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Thermodynamics and extrathermodynamics of organic solute liquid-liquid distribution between water and 2,2,4-trimethylpentane

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Summary

The temperature dependencies of the distribution of substituted benzenes and methylbenzoates between aqueous phosphate buffer (pH 7.0) and 2,2,4-trimethylpentane have been determined using a rapid mix/filter probe system which enables short equilibration and measurement times to be achieved. Except for nitrosubstituted compounds, distribution increases with temperature. A single unique relationship between distribution coefficients and enthalpies of distribution could be described which indicates true linear enthalpy-entropy compensation, the origin of which is suggested as being almost entirely due to the properties of water. Examination of the theory implicit in the use of van 't Hoff operators, indicates that it is inappropriate to obtain thermodynamic quantities from a study of the temperature dependency of distribution when the solvent pair studied have: (i) high mutual solubility; and (ii) various intermolecular and molecular states which are temperature sensitive. The water/octan-1-ol system is exemplified as suffering from these limitations and linear enthalpy-entropy compensation previously reported for this system is shown to be due to probable statistical and experimental effects.

Introduction

Contemporary pharmaceutical science relies much on knowledge of the physicochemical properties of drug molecules. Particular utility has been made of solute liquid-liquid distribution coefficients, (i.e. oil/water partition coefficients), which, if considered as a descriptor of *hydrophobicity*, may be used in preformulation, drug design, analysis and separation science. Additionally, distribution coefficients can give information on the solution thermodynamics of molecules of pharmaceutical

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interest, which can enable thermodynamic data to be derived for use in prediction of behaviour in such phenomena as solubility, compatability, membrane permeability, etc. This follows from, (Davis et al., 1974), the definition of liquid–liquid distribution coefficients as being the ratio of symmetrical (i.e. Raoult's law) activity coefficients (or of Henry's law constants).

Although solute oil/water distribution has been studied since the last century, and a large collection of distribution coefficients exist, (Hansch and Leo, 1979), most work has concentrated on determination of the free-energy-based coefficient itself, with few workers even reporting the temperature of measurement. Although such information indicates the extent of distribution, it yields little information on why the process occurs. This can be afforded by a more complete thermodynamic description of the system to include, for example, the enthalpic and entropic contributions towards the distribution. Some workers have reported either these particular quantities or the effect of temperature on the distribution coefficient for various solutes and solvent pairs, (Hantzsch and Sebalt, 1899; Farmer and Warth, 1904; Moore and Winmill, 1912; Forbes and Coolidge, 1919; Synge, 1939; Davies et al., 1951; Renkin, 1952; Kato, 1964; Mindowicz and Biallozor, 1964; Mindowicz and Uruska, 1964; Crook et al., 1965; Shamsal and Lodhi, 1966; Christensen et al., 1968; Aveyard and Mitchell, 1969; Crugman, 1971; Harris et al., 1973; Korenman and Karyakina, 1973; Marcus and Kolarik, 1973; Breslauer et al., 1974; Davis et al., 1974; Schumacher and Nagwekar, 1974; Kaufman et al., 1975; Brodin et al., 1976; Davis et al., 1976 and Cooke and Gonda, 1977), though only those by Harris et al. (1973) on ion-pair transfer and two very recent studies using octan-1-ol as the oil phase (Beezer et al., 1980; and Rogers and Wong, 1980) can be considered as attempts at a systematic examination of the thermodynamics of solute distribution. All reported studies save those by Marcus and Kolarik and by Breslauer et al. (microcalorimetry), have used the temperature dependence of the distribution process to determine enthalpies and thence entropies of solute transfer. As discussed later the choice of solvent pair can be critical in such studies.

We report here attempts to determine the thermodynamics of organic solute distribution from knowledge of the temperature dependence of the process using as simple a two-phase system as possible. Also we have addressed the question posed by our previous studies on the thermodynamics of drug behaviour (e.g. Tomlinson and Davis, 1980; Tomlinson et al., 1981)—do distributing systems exhibit linear enthalpy/entropy compensation behaviour, and, if so, is such behaviour both unique to that system and consistent with that found for other phenomena. To examine for this we have studied the effect of temperature on the liquid–liquid distribution coefficients, K_d, of 11 simple organic solutes using buffer (pH 7.0)/2,2,4-trimethylpentane as solvent pair, with rapid, semi-automated methods of determination. In addition the effects of solute concentration on both K_d and the miscibility of water with 2,2,4-trimethylpentane over the temperature range used have been examined.

