Solubility in Amide–Water Cosolvent Systems II: Cosolvent Excess at Solute Surface

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Abstract □ The solubility of methylparaben was determined at 25° in a series of amide–water cosolvent systems. The data were used to demonstrate the possibility of an amide excess at or near the ester solute over that in the bulk solvent. The analysis, stemming from an interfacial tension–solute area solubility model proposed by earlier workers, involved data obtained as a function of amide concentration and as a function of amide alkylation. Both sets of data support the basic contention of the paper.

Keyphrases □ Solubility—methylparaben in amide–water cosolvent systems, cosolvent excess □ Methylparaben—solubility in amide–water cosolvent systems, cosolvent excess □ Amide–water cosolvent systems—methylparaben solubility, cosolvent excess

An interesting approach to explaining the solubility of nonelectrolytes in polar solvents was proposed and tested by previous investigators (1–6). The idea stems from the concepts of regular solutions (7), and it describes the excess work of cohesion and adhesion in forming those solutions in terms of the tension and surface area at the solute–solvent interface. The apparent success of the model has prompted an extension of these relatively new concepts.

BACKGROUND

The mole fraction solubility of a solid nonelectrolyte, X_3, may be represented as:

$$\ln X_3 = -\left[\frac{\Delta H_f(T_m - T)}{RTT_m}\right] + [-V_3\phi_1^2(\delta_2 - \delta_1)^2/RT] \quad \text{(Eq. 1)}$$

where the first term on the right is the ideal solubility of the solid material in any solvent as calculated using the heat of fusion, ΔH_f, the melting point of the solid, T_m, and the temperature, T, at which the solubility is desired.

The second term on the right in Eq. 1 represents the natural logarithm of the activity coefficient, $\ln Y_3$, which adjusts for solute–solvent interactions. In that expression, V_3 is the molar volume of the solute, ϕ_1 is the volume fraction of solvent in the solution, and δ_1 and δ_2 are the solubility parameters for the solvent and solute, respectively. The latter are the subject of an excellent review (8). This approach to describing the activity coefficient is based on a summation of the energies associated with: (a) the removal of a solute molecule from the bulk solute, (b) creation of a hole or cavity in the solvent, and (c) subsequent adhesive interactions between the solute and the solvent.

Amidon et al. (2), using arguments of Langmuir (9) and Scatchard (10), suggested the following relationship as a workable alternative for the activity coefficient expression:

$$\ln Y_3 = -\gamma_{12}(SA_3) \quad \text{(Eq. 2)}$$

where γ_{12} is the tension at the interface between the solute molecule and the surrounding solvent, and (SA_3) is the surface area that the solute molecule presents to the solvent. According to this model, the nonideal energy of interaction is due to the creation of new surface, (SA_3), against the interfacial tension, γ_{12}.

Equation 2 has been discussed and tested in various forms, which permit some helpful analyses of solvent interactions with the polar and nonpolar portions of numerous nonelectrolyte solutes. One form of the expression particularly relevant to cosolvent systems is (4):

$$\log X_f = \log X_w + \sigma f_c \quad \text{(Eq. 3)}$$

in which X_f is the mole fraction solubility of the solute at volume fraction,

f_c, of the cosolvent, and X_w is the mole fraction solubility of the solute in water. The term σ is defined as:

$$\sigma = \frac{C(\gamma_w^0 - \gamma_c^0)(HYSA_3)}{2.303kT} \quad \text{(Eq. 4)}$$

where γ_w^0 and γ_c^0 are the macroscopic interfacial tensions between tetradecane (a model hydrophobic surface) and water and between tetradecane and pure cosolvent, respectively. The hydrophobic surface area for the solute is $(HYSA_3)$, and C is a correction for the extremely small radius of curvature at the solute molecule surface. Tests using aqueous cosolvent mixtures with glycerin, propylene glycol, ethylene glycol, formamide, methanol, and ethanol over the range from pure water to pure cosolvent suggest that Eq. 4 is a reliable representation and that C has a relatively constant value near 0.5.

While there is general agreement that theory predicts a reduced surface tension at the solute–solvent interface because of the small radius of curvature, some disagreement exists (11) as to whether the reductions should be as great as 50%. Arguments for the curvature effects as they relate to cosolvent systems have assumed that the solvent mixture at the solute surface is of the same composition and character as it is in the bulk. Indeed, it was suggested (3, 4) that the thermal motion of the solute molecules and the already lowered tension at the curved interface with the solvent preclude the accumulation of cosolvent molecules at the solute surface over that in the bulk of the mixed solvent. These researchers (3, 4) showed compelling evidence that this hypothesis may be true in reporting rather constant values for C in Eq. 4 and σ in Eq. 3 for several cosolvent–solute systems.

