolonged contact of immiscible phases both containing varying initial amounts of solute. The method appears laborious and requires (a) solute distribution to be complete within the time of the measurement, (b) reasonable solute solubility in both phases and (c) (particularly for solvent pairs with significant mutual saturation) knowledge of the densities of both mutually saturated cosolvents. A third calorimetric technique is to estimate the difference between heats of solute solution in both oil and water (refs. 34,35). This is again tedious and suffers from the disadvantage that this generally involves subtraction of large similar numbers. We have recently developed a novel flow-microcalorimetric procedure for determining the enthalpies of solute transfer between immiscible solvents (ref. 26). The procedure enables the concentration of solute in the phases to be measured immediately after extraction within a flow-mix cell, so that the observed heat change can be directly related to the amount of solute transferred. Consequently the problems described above for other calorimetric methods are obviated. In brief this approach involves the bringing together of two (pre-saturated) immiscible phases within a flow-microcalorimeter via a T-junction, which, together with the coiled nature of the flow-mix cell tubing employed, results in turbulent and segmented flow (ref. 36), during which the solute is distributed between the two immiscible phases. At the outlet of the cell a phase-splitting device is used to separate the phases, which are then analysed for solute content either spectrophotometrically or using gas chromatography. Fig. 1 is a flow diagram of the liquid/liquid distribution experiment carried out in the flow-microcalorimeter.

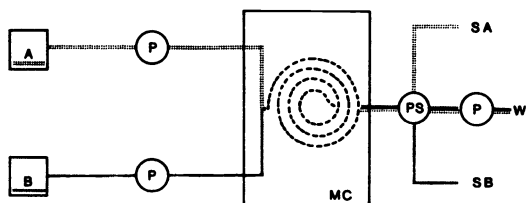


Fig. 1. Flow-microcalorimetry procedure, where A,B are thermostatted solutions; P = peristaltic pump; MC = micro-calorimeter with flow-mix cell; PS = phase splitter; SA,SB = samples of single phases A and B; W = mixed phases to waste

The method permits $\Delta_t H$ to be determined; the free-energy values are determined using a conventional shake-flask technique.

DISCUSSION

Water/non-polar solvents

Fig. 2 gives the relationship between enthalpies of transfer from 2,2,4-trimethylpentane to aqueous buffer using the microcalorimetric procedure described above, and values obtained from the literature (ref. 28). (The enthalpies of solute transfer from the literature have been obtained either directly or indirectly by calculation). Three methods have been used: (1) calorimetric determination of the integral heats of solutes in pure hydrocarbon solvent and pure water; (2) calorimetric measurements of the heat of extraction with either (a) continuous complete-flow extraction of ionizable solutes by either acid or alkaline solution (ref. 22), or (b) discontinuous liquid/liquid distribution in a rotating bath mix cell (ref. 23); and (3) indirect determination from the derivative of the distribution constant with temperature (van't Hoff isochore). The figure shows that less than half of the datum points fall within the 10% confidence limits of the theoretical line, with some large variations being found both between our values and literature values and also within literature values.

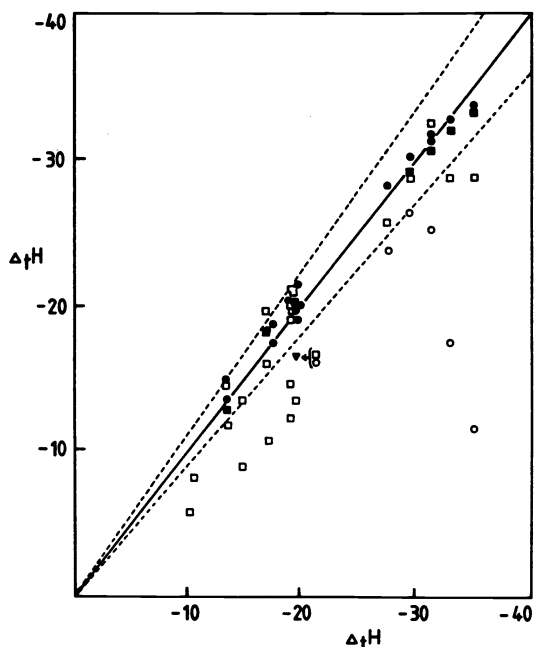


Fig. 2. Relationship between enthalpies of solute transfer between 2,2,4-trimethyl pentane and aqueous buffer (pH 7) determined in this study by a direct microcalorimetric method (abscissa) and those between alkanes and water either determined by other methods using either calorimetry (open circles and open triangles refer to values from refs. 23, 25 and 22, respectively) or van't Hoff plots (open squares) or calculated by us from literature values for enthalpies of solution according to eq 3-5 (closed circles). Values represented by closed squares are those determined by us for transfer between n-octane and aqueous buffer (pH 7). (ref. 28).

Apart from anisole, all enthalpies of transfer estimated from enthalpy of solution data agree within 10% of the experimental values of our study, with most being within 3%. Also, the majority of enthalpies of transfer derived from van't Hoff plots are between 5% and 40% more endothermic than values obtained by us, and in addition, the enthalpies of transfer obtained microcalorimetrically by others (refs. 22-25) are at considerable variance with both the values estimated from enthalpies of solution and our values. We have discussed previously (ref. 26) the possible inaccuracies associated with the determination of $\Delta_t H$ using calorimetric methods 2a (ref. 22) and 2b (refs. 23-25). The method due to Bresläuer (ref. 22) involves subtracting several large values from one another (i.e. heats of water formation, protonation and ionization). That due to the group of Goffredi could be due to incomplete equilibrium within their batch microcalorimeter. Further, alcohols and phenol have been shown to self-associate in nonaqueous solvents. Such studies have indicated that association below 10^{-2} mol.L⁻¹ is extremely small, and although this indicates that in the present study such effects are not significant, it is not possible to determine whether this has been a problem during the microcalorimetric studies of others.

