Enthalpy and Entropy Contributions to the Solubility of Sulphamethoxypyridazine in Solvent Mixtures Showing Two Solubility Maxima

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Abstract

The solubility of sulphamethoxypyridazine was measured at several temperatures in mixtures of water:ethanol and ethanol:ethyl acetate. Sulphamethoxypyridazine was chosen as a model drug to compare the solvation effects of proton donor-proton acceptor (water and ethanol) and proton acceptor (ethyl acetate) solvents and mixtures of these solvents because this drug contains functional groups capable of Lewis acid-base interaction.

A plot of the mole fraction solubility against the solubility parameter (δ_1) of these solvent mixtures showed two solubility maxima, one at $\delta_1 = 30{\cdot}87\,MPa^{1/2}$ (20:80 v/v water:ethanol) and another at $\delta_1 = 20{\cdot}88\,MPa^{1/2}$ (30:70 v/v ethanol:ethyl acetate) at all the temperatures under study. The enthalpies and entropies of mixing as well as the enthalpies and entropies of transfer of sulphamethoxypyridazine from ethanol to water:ethanol and ethanol:ethyl acetate mixtures were calculated to compare solvation characteristics of the solvent mixtures toward the drug. As ethanol is added to water, the entropy increases and the structure of the solvent mixture became less ordered, favouring the interaction of the drug with the solvent mixture. On the other hand, in the case of the ethanol:ethyl acetate mixture, solubility is favoured by the more negative enthalpy values. This way, the same result, i.e. a solubility maximum, is obtained by different routes.

In the ethanol:water mixtures, the dissolution process is entropy-controlled while enthalpy is the driving force in the case of ethanol:ethyl acetate mixtures. The two solvent systems show enthalpy-entropy compensation. Water deviates from the linear relationship due possibly to its hydrophobic effect.

When the solubility of a drug in pure solvents or solvent mixtures is compared at several temperatures, the enthalpies and entropies of solution directly reflect changes in solvation (Rogers 1982; Tomlinson 1983; Somsen 1991). Solvation effects are important in solubility as well as in other fields. They may or may not favour complexation of a drug to a macromolecule and they may mask donor-acceptor contributions to complexation strength (Ferguson et al 1991). Solubility measurements are particularly useful in the investigation of sparingly-soluble solutes such as the sulphonamide studied in this work. In such cases the enthalpy of mixing is difficult to measure calorimetrically, whereas solubility provides a reliable estimate of the free energy of transfer (Hefter 1991). Mixed solvents have many practical applications. They are used in pharmacy to increase the solubility of a drug over that obtained in a single solvent, and to enhance or limit the penetration of a drug through the skin and across various other living membranes.

Sulphamethoxypyridazine was chosen as a model drug to compare the solvation effects of proton donor and proton acceptor solvents and solvent mixtures because this drug contains functional groups such as NH_2, NH, O, capable of Lewis acid base interaction (Fig. 1). A plot of the solubility of sulphamethoxypyridazine at 25°C in mixtures of water:ethanol and ethanol:ethyl acetate against the solubility parameter of the solvent mixtures showed two
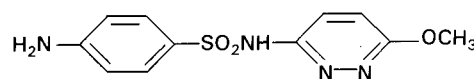
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FIG. 1. Structure of sulphamethoxypyridazine.

solubility maxima, one at $\delta_1 = 30{\cdot}87\,MPa^{1/2}$ (20:80 v/v water:ethanol) and another at $\delta_1 = 20{\cdot}88\,MPa^{1/2}$ (30:70 v/v ethanol:ethyl acetate) (Escalera et al 1994). The solubility parameter, δ, defined as the square root of the cohesive energy density (Hildebrand et al 1970) is a measure of polarity. Two solubility peaks were also found for other sulphonamides (Bustamante et al 1994) but they are not reported for other drugs in these solvent mixtures. For example, benzoic acid shows only a solubility maximum (Chertkoff & Martin 1960) and paracetamol displays small irregularities (shoulders) and a unique solubility maximum in the solvent mixtures of similar nature to that studied here, methanol–ethyl acetate and methanol–water (Subrahmanyam et al 1992). This interesting behaviour of sulphonamides demonstrated the chameleonic effect first described by Hoy (1970). Sulphonamides are amphoteric but they behave as weak acids rather than amphoteric at physiological pH (Schott & Astigarrabia 1988). The solubility of sulphamethoxypyridazine is very low at neutral or slightly acidic pH and the drug is freely soluble in solutions of alkaline hydroxides. The pK_2 of sulphonamides is attributed to the ionization of the N^4 group and fall in a narrow range $(pK_2 = 2$–$2{\cdot}5)$, while the pK_1 corresponds to the ionization of the substituted N^1 and varies among the sulphonamides. In

