

John T. Slattery

Department of Pharmaceutics  
University of Washington  
Seattle, WA 98105

Received February 18, 1981.

Accepted for publication June 10, 1981.

Discussions with Dr. René Levy and Dr. Milo Gibaldi are gratefully acknowledged.

## Correlation of Water Solubility with Octanol-Water Partition Coefficient

**Keyphrases** □ Solubility—water, correlation with octanol-water partition coefficient □ Partition coefficient—octanol-water, correlation with water solubility □ Melting-point effect—correlation between water solubility and octanol-water partition coefficient

### To the Editor:

Yalkowsky and Valvani (1) made a valuable analysis of the melting-point effect on the solubility of solid compounds and discussed the correlation between water solubility ( $S$ ) and the octanol-water partition coefficient ( $P$ ). Regression equations between  $\log S$  and  $\log P$  were constructed using  $\log P$  values calculated primarily from molecular fragment constants developed by Nys and Rekker (2).

We have found several points relevant to the Yalkowsky-Valvani analysis (1). First, part of their conclusions for a particular class of compounds was based on a linear regression between the values of  $\log S_{\text{obs}}$  and  $\log P_{\text{estim}}$  obtained from the correlation equation for that class of compounds. Regression of this kind must, in principle, yield  $\log S_{\text{obs}} = 1.0 \log S_{\text{estim}}$  with an intercept equal to 0.0. The correlation coefficient will then be a measure of how

for the compounds in Table VI, *i.e.*,  $\log S = -0.9874 \log P - 0.0095(MP) + 0.7178$ , the estimated  $S$  values then deviate appreciably from the experimental data.

It is understood that  $\log P$  values calculated by various fragment approaches are only as accurate as the values used to define each fragment. At this time, the rules to calculate  $\log P$  values are empirically derived. This approach has led to numerous correction factors for such things as branching, flexibility, chain length, bond unsaturation, and substituent polarity. In general, the fragment approach works reasonably well for simple low molecular weight molecules. It tends to be less accurate for more complex molecules.

Third, Yalkowsky and Valvani assumed that the effect of octanol-water mutual saturation on the partition coefficient was small and thus ignored it in their treatment. Banerjee *et al.* (3) also reported no observable effect of octanol-water mutual saturation. Although this effect is expected to be small for compounds with relatively high solubilities in both octanol and water, it becomes significant for solutes with limited solubilities. Consequently, it would be a factor in the correlation of  $\log S$  versus  $\log P$  at the low  $S$  (high  $P$ ) region.

The significance of octanol-water mutual saturation may be evaluated by comparing experimental  $P$  values with those calculated from solute solubilities in octanol and water for some high melting solid compounds. Because of the high melting-point effect, solids have limited solubilities in both solvents and their partition coefficients can be determined directly from the ratios of solute solubilities in the two solvents. Note that at low (mole fraction) concentrations, solute activity coefficients are essentially constant and the  $\log P$  of a solute would be practically constant at all concentrations.

We selected *p,p'*-dichlorodiphenyltrichloroethane (I)<sup>1</sup>, hexachlorobenzene (II)<sup>2</sup>, and anthracene (III) for illustration. The experimental and estimated octanol-water partition coefficients and the determined solubilities in water, octanol, and water-saturated octanol for these

Table I—Solubilities and Octanol-Water Partition Coefficients of I, II, and III

Compound	Melting Point	$S_w$ ( $\mu\text{g/liter}$ ) <sup>a</sup>	$S_o$ (g/liter)	$S_{o/w}$ (g/liter)	$\log S_o/S_w$	$\log P_{\text{exp}}$	$\log P_{\text{est}}$ <sup>b</sup>
I	108.5°	5.5 (25°) <sup>c</sup> 5.0 (20°)	41.5 (24°)	31.9 (24°)	6.88	6.36	—
II	230°	5.0 (25°) <sup>c</sup>	3.53 (23°)	2.65 (23°)	5.85	5.50	6.53
III	216°	45 (25°) <sup>d</sup>	2.44 (23°)	2.22 (23°)	4.73	4.45 <sup>e</sup>	4.63