The use of van't Hoff plots to obtain $\Delta_t H$ leads to values that are usually much smaller than those obtained by microcalorimetry. Use of these plots depends upon the heat capacity of transfer being negligible. Frequently, we have observed a curvature in literature van't Hoff plots, which seems to suggest that these conditions do not always hold. Although, for example, Franks and Reid have noted that the principal differences between calorimetric integral heats and van't Hoff differential heats (of solution) should disappear at infinite dilution, for two-phase systems where the mutual solubility of solvents is large or where there are molecular associations which are sensitive to temperature, it is to be expected that standard states will change with temperature (ref. 17). That heat capacity effects are not negligible for solute liquid/liquid distribution may be shown by an examination of heat

capacities of solutions at high dilution. Arnett, et al. (ref. 38) have reported large positive changes in heat capacities for a number of alcohols in water as derived from the partial molar heat capacity of the solutes at high dilution and the heat capacities of the pure (liquid) solutes, and indicated a large contribution of solvation to the heat capacity of solution. Since enthalpies of transfer are considered to represent the difference in solvation in two phases (Eqn. 3), it cannot be expected that the resulting values for $\Delta_t H$ will be constant if one (or both) of the $\Delta_{\text{sol}} H$ terms varies with temperature. Clearly for the solutes we have studied, distribution from hydrocarbon solvents to an aqueous pH 7 buffer is exothermic. This implies that solvation in water is more favoured than solvation in the hydrocarbon solvent. Thus, the most negative $\Delta_t H$ values have been found for short-chain alcohols, whereas benzene derivatives and more apolar solutes gave relatively smaller heat effects.

Our studies have proven that $\Delta_t H_{(b+a)}$, as defined in pure solvents a and b, is equal to the enthalpy of extraction determined with mutually saturated solvents like alkanes and water. It is not expected that this will be the case when solvent pairs having high mutual solubilities are studied (see later). Moreover, the low mutual solubilities of water and hydrocarbon (e.g. water in 2,2,4-trimethylpentane and vice versa at 298.15 K have mole fraction solubilities of 8.76×10^{-4} and 3.84×10^{-7} , respectively), suggest that at the low concentrations of solutes used any adjustments in these solubilities due to transferring solutes will be small. Indeed, for the benzene derivatives we have found (ref. 27) that only concentrations of cresol and p-chlorophenol greater than 10^{-2} mol.L⁻¹ significantly alter the solubility of water in 2,2,4-trimethylpentane. In addition, the work of Aveyard and Heselden (ref. 39) has shown that heats of solution will be little changed by the concentrations of buffer salts employed.

Group contribution effects on $\Delta_t H$. In common with other findings for solute solution, vaporisation and solvation, we have found linear relationships between the heats of transfer from aqueous to non-polar organic phase and alkyl chain carbon number (n_c) (ref. 28). Not all of the enthalpies of transfer for primary alcohols reported in the literature show such linearity (Fig. 3). These effects may be because of errors in measurement due to solute volatility (ref. 28).

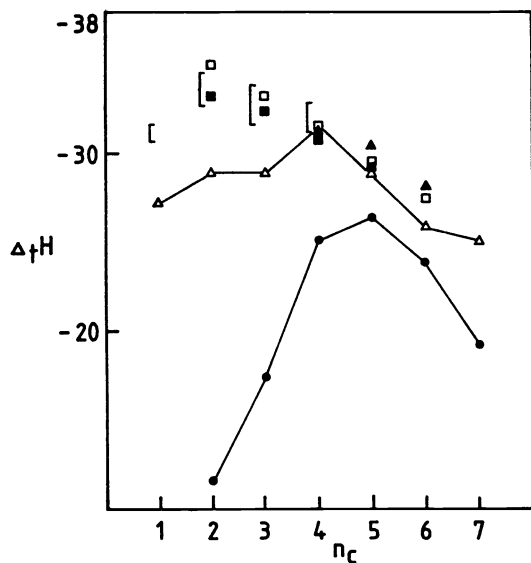


Fig. 3. Comparative relationship between the carbon number of the alkyl chain n_c , for primary alcohols, and the enthalpies of transfer, $\Delta_t H$ (kJ.mol⁻¹), estimated in this study for transfer from 2,2,4-trimethylpentane to aqueous buffer (pH 7) (open squares) and between n-octane and aqueous buffer (pH 7) (closed squares), estimated calorimetrically by others (closed circles), and estimated via van't Hoff plots for solute transfer from n-heptane to water (refs. 23-25) (open triangles). Parentheses (ref. 40) indicate the spread of $\Delta_t H$ values calculated from either $\Delta_{\text{sol}} H$ or $\Delta_{\text{sol}}^t H$ values for various hydrocarbons (ref. 17). Closed triangles refer to $\Delta_t H$ values calculated from reported $\Delta_{\text{sol}}^t H$ values for n-octane, and n-hexadecane.