earlier work (Bustamante et al 1994) a single equation was able to predict the two solubility peaks of sulphanilamide ($pK_{a1} = 10\cdot8$), sulphamethazine ($pK_{a1} = 6\cdot65$) and sulphamethoxypyridazine ($pK_{a1} = 6\cdot7$) found in ethanol–water and ethanol–ethyl acetate mixtures. The solubility peak in the ethanol–water mixtures appears at the same solvent composition (80% ethanol in water, $\delta_1 = 30\cdot87\,MPa^{1/2}$) for these sulphonamides. The variation of solubility is a function of the solubility parameter of the solvent mixtures and the Lewis acid and Lewis base characteristics of these solvent mixtures, as measured by their acidic and basic partial solubility parameters (Bustamante et al 1994).

The solubility of sulphamethoxypyridazine is studied in this work at several temperatures as a function of solvent composition to investigate whether the enthalpy or entropy of mixing provides an explanation for the existence of the two solubility maxima found. These thermodynamic quantities may also be related to solute–solvent and solvent–solvent interactions in terms of the water structure as compared with ethanol, a nonaqueous hydrogen-bonded solvent and ethyl acetate, a Lewis-base solvent.

Materials and Methods

The solubilities of sulphamethoxypyridazine in ethanol–water and ethyl acetate–ethanol mixtures (Table 1) were determined at 20, 25, 30, 35 and 40°C. The pH of the ethanol–water mixtures ranged between 6·64 and 7·56 and the pH of the saturated solution in water was 6·04 at 25°C. The solute (Interchimia, Hamburg, Germany) and solvents (analytical or UV-IR grade, Panreac, Monplet & Esteban, Barcelona) were used as received. The solute was tested for purity in a differential scanning calorimeter (DSC; Mettler TA 3000) and the experimental heat and temperature of fusion were $22\cdot3\,kJ\,mol^{-1}$ and $453\cdot4\,K$, respectively. The solubility was determined as follows. Samples (20 mL) containing an excess of solute were shaken for 72 h and allowed to reach equili-

brium in a constant temperature bath held at 20, 25, 30, 35 or $40 \pm 0\cdot2°C$. Preliminary experiments showed that 72 h was sufficient to ensure saturation at the temperatures under study. The excess solute was eliminated by filtration through Durapore or Fluoropore filters (pore size $< 1\,\mu m$), depending on the compatibility of the solvent with the filter. Four samples of each solution were diluted with methanol and assayed in a double-beam spectrophotometer (Bausch and Lomb 2000) at 268 nm. The small amount of solvent present after dilution with methanol did not affect the absorbance readings. The concentration (molarity units) of the solute in methanol was determined from Beer's law. The densities of the saturated solutions, needed to express the results in mole fractions, were measured in 10-mL pycnometers at 25°C. The results are the average of at least four solubility determinations. The experimental variation in solubility was less than 3% in replicated samples.

