Solubility of Nonelectrolytes in Polar Solvents II: Solubility of Aliphatic Alcohols in Water

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Abstract ☐ The surface areas for 73 aliphatic hydrocarbons and alcohols, for which solubility and boiling point data are available, were calculated. The solubility of the alcohols and hydrocarbons can be quantitatively related to a combination of the hydrocarbon and hydroxyl surface areas of the molecules. The boiling points of the alcohols also correlated well with these two parameters. Isomeric alcohols, having a lower hydrocarbon surface area and/or a lower hydroxyl group surface area, are more soluble in water. The correlations show that branching, cyclization, and positional isomerism can be accounted for without introducing additional terms.

Keyphrases ☐ Solubility—73 aliphatic alcohols in water, correlated with surface areas and boiling points ☐ Alcohols, aliphatic—solubility in water, correlated with surface areas and boiling points ☐ Aliphatic hydrocarbons and alcohols—solubility of 73 determined, correlated with surface areas and boiling points ☐ Surface areas—73 aliphatic hydrocarbons and alcohols, correlated with solubility in water and boiling points

The ability to predict the effects of even simple structural modifications on aqueous solubility could be of great value in the design of improved drugs and drug delivery systems. At present, theoretical descriptions of solubility are mainly restricted to either nonpolar solutes in nonpolar solvents (1) or to salts and other highly polar compounds in water and other polar solvents (2) and are not generally applicable to most compounds of pharmaceutical interest.

In this paper, the solubility of semipolar and nonpolar compounds in water is discussed in terms of the molecular surface area of the solute and a corresponding "interfacial tension" term. This approach, initially suggested by Langmuir (3) and discussed further (4–6) for aqueous systems, was recently shown (7) to be successful in correlating the solubilities of hydrocarbons in water.
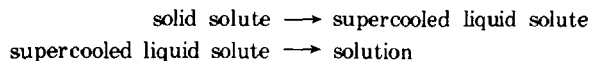
In the present paper, this approach is applied to the aqueous solubilities of primary, secondary, and tertiary linear and branched alcohols. While the primary purpose is to analyze the effects of relatively simple structural variations on the water solubility of alcohols, the approach appears to be generally applicable to semipolar and nonpolar compounds of arbitrary structure.

THEORETICAL

Ideal Solutions—In an ideal solution, one in which the activity equals the mole fraction over the entire composition range, there is no change in enthalpy or volume on mixing. The only term contributing to the free energy of mixing is the entropy of mixing. For two liquids, this quantity is always negative and results in infinite miscibility. From a molecular viewpoint, the molecules must be alike insofar as they are under the same forces in the mixture as in the pure liquids.

If one component of the mixture is a solid at the temperature of interest, the ideal solubility may be a good approximation to the actual solubility, provided that the molecules are "sufficiently" alike, e.g., naphthalene in benzene. In this case, the solubility pro-

cess may be considered as the sum of the two steps in Scheme I:

$$\text{solid solute} \longrightarrow \text{supercooled liquid solute}$$
$$\text{supercooled liquid solute} \longrightarrow \text{solution}$$

Scheme I

If the second step is considered as an ideal process, $\Delta G = RT \ln X$ for this step. The free energy change for the first step is obtained by integrating $(\partial \Delta G / \partial T)_p$ from T_m (the melting point) to the temperature of interest, T. When assuming that the enthalpy and entropy changes are constant over this temperature range, the free energy change for this step is $\Delta G = \Delta H_f[(T_m - T)/T_m]$.

The total free energy change is $\Delta G = \Delta H_f[(T_m - T)/T_m] + RT \ln X$ and at equilibrium ($\Delta G = 0$) the ideal solubility is given by Eq. 1:

$$\log X = \frac{-\Delta H_f}{2.3 RT}\left(\frac{T_m - T}{T_m}\right) \tag{Eq. 1}$$

where X is the mole fraction of the solute, ΔH_f is the heat of fusion, T_m is the melting point, and T is the temperature of interest (below the melting point).

Regular Solution Approach—The next step in solution theory is to admit an excess enthalpy while maintaining the random or ideal entropy of mixing (i.e., zero excess entropy of mixing). This is the regular solution approach (1, 8). In this model, the enthalpy (energy) of transfer of a mole of liquid 2 from pure liquid to solution is set equal to $v_2 \phi_1^2(\delta_1 - \delta_2)^2$, where v_2 is the molar volume of liquid 2, ϕ_1 is the volume fraction of liquid 1, and δ is the solubility parameter that equals the square root of the energy of vaporization divided by the molar volume.

Therefore, the free energy of transfer of a mole of liquid solute 2 from pure liquid 2 to solution is:

$$\Delta \bar{G}_2 = RT \ln a_2 = v_2 \phi_1^2(\delta_2 - \delta_1)^2 + RT \ln X_2 \tag{Eq. 2}$$

or:

$$RT \ln (a_2/X_2) = v_2 \phi_1^2(\delta_2 - \delta_1)^2 \tag{Eq. 3}$$

For a dilute solution ($\phi_1 = 1$), this becomes:

$$RT \ln (a_2/X_2) = v_2(\delta_2 - \delta_1)^2 \tag{Eq. 4}$$

or:

$$RT \ln X_2 = -v_2(\delta_2 - \delta_1)^2 \tag{Eq. 5}$$

for the solubility of two immiscible liquids. If solute 2 is a solid at the temperature of interest, the correction discussed for the ideal solution case must be applied. For a pure solid solute in equilibrium with saturated solution, the solubility is given by:

$$\ln X_2 = -\frac{\Delta H_f(T_m - T)}{RT_m T} - v_2 \phi_1^2(\delta_2 - \delta_1)^2 \tag{Eq. 6}$$

(using the pure supercooled liquid as the standard state).

This approach is applicable to nonpolar compounds but must be further modified for polar substances. Four modifications have been proposed: (a) divide the solubility parameter into polar (τ) and nonpolar (λ) parts, (b) incorporate a factor to account for deviation from the geometric mean rule, (c) determine a correction factor for the entropy of mixing to account for differences in molecular size (Flory–Huggins correction term), and (d) include a correction term for the additional entropy effects associated with hydrogen bonding substances (1).

