

The apparent  $K_{eq}$  in plasma may be greater because I is more extensively protein bound. It also may result from the use of trichloroacetic acid as a protein precipitant.

### CONCLUSIONS

Chloramphenicol-3-monosuccinate (III) exists in rapid equilibrium with chloramphenicol-1-monosuccinate (I) under physiological conditions and in intravenous solutions prepared for administration. The analytical technique developed permits the quantification of chloramphenicol, I, and III in biological fluids and reconstituted commercial preparations. The methodology may be adapted for certifying chloramphenicol sodium succinate and offers advantages over the current FDA spectrophotometric method, which does not differentiate between these compounds. The analysis of I was simplified by demonstrating that I and III have similar molar absorptivities.

The results of previous investigators who reported that chloramphenicol succinate is not rapidly hydrolyzed by plasma esterases were confirmed. A rapid analytical technique is offered that will allow future studies of the effects of renal and hepatic disease on the pharmacokinetics and bioavailability of chloramphenicol sodium succinate.

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### ACKNOWLEDGMENTS

Supported in part by Faculty Research Council Grant VF648 from the University of North Carolina at Chapel Hill.

## Solubility and Partitioning I: Solubility of Nonelectrolytes in Water

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Received July 6, 1979, from the *Pharmacy Research Unit, The Upjohn Company, Kalamazoo, MI 49001*. Accepted for publication March 17, 1980.

**Abstract** □ On the basis of a semiempirical analysis, an equation was obtained that enables the estimation of the aqueous solubility of either liquid or crystalline organic nonelectrolytes:

$$\log S_w \approx -1.00 \log PC - 1.11 \frac{\Delta S_f(MP - 25)}{1364} + 0.54$$

where  $\log PC$  and  $\Delta S_f$  are estimated from the chemical structure and  $MP$  is either known or experimentally determined. Analysis of this equation provides a means of assessing the role of crystal structure [as reflected by the melting point ( $MP$ ) and the entropy of fusion ( $\Delta S_f$ )] and of the activity coefficient [as reflected by the octanol-water partition coefficient ( $PC$ )] in controlling the aqueous solubility of a drug. Techniques are also provided for estimating the entropy of fusion of organic compounds.

**Keyphrases** □ Solubility—nonelectrolytes in water, estimation techniques □ Nonelectrolytes—estimation of solubility in water □ Aqueous solubility—nonelectrolytes, estimation techniques

Aqueous solubility has long been recognized as a key factor in controlling drug efficacy. Before an orally administered drug can become available to its receptor, it first must dissolve in the GI fluid. Both the dissolution rate and the maximum amount of drug that can be dissolved are governed by the solubility of the drug in the medium (1).

The design of orally active drugs must account for the effects of structural modifications on solubility. The lack

of sufficient aqueous solubility often causes a drug to appear inactive or less active than some reference compound of a series. Aqueous solubility is a key factor in the design of parenteral and ophthalmic formulations, and it also is important in controlling taste. For these reasons, some appreciation of the relationship between aqueous solubility and chemical structure is needed.

### THEORETICAL

In spite of the tremendous importance of aqueous solubility in pharmacy and other applied chemical disciplines, it is a poorly understood phenomenon. There are no generally useful guidelines for estimating the solubility of a substance in water from a consideration of its structure and physical properties. One reason that solubility of crystalline compounds has successfully defied attempts to make it predictable is that it is not a simple equilibrium but rather a combination of equilibria.

This report attempts to provide some guidelines for understanding the factors that govern aqueous solubility and for estimating the aqueous solubility of nonelectrolytes. Subsequent reports will deal with the estimation of the solubility of weak electrolytes.

**Factors Influencing Aqueous Solubility**—The aqueous solubility of a drug is governed by three major factors: (a) the entropy of mixing; (b) the difference between the drug-water ( $DW$ ) adhesive interactions and the sum of the drug-drug ( $DD$ ) and water-water ( $WW$ ) cohesive interactions; and (c) the additional drug-drug interactions associated with the lattice energy of crystalline drugs, which are designated  $\bar{D}D$  and are not applicable to liquids.

The entropy of mixing can be thought of as a force that favors complete

miscibility of all components. If  $DD + WW - 2DW = 0$  for a liquid solute (*i.e.*,  $\overline{DD} = 0$ ), the solubility is governed only by the entropy of mixing, which is assumed to be ideal. On a mole fraction scale, the ideal solubility of a liquid,  $X_i^l$ , is equal to unity and  $\log X_i^l = 0$ .

In general, the liquid interaction term and the crystal interaction term combine to reduce the aqueous solubility of most drugs by:

$$2.303RT \log X = -(DD + WW - 2DW) - \overline{DD} \quad (\text{Eq. 1})$$

If the material is crystalline, the crystalline interactions reduce the solubility by  $\overline{DD} = -2.303RT \log X_i^c$ , where  $X_i^c$  is the ideal solubility of a crystalline compound.

The difference between the adhesive and cohesive forces usually is described (2) by an activity coefficient for the drug in water,  $\gamma_w$ , by:

$$(DD + WW - 2DW) = 2.303RT \log \gamma_w \quad (\text{Eq. 2})$$

If the left side is equal to zero,  $\gamma_w$  must equal unity. If  $DD + WW - 2DW > 0$ , the solubility will be less than ideal. If  $DD + WW - 2DW \gg 0$  (as usually is the case for nonelectrolytes in water), there usually will be less than total miscibility and the drug will have a finite solubility in water,  $X_w$ . These equations assume that there is no significant mutual miscibility of the drug and water phases. Therefore,  $DD$  and  $WW$  refer to the pure phases. A more sophisticated treatment would account for the fact that each phase contains some of the other phase. This treatment would have the effect of increasing  $DD$  and decreasing  $WW$ . Mathematically,  $X_w$ ,  $X_i$ , and  $\gamma_w$  are related by:

$$\log X_w = \log X_i - \log \gamma_w \quad (\text{Eq. 3})$$

The greater the difference between the adhesive and cohesive forces, the greater is the deviation from ideality and, in general, the lower is the solubility.

If  $DD + WW - 2DW = 0$  and the drug is crystalline,  $\overline{DD}$  will cause the ideal mole fractional solubility to be less than unity. In most instances, both  $DD + WW - 2DW$  and  $\overline{DD}$  are greater than zero, so solubility is inhibited by a combination of the liquid interaction term,  $\log \gamma_w$ , and the crystal interaction term,  $\log X_i$ . To understand the aqueous solubility of crystalline drugs, it is necessary to consider these terms separately. This report will attempt to provide some insight into the dependence of these terms on chemical structure and, thereby, to present a means for their estimation and thus the estimation of the aqueous solubility of a variety of nonelectrolytes.

**Ideal Solubility of Crystals**—As already stated, the ideal solubility of a crystalline drug (*i.e.*, its solubility in an ideal solvent) is dependent only on the nature of the crystal. According to Hildebrand and Scott (2), the ideal solubility of a crystalline substance expressed as its mole fraction,  $X_i^c$ , is:

$$\log X_i^c = \frac{-\Delta H_f (T_m - T)}{2.303R (T_m T)} + \frac{\Delta C_p}{2.303R} \left[ \frac{(T_m - T)}{T} - \log \frac{T_m}{T} \right] \quad (\text{Eq. 4})$$

where  $\Delta H_f$  is the molar heat of fusion of the solid;  $R$  is the gas constant;  $T_m$  and  $T$  are the absolute melting point and temperature of interest, respectively; and  $\Delta C_p$  is the difference in heat capacity of the crystalline and molten forms of the drug. Since  $\Delta C_p$  usually is quite small, and since  $(T_m - T)/T$  is approximately equal to  $\ln(T_m/T)$ , the last term in Eq. 4 usually can be ignored without any significant loss in accuracy. Therefore, as a reasonable approximation,  $X_i^c$  can be approximated from  $T_m$  ( $^{\circ}\text{K}$ ),  $T$  ( $^{\circ}\text{K}$ ), and  $\Delta H_f$  by:

$$\log X_i^c \approx -\frac{\Delta H_f (T_m - T)}{2.303RT_m T} \quad (\text{Eq. 5})$$

Both  $\Delta H_f$  and  $T_m$  depend on the chemical structure of the solute, and both of these parameters tend to increase with increasing molecular weight and increasing polarity. However, these relationships have not proven to be amenable to estimation with any degree of reliability.

Since the free energy of fusion,  $\Delta G$ , is equal to zero at the melting point,  $\Delta H_f/T_m$  can be replaced with  $\Delta S_f$ , where  $\Delta S_f$  is the entropy of fusion. At 25  $^{\circ}\text{C}$ , Eq. 5 becomes:

$$\log X_i^c = -\frac{\Delta S_f}{1364} (T_m - 298) \quad (\text{Eq. 6})$$

For convenience, the difference in absolute temperatures can be replaced with the difference in centigrade temperatures:

$$\log X_i^c = -\frac{\Delta S_f}{1364} (MP - 25) \quad (\text{Eq. 7})$$

where  $MP$  is the melting point of the drug on the conventional centigrade scale.

The advantage of Eq. 7 over Eq. 5, in addition to its greater simplicity, is that  $\Delta S_f$  is more understandable and more predictable than  $\Delta H_f$  (1).

The real aqueous solubility of a crystalline drug,  $X_w^c$ , differs from the ideal solubility in the same manner as described for liquids. Thus:

$$\log X_w^c = -\frac{\Delta S_f}{1364} (MP - 25) - \log \gamma_w \quad (\text{Eq. 8})$$

From Eq. 8, it is apparent that the estimation of aqueous solubility requires the estimation of two parameters,  $\Delta S_f$  and  $\log \gamma_w$ . The remainder of this report deals with the estimation of these parameters for nonelectrolytes and their application to the estimation of aqueous solubility.

## EXPERIMENTAL

**Entropies of Fusion**—All entropies of fusion were calculated from the heats of fusion and melting points. These quantities were either obtained from the literature (3) or were determined experimentally on a differential thermal analyzer with a high-pressure differential scanning calorimeter cell<sup>1</sup>. The literature values were obtained at atmospheric pressure. The experimentally determined values were obtained at 500 psi as described by Martin *et al.* (4) to inhibit sublimation of the more volatile compounds. It was determined that this pressure had little or no effect on the entropy of fusion of nonvolatile compounds; thus, it was assumed that it had no effect on the entropy of fusion of the volatile crystals studied.

Reliable values for the entropy of fusion of three solids could not be determined experimentally. *p*-Aminophenol decomposed before melting, even under 1000 psi of nitrogen. Phthalic acid dehydrated upon melting to form phthalic anhydride. Terephthalic acid sublimed, even under 1000 psi of nitrogen, as evidenced by a coating of the compound around the inside of the calorimeter cell. However, this coating was insoluble in dilute sodium hydroxide and had the texture of a polymer, suggesting that some chemical change (possibly to a linear anhydride) occurred as well. Therefore, the data were excluded from the analysis.

**Partition Coefficients**—Octanol-water partition coefficients were calculated from the fragment constants,  $f$ , developed by Nys and Rekker (5) with the following modifications. Secondary and tertiary hydroxyl groups were given  $f$  values of  $-1.14$  and  $-0.71$ , respectively. For the steroids, the experimentally determined values of Tomida *et al.* (6) were used. These values (which were determined under the same conditions as were used to determine the aqueous solubilities) were used because current methods of estimating partition coefficients are unreliable when applied to steroids.

