Solubility and Partitioning VI: Octanol Solubility and Octanol–Water Partition Coefficients

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Abstract □ A simple equation for the estimation of the aqueous solubility of crystalline solutes was previously derived based on the assumption that the presence of water does not significantly alter the crystal properties of the solute. The data presented verify the solubility equation for a set of 36 nonelectrolytes and weak electrolytes. Using the same set of solutes, the two major assumptions used to derive the equation were also verified: that the octanol solubility of nonelectrolytes is exponentially proportional to the melting point of the solute and that the octanol–water solubility ratio is a good approximation of the octanol–water partition coefficient.

Keyphrases □ Solubility—of nonelectrolytes and weak electrolytes in octanol, determination using melting points and partition coefficients □ Partition coefficient—of nonelectrolytes and weak electrolytes in octanol–water, use with melting point to determine solubility □ Octanol—determination of the solubility of nonelectrolytes and weak electrolytes, partition coefficients with water

In previous publications (1–6) a simple equation for the estimation of the aqueous solubility of crystalline solutes was derived on the basis of the following rationale:

1. The solubility of nonpolar and semipolar solutes in octanol is approximately equal to the ideal solubility.
2. The ideal solubility can be estimated from the melting point and entropy of fusion of the solute.
3. The entropy of fusion of the solute is constant for rigid molecules.
4. The octanol–water solubility ratio of a solute is equivalent to the octanol–water partition coefficient.
5. The aqueous solubility is equal to the octanol solubility divided by the octanol–water partition coefficient.

The above strategy is based on the assumption that the presence of water does not significantly alter the crystal properties of the solute. This assumption is usually valid; however, its failure can occasionally be the source of an incorrect estimate of the aqueous solubility of a semipolar substance.

THEORETICAL

An equation enables the estimation of the aqueous solubility (S_w in moles/liter) of rigid organic compounds from melting point (mp) and octanol–water partition coefficient (PC) data. This equation has the simple form:

$$\log S_w(\text{calc}) = -0.01\ \text{mp} - \log \text{PC} + 1.05 \qquad \text{(Eq. 1)}$$

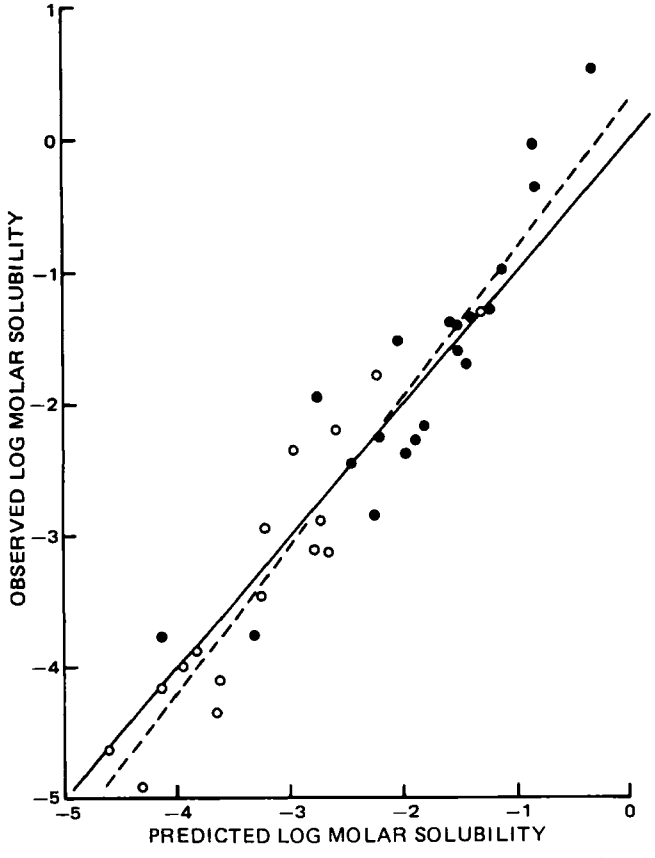

Figure 1—*Observed and predicted aqueous solubilities of nonelectrolytes (○) and weak electrolytes (●). Key: (—) theoretical line described by Eq. 1; (- - - -) regression line described by Eq. 6.*