Since all of these factors must be considered for aqueous sys-

tems, this approach is of limited predictive value due to the lack of adequate estimates of the various terms.

Molecular Surface Area Approach—An alternative approach to aqueous solutions (9–11) suggests that the number of water molecules that can be packed around the solute molecule plays an important role in the theoretical calculation of the thermodynamic properties of the solution. Hence, the molecular surface area of the solute is an important parameter in the theory. Hermann (7) applied this approach to the solubilities of hydrocarbons in water with good results. For an arbitrary semipolar molecule, the total molecular surface area can be divided into polar and nonpolar parts. The contribution of each part to the solubility can then be calculated by multiplying the respective surface areas by the appropriate free energy per unit area terms.

This approach has the advantage that, once the free energy per unit area terms for various functional groups are known, an estimate of the solubility of a new structure can be made simply by calculating the molecular (group) surface area(s). An additional advantage over other group contribution methods is that the effects of branching and stereochemistry (e.g., diastereoisomer solubility differences) are accounted for without resorting to different factors for each structural variation.

Historically, Langmuir (3) was the first to approach solubility from a consideration of the molecular surface area of a molecule. He split the energy of vaporization into three parts, polar–polar, nonpolar–nonpolar, and nonpolar–polar interactions, and calculated the energy of vaporization as a sum of the fractional surface areas times the corresponding "interfacial energies." A solution of two different species was treated in a similar manner by considering the various interfacial energies. The mutual solubilities of two immiscible liquids could then be calculated.

Scatchard (8) noted that Langmuir's equation could be put into the same form as that of the regular solution theory by replacing the energy density with energy per unit surface area and the volume fraction by surface fraction. However, he criticized two assumptions in Langmuir's approach; one is that the surface of contact between two surfaces is proportional to the product of the surfaces, and the second is the assumption that the surface area of any molecule is proportional to the two-thirds power of its volume. The second criticism is resolved using the surface area approach developed by Hermann (7) and discussed here. The first criticism, while valid in general, is not necessary for dilute solutions of semipolar compounds in water since each solute is only surrounded by water molecules; i.e., solute–solute interactions are negligible.

A related approach (4–6, 10, 11), based on a cavity model for the solvent, considers the energy required to create a cavity in the solvent as an important determinant of the solubility of a gas molecule in the solvent and the surface area of the molecule enters into the calculation along with the surface tension of the solvent. This approach has been used successfully for water (10) as well as other solvents (6, 12). Similar approaches to the complexation in liquid systems have also been used successfully (13, 14).

Comparison of Area and Volume Theories—Returning to the analogy between the regular solution approach and Langmuir's approach suggested by Scatchard (8), the equation for the solubility of one liquid in another according to regular solution theory is:

$$RT \ln X_2 = -v_2 \phi_1{}^2 (\delta_2 - \delta_1)^2 \qquad \text{(Eq. 7)}$$

Assuming low solubility ($\phi_1 = 1$), the analogy gives:

$$RT \ln X_2 = -SA_2(\gamma_2{}^{1/2} - \gamma_1{}^{1/2})^2 \qquad \text{(Eq. 8)}$$

where SA_2 is the surface area of molecule 2, and γ_1 and γ_2 are the surface tensions of liquids 1 and 2, respectively. The term in parenthesis $(\gamma_2{}^{1/2} - \gamma_1{}^{1/2})^2$ resembles Antonow's rule for the interfacial tension, γ_{12} (15). This then suggests that for two very different liquids, where an experimental interfacial tension can be measured, the solubility prediction may be improved by using:

$$RT \ln X_2 = (-SA_2)(\gamma_{12}) \qquad \text{(Eq. 9)}$$

This equation can also be developed by considering the work of cohesion of the two pure liquids (W_{11} and W_{22}) and the work of adhesion (W_{12}). The reversible work required to remove a solute molecule from bulk liquid to vapor is one-half the work of cohesion

times the surface area, $(\frac{1}{2} W_{11})(SA)$. The work required to create a cavity in the solvent is $(\frac{1}{2} W_{22})(SA)$. The free energy change in placing the solute molecule into the solvent cavity is $(-\gamma_{12})(SA)$. Thus, the reversible work for the process of transferring a solute molecule from bulk liquid to solution is: $(\frac{1}{2}W_{11} + \frac{1}{2}W_{22} - W_{12})(SA)$.

At this point all energy and entropy terms have been accounted for in the transfer process (unitary terms). However, the solute is still fixed in position in solution. Thus, the cratic (mixing) term of the molecule (or molecule plus cosphere) must be added to obtain the total free energy change (2):

$$\Delta G_2 = RT \ln a_2 = (\frac{1}{2} W_{11} + \frac{1}{2} W_{22} - W_{12})(SA_2) + RT \ln X_2$$
$$\text{(Eq. 10)}$$

For a pure liquid in equilibrium with solution, the solubility is then given by:

$$RT \ln X_2 = -(\frac{1}{2} W_{11} + \frac{1}{2} W_{22} - W_{12})(SA_2) \quad \text{(Eq. 11)}$$

If the work of adhesion and cohesion terms are replaced with the bulk interfacial tensions, the solubility expression becomes:

$$RT \ln X_2 = (-\gamma_{12})(SA_2) \qquad \text{(Eq. 12)}$$

which is identical to Eq. 9. Implicit in this approach are the requirements that the solution be dilute, so the solute–solute interaction terms in solution can be neglected, and that the molecular cospheres do not overlap.

Microscopic Surface Tension—A second point to consider is the use of bulk surface tensions for molecular cavities. It is well known that for surfaces of molecular dimensions, a curvature correction must be applied (15). In general, this has the effect of lowering the surface tension at a curved surface from that of a bulk planar surface. In this approach, the curvature correction for the pure liquid phase surface tensions, γ_1 and γ_2, need not be considered since they cancel out of the final equation. However, the interfacial tension term, γ_{12}, that remains must be considered.

