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Solubility of Nonelectrolytes in Polar Solvents III: Alkyl *p*-Aminobenzoates in Polar and Mixed Solvents

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Abstract □ The relative solubilities of *n*-alkyl *p*-aminobenzoates in water, propylene glycol–water mixtures, propylene glycol, and several other pharmaceutically important solvents can be predicted on the basis of a theoretical equation. This equation relates the activity coefficient of the hydrophobic portion of the molecule to the product of its surface area and its interfacial tension [free energy per unit area of a hydrocarbon (tetradecane) against the polar or semipolar solvent of interest]. The assumptions, conclusions, and applicability of the theoretical relationship are compared to those of the Scatchard–Hildebrand approach.

Keyphrases □ *p*-Aminobenzoates, alkyl—solubility in polar and mixed solvents, equation developed for predicting solubility □ Alkyl *p*-aminobenzoates—solubility in polar and mixed solvents, equation developed for predicting solubility □ Solubility—alkyl *p*-aminobenzoates in polar and mixed solvents, equation developed for predicting solubility, compared to Scatchard–Hildebrand approach □ Solvents, polar—solubility of nonelectrolytes (alkyl *p*-aminobenzoates)

From a pharmaceutical point of view, the most important physical-chemical property of a substance is its aqueous solubility. In addition to designating the maximum concentration (blood level) attainable for a drug, aqueous solubility is a dominant factor in partitioning and adsorption onto biological surfaces. Solubility in water-miscible polar solvents and in mixed aqueous solvents is also of great potential utility in the design of parenteral, topical, and liquid vehicles for drugs.

The ability to predict the effects of even simple structural modifications or vehicle modifications on solubility can be of great value in the design of improved drugs and drug delivery systems. Theoretical descriptions of solubility have mainly been restricted to either nonpolar solutes in nonpolar solvents (1–4) or to salts and other highly polar solutes in water (5) and are thus not directly applicable to either aqueous (or polar) solvents of pharmaceutical interest. Several empirical correlations between structure and aqueous solubility have been published (6–8) but have not received wide acceptance.

Recently, the authors (9, 10) applied an "interfacial" model to the solubilities of aliphatic alcohols and hydrocarbons in water. This model equates the combined attractive and repulsive forces between the hydrocarbon portion of the molecule and water with the product of the molecular surface area and the free energy per unit area (the latter being related to the curvature corrected hydrocarbon–water interfacial tension). It has been used successfully for primary, secondary, tertiary, linear, branched, and cyclic alcohols and hydrocarbons (10) and also for other liquid series[1]. It is also applicable to series whose members are crystalline provided that the ideal solubility (determined from thermal data) is taken into account.

THEORETICAL

In an ideal solution, the solute–solute and solvent–solvent interactions are equivalent to the solute–solvent interactions, and there is no change in heat or volume on mixing. Thus, the only thermodynamic factor affecting solubility is the entropy of mixing, which results in infinite miscibility or a mole fractional solute solubility (X_2) of unity. This is frequently written as:

$$-\log (X_2)^{\text{ideal}} = 0 \qquad \text{(Eq. 1)}$$

If the solute is a solid, the crystal lattice energy opposes the solution process. The magnitude of this effect on solubility is approximately:

$$-\log (X_2)^{\text{ideal}} = \frac{\Delta H_f}{2.303R} \frac{(T_f - T)}{T_f T} \qquad \text{(Eq. 2)}$$

where ΔH_f is the molar heat of fusion of the crystal having an absolute melting point of T_f, R is the gas constant, and T is the absolute temperature. At the melting point, where the solute becomes a liquid, $(T_f - T)$ vanishes and Eq. 2 becomes Eq. 1.