The results obtained are compared to those derived from values reported elsewhere for other solvent pairs, including water/cyclohexane and water/octan-1-ol systems.

Materials and methods

Chemicals

Benzene, and mono- and di-substituted benzenes were obtained from Fluka (Hicol, Rotterdam, The Netherlands) and B.D.H. Chemicals (Brunschwig, Amsterdam, The Netherlands). Substituted methylbenzoates were obtained from Eastman-Kodak (Tramedico, Weesp, The Netherlands). 2,2,4-Trimethylpentane (analytical grade) and buffer components were from Merck (Amsterdam, The Netherlands). Modified Karl-Fischer titration reagent was from Baker Chemicals (Deventer, The Netherlands). All these chemicals were of high purity and were used as supplied. Water was freshly distilled from an all-glass still after de-ionization over a mixed bed ion exchanger.

Determination of liquid–liquid distribution coefficients

Apparatus and procedures

Liquid–liquid distribution coefficients, were determined using a rapid mix/filter probe system, (as given in Fig. 1). This was a modification of that developed recently (Cantwell and Mohammed, 1979) for two phase acid–base titrations. It consisted of a thermostated (±0.1°C) mixing chamber (200 ml volume) whose contents could be vigorously stirred using a magnetic stirring bar and motor. Using filters of hydrophilic (589/3 blauband filter paper, Schleicher and Schüll, Tamson, Zoetermeer, The Netherlands) or hydrophobic (teflon film, Mitex LC 10 μ with 68% porosity, from Millipore, Brussels, Belgium) material, the water or oil phases, respectively, could be probed by linking the filters to a high performance pump (Orlita DMP, 1515) and then examining the phase under study by on-line detection using an ultraviolet spectrophotometer, (Pye-Unicam, SP 8-100), fitted with a 80 μl flow-though cell thermostatted at 25°C. Flow exiting from this cell was returned to the mixing chamber. All connecting tubes (Fig. 1), together with the pump membrane were

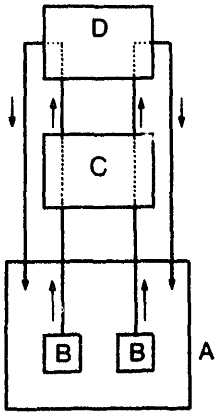

Fig. 1. Rapid mix/filter probe assembly. A = thermostatted mixing chamber; B = hydrophilic and hydrophobic filter probes; C = high performance pump, (flow: 1.5 ml·min^{-1}); and D = thermostatted spectrophotometric flow-through cell. The direction of flow is indicated.

constructed of stainless steel. (Although the hydrophobic probe was used occasionally to check mass balance, for K_d measurements only the aqueous phase was probed). Using this arrangement to determine distribution coefficients, first both solvents were pre-equilibrated at 20°C by gentle shaking for 24 h. The aqueous phase (Clark-Lubs constant ionic strength phosphate buffer at pH 7.0) was added to the mixing chamber and probed to give a blank reading (A_b); then a second addition of aqueous phase containing solute was made to obtain an unextracted sample reading (A_u). The organic phase was then added and the absorbance of the aqueous phase monitored continuously (A_e). To examine the effect of temperature on the solute liquid–liquid distribution coefficient, the temperature of the mixing chamber was raised several times over a range of 20–50°C and the A_e values determined at equilibrium. Thus:

$$K_d = (A_u - A_e) \cdot (A_e - A_b)^{-1} R^{-1} \tag{1}$$

where R is the oil/water phase volume ratio, and which was between 0.01 and 5.00. The UV absorbance of each solute was examined in the system at the different mixing chamber temperatures in the absence of the oil phase. In no case did the absorbance in the flow-through cell (at 25°C) change. All measurements were carried out in the linear portion of the Beer-Lambert plots. The accuracy and precision of the method compared to a conventional shake-flask procedure were examined for *p*-chloroaniline and results were found to be indistinquishable from one another. All determinations were carried out in triplicate and were performed at least at two different concentrations (approximately 1×10^{-4} and 1×10^{-3} mol·dm^{-3}).