If, as discussed later, a molecule is divided into groups, the only meaningful interfacial tension terms would be those between the hydrophobic portions of the molecule and water. In the case of aliphatic hydrocarbon portions, the experimental hydrocarbon–water interfacial tension is about 50 ergs/cm² [and relatively independent of the actual hydrocarbon (16)] and should provide an upper limit for the slope of ln (sol) versus hydrocarbon surface area plot. From the significant structure theory applied to the solution of hydrocarbons in water (11), the interfacial tension is calculated to be about 15 ergs/cm². Hence, the curvature correction is significant.

However, the actual energetics of cavity formation are considerably more complex than the preceding discussion, based on free energies, would suggest (particularly for the short-chain compounds). An analysis similar to this for the energy and entropy changes would suggest that, since the bulk hydrocarbon–water interfacial tension decreases with increasing temperature (17), the entropy of cavity formation as well as the energy of surface formation would be positive.

On the other hand, transfer of small hydrocarbons from nonpolar liquids to water is accompanied by large negative entropies and small heat effects (18). These effects are usually attributed to water structuring; however, it is not clear whether this effect is intrinsic to the creation of a small cavity in water or to the introduction of the nonpolar solute into the cavity (19). For the longer chain length alcohols (lengths greater than four carbons), the entropy effect levels off, with more than two-thirds of the free energy of solution coming from the enthalpy of solution (20). This is in line with the notion that interfacial effects should increase with increasing chain lengths (21) and the approach taken in this work.

Molecular Surface Area—The definition of molecular surface area adopted in this paper is that of Hermann (7). A molecule is considered as a collection of spheres with each radius located at the nuclear center. To each radius on the solute (alcohol) molecule, a radius for the solvent (water) is added to give a surface shown schematically in Fig. 1 for ethanol and tert-butanol. This approach has the desirable property of eliminating from the total surface area of a molecule those areas not exposed (or accessible) to the solvent.

Table I—Experimental Solubilities, Boiling Points, Surface Area Results, and Predicted Solubilities

Number	Compound	Structure	Solubility[a], molal	TSA^b, Å²	OHSA, A	Tb^c	Predicted Solubility[d], molal
1	n-Butanol		1.006 (1.1)	272.1	59.2	117.7°	0.821
2	2-Methyl-1-propanol		1.023	263.8	52.4	107.9°	1.299
3	2-Butanol		1.068	264.1	42.8	99.5°	1.496
4	n-Pentanol		2.6 (2.5) × 10⁻¹	303.9	59.2	137.8°	2.09 × 10⁻¹
5	3-Methyl-1-butanol		3.11 × 10⁻¹	291.4	59.2	131.2°	3.57 × 10⁻¹
6	2-Methyl-1-butanol		3.47 × 10⁻¹	289.4	52.4	128.7°	4.33 × 10⁻¹
7	2-Pentanol		5.3 × 10⁻¹	295.9	42.8	119°	3.81 × 10⁻¹
8	3-Pentanol		6.15 × 10⁻¹	293.5	36.0	115.3°	4.70 × 10⁻¹
9	3-Methyl-2-butanol		6.67 × 10⁻¹	284.3	40.2	111.5°	6.54 × 10⁻¹
10	2-Methyl-2-butanol		1.403	282.5	38.6	102.0°	7.25 × 10⁻¹
11	2,2-Dimethyl-1-propanol[e,f]		4.11 × 10⁻¹ [5.24 × 10⁻¹]	283.5	47.3	113.1°	6.05 × 10⁻¹
12	n-Hexanol		6.14 (6.1, 6.6) × 10⁻²	335.7	59.2	157°	5.32 × 10⁻²
13	2-Hexanol		1.36 (1.69) × 10⁻¹	327.7	42.8	139.9°	9.69 × 10⁻²
14	3-Hexanol		1.6 × 10⁻¹	325.3	36.0	135.4°	1.20 × 10⁻¹
15	3-Methyl-3-pentanol		4.36 × 10⁻¹	305.8	32.7	122.4°	2.91 × 10⁻¹
16	2-Methyl-2-pentanol		3.27 × 10⁻¹	314.3	38.6	121.4°	1.84 × 10⁻¹
17	2-Methyl-3-pentanol		2 × 10⁻¹	314.3	37.9	126.5°	1.86 × 10⁻¹
18	3-Methyl-2-pentanol		1.94 × 10⁻¹	311.3	45.1	134.2°	1.89 × 10⁻¹
19	2,3-Dimethyl-2-butanol		4.27 × 10⁻¹	301.2	34.77	118.6°	3.44 × 10⁻¹
20	3,3-Dimethyl-1-butanol		7.5 × 10⁻²	307.5	59.2	143°	1.79 × 10⁻¹
21	3,3-Dimethyl-2-butanol		2.44 × 10⁻¹	296.7	36.6	120°	4.05 × 10⁻¹
22	4-Methyl-1-pentanol		1.02 × 10⁻¹	323.0	59.2	151.8°	9.20 × 10⁻²
23	4-Methyl-2-pentanol		1.63 × 10⁻¹	314.9	41.5	131.7°	1.71 × 10⁻¹
24	2-Ethyl-1-butanol		6.16 × 10⁻²	308.6	51.1	146.5°	1.93 × 10⁻¹
25	Cyclohexanol		3.83 × 10⁻¹	290.5	49.6	161°	4.3 × 10⁻¹