Results

Table 1 lists the logarithm of the mole fraction solubility of sulphamethoxypyridazine in ethanol:water and ethanol:ethyl acetate at the five temperatures studied. A plot of the mole fraction solubility of the drug X_2, against the solubility parameter of the solvent mixtures, δ_1, shows two solubility peaks at all temperatures tested (Fig. 2). The different curves obtained when water or ethyl acetate was added as the cosolvent to ethanol may be assumed to be the result of changes in the enthalpy and entropy of mixing. The partial molar heat and entropy of mixing of sulphamethoxypyridazine at 25°C were calculated according to the expressions:

$$\Delta\bar{H}_{2mix} = \Delta\bar{H}_{2soln} - \Delta H_F^{25} \qquad (1)$$

$$\Delta\bar{S}_{2mix} = \Delta\bar{S}_{2soln} - \Delta S_F^{25} \qquad (2)$$

where ΔH_F^{25} and ΔS_F^{25} are the heat and entropy of fusion

Table 1. Experimental solubility (ln X_2) of sulphamethoxypyridazine in ethanol:water and ethanol:ethyl acetate mixtures.

v/v	Ethanol:water ratios					
	93:7	80:20	70:30	60:40	30:70	0:100
δ_1^a	27·57	30·87	32·91	35·04	41·44	47·86
T,°C						
20	−6·3067	−6·0438	−6·1579	−6·5096	−8·3959	−10·2914
25	−6·1610	−5·9096	−6·0044	−6·4098	−8·1611	−10·1959
30	−5·8680	−5·6617	−5·7906	−5·9915	−7·8314	−9·8950
35	−5·7357	−5·5516	−5·6020	−5·7747	−7·5230	−9·6916
40	−5·5306	−5·2979	−5·2829	−5·5176	−7·2902	−9·5883
v/v	Ethanol:ethyl acetate ratios					
	100:0	65:35	30:70	13:87	0:100	
δ_1^a	26·51	23·67	20·88	19·51	18·49	
T,°C						
20	−6·7055	−5·5491	−5·2621	−5·5555	−6·3127	
25	−6·5384	−5·4762	−5·2320	−5·4947	−6·1859	
30	−6·4773	−5·3628	−5·1687	−5·3266	−6·0464	
35	−6·2097	−5·2092	−5·1321	−5·3078	−5·8406	
40	−6·2320	−5·0803	−5·0327	−5·2445	−5·5919	

^{a} Calculated from δ_1 (mixture) $= \Sigma\delta_i\phi_i$, where δ_i is the solubility parameter of the pure solvent ($MPa^{1/2}$) ($\delta_{water} = 47\cdot86$, $\delta_{ethanol} = 26\cdot51$, $\delta_{ethyl\ acetate} = 18\cdot49$) and ϕ_i is the volume fraction of the solvent in the solvent mixture.
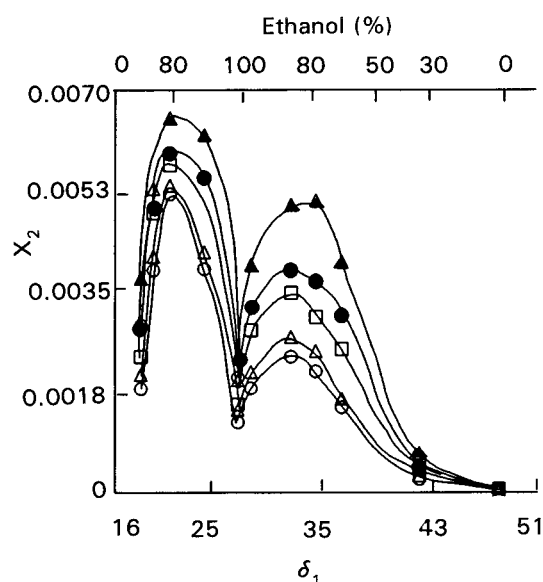
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Ethanol (%)

FIG. 2. Mole fraction solubility of sulphamethoxypyridazine in ethanol:water (right curve) and ethanol:ethyl acetate mixtures (left curve). $\bigcirc$ 20°C, $\triangle$ 25°C, $\square$ 30°C, $\bullet$ 35°C, $\blacktriangle$ 40°C.