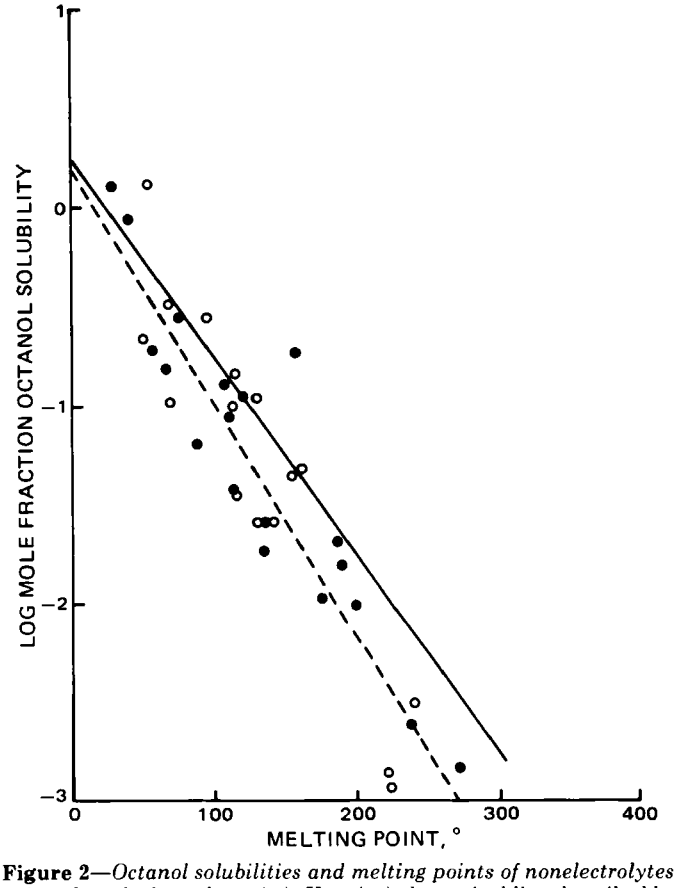

Figure 2—*Octanol solubilities and melting points of nonelectrolytes (○) and weak electrolytes (●). Key: (—) theoretical line described by Eq. 2; (- - - -) regression line described by Eq. 11.*

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Table I—Estimation of Aqueous Solubility [a]

Solute	log PC (obs)	mp°, [b]	log S_w (obs)	log S_w (calc)	Difference
Acetylsalicylic acid	(1.21)	135	(−1.60)[c]	−1.51	0.094
p-Aminobenzoic acid	(0.58)	187	−1.35	−1.40	−0.048
Aminopyrine	(0.80)	108	(−0.36)[d]	−0.83	−0.470
Antipyrine	(0.26)	112	0.53	−0.33	−0.865
Barbital	(0.67)	190	(−1.41)[e]	−1.52	−0.106
Benzoic acid	(1.87)	122	−1.53	−2.04	−0.507
Butyl-*p*-aminobenzoate	2.72	58	−2.84	−2.25	0.593
Caffeine	−0.20	238	−0.98	−1.13	−0.154
Flurbiprofen	3.26	111	−3.74	−3.32	0.424
Ethyl-*p*-aminobenzoate	1.96	89	−2.17	−1.80	0.368
Fumaric acid	0.28	200	−1.29	−1.23	0.062
Ibuprofen	4.43	76	−3.76	−4.14	−0.382
Methyl-*p*-aminobenzoate	1.35	114	−1.70	−1.44	0.259
Phenobarbital	(1.48)	176	−2.26	−2.19	0.072
Phenacetin	(1.58)	135	−2.28	−1.88	0.399
Phenol	(1.48)	41	(−0.04)[f]	−0.84	−0.796
Prostaglandin E_2	2.82	67	−2.47	−2.44	0.017
Prostaglandin $F_{2\alpha}$	2.72	30	−2.38	−1.97	0.409
Salicylic acid	(2.23)	158	−1.95	−2.76	−0.813
Theophylline	−0.09	272	−1.38	−1.58	−0.200
Acetanilide	(1.21)	114	−1.31	−1.30	0.007
Biphenyl	(3.98)	70	−4.34	−3.63	0.710
Butyl-*p*-hydroxybenzoate	3.57	69	−2.93	−3.21	−0.283
Cortisone	1.47	222	−3.12	−2.64	0.479
Desoxycorticosterone	2.88	142	(−3.45)[g]	−3.25	0.201
Ethyl-*p*-hydroxybenzoate	2.47	116	−2.20	−2.58	−0.380
Fluorene	4.18	117	−4.91	−4.30	0.607
Methyl-*p*-hydroxybenzoate	1.96	131	−1.78	−2.22	−0.438
15-*s*-15-Methyl prostaglandin $F_{2\alpha}$ methyl ester	3.21	55	−2.88	−2.71	0.173
Methyltestosterone	3.36	163	−3.99	−3.94	0.046
Prednisolone	(1.42)	240	−3.10	−2.77	0.335
Propyl-*p*-hydroxybenzoate	(3.04)	96	−2.35	−2.95	−0.600
Progesterone	3.87	131	(−4.15)[h]	−4.13	0.023
Testosterone	3.32	155	(−3.87)[h]	−3.82	0.048
Triazolam	2.42	224	−4.09	−3.61	0.485