Virtually all pharmaceutically important solutes have aqueous and polar solvent solubilities well below their ideal values. For these solutes, the deviation from ideality is described by an activity coefficient (ac) defined so that:

$$-\log X_2^{\text{exp}} = \log X_2^{\text{ideal}} + \log (ac) \qquad \text{(Eq. 3)}$$

The activity coefficient reflects the sum of: *(a)* the work required to remove a solute molecule from its surrounding of other solute molecules, W_{22}; *(b)* the work required to create a cavity in the sol-

[1] S. H. Yalkowsky and G. L. Amidon, unpublished observations.

vent large enough to contain a solute molecule, W_{11}; and *(c)* the work gained on the insertion of the solute molecule into the cavity, W_{12}. Mathematically, it can be shown that (1, 2):

$$-\log(ac) = (W_{22} + W_{11} - 2W_{12})\frac{V_2\phi_1^2}{2.303RT} \qquad \text{(Eq. 4)}$$

where V_2 is the solute partial molal volume, and ϕ_1 is the solvent volume fraction. For dilute solutions, ϕ_1 and ϕ_1^2 can be approximated by unity.

Systems for which the size and polarity of the solute and solvent do not differ greatly are termed regular solutions. For these regular solutions, the term W_{12} (which is difficult to evaluate) can be accurately approximated by the geometric mean of W_{11} and W_{22} (which are easily measured):

$$W_{12} = \sqrt{W_{11}W_{22}} \qquad \text{(Eq. 5)}$$

and Eq. 4 becomes:

$$\log(ac) = -(W_{11}^{1/2} - W_{22}^{1/2})^2\frac{V_2}{2.303RT} \qquad \text{(Eq. 6)}$$

for dilute solutions. The square roots of the work terms are frequently designated as solubility parameters, δ_1 and δ_2. Thus:

$$\log(ac) = -(\delta_1 - \delta_2)^2\frac{V_2}{2.303RT} \qquad \text{(Eq. 7)}$$

For aqueous or polar solvent solutions of most drugs, the geometric mean approximation (Eq. 5) is not valid and Eqs. 6 and 7 are thus not applicable. However, Eq. 4 is still valid and would be useful if it were possible to measure W_{12} (or δ_{12}) conveniently.

In a previous publication (10), the authors discussed a two-dimensional analogy to Eq. 4, where W_{11}, W_{12}, and W_{22} are replaced by the surface and interfacial tensions γ_1, γ_2, and γ_{12} and the partial molal volume is replaced by molar surface area A_2.

Mathematically, the work required to remove a solute molecule from a bulk phase is equal to the surface area created times the surface tension of the liquid. (Curvature corrections will be discussed later.) Since removal of a single molecule from a bulk liquid phase does not measurably change the bulk phase surface area, it is only necessary to consider half of the work of cohesion:

$$\tfrac{1}{2}WC = \gamma_2 A_2 \qquad \text{(Eq. 8)}$$

Likewise, the work required to create a cavity in the solute phase capable of accommodating the solute is equal to half the solvent work of cohesion:

$$\tfrac{1}{2}WC = \gamma_1 A_2 \qquad \text{(Eq. 9)}$$

Finally, the work involved in the insertion of the solute molecule into the solvent cavity is given by the work of adhesion between the two species:

$$WA = -(\gamma_1 + \gamma_2 - \gamma_{12})A_2 \qquad \text{(Eq. 10)}$$

These three steps, which are strictly analogous to those used in deriving Eq. 4, can be summed and used to give:

$$\log(ac) = -\frac{\gamma_{12}A_2}{2.303RT} \qquad \text{(Eq. 11)}$$

The main advantage of using the two-dimensional model over the more commonly used three-dimensional one is that, for the systems of interest, the term γ_{12} is experimentally measurable whereas δ_{12} is not. Interestingly, the interfacial tension is difficult to measure for substances of similar polarity where the geometric mean rule is valid; conversely, Eq. 11 is useful for situations where Eq. 7 is inapplicable so that the two equations are complimentary rather than competitive.

Equation 11 can be obtained more intuitively by a modification of standard cavity theories of solubility. In general, these theories consider the energy required to create a cavity or hole in the solvent and then add a solute–solvent interaction term. The use of the interfacial rather than the surface tension eliminates the need to use a specific interaction term because γ_{12} is already dependent upon solute–solvent interactions.