of sulphamethoxypyridazine at 25°C. For non-ideal solutions, the slope and intercept of the vant'Hoff plots do not give directly the heat and entropy of solution. The asterisks in equations 3 and 4 indicate apparent enthalpies and entropies (Hollenbeck 1980):

$$\Delta \bar{H}_{2soln} = \left(\frac{\partial \ln a_2}{\partial \ln X_2}\right)_{T,P} \times \Delta \bar{H}^*_{2soln} \qquad (3)$$

$$\Delta \bar{S}_{2soln} = \left(\frac{\partial \ln a_2}{\partial \ln X_2}\right)_{T,P} \times \Delta \bar{S}^*_{2soln} \qquad (4)$$

where the partial derivative is the correction for the variation of thermodynamic activity (a_2) with concentration (X_2) at constant temperature and pressure. Only for ideal solutions is this term equal to unity (Hollenbeck 1980; Grant & Higuchi 1990) and $\Delta \bar{H}_{2(soln)} = \Delta \bar{H}^*_{2(soln)}$. Since

($\partial \ln a_2/\partial \ln X_2$) is always positive, the sign obtained for $\Delta \bar{H}^*_2$ from a vant'Hoff plot indicates whether the process is exothermic or endothermic. The variation of activity with concentration may be estimated from the expression (Manzo & Ahumada 1990):

$$\left(\frac{\partial \ln a_2}{\partial \ln X_2}\right)_{T,P} = 1 - \frac{2\phi_2}{X_1}\ln\left(\frac{a_{2sat}}{X_{2sat}}\right) \qquad (5)$$

where ϕ_2 is the volume fraction of the solute and X_1 the mole fraction of the solvent. The subscript, sat, indicates saturated solution. The activity of the solute at 25°C, a_{2sat} (eqn 5) is given by the expression (Hildebrand et al 1970; Hollenbeck 1980):

$$\ln a_{2sat} = -\frac{\Delta H^M_F}{R}\left(\frac{T_M - T}{T_M T}\right) \qquad (6)$$

where ΔH^M_F is the heat of fusion of the solute at the melting point (T_M) and T the absolute temperature (298 °K). Equation 6 assumes $\Delta C_p = 0$ and is as good as an approximation as assuming $\Delta C_p = \Delta S^M_F$ (Grant & Higuchi 1990).

The negative slopes obtained in Fig. 3 show that the heat of solution is endothermic for all the solvent mixtures studied. The slopes of the lines are not parallel indicating that the heat of mixing varies with solvent composition in the ethanol:water and in the ethanol:ethyl acetate mixtures. The linear relationship of ln X_2 against 1/T for all the solvent mixtures suggests that $\partial \ln a_2/\partial \ln X_2$ is reasonably constant over the temperature range of the experiment. These values are close to unity, ranging between 0·980 and 0·996 (Table 2).

Discussion

The net $\Delta \bar{H}_{2mix}$ results from the contribution of several kinds of interaction in solution (Arnett et al 1970) and may be expressed as:

$$\Delta \bar{H}_{2mix} = \Delta H_{CAV} + \Delta H_{VDW+AB} + \Delta H_H \qquad (7)$$

The enthalpy of cavity formation ΔH_{CAV} is endothermic because work must be done against the cohesive forces of

Table 2. Variation of thermodynamic activity with concentration, enthalpies and entropies at 25°C for sulphamethoxypyridazine in solvent mixtures and pure solvents[a].

No.	Solvent mixture (%)			$\partial \ln a_2/\partial \ln X_2$	$\Delta \bar{H}_{2soln}$ $\Delta \bar{H}_{2mix}$		$\Delta \bar{S}_{2soln} \Delta \bar{S}_{2mix}$	
	Ethanol	Ethyl acetate	Water		(kJ mol^{-1})		(J deg^{-1} mol^{-1})	
1	100	—	—	0·9843	19·18	−14·76	10·65	−64·18
2	93	—	7	0·9803	29·58	−4·35	49·38	−25·47
3	80	—	20	0·9761	27·52	−6·42	44·61	−30·23
4	70	—	30	0·9740	31·90	−2·04	58·56	−16·28
5	60	—	40	0·9748	38·92	4·98	79·48	4·64
6	30	—	70	0·9875	42·92	8·98	77·27	2·42
7	—	—	100	0·9961	20·04	−4·89	13·60	−61·24
8	65	35	—	0·9846	18·05	−15·89	15·88	−58·96
9	30	70		0·9887	8·40	−25·54	−14·73	−89·57
10	13	87		0·9894	12·25	−21·69	−3·88	−27·72
11	—	100		0·9892	26·90	−7·38	39·38	−35·46