[a] *Values in parentheses were obtained from the literature.* [b] Melting point data taken from Ref. 8 or the manufacturers' specifications. [c] L. J. Edwards, *Trans. Faraday Soc.*, **57**, 1191 (1951). [d] R. Charonnat, *Compt. Rend.*, **185**, 284 (1927). [e] F. A. Long and W. F. McDevitt, *Chem. Rev.*, **51**, 119 (1952). [f] L. Erichsen and E. Dobbert, *Brennstoff Chem.*, **36**, 338 (1955). [g] H. Tomida, T. Yotsuyanagi, and K. Ikeda, *Chem. Pharm. Bull. Tokyo*, **26**, 2832 (1978). [h] K. Uekema, T. Fujinaga, F. Hirayama, M. Otagiri, and M. Tamasaki, *Int. J. Pharm.*, **10**, 1 (1982).

In the derivation of this equation, several important assumptions were made:

1. Octanol is a nearly ideal solvent for the solutes of interest, so that the octanol solubility (X_o in moles fraction) is given by:

$$\log X_o(\text{calc}) = -0.01\ \text{mp} + 0.25 \qquad \text{(Eq. 2)}$$

2. The octanol–water partition coefficient is equal to the octanol–water solubility ratio (SR), which is defined as the octanol solubility (S_o in moles/liter) divided by the aqueous solubility (S_w in moles/liter):

$$\text{PC} = \text{SR} = S_o/S_w \qquad \text{(Eq. 3)}$$

or

$$\log (S_w/S_o) = -\log \text{PC} = -\log \text{SR} \qquad \text{(Eq. 4)}$$

3. The melting point of the drug in equilibrium with octanol is the same as the melting point of the drug in equilibrium with water. The overall strategy of this approach can be expressed as:

$$S_w = S_o\,(S_w/S_o) \qquad \text{(Eq. 5)}$$

with S_o and the solubility ratio being determined by Eqs. 2 and 4, respectively.

In this report, an attempt was made to extend Eq. 1 to include some pharmaceutically important solutes and to verify the assumptions that were used in its derivation. A single set of solutes was chosen for these purposes, including both nonelectrolytes and weak electrolytes of widely varying chemical structure.

EXPERIMENTAL

Materials—The octanol was reagent grade[1]. All other compounds were of the purest grade available from commercial sources[2] and were used as received.

[1] Aldrich.
[2] Aldrich, Eastman, Fluka.