Another means of obtaining Eq. 11 utilizes the relationship (1) that $\gamma A = \delta^2 V$ which, when substituted into Eq. 4, gives:

$$-\log(ac) = \frac{(\gamma_1 + \gamma_2 - 2\gamma_{12})A}{2.303RT} \qquad \text{(Eq. 12)}$$

for dilute solutions. With Antanow's rule, which states that $\gamma_1 + \gamma_2 - \gamma_{12} = 0$, Eq. 11 derives directly from Eq. 4. This derivation is not to be preferred because it relies upon the geometric mean rule and Antanow's rule, both of which are not generally valid. It is presented only to illustrate the parallelism between the two approaches.

To make Eq. 11 applicable to solutions of nonelectrolytes in polar solvents, consider how both γ_{12} and A_2 vary with structure. It is convenient to consider, as did Langmuir (11), the aliphatic and nonaliphatic portions of the solute separately. The total surface area A_2 of each solute is then equal to the area of the polar (*p*-aminobenzoate) moiety A_p plus the area of the aliphatic hydrocarbon chain A_h:

$$A_2 = A_p + A_h \qquad \text{(Eq. 13)}$$

When using this relationship, Eq. 11 becomes:

$$\log(ac) = \frac{\gamma_{1p}A_p + \gamma_{1h}A_h}{2.303RT} \qquad \text{(Eq. 14)}$$

where γ_{1h} is the microscopic aliphatic hydrocarbon–solvent interfacial tension, and γ_{1p} is an analogous two-dimensional term dependent upon the interactions between the solvent and the polar portion of the solute. These terms are similar to those first proposed by Langmuir (11) in his principle of independent surface activity.

If γ_{1p} and A_p are both independent of the size of the alkyl group, the change in activity coefficient with homologation would be expected to be directly proportional to the change in the hydrocarbon surface area A_h. The quantity $\gamma_{1p}A_p$ could then be determined from the intercept at A_p. These values are presently under study for a large number of polar groups. However, the present paper considers only changes in the hydrophobic portion of semipolar solutes with particular emphasis on normal aliphatic chains [branched chains were considered previously (10)].

The method of calculating the surface area of a molecule has been described in detail (10, 12). Briefly, the calculation involves determining the most likely molecular conformation of the atomic centers and then determining the areas from the van der Waals radii of the atoms and the solvent. Overlapping areas and areas not accessible to solvent are not included.

In the calculation of the interfacial tension, two factors must be considered: *(a)* the dependence of γ_{12} on the hydrocarbon moiety, and *(b)* its dependence on both the high curvature that exists at the microscopic interface surrounding a single molecule and the density difference associated with the change from a macroscopic to microscopic interface. Studies (13–15) have shown that hydrocarbon–water interfacial tension, although definitely dependent on hydrocarbon structure, falls within a narrow range and is not greatly affected by branching. Some selected values are listed in

Table I—Selected Hydrocarbon–Water Interfacial Tensions

Hydrocarbon	Interfacial Tension Reported		
	Ref. 14	Ref. 15	Ref. 13
n-Pentane	49.0[a]	—	—
	50.2[a]		
2-Methylbutane	49.64[a]	—	—
n-Hexane	50.8[a]	51.1	49.5
	51.25[a]		
Cyclohexane	—	51.2	—
n-Octane	51.7[a]	50.8	—
	50.8[a]		
	51.68[a]		
2,2,4-Trimethylpentane	50.1[a]	—	—
n-Decane	—	51.2	—
Decalin	—	51.4	—
Tetradecane	—	52.2	51.9
White mineral oil	—	51.3	—

[a] These are literature values gathered by Pomerantz *et al.* (14).

Table II—Logarithms of Mole Functional Solubilities of Alkyl *p*-Aminobenzoates in Various Solvents