Table I—*Continued*

Num-ber	Compound	Structure	Solubility[a], molal	TSA^b, Å^2	OHSA, A	Tb^c	Predicted Solubility[d], molal
26	*n*-Heptanol		$1.55\ (1.45, 1.7) \times 10^{-2}$	367.5	59.2	176.3°	1.36×10^{-2}
27	2-Methyl-2-hexanol		8.43×10^{-2}	346.1	38.6	142.5°	4.69×10^{-2}
28	3-Methyl-3-hexanol		1.04×10^{-1}	337.7	32.7	142.4°	7.41×10^{-2}
29	3-Ethyl-3-pentanol		1.47×10^{-1}	324.4	32.7	142.5°	1.31×10^{-1}
30	2,3-Dimethyl-2-pentanol		1.35×10^{-1}	323.8	38.6	139.7°	1.22×10^{-1}
31	2,3-Dimethyl-3-pentanol		1.44×10^{-1}	321.8	32.7	139°	1.46×10^{-1}
32	2,4-Dimethyl-2-pentanol		1.17×10^{-1}	328.6	28.1	133°	1.17×10^{-1}
33	2,4-Dimethyl-3-pentanol		6.07×10^{-2}	331.7	33.9	138.8°	9.39×10^{-2}
34	2,2-Dimethyl-3-pentanol		7.11×10^{-2}	326.1	29.8	136°	1.27×10^{-1}
35	3-Heptanol		4.1×10^{-2}	57.1	36.0	156.8°	3.05×10^{-2}
36	4-Heptanol		4.09×10^{-2}	357.1	36.0	155.0°	3.05×10^{-2}
37	1-Octanol		$4.51\ (3.68, 4.1) \times 10^{-3}$	399.4	59.2	195.2°	3.45×10^{-3}
38	2,2,3-Trimethyl-3-pentanol		5.33×10^{-2}	335.2	26.7	152.5°	9.05×10^{-2}
39	2-Octanol		8.6×10^{-3}	391.0	42.8	179.8°	6.39×10^{-3}
40	2-Ethyl-1-hexanol		6.76×10^{-3}	371.3	51.1	184.6°	1.31×10^{-2}
41	1-Nonanol		$1.0\ (0.934) \times 10^{-3}$	431.2	59.2	213.1°	8.79×10^{-4}
42	2-Nonanol		1.8×10^{-3}	423.2	42.8	198.5°	1.60×10^{-3}
43	3-Nonanol		2.2×10^{-3}	420.8	36.0	194.7°	1.97×10^{-3}
44	4-Nonanol		2.6×10^{-3}	420.8	36.0	193°	1.97×10^{-3}
45	5-Nonanol		3.2×10^{-3}	420.8	36.0	195.1°	1.97×10^{-3}
46	2,6-Dimethyl-4-heptanol		3.1×10^{-3}	394.0	33.4	178°	6.50×10^{-3}
47	3,5-Dimethyl-4-heptanol		5.0×10^{-3}	379.3	29.8	187°	1.29×10^{-2}
48	2,2-Diethyl-1-pentanol		3.8×10^{-3}	372.5	44.6	192°	1.38×10^{-2}

(continued)

Table I—*Continued*

Number	Compound	Structure	Solubility[a], molal	TSA[b], Å²	OHSA, A	Tb[c]	Predicted Solubility[d], molal
49	7-Methyl-1-octanol		3.2×10^{-3}	418.7	59.2	206°	1.50×10^{-3}
50	3,5,5-Tri-methyl-1-hexanol		3.12×10^{-3}	376.6	59.2	193.0°	9.19×10^{-3}
51	1-Decanol		$2.0 \ (2.69) \times 10^{-4}$	463	59.2	230.2°	2.24×10^{-4}
52	1-Dodecanol		2.3×10^{-5}	527	592	—	1.43×10^{-5}
53	1-Tetradecanol[e]		1.46×10^{-6} $[2.84 \times 10^{-6}]$	591	59.2	263.5°	9.38×10^{-7}
54	1-Penta-decanol[e]		4.5×10^{-7} $[1.02 \times 10^{-6}]$	623	59.2	—	2.36×10^{-7}
55	1-Hexa-decanol[e]		1.7×10^{-7} $[4.55 \times 10^{-7}]$	655	59.2	—	5.87×10^{-8}
56	n-Butane		2.34×10^{-3}	255.2	—	—	1.43×10^{-3}
57	Isobutane		2.83×10^{-3}	249.1	—	—	1.86×10^{-3}
58	n-Pentane		5.37×10^{-4}	287.0	—	—	3.65×10^{-4}
59	2-Methyl-butane		6.61×10^{-4}	274.6	—	—	6.21×10^{-4}
60	3-Methyl-pentane		1.48×10^{-4}	300.1	—	—	2.08×10^{-4}
61	Neopentane		7.48×10^{-4}	270.1	—	—	7.52×10^{-4}
62	2,2-Dimethyl-butane		2.14×10^{-4}	290.8	—	—	3.10×10^{-4}
63	2,4-Dimethyl-pentane		4.07×10^{-5}	324.7	—	—	7.20×10^{-5}
64	2,2,4-Tri-methyl-pentane		7.48×10^{-5}	338.9	—	—	3.91×10^{-5}
65	2,2,5-Tri-methyl-hexane		8.95×10^{-6}	373.0	—	—	9.03×10^{-6}
66	Cyclohexane		6.61×10^{-4}	279.1	—	—	5.11×10^{-4}
67	(e)-Methyl-cyclohexane		1.41×10^{-4}	304.9	—	—	1.69×10^{-4}
68	1-cis-2-Di-methyl-cyclohexane		5.38×10^{-5}	315.5	—	—	1.07×10^{-4}
69	Cycloheptane		3.05×10^{-4}	301.9	—	—	1.92×10^{-4}
70	Cyclooctane		7.05×10^{-5}	322.58	—	—	7.89×10^{-4}
71	n-Hexane		1.11×10^{-5}	319	—	—	1.23×10^{-4}
72	n-Heptane		2.93×10^{-5}	351	—	—	2.33×10^{-5}
73	n-Octane		5.79×10^{-6}	383	—	—	5.87×10^{-6}

[a] Solubilities were taken from the following references and references cited therein: C. Hansch, J. E. Quinlar, and G. L. Lawrence, *J. Org. Chem.*, **33**, 347 (1968); G. H. Bell, *Chem. Phys. Lipids*, **10**, 1(1973); J. R. Hommelen, *J. Colloid. Sci.*, **14**, 385(1959); R. Vochten and G. Petre, *J. Colloid. Interface Sci.*, **42**, 320(1973); and C. McAuliffe, *J. Phys. Chem.*, **70**, 1267(1966). The first listed values were used in the regression analysis, values in parentheses are other reported values. [b] Hydrocarbon surface areas were taken from Ref. 7. [c] Reference 23. [d] From Eq. 16 in text. [e] Solids at room temperature; the solubility in brackets [ ] is the solubility of the pure supercooled liquid at 25°. [f] The ΔH_f for this compound was calculated from the cryoscopic constant (29).