Solubilities—The aqueous solubilities of some of the solutes were taken from the literature or previous work in this laboratory[3]. Only values in the 20–30° range were used. Solubilities for those compounds for which literature data were not available were determined experimentally in the following manner. An excess amount of solute was allowed to equilibrate with water in a sealed vial for 24 hr at 30°. After equilibration the samples were filtered through either a 0.22-μm porous filter[4] or a 1.2-μm silver membrane filter[5] which was preequilibrated at 30°. Analysis of the filtrate was performed using UV spectrophotometry[6]. Octanol solubilities were determined in the same manner as the aqueous solubilities, except that dilutions were made with 2-propanol.

Partition Coefficients—For many of the solutes the partition coefficients were taken from the literature (7). For selected solutes, the partition coefficients were determined in the following manner. A known amount of solute was dissolved in water-saturated octanol or octanol-saturated water. The two phases were shaken for 3 hr and then allowed to equilibrate at 30° for 3–6 days. The phases were separated by centrifugation at 1500 rpm for 15 min, and the concentration in each phase was determined spectrophotometrically.

Solubility Ratio in Mutually Saturated Solvents—Water-saturated octanol and octanol-saturated water were prepared by shaking an excess of water or octanol with the pure solvent for 8 hr. After equilibration, the two layers in each of the solvent mixtures were separated to yield the mutually saturated octanol and water. These solvents were used to determine the aforementioned saturation solubilities for antipyrine, ethyl-*p*-aminobenzoate, caffeine, and theophylline. All determinations were run in duplicate.

RESULTS AND DISCUSSION

Water Solubility—The logarithms of the aqueous solubilities calculated by Eq. 1 for the solutes studied are listed in Table I, along with

[3] S. H. Yalkowsky and S. C. Valvani, unpublished compilation.
[4] Millipore.
[5] Selas.
[6] Zeiss DMR 21.

Table II—Estimation of Octanol Solubility

Solute	mp°, [a]	log X_o (obs)	log X_o (calc)	Difference
Acetylsalicylic acid	135	−1.58	−0.30	0.395
p-Aminobenzoic acid	187	−1.68	−0.82	−0.023
Aminopyrine	108	−0.89	−0.03	−0.029
Antipyrine	112	−1.06	−0.07	0.122
Barbital	190	−1.80	−0.85	0.071
Benzoic acid	122	−0.95	−0.17	−0.109
Butyl-*p*-aminobenzoate	58	−0.72	0.47	0.340
Caffeine	238	−2.61	−1.33	0.395
Flurbiprofen	111	−1.05	−0.06	0.140
Ethyl-*p*-aminobenzoate	89	−1.19	0.16	0.469
Fumaric acid	200	−2.00	−0.95	0.169
Ibuprofen	76	−0.55	0.29	0.017
Methyl-*p*-aminobenzoate	114	−1.42	−0.09	0.444
Phenobarbital	176	−1.97	−0.71	0.382
Phenacetin	135	−1.73	−0.30	0.543
Phenol	41	−0.06	0.64	−0.300
Prostaglandin E_2	67	−0.81	).38	0.406
Prostaglandin $F_{2\alpha}$	30	0.11	0.75	0.263
Salicylic acid	158	−0.73	−0.53	−0.679
Theophylline	272	−2.83	−1.67	0.276
Acetanilide	114	−1.00	−0.09	0.027
Biphentl	70	−0.98	0.35	0.448
Butyl-*p*-hydroxybenzoate	69	−0.48	0.36	0.021
Cortisone	222	−2.85	−1.17	0.797
Desoxycorticosterone	142	−1.58	−0.37	0.340
Diphenylethane	52	−0.66	0.53	0.337
Ethyl-*p*-hydroxybenzoate	116	−0.83	−0.11	−0.150
Fluorene	117	−1.45	−0.12	0.445
Methyl-*p*-hydroxybenzoate	131	−0.96	−0.26	−0.182
15-*s*-15-Methyl prostaglandin $F_{2\alpha}$, methyl ester	55	0.12	0.50	0.046
Methyltestosterone	163	−1.31	−0.58	−0.130
Prednisolone	240	−2.50	−1.35	0.270
Propyl-*p*-hydroxybenzoate	96	−0.55	0.09	−0.267
Progesterone	131	−1.58	−0.26	0.447
Testosterone	155	−1.35	−0.50	−0.013
Triazolam	224	−2.93	−1.19	0.856