Table 1

Thermodynamics of solute liquid–liquid distribution between phosphate buffer (pH 7.0) and 2,2,4-trimethylpentane at 35°C

Solute[a]	Thermodynamics[b]		
	ΔG^x	ΔH^x	ΔS^x
A. Phenol	−0.57	16.4	55.0
B. *p*-chlorophenol	−3.17	10.6	44.6
C. *p*-cresol	−3.84	14.7	60.1
D. aniline[c]	−4.85	11.8	54.1
E. *p*-chloroaniline[c]	−8.70	5.84	47.2
F. *p*-methylaniline[c]	−7.98	8.87	54.7
G. nitrobenzene	−14.0	−1.61	40.3
H. *p*-nitrotoluene	−16.8	−2.55	46.2
I. *o*-aminomethylbenzoate	−12.5	3.46	51.7
J. *m*-aminomethylbenzoate	−3.97	12.1	52.1
K. *o*-ethoxymethylbenzoate	−13.6	2.27	46.2

[a] Benzene (evaporation) and *p*-chloronitrobenzene (absorption), could not be examined for the temperature effect on their K_d using the rapid mix/filter probe system.

[b] Units for ΔG^x, ΔH^x and ΔS^x are kJ·mol^{-1}, kJ·mol^{-1} and J·mol^{-1}·K^{-1}, respectively.

[c] Values corrected for $\Delta pK_a/T$ effects on both solute (Sergeant and Dempsey, 1979) and buffer (Perrin, 1972).

Water content determination in binary and ternary mixtures

The effect of solute on the solubility of water in the 2,2,4-trimethylpentane layer was examined by equilibrating buffered water with the oil for 24 h by gentle shaking at 20, 30, 40 and 50°C both in the absence of solute and with initial solute aqueous concentrations of 10^{-1}, 10^{-2}, 10^{-3} and 10^{-4} mol dm^{-3}. After this time the water content of the 2,2,4-trimethylpentane layer was determined using the modified Karl-Fischer titration method of Verhoef et al. (1977). The K_d value of solute was also determined for these systems. Solutes examined were as given in Table 1 except for nitrobenzene, *p*-nitrotoluene and *o*-aminomethylbenzoate.

Results and discussion

Assuming simple Nernst law distribution of a neutral solute, N, between two immiscible solvents we may write:

$$K_d = [\mathrm{N}]_o/[\mathrm{N}]_w \tag{2}$$

where the phase volume ratio is unity and subscripts o and w refer to the oil and water phases, respectively. Eqn. 2 holds only for systems which are ideal, and for which the solute is in the same molecular state in both phases; and where K_d is described as the thermodynamic liquid–liquid distribution coefficient, K_d^x, when concentrations are expressed in mole fractions. For sufficiently dilute solutions, a good approximation is (Aveyard and Mitchell, 1969):

$$\ln K_d^x = \ln K_d + \ln(\mathrm{V}_o/\mathrm{V}_w) \tag{3}$$

where V is the molar volume. Although the use of a molarity scale has been proposed for examining the thermodynamics of distribution, (Ben-Naim, 1978), the mole fraction scale enjoys freedom from both temperature and density effects (Arnett and McKelvey, 1969). Thus using mole fraction units, as the ratio $(\mathrm{V}_o/\mathrm{V}_w)$ changes this is countered by an opposite and equal change in the nominal phase volume ratio. Hence, with water 2,2,4-trimethylpentane as the solvent pair,

$$\mathrm{RT} \ln K_d^x = \mathrm{RT} \ln K_d + 5.491\ (\mathrm{kJ \cdot mol^{-1}}) = -\Delta \mathrm{G}^x \tag{4}$$

where $\Delta \mathrm{G}^x$ is the free-energy change upon solute distribution, and R and T are the gas constant and absolute temperature. Enthalpies of distribution, $\Delta \mathrm{H}^x$, may be obtained from the slopes of $\ln K_d^x$ versus T^{-1} plots via the van 't Hoff equation, and entropy changes upon distribution, $(\Delta \mathrm{S}^x)$, from the Gibbs equation.