[a] $\Delta \bar{H}_{2soln}$ from equation 3 using $\partial \ln a_2/\partial \ln X_2$ (5th column) and $\Delta \bar{H}^*_{2soln} = 8\cdot3143 \times$ slopes of Fig. 3. $\Delta \bar{H}_{2mix}$ from equation 1 with $\Delta H^{25}_F = 22307$ J mol^{-1}. $\Delta \bar{S}_{soln}$ from equation 4 using $\partial \ln a_2/\partial \ln X_2$ and $\Delta \bar{S}^*_{2soln} = 8\cdot3143 \times$ intercepts of Fig. 3. $\Delta \bar{S}_{2mix}$ from equation 2, where $\Delta S^{25}_F = 74\cdot81$ J deg^{-1} mol^{-1}.

the solute (Arnett et al 1970; Riddle & Fowkes 1990). The enthalpy of solute-solvent interaction ΔH_{VDW+AB} is exothermic and results mainly from van der Waals and Lewis acid-base interactions. Dipole-dipole forces are not as important in solution as in the gaseous state (Fowkes 1984). The magnitude of the solute-solvent interaction enthalpy is largely determined by the strength of hydrogen bonding. Solvation in pure water contains an additional term, ΔH_H (eqn 7), due to the structuring of water molecules around the nonpolar parts of the solute. The sign on this term is negative and contributes to lower the net ΔH_{2mix} to small positive or even negative values in aqueous solutions (Yalkowsky & Banerjee 1992).

Enthalpies and entropies of mixing

The net negative ΔH_{2mix} values (Table 2) are the result of positive enthalpy values arising from cavity formation and solute-solvent exothermic contributions. These values are reasonable because sulphamethoxypyridazine may undergo hydrogen bonding with the solvent mixtures which, in addition to the van der Waals interaction, is a possible source of negative heat of mixing. However, these values are not large enough to overcome the entropy loss. As a result, the free energy of mixing is positive and the solubility is low. The values given in Table 2 may not be absolute values, but the relative comparison among solvents is not dependent on the accuracy of $\Delta H_F{}^{25}$ and a_{2sat} since they are constant at constant T and are equally applied to each calculation.

For the ethanol-water mixtures, as water is added to ethanol (0 to 70% in ethanol, Table 2), both ΔS_{2mix} and ΔH_{2mix} increase. This suggests that dilution of ethanol breaks the hydrogen bonding between ethanol and the solute, and the system becomes less ordered. However, from the 30:70 ethanol-water mixture to pure water, the trend changes and both ΔS_{2mix} and ΔH_{2mix} decrease, suggesting hydrophobic solvation in water (eqn 7). If this effect did not take place, the ΔH_{2mix} value would be larger in water than in the ethanol-water mixtures (Table 2) due to the unfavourable contribution of the cavity term, which is larger in water than in organic solvents (Pohorille & Pratt 1990). For the solvent mixtures of higher water content (5-7, Table 2) ionization of sulphamethoxypyridazine does not seem to play an important role because for sulphonamides the standard entropy of ionization shows the opposite trend; i.e. it decreases as the dielectric constant of the solvent is lowered, whereas the standard enthalpy of ionization remains almost constant (Agrawal et al 1987). The exothermic contribution of hydrophobic solvation makes the net ΔH_{2mix} (eqn 7) smaller than expected. Hydrophobic solvation is accompanied by a large entropy loss and as a result the aqueous solubility of sulphamethoxypyridazine in water is low.