Another advantage of this method is that individual atom contributions to the total area are calculated. This allows the total area of a molecule to be divided into group contributions (*e.g.*, hydrocarbon and hydroxyl group portions for alcohols), and the group contribution to the solubility can be evaluated. Standard bond angles and distances were used for all molecules considered in this study (22). The van der Waals radii were taken to be C = 1.6 Å, H = 1.2 Å, O = 1.4 Å, and H_2O = 1.5 Å (solvent radius). The
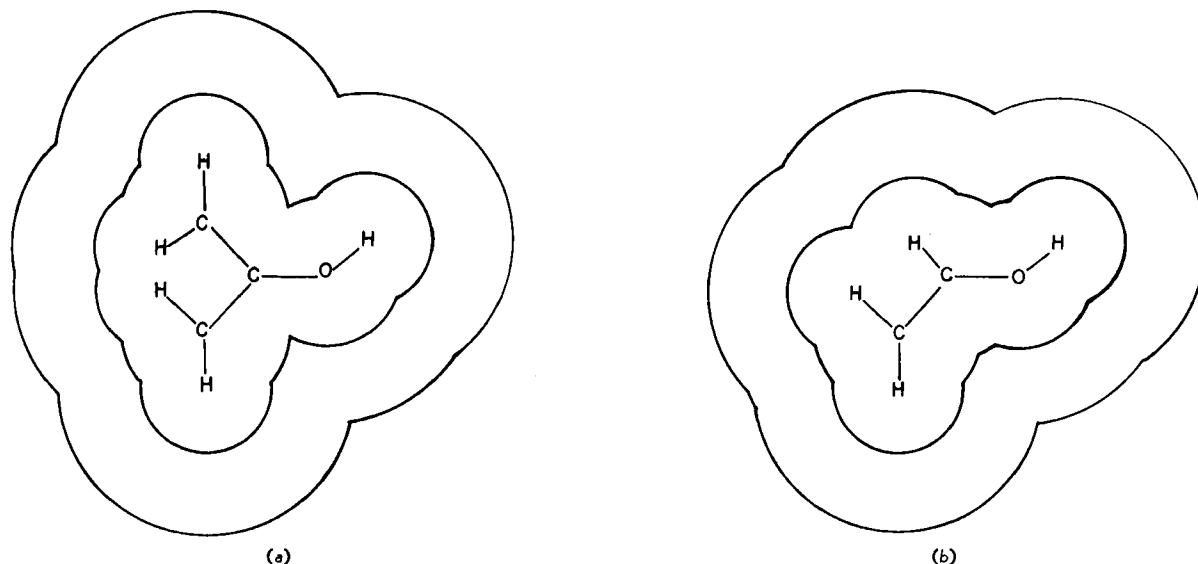
Figure 1—*Planar sections of* tert-*butanol* (a) *and* ethanol (b). *The inner surface represents surface area with the van der Waals radius of the solvent equal to zero. The outer surface includes a 1.5 Å solvent radius.*

main chain of all compounds was placed in an all-*trans*-conformation.

RESULTS

Solubility and Boiling Point Data—The solubilities of the alcohols considered are given in Table I. The overall decrease in solubility with increasing hydrophobicity is obvious. There are, however, more subtle changes in solubility with structure which can best be illustrated by considering a set of isomers such as the pentanols (Compounds 4–11).

From Table I, it is apparent that the primary pentanols are less soluble than the secondary pentanols and that the tertiary pentanols have the greatest solubilities in this group. It is also evident that, for the primary pentanols (Compounds 4–6 and 11), branching of the normal chain increases solubility; it can also be seen that 3-pentanol is more soluble than 2-pentanol, which is more soluble than 1-pentanol. These same trends are present in each set of isomers in Table I, *i.e.*, butanols, hexanols, heptanols, octanols, and nonanols.

In addition, the boiling points of the alcohols are listed in Table I. These values are also dependent upon the described structural features. In general, boiling points increase with chain length and decrease with branching and substitution on the α-carbon.

Surface Area—The surface area of each alcohol was calculated as discussed[1]. The total surface areas *(TSA)* as well as the hydroxyl group areas *(OHSA)*, the sum of the oxygen and hydroxyl hydrogen exposed areas, are presented in Table I. From these values it is apparent that substitution on either the α- or β-carbon reduces the *OHSA* from its value in a normal alcohol (*OHSA* = 59.2 Å^2). Qualitatively, the surface area, solubility, and boiling point seem to be dependent on the same structural features.

DISCUSSION

Before discussing the relationship between solubility and surface area, it should be noted that Compounds 11 and 51–53 are solids at room temperature. Since the solubility estimate refers to that of the supercooled liquid, the observed solubility for these compounds must be corrected by multiplying by the factor $\exp[+\Delta H_f(T_m - T)/RT_m T]$ (see Eq. 2).

The heat of fusion data were taken from Wilhoit and Zwolinski (23). The corrected solubilities are given in parentheses in Table I.

To evaluate the proposed relationship between solubility and

surface area, regression analysis was performed on the 51 alcohols, Compounds 1–55 in Table I omitting the solid alcohols. This analysis gives:

$$\ln(\text{sol}) = -0.043TSA + 11.78 \qquad \begin{matrix} r & s \\ 0.974 & 0.499 \end{matrix} \quad (\text{Eq. 13})$$

where sol is the molar solubility, *TSA* is the total surface area in Å^2, *r* is the correlation coefficient, and *s* is the standard error.

If the hydroxyl group were to make a constant contribution to the solubility, a correlation with hydrocarbon surface area, *HYSA* = *TSA* − *OHSA* should give a similar correlation. However, the analysis gives:

$$\ln(\text{sol}) = -0.0396HYSA + 8.94 \qquad \begin{matrix} r & s \\ 0.94 & 0.706 \end{matrix} \quad (\text{Eq. 14})$$

which is considerably poorer than the correlation with *TSA*. This can be observed in Fig. 2 where there is considerably more scatter in the *HYSA* plot than in the *TSA* plot.

A third analysis, which includes both the *HYSA* and *OHSA*, gives the following equation:

$$\ln(\text{sol}) = -0.043HYSA - 0.060OHSA + 12.41$$
$$\begin{matrix} r & s \\ 0.978 & 0.462 \end{matrix} \quad (\text{Eq. 15})$$

which in spite of having an additional parameter is not significantly better than Eq. 13. This suggests that the hydroxyl group is making a variable contribution to the solubility.