[a] Melting point data taken from Ref. 8 or the manufacturers' specifications.

the experimentally determined values (log S_w and log PC) and the melting point data; the last column lists the difference between the observed and calculated solubilities. In no case is the error in the estimate greater than an order of magnitude, and in over three-quarters of the examples it is less than a factor of 3.

The relationship between the observed and predicted values is shown in Fig. 1. The regression line is described by:

$$\log S_w = 1.129 \log S_w(\text{calc}) + 0.32$$
$$r = 0.954 \quad s = 0.400 \quad n = 36 \qquad \text{(Eq. 6)}$$

It is clear that there is no systematic deviation from the regression line for the nonelectrolytes or the weak electrolytes. The regression lines for the weak electrolytes [log S_w = 1.124 log S_w(calc) + 0.308] and for the nonelectrolytes [log S_w = 1.143 log S_w(calc) + 0.371] are both in good agreement with the line described by Eq. 6.

The multiple-regression equation for the aqueous solubility in terms of the melting point and the octanol–water partition coefficient is:

$$\log S_w = -0.012\ \text{mp} - 1.13 \log \text{PC} + 1.62$$
$$r = 0.955 \quad s = 0.402 \quad n = 36 \qquad \text{(Eq. 7)}$$

This compares favorably with the theoretical line from Eq. 1. In spite of an added parameter, Eq. 7 is virtually equivalent to Eq. 6 in estimating the aqueous solubilities of the compounds studied.

Octanol Solubility—If octanol is an ideal solvent for a drug, then the mole fractional solubility of that drug in octanol (X_o) should be equal to the ideal mole fractional solubility (X_i) as given by the van't Hoff equation:

$$\log X_o = \log X_i = [\Delta S_f/(2.303\,RT)]\,(T_m - T) \qquad \text{(Eq. 8)}$$

where ΔS_f is the entropy of fusion of the solute, T_m is the solute melting point in °K, R is the gas constant, and T is the temperature of interest in °K. It has been shown that, for rigid molecules (molecules with little or no conformational flexibility), the entropy of fusion can be approximated by 13.5 eu (9). Thus, for rigid molecules at room temperature (298 °K), Eq. 8 becomes:

$$\log X_o = -0.01\,(T_m - 298) \qquad \text{(Eq. 9)}$$

If the melting point and temperature in Eq. 9 are converted to the centigrade scale (by subtracting 273 from T_m and from 298°), Eq 9 becomes identical to Eq. 2.

If the intercept is expressed in moles per liter rather than in mole fraction, then 0.80 (the logarithm of the molarity of pure octanol) must be added to the left hand side of Eq. 9, so that it becomes:

$$\log S_o = -0.01\,(T_m - 298) + 0.8 = -0.01\,(T_m - 378) \qquad \text{(Eq. 10)}$$

The use of 0.80 is only an approximation of log $\{[(1000\rho - M{\cdot}W)/130.22] + M\}$, where ρ is the density of solution, M is the molarity of the solute, W is the molecular weight of the solute, and 130.22 is the molecular weight of octanol. When the solute molarity (M) is low or when the molecular weight of the solute (W) is close to that of octanol, the exact expression reduces to 0.80. The mole fractional solubilities in octanol (X_o) can be estimated by assuming that the density of the solution (ρ) is equal to the density of octanol (ρ_o) by:

$$X_o = \frac{M}{\left(\frac{1000\,\rho_o - M{\cdot}W}{130.22}\right)+M}$$

Regression analysis of the octanol solubility data (Table II) against melting point for the 36 solutes gives:

$$\log X_o = -0.012\ \text{mp} + 0.26$$
$$r = 0.92 \quad s = 0.32 \quad n = 36 \qquad \text{(Eq. 11)}$$

which is in good agreement with Eq. 2. The relationship between the octanol solubilities and the predicted values is illustrated in Fig. 2. No adjustable parameters were used in the analyses. The data cover three orders of magnitude, and there is no systematic difference in the data for nonelectrolytes and weak electrolytes.