It is interesting to note that enthalpy and entropy of mixing can differ dramatically in solvents showing similar free energy of mixing. For example, ΔH_{2mix} in the 60:40 ethanol-water mixture is $+4.98$ kJ mol^{-1} and ΔS_{2mix} is $+4.64$ J deg^{-1} mol^{-1}, whereas in ethanol ΔH_{2mix} is -14.76 kJ mol^{-1} and ΔS_{2mix} is -64.18 J deg^{-1} mol^{-1} (Table 2). The free energies of mixing are similar, $\Delta G_{2mix} = \Delta H_{2mix} - T \Delta S_{2mix} = 3.6$ and 4.37 kJ mol^{-1},
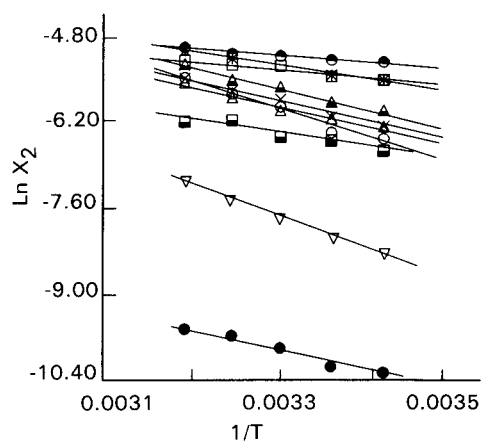

FIG. 3. Vant'Hoff plots of sulphamethoxypyridazine in solvent mixtures. ● water, ▽, 30:70 ethanol-water, ■ ethanol, ○ 60:40 ethanol-water, △ ethyl acetate, × 70:30 ethanol:water, ▲ 80:20 ethanol:water, □ 13:87 ethanol:ethyl acetate, ✶ 65:35 ethanol:ethyl acetate, ◐ 30:70 ethanol:ethyl acetate.

respectively. This fact is usually due to enthalpy-entropy compensation (Hepler 1963; Schowen 1967):

$$\Delta H_{2mix} = \Delta H_{2mix}{}^{int} + \beta \Delta S_{2mix} \qquad 8$$

where $\Delta H_{2mix}{}^{int}$ is a constant (J mol^{-1}) and β is the isoergonic temperature (K). Enthalpy-entropy compensation is a characteristic of the hydrogen bond and causes the free energy to be relatively small for this kind of interaction (Grant & Higuchi 1990). Fig. 4 shows a good linear relationship of ΔH_{2mix} and ΔS_{2mix} except for water. The equation (excluding water) is:

$$\Delta H_{2mix} = 4840.1 + 337.3 \Delta S_{2mix} \qquad 9$$
$$r = 0.981$$

The correlation covers a wide polarity range, from ethyl acetate ($\delta_1 = 18.49$) to 30% ethanol in water ($\delta_1 = 41.44$) (Table 1) and the isergonic temperature, $\beta = 337.3$ K, is reasonable for processes involving hydrogen bonding. It should be noted that the slope of equation 9 does not vary if ΔH_{2mix} and ΔS_{2mix} are calculated with the assumption that $\Delta C_p = \Delta S_F{}^M$. For the separate set of ethanol:water mixtures (excluding water), the isergonic temperature is $\beta = 324.5$ K (Fig. 3) which is in striking agreement with the isergonic temperature reported for solvation phenomena in methanol, $\beta = 320$ K (Schowen 1967). Similar isergonic temperatures may involve similar solvation processes, and the deviation of water from the general trend (Fig. 4) could be the result of the additional hydrophobic solvation effect. Hermann (1971) gives $\Delta H_{2mix} = -11.97$ kJ mol^{-1} and $\Delta S_{2mix} = -76.98$ J deg^{-1} mol^{-1} for methane in water. These values may be taken roughly as the hydrophobic effect of water on the CH_3 group of sulphamethoxypyridazine to crudely estimate the sum of cavity plus solute-solvent interaction terms for sulphamethoxypyridazine in water. Using equation 7 and Table 2, $\Delta H_{CAV} + \Delta H_{VDW+AB} = \Delta H_{2mix} - \Delta H_H = -4.89 - (-11.97) = +7.08$ kJ mol^{-1}. A similar
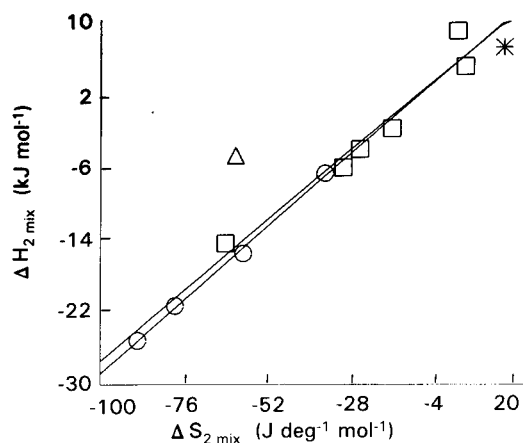
Fig. 4. Enthalpy–entropy relationship. O Ethanol–ethyl acetate, □ ethanol–water, △ water, * water, after subtracting the hydrophobic contribution of $\Delta \bar{H}_{2mix}$ (ΔH_H). The solid lines are the regression lines for each data set.