Solvent[a]	Ester (Surface Area)				
	Ethyl (391.5 Å²)	Butyl (455.2 Å²)	Hexyl (518.8 Å²)	Octyl (582.4 Å²)	Dodecyl (709.6 Å²)
Ideal: 25°	−0.619	−0.406	−0.669	−0.933	−1.731
37°	−0.490	−0.239	−0.426	−0.680	−1.438
Water: 25°	−4.060	−4.378	−5.252	−7.647	
37°	−3.734	−4.508	−5.715	−8.124	−9.544
Methanol	−0.950	−0.519	−1.039	−1.729	−2.798
Ethanol	−1.080	−0.615	−1.027	−1.509	−2.370
Ethylene glycol	−1.588	−1.576	−2.374	−3.139	−4.750
Propylene glycol, 37°	−1.161	−0.710	−1.153	−1.688	−2.968
Glycerin	−1.952	−2.660	−3.494	−4.520	−6.733
Formamide	−1.671	−1.826	−2.656	−3.466	−5.063
N-Methylformamide	−0.695	−0.542	−0.678	−1.168	−2.388
N,*N*-Dimethylformamide	−0.371	−0.242	−0.359	−0.530	−2.113
Hexane, 37°	−2.778	−2.222	−2.285	−2.495	−3.015
Silicone oil, 37°	−1.005	−0.721	−0.890	−1.138	−1.771

[a] All data for 25° unless otherwise indicated.

Table I, from which it is seen that 50 dynes/in. is a good representative value. Zografi and Yalkowsky (13) made similar observations for all other solvents used in this study.

A water molecule at a highly convex surface is in contact with more water molecules than if it were at a planar surface. Since some of these neighboring molecules are on the hydrocarbon side of a plane tangent to the interface, there are stronger inward (toward the hydrocarbon) forces than there are at a flat surface. These inward forces counterbalance some outward attractive forces and thus reduce the interfacial tension. Also, a bulk interfacial tension involves void spaces in the hydrocarbon phase, which cannot be present at the microscopic interface as it has been defined here.

On this basis, Eq. 11 is modified to give:

$$\log(ac) = \frac{-C\gamma_{1h}A_h}{2.303RT} \qquad \text{(Eq. 15)}$$

where C is a curvature correction factor [due cognizance is given to the complex nature of the molecular interface in defining C (10)].

The important feature of Eq. 15 is that if C is a constant, the bulk hydrocarbon–solvent interfacial tension is a meaningful parameter with which to correlate solubility. The exact value of C may be dependent upon the size of the solvent molecule and the degree of curvature (16, 17). However, since the solvents being considered do not vary greatly in size, this variation will be ignored in the present paper.

From Eq. 15, one would expect the ability of each member of a group of solvents to solubilize a methylene group, *i.e.*, the activity coefficient of a methylene group, to be directly proportional to the hydrocarbon–solvent interfacial tension. This could be extended to mixed solvents, provided that there is no preferential localization of either component at the bulk or molecular interface.

EXPERIMENTAL

Materials—The *p*-aminobenzoate esters studied were selected from those used in Ref. 18. All solvents were of reagent grade and were used as received. The water was deionized.

Solubility Measurements—Solutions containing excess solid were allowed to equilibrate for 3 days with mild agitation. They were then filtered through a thermally equilibrated filter, diluted with methanol or hexane, and read spectrophotometrically.

Table III—Logarithms of Mole Fractional Activity Coefficients of Alkyl *p*-Aminobenzoates in Various Solvents

Solvent[a]	Ester					Slope, $\Delta \log(ac)$ / Δn
	Ethyl	Butyl	Hexyl	Octyl	Dodecyl	
Water	−3.441	−4.472	−5.583	−6.654	—	−0.537
Water, 37°	−3.245	−4.269	−5.299	−6.444	−8.106[b]	−0.525
Methanol	−0.331	−0.114	−0.370	−0.737	−1.068	−0.089
Ethanol	−0.461	−0.209	−0.359	−0.516	−0.639	−0.029
Ethylene glycol	−0.969	−1.170	−1.706	−2.146	−3.019	−0.212
Propylene glycol, 37°	−0.372	−0.472	−0.728	−1.009	−1.530	−0.120
Glycerin	−1.334	−2.254	−2.825	−3.509	−5.002	−0.358
Formamide	−1.053	−1.421	−1.987	−2.474	−3.332	−0.233
N-Methylformamide	−0.077	−0.046	−0.010	−0.175	−0.658	−0.059
N,*N*-Dimethylformamide	+0.248	+0.164	+0.309	+0.463	−0.383	−0.050
Hexane, 37°	−2.288	−1.983	−1.859	−1.815	−1.668	+0.056
Silicone oil, 37°	−0.515	−0.482	−0.465	−0.458	−0.333	+0.017

[a] All data for 25° unless otherwise noted. [b] Not used in calculation of slope because of uncertainty of experimental measurement.