In spite of the evidence, however, it seems reasonable to reconsider the possibility of a cosolvent excess at or near the solute. In this regard, one must ask if the shearing force on a diffusing semipolar solute is sufficient to overcome the van der Waal's interactions between it and the water and cosolvent molecules, as has been suggested (3, 4). These interactions, often referred to as nonspecific because they are nondirectional and lack a definite stoichiometry (12), can be significant. Thus, it is difficult to accept solute diffusion that is completely independent of some solvation shell or environment. Furthermore, it can be argued that the tendency for a cosolvent to partition to the molecule–solvent interface is not controlled so much by the existing tension at that interface as by the need to minimize the energy of the entire system. Thus, the lowered tension at the solute–solvent interface does not preclude cosolvent adsorption to that surface with consequent further tension lowering.

The latter contentions have significant possibilities with regard to cosolvency mechanisms. Accordingly, it seemed desirable to investigate the conditions further. The present paper is a supplemental and, perhaps, more detailed view of the solute–cosolvent microinterface in that it focuses on very water-rich systems where more characteristic cosolvent effects may be evident.

EXPERIMENTAL

The data used in the preparation of this paper were reported previously (13, 14). In brief, the procedures for obtaining these data entailed: (a) preparation of the amide–water solvent systems by careful weighing of the two ingredients, (b) equilibration of excess methylparaben with the cosolvents at 25.0°, and (c) determination of the ester concentration in the resulting solutions using a standard UV spectrophotometric procedure. The results pertinent to the present study are listed in Tables I and II.

The volume fraction values, f_a, shown in Tables I and II were calculated according to:

$$f_a = \frac{X_a \overline{V}_a}{X_a \overline{V}_a + X_w \overline{V}_w} \quad \text{(Eq. 5)}$$

where X and $\overline{V}$ refer to mole fractions and partial molar volumes, respectively, of the amide, a, and the water, w, in the binary mixtures. The

Table I—Mole Fraction Solubility of Methylparaben, X_f, in Various Amide-in-Water Cosolvent Systems at 25°

Amide	$X_a{}^a$	$f_a{}^b$	$\dfrac{X_f}{\times 10^3}$	$\dfrac{\log X_f{}^c}{-\log X_w}$	σ^d
Formamide	0	0	0.246	—	—
	0.0100	0.0213	0.306	0.095	4.46
	0.0258	0.0573	0.368	0.175	3.26
	0.0506	0.1029	0.534	0.337	3.38
	0.0746	0.1483	0.712	0.462	3.12
	0.1002	0.1946	0.948	0.586	3.01
	0.1248	0.2371	1.23	0.699	2.95
	0.1490	0.2768	1.55	0.799	2.89
	0.1747	0.3169	1.84	0.874	2.76
	0.1997	0.3538	2.35	0.980	2.77
Methylformamide	0	0	0.246	—	—
	0.0100	0.0307	0.344	0.146	4.76
	0.0247	0.0734	0.523	0.328	4.47
	0.0497	0.1406	0.939	0.582	4.14
	0.0754	0.2036	1.61	0.816	4.01
	0.0998	0.2598	2.51	1.009	3.88
	0.1245	0.3105	3.83	1.192	3.84
	0.1490	0.3572	5.44	1.345	3.77
	0.1736	0.4011	8.29	1.528	3.81
	0.1981	0.4416	11.72	1.678	3.80
Dimethylformamide	0	0	0.246	—	—
	0.0100	0.0409	0.431	0.244	5.95
	0.0249	0.0969	0.830	0.528	5.45
	0.0499	0.1799	2.04	0.919	5.11
	0.0745	0.2513	4.57	1.269	5.05
	0.0992	0.3150	10.39	1.626	5.16
	0.1224	0.3686	22.07	1.953	5.30
	0.1440	0.4137	40.71	2.219	5.36
	0.1644	0.4534	61.07	2.395	5.28
	0.1833	0.4869	83.60	2.531	5.20

[a] Mole fraction of amide in the binary aqueous cosolvent system. [b] Volume fraction of amide in the binary aqueous cosolvent system. [c] Corresponding terms in Eq. 3. [d] Calculated according to Eq. 3.

partial molar values employed were those corresponding to the appropriate amide mole fraction. Measurements equivalent to density determinations to 1 ppm were the bases for these volume data (13).

DISCUSSION

The data in Table I report cosolvency effects produced by changes in cosolvent concentration. Those in Table II report the analogous effects as the hydrophobic nature of the cosolvent was varied. Both sets of data strongly suggest that an excess of cosolvent in these aqueous solutions may be found at or near the solute–solvent interface.