**Aqueous Solubilities**—The aqueous solubilities of the various classes of compounds were obtained as follows.

The solubilities of halobenzenes were determined spectrophotometrically after equilibration for 24 hr and filtration through sintered glass as described by Yalkowsky *et al.* (7).

Alkyl *p*-aminobenzoate solubilities were determined in the manner described by Yalkowsky *et al.* (8).

The solubilities of polycyclic aromatic compounds were determined as described by MacKay and Shiu (9).

Steroid solubilities were determined as described by Tomida *et al.* (6).

The alcohol solubility data were obtained by averaging data from over 30 sources taken from a compilation<sup>2</sup> of solubility data.

**Statistical Analysis of Data**—Multiple regression analysis of the data was performed using standard statistical procedures.

## RESULTS AND DISCUSSION

**Estimation of Entropy of Fusion**—In this section, a strictly geometric interpretation of the melting process will be utilized to provide a simple and easily understood means of estimating entropy. Since entropy is a state function, consideration of how the process occurs is not required. Only the initial and final states, *i.e.*, the crystal and the melt, are important. On a molecular level, the most obvious difference between these states is their relative degree of geometric order. The intermolecular distance, the packing arrangement, the orientation, and the conformation of crystalline molecules are held within a much narrower range in the crystal than for the liquid.

<sup>1</sup> DuPont model 910.

<sup>2</sup> S. H. Yalkowsky and S. C. Valvani, unpublished data.

$$\Delta S_f = \Delta S_{\text{trans}} + \Delta S_{\text{rot}} + \Delta S_{\text{int}} \quad (\text{Eq. 11})$$

Thus, the total entropy of fusion can be estimated from the probabilities of the component processes of fusion.

**Translational Entropy of Fusion**—The translational entropy of fusion can be visualized by a two-dimensional analogy. Consider a field of disks or checkers that have been trapped into a nearly closest packed arrangement (Fig. 1a) as representing a two-dimensional crystal. When this crystal melts, a slight expansion and a randomization of the positions of the disks occur (Fig. 1b). The probability of two-dimensional fusion taking place is equal to the number of arrangements of the disks that are possible within the area allotted for the solid divided by the much greater number of arrangements that are possible within the area allowed for the liquid. This, in turn, is related to the ratio of the areas available within each phase for the disks to occupy, *i.e.*, to the ratio of free areas. In a three-dimensional arrangement of molecules, the ratio of free volumes rather than free areas would be of concern.

As already stated, spherical molecules can gain only translational entropy when they melt. The entropies of fusion for spherical molecules such as the inert gases and for pseudospherical molecules such as methane and carbon tetrachloride usually fall within the range of 3–4 eu. A value of 3.5 eu can be considered as a reasonable approximation for the translational entropy of fusion of all molecules (although nonspherical molecules tend to have a somewhat larger volume change associated with fusion).

**Rotational Entropy of Fusion**—The rotational entropy of fusion is a component of the total entropy of fusion of all nonspherical molecules. For rigid molecules, it is the only term in addition to the translational entropy that needs to be considered. From the data in Tables I and II, it appears that most rigid aromatic molecules have entropies of fusion between 11 and 16 eu. This constancy of the entropy of fusion has been noted repeatedly in the literature (10–13) but has not been explained.

If it is assumed that the translational contribution to the entropy of fusion is ~3.5 eu, as noted earlier, then the rotational entropy of rigid aromatic molecules must be ~10 ± 3 eu.

An intuitive justification of the nearly constant rotational entropy of fusion is based on the following two assumptions:

1. In the crystal, the molecules (with their centers of mass fixed and accounted for by  $\Delta S_{\text{int}}$ ) can wobble or vibrate (~10° in the spherical coordinates  $\phi$  and  $\theta$  from their most stable position after averaging over all axes).

2. In the liquid, the individual molecules have much greater orientational freedom and can rotate over a much wider range of  $\phi$  and  $\theta$ .

The probability difference between the two degrees of rotational freedom can be evaluated easily by comparing the areas available to a point on the molecular surface in each phase, provided that the range of  $\phi$  and  $\theta$  in the two phases is known. If it is assumed for simplicity that a liquid molecule can rotate freely, any reference point will trace out a sphere about the center of gravity of the molecule. If the molecule is restricted orientationally, as it is in the crystal, the reference point will trace out only a spherical segment.

For example, the area of a spherical segment obtained by a ±10° variation in  $\theta$  and  $\phi$  is 0.00754 times that of a sphere of the same radius. Thus, the probability of  $n$  molecules being oriented within the allowed limits for crystallinity is 0.00754<sup>n</sup> and the entropy contribution is  $-k \ln 0.00754^n$  or ~10 eu. Similarly, the entropy associated with  $\theta = \phi = 20^\circ$  is 7 eu. Although the actual values of  $\theta$  and  $\phi$  probably will depend on the overall geometry of the molecules and their degree of interaction, the relative constancy of  $\Delta S_f$  for rigid molecules suggests that the variation is not too large or, more likely, that factors inhibiting rotation in the liquid also inhibit rotation in the crystal.

The assumption of free rotation in the liquid is used only for mathematical convenience and probably is physically inappropriate in many cases. However, the entropy estimate is based on the ratio of areas available to the reference point in the two phases. If the liquid rotation is restricted, as it would be in highly elongated or hydrogen-bonded molecules, then the rotation in the solid also is more restricted for the same reasons. The constancy of the entropy of fusion of rigid molecules suggests that, in these cases, the ratio of the rotational freedom in the liquid to the solid is the same.

Pirsch (14, 15) suggested that elongated molecules have higher entropies of fusion; Bondi (10) postulated that, because of their restricted motion in the liquid, hydrogen-bonded molecules have lower entropies of fusion than their hydrocarbon homomorphs. These postulates are not supported by the data available for rigid molecules.

As can be seen in Table I, there is no systematic effect of hydrogen bonding on entropy of fusion. Specifically, the isomeric xylenes and their

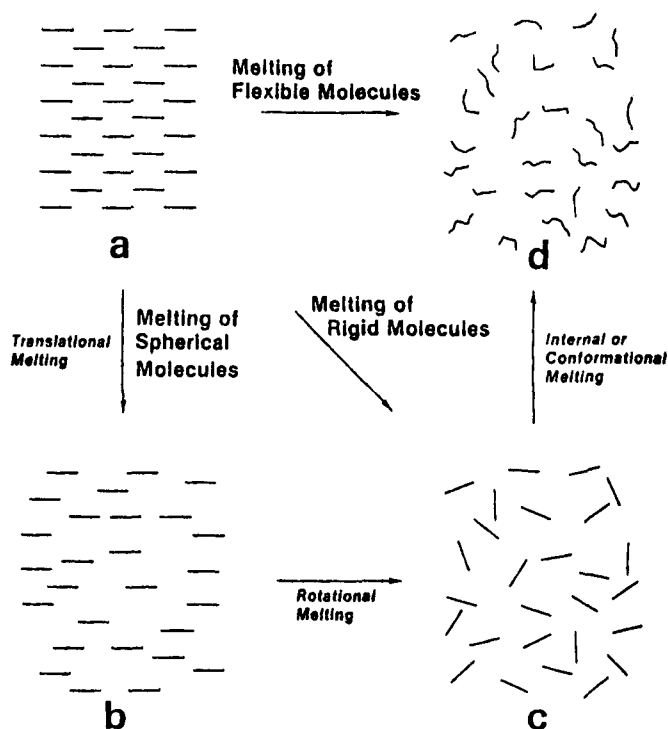


Figure 1—Hypothetical stages of melting.

For conceptualization, the melting process can be divided into three subprocesses (4):

1. Translational melting—the change from the ordered arrangement of the molecular centers of gravity in the crystal to the expanded and more randomized arrangement in the liquid.

2. Rotational melting—the change from the ordered arrangement of the major axes of crystalline molecules to the randomly oriented arrangement in the liquid. (This process is not applicable to spherical molecules.)

3. Internal melting—the change from the uniform conformation of flexible molecules of the crystal to the random conformation of such molecules in the liquid. (This process is not applicable to rigid molecules and, thus, to most drugs. However, it does become important for long chain molecules.)

These subprocesses are illustrated in Fig. 1. Since the total entropy is dependent only on the initial and final states, these processes can be treated for convenience as occurring sequentially. For spherical molecules, only translational melting can occur. For rigid nonspherical molecules, both translational and rotational melting exist. All three steps are applicable to the melting of flexible molecules, *i.e.*, those that can undergo conformational changes to an appreciable extent.

The geometrical entropy of a liquid,  $S_L$ , is related to the number of ways,  $W_L$ , in which its molecules can be arranged that would be consistent with the liquid state by  $S_L = R \ln W_L$ . Similarly, the geometrical entropy of a crystalline solid,  $S_c$ , is related to the number of ways,  $W_c$ , of arranging the molecules in the crystal by  $S_c = R \ln W_c$ . It is assumed that  $W_c$  is a subset of  $W_L$ ; *i.e.*, the crystal arrangement is a special case of the more general, less constrained liquid arrangement.

The molar entropy of fusion,  $\Delta S_f$ , is equal to the entropy of the liquid minus the entropy of the crystal:

$$\Delta S_f = S_L - S_c = -R \ln \left( \frac{W_c}{W_L} \right) = -R \ln P_f \quad (\text{Eq. 9})$$

where  $P_f$  is the ratio of the number of ways of achieving the crystal to the number of ways of achieving the liquid. It is equal to the probability (above the melting point) of a collection of 1 mole of liquid molecules spontaneously arranging themselves in such a way as to fulfill the geometrical requirements of the crystal. This quantity will be referred to as the total geometrical probability of fusion and is assumed to be equal to the product of the subprocess probabilities:

$$P_f = P_{\text{trans}} P_{\text{rot}} P_{\text{int}} \quad (\text{Eq. 10})$$

Since the entropies of the subprocesses are related to their probability of occurrence by equations analogous to Eq. 9, and since the probabilities are assumed to be multiplicative, the entropies must be additive:

Table I—Entropy of Fusion Values for Disubstituted Benzenes

| Position     | No H-Bonding Groups |                 | One H-Bonding Group |                 | Two H-Bonding Groups |              |                 |                 |      |
|--------------|---------------------|-----------------|---------------------|-----------------|----------------------|--------------|-----------------|-----------------|------|
|              | Substituents        | $\Delta S_f$    | Substituents        | $\Delta S_f$    | Substituents         | $\Delta S_f$ |                 |                 |      |
| <i>ortho</i> | CH <sub>3</sub>     | CH <sub>3</sub> | 13.2                | OH              | CH <sub>3</sub>      | 12.4         | OH              | OH              | 14.4 |
| <i>meta</i>  |                     |                 | 12.4                |                 |                      | 9.0          |                 |                 | 13.2 |
| <i>para</i>  |                     |                 | 14.2                |                 |                      | 9.6          |                 |                 | 14.6 |
| <i>ortho</i> | CH <sub>3</sub>     | Cl              | —                   | OH              | Cl                   | 9.1          | OH              | NH <sub>2</sub> | 12.8 |
| <i>meta</i>  |                     |                 | —                   |                 |                      | 9.2          |                 |                 | 11.2 |
| <i>para</i>  |                     |                 | 12.9                |                 |                      | 11.1         |                 |                 | —    |
| <i>ortho</i> | CH <sub>3</sub>     | Br              | —                   | OH              | Br                   | 9.7          | OH              | COOH            | 10.8 |
| <i>meta</i>  |                     |                 | —                   |                 |                      | —            |                 |                 | 14.7 |
| <i>para</i>  |                     |                 | 12.0                |                 |                      | 10.5         |                 |                 | 12.2 |
| <i>ortho</i> | CH <sub>3</sub>     | NO <sub>2</sub> | —                   | OH              | NO <sub>2</sub>      | 12.5         | NH <sub>2</sub> | NH <sub>2</sub> | 12.0 |
| <i>meta</i>  |                     |                 | 14.6                |                 |                      | 13.8         |                 |                 | 11.5 |
| <i>para</i>  |                     |                 | 13.9                |                 |                      | 13.0         |                 |                 | 10.4 |
| <i>ortho</i> | Cl                  | Cl              | 12.1                | NH <sub>2</sub> | CH <sub>3</sub>      | —            | NH <sub>2</sub> | COOH            | 11.8 |
| <i>meta</i>  |                     |                 | 12.2                |                 |                      | —            |                 |                 | 11.5 |
| <i>para</i>  |                     |                 | 13.4                |                 |                      | 13.5         |                 |                 | 10.8 |
| <i>ortho</i> | Cl                  | Br              | —                   | NH <sub>2</sub> | Cl                   | —            | COOH            | COOH            | —    |
| <i>meta</i>  |                     |                 | 12.2                |                 |                      | —            |                 |                 | 18.9 |
| <i>para</i>  |                     |                 | 13.3                |                 |                      | 13.8         |                 |                 | —    |
| <i>ortho</i> | Cl                  | NO <sub>2</sub> | 13.7                | NH <sub>2</sub> | Br                   | 13.0         |                 |                 | —    |
| <i>meta</i>  |                     |                 | 16.1                |                 |                      | —            |                 |                 | —    |
| <i>para</i>  |                     |                 | 11.7                |                 |                      | 14.4         |                 |                 | —    |
| <i>ortho</i> | Br                  | Br              | 11.0                | NH <sub>2</sub> | NO <sub>2</sub>      | 11.2         |                 |                 | —    |
| <i>meta</i>  |                     |                 | 12.1                |                 |                      | 12.0         |                 |                 | —    |
| <i>para</i>  |                     |                 | 13.5                |                 |                      | 14.6         |                 |                 | —    |
| <i>ortho</i> | Br                  | NO <sub>2</sub> | 16.3                | COOH            | CH <sub>3</sub>      | 14.9         |                 |                 | —    |
| <i>meta</i>  |                     |                 | 13.7                |                 |                      | 9.8          |                 |                 | —    |
| <i>para</i>  |                     |                 | 10.0                |                 |                      | 12.0         |                 |                 | —    |
| <i>ortho</i> | NO <sub>2</sub>     | NO <sub>2</sub> | 13.9                | COOH            | Cl                   | 14.9         |                 |                 | —    |
| <i>meta</i>  |                     |                 | 11.5                |                 |                      | 13.3         |                 |                 | —    |
| <i>para</i>  |                     |                 | 15.1                |                 |                      | 15.0         |                 |                 | —    |
|              |                     |                 |                     | COOH            | Br                   | 13.2         |                 |                 | —    |
|              |                     |                 |                     |                 |                      | 11.9         |                 |                 | —    |
|              |                     |                 |                     | COOH            | NO <sub>2</sub>      | 15.5         |                 |                 | —    |
|              |                     |                 |                     |                 |                      | 15.9         |                 |                 | —    |
|              |                     |                 |                     |                 |                      | 11.3         |                 |                 | —    |
|              |                     |                 |                     |                 |                      | 17.2         |                 |                 | —    |
| Average      |                     |                 | 13.1                |                 |                      | 12.6         |                 |                 | 12.7 |

corresponding dihydroxybenzenes have nearly identical entropies of fusion. The degree of substitution of the benzene ring does not have any systematic effect, as is evidenced by the data for the halobenzenes. Molecular size and shape also appear to have no effect on the entropy of fusion (for compounds larger than benzene).

Surprisingly, there is no systematic difference in entropy with respect to the position of substitution (Table I). The decreased rotational entropy of the more symmetrical compounds evidently is offset by the increased translational entropy that results from their greater packing efficiency. Highly prolate ellipsoids such as diphenyl, anthracene, and naphthalene and highly oblate ellipsoids such as hexamethylbenzene, hexachlorobenzene, and coronene all have entropies of fusion in the range discussed.

**Internal Entropy of Fusion**—The internal or conformational entropy of fusion results from the fact that molecular configuration is fixed invariably in the crystal but not in the liquid. For example, a molecule of stearic acid is likely to be found only in the *anti*-conformation in a crystal, whereas many bonds are likely to be *gauche* in the liquid.

If twist angles of only 60° (*gauche*), 180° (*anti*), and 300° (*gauche*) are possible and if these three angles are equally probable, then the probability of finding a long chain molecule in the completely outstretched conformation is equal to  $(\frac{1}{3})^{n-3}$ , where  $n$  is the number of carbon and heteroatoms in the chain and  $n - 3$  is the number of twist angles. The entropy associated with this probability is:

$$\Delta S_{\text{int}} = -R(n - 3) \ln (\frac{1}{3}) = 2.2(n - 3) \quad (\text{Eq. 12})$$

For reasons discussed previously (16), the internal entropy of fusion is better approximated by  $2.5(n - 5)$ . Molecules having less than five units in a flexible chain can be treated as rigid molecules as a first approximation.

**Total Entropy of Fusion**—On the basis of the preceding discussion, the entropy of fusion is dependent primarily on molecular geometry. For spherical or nearly spherical molecules:

$$\Delta S_f = \Delta S_{\text{trans}} = 3.5 \text{ eu} \quad (\text{Eq. 13})$$

For rigid molecules:

$$\Delta S_f = \Delta S_{\text{trans}} + \Delta S_{\text{rot}} = 13.5 \text{ eu} \quad (\text{Eq. 14})$$

For molecules having  $n > 5$  nonhydrogen atoms in a flexible chain:

$$\Delta S_f = \Delta S_{\text{trans}} + \Delta S_{\text{rot}} + \Delta S_{\text{int}} = 13.5 + 2.5(n - 5) \text{ eu} \quad (\text{Eq. 15})$$

Some small nonspherical molecules have very small rotational entropies and thus have entropies of fusion falling between 3.5 and 13 eu. Fortunately, these compounds, like spherical molecules, melt below room temperature and thus have ideal mole fractional solubilities of unity. In other words, the term involving  $\Delta S_f$  is equal to zero.

**Estimation of Ideal Solubility**—The ideal room temperature solubility of the various classes of molecules can be calculated by simply inserting the entropy of fusion approximation into Eq. 7 to give:

$$-\log X_i = 0.01(MP - 25) \quad (\text{Eq. 16})$$

for rigid nonspherical molecules and:

$$-\log X_i = [0.01 + 0.0018(n - 5)](MP - 25) \quad (\text{Eq. 17})$$

for partially flexible molecules. The logarithms of the ideal solubilities of a wide variety of compounds calculated from experimentally measured entropies of fusion and from these approximations are listed in Table II. The two values rarely differ by more than 0.3 log unit (*i.e.*, by a factor of two). In fact, the solubility estimates frequently are better than the entropy estimates from which they were generated.

The high accuracy of this approach results in part because compounds that are more spherical or that are highly flexible and thus are likely to have the greatest error in  $\Delta S_f$  estimation are compounds that tend to have low melting points, so the product  $(MP - 25) \Delta S_f$  is small and thus does not contribute greatly to the calculation, *i.e.*,  $\log X_i$  is near zero.

Statistical analysis of the calculated (from Eq. 7) and approximated (from Eq. 16 or 17) ideal solubilities of the compounds in Table II gives the following:

$$\log X_{\text{calc}} = 0.962 \log X_{\text{estim}} - 0.020 \quad (\text{Eq. 18})$$

$$r = 0.96 \quad s = 0.16$$

Since the compounds considered were chosen previously (3) (*i.e.*, there was no subjective selection by the present investigators), this analysis probably can be regarded as an objective test of the relationships dis-

