Solubility in amide-water cosolvent systems: a thermodynamic view

RICHARD E. LINDSTROM* AND CHI HO LEE

School of Pharmacy, The University of Connecticut, Storrs, CT 06268 U.S.A.

The solubility of methyl *p*-hydroxybenzoate was determined in a series of amide-water cosolvents in the temperature range 25–40 °C. Thermodynamic values for the transfer of the ester between the cosolvent system were calculated using a method which permits a focus on the effects of amide alkylation. The results are interpreted in terms of hydrophobic bonding principles which suggest that the alkyl groups on the amide detract from amide-water interaction and enhance amide-ester interaction.

The nature of the solvent-cosolvent interactions which lead to the increased solubility of a solute in cosolvent systems is uncertain. Accordingly, a need for further information on the phenomenon exists. The present report relates to aspects of interactions in cosolvent systems comprised of water and low molecular weight amides (Giaquinto 1972; Lindstrom 1979).

If it is assumed that the enhanced ester solubility in amide-water cosolvent systems is ultimately due to the amide-ester interactions that promote the formation of cooperative bonds and a reduction of hydrophobic surface energy, then several conditions may be anticipated. First, the free energy of the system should decrease as the availability of amide alkyl groups increases. Second, the entropy associated with the solution of an ester (the methyl *p*-hydroxybenzoate) should be greater in water-alkylated amide cosolvent systems than in water alone. The former would involve a degree of hydrophobic bonding, while the latter entails, in all probability, significant water structuring near the non-polar areas of the ester. Finally, the enthalpy of the ester–amide–water system will be somewhat greater than that of the ester–water system, the difference corresponding to the reduced solvent structure near the ester in the amide-water systems.

We have investigated these possibilities through determination of methyl *p*-hydroxybenzoate solubility in various amide-water cosolvent systems as a function of temperature.

METHODS

The solubility of methyl *p*-hydroxybenzoate in thirteen amide cosolvent systems was determined

* Correspondence.

at various temperatures in the range 25–41·56 °C according to the procedure outlined previously (Giaquinto et al 1977). Results of the determinations are summarized as smoothed values in Table 1. The hard data may be obtained from the authors.

Table 1. The solubility of methyl *p*-hydroxybenzoate in water and in various 0·01 mol fraction amide-in-water cosolvent systems within the temperature range 25–40 °C.

| Cosolvent | Ester solubility[a], $X_2 \times 10^4$ | | | |
	25 °C	30 °C	35 °C	40 °C
Water	2·61	3·24	4·01	4·92
Formamide	2·84	3·52	4·33	5·29
N-Methylform-amide	3·36	4·17	5·15	6·31
N-Ethyl formamide	3·69	4·59	5·68	6·99
N-Propylform-amide	4·30	5·36	6·62	8·14
N-Methylacet-amide	3·91	4·83	5·92	7·21
N-Ethylacetamide	4·11	5·13	6·36	7·82
N-Methylpropion-amide	4·15	5·18	6·41	7·88
N-Propylpropion-amide	5·22	6·25	7·45	8·83
Dimethylform-amide	4·15	5·17	6·41	7·89
Diethylformamide	5·49	7·01	8·87	11·13
Dimethylacet-amide	4·82	6·02	7·46	9·18
Diethylacetamide	6·50	8·02	9·83	11·97
Dimethylpropion-amide	5·57	7·06	8·89	11·10

[a] Smoothed values calculated from a linear least squares treatment of experimental data.

DISCUSSION

It is convenient to view the results of this study through standard free energies of transfer, ΔG_t°, as they are defined by

$$\Delta G^\circ = 2 \cdot 303 \, RT \log \frac{X_{2,f}}{X_{2,a}} \qquad (1)$$

where $X_{2,f}$ and $X_{2,a}$ are the mole fraction solubilities of methyl p-hydroxybenzoate in formamide and in alkylated amide cosolvent systems, respectively. The nature of equation 1 (Nozaki & Tanford 1963) is that it represents interactions solely between the ester and the solvents. Since the latter differ only in the degree of alkylation of the amide cosolvent, ΔG_t° are clearly a measure of alkylation effects.

For purposes of this report, it is assumed that the ester activity coefficient is unity in all solutions under consideration. This is not a particularly risky assumption since (i) the ester concentration is extremely low in all cases; and (ii) the solvent systems share many common features including the fact that they are 99% water.

Values for the standard entropy of transfer, ΔS_t°, are calculated according to the expression:

$$\Delta S_t^\circ = -[d(\Delta G_t^\circ)/dT] \qquad (2)$$

The Gibbs-Helmoltz relationship will then yield the standard free enthalpies of transfer, ΔH_t°.