Table I presents the results of a study in which the solubility of methylparaben was determined in aqueous cosolvents of increasing formamide, methylformamide, or dimethylformamide concentration. The last column of the table lists the σ values calculated according to Eq. 3 for each solution system. The trends in all three data sets are similar. The σ value is highest at the low amide concentrations and decreases to a somewhat constant value which appears to be characteristic of the particular amide involved. This result contrasts with the findings and suggestions of Yalkowsky et al. (3, 4) indicating that σ would be a constant as described in Eq. 4.

Inspection of the parameters in Eq. 4 reveals little that may change to meet the present circumstance if one is to subscribe to the interfacial tension-solute surface area model for solubility predictions. Both γ_w^0 and γ_a^0, whatever their precise value against a suitable hydrophobic surface, are constants for the particular amide–water cosolvent systems; HYSA₃ is a constant for this study since only the solute methylparaben was used. The theoretical meaning and constancy of the curvature correction, C, are uncertain. Nevertheless, previous results involving numerous solvent systems strongly support a relatively constant, although empirical, value near 0.55 (4).

An additional point should be considered. If σ is in fact a constant, then theory may be reconciled with observation if the volume fraction of the amide in the cosolvent, f_a, is larger than that shown for the lower amide concentrations in Table I. Practically speaking, this can occur if the amide cosolvent accumulates at or near the solute molecules as an excess over that in the bulk. The result would be a higher "effective" cosolvent volume fraction, as well as a tendency toward the constant σ. Water–amide interactions and steric effects should limit this cosolvent excess and, in all probability, account for the decrease in the apparent σ to the characteristic and relatively constant values shown at higher amide concentrations in Table I. Moreover, no exception need be taken with the results

of the earlier studies since the cosolvent concentrations employed were all undoubtedly high enough to be in the range where the σ values had plateaued.

Table II presents the results of a study in which the solubility of methylparaben was determined in several 0.01 mole fraction amide-in-water cosolvent systems. The amides used were relatively simple and differed only in the degree of alkylation on the nitrogen and on the carbonyl carbon.

Values for σ (not shown) were calculated according to Eq. 3. They varied from 3.40 for acetamide to 6.43 for dimethylpropionamide. The surface tensions of several of the pure amides against air were obtained from the literature (3, 15). While some correspondence between these values and an amide–tetradecane interfacial tension might be anticipated (3), there was no obvious correlation with the calculated σ.

An inspection of the data in Table II indicates that $(\log X_f - \log X_w)$ does bear some dependence on the degree of alkylation. This relation is seen more clearly in Fig. 1 where $(\log X_f - \log X_w)$ is plotted against the number of methylene groups in the various amides. The line in the figure is a linear least-squares representation of the data, having its origin at $(\log X_f - \log X_w)$ for formamide and a slope of 0.0495.

Since $(\log X_f - \log X_w)$ is the logarithm of the activity coefficient of the solute, the slope of the line in Fig. 1 permits the calculation of the standard partial molar free energy change, $\Delta \overline{G}_t^0$, accompanying the transfer of 1 mole of solute from a saturated solution in an amide–water cosolvent to a second saturated solution in which the amide cosolvent possesses an additional methylene group per molecule. The expression is given by:

$$\Delta \overline{G}_t^0 = -2.303RT \frac{(\log X_f/X_w)}{CH_2} \qquad \text{(Eq. 6)}$$

which, upon insertion of the least-squares slope on the right, gives $\Delta \overline{G}_t^0 = -1780$ cal/methylene group.

It is interesting to consider this free energy change in contrast with several possible events. For example, a straightforward application of the interfacial tension-solute area model, using 130 Å² as the approximate (HYSA₃) for methylparaben[1], would require a decrease in γ_a^0 of -9.4 dynes/cm as each methylene group is added to the amide cosolvent to produce the energy change. If a curvature correction of 0.55 is included, the required change in γ_a^0 becomes nearly 18. Intuition and the surface

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[1] S. H. Yalkowsky, personal communication.