Table II—Calculation of Ideal Solubility of Some Model Compounds<sup>a</sup>

| Compound                     | MP     | $\Delta S_f$<br>Obs., eu | $n - 5$ | $\Delta S_f$<br>Estim., eu | log X Ideal      |                          | Residual |
|------------------------------|--------|--------------------------|---------|----------------------------|------------------|--------------------------|----------|
|                              |        |                          |         |                            | Calc.<br>(Eq. 7) | Estim.<br>(Eq. 16 or 17) |          |
| Cyclohexanol                 | 25.5°  | 1.41 <sup>a</sup>        | —       | 13.5 <sup>a</sup>          | 0.001            | 0.005                    | -0.004   |
| Cyanamide                    | 44.0°  | 1.69                     | —       | 13.5                       | 0.024            | 0.190                    | -0.166   |
| Succinonitrile               | 54.5°  | 2.86                     | —       | 13.5                       | 0.062            | 0.295                    | -0.233   |
| Trichloroacetic acid         | 57.5°  | 4.25                     | —       | 13.5                       | 0.101            | 0.325                    | -0.224   |
| <i>tert</i> -Butyl alcohol   | 25.4°  | 5.44                     | —       | 13.5                       | 0.002            | 0.004                    | -0.002   |
| Crotonic acid                | 72.0°  | 6.32                     | —       | 13.5                       | 0.218            | 0.470                    | -0.252   |
| Levulinic acid               | 33.0°  | 7.20                     | —       | 13.5                       | 0.042            | 0.080                    | -0.038   |
| Phenol                       | 40.9°  | 8.60                     | —       | 13.5                       | 0.100            | 0.159                    | -0.059   |
| <i>cis</i> -Crotonic acid    | 71.2°  | 8.73                     | —       | 13.5                       | 0.296            | 0.462                    | -0.166   |
| $\alpha$ -Chloroacetic acid  | 61.2°  | 8.78                     | —       | 13.5                       | 0.23-            | 0.362                    | -0.129   |
| Menthol                      | 43.5°  | 9.20                     | —       | 13.5                       | 0.125            | 0.185                    | -0.060   |
| <i>p</i> -Cresol             | 34.6°  | 9.24                     | —       | 13.5                       | 0.065            | 0.096                    | -0.031   |
| <i>m</i> -Toluic acid        | 108.8° | 9.84                     | —       | 13.5                       | 0.605            | 0.838                    | -0.233   |
| Phenylacetic acid            | 76.7°  | 9.90                     | —       | 13.5                       | 0.376            | 0.517                    | -0.141   |
| $\alpha$ -Naphthylamine      | 50.0°  | 9.90                     | —       | 13.5                       | 0.182            | 0.250                    | -0.068   |
| $\beta$ -Chloroacetic acid   | 56.0°  | 10.09                    | —       | 13.5                       | 0.229            | 0.310                    | -0.081   |
| Hydrazobenzene               | 134.0° | 10.36                    | —       | 13.5                       | 0.828            | 1.090                    | -0.262   |
| Benzoic acid                 | 122.4° | 10.47                    | —       | 13.5                       | 0.748            | 0.974                    | -0.226   |
| <i>p</i> -Bromophenol        | 63.5°  | 10.54                    | —       | 13.5                       | 0.298            | 0.385                    | -0.087   |
| Diphenyl                     | 165.5° | 10.69                    | —       | 13.5                       | 1.102            | 1.405                    | -0.303   |
| <i>DL</i> -Carvoxime         | 91.0°  | 10.72                    | —       | 13.5                       | 0.519            | 0.660                    | -0.141   |
| <i>p</i> -Aminobenzoic acid  | 188.5° | 10.83                    | —       | 13.5                       | 1.299            | 1.635                    | -0.336   |
| Thiosinamine                 | 77.0°  | 11.10                    | —       | 13.5                       | 0.423            | 0.520                    | -0.097   |
| <i>m</i> -Nitrobenzoic acid  | 141.1° | 11.13                    | —       | 13.5                       | 0.948            | 1.161                    | -0.213   |
| <i>D</i> -Carvoxime          | 71.5°  | 11.17                    | —       | 13.5                       | 0.381            | 0.465                    | -0.084   |
| <i>o</i> -Nitroaniline       | 71.2°  | 11.19                    | —       | 13.5                       | 0.379            | 0.462                    | -0.083   |
| <i>L</i> -Carvoxime          | 70.0°  | 11.28                    | —       | 13.5                       | 0.372            | 0.450                    | -0.078   |
| Urethan                      | 48.7°  | 11.31                    | —       | 13.5                       | 0.197            | 0.237                    | -0.040   |
| <i>m</i> -Dinitrobenzene     | 89.7°  | 11.45                    | —       | 13.5                       | 0.543            | 0.647                    | -0.104   |
| $\beta$ -Naphthol            | 120.6° | 11.46                    | —       | 13.5                       | 0.804            | 0.956                    | -0.152   |
| Benzoquinone                 | 112.9° | 11.48                    | —       | 13.5                       | 0.740            | 0.879                    | -0.139   |
| <i>m</i> -Aminobenzoic acid  | 179.5° | 11.53                    | —       | 13.5                       | 1.306            | 1.545                    | -0.239   |
| <i>o</i> -Nitrophenol        | 45.1°  | 11.70                    | —       | 13.5                       | 0.172            | 0.201                    | -0.029   |
| <i>o</i> -Aminobenzoic acid  | 145.0° | 11.80                    | —       | 13.5                       | 1.039            | 1.200                    | -0.161   |
| <i>p</i> -Bromotoluene       | 28.0°  | 11.85                    | —       | 13.5                       | 0.026            | 0.030                    | -0.004   |
| Alloinnamic acid             | 68.0°  | 11.88                    | —       | 13.5                       | 0.375            | 0.430                    | -0.055   |
| <i>D</i> -Dimethyl tartrate  | 49.0°  | 11.89                    | —       | 13.5                       | 0.209            | 0.240                    | -0.031   |
| <i>m</i> -Nitroaniline       | 147.0° | 12.00                    | —       | 13.5                       | 1.074            | 1.220                    | -0.146   |
| <i>p</i> -Toluic acid        | 179.6° | 12.00                    | —       | 13.5                       | 1.361            | 1.546                    | -0.185   |
| Phenanthrene                 | 96.3°  | 12.07                    | —       | 13.5                       | 0.631            | 0.713                    | -0.082   |
| 2,4,6-Tribromophenol         | 93.0°  | 12.09                    | —       | 13.5                       | 0.603            | 0.680                    | -0.077   |
| <i>m</i> -Diiodobenzene      | 34.2°  | 12.39                    | —       | 13.5                       | 0.084            | 0.092                    | -0.008   |
| Succinic anhydride           | 119.0° | 12.44                    | —       | 13.5                       | 0.858            | 0.940                    | -0.082   |
| <i>p</i> -Bromoiodobenzene   | 90.1°  | 12.59                    | —       | 13.5                       | 0.601            | 0.651                    | -0.050   |
| Benzil                       | 95.2°  | 12.65                    | —       | 13.5                       | 0.651            | 0.702                    | -0.051   |
| Naphthalene                  | 80.2°  | 12.72                    | —       | 13.5                       | 0.515            | 0.552                    | -0.037   |
| Thymol                       | 51.5°  | 12.72                    | —       | 13.5                       | 0.247            | 0.265                    | -0.018   |
| <i>o</i> -Toluic acid        | 103.7° | 12.79                    | —       | 13.5                       | 0.738            | 0.787                    | -0.049   |
| <i>p</i> -Dichlorobenzene    | 53.1°  | 13.10                    | —       | 13.5                       | 0.270            | 0.281                    | -0.011   |
| Diphenylamine                | 53.0°  | 13.10                    | —       | 13.5                       | 0.269            | 0.280                    | -0.011   |
| Hydrocinnamic acid           | 48.0°  | 13.17                    | —       | 13.5                       | 0.222            | 0.230                    | -0.008   |
| <i>D</i> -Diiodobenzene      | 129.0° | 13.29                    | —       | 13.5                       | 1.014            | 1.040                    | -0.026   |
| Resorcinol                   | 110.0° | 13.29                    | —       | 13.5                       | 0.828            | 0.850                    | -0.022   |
| <i>p</i> -Iodotoluene        | 84.0°  | 13.32                    | —       | 13.5                       | 0.088            | 0.090                    | -0.002   |
| Cinnamic acid                | 133.0° | 13.32                    | —       | 13.5                       | 1.055            | 1.080                    | -0.025   |
| <i>m</i> -Chlorobenzoic acid | 154.2° | 13.34                    | —       | 13.5                       | 1.264            | 1.292                    | -0.028   |
| Nitronaphthalene             | 56.7°  | 13.36                    | —       | 13.5                       | 0.311            | 0.317                    | -0.006   |
| Benzophenone                 | 47.9°  | 13.36                    | —       | 13.5                       | 0.224            | 0.229                    | -0.005   |
| <i>p</i> -Dibromobenzene     | 86.0°  | 13.50                    | —       | 13.5                       | 0.604            | 0.610                    | -0.006   |
| Benzylaniline                | 23.4°  | 13.52                    | —       | 13.5                       | -0.016           | -0.016                   | 0.000    |
| Carbazole                    | 243.0° | 13.63                    | —       | 13.5                       | 2.178            | 2.180                    | -0.002   |
| <i>p</i> -Toluidine          | 43.3°  | 13.77                    | —       | 13.5                       | 0.185            | 0.183                    | 0.002    |
| Chloral hydrate              | 47.4°  | 13.82                    | —       | 13.5                       | 0.227            | 0.224                    | 0.003    |
| Azoxybenzene                 | 36.0°  | 13.87                    | —       | 13.5                       | 0.112            | 0.110                    | 0.002    |
| <i>o</i> -Dinitrobenzene     | 116.9° | 13.90                    | —       | 13.5                       | 0.937            | 0.919                    | 0.018    |
| <i>p</i> -Chloronitrobenzene | 33.5°  | 13.93                    | —       | 13.5                       | 0.597            | 0.585                    | 0.012    |
| Methyl cinnamate             | 36.0°  | 13.93                    | —       | 13.5                       | 0.112            | 0.110                    | 0.002    |
| Hydroxyacetanilide           | 91.3°  | 13.94                    | —       | 13.5                       | 0.678            | 0.663                    | 0.015    |
| Anthraquinone                | 284.8° | 13.99                    | —       | 13.5                       | 2.665            | 2.598                    | 0.067    |
| 2,4-Dinitrotoluene           | 70.1°  | 14.01                    | —       | 13.5                       | 0.463            | 0.451                    | 0.012    |
| Anthracene                   | 216.5° | 14.09                    | —       | 13.5                       | 1.979            | 1.915                    | 0.064    |
| Durene                       | 79.3°  | 14.25                    | —       | 13.5                       | 0.567            | 0.543                    | 0.024    |
| <i>D</i> -Tetrachloroxylene  | 86.0°  | 14.28                    | —       | 13.5                       | 0.639            | 0.610                    | 0.029    |
| 2,4,6-Trinitrotoluene        | 80.8°  | 14.34                    | —       | 13.5                       | 0.587            | 0.558                    | 0.029    |
| Pyrocatechol                 | 105.0° | 14.39                    | —       | 13.5                       | 0.844            | 0.800                    | 0.044    |
| Glutaric acid                | 97.5°  | 14.54                    | —       | 13.5                       | 0.773            | 0.725                    | 0.048    |
| Quinol                       | 172.3° | 14.55                    | —       | 13.5                       | 1.572            | 1.473                    | 0.099    |
| <i>m</i> -Chloronitrobenzene | 44.4°  | 14.58                    | —       | 13.5                       | 0.207            | 0.194                    | 0.013    |
| <i>p</i> -Nitroaniline       | 114.0° | 14.62                    | —       | 13.5                       | 0.954            | 0.890                    | 0.064    |
| <i>p</i> -Tetrachloroxylene  | 95.0°  | 14.65                    | —       | 13.5                       | 0.752            | 0.700                    | 0.052    |