Table IV—Logarithms of Mole Fractional Solubilities of Alkyl *p*-Aminobenzoates in Propylene Glycol–Water Mixtures

Solvent[a]		Ester				
Water, %	Propylene Glycol, %	Ethyl	Butyl	Hexyl	Octyl	Dodecyl
100	0	−3.734	−4.500	−5.715	−7.142	−9.540
80	20	−3.329	−3.909	−5.086	−6.168	−8.433
60	40	−2.720	−3.108	−4.234	−5.245	−7.347
40	60	−2.337	−2.250	−3.115	−3.987	−5.470
20	80	−1.828	−1.345	−2.321	−2.961	−4.386
0	100	−1.161	−0.710	−1.153	−1.688	−2.968

[a] All data for 37°.

Table V—Logarithms of Mole Fractional Activity Coefficients of Alkyl *p*-Aminobenzoates in Propylene Glycol–Water Mixtures

Solvent[a] Composition	Ester					Slope, $\Delta \log (ac)$ / Δn
	Ethyl	Butyl	Hexyl	Octyl	Dodecyl	
Water	−3.245	−4.268	−5.289	−6.444	−8.106[b]	−0.525
20% Propylene glycol	−2.840	−3.671	−4.661	−5.488	−6.995	−0.419
40% Propylene glycol	−2.230	−2.870	−3.809	−4.566	−5.910	−0.375
60% Propylene glycol	−1.848	−2.012	−2.690	−3.307	−4.032	−0.234
80% Propylene glycol	−1.339	−1.107	−1.895	−2.281	−2.948	−0.183
Propylene glycol	−0.372	−0.472	−0.728	−1.009	−1.530	−0.120

[a] All data for 37°. [b] Not used in calculation of slope because of uncertainty of experimental measurement.

Ideal Solubility Determinations—These values were calculated using Eq. 2, the heat of fusion, and the melting temperature. The heats of fusion were determined by a differential scanning calorimeter. The melting points were determined by hot-stage microscopy and differential scanning calorimetry, both as described previously (18).

Interfacial Tensions—The interfacial tensions were determined against tetradecane using the Wilhelmy plate method. The experimental details along with the dependence of interfacial tension on hydrocarbon density were described in a separate publication (13).

RESULTS

The ideal mole fractional solubilities of ethyl, butyl, hexyl, octyl, and dodecyl *p*-aminobenzoates at 25 and 37° are given in Table II. These values were calculated from the experimentally measured heats and temperatures of fusion as described. Their relationship to changes in crystal structure with chain length was discussed previously (18). The experimental mole fractional solubilities of the five esters in each of the 11 pure polar solvents considered are also given in Table II.

The experimental and ideal mole fractional solubilities of Table II and Eq. 3 were used to calculate the activity coefficients of each ester in each solvent. The logarithms of these values are listed in Table III. The expected linear decline in log *(ac)* with increasing chain length was observed in nearly all solvents. The sensitivity, σ, of the solvent to an additional methylene unit can be defined as:

$$\sigma = \frac{\Delta \log (ac)}{\Delta n} \qquad \text{(Eq. 16)}$$

(This relationship is generally not valid for $n = 0$ because the free acid can undergo donor hydrogen bonding and cannot be considered part of the series.) The value of σ for each solvent is given in the last column of Table III. The values of σ for water at 25 and 37° are close to each other and to the value determined for the alcohols and hydrocarbons (10, 11) and other series (6–8).

The logarithms of the solubilities and activity coefficients of the esters in mixed propylene glycol–water solutions are given in Tables IV and V. Each mixed solvent behaves as a pure solvent having a value of σ which is directly dependent upon its composition.