analysis gives $\Delta S_{CAV}+ \Delta S_{VDW+AB} = -61\cdot24 - (-76\cdot98) = +15\cdot74$ J deg^{-1} mol^{-1}. When these values are plotted in Fig. 4, water follows the general trend.

Enthalpies and entropies of transfer

The enthalpies and entropies of transfer of sulphamethoxypyridazine from solvent A to solvent B provide direct comparison of solvation characteristics of the solvent. They do not depend on accuracy of $\Delta H_F{}^{25}$ because this term is a constant and cancels out:

$$\Delta H_{tr}(A \rightarrow B) = \Delta \bar{H}_{2soln}(B) - \Delta \bar{H}_{2soln}(A) \qquad 10$$

$$\Delta S_{tr}(A \rightarrow B) = \Delta \bar{S}_{2soln}(B) - \Delta \bar{S}_{2soln}(A) \qquad 11$$

The enthalpies and entropies of transfer of sulphamethoxypyridazine from ethanol to ethanol–water and from ethanol to ethanol–ethyl acetate mixtures are calculated at 25°C from Table 2 and plotted against the percent of cosolvent (water or ethyl acetate) in Figs 5 and 6. The relationships are not linear with the composition of the solvent mixture and the values shift from negative to positive from 87% ethyl acetate in ethanol to pure ethyl acetate. Literature results also report nonlinear relationships and shifts from negative to positive values for the transfer of tetraalkylammonium compounds, alkanols, urea (Somsen 1991) and the fluoride ion (Hefter 1991) in solvent mixtures. The literature also reports curves displaying minima and maxima at certain compositions of the solvent mixture, depending on the interplay of solvent-solvent and solute-solvent interactions (Hefter 1991).

The entropy of transfer of sulphamethoxypyridazine from ethanol to water is nearly zero (from Table 2, $13\cdot60 - 10\cdot65 = 2\cdot95$) which is in striking agreement with the close zero value found for the transfer of the fluoride ion between these solvents. F$^-$ is the only ion known where solvation was suggested to be entropy controlled (Hefter 1991), and this similar behaviour of F$^-$ and sulphamethoxypyridazine shows the large influence of solvent structure in determining the solvation process. The entropy of transfer of sulphamethoxypyridazine from aprotic to protic solvents
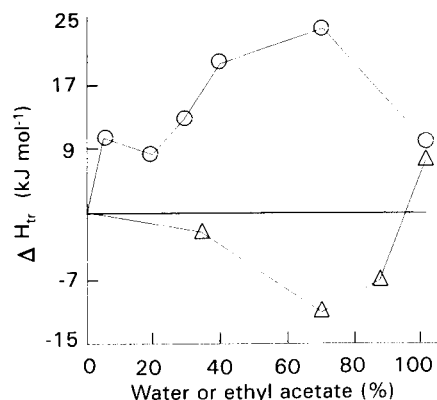

Fig. 5. Enthalpy of transfer of sulphamethoxypyridazine from ethanol to ethanol–water mixtures (O) and from ethanol to ethanol-ethyl acetate mixtures (△).

is negative (unfavourable). From Table 2, ΔS_{tr}(ethyl acetate $\rightarrow$ water) is $13\cdot60 - 39\cdot38 = -25\cdot78$ J deg^{-1} mol^{-1}, and ΔS_{tr}(ethyl acetate $\rightarrow$ ethanol) is $10\cdot65 - 39\cdot38 = -28\cdot73$. As contrasted, the transfer of F$^-$ from aprotic to protic systems shows the opposite sign (Hefter 1991). This differentiates the behaviour of an ion, preferentially solvated by water, and sulphamethoxypyridazine preferentially solvated by a less structured solvent, ethyl acetate.