Fig. 2 gives the van 't Hoff plots for 11 solutes examined using the rapid mix/filter probe system. The excellent linearity found, (as reflected by correlation coefficients > 0.995), indicates that in all cases the enthalpies of distribution were constant over the studied temperature range. Thermodynamic descriptions of distribution at a fixed temperature (35°C), are given in Table 1, from which K_d^x at any temperature between 20 and 50°C may be found. Any compounds showing evidence of either evaporation or adsorption during the comparatively short equilibration times (2–5 min) were not studied further (Table 1). Values given in Table 1 are for solute concentrations below 10^{-2} mol·dm^{-3}, where no concentration dependency of

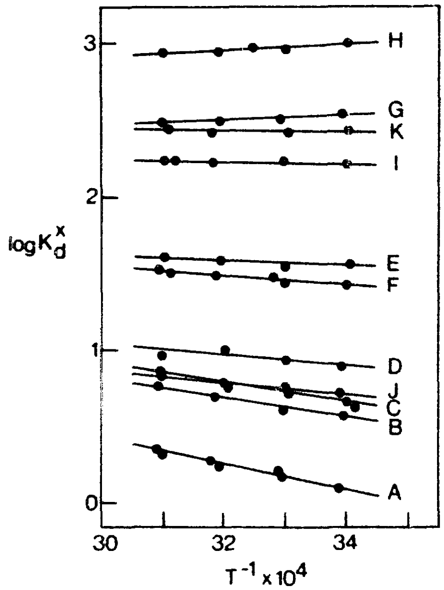

Fig. 2. Van 't Hoff plots for substituted benzenes and methylbenzoates distributing between phosphate buffer (pH 7.0) and 2,2,4-trimethylpentane, showing log mean thermodynamic liquid–liquid distribution coefficients, K_d^x, as a function of reciprocal absolute temperature, T^{-1}. Overlapping points have been omitted for clarity purposes. Solute code A–K is as Table 1.

K_d was observed. We have used a rapid method for determining K_d to obviate both the tedium of measurement and the possibilities of either incomplete distribution and chemical instability encountered during conventional shake flask methods.

Except for the nitrosubstituted compounds, K_d increases with increase in temperature. A survey of the literature shows that this is a common feature for distribution between solvent pairs which have little mutual solubility, (e.g. cyclohexane), whereas for solvent pairs having high mutual solubility an exothermic effect is often reported. At this stage we will not examine the individual thermodynamic descriptions of distribution nor comment on their origin, but rather will examine trends in the data. To do this it is convenient to use extrathermodynamics.

Extrathermodynamic relationships in distributing systems

Leo and Hansch (1971) have discussed the existence of linear free-energy relationships in partitioning solvent systems, as first formalized by Collander (1951). These are examples of *extrathermodynamic* relationships (Leffler and Grunwald, 1963), where although the relationships themselves are outside the formal structure of thermodynamics, their approach resembles that of thermodynamics in that the detailed microscopic mechanisms need not be explicitly identified. Availability of thermodynamic quantities other than the free energy enables the extrathermodynamic approach to be used to give information for a single system or process. Leffler and Grunwald (1963) have argued that to identify a single unique mechanism for a series of solutes, if ΔH and ΔS are approximated as being constant then $\delta\Delta H$ should be simply proportional to $\delta\Delta S$, (where δ denotes a change caused in the thermodynamic parameter by either a medium effect, or, as for the present study, by

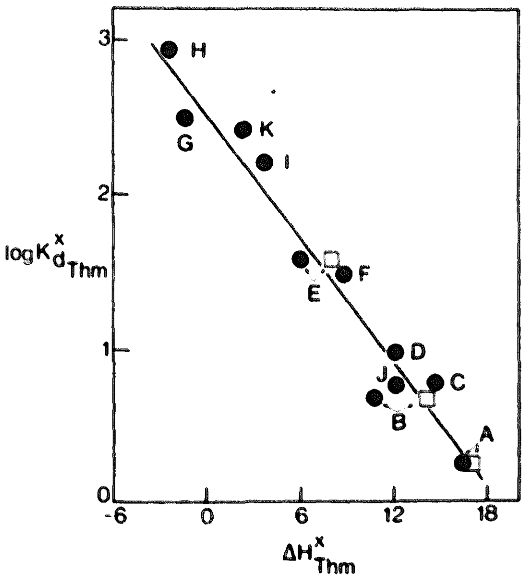

Fig. 3. Relationship between thermodynamic liquid-liquid distribution constants and the enthalpies of distribution ΔH^{x} ($kJ \cdot mol^{-1}$), (developed according to Eqn. 7 using harmonic mean temperature (Thm) values), for distribution between phosphate buffer and 2,2,4-trimethylpentane. Solute code is as Table 1. Data indicated by squares have been obtained by direct microcalorimetric determination of the enthalpies of distribution (Riebeschl and Tomlinson, 1981).