The regression equations for the 21 weak electrolytes (log X_o = −0.011 mp + 0.15) and for the 15 nonelectrolytes (log X_o = −0.013 mp + 0.44) are both consistent with Eq. 11. This confirms the applicability of the first assumption to the solutes selected for this study. The reason for the near ideal solubility of this wide range of solutes in octanol has been explained on the basis of regular solution theory and the fact that the sol-

Table III—Estimation of Partition Coefficient [a]

Solute	log S_o (obs)	log S_w (obs)	log PC (obs)	log SR (calc)	Difference
Acetylsalicylic acid	−0.69	(−1.60)[b]	1.21	0.91	0.301
p-Aminobenzoic acid	−0.80	−1.35	(0.58)	0.56	0.024
Aminopyrine	−0.00	(−0.36)[c]	(0.80)	0.36	0.441
Antipyrine	−0.19	0.53	(0.26)	−0.73	0.987
Barbital	−0.92	(−1.41)[d]	(0.67)	0.49	0.177
Benzoic acid	−0.06	−1.53	(1.87)	1.47	0.399
Butyl-*p*-aminobenzoate	0.13	−2.84	2.72	2.97	−0.253
Caffeine	−1.72	−0.98	−0.20	−0.75	0.548
Flurbiprofen	−0.20	−3.74	3.26	3.54	−0.284
Ethyl-*p*-aminobenzoate	−0.31	−2.17	1.96	1.86	0.101
Fumaric acid	−1.12	−1.29	0.28	0.17	0.107
Ibuprofen	0.27	−3.76	4.43	4.03	0.399
Methyl-*p*-aminobenzoate	−0.53	−1.70	1.35	1.17	0.185
Phenobarbital	−1.09	−2.26	(1.48)	1.17	0.310
Phenacetin	−0.84	−2.28	(1.58)	1.44	0.145
Phenol	0.94	(−0.04)[e]	(1.48)	0.98	0.496
Prostaglandin E_2	−0.03	−2.46	2.82	2.43	0.389
Prostaglandin $F_{2\alpha}$	0.49	−2.38	2.72	2.87	−0.146
Salicylic acid	0.15	−1.95	2.23	2.10	0.134
Theophylline	−1.95	−1.38	−0.09	−0.57	0.476
Acetanilide	−0.12	−1.31	(1.21)	1.19	0.021
Biphenyl	−0.10	−4.34	(3.98)	4.24	−0.262
Butyl-*p*-hydroxybenzoate	0.34	−2.93	3.57	3.27	0.304
Cortisone	−1.97	−3.12	1.47	1.15	0.318
Desoxycorticosterone	−0.71	(−3.45)[f]	2.88	2.74	0.139
Diphenylethane	0.19	−4.63	5.12	4.82	0.299
Ethyl-*p*-hydroxybenzoate	0.04	−2.20	2.47	2.24	0.229
Fluorene	−0.56	−4.91	4.18	4.34	−0.162
Methyl-*p*-hydroxybenzoate	−0.08	−1.78	1.96	1.70	0.256
15-*s*-15-Methyl prostaglandin $F_{2\alpha}$ methyl ester	0.45	−2.88	3.21	3.34	−0.127
Methyltestosterone	−0.45	−3.99	3.36	3.54	−0.176
Prednisolone	−1.62	−3.10	1.42	1.49	−0.065
Propyl-*p*-hydroxybenzoate	0.36	−2.35	(3.04)	2.71	0.333
Progesterone	−0.71	(−4.15)[g]	3.87	3.45	0.424
Testosterone	−0.49	(−3.87)[g]	3.32	3.38	−0.061
Triazolam	−2.05	−4.09	2.42	2.05	0.371