Table II—Continued

| Compound                     | MP     | $\Delta S_f$<br>Obs., eu | $n - 5$ | $\Delta S_f$<br>Estim., eu | log X Ideal      |                          | Residual |
|------------------------------|--------|--------------------------|---------|----------------------------|------------------|--------------------------|----------|
|                              |        |                          |         |                            | Calc.<br>(Eq. 7) | Estim.<br>(Eq. 16 or 17) |          |
| <i>o</i> -Chlorobenzoic acid | 140.2° | 14.88                    | —       | 13.5                       | 1.257            | 1.152                    | 0.105    |
| <i>p</i> -Nitrophenol        | 113.8° | 15.00                    | —       | 13.5                       | 0.977            | 0.888                    | 0.089    |
| <i>p</i> -Chlorobenzoic acid | 239.7° | 15.03                    | —       | 13.5                       | 2.367            | 2.147                    | 0.220    |
| <i>p</i> -Dinitrobenzene     | 173.5° | 15.06                    | —       | 13.5                       | 1.640            | 1.485                    | 0.155    |
| <i>m</i> -Xylene dichloride  | 34.0°  | 15.19                    | —       | 13.5                       | 0.100            | 0.090                    | 0.010    |
| $\alpha$ -Naphthol           | 95.0°  | 15.26                    | —       | 13.5                       | 0.783            | 0.700                    | 0.083    |
| <i>p</i> -Xylene dichloride  | 100.0° | 15.36                    | —       | 13.5                       | 0.845            | 0.750                    | 0.095    |
| Methyl oxalate               | 54.4°  | 15.38                    | —       | 13.5                       | 0.332            | 0.294                    | 0.038    |
| <i>o</i> -Xylene dichloride  | 55.0°  | 15.49                    | —       | 13.5                       | 0.341            | 0.300                    | 0.041    |
| Azobenzene                   | 61.7°  | 15.74                    | —       | 13.5                       | 0.424            | 0.367                    | 0.057    |
| <i>o</i> -Nitrobenzoic acid  | 148.5° | 15.88                    | —       | 13.5                       | 1.438            | 1.235                    | 0.203    |
| <i>m</i> -Xylene dibromide   | 77.0°  | 16.18                    | —       | 13.5                       | 0.617            | 0.520                    | 0.097    |
| Dimethylpyrone               | 132.0° | 16.59                    | —       | 13.5                       | 1.302            | 1.070                    | 0.232    |
| <i>p</i> -Nitrobenzoic acid  | 239.2° | 17.23                    | —       | 13.5                       | 2.706            | 2.142                    | 0.564    |
| DL-Dimethyl tartrate         | 87.0°  | 17.38                    | —       | 13.5                       | 0.790            | 0.620                    | 0.170    |
| <i>o</i> -Xylene dibromide   | 95.0°  | 17.39                    | —       | 13.5                       | 0.893            | 0.700                    | 0.193    |
| Stilbene                     | 124.0° | 18.16                    | —       | 13.5                       | 1.318            | 0.990                    | 0.328    |
| Apiol                        | 29.5°  | 18.95                    | —       | 13.5                       | 0.063            | 0.045                    | 0.018    |
| Undecilic acid               | 28.3°  | 19.91                    | 5       | 26                         | 0.048            | 0.063                    | 0.015    |
| Capric acid                  | 32.0°  | 21.95                    | 6       | 28.5                       | 0.113            | 0.147                    | 0.034    |
| Methyl fumarate              | 102.0° | 22.26                    | 1       | 17                         | 1.257            | 0.963                    | 0.295    |
| Camphene                     | 51.0°  | 23.26                    | —       | 13.5                       | 0.443            | 0.260                    | 0.183    |
| Cinnamic anhydride           | 48.0°  | 24.40                    | —       | 13.5                       | 0.411            | 0.230                    | 0.181    |
| Cetyl alcohol                | 49.3°  | 25.43                    | 12      | 43.5                       | 0.453            | 0.777                    | -0.324   |
| Lauric acid                  | 43.2°  | 27.70                    | 6       | 28.5                       | 0.370            | 0.381                    | -0.011   |
| Palmitic acid                | 61.8°  | 30.01                    | 10      | 38.5                       | 0.810            | 1.042                    | -0.232   |
| Tricosane                    | 47.6°  | 31.13                    | 18      | 58.5                       | 0.516            | 0.972                    | -0.456   |
| Myristic acid                | 54.0°  | 33.17                    | 8       | 33.5                       | 0.705            | 0.714                    | -0.007   |
| Nonadecane                   | 32.1°  | 35.89                    | 14      | 48.5                       | 0.187            | 0.253                    | -0.066   |
| Heneicosane                  | 40.5°  | 36.37                    | 16      | 53.5                       | 0.413            | 0.610                    | -0.197   |
| Docosane                     | 44.4°  | 36.86                    | 17      | 56                         | 0.524            | 0.799                    | -0.175   |
| Stearic acid                 | 68.8°  | 39.57                    | 12      | 43.5                       | 1.271            | 1.401                    | -0.130   |
| Tetracosane                  | 50.9°  | 40.51                    | 19      | 61                         | 0.769            | 1.162                    | -0.393   |
| Pentacosane                  | 53.7°  | 42.24                    | 20      | 63.5                       | 0.889            | 1.340                    | -0.451   |
| Heptacosane                  | 59.0°  | 43.50                    | 21      | 66                         | 1.085            | 1.650                    | -0.565   |
| Octacosane                   | 61.4°  | 46.21                    | 22      | 68.5                       | 1.233            | 1.833                    | -0.600   |
| Elaidic acid                 | 44.4°  | 46.35                    | 13      | 46                         | 0.659            | 0.656                    | 0.003    |
| Octadecane                   | 28.2°  | 48.71                    | 13      | 46                         | 0.114            | 0.108                    | 0.006    |
| Eicosane                     | 36.8°  | 53.91                    | 15      | 51                         | 0.467            | 0.443                    | 0.024    |
| Tristearin                   | 54.5°  | 122.67                   | 49      | 135                        | 2.654            | 2.928                    | -0.274   |

<sup>a</sup> The compounds listed have melting points above 25° for which heat of fusion data are given in Ref. 3. The list therefore is not in any way weighted toward good agreement with theory. All entropy data are in entropy units.

Table III—Calculated Entropies of Fusion and Ideal Solubilities of Alkyl *p*-Aminobenzoates at 37°

| Ester     | MP   | $\Delta S_f$<br>Obs.<br>(Ref. 3) | $n - 5$ | 13.5 +<br>2.5<br>( $n - 5$ ) | log $X_i$        |                   | $\Delta \log X_i$<br>(Residual) |
|-----------|------|----------------------------------|---------|------------------------------|------------------|-------------------|---------------------------------|
|           |      |                                  |         |                              | Calc.<br>(Eq. 6) | Estim.<br>(Eq. 7) |                                 |
| Methyl    | 112° | 15.1 <sup>a</sup>                | 0       | 13.5                         | 0.80             | 0.75              | 0.05                            |
| Ethyl     | 89°  | 13.1                             | 0       | 13.5                         | 0.49             | 0.53              | -0.04                           |
| Propyl    | 74°  | 14.6                             | 0       | 13.5                         | 0.37             | 0.36              | 0.01                            |
| Butyl     | 56°  | 17.8                             | 1       | 16.0                         | 0.24             | 0.24              | 0.00                            |
| Pentyl    | 52°  | 17.8                             | 2       | 18.5                         | 0.20             | 0.26              | -0.06                           |
| Hexyl     | 61°  | 25.2                             | 3       | 21.0                         | 0.43             | 0.44              | -0.01                           |
| Heptyl    | 75°  | 18.1                             | 4       | 23.5                         | 0.50             | 0.76              | -0.26                           |
| Octyl     | 71°  | 28.3                             | 5       | 26.0                         | 0.68             | 0.78              | -0.10                           |
| Nonyl     | 69°  | 31.4                             | 6       | 28.5                         | 0.69             | 0.78              | -0.09                           |
| Dodecyl   | 82°  | 41.5                             | 9       | 36.0                         | 1.44             | 1.39              | 0.05                            |
| Hexadecyl | 87°  | 55.5                             | 13      | 46.0                         | 1.88             | 1.99              | -0.11                           |

<sup>a</sup> All entropy values are expressed in entropy units.

cussed in this report. If so, Eq. 16 offers a 95% probability of estimating the ideal solubility of a substance to within a factor of two.

The contribution of increasing chain length to the internal entropy of fusion and to the ideal solubility is illustrated specifically for the alkyl *p*-aminobenzoates in Table III.

Experimentally, ideal solubilities can be demonstrated only for solutes in solvents of very similar polarity. The most convenient system for demonstrating the ideal solubility for solids is the aromatic and haloaromatic hydrocarbons in benzene. The observed solubilities of a number of polycyclic aromatics and substituted benzenes in benzene are listed in Table IV along with the ideal solubilities estimated by Eq. 7. The estimated values are in excellent agreement with the experimentally determined values.

Because this treatment is based on many assumptions and approximations, it cannot be expected to provide highly accurate ideal solubility estimates for all compounds. However, it does provide a simple means of obtaining a reasonable estimate of ideal solubility from nothing more than the structure and melting point of the compound in question.

From a pharmaceutical point of view, the value of being able to estimate ideal solubility is not that it enables calculation of the solubility of compounds in ideal solvents but rather that the ideal solubility of a substance is a factor which partially determines its solubility in water and other pharmaceutically important solvents.

**Estimation of Aqueous Activity Coefficient**—The estimation of the activity coefficient is somewhat more difficult than estimation of the entropy of fusion. The former value is dependent on the nature of two

Table IV—Mole Fraction Solubility of Aromatic Compounds in Benzene

| Solute                                      | MP     | I     | X      | log X<br>Obs. | log X <sub>i</sub><br>Estim.,<br>0.01(MP - T) |
|---|--------|-------|--------|---------------|---|
| Diphenyl                                    | 68.9°  | 37.0° | 0.5118 | -0.29         | -0.32   |
| <i>o</i> -Terphenyl                         | 55.5°  | 28.0° | 0.5852 | -0.23         | -0.28   |
| <i>m</i> -Terphenyl                         | 87.0°  | 36.8° | 0.2827 | -0.55         | -0.50   |
| <i>p</i> -Terphenyl                         | 213.0° | 38.0° | 0.0071 | -2.15         | -1.75   |
| <i>s</i> -Triphenylbenzene                  | 174.9° | 25.2° | 0.0299 | -1.52         | -1.50   |
| Naphthalene                                 | 80.0°  | 35.0° | 0.3766 | -0.42         | -0.45   |
| Anthracene                                  | 218.0° | 35.8° | 0.0103 | -1.99         | -1.82   |
| Phenanthrene                                | 98.4°  | 32.0° | 0.2239 | -0.65         | -0.62   |
| Pyrene                                      | 150.2° | 32.4° | 0.0734 | -1.13         | -1.18   |
| Triphenylene                                | 198.1° | 39.4° | 0.0140 | -1.85         | -1.59   |
| Chrysene                                    | 254.0° | 35.6° | 0.0021 | -2.68         | -2.18   |
| Fluorene                                    | 113.2° | 33.5° | 0.1604 | -0.79         | -0.80   |
| Acenaphthene                                | 94.1°  | 30.6° | 0.1815 | -0.74         | -0.63   |
| Fluoranthrene                               | 110.2° | 44.8° | 0.2174 | -0.66         | -0.65   |
| Hexachlorobenzene                           | 226.0° | 29.9° | 0.0147 | -1.83         | -1.96   |
| Hexamethylbenzene                           | 166.0° | 29.9° | 0.0583 | -1.23         | -1.36   |
| 1,3,5-Trimethyl-<br>2,4,6-trichlorobenzene  | 205.0  | 29.9° | 0.0190 | -1.72         | -1.75   |
| 1,2,5-Trimethyl-<br>3,4,6-trichlorobenzene  | 210.0° | 29.9° | 0.0153 | -1.82         | -1.94   |
| Tetrachloro- <i>o</i> -xylene               | 228.0° | 29.9° | 0.0150 | -1.82         | -1.98   |
| 1,2,3,4-Tetramethyl-<br>5,6-dichlorobenzene | 193.0° | 29.9° | 0.0370 | -1.43         | -1.63   |
| Pentamethylchlorobenzene                    | 154.0° | 29.9° | 0.0737 | -1.13         | -1.34   |
| Pentachlorobenzene                          | 86.0°  | 29.9° | 0.242  | -0.62         | -0.54   |
| 4,5-Dichloro- <i>m</i> -xylene              | 76.0°  | 29.9° | 0.305  | -0.52         | -0.46   |
| Ethylpentachlorobenzene                     | 56.0°  | 32.4° | 0.645  | -0.19         | -0.24   |

species, the solute and the solvent (in this case, water), whereas the latter quantity is dependent only on the nature of the solute. Most theoretical treatments of activity coefficients apply to nonpolar solutes in nonpolar solvents [*cf.*, the Scatchard-Hildebrand approach (2)] or to electrolytes in water (*cf.*, Ref. 17).

This report will attempt to develop a practical and easily used semi-empirical approach. This approach relates the aqueous activity coefficient to the octanol-water partition coefficient,  $PC$ , which can in turn be estimated from the chemical structure by established techniques. Some of the more useful schemes used to estimate  $\log PC$  were summarized previously (4).

The aqueous activity coefficient of a drug and its octanol-water partition coefficient are related by:

$$PC_x = \frac{\gamma_w}{\gamma_0} \quad (\text{Eq. 19})$$

where  $\gamma_0$  is the activity coefficient of the drug in octanol. All three terms are expressed in mole fractions. (In its strictest sense, the partition coefficient is the ratio of the activity coefficients of the solute in water-saturated octanol to octanol-saturated water. Since it was shown that the effects of mutual saturation usually are quite small<sup>3</sup>, they will be ignored in this report.)