a change in solute(s) structure(s). Krug et al. (1976a and b) have recommended that, for thermodynamic quantities obtained using van 't Hoff relationships, regressions between these quantities should be carried out in $\Delta H_{Thm} - \Delta G_{Thm}$ coordinates, (where Thm refers to the harmonic mean temperature of the experiments); for linear enthalpy–entropy compensation can arise as statistical artefacts, since ΔH and ΔS are derived from the same set of data, and where the use of Thm values minimizes any statistical bias in the subsequent analysis. Enthalpy–entropy compensation can be expressed (Krug et al., 1976b) by:

$$\Delta H = \beta \Delta S + \Delta G \ (\text{at } T = \beta) = \beta \Delta S + \Delta G_{\beta} \tag{5}$$

(where β is a proportionality factor having dimensions of absolute temperature—Leffler and Grunwald, 1963). Using the Gibbs equation in re-writing Eqn. 5 to express the free-energy change measured at a fixed temperature T, (ΔG_T), we obtain:

$$\Delta G_T = \Delta H \, (1 - T/\beta) + T \, \Delta G_{\beta} / \beta \tag{6}$$

Combination of Eqns. 4, 5 and 6 gives

$$\ln K_d^{x} = -(\Delta H^{x}/R) \cdot (1/T - 1/\beta) - \Delta G_{\beta}^{x}/R\beta \tag{7}$$

Using 35°C as the harmonic mean temperature we have examined all data from the present study using the water/2,2,4-trimethylpentane system for true linear enthalpy–entropy compensation according to Eqns. 6 or 7. Fig. 3 gives the relationship found for 11 simple substituted benzenes. This has a correlation coefficient of 0.973, which compares well with other values reported for simple physicochemical

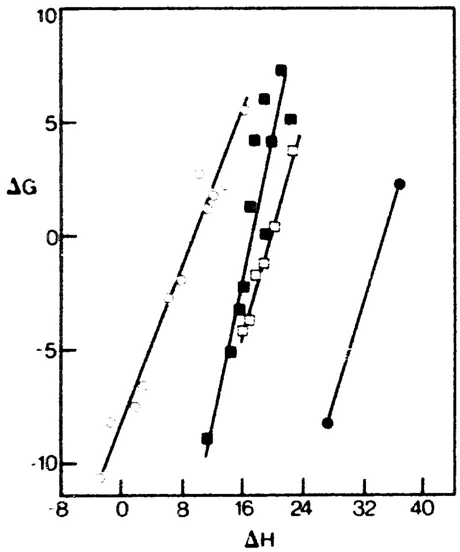

Fig. 4. Enthalpy-entropy compensation plots according to Eqn. 6 (free-energy change, ΔG, enthalpy change, ΔH, coordinates) for solute distribution between solvent pairs having little mutual solubility. Thermodynamic quantities are in kJ·mol^{-1} units based on a molar concentration scale at 298°K. (Key: open and closed circles are from this study and that by Brodin et al., 1976 (water/cyclohexane), respectively; open and closed squares are from Davis et al., 1976 and Crugman, 1971, respectively (both water/cyclohexane).

processes using van 't Hoff operators, (Melander et al., 1978; Riley and Tomlinson, 1980; Tomlinson and Davis, 1980; Vigh and Varga-Puchony, 1980; and Tomlinson et al., 1981), and can be expressed by

$$\Delta G^{x}_{\mathrm{Thm}} = 0.81\,\Delta H^{x}_{\mathrm{Thm}} - 14.2 \quad n = 11 \quad r = 0.973 \tag{8}$$

where n and r refer to the number of data points and the correlation coefficient. From theory (Leffler and Grunwald, 1963), it is now suggested that all solutes studied here distribute by the same mechanism, and one can postulate (based on a consideration of the nature of both the oil phase and the solutes), that this is due to a hydrophobic effect (Scheraga, 1979), with solvation in the oil phase (Smith et al., 1975) having little role. It is pertinent to the present discussion to examine for ΔH-ΔS compensation in other distributing systems where, like in the present system, there is little mutual solvent pair solubility, and Fig. 4 shows plots of free-energy changes versus enthalpies developed by us from data reported for the water/cyclohexane system. The remarkable feature of this figure is that all reported studies suggest linear enthalpy-entropy compensation.

It has been argued (e.g. Scheraga, 1979) that the strength of hydrophobic effects should increase with temperature; however, Fig. 4 shows that this is the case only over a certain domain of ΔG and ΔH values, and that at high K_d values an exothermic process exists, although for all solutes a positive entropy change upon distribution exists (Table 1).