To investigate the hydroxyl group contribution to the solubility more thoroughly, regression analysis was performed using the solubility data for both the alcohols and hydrocarbons in Table I. The analysis gives the following equation:

$$\ln(\text{sol}) = -0.0430HYSA + 8.003IOH - $$
$$0.0586OHSA + 4.420 \qquad \begin{matrix} r & s \\ 0.992 & 0.452 \end{matrix} \quad (\text{Eq. 16})$$

where the *IOH* term equals 1 if the compound is an alcohol and zero if the hydroxyl group is not present[2]. The predicted solubilities in Table I were calculated using this equation, and Fig. 3 shows a plot of ln(sol) observed *versus* ln(sol) predicted. This equation gives an excellent estimate of the solubilities of the alcohols and hydrocarbons in Table I without the need to include additional correction factors for branching, cyclization, positional isomers, *etc.*

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[1] The computer program utilized in this study was a modified version of a program written by Dr. Robert Hermann. The original program (QCPE 225) was obtained through the Quantum Chemistry Program Exchange, Chemistry Department, Indiana University, Bloomington, Ind.

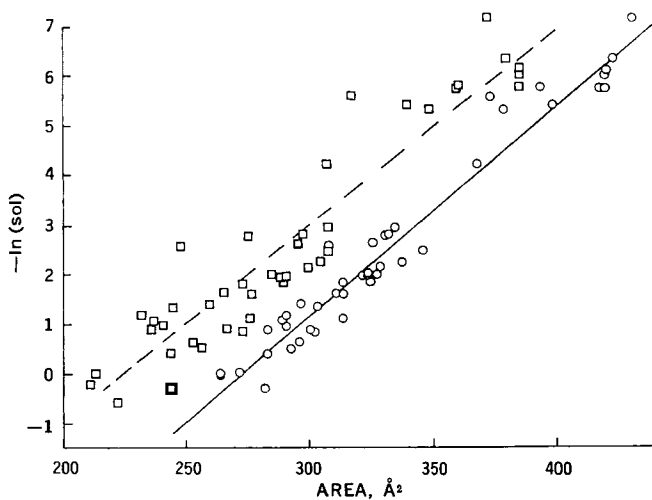[2] It would equal zero or the number of (independent) hydroxyl groups in a polyhydroxy alcohol.

Figure 2—*Plot of* $-\ln$ *(sol) versus total surface area* (○) *and hydrocarbon surface area* (□) *for the alcohols.*

In view of the success of Eq. 16, a discussion of each term in the equation is appropriate. The *HYSA* term represents the incremental effect on solubility (per Å²) of increasing the hydrocarbon surface area in the molecule. The coefficient of this term is negative, as expected; when converted into a corresponding interfacial tension (see Eq. 9), it gives a value of 17.7 ergs/cm². While this coefficient is only an adjusted parameter from Eq. 16, if it is considered as a microscopic interfacial tension, it is well within the range expected for such a term as discussed.

The constant, 4.420, in Eq. 16 is related to the concentration units used for the solubility data. Equation 9 predicts a zero intercept on a mole fraction basis; converting to a molal concentration scale gives an approximate theoretical intercept of 4.0 (on a natural log scale), in good agreement with the observed intercept.

The *IOH* and *OHSA* terms collectively represent the effect of the hydroxyl group on the solubility of the hydrocarbon (there is also an effect on the *HYSA* term as discussed later). If for comparative purposes the normal alcohols are considered as reference alcohols with a constant *OHSA* equal to 59.2 Å² (Table I), the effect of structural variation in the alcohol on its solubility can be discussed on a comparative basis. For this purpose, it is convenient to rearrange the *IOH* and *OHSA* terms to give:

$$8.003IOH - 0.0586OHSA = 0.0767NOHSA +$$
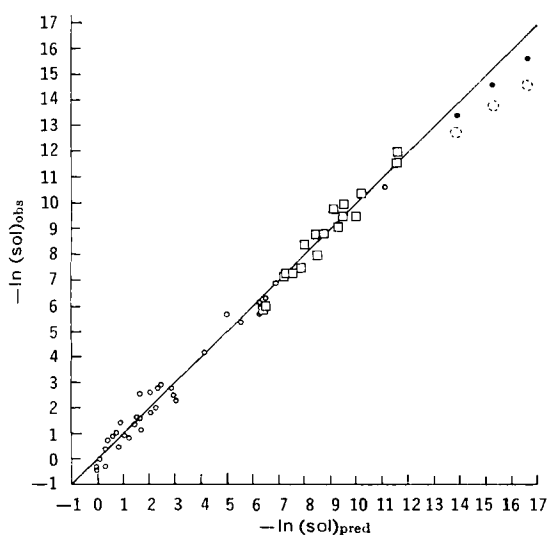$$0.0586(NOHSA - OHSA) \quad \text{(Eq. 17)}$$

Figure 3—*Plot of* $-\ln$ *(sol) observed versus* $-\ln$ *(sol) predicted, from Eq. 16, for alcohols* (○) *and hydrocarbons* (□). *Solid circles* (●, *experimental solubility*) *and dashed circles* (◌, *solubility of pure supercooled liquids*) *are the points for the 14-, 15-, and 16 carbon alcohols* (*see text*).

Table II—Free Energy Contribution of Hydroxyl Group to Solution Process

OH Position	ΔG, kcal/molal		
	Loss of *HYSA*[a]	Presence of OH[a]	Total
1°	−1.12	−2.69	−3.81
2°	−0.78	−3.49	−4.27
3°	−0.70	−3.59	−4.29

[a] This division will vary somewhat depending on the structure of the hydrocarbon portion of the alcohol and the position of the OH.

where *NOHSA* represents the exposed surface area of the hydroxyl group in the normal alcohol (59.2 Å²). By referring to the right-hand side of Eq. 17, it can be seen that, as expected, in the normal position the hydroxyl group increases the solubility since *NOHSA* = *OHSA* = 59.2 and the coefficient of the *NOHSA* term is positive. This corresponds to a free energy contribution to solubility of −2.69 kcal/mole for the addition of the hydroxyl group to the hydrocarbon, with the *HYSA* term remaining constant.