The enthalpy of transfer of sulphamethoxypyridazine from ethanol to ethanol:water mixtures is positive (unfavourable, upper curve of Fig. 5). The entropy of transfer follows a similar pattern but the positive values favour the process (upper curve of Fig. 6). This suggests that the solubility maximum found in the ethanol–water mixtures (Fig. 2) is largely determined by the structure of the solvent mixture (more positive entropy values). Fini et al (1986) found that the transfer of anti-inflammatory drugs from an alcohol, octanol, to water was also essentially entropic.

The transfer of sulphamethoxypyridazine from a hydrogen-bonded solvent, ethanol, to a proton acceptor solvent, ethyl acetate, has different characteristics from those involving ethanol and water. The small initial increase of ΔS_{tr} from 100% ethanol to 35:65 ethyl acetate:ethanol (Fig. 6,
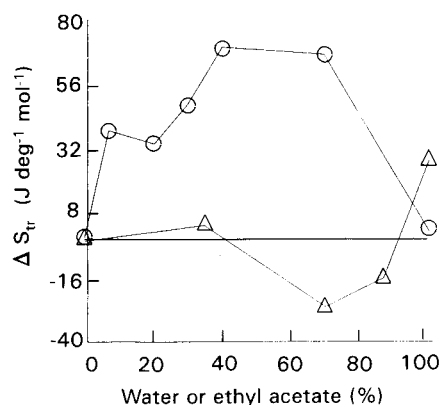

Fig. 6. Entropy of transfer of sulphamethoxypyridazine from ethanol to ethanol–water mixtures (O) and from ethanol to ethanol–ethyl acetate mixtures (△).

lower curve) suggests that the breaking of self-association of ethanol does not increase the entropy of the system as much as found when ethanol is added to water (Fig. 6, upper curve). The structural effect of ethanol is much smaller than that of water since ethanol associates as chains rather than as networks (James 1986). As ethyl acetate is added to ethanol, the solute-solvent interaction, possibly hydrogen bonding, is facilitated and the enthalpy and entropy of transfer become more negative. The lower curves of Figs 5 and 6 show minimum enthalpy and entropy values at 30:70 ethanol:ethyl acetate. The free energy has the lowest value and this point corresponds to the solubility maximum found in this solvent mixture (Fig. 2). Beyond 70% ethyl acetate, the ordering of the system decreases as shown by the less negative entropy values which shifts to positive values in pure ethyl acetate. At these higher concentrations of ethyl acetate, the enthalpy also increases. This suggests that the cavity term (eqn 7) becomes larger, due possibly to a more effective solvent-cosolvent interaction, and the sulphamethoxypyridazine solubility decreases. As contrasted with the water–ethanol system, the solubility maximum found for sulphamethoxypyridazine in ethanol:ethyl acetate (Fig. 2) is due to the favourable enthalpy contribution to the free energy of mixing.

This study has shown the different behaviour of aqueous solutions and nonaqueous solutions of solvents capable of undergoing Lewis acid-base interaction toward a solute with donor-acceptor ability. The two solubility maxima found in ethanol–water and ethanol–ethyl acetate are produced by different causes. In the ethanol-water mixtures, solvation is entropically driven, whereas in the ethanol–ethyl acetate mixtures enthalpy is the driving force that increases the solubility. The smooth solubility curves obtained for each solvent mixture are the result of cancellation of largely opposing changes in enthalpy and entropy. The systems show the enthalpy-entropy compensation characteristics of hydrogen bonding. Water deviates from the general linear relationship due possibly to its structural effects.

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