Interpretation of the experimental determination of the temperature dependence of distribution by the van 't Hoff equation to provide ΔH and ΔS quantities are common (Introduction). However, as is well discussed for the micellization process

(Holtzer and Holtzer, 1974), macroscopic operational van 't Hoff relationships fail if the system itself changes, (in the case of micellization the micellar number may change). Considering the distributing system this could be interpreted (Christian et al., 1963, 1970) in terms of: (i) the water solubility in the oil and vice versa; (ii) the state of any oil/water complexes; (iii) the molecular state of the oil; and (iv) the effect of solute on (i)–(iii). For the phosphate buffer/2,2,4-trimethylpentane system we have determined the mole fraction water solubility in the oil (at 25°C) as 8.76×10^{-4} with an enthalpy of solution of 16.64 $\mathrm{kJ \cdot mol^{-1}}$, which compares with a reported (Leo et al., 1971) mole fraction solubility of water in cyclohexane of 2.65×10^{-4} (ΔH; 13.2 $\mathrm{kJ \cdot mol^{-1}}$, Reid et al., 1969) and where the water is considered (Smith et al., 1975) as being unassociated with the oil. Conversely, the mole fraction solubilities of oil in water for 2,2,4-trimethylpentane and cyclohexane at 25°C are (McAuliffe, 1966) 3.84×10^{-7} and 1.17×10^{-5} (ΔH; 0.3 $\mathrm{kJ \cdot mol^{-1}}$; Reid et al., 1969), respectively. These data, and an exhaustive search of the literature show, that for the water/2,2,4-trimethylpentane system the above conditions (i)–(iii) either do not exist or are insignificant with respect to temperature changes altering the nature of either phase. We shall consider factor (iv) later.

Distribution between solvent pairs having high mutual solubility

A much studied solvent pair in distribution studies are water/octan-1-ol (see Hansch and Leo, 1979). Although as a medium for describing solute hydrophobicity (sic) this system has its uses, the complex nature of the system has led to its criticism (Rytting et al., 1970) as a standard state. It has been suggested (Lippold and Adel, 1972) that water-centered aggregates exist in octan-1-ol with a 4:1 alcohol–water ratio, and that a solute transferring to this phase may replace one octan-1-ol in the complex (Smith et al., 1975). In addition, linear aliphatic alcohols (including octan-1-ol) have been shown to exist in monomeric and polymeric forms (Anderson, 1978). For reference, the corresponding values (Brodin et al., 1976) of solubility at 25°C (mole fraction) and enthalpies of solution for water in octan-1-ol and vice versa are 0.27; 5.7 $\mathrm{kJ \cdot mol^{-1}}$ and 7.29×10^{-5}; 3.9 $\mathrm{kJ \cdot mol^{-1}}$, respectively. This shows that at 25°C, upon equilibration octan-1-ol is comprised (on a mole fraction scale) of 27% water which rises to 32% water at 50°C. In relation to this Lippold and Adel (1972) show that the dielectric constant of octan-1-ol changes negatively with both temperature and its water content (whereas the dielectric constant for cyclohexane at 25°C does not change upon saturation).

Thus the arguments against the use of van 't Hoff operators for obtaining ΔH and ΔS quantities would appear to hold for the water/octan-1-ol system and similar solvent pairs. Two recent studies have examined the temperature dependence of the distribution of resorcinol monoalkylethers (Beezer et al., 1980) and substituted phenols (Rogers and Wong, 1980) between octan-1-ol and, respectively, water and 0.15 $\mathrm{mol \cdot dm^{-3}}$ aqueous sodium chloride. It is of considerable interest to this present study to examine whether linear enthalpy–entropy compensation exists in these reported systems. Thus Fig. 5 gives the relationships between enthalpy and free-energy change quantities from these two studies and from the present study using phosphate buffer/2,2,4-trimethylpentane. The phenol system does not exhibit true