However, when the hydroxyl group is added to a hydrocarbon, the *HYSA* of the molecule is reduced by about 43 Å² for the normal alcohols (compare normal hydrocarbons and alcohols in Table I). This gives an additional free energy increment of −1.12 kcal/mole for a total free energy increment of −3.81 kcal/mole to the solubility for the addition of a hydroxyl group to a normal hydrocarbon in the 1-position (see also Table II).

For the isomeric alcohols, the *OHSA* term is, in general, less than 59.2 (Table I). Referring to Eq. 17, this indicates that the higher solubility of the isomeric alcohols over the normal alcohols is due to a reduced *OHSA*, since the *OHSA* is less than the *NOHSA* and the coefficient of this term, +0.0586, is positive, indicating a positive contribution to the solubility. This reduction in the *OHSA* for the isomers is a result of the hydroxyl group being less exposed than in the normal position. Since this reduced accessibility of the hydroxyl group, in other than normal alcohol, would not be expected to favor its interaction with water, the effect of branching, *etc.*, would seem to reside in its effect on the properties of the pure liquid alcohol phase (or possible electronic effects).

Alcohols are known to be associated through hydrogen bonding in the liquid state, with the association decreasing in the order primary, secondary, and tertiary due to steric limitations (24, 25). The effect of this reduced association would be to increase the vapor pressure and reduce the boiling point. In addition to the steric effects, these structural changes also affect the proton-donating and proton-accepting abilities of the hydroxyl group through electronic changes.

Experimental data suggest that branching reduces the proton-donating ability of the hydroxyl group and increases the proton-accepting ability (24). While the net effect of the electronic changes on the interaction of the alcohol with itself and with water is not certain, the steric effect on the self-association of the alcohol appears to be a dominant factor in the formation of alcohol-water mixtures (25).

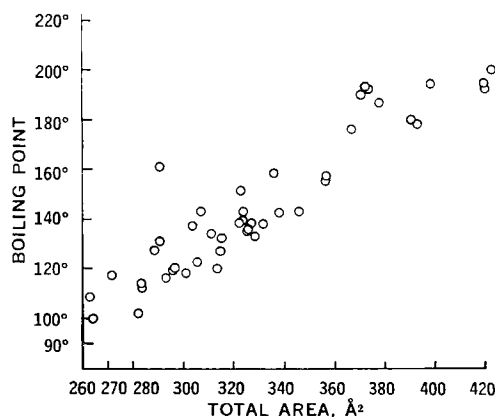The overall correlation of boiling point with total surface area

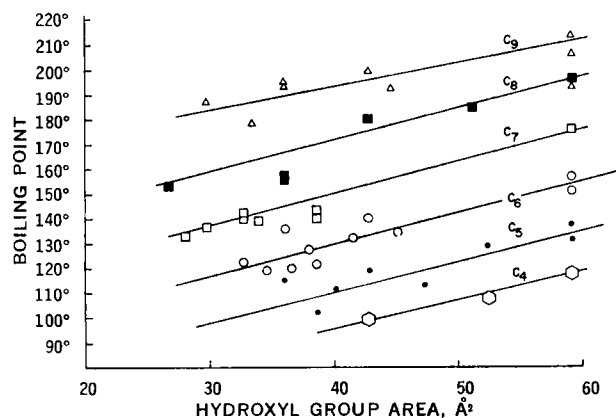**Figure 4**—*Plot of boiling point versus total surface area for the alcohols.*

Figure 5—*Plot of boiling point versus hydroxyl group surface area for the various chain length alcohols.*

Table III—Methylene and Methyl Group Surface Areas in 1-Nonanol

$$CH_3-CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-OH$$
$$9 \quad 8 \quad 7 \quad 6 \quad 5 \quad 4 \quad 3 \quad 2 \quad 1$$

Group	Exposed Surface Area
OH	59.15
CH_2 (1)	45.43
CH_2 (2)	39.80
CH_2 (3)	31.82
CH_2 (4)	31.82
CH_2 (5)	31.82
CH_2 (6)	31.82
CH_2 (7)	31.82
CH_2 (8)	42.75
CH_3 (9)	84.92
Total	431.15

(TSA) is apparent in Fig. 4. To analyze further the effect of the OHSA term on the properties of the pure liquid alcohols, a regression analysis was performed on the boiling point data (Table I) which gives:

$$\text{boiling point} = 0.632 HYSA + 1.182 OHSA - 87.78 \qquad \begin{array}{cc} r & s \\ 0.982 & 6.37 \end{array} \qquad (\text{Eq. 18})$$

The positive coefficient of the OHSA term indicates that reducing the OHSA (relative to that of a normal alcohol) reduces the boiling point. This effect is shown in Fig. 5, where for a given number of carbon atoms the decrease in boiling point with decreasing OHSA is very evident. Hence, the increased solubility of, for example, 2-pentanol (Compound 7) over 1-pentanol (Compound 4) is due to both a reduction in the hydrocarbon area and a reduction in the hydroxyl surface area.

The free energy contributions of the hydroxyl group to the solubility of a given chain length hydrocarbon are summarized in Table II. The contribution from the reduction of hydrocarbon surface area was calculated by comparing the appropriate alcohols and hydrocarbons in Table I. The contribution of the hydroxyl group is the sum of the IOH and OHSA terms in Eq. 16. While the division will vary somewhat depending on the structure of the hydrocarbon portion of the alcohol, it is evident from Table II that secondary and tertiary hydroxyl groups cause a larger relative increase in solubility than primary hydroxyl groups. This effect is due presumably to the reduced association in the pure liquid alcohol as discussed earlier.