Fig. 3 shows that there is a regular, though slight, influence of the nature of the hydrocarbon solvent on the determined enthalpies of transfer, with less exothermic values being obtained with hydrocarbons in the order n-hexane, n-heptane, 2,2,4-trimethylpentane, and n-octane being found. A similar trend can be found for the transfer of butanol between hydrocarbons and water using $\Delta_{\text{sol}}^t H$ values to calculate $\Delta_t H$ values (ref. 28). Also, the larger n_c the less this solvation effect becomes, such that at n_c equal to 6 the linear relationships between $\Delta_t H$ and n_c appear to be converging.

Arguments presented elsewhere (ref. 28) give that a simple, additive group contribution model for calculating enthalpies of solution between hydrocarbons and water is improbable, since group contribution values are highly dependent upon vicinal effects and (differing) solvation energies in both hydrocarbon and aqueous solvents.

Extrathermodynamics. Previously we have shown from independently determined free-energy of transfer values and enthalpies of transfer values that transfer from 2,2,4-trimethylpentane to water is exothermic (i.e. favourable for the process of hydration), and that although free-energies are either negative or positive, the entropic term is always negative, (ref. 29). To understand these effects we have applied an extrathermodynamic approach, (namely enthalpy/entropy compensation analysis) to both transfer and solution data. Extrathermodynamic analysis has often been applied to the study of solute transfer between oil and water. Tomlinson has described enthalpy/entropy compensation behavior during solute liquid/liquid distribution (ref. 11). It is now well recognised that to examine for enthalpy/entropy compensation, the extrathermodynamic analysis needs to be performed in the statistically correct plane of enthalpy versus free energy coordinates (with data obtained from the temperature coefficient of the free energy of the process being analysed at the harmonic means of the experimental temperatures). Fig. 5 is such a construct for solute transfer from 2,2,4-trimethylpentane to aqueous buffer (pH 7). It is seen that although an increasingly favored transfer is generally accompanied by an increasingly more negative enthalpy of transfer, linear enthalpy/entropy compensation can be described only for the homologous series of primary alcohols, alkyl ketones, and phenyl alcohols. Substituted benzenes exhibit a trend in their values which is different from that described for the aliphatic solutes. We have also determined the enthalpies of transfer of a limited series of substituted benzenes between 2,2,4-trimethylpentane and aqueous buffer (pH 7) using van't Hoff plots, which gave a good linear relationship between $\Delta_t H$ and $\Delta_t G$ (ref. 27). It is clear from Fig. 4 that examination of a larger series of diverse benzenes shows that there exists only an approximate linear relationship between the free energies and enthalpies of transfer and that, hence, as a class, substituted benzenes do not exhibit linear enthalpy/entropy compensation during their transfer between 2,2,4-trimethylpentane and water. Also, Fig. 4 shows that extending a solute alkyl chain has a much greater influence on the free energy of transfer than it does on the enthalpy term, indicating a strong entropic contribution to the extent of alkyl-substituted solute liquid/liquid distribution.

As the enthalpies and free energies of transfer have been determined independently, there is some justification for examining the entropies of transfer. Thus, entropy changes for solutes bearing an alkyl chain are greater than those for benzene derivatives of similar size (-50 to $-105 \text{ J.mol}^{-1}.\text{K}^{-1}$ compared to -34 to $-57 \text{ J.mol}^{-1}.\text{K}^{-1}$). Interestingly, whereas for alkyl-substituted solutes there exist linear relationships between V and $\Delta_t S$ no such relationship can be demonstrated for the other solutes, although a priori one might consider molar volume to be related to solvation of the solute in both phases. In addition, we have shown that for aliphatic solutes there is an almost constant contribution of the methylene group to $\Delta_t S$, with the different alkyl-substituted solute series having relationships with similar slopes and intercept values reflecting the differing (polar) head groups of the series (ref. 29).

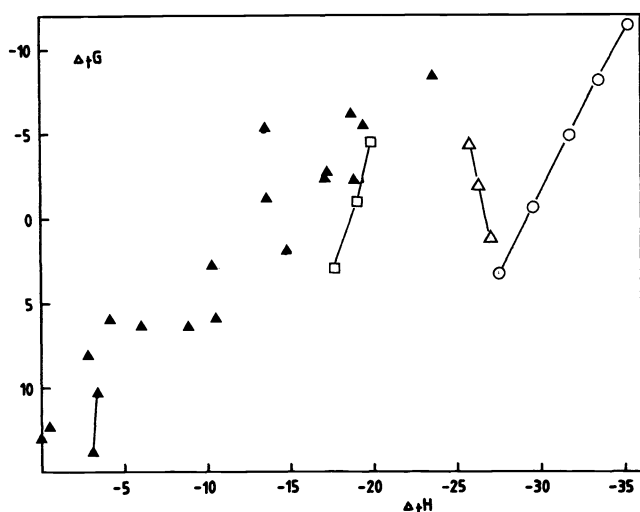


Fig. 4. Relationship between measured enthalpies and free energies of solute transfer between 2,2,4-trimethylpentane and aqueous buffer (pH 7) at 298.15 K. Units are all kJ.mol^{-1} . Open circles and squares are primary aliphatic alcohols and aliphatic ketones, respectively. Triangles are benzene derivatives, with open datum points representing the values for phenyl alcohols. Datum points connected by lines are for solutes with alkyl chains.