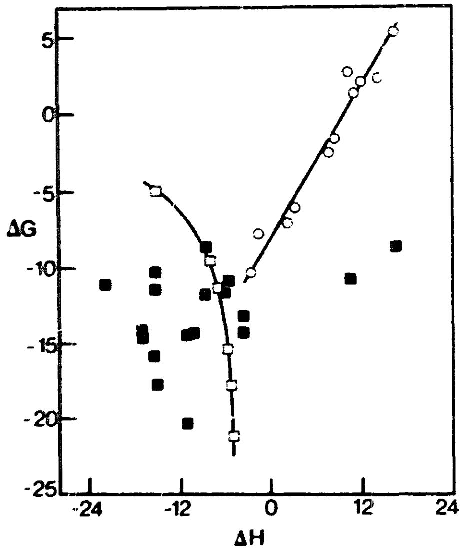

Fig. 5. Relationships between free-energy changes and enthalpies upon solute distribution between an aqueous phase and octan-1-ol. Open squares are for resorcinol monoalkylethers and have been derived using a molar concentration scale at 298°K (Beezer et al., 1980); closed squares are for phenol and have been derived using a molar concentration scale at 293°C (Rogers and Wong, 1980). Data from this present study using water/2,2,4-trimethylpentane as the solvent pair (molar scale (circles), 298°K), are included for comparison.

linear compensation behaviour with a correlation coefficient of 0.402 being found, and although for the resorcinol monoalkylethers the ΔH–ΔG relationship has a correlation coefficient of 0.876, the small number of data points show considerable non-linearity. Rogers and Wong (1980) have reported an excellent correlation (0.942, $n = 18$) between ΔH and ΔS data; the previous discussion and Fig. 5 show that this is probably due to statistical and experimental reasons and that true enthalpy–entropy compensation has not been exhibited for the octan-1-ol system, which also implies that van 't Hoff operators should not be used to obtain thermodynamic quantities in such systems. (Table 2 gives the regression coefficients for a similar analysis of the distribution of ion pairs from phosphate buffer to a chloroform/carbon tetrachloride mixture. The variance between the quantities unexplained by the relationship may be due again to a significant mutual solubility/temperature effect.)

Effect of solute on solubility of water in 2,2,4-trimethylpentane

For the present solvent pair we have considered the possibility of an increase in the solubility of water in the oil due to the formation of hydrate complexes (Staveley et al., 1943; Christian et al., 1970) such that the non-polar nature of 2,2,4-trimethylpentane itself can be altered by the distribution process itself. Thus we have chosen solutes which will tend to hydrogen bond well with water and examined the effect of various concentrations at different temperatures on the solubility of water in 2,2,4-trimethylpentane. Without solute we have found a direct relationship between the changes in water's oil solubility and its vapour pressure (Weast, 1979)

Table 2

Enthalpy–entropy compensation relationships for solute distribution between various solvent pairs

Solute	Solvent pair	Mole fraction water solubility in the oil at 25°C	Compensation according to $\Delta G_T = a\,\Delta H + b$					β(°K)
			T(°K)	a	b	n	r	
Substituted benzenes and methylbenzoates[a]	Phosphate buffer (pH 7.0)/ 2,2,4-trimethylpentane	8.76×10^{-4a}	308	0.81	−14.2	11	0.973	1620
Phenols[b]	Water/cyclohexane	2.65×10^{-4g}	298	1.12	−21.2	6	0.987	−2508
Phenols[c]	Water/cyclohexane		298	1.43	−24.3	12	0.832	−679
Straight-chain alkysulphates[d]	Phosphate buffer (pH 2.4) 25°C v/v $CHCl_3$ in CCl_4	0.0048($CHCl_3$)[h]	298	1.26	7.54	7	0.964	−1138
Polyfunctional alkysulphates[d]	Phosphate buffer (pH 2.4) 25% v/v $CHCl_3$ in CCl_4	0.0084(CCl_4)[h]	298	0.99	3.74	26	0.837	29,800
Resorcinol monoalkylethers[e]	Water/octan-1-ol	0.27[h]	298	1.38	−24.1	6	0.876	124
Phenols[f]	Aqueous NaCl/octan-1-ol		293	0.13	−12.0	18	0.402	341

[a] This study—mole fraction units.

[b] Davis et al., (1976)—$mol \cdot dm^{-3}$ units.

[c] Crugman, (1971)—$mol \cdot dm^{-3}$ units.

[d] Harris et al., (1973); (as the dextromethorphan ion pair)—$mol \cdot dm^{-3}$ units.

[e] Beezer, et al., (1980)—$mol \cdot dm^{-3}$ units.

[f] Rogers and Wong, (1980)—molal units.

[g] Leo et al., (1971).

[h] Davis, (1975).