Returning to the overall correlation of the solubilities of the alcohols and hydrocarbons (Fig. 3), it can be observed that the solubilities of the C_{14}, C_{15}, and C_{16} alcohols (Compounds 53–55, Table I) lie below the predicted line, indicating a higher aqueous solubility than predicted. For n-hexadecanol, the predicted solubility (Table I and Eq. 16) is 6.3×10^{-8} M while the solubility of the pure supercooled liquid is 4.6×10^{-7} M. Hence, the supercooled C_{16} alcohol is about 10-fold more soluble than expected on the basis of the extrapolation from the shorter chain alcohols (C_4-C_{12}). Aside from possible experimental error, two of the possible reasons are self-association and intramolecular coiling of the hydrocarbon chain.

Recent experimental data (26) indicate that the free energy of transfer of n-alkyl carboxylic acids from heptane to aqueous buffer is linear for all acids up to behenic acid ($C_{21}H_{43}COOH$), suggesting that preferential coiling does not occur in either phase. On the other hand, dimerization of fatty acid anions is known to occur in aqueous solutions (21, 27). Using the estimated dimerization constant for an uncharged dimer (assuming only dimers exist) to calculate the solubility of the 1-hexadecanol monomer gives a solubility estimate of 1.67×10^{-7} M. This accounts for about half of the observed difference between the experimental and predicted values.

Since the formation of higher aggregates is more likely to occur for the alcohols than the fatty acid anions, this estimated solubility of the monomer is likely to be an overestimate. While more accurate estimates cannot be made at present, it appears that self-asso-

ciation can account for most, if not all, of the observed deviation in the solubility of the longer chain (C_{14}, C_{15}, and C_{16}) alcohols. However, the possibility of some preferential coiling cannot be completely eliminated.

It has frequently been noted that a methyl group and a methylene unit should make different contributions to the free energy of solution (28). The method of surface area calculation employed in this study allows an easy assessment of these differences. Table III presents the group contributions to the total surface area of n-nonanol. From this table it is clear that the exposed surface area of a terminal methyl group (84.9 $Å^2$) is about three times that of the methylene unit (31.8 $Å^2$). From the slope of Eq. 16, these values correspond to contributions to the free energy of solution of 810 cal/mole/methylene group and 2.16 kcal/mole/terminal methyl group. Clustered methyl groups such as in tert-butanol or neopentanol have somewhat lower surface areas than a terminal group. It may also be noted in Table III that not all of the methylene units are identical.

While this study was limited to those alcohols showing limited miscibility with water, the results can be extrapolated to the miscible alcohols. Table IV presents the experimental and theoretically calculated activity coefficients for the miscible as well as some immiscible alcohols studied. The agreement is good, with a general tendency to overestimate the activity coefficient. However, particularly for the lower molecular weight alcohols, the surface area approach must be viewed as only providing good estimates of the free energy of solution since, as discussed previously, a direct application of the interfacial approach fails to give good estimates of the enthalpy and entropy of solution.

SUMMARY

The aqueous solubilities of 73 aliphatic alcohols and hydrocarbons can be correlated with a simple linear equation involving the functional group surface areas, and the coefficients of each term

Table IV—Experimental and Predicted Activity Coefficients of Alcohols at Infinite Dilution

Alcohol	Activity Coefficients, M	
	Experimental[a]	Predicted
Methanol	3.42×10^{-2}	1.75×10^{-2}
Ethanol	8.54×10^{-2}	7.89×10^{-2}
Propanol	0.250	0.310
Isopropanol	0.157	0.252
n-Butanol	0.923	1.22
2-Butanol	0.500	0.668
tert-Butanol	0.237	0.550
n-Pentanol	3.12	4.78
2-Pentanol	2.05	2.62
n-Octanol	1.98×10^2	2.90×10^2
2-Octanol	1.35×10^2	1.56×10^2
n-Decanol	3.78×10^3	4.46×10^3

[a] R. A. Pierotti, C. H. Deal, and E. L. Derr, *Ind. Eng. Chem.*, **51**, 95 (1959), and supplementary tables. Mole fraction activity coefficients were converted to molar activity coefficients using partial molar volumes calculated from Ref. 30.

can be related to other physical–chemical data. The analysis indicates that the hydroxyl group contribution to the solubility is variable and depends significantly on the properties of the pure liquid alcohols. Aliphatic alcohols of varying structure are conveniently handled without the need to introduce additional parameters for branching, cyclization, etc. The method appears to be general enough to be extended to other functional groups as well as more complex organic molecules with limited solubility in water.

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Vanadyl Complexes of Antiamebic Drugs: Electronic Absorption Spectra

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Abstract □ The complexing properties of the antiamebic drugs iodochlorhydroxyquin and diiodohydroxyquin with vanadium as VO^{+2} were investigated using spectrophotometric methods. The composition of the complexes and their stability constants were determined by more than one procedure. When ethanol was the solvent and the pH of the solution was 2.0–6.0, the 1:2 complexes were predominant.

Keyphrases □ Iodochlorhydroxyquin—complexing properties, electronic absorption spectra of vanadyl complexes □ Diiodohydroxyquin—complexing properties, electronic absorption spectra of vanadyl complexes □ Vanadyl complexes—iodochlorhydroxyquin and diiodohydroxyquin, complexing properties investigated using electronic absorption spectra □ Complexes—vanadium with iodochlorhydroxyquin and diiodohydroxyquin, complexing properties investigated using electronic absorption spectra

Quinoline derivatives were among the earliest synthetic compounds found active in amebiasis. Greatest success was achieved with iodinated 8-hydroxyquino-lines. Among the commonly used drugs are iodochlorhydroxyquin, chiniofon, and diiodohydroxyquin; the early work on these drugs was reviewed previously (1).

Testing of these drugs in vitro is complicated by their low solubility (2). Bradner and Rawson (3) reported that iodochlorhydroxyquin is active at 125 µg/ml in Entameba histolytica-T. cruzi cultures. It appears, therefore, that these drugs have a direct amebicidal activity of a relatively low order (3) and are effective to some degree when given orally to cyst-passing patients but less effective in acute amoebic dysentery. Iodochlorhydroxyquin and diiodohydroxyquin are effective only in intestinal amebiasis (4).

Quinoline derivatives are strong chelating agents. At pH 2.5, the 1:2 iron (III)–chiniofon was obtained with log K_f 7.5 (5). The same ligand forms different complexes with Co^{+2}, Ni^{+2}, Mo^{+4} (6, 7), and V^{+5}