The molecular surface areas of each normal alkyl ester of *p*-aminobenzoic acid were calculated by Hermann's (12) method using an effective solvent radius of 1.5 Å as described previously (10). From these values, it is found that the surface area of the esters above propyl, like the alcohols and hydrocarbons, increases by 31.8 Å^2/methylene unit (see Table II). The interfacial tensions of each solvent against tetradecane (a representative hydrocarbon) are listed in Table VI. For mixed solvent systems the interfacial tensions were also calculated as the composition weighted average of the pure solvent values:

$$\gamma_{1h} = \gamma_{wh} f_w + \gamma_{ch} f_c \qquad \text{(Eq. 17)}$$

where w and c represent water and cosolvent, respectively. The corresponding surface tensions, solubility parameters, and dielectric constants are also listed in Table VI for comparative purposes.

DISCUSSION

Semilogarithmic plots of mole fractional solubility *versus* chain length for the alkyl *p*-aminobenzoates in any of the solvents studied (mixed or pure) show a break in linearity at $n = 4$ (see Fig. 2 of Ref. 9 and Figs. 2–4 of Ref. 18). This break has been shown to be due to the fact that the butyl ester has the weakest crystal lattice energy of the series and thus has the greatest ideal solubility. When the ideal solubility is divided into the observed solubilities, good linearity between log *(ac)* and chain length is found.

The slopes of these lines (Tables III and V) can be seen to be roughly dependent upon solvent polarity: $\sigma_{hexane} = +0.06$, $\sigma_{glycerin} = -0.36$, and $\sigma_{water} = -0.53$. Comparisons of σ with each parameter in Table VI were considered, but the best correlation was obtained with interfacial tension; therefore, the discussion will be confined to interfacial tension for which linearity may be expected.

Since the increase in surface area per methylene unit is a constant (31.8 Å^2 above the propyl ester), Eqs. 15 and 16 can be combined to give:

$$\sigma = \frac{-C\gamma_{1h}}{2.303RT} \qquad \text{(Eq. 18)}$$

Table VI—Solvent Properties

Solvent	Solubility Parameter	Dielectric Constant	Surface Tension	Interfacial Tension against Tetradecane
Water	23.4	78.5	72.0	51.9
Methanol	14.5	33	23.0	4.2
Ethanol	12.8	24.3	22.2	—
Ethylene glycol	17.1	37.7	48.8	19.3
Propylene glycol	15.0	32.1	37.1	12.5
Glycerin	17.7	42.5	64.9	35.2
Formamide	19.4	109.5	58.7	31.2
N-Methylformamide	16.1	190	40.1	12.3
N,*N*-Dimethylformamide	12.2	36.7	36.6	4.6
Hexane	7.3		18.5	0.0
Silicone oil	—	—	—	0.0
20% Propylene glycol	21.4[a]	77.6[a]	65.2[a]–53.3[b]	44.1[a]–34.2[b]
40% Propylene glycol	19.8[a]	59.9[a]	58.4[a]–47.0[b]	36.2[a]–28.9[b]
60% Propylene glycol	18.2[a]	48.7[a]	51.6[a]–42.9[b]	28.3[a]–22.9[b]
80% Propylene glycol	16.5[a]	41.4[b]	44.8[a]–39.1[b]	20.4[a]–17.1[b]

[a] Estimated as the sum of the properties of the pure solvent times their volume fraction. [b] Experimentally measured.

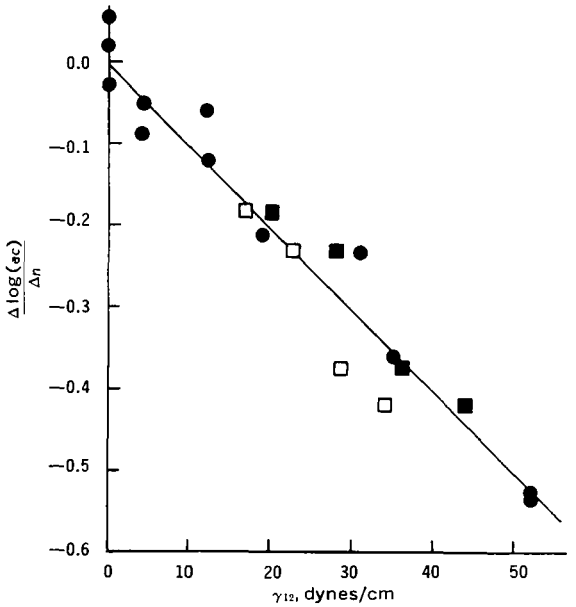

Figure 1—*Dependence of methylene group activity coefficient in a solvent upon the solvent–tetradecane interfacial tension. Key: ●, pure solvents; □, experimental interfacial tension of mixtures; and ■, calculated interfacial tension of mixtures.*