By analogy to the aqueous activity coefficient, the activity coefficient of the drug in octanol can be described by:

$$2.303RT \log \gamma_0 = DD + OO - 2DO \quad (\text{Eq. 20})$$

where  $OO$  represents the octanol cohesive interactions and  $DO$  is the drug-octanol adhesive interaction term. By combining Eqs. 19 and 20, the following relationship is obtained:

$$2.303RT \log \gamma_w = \log PC_x + DD + OO - 2DO \quad (\text{Eq. 21})$$

If the drug has a molar cohesive energy that is similar to that of octanol, the adhesive interactions can be assumed to be equal to the average of the drug and octanol adhesive interactions, so that:

$$DD + OO \cong 2DO \quad (\text{Eq. 22})$$

and thus:

$$\log \gamma_w \cong \log PC_x \quad (\text{Eq. 23})$$

This treatment is somewhat similar in concept to the Hildebrand and Scott (2) treatment of regular solution theory, with an arithmetic mean being used instead of a geometric mean.

The fact that most available partition coefficient data are for the octanol-water system is fortuitous. Octanol is a solvent of moderate polarity and is not very different in polarity from most drugs. Octanol has a solubility parameter ( $\delta$ ) of 10.3; for most drugs, this value is  $8 \leq \delta \leq 12$ . Extremely nonpolar compounds such as hexane have a  $\delta$  value of  $>7$ , and very polar compounds such as ethanol have a  $\delta$  value of  $<13$ . This similarity of polarities is responsible for the near equivalence of  $DD$  and  $OO$  and thus for the success of Eqs. 22 and 23. Additional support for the applicability of Eq. 22 is provided by the fact that most organic liquids are miscible in all proportions with octanol<sup>3</sup>, indicating that  $\gamma_0$  is near unity and thus that  $\log \gamma_0$  in Eq. 20 is near zero.

The requirement described by Eq. 22 is important in that it restricts this treatment to nonelectrolytes. If ionized, weak electrolytes can self-interact much more strongly than octanol, the sum of the cohesive forces will be greater than the adhesive forces and the calculated solubility will be erroneous.

**Estimation of Aqueous Solubility of Liquids**—Equation 23 can be tested on organic liquids that do not self-associate. For these liquids, the activity coefficient can be approximated by the reciprocal of the mole fraction solubility in water,  $X_w^l$ :

$$\log \gamma_w \approx -\log X_w^l \quad (\text{Eq. 24})$$

By merging the aqueous solubility file of Yalkowsky and Valvani<sup>2</sup> with the octanol-water partition coefficient data of Hansch and Leo (18), over 100 liquids have been found<sup>2</sup> for which apparently reliable solubility and partition coefficient data have been published. The result of regression analysis on these data (which include multiple values for most of the liquids) is:

$$-\log \gamma_w = \log X_w^l = -1.08 \log PC - 1.04 \quad (\text{Eq. 25})$$

$$n = 417 \quad r = 0.946 \quad s = 0.356$$

which is in good agreement with Eq. 24.

The slight deviation of the slope from unity is believed to be due to a systematic decrease in  $DD$  with increasing values of  $\log PC$ , *i.e.*, with decreasing polarity. The intercept of 1.04 is due to the fact that Eq. 23 refers to the mole fractional partition coefficient, which is equal to the conventionally defined partition coefficient minus 0.94 (the logarithm of the ratio of the molarity of pure octanol to that of pure water). This distinction has been discussed more fully (19).

Although verified in this case for liquids, Eq. 25 is not restricted to liquid solutes. It can be expected to hold equally well for crystalline compounds. Therefore, a method has been obtained for estimating  $\log \gamma_w$  for all organic nonelectrolytes that do not self-associate.

The reason for the exercise that equated  $\log \gamma$  with  $\log PC$  is that the

<sup>3</sup> T. J. Roseman and S. H. Yalkowsky, unpublished data.

Table V—Solubility Estimates for Some Polycyclic Hydrocarbons

| Name                             | MP   | log PC<br>Estim. | log S |        | Residual |
|----------------------------------|------|------------------|-------|--------|----------|
|                                  |      |                  | Obs.  | Estim. |          |
| Indan                            | 25°  | 3.57             | -3.03 | -3.40  | 0.369    |
| Naphthalene                      | 80°  | 3.35             | -3.61 | -3.71  | 0.108    |
| 1-Methylnaphthalene              | 25°  | 3.86             | -3.70 | -3.67  | -0.030   |
| 2-Methylnaphthalene              | 35°  | 3.86             | -3.75 | -3.77  | 0.017    |
| 1,3-Dimethylnaphthalene          | 25°  | 4.38             | -4.29 | -4.16  | -0.129   |
| 1,4-Dimethylnaphthalene          | 25°  | 4.38             | -4.14 | -4.16  | 0.024    |
| 1,5-Dimethylnaphthalene          | 81°  | 4.38             | -4.68 | -4.69  | 0.010    |
| 2,3-Dimethylnaphthalene          | 102° | 4.38             | -4.72 | -4.89  | 0.171    |
| 2,6-Dimethylnaphthalene          | 108° | 4.38             | -4.89 | -4.94  | 0.055    |
| 1-Ethylnaphthalene               | 25°  | 4.39             | -4.16 | -4.17  | 0.011    |
| 1,4,5-Trimethylnaphthalene       | 25°  | 4.90             | -4.92 | -4.65  | -0.271   |
| Diphenyl                         | 71°  | 4.03             | -4.34 | -4.27  | -0.078   |
| Acenaphthene                     | 96°  | 4.03             | -4.59 | -4.50  | -0.091   |
| Fluorene                         | 116° | 4.47             | -4.92 | -5.10  | 0.178    |
| Phenanthrene                     | 101° | 4.63             | -5.15 | -5.11  | -0.038   |
| Anthracene                       | 216° | 4.63             | -6.38 | -6.19  | -0.183   |
| 2-Methylantracene                | 209° | 5.15             | -6.69 | -6.62  | -0.076   |
| 9-Methylantracene                | 82°  | 5.15             | -5.87 | -5.42  | -0.450   |
| 9,10-Dimethylantracene           | 182° | 5.67             | -6.57 | -6.85  | 0.284    |
| Pyrene                           | 156° | 5.22             | -6.18 | -6.18  | 0.007    |
| Fluoranthene                     | 111° | 5.22             | -5.90 | -5.76  | -0.138   |
| 1,2-Benzofluorene                | 187° | 5.75             | -6.68 | -6.97  | 0.290    |
| 2,3-Benzofluorene                | 209° | 5.75             | -7.27 | -7.18  | -0.096   |
| Chrysene                         | 255° | 5.01             | -8.06 | -7.76  | -0.296   |
| Triphenylene                     | 199° | 5.45             | -6.73 | -6.80  | 0.077    |
| Naphthacene                      | 357° | 5.91             | -8.69 | -8.72  | 0.032    |
| 1,2-Benzanthracene               | 160° | 5.91             | -7.21 | -6.87  | -0.345   |
| 9,10-Dimethyl-1,2-benzanthracene | 122° | 6.95             | -6.63 | -7.49  | 0.863    |
| Perylene                         | 277° | 6.50             | -8.80 | -8.52  | -0.282   |
| 3,4-Benzopyrene                  | 175° | 6.50             | -7.82 | -7.56  | -0.256   |
| 3-Methylcholanthrene             | 178° | 7.11             | -7.97 | -8.17  | 0.192    |
| Benzo[ghi]perylene               | 277° | 7.10             | -9.02 | -9.09  | 0.068    |

Table VI—Solubility Estimates for Halobenzenes

| Name                       | MP   | log PC<br>Estim. | log S |        | Residual |
|----------------------------|------|------------------|-------|--------|----------|
|                            |      |                  | Obs.  | Estim. |          |
| Hexachlorobenzene          | 230° | 6.53             | -7.76 | -7.92  | 0.165    |
| Pentachlorobenzene         | 86°  | 5.79             | -5.65 | -5.82  | 0.170    |
| 1,2,3,4-Tetrachlorobenzene | 47°  | 5.05             | -4.70 | -4.72  | 0.017    |
| 1,2,3,5-Tetrachlorobenzene | 54°  | 5.05             | -4.79 | -4.78  | -0.006   |
| 1,2,4,5-Tetrachlorobenzene | 140° | 5.05             | -5.56 | -5.60  | 0.045    |
| 1,2,4,5-Tetrabromobenzene  | 182° | 6.01             | -6.98 | -6.95  | -0.027   |
| 1,2,3-Tribromobenzene      | 87°  | 4.98             | —     | -5.03  | —        |
| 1,2,4-Tribromobenzene      | 44°  | 4.98             | -4.50 | -4.62  | 0.119    |
| 1,3,5-Tribromobenzene      | 122° | 4.98             | -5.60 | -5.36  | -0.236   |
| 1,2,3-Trichlorobenzene     | 53°  | 4.27             | -3.76 | -4.00  | 0.244    |
| 1,2,4-Trichlorobenzene     | 25°  | 4.27             | -3.72 | -3.74  | 0.017    |
| 1,3,5-Trichlorobenzene     | 63°  | 4.27             | -4.44 | -4.10  | -0.340   |
| 1,2,3-Triiodobenzene       | 116° | 5.86             | —     | -6.18  | —        |
| 1,2,4-Triiodobenzene       | 91°  | 5.85             | —     | -5.93  | —        |
| 1,3,5-Triiodobenzene       | 184° | 5.85             | —     | -6.81  | —        |
| 1,2-Dibromobenzene         | 25°  | 4.07             | -3.50 | -3.54  | 0.039    |
| 1,3-Dibromobenzene         | 25°  | 4.07             | -3.38 | -3.54  | 0.159    |
| 1,4-Dibromobenzene         | 87°  | 4.07             | -4.07 | -4.13  | 0.061    |
| 1,2-Dichlorobenzene        | 25°  | 3.59             | -3.20 | -3.07  | -0.135   |
| 1,3-Dichlorobenzene        | 25°  | 3.59             | -3.09 | -3.07  | -0.025   |
| 1,4-Dichlorobenzene        | 53°  | 3.59             | -3.21 | -3.33  | 0.123    |
| 1,2-Difluorobenzene        | 25°  | 2.59             | -2.00 | -2.08  | 0.078    |
| 1,3-Difluorobenzene        | 25°  | 2.58             | -2.00 | -2.07  | 0.068    |
| 1,4-Difluorobenzene        | 25°  | 2.58             | -1.97 | -2.07  | 0.098    |
| 1,2-Diiodobenzene          | 27°  | 4.65             | -4.24 | -4.13  | -0.109   |
| 1,3-Diiodobenzene          | 40°  | 4.64             | -4.57 | -4.25  | -0.325   |
| 1,4-Diiodobenzene          | 132° | 4.64             | -5.25 | -5.12  | -0.127   |
| Bromobenzene               | 25°  | 3.07             | -2.64 | -2.55  | -0.088   |
| Chlorobenzene              | 25°  | 2.83             | -2.35 | -2.32  | -0.035   |
| Fluorobenzene              | 25°  | 2.33             | -1.79 | -1.82  | 0.031    |
| Iodobenzene                | 25°  | 3.36             | -2.95 | -2.84  | -0.112   |
| Benzene                    | 25°  | 2.13             | -1.64 | -1.62  | -0.016   |
| 2-Bromochlorobenzene       | 25°  | 3.83             | -3.19 | -3.30  | 0.112    |
| 3-Bromochlorobenzene       | 25°  | 3.83             | -3.21 | -3.30  | 0.092    |
| 4-Bromochlorobenzene       | 68°  | 3.83             | -3.63 | -3.71  | 0.083    |
| 2-Bromoiodobenzene         | 25°  | 4.36             | —     | -3.83  | —        |
| 3-Bromoiodobenzene         | 25°  | 4.36             | —     | -3.83  | —        |
| 4-Bromoiodobenzene         | 92°  | 4.36             | -4.56 | -4.47  | -0.095   |
| 2-Chloroiodobenzene        | 25°  | 4.12             | -3.54 | -3.59  | 0.049    |
| 3-Chloroiodobenzene        | 25°  | 4.12             | -3.55 | -3.59  | 0.039    |
| 4-Chloroiodobenzene        | 57°  | 4.12             | -4.03 | -3.89  | -0.136   |