[a] Values in parentheses taken from the literature. [b] L. J. Edwards, *Trans. Faraday Soc.*, **57**, 1191 (1951). [c] R Charonnat, *Compt. Rend.*, **185**, 284 (1927). [d] F. A. Long and W. F. McDevitt, *Chem. Rev.*, **51**, 119 (1952). [e] L. Erichsen and E. Dobbert, *Brennstoff Chem.*, **36**, 338 (1955). [f] H. Tomida, T. Yotsuyanagi, and K. Ikeda, *Chem. Pharm. Bull., Tokyo*, **26**, 2832 (1978). [g] K. Uekema, T. Fujinaga, F. Hirayama, M. Otagiri, and M. Yamasaki, *Int. J. Pharm.*, **10**, 1 (1982).

ubility parameter of octanol (10.3) is within 3.3 units of the solubility parameter of each compound.

Solubility Ratio and Partition Coefficient—The second major assumption that is used to obtain Eq. 1 is that the octanol–water partition coefficient is equivalent to the octanol–water solubility ratio. Regression analysis clearly indicates a linear relationship between the logarithms of the two parameters:

$$\log PC = 0.900 \log SR + 0.390 \qquad \text{(Eq. 12)}$$
$$r = 0.985 \quad s = 0.233 \quad n = 36$$

For most of the compounds studied, the solubility ratio does not differ greatly from the partition coefficient (Table III). Antipyrine is a notable and inexplainable exception; this difference is concentration dependent.

Figure 3 shows the observed partition coefficients and solubility ratios for the solutes studied. If the regression line is forced through the origin, it becomes:

$$\log PC = 1.027 \log SR \qquad \text{(Eq. 13)}$$
$$r = 0.992 \quad s = 0.326 \quad n = 36$$

which is in agreement with the theoretical expectation. Again the weak electrolytes and the nonelectrolytes conform to regression equations similar to the equation for the entire data set. For weak electrolytes the equation is log PC = 0.868 log SR + 0.421; for nonelectrolytes it is log PC = 0.942 log SR + 0.281.

Experimentally the octanol–water partition coefficient is the ratio of the concentrations of the solute in each of the two phases determined in dilute solution, *i.e.*, PC = C_o/C_w. This differs from the solubility ratio in two respects. The solubility ratio (SR) is the ratio of the solubilities determined in pure octanol and pure water (or buffer), whereas the partition coefficient is based on the concentration ratio determined in water-saturated octanol and octanol-saturated water. The solute–solute interactions, which are concentration dependent, are more significant in the solute-saturated solutions used to determine the solubility ratio than in the dilute solutions used to determine the partition coefficient.

Fortunately these factors are not usually large, and for nonpolar and semipolar solutes (log PC > 0) they tend to negate each other. For polar solutes (log PC < 0), however, these effects amplify each other and increase the difference between the solubility ratio and the partition coefficient.

The effect of self-association of polar solutes at high concentration in octanol will generally increase the partition coefficient by increasing the ability of the octanol to accomodate the solute. This can be seen from a comparison of the partition coefficients determined in dilute solution and at saturation in Table IV. The effect of increasing the concentration of nonpolar solutes is to encourage their self-association in the aqueous phase. This, in turn, usually decreases the octanol–water partition coefficient by increasing the relative proportion of solute in the water. The effect of mutual saturation of the partitioning phases is to decrease the partition coefficient compared to the solubility ratio for nonpolar and semipolar solutes. Mutual saturation makes the octanol more water-like and the water more octanol-like. This tends to decrease the absolute value of log PC by bringing the partition coefficient closer to unity. For three of the four solutes in Table IV, the solubility ratio determined in mutually saturated solvents is closer to unity than the value determined in pure solvents. The mutual cancellation of the above effects can also be seen from the data in Table III, where the partition coefficients determined in dilute solution are quite close to the solubility ratio.