Table II—Mole Fraction Solubility of Methylparaben, X_f, in 0.01-Mole Fraction Amide-in-Water Cosolvent Systems at 25°

Amide	$f_a{}^a$	X_f $\times 10^3$	$\log X_f{}^b$ $-\log X_w$	γ^c
Formamide	0.0213	0.306	0.095	(58)
Methylformamide	0.0307	0.344	0.146	39 (40)
Ethylformamide	0.0394	0.388	0.198	—
Propylformamide	0.0466	0.455	0.257	—
Acetamide	0.0300	0.311	0.102	—
Methylacetamide	0.0394	0.389	0.199	35
Ethylacetamide	0.0477	0.427	0.239	—
Propylacetamide	0.0546	0.524	0.328	—
Propionamide	0.0384	0.362	0.168	—
Methylpropionamide	0.0472	0.415	0.227	32
Ethylpropionamide	0.0548	0.442	0.254	—
Propylpropionamide	0.0624	0.512	0.318	—
Dimethylformamide	0.0409	0.431	0.244	35 (37)
Diethylformamide	0.0560	0.551	0.350	28
Dimethylacetamide	0.0473	0.481	0.291	33
Diethylacetamide	0.0628	0.669	0.281	—
Dipropylacetamide	0.0785	—^{d}	—	—
Dimethylpropionamide	0.0549	0.554	0.353	—
Diethylpropionamide	0.0703	—^{d}	—	—

^{a} Volume fraction of amide in the cosolvent system. ^{b} Corresponding terms in Eq. 3. ^{c} Surface tension of pure liquid amides obtained from Ref. 15. Numbers in parentheses are the values of Yalkowsky *et al.* (3). ^{d} Separation into two phases on equilibration.

tension data shown in Table II indicate that neither change is probable. Complexation between the solute and the amides seems to be a remote possibility given the relatively low energy change and the fact that the change is related only to the degree of amide alkylation. This once again points to the possibility of an accumulation of excess cosolvent at or near the solute.

According to Traube's rule (16), the free energy of a system is reduced by 640 cal for every mole of methylene group that partitions to the air–water interface. While the reduction in the case of partitioning to a solvent–hydrophobic solute interface will undoubtedly be greater due to the enhanced dispersion interactions, this added effect probably would not triple the energy reduction needed to give the observed value. Obviously, factors other than, or in addition to, adsorption to an interface are involved.

The phase separations noted in Table II support the view that a cosolvent excess probably exists at the solute surface. Dipropylacetamide is miscible with water in all proportions, as is diethylpropionamide (13). However, the introduction of methylparaben at less than one-tenth the amide concentration leads to a separation of the otherwise stable water–amide mixtures into two systems. Again, no distinct explanation is apparent. Nevertheless, the largely hydrophobic ester indisputably provides a focus for the amide molecules in these solutions.

Presumably, the same type of amide–solvent, amide–solute, and amide–amide interactions that lead to the observed phase separations exist to varying degrees in each single-phase system obtained and studied in this work. Further investigation is necessary to characterize these interactions, which apparently promote the cosolvent excess.

SUMMARY

The solubility of methylparaben in various water-rich, amide–water cosolvent systems was studied. The findings cannot be explained on the basis of the interfacial energy-solubility model proposed by earlier workers. The present analysis finds evidence suggesting the existence of excess amide molecules near the dissolved ester over those in the bulk. Such an excess might explain the effects on solute–solvent interfacial tension and/or a decrease in the free energy of the systems through some cooperative hydrophobic effect. This matter is being studied.
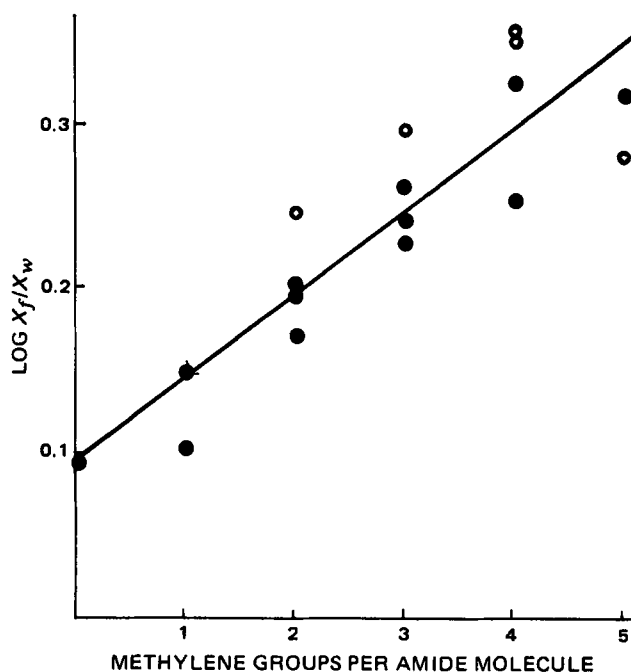

Figure 1—*Logarithm of the activity coefficient of methylparaben in its saturated solutions with 0.01-mole fraction amide-in-water cosolvents, log X_f/X_w, as a function of the number of methylene groups on the amide molecule in the respective cosolvent system. Key:* ●, *N-substituted amides; and* ○, *N,N₁-disubstituted amides.*

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