Table VII—Solubility Estimates of Alkyl *p*-Substituted Benzoates

| Name                             | MP   | log PC<br>Estim. | log S |        | Residual |
|----------------------------------|------|------------------|-------|--------|----------|
|                                  |      |                  | Obs.  | Estim. |          |
| Methyl <i>p</i> -aminobenzoate   | 112° | 1.12             | -1.60 | -1.49  | -0.112   |
| Ethyl <i>p</i> -aminobenzoate    | 89°  | 1.65             | -1.99 | -1.78  | -0.213   |
| Propyl <i>p</i> -aminobenzoate   | 74°  | 2.18             | -2.33 | -2.14  | -0.189   |
| Butyl <i>p</i> -aminobenzoate    | 56°  | 2.70             | -2.76 | -2.57  | -0.194   |
| Pentyl <i>p</i> -aminobenzoate   | 52°  | 3.23             | -3.35 | -3.12  | -0.231   |
| Hexyl <i>p</i> -aminobenzoate    | 61°  | 3.76             | -3.95 | -3.85  | -0.100   |
| Heptyl <i>p</i> -aminobenzoate   | 75°  | 4.29             | -4.60 | -4.70  | 0.095    |
| Octyl <i>p</i> -aminobenzoate    | 71°  | 4.81             | -5.40 | -5.25  | -0.148   |
| Nonyl <i>p</i> -aminobenzoate    | 69°  | 5.34             | -6.00 | -5.84  | -0.157   |
| Dodecyl <i>p</i> -aminobenzoate  | 82°  | 6.92             | -7.80 | -7.90  | 0.102    |
| Methyl <i>p</i> -hydroxybenzoate | 131° | 1.66             | -1.84 | -2.18  | 0.344    |
| Ethyl <i>p</i> -hydroxybenzoate  | 116° | 2.19             | -2.22 | -2.55  | 0.329    |
| Propyl <i>p</i> -hydroxybenzoate | 96°  | 2.71             | -2.59 | -2.86  | 0.266    |
| Butyl <i>p</i> -hydroxybenzoate  | 68°  | 3.24             | -2.89 | -3.10  | 0.207    |

latter value can be estimated by linear free energy (*i.e.*, group contribution) approaches. Due to the efforts of Hansch and coworkers (20, 21) and Nys and Rekker (5), it is possible to estimate, with reasonable accuracy, the value of log PC for most organic compounds. The fragment contributions to log PC (*f* values) developed by Nys and Rekker for the most common functional groups are summarized in Ref. 5. These *f* values can be used to obtain an approximate log PC value for most compounds.

**Estimation of Aqueous Solubility of Organic Nonelectrolytes**—If the estimations of  $\Delta S_f$  and  $\gamma_w$  are valid for drugs, they can be inserted into Eq. 8 to give:

$$\log X_w^c \approx -\log PC - \left( \frac{\Delta S_f}{1364} \right) (MP - 25) - 0.94 \quad (\text{Eq. 26})$$

which simplifies to:

$$\log X_w \approx -\log PC - 0.01MP - 0.69 \quad (\text{Eq. 27})$$

for rigid molecules.

Equations 26 and 27 can be made applicable to liquids simply by replacing the melting point by 25° for compounds that melt below this

temperature. This process effectively eliminates the crystal interaction term and causes the equations to revert back to Eq. 25.

The aqueous solubility of drugs by convention is reported on a molar rather than a mole fraction scale. For poorly soluble compounds, the molar solubility is simply the mole fraction solubility multiplied by 55.5 (the molarity of water) so that:

$$\log S_m = \log X + 1.74 \quad (\text{Eq. 28})$$

where  $S_m$  is the solubility in moles per liter. Thus, on a molar scale, Eqs. 26 and 27 become:

$$\log S_m^c \approx -\log PC - \frac{\Delta S_f(MP - 25)}{1364} + 0.80 \quad (\text{Eq. 29})$$

in general for nonelectrolytes and:

$$\log S_m^c \approx -\log PC - 0.01MP + 1.05 \quad (\text{Eq. 30})$$

for rigid and short chain molecules.

For the more soluble solutes, it is necessary to account for the volume of water displaced by the dissolved solute. The more precise relationship between molar and mole fraction solubilities is:

$$S_w = \frac{1000\rho X_w}{18 + (MW - 18)X_w} \quad (\text{Eq. 31})$$

where  $\rho$  is the density of the saturated solution and  $MW$  is the molecular weight of the solute. Note that as  $X_w$  approaches zero and as  $\rho$  approaches unity, Eq. 31 approaches Eq. 28. Since  $S_w$  is not a truly linear function of  $X_w$ , it is not a strictly linear function of  $MP$  and  $\log PC$ , especially at high values of  $S_w$ . However, it can be approximated by a linear function with slightly altered coefficients. As long as very soluble solutes are avoided, no serious errors will be encountered as a result of this approximation.

**Applications**—To test the ability of Eqs. 29 and 30 to estimate the aqueous solubilities of organic nonelectrolytes, several series of compounds will be considered: polycyclic aromatic hydrocarbons; mono- and multihalobenzenes; steroid hormones; normal, branched, and cyclic alcohols; and alkyl *p*-hydroxybenzoates and alkyl *p*-aminobenzoates. These series enable coverage of a wide variety of melting points, partition coefficients, and solubilities. The regression equations of the estimated and observed solubilities for each series and for the combination of all compounds will be given.

Tables V and VI contain the aqueous solubility data for two classes of compounds containing only rigid molecules (the polycyclic aromatic compounds and the halobenzenes). Tables V and VI also contain the estimated partition coefficients and the melting points. In the case of liquids, 25° is used in place of the melting point. For the polycyclic aromatic compounds, the results of regression analysis between the observed and estimated solubilities are:

$$\log S_{\text{obs}} = 0.944 \log S_{\text{estim}} - 0.785 \quad (\text{Eq. 32})$$

$$n = 32 \quad r = 0.989 \quad s = 0.252$$

and for the halobenzenes:

$$\log S_{\text{obs}} = 0.980 \log S_{\text{estim}} - 0.32 \quad (\text{Eq. 33})$$

$$n = 35 \quad r = 0.995 \quad s = 0.136$$

Table VII contains the same type of data for the alkyl *p*-substituted benzoates, a series of both rigid and flexible molecules, all of which are

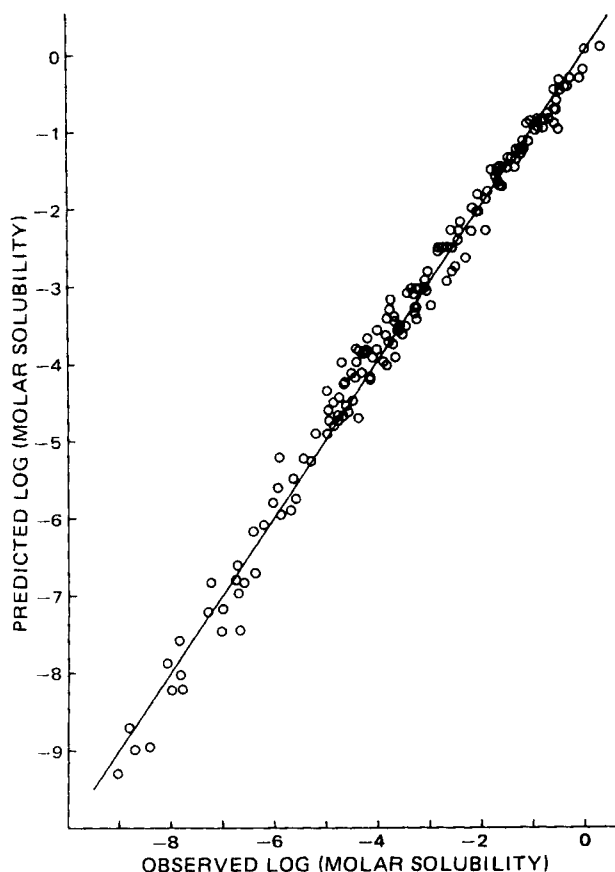


Figure 2.—Predicted (Eq. 38) versus observed aqueous solubility of 167 organic nonelectrolytes.