Origin of the thermodynamics of transfer. To examine for the origin of the thermodynamics of solute transfer between nonpolar solvents and aqueous phases, we have combined our data for the transfer between 2,2,4-trimethylpentane and aqueous buffer (pH 7) with literature data for solute solvation in water, so as to obtain the thermodynamics of solvation of numerous solutes in 2,2,4-trimethylpentane. Examining first the thermodynamics of transfer of aliphatic solutes, we have constructed plots between their thermodynamics of solvation in

2,2,4-trimethylpentane, and in water, and their carbon number which show (ref. 29) that (a) in 2,2,4-trimethylpentane, all solvation energies become increasingly negative with increase in alkyl chain carbon number and (b) in water, although all terms are also negative, hydration of aliphatic alcohols becomes increasingly less favorable with increasing alkyl chain length. These effects indicate that for the aliphatic alcohols studied by us both solvation in 2,2,4-trimethylpentane and hydration exhibit linear enthalpy/entropy compensation behavior, which leads to liquid/liquid transfer between 2,2,4-trimethylpentane also exhibiting enthalpy, entropy compensation behavior. This indicates that all the aliphatic alcohols studied by us are distributing by the same mechanism, which is not surprising due to the fact that they differ only in their number of methylene groups. Molecules substituted with differing types of functional groups would not be expected to exhibit similar thermodynamics due to the occurrence of additional specific solvation effects in both oil and water. To confirm this we have examined the thermodynamics of solvation of a

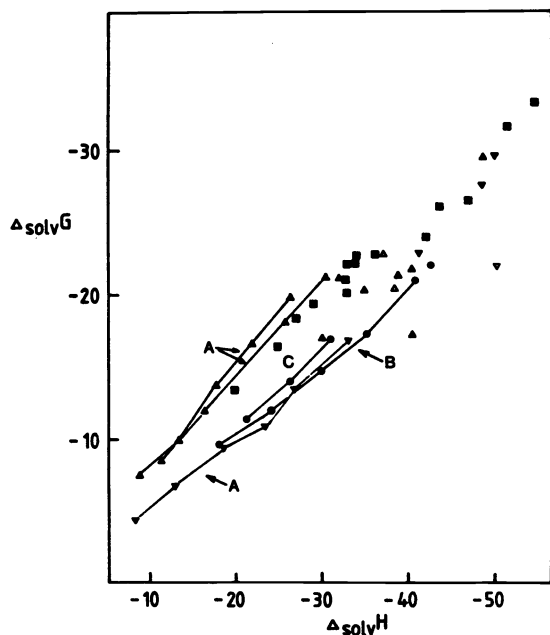


Fig. 5. Relationship between enthalpy of solvation $\Delta_{\text{solv}}H$ (kJ.mol^{-1}), and free energy of solvation $\Delta_{\text{solv}}G$ (kJ.mol^{-1}), for non-electrolytes in non-aqueous solvents at 298.15 K. Datum points for n-alkanes, primary alcohols and aliphatic ketones are indicated by A, B and C respectively. Solvents are 2,2,4-trimethylpentane (closed circles), cyclohexane (open triangles), benzene (closed triangles), chloroform (inverted open triangles) and methanol (inverted closed triangles).

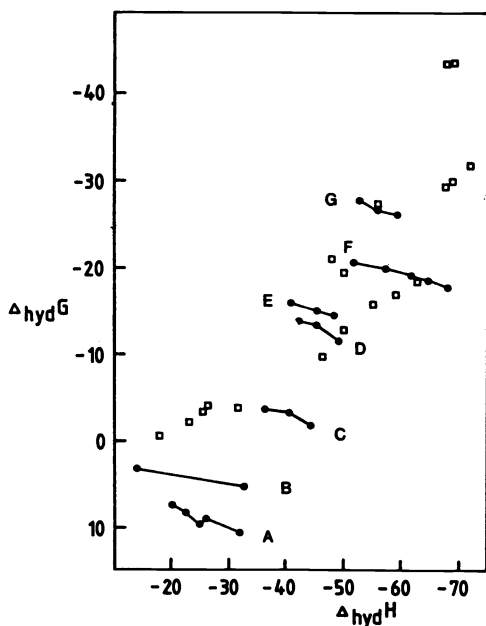


Fig. 6. Relationship between enthalpy of hydration, $\Delta_{\text{hyd}}H$ (kJ.mol^{-1}), and free energy of hydration, $\Delta_{\text{hyd}}G$ (kJ.mol^{-1}), of organic non electrolytes at 298.15 K. Solutes consisting of an alkyl chain are denoted by closed circles, with A-G being n-alkanes, cyclo-alkanes, n-alkylbenzenes, n-alkylbenzoates, aliphatic lactones, primary alcohols and alkanolic acids.

large number of the solutes studied using free energy versus enthalpy plots. Figs. 5 and 6 are the plots for solvation in various oils and the hydration, respectively. In 2,2,4-trimethylpentane, cyclohexane, benzene, chloroform, and methanol, the $\Delta_{\text{sol}}^{\text{G}}$ versus $\Delta_{\text{sol}}^{\text{H}}$ plot shows that for aliphatic and aromatic nonelectrolytes there exists an overall trend in the data, with a favourable free energy of solvation being due to an increasingly exothermic enthalpy of solvation. Linear compensation behavior is found for alkyl-substituted solutes. Nonpolar solutes exhibit similar patterns of compensation for solvation in cyclohexane and benzene, with a lateral displacement of the pattern in methanol. Data for benzene derivatives fit into the general trend, though as a group they do not exhibit linear compensation in any of the oils for which data exist. It should be recognised here that the solutes used to construct the plot given in Fig. 5 will not generally interact strongly with their solvating solvents and that non-regular behaviour could be expected were this to be the case.