For the most part, the changes reported in Table 2 are small. This should be expected in view of the rather small differences in the nature of the co-solvent systems. However, the thermodynamic values are significant. The magnitude of the values suggest, for example, that complexation involving the formation of covalent or coordinate covalent bonds seems an unlikely factor in explaining the observations. An inspection of the data in Table 1 suggests this to be the case for the water-to-formamide transfer as well.

The enthalpies of transfer, ΔH_t°, are relatively small, as is generally observed in hydrophobic events. Most of the values are positive, suggesting that there is a net breaking of water-solute (amide or ester) bonds as the ester is transferred to the alkylated amide cosolvents. The same results are seen if the present treatment is applied to the sulfadiazine-water-dimethylformamide data of Elworthy & Worthington (1968).

The entropy changes of transfer, ΔS_t°, with one exception are positive. This fact further detracts from the possibility of a complexation mechanism for the observed events. Instead, the ester finds itself at a higher entropy state, a situation quite compatible with hydrophobic bonding principles. Within an amide family, the formamides for example, the entropy change generally becomes more positive with the degree of alkylation.

Table 2. Thermodynamic values for the transfer of methyl p-hydroxybenzoate from a 0·01 mol fraction formamide-in-water cosolvent system to systems in which other alkylated amides replace the formamide cosolvent on a mol-for-mol basis.

ΔG_t°, cal mol⁻¹* with cosolvent				ΔS_t°	ΔH_t°
25 °C	30 °C	35 °C	40 °C	e.u.	cal mol⁻¹
Formamide					
0	0	0	0	0	0
N-Methylformamide					
-100	-102	-106	-110	0·68	103
N-Ethylformamide					
-155	-160	-166	-173	1·20	203
N-Propylformamide					
-246	-253	-260	-268	1·46	189
N-Methylacetamide					
-189	-191	-191	-193	0·24	-117
N-Ethylacetamide					
-219	-227	-235	-243	1·60	258
N-Methylpropionamide					
-225	-233	-240	-248	1·52	228
N-Propylpropionamide					
-360	-346	-332	-319	-2·74	-1177
Dimethylformamide					
-225	-231	-240	-249	1·62	258
Diethylformamide					
-390	-415	-439	-463	4·86	1058
Dimethylacetamide					
-313	-323	-333	-343	2·00	283
Diethylacetamide					
-490	-496	-502	-508	1·20	-132
Dimethylpropionamide					
-399	-419	-440	-461	4·14	835

* × 4·186 for J mol⁻¹

Values for the free energy change of transfer, ΔG_t°, show (i) that amide alkylation provides a more thermodynamically suitable environment for the ester, and (ii) that the conditions for the ester generally improved as the temperature increases. The N-propylpropionamide system is, again, an exception to the rule in the latter case.

The continual decrease in the free energy of transfer with amide alkylation at any one temperature must result from an increased potential for cooperative, or hydrophobic interactions between the amide and the ester. The result may lead to the promotion of the amide excesses which have been suggested to exist near the ester molecules in these solutions (Lindstrom 1979). It is also apparent from the present data that the amide-ester interaction in these solutions is important. This is seen from the fact that, on the average, (i) each methylene group added to the nitrogen in N-substituted amides reduces the free energy by approximately 90 cal mol⁻¹ (377 J mol⁻¹); and (iii) each methylene added to the second alkyl on nitrogen in NN-disub-

stituted amide reduces the free energy by approximately 120 cal mol⁻¹ (502 J mol⁻¹).

The further general decrease in $\Delta G_t°$ for each amide system as the temperature increases is undoubtedly related to changes in the solvent structure. This, in turn, permits more intimate contact between the ester and the amide. Another view of the data in Table 2 is interesting in this regard. On subtracting the mole fraction ester solubility in water from the solubility in the amide cosolvent systems, the amount of ester that is in solution because of the presence of the amide is obtained. Dividing that figure by the mole fraction amide in the system gives the number of amide molecules "needed" to accommodate the extra ester. At 25 °C, the numbers range from approximately 170 in the case of formamide, down to 25 in solutions containing diethylacetamide. When the temperature is raised to 40 °C, those numbers decrease by sone 30–40%. It is unlikely that each ester molecule is associated directly with that many amide molecules. However, it is apparent from these data that the amides find the ester more accessible at the higher temperature.

CONCLUSION

The results of this study lend support to a view that cosolvency in amide-water systems is due to a relatively strong interaction between the amide and the solute that is mediated by the degree of amide-water interaction. The net attraction in the latter is apparently reduced through alkylation of the amide, leading to enhanced amide-ester interaction and a possible excess of amide in the region of the solute molecule.

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