Table VIII—Solubility Estimates for Aliphatic Alcohols

| Name                       | MP  | $\Delta S_f$<br>Estim. | log PC<br>Estim. | log S |        | Residual |
|----------------------------|-----|------------------------|------------------|-------|--------|----------|
|                            |     |                        |                  | Obs.  | Estim. |          |
| 1-Butanol                  | 25° | 13.5                   | 0.84             | -0.01 | 0.05   | -0.064   |
| 2-Methyl-1-propanol        | 25° | 13.5                   | 0.73             | 0.06  | 0.16   | -0.101   |
| 2-Butanol                  | 25° | 13.5                   | 0.73             | 0.39  | 0.16   | 0.232    |
| 1-Pentanol                 | 25° | 13.5                   | 1.37             | -0.61 | -0.46  | -0.152   |
| 2-Methyl-1-butanol         | 25° | 13.5                   | 1.25             | -0.48 | -0.34  | -0.143   |
| 3-Methyl-1-butanol         | 25° | 13.5                   | 1.25             | -0.51 | -0.34  | -0.174   |
| 2,2-Dimethyl-1-propanol    | 54° | 13.5                   | 1.33             | -0.42 | -0.69  | 0.277    |
| 2-Pentanol                 | 25° | 13.5                   | 1.25             | -0.31 | -0.31  | 0.031    |
| 3-Pentanol                 | 25° | 13.5                   | 1.25             | -0.24 | -0.34  | 0.097    |
| 3-Methyl-2-butanol         | 25° | 13.5                   | 1.14             | -0.21 | -0.24  | 0.022    |
| 2-Methyl-2-butanol         | 25° | 13.5                   | 1.33             | 0.09  | -0.42  | 0.503    |
| 1-Hexanol                  | 25° | 13.5                   | 1.90             | -1.24 | -0.96  | -0.278   |
| 2-Methyl-1-pentanol        | 25° | 13.5                   | 1.78             | -1.11 | -0.85  | -0.267   |
| 4-Methyl-1-pentanol        | 25° | 13.5                   | 1.78             | -1.14 | -0.85  | -0.294   |
| 2,2-Dimethyl-1-butanol     | 25° | 13.5                   | 1.57             | -1.04 | -0.65  | -0.390   |
| 3,3-Dimethyl-1-butanol     | 25° | 13.5                   | 1.57             | -0.50 | -0.65  | 0.146    |
| 2-Ethyl-1-butanol          | 25° | 13.5                   | 1.78             | -1.17 | -0.85  | -0.325   |
| 2-Hexanol                  | 25° | 13.5                   | 1.78             | -0.88 | -0.85  | -0.036   |
| 3-Hexanol                  | 25° | 13.5                   | 1.78             | -0.82 | -0.85  | 0.029    |
| 3-Methyl-2-pentanol        | 25° | 13.5                   | 1.67             | -0.74 | -0.74  | 0.004    |
| 4-Methyl-2-pentanol        | 25° | 13.5                   | 1.67             | -0.81 | -0.74  | -0.065   |
| 2-Methyl-3-pentanol        | 25° | 13.5                   | 1.67             | -0.71 | -0.74  | 0.029    |
| 3,3-Dimethyl-2-butanol     | 25° | 13.5                   | 1.74             | -0.64 | -0.81  | 0.165    |
| Cyclohexanol               | 25° | 13.5                   | 1.43             | -0.45 | -0.51  | 0.058    |
| 2-Methyl-2-pentanol        | 25° | 13.5                   | 1.86             | -0.51 | -0.92  | 0.414    |
| 3-Methyl-3-pentanol        | 25° | 13.5                   | 1.86             | -0.39 | -0.92  | 0.529    |
| 2,3-Dimethyl-2-butanol     | 25° | 13.5                   | 1.74             | -0.41 | -0.81  | 0.403    |
| 2,4-Dimethyl-2-pentanol    | 25° | 13.5                   | 2.27             | -0.96 | -1.32  | 0.351    |
| 1-Heptanol                 | 25° | 13.5                   | 2.42             | -1.83 | -1.46  | -0.373   |
| 2,2-Dimethyl-1-pentanol    | 25° | 13.5                   | 2.39             | -1.52 | -1.43  | -0.091   |
| 2,4-Dimethyl-1-pentanol    | 25° | 13.5                   | 2.19             | -1.60 | -1.24  | -0.360   |
| 4,4-Dimethyl-1-pentanol    | 25° | 13.5                   | 2.39             | -1.55 | -1.43  | -0.116   |
| 2-Heptanol                 | 25° | 13.5                   | 2.31             | -1.55 | -1.35  | -0.193   |
| 3-Heptanol                 | 25° | 13.5                   | 2.31             | -1.44 | -1.35  | -0.088   |
| 4-Heptanol                 | 25° | 13.5                   | 2.31             | -1.40 | -1.35  | -0.048   |
| 5-Methyl-2-hexanol         | 25° | 13.5                   | 2.19             | -1.38 | -1.24  | -0.145   |
| 2-Methyl-3-hexanol         | 25° | 13.5                   | 2.19             | -1.32 | -1.24  | -0.076   |
| 2,2-Dimethyl-3-pentanol    | 25° | 13.5                   | 2.27             | -1.16 | -1.32  | 0.155    |
| 2,4-Dimethyl-3-pentanol    | 25° | 13.5                   | 2.08             | -1.23 | -1.13  | -0.092   |
| 2-Methyl-2-hexanol         | 25° | 13.5                   | 2.39             | -1.09 | -1.43  | 0.336    |
| 3-Methyl-3-hexanol         | 25° | 13.5                   | 2.39             | -1.00 | -1.43  | 0.432    |
| 2,3-Dimethyl-2-pentanol    | 25° | 13.5                   | 2.27             | -0.91 | -1.32  | 0.410    |
| 2,3-Dimethyl-3-pentanol    | 25° | 13.5                   | 2.27             | -0.86 | -1.32  | 0.451    |
| 3-Ethyl-3-pentanol         | 25° | 13.5                   | 2.39             | -0.87 | -1.43  | 0.558    |
| 2,3,3-Trimethyl-2-butanol  | 25° | 13.5                   | 2.35             | -0.72 | -1.39  | 0.670    |
| 1-Octanol                  | 25° | 13.5                   | 2.95             | -2.37 | -1.97  | -0.404   |
| 2-Ethyl-1-hexanol          | 25° | 13.5                   | 2.84             | -2.11 | -1.86  | -0.254   |
| 2-Octanol                  | 25° | 13.5                   | 2.84             | -2.09 | -1.86  | -0.228   |
| 2-Methyl-2-heptanol        | 25° | 13.5                   | 2.91             | -1.72 | -1.93  | 0.211    |
| 3-Methyl-3-heptanol        | 25° | 13.5                   | 2.91             | -1.60 | -1.93  | 0.325    |
| 2,2,3-Trimethyl-3-pentanol | 25° | 13.5                   | 2.88             | -1.27 | -1.90  | 0.625    |
| 1-Nonanol                  | 25° | 13.5                   | 3.48             | -3.01 | -2.47  | -0.533   |
| 7-Methyl-1-octanol         | 25° | 13.5                   | 3.36             | -2.49 | -2.36  | -0.137   |
| 2,2-Diethyl-1-pentanol     | 25° | 13.5                   | 3.44             | -2.42 | -2.43  | 0.015    |
| 2-Nonanol                  | 25° | 13.5                   | 3.36             | -2.74 | -2.36  | -0.386   |
| 3-Nonanol                  | 25° | 13.5                   | 3.36             | -2.66 | -2.36  | -0.299   |
| 4-Nonanol                  | 25° | 13.5                   | 3.36             | -2.59 | -2.36  | -0.227   |
| 5-Nonanol                  | 25° | 13.5                   | 3.36             | -2.49 | -2.36  | -0.137   |
| 2,6-Dimethyl-4-heptanol    | 25° | 13.5                   | 3.13             | -2.51 | -2.14  | -0.370   |
| 3,5-Dimethyl-4-heptanol    | 25° | 13.5                   | 3.13             | -2.51 | -2.14  | -0.370   |
| 1-Decanol                  | 25° | 13.5                   | 4.01             | -3.60 | -2.98  | -0.622   |
| 2-Undecanol                | 25° | 13.5                   | 4.42             | -2.94 | -3.37  | 0.437    |
| 1-Dodecanol                | 25° | 13.5                   | 5.06             | -4.80 | -3.98  | -0.814   |
| 1-Tetradecanol             | 38° | 38.5                   | 6.11             | -5.84 | -5.78  | -0.056   |
| 1-Pentadecanol             | 44° | 41.0                   | 6.64             | -6.35 | -6.53  | 0.180    |
| 1-Hexadecanol              | 49° | 43.5                   | 7.17             | -7.00 | -7.26  | 0.264    |
| 1-Octadecanol              | 58° | 48.5                   | 8.22             | -8.40 | -8.75  | 0.350    |

crystalline. The statistics for this series are:

$$\log S_{\text{obs}} = 1.008 \log S_{\text{estim}} - 0.270 \quad (\text{Eq. 34})$$

$$n = 14 \quad r = 0.990 \quad s = 0.264$$

Table VIII concerns the aliphatic alcohols. The series contains rigid and flexible molecules, most of which are liquids at room temperature. For this series, the observed and estimated solubilities are related by:

$$\log S_{\text{obs}} = 0.989 \log S_{\text{estim}} - 0.203 \quad (\text{Eq. 35})$$

$$n = 67 \quad r = 0.994 \quad s = 0.178$$

Table IX lists the data for some steroid hormones. The data for this group of rigid solids were taken from a study by Tomida *et al.* (6) in which both aqueous solubilities and octanol-water partition coefficients were determined. The experimental data for these cases were used because the group contribution approaches (20, 21) worked poorly for steroids (1). The regression equation for this series is:

$$\log S_{\text{obs}} = 0.879 \log S_{\text{estim}} - 0.863 \quad (\text{Eq. 36})$$

$$n = 19 \quad r = 0.847 \quad s = 0.309$$

In each of the five classes of compounds, there is a definite relationship

Table IX—Solubility Estimates for Some Steroids

| Name                             | MP   | log PC<br>Obs. | log S |        | Residual |
|----------------------------------|------|----------------|-------|--------|----------|
|                                  |      |                | Obs.  | Estim. |          |
| Hydrocortisone                   | 213° | 1.55           | -2.97 | -3.26  | 0.292    |
| Corticosterone                   | 181° | 1.94           | -3.24 | -3.32  | 0.084    |
| Deoxycorticosterone              | 141° | 2.90           | -3.45 | -3.82  | 0.366    |
| Cortisone                        | 222° | 1.42           | -3.27 | -3.23  | -0.043   |
| Hydrocortisone acetate           | 223° | 2.19           | -4.34 | -3.91  | -0.427   |
| Cortisone acetate                | 236° | 2.10           | -4.21 | -3.95  | -0.262   |
| Deoxycorticosterone acetate      | 157° | 3.08           | -4.63 | -4.11  | -0.515   |
| 11 $\alpha$ -Hydroxyprogesterone | 222° | 2.36           | -3.82 | -4.05  | 0.233    |
| Progesterone                     | 131° | 3.87           | -4.42 | -4.58  | 0.161    |
| Testosterone                     | 155° | 3.29           | -4.08 | -4.28  | 0.202    |
| Prednisolone                     | 240° | 1.62           | -3.18 | -3.56  | 0.381    |
| Prednisolone acetate             | 238° | 2.40           | -4.37 | -4.23  | -0.141   |
| Triamcinolone                    | 270° | 1.03           | -3.68 | -3.31  | -0.374   |
| Triamcinolone acetonide          | 293° | 2.31           | -4.31 | -4.63  | 0.323    |
| Triamcinolone diacetate          | 235° | 1.92           | -4.13 | -3.78  | -0.349   |
| Dexamethasone                    | 266° | 1.83           | -3.59 | -3.97  | 0.384    |
| Betamethasone                    | 230° | 1.94           | -3.77 | -3.75  | -0.016   |
| Dexamethasone acetate            | 230° | 2.91           | -4.90 | -4.61  | -0.293   |
| Betamethasone-17-valerate        | 183° | 3.49           | -4.71 | -4.70  | -0.006   |

between the observed and estimated values of log S. In four of the five groups, the coefficient of log  $S_{\text{estim}}$  is close to 0.96. For the steroids, a lower value is observed. The major variation is observed in the value of the intercept, which varies from -0.863 to -0.203. The reason for the variation (which would be equal to zero if Eqs. 29 and 30 were absolutely correct) is not clear. However, it is clear that the average of Eqs. 32-36:

$$\log S_{\text{obs}} \approx \log S_{\text{estim}} - 0.5 \quad (\text{Eq. 37})$$

can be used as a means of estimating the solubility of nearly any rigid nonelectrolyte regardless of whether it is liquid or solid.

In each of the five classes of compounds, there is a similar relationship between the observed and predicted solubilities. Whether the differences observed are real or are due to systematic errors in calculating log PC is not clear.

The complete data set was fitted by multiple linear regression to a function of log PC and  $\Delta S_f(MP - 25)$ . This analysis yielded the following semiempirical equation:

$$\log S_w \sim -1.00 \log PC - 1.11 \frac{\Delta S_f(MP - 25)}{1364} + 0.54 \quad (\text{Eq. 38})$$

$$n = 167 \quad r = 0.994 \quad r^2 = 0.988 \quad s = 0.242$$

Equation 38 estimates the solubilities of all but eight of the solutes listed in Tables V-IX to within 0.5 log unit. The agreement between the observed solubilities and the solubilities estimated by Eq. 38 is illustrated in Fig. 2. Although the solubility values span nine orders of magnitude, the error in no case reached a factor of 10.

The pooled data for the rigid molecules gave:

$$\log S_w = -1.05 \log PC - 0.012MP + 0.87 \quad (\text{Eq. 39})$$

$$n = 155 \quad r = 0.989 \quad r^2 = 0.979 \quad s = 0.308$$

These equations are believed to be useful because they enable the estimation of aqueous solubility on the basis of a single physical measurement, the melting point. They also enable the chemist to appreciate the likely effect of a structural modification on aqueous solubility.

Although this study was restricted to nonelectrolytes, it appears that Eqs. 38 and 39 can be extended to cover weak electrolytes with only slight modification (22).

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## ACKNOWLEDGMENTS

The authors thank Dr. Gary L. Bertrand for many helpful comments and criticisms.