The energetics of hydration of aliphatic and aromatic non-electrolytes are shown by Fig. 6 to be much more complicated than solvation in nonpolar or proton-donation oils. There is a general trend in the data, with a more favourable hydration free energy being accompanied by an increasingly more exothermic enthalpy change. Solute possessing an alkyl chain intersect this relationship, such that an increase in alkyl chain length makes hydration less favourable even though this is accompanied by an increase in the enthalpy of hydration. For alkyl-substituted solutes these patterns are presumed to be due to the phenomenon of hydrophobic hydration. Conversely, increasingly favorable enthalpies and free energies of hydration and solvation are considered to be reflections of the increases in solute and solvent polarisability, polarity, and their ability to form hydrogen bonds.

Water/chloroform solvent pair

It is to be expected that as the solvent pair are able either to mutually interact or to solvate the solutes to a relatively greater extent that the rather simple relationships found with transfer from apolar solvents to water will not occur here.

Figure 7 is the derived enthalpy/entropy compensation analysis for solute transfer between water-saturated chloroform and aqueous buffer (at 298.15 K).

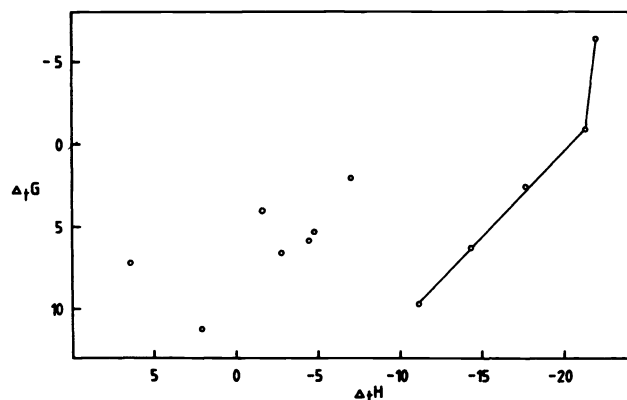


Fig. 7. Relationship between measured enthalpy of transfer, $\Delta_t H$ (kJ.mol⁻¹), and free energy of transfer, $\Delta_t G$ (kJ.mol⁻¹), from water-saturated chloroform to aqueous buffer at 298.15 K. Datum points connected by a line denote the primary alcohols.

A linear relationship is seen with an homologous series of alcohols, with other solutes exhibiting a less than linear relationships (ref. 30). In order to obtain an estimate of the contribution of the hydroxy group to transfer, values for various solutes have been extrapolated to zero carbon number (ref. 30). It is found that transfer from chloroform to water is accompanied by a large entropy loss of $-62 \text{ J.mol}^{-1}.\text{K}^{-1}$, which is much larger than that found for alkyl and methylene group transfers. This surprising result can be explained in two ways. Either there is no structure-promoting effect on transfer of apolar group to water, or, more likely, there exist two opposing effects of similar magnitude. As nonpolar molecules interact merely through weak dispersion forces, the interaction enthalpies within a nonpolar solvent and between a solute methylene group and any solvent are small. Also, in an unassociated and nonpolar solvent the solvation entropy of a solute is expected to be small. Therefore, any entropy change on transfer of a nonpolar solute (or group) from water into chloroform or 2,2,4-trimethylpentane may be primarily attributed to solvation changes in the aqueous phase, and should give similar values for one compound. The observed differences we have found (refs. 28, 29, 30) should therefore result from different solvent-solvent interactions in the aqueous phase, or in both aqueous and chloroform phases, and may be indicative of an influence of the mutual solubility of the solvent phases. To substantiate these presumptions, heats of solution in pure chloroform would be needed in order to compare heats of transfer observed in this study with calculated $\Delta_{\text{sol}}^{\text{H}}$ values. Fig. 7 shows a further $\Delta H - \Delta S$ compensation line for three phenols, which has almost the same slope as the alcohol series. The methyl and chloro groups in the para position of the simple benzenes

studied promote the water to chloroform transfer to the same extent, with the methyl group having a slightly stronger effect on the energy terms than the chloro group. A different methyl increment results from substitution at the aniline nitrogen, with the large entropy effect indicating a special mechanism of solvation of aniline and N-methylaniline in both solvents. Found exothermic enthalpies of transfer of aniline and N-methylaniline suggest that there are specific interactions between chloroform and these solutes. Most likely these interactions are between the chloroform hydrogen and the basic aniline nitrogen. This interaction must be related to a loss of entropy which compensates the gain in entropy on leaving the aqueous phase. It is likely that the decrease in specific interactions for N-methylaniline is due to an inaccessibility of the N-atom because of steric hindrance, the more so as the basicity increases upon methylation. As a result, the enthalpy change is less exothermic and the entropy change is again comparable to that shown by other benzene derivatives. Similarly, Spencer *et al.* have studied the solvation of anilines (ref. 41) and pyridines (ref. 42) by chloroform, carbon tetrachloride and cyclohexane. They find a difference in the solvation by the two inert solvents and between CCl_4 and chloroform which they attribute to specific interaction with the solutes. The thermodynamics of liquid/liquid distribution in the system chloroform/water show features which are similar to those observed for the system 2,2,4-trimethylpentane/water. Changes in enthalpy and free energy are roughly parallel to one another, following the trends in the thermodynamics of solvation discussed above.