The slope of σ *versus* γ_{1h} (Fig. 1) is equal to $-C/2.303RT$ (or $-0.033C$ at 25°). The observed slope is 0.01, which corresponds to a value of about one-third for C. This value is in good agreement with theoretical estimates (16, 17) and with the value obtained (10) for alcohols and hydrocarbons in water. Furthermore, the good linearity of Fig. 1 lends support to the assumption of a constant curvature correction factor and thus to the use of interfacial tension as a parameter with which to correlate solubility. The effects of chain branching and positional isomerism in each solvent having positive hydrocarbon–water interfacial tensions should be the same; reducing the surface area reduces the interfacial area and, by Eq. 11, increases solubility.

In Fig. 1, both the experimentally measured and the calculated interfacial tensions are shown for the propylene glycol–water mixtures against tetradecane. The difference between the two is not unexpected. It is well known that semipolar components of aqueous solutions tend to be absorbed onto nonpolar interfaces. This accumulation of a surface excess of the less polar component causes a greater lowering of the surface or interfacial tension than would be observed for a completely homogeneous mixture. Since the calculated values are based upon complete homogeneity, they are, of necessity, higher than the measured values. At a microscopic interface within the bulk of the solution, it seems likely that there will be little or no accumulation of a surface excess of the cosolvents being considered. (Such an accumulation would effectively amount to complexation if it did occur to an appreciable extent.)

While this postulate cannot be proved, it is interesting to consider the following possible reasons for its justification:

1. The development of a surface excess is a slow diffusion-dependent process. The thermal motion of the particles (molecules) would tend to hinder the build-up of an absorbed layer.

2. At the highly curved molecular interface, the interfacial tension is much less than at a microscopic hydrocarbon or air interface. Thus, there would be a much smaller change in free energy per unit area when a third component (cosolvent) goes to the interface.

The theory of regular solutions (Eqs. 2 and 7) has been used successfully to describe the solubilities of methyl through nonyl and dodecyl *p*-aminobenzoates in hexane (18) but was unable to handle the aqueous solubilities of these same compounds. The present approach (Eqs. 2 and 11), while giving satisfactory results for hexane, is not sensitive to changes in nonpolar solvents. This is because it is mechanically impossible to obtain accurate interfacial tension of such solvents against pure hydrocarbon surfaces.

Furthermore, since γ_{12} cannot be less than zero, it is not possible to predict the slight increase in log *(ac)* with chain length in some solvents, nor can the curvature of such data be predicted. Fortunately, as mentioned previously, these properties are handled well by regular solution theory. On the other hand, the use of Eq. 7 cannot predict the linearity of the log *(ac) versus n* data observed in the polar solvents and the mixed solvents in this study.

The limiting factor to the validity of the theory presented and of regular solution theory is the evaluation of the solute–solvent term, γ_{12} or δ_{12}. The former can be measured for substances whose polarity is significantly different from one another while the latter is calculable for substances similar in polarity. Together, the two equations cover a wide range of solvents and solutes and bring one a step closer to being able to predict solubility *a priori*. Investigations are already underway to determine the effects of common organic substituents on activity coefficients. However, for the present, γ_{12} applies only to saturated hydrocarbons which represent the alkyl portion of the solute.

CONCLUSION

A derivation is presented which equates RT log *(ac)* to $\gamma_{1h}A_h$, the hydrocarbon–solvent interfacial tension times the molecular surface area of the hydrocarbon portion of a molecule. This equation, which is a two-dimensional analogy to the Scatchard–Hildebrand equation, avoids the need to rely upon the geometric mean rule and overcomes certain limitations on the application of the latter. It has been shown to be useful for predicting the effects of hydrophobic substituents on the activity coefficients of various semipolar substances in water, mixed aqueous solvents, and pure nonaqueous polar and semipolar solvents.

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