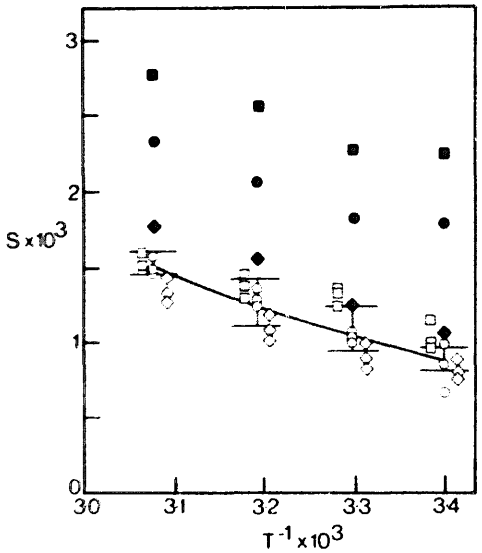

Fig. 6. Effect of temperature and solute concentration on the mole fraction solubility, S, of water in 2,2,4-trimethylpentane after equilibiation of equal volumes. Data are for phenol (diamonds), *p*-chlorophenol (squares) and cresol (circles). Closed points are for initial aqueous solute concentrations of 1×10^{-3} mol·dm^{-3}; open points indicate the 3 lower concentrations studied (Methods) and have been laterally spread for clarity purposes. The line drawn is for solubility in the absence of solute, with bars indicating the standard deviations of the means.

caused by temperature; i.e.

$$S(\times 10^{-4}) = 0.098\mathrm{VP} + 7.09 \quad n = 4 \quad r = 0.995 \qquad (9)$$

where S is the mole fraction solubility and VP is the vapour pressure in mm. This may indicate that there is no complexation between the water and oil molecules. For all studied concentrations (Materials and Methods) only concentrations of cresol, *p*-chlorophenol, and *m*-amino- and *o*-ethoxymethylbenzoates greater than 1×10^{-2} mol·dm^{-3} significantly perturb the relationship between water's 2,2,4-trimethylpentane solubility and temperature. Fig. 6 shows data for 3 representative compounds. For *p*-cresol the K_d is raised with initial solute concentrations of 10^{-1} mol·dm^{-3}, though the values for the other solutes remain constant over the studied concentration range and are consistent with our other findings.

Conclusions

For the water/2,2,4-trimethylpentane solvent pair a single unique relationship between distribution coefficients and enthalpies of transfer can be described, which may be of use in a priori predictions of solute behaviour in distributing systems. The linear plots given in Fig. 4 have a slope coefficient ϕ, which is related to the proportionality factor β (Eqn. 6) by

$$\beta = \mathrm{Thm}/(1 - \phi) \qquad (10)$$

Table 2 gives the β values for the present study and for the water/cyclohexane (Fig. 4) and water/octan-1-ol (Fig. 5) systems. The β term has become known as the compensation temperature (since its units are absolute temperature), and although it has been used (e.g. Leffler and Grunwald, 1963; Riley and Tomlinson, 1980) to relate systems to one another, its meaning is uncertain (Krug et al., 1976b). As ϕ approaches unity β is subject to very large error in determination. Since this is the case for the distribution systems examined here (Table 2), a direct comparison with β values from studies on other physicochemical behaviour (e.g. Melander et al., 1978; Tomlinson and Davis, 1980) is not valid.

The origin of the linear compensation behaviour can be postulated as due to the unique properties of water (Némethy et al., 1963; Lumry and Rajender, 1970; Tanford, 1973) suggesting that 2,2,4-trimethylpentane behaves almost as an ideal 'inert' hydrocarbon (Davis et al., 1974). We take note here of a recent study (Kühne et al., 1981) which has postulated that 70% of the transfer of a methylene group from water to oleyl alcohol is due to solvation in the oil and that only about 30% is due to repulsion by water. However, the work totally ignores the mutual solubility effect and is at variance with results implicit in the study by Davis (1975) on the effect of mutual solubility on methylene group transfer between water and various oils.

Finally, arguments presented in this contribution suggest that the use of van 't Hoff operators for obtaining thermodynamic quantities is inappropriate when solvent pairs with high mutual solubility etc. are examined, and that for the water/octan-1-ol system true linear enthalpy–entropy compensation cannot be demonstrated from the results of others (Beezer et al., 1980; Rogers and Wong, 1980). This does not preclude such compensation existing and, as suggested by Beezer et al. (1980), this could be examined using direct microcalorimetric measurements. Our present studies are directed to this aim and some initial findings using microcalorimetry for the phosphate buffer/2,2,4-trimethylpentane system are given in Fig. 3, (Riebesehl and Tomlinson, 1981).

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