The linear relationship between free energy and enthalpy of transfer of the primary alcohols shows that the occurrence of enthalpy-entropy compensation in liquid/liquid distribution is not restricted to solvent systems of low mutual solubility. The enthalpies of solvation in water-saturated chloroform are not very much influenced by the water content of chloroform, which suggests that the measured apparent enthalpy changes are reasonable estimates for the enthalpy of transfer in this solvent system.

2,2,4-Trimethylpentane/chloroform solvent pair

In order to compare the distribution systems 2,2,4-trimethylpentane/aqueous and chloroform/aqueous, the thermodynamics for the transfer from the inert solvent 2,2,4-trimethylpentane to chloroform have been estimated. Here, instead of choosing the ideal gas phase as a reference, an inert solvent has been used to study solvation in various solvents. The Pure Base Method introduced by Arnett (ref. 43) to determine hydrogen-bond formation enthalpies, makes use of heats of solution in a reference solvent (which is employed to compensate for non-specific interaction terms in the solution process).

The experimentally obtained values (TABLE 1) for transfer from 2,2,4-trimethylpentane to chloroform all favor solvation of the compounds in chloroform, except for the transfer of ethanol.

TABLE 1. Thermodynamics of solute transfer from 2,2,4-trimethylpentane to chloroform, at 298.15 K. (from ref. 30).

Solute	$\Delta_t H$	$\Delta_t G$	$T\Delta_t S$
Ethanol	-13.13	-5.01	-8.12
Propanol	-11.89	-7.15	-4.74
Butanol	-13.92	-7.49	-6.43
Pentanol	-15.33	-7.15	-8.18
Hexanol	-16.40	-6.62	-9.78
Acetone	-18.26	-8.67	-9.59
Phenol	-12.46	-7.53	-4.93
4-Chlorophenol	-12.45	-8.08	-4.37
4-Methylphenol	-14.41	-8.13	-6.28
Aniline	-20.01	-8.39	-11.62
N-Methylaniline	-12.65	-5.31	-7.34
Pyridine	-14.21	-8.92	-5.29

Energy changes in $\text{kJ}\cdot\text{mol}^{-1}$

The large exothermic enthalpies and free energies given in TABLE 1 may be attributed to the better solvation in chloroform due to both dipole-dipole and dipole-induced dipole interaction and hydrogen bonding.

As these transfer quantities represent the different in solvation of the solute in the respective solvents, it is necessary to recall the solvation process and the energy contributions connected with it in order to distinguish between non-specific interactions and specific ones. The former are comprised of the contributions needed to create a cavity of the size of the solute in the solvent plus a gain by solvent-solvent dispersion interactions, dipole-dipole and dipole-induced dipole interactions. The latter consist of solute-solvent interactions of either the donor-acceptor type or of the hydrogen-bonding type.

According to the solubility parameter concept it should be possible using solubility parameters to calculate those non-electric parts of the solvation enthalpy which depend on the solute molecular volume. The enthalpy of cavity formation in the solvent may be calculated as

$$\Delta H_{\text{cav}} = V_y \cdot \delta_s^2 \quad (4)$$

with V_y the volume of the solute and δ_s the solubility parameter of the solvent. The solute-solvent interaction term due to dispersion forces is calculated as

$$\Delta H_{\text{disp}} = 2 \cdot V_y \cdot \delta_y \cdot \delta_s \quad (5)$$

(We have omitted calculation of the electric parts of the solute-solvent interaction (dipole-induced dipole) as there is reason to believe that these are very small and nearly constant for the small dipole moments of the compounds studied).

We find that the experimentally determined solvation enthalpies are, with one exception, less exothermic than the sum of calculated cavity and dispersion terms (TABLE 2). The calculation properly predicts the solvation of the methylene group in 2,2,4-trimethylpentane but not in chloroform, (as is shown by constructing plots of the number of carbon atoms versus enthalpies of solvation - ref. 30).

TABLE 2. Enthalpies of solvation from experimental enthalpies of transfer and calculated values from solubility parameters using Eqns. 4 and 5.

Solute	δ	V	Δ_{soln}^H a		Δ_{soln}^H b		Δ_{soln}^H b		Δ_{soln}^H c	
			TMP	CHCl ₃	CHCl ₃ +TMP	TMP	CHCl ₃	CHCl ₃ +TMP	CHCl ₃	TMP
Ethanol	12.78	58.3	-31.13	-36.44	-5.31	-17.41	-31.16	-13.15	5.82	13.72
Propanol	12.18	75.0	-37.66	-43.72	-6.06	-24.32	-36.21	-11.89	7.51	13.34
Butanol	11.6	91.5	-42.89	-49.25	-6.36	-30.09	-44.01	-13.92	5.24	12.80
Pentanol	11.12	109.0	-48.62	-54.64	-6.02	-35.19	-50.52	-15.33	4.12	13.43
Hexanol	10.77	126.0	-53.09	-59.78	-6.69	-40.71	-57.11	-16.04	2.67	12.38
Acetone	9.62	73.5	-26.11	-28.41	-2.30	-20.87	-39.13	-18.20	-10.72	5.24

Enthalpies in $\text{kJ} \cdot \text{mol}^{-1}$, molecular volume (V) in mL, solubility parameter (δ) in $(\text{kcal}/\text{mL})^{1/2}$, $\delta_{\text{TMP}} = 6.86$, $\delta_{\text{CHCl}_3} = 9.16$; (a) calculated; (b) experimental; (c) difference between experimental and calculated values.