State of Undissolved Solute—The third assumption used for Eq. 1

Table IV—Effect of Mutual Saturation on Solubility Ratio

Solute	log (S_o/S_w) (pure phases)[a]	log (S_o/S_w) (mutually saturated)	log (C_o/C_w) (dilute)[b]
Antipyrine	−0.73	−0.50	0.26
Ethyl-*p*-aminobenzoate	1.86	2.21	1.96
Caffeine	−0.75	−0.42	−0.20
Theophylline	−0.57	−0.08	−0.09

[a] log SR. [b] log PC.

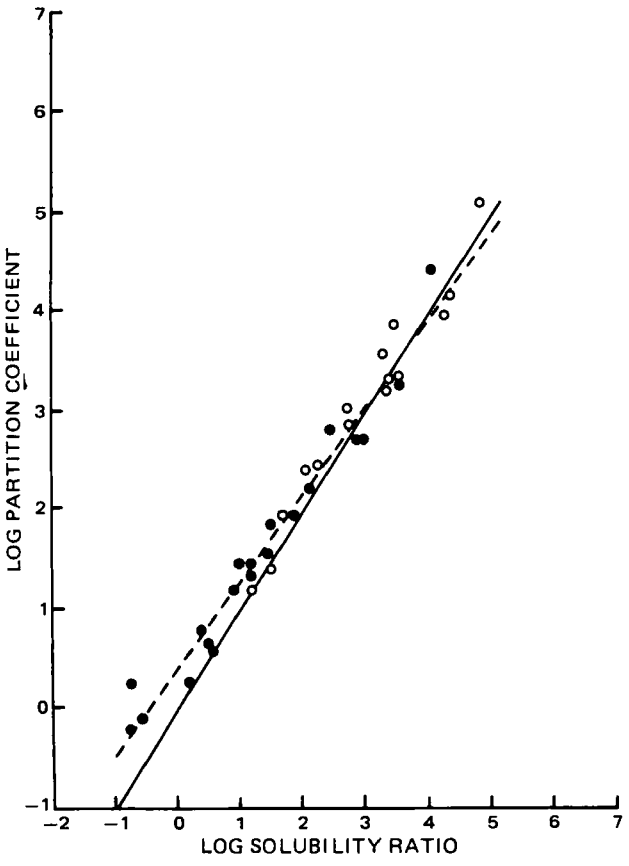

Figure 3—*Partition coefficients and solubility ratios of nonelectrolytes* (○) *and weak electrolytes* (●). *Key:* (—) *theoretical line described by Eq. 3;* (- - - -) *regression line described by Eq. 13.*

is that the melting point of the pure solute is the same as the melting point of the solute in equilibrium with its saturated solution in water. If this is not true, then the melting point used in Eq. 1 would be wrong. Fortunately, most organic compounds do not take up sufficient amounts of water to invalidate this assumption. Some compounds, however, can accomodate large enough amounts of water to significantly alter their physical properties. Phenol, for example, can take up enough water to cause liquification. The use of the normal melting point of phenol in Eq. 1 introduces a systematic error which results in an underestimation of the aqueous solubility of phenol. Still other organic compounds form crystalline hydrates which have melting points that are significantly different from the anhydrous parent compounds. If a substance is known to form a hydrate, the melting point of the hydrate should be used in Eq. 1. If a substance forms an undetected hydrate and if the melting point of this hydrate is different from the melting point of the unequilibrated material, then the use of the melting point of the latter would result in an erroneous estimation of the aqueous solubility.

It is not always feasible to isolate the exact species of a solute that is in equilibrium with its saturated solution. Recrystallization and drying can alter the water content and even the crystal form of the solute. Even the act of determining the melting point can alter the crystal in favor of a more anhydrous or a more stable form. For these reasons it appears likely that the use of an inappropriate melting point is the most likely source of error in the use of Eq. 1.

Fortunately, melting point alterations caused by water are rarely a problem with nonpolar solutes and are only infrequently significant for semipolar solutes. This is confirmed by the highly successful application of Eq. 1 to nonpolar solutes (1) and to a mixture of nonpolar and semipolar solutes (2), as well as to the compounds used herein.

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