For the enthalpies of transfer from 2,2,4-trimethylpentane to chloroform the calculations correctly predict an exothermic effect, but this accounts for only 30-50% of the measured value. The remaining difference agrees roughly with the group value of $-7.75 \text{ kJ} \cdot \text{mol}^{-1}$ which we have calculated for the transfer of an alcoholic hydroxy group from 2,2,4-trimethylpentane to chloroform, reflecting probably its exothermic hydrogen-bonding interaction with chloroform.

Thus, the thermodynamics of transfer from 2,2,4-trimethylpentane to chloroform give that chloroform interacts much stronger than the hydrocarbon with the solutes studied. However, for these thermodynamic values the solutes are not as well distinguished from one another as in the thermodynamics of transfer involving water as a solvent phase. Also, solubility parameters appear not to be totally suitable for calculating the contribution of solvent-solvent interactions to the enthalpies of either solvation or of transfer.

Water/octan-1-ol solvent pair

In the pharmaceutical sciences the octan-1-ol/water system has assumed a significant importance due to its (putative) ability to mimic biological solution processes. The thermodynamics of solute transfer have been determined by us for both primary alcohols and mono- and di-substituted benzene derivatives. From the enthalpy/entropy compensation analysis for these solutes (ref. 31) it is seen that in going from one compound to another, an increase in free energy is not generally accompanied by a parallel change in enthalpy. The benzene derivatives have free-energy changes with a spread of $10 \text{ kJ} \cdot \text{mol}^{-1}$, and are far more distinguished by their enthalpy change, which covers a range twice as large. The opposite is found for the primary alcohols. Ascending the series from ethanol to octanol the free-energy change decreases much more strongly than does the enthalpy change, which indicates a strong entropic contribution of the methylene group. For the alcohols ethanol to butanol, a curvilinear relationship is observed, which extends into a straight line for the solutes butanol and octanol. Methanol does not follow this trend and shows an extremely small entropy change on transfer. The linear enthalpy/entropy relationship found for the alcohols butanol to octanol indicates an occurrence of $\Delta H - \Delta S$ compensation. The change in molecular structure of the solutes, i.e. chain prolongation, results in proportional changes in ΔH and ΔG . According to theory this means that the solutes have the same mechanism of distribution, which is not surprising as the structural changes are repetitive and the solvation interactions should be similar in nature.

With transfer quantities, we always deal with the sum of two effects, and hence the origin of a certain feature cannot be fully described. Thus, again we may relate the thermodynamics of solute transfer to their thermodynamics of solvation in the corresponding solvent phases. Above, we have calculated the enthalpies and free energies of solvation of the alcohols in octanol. (The data for alcohol hydration were used by neglecting the small constant effect on the energies of transfer caused by the buffer salts used). An excellent linear relationship between enthalpy and free-energy changes for the solvation of the alcohols ethanol to heptanol has been found (ref. 31). This has the same slope value as the corresponding line found for solvation in 2,2,4-trimethylpentane, and is very similar to that found for solvation in chloroform. This is remarkable as the high water content of the octanol phase ($X[\text{H}_2\text{O}] = 0.28$) does not seem to have any influence on the enthalpy-entropy compensation line obtained from transfer of homologous solutes between pure solvent phases. As the enthalpy-entropy compensation lines for the hydration of homologous solutes are characteristically different from those of solvation in non-aqueous solvents (ref. 29), a marked influence on the slope value could be expected. On the other hand, the found effect agrees with the observation that aqueous solutions of non-electrolytes at mole fractions $X[\text{H}_2\text{O}] = 0.7$ do not show the characteristic thermodynamic feature of pure water, this being interpreted as a breakdown of water-structure.

It is now interesting to discuss the deviation from the linear relationship between the free energy and enthalpy of transfer observed with methanol. On inspection of Fig. 8 one sees curvatures for both the enthalpy and the entropy of hydration which nicely compensate to give a regular free-energy change. The peculiar effect of methanol is supported by the thermodynamics of transfer which we have calculated for water. It is found that for solvation in the octanol phase, (Fig. 8), there is no difference enthalpically between water and methanol, and that in entropic terms only very small differences between water, methanol and ethanol exist. This suggests that water behaves in octanol similar to methanol, which leads to the possibility that methanol has a similar role as water does in octanol. Water-saturated octanol has been described as consisting of water-centred tetramers (ref. 44), whereas for pure liquid alcohols various hydrogen-bonded aggregates have been reported (ref. 45). For the present data it is not possible to draw definite conclusions on the configuration of the solvated species. In comparison, the enthalpy of hydration of the alcohols resembles very much that of solvation in octanol, having the same slope value for the relation between enthalpy change and carbon number - which suggests that the same interactions are occurring. However, entropy changes due to the solvation of the alkyl chain are much stronger in water than in octanol, and are evident even with the first member of the series. In summary: (i) the transfer of water and methanol, in which the enthalpy change dominates the entropy change, is determined by almost equal changes in enthalpy in both the oil and the water phases; and (ii) the entropically-dominated transfer of the alcohols propanol and the following alcohols is determined by the entropy of hydration. Nevertheless it is obvious from this comparison that both solvating phases have about equal roles in the transfer thermodynamics, and that hydrophobic effects cannot be considered as the origin of the linear free-energy enthalpy relationship.

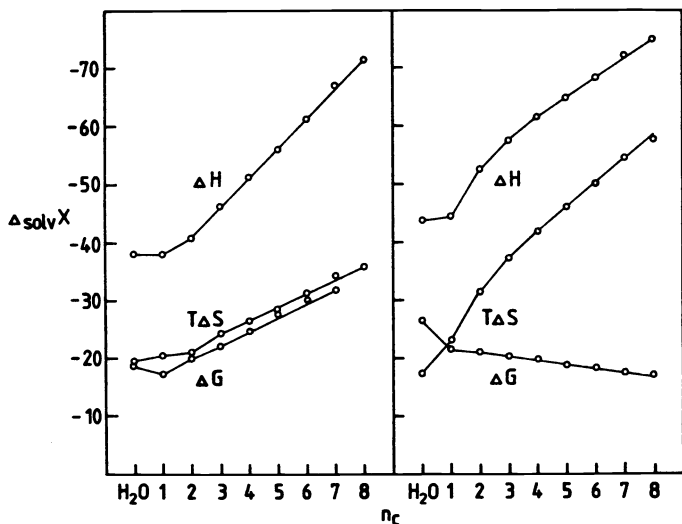


Fig. 8. Relationship between number of carbon atoms, n_c , and the thermodynamics of solvation, $\Delta_{\text{solv}} X$ (kJ.mol⁻¹) at 298.15 K, for water and the primary alcohols in water-saturated octanol (left) and in water (right).

2,2,4-Trimethylpentane/octan-1-ol solvent pair

The thermodynamics of solute transfer from 2,2,4-trimethylpentane to water-saturated octanol may be calculated by adding the thermodynamics of transfer from aqueous buffer to water-saturated octanol to the thermodynamics of transfer from 2,2,4-trimethylpentane to aqueous buffer, viz:

$$\Delta_t^X(\text{octanol} + \text{TMP}) = \Delta_t^X(\text{octanol} + \text{water}) + \Delta_t^X(\text{water} + \text{TMP}) \quad (6)$$

Thus, Fig. 9 is the derived enthalpy/entropy compensation plot for transfer from 2,2,4-trimethylpentane to octan-1-ol. As we compare the thermodynamics of transfer from 2,2,4-trimethylpentane to water-saturated octanol with the corresponding thermodynamics of transfer to water-saturated chloroform and to aqueous buffer we see that:

- (i) solute transfer between non-aqueous solvents results in enthalpy changes which are roughly parallel to free-energy changes, and correspond to the picture exhibited by the thermodynamics of solvation in non-aqueous solvents. Also,
- (ii) transfer from 2,2,4-trimethylpentane to aqueous buffer differs characteristically from the transfer between non-aqueous solvents for solutes bearing an alkyl chain, for which large positive free-energy changes have been found, due to large negative entropy changes and,
- (iii) relative positions of some solute classes in the compensation plots differ.

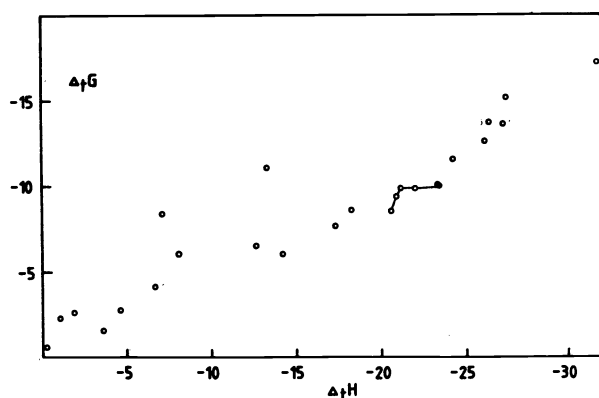


Fig. 9. Relationship between the enthalpy of transfer, $\Delta_t H$ (kJ mol^{-1}), and the free energy of transfer, $\Delta_t G$ (kJ mol^{-1}) at 298.15 K, from 2,2,4-trimethylpentane to octanol. The connected datum points represent the primary alcohols.

The transfer to chloroform gives enthalpy and free-energy changes of similar magnitude for the primary alcohols, phenols, pyridine and N-methylaniline. In contrast, for the same set of solutes, the transfer to octanol and to water gives a much larger range of energy changes. These enthalpy changes increase in the order of the solute classes:

$\Delta_t H(\text{octanol} + \text{TMP})$ anilines < primary alcohols < phenols, and

$\Delta_t H(\text{aq.buffer} + \text{TMP})$ anilines < phenol < primary alcohols.

The enthalpies of transfer of the phenylalcohols appear to be almost the same for both transfer, however, the enthalpy changes for the benzene derivatives (here characterised as pure hydrogen-bond acceptors) appear to be stronger on transfer to water. Most surprisingly, it is found that the enthalpies of transfer within the series of alcohols increase with chain length with their transfer to chloroform and to water, but decrease with their transfer to octanol.

CONCLUDING REMARKS

Using the thermodynamics of solute transfer between 2,2,4-trimethylpentane and water-saturated chloroform, water-saturated octanol and aqueous buffer, we have isolated and identified those specific solvation interactions which determine the thermodynamics of transfer. Hydrogen-bonding interactions were found to discriminate the strongest between both the solutes of one distribution system and between solvents.

It has been shown that changes in the enthalpy of transfer on substitution may be a direct consequence of changes in hydrogen-bonding interaction between solutes and solvents. If the thermodynamics of transfer of a solute and a suitable model compound are available, an estimate of the solute-solvent interaction energy can be given.

From the agreement of the solute-water-saturated solvent interactions determined in this work and solute-pure solvent interactions calculation from literature values, it can be concluded that the co-solvent water does not contribute significantly to either the enthalpies of solvation and of transfer, respectively.

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