<sup>a</sup> Key:  $S_w$ , solubility in water;  $S_o$ , solubility in octanol;  $S_{o/w}$ , solubility in water-saturated octanol; and  $P_{\text{exp}}$ , experimental octanol-water partition coefficient. <sup>b</sup> Estimated values from fragment constants given in Ref. 1. <sup>c</sup> Reference 7. <sup>d</sup> Reference 8. <sup>e</sup> Reference 6.

well  $\log S_{\text{obs}}$  fits  $\log S_{\text{estim}}$ . For reasons unspecified, this condition was not met in their Eqs. 32–36.

Second, the calculated values of  $\log P$  for some low solubility compounds are highly imprecise. For instance, the values of  $\log P$ , 5.05, 5.79, and 6.53, estimated for 1,2,3,5-tetra-, penta-, and hexachlorobenzene, respectively, in their Table VI, are considerably greater than the corresponding experimental values of 4.46 (3), 4.94 (3), and 5.50 (4). It is surprising that the molar solubilities ( $\log S$ ) predicted from these calculated  $\log P$  values and the solute melting points ( $MP$ ) fall into close agreement with the experimental  $\log S$ . If experimental  $\log P$  values are entered into the correlation derived by Yalkowsky *et al.* (5)

compounds are given in Table I. If it is assumed that mutual saturation has no effect on solute partitioning, the partition coefficients should be equal to the ratios of solute solubilities in pure octanol and water ( $S_o/S_w$ ); *i.e.*,  $\log P = 6.88$  for I, 5.85 for II, and 4.73 for III. These calculated  $P$  values are larger than the experimental values by factors of 3.3, 2.2, and 1.9 for I, II, and III, respectively. The difference between experimental and calculated  $P$  values results presumably from an alteration of the solute solubilities in the two solvents due to their mutual saturation.

<sup>1</sup> Commonly referred to as DDT.

<sup>2</sup> Commonly referred to as HCB.

Water (2.3 M) dissolved in octanol (6) reduces solute solubility in octanol, while octanol ( $4.5 \times 10^{-3}$  M) in water (9) enhances solute solubility in water. To support this point, the solubilities of these three compounds in water-saturated octanol are shown to be reduced by ~10–30% because of water saturation. These results suggest that octanol in water promotes water solubility by ~75% for III, 70% for II, and 150% for I.

Based on these findings, the use of experimental partition coefficients probably would improve the reliability of the log *S*–log *P* correlation at the high *P* region.

- (1) S. H. Yalkowsky and S. C. Valvani, *J. Pharm. Sci.*, **69**, 912 (1980).
- (2) G. G. Nys and R. F. Rekker, *Eur. J. Med. Chem.*, **9**, 361 (1974).
- (3) S. Banerjee, S. H. Yalkowsky, and S. C. Valvani, *Environ. Sci. Technol.*, **14**, 1227 (1980).
- (4) C. T. Chiou and D. W. Schmedding, in "Test Protocols for Environmental Fate and Movement of Toxicants," Association of Official Analytical Chemists, Arlington, Va., 1981, p. 28.
- (5) S. H. Yalkowsky, R. J. Orr, and S. C. Valvani, *Ind. Eng. Chem. Fundam.*, **18**, 351 (1979).
- (6) A. Leo, C. Hansch, and D. Elkins, *Chem. Rev.*, **71**, 525 (1971).
- (7) L. Weil, G. Duré, and K. Quentin, *Z. Wasser-Abwasser Forsch.*, **7**, 169 (1974).
- (8) W. E. May, in "Petroleum in the Marine Environment," L. Petrakis and F. T. Weiss, Eds., *Advances in Chemistry Series*, **185**, 143 (1980).
- (9) R. Collander, *Acta Chem. Scand.*, **5**, 774 (1951).

Cary T. Chiou<sup>x</sup>  
David W. Schmedding  
Environmental Health Sciences Center  
Oregon State University  
Corvallis, OR 97331  
John H. Block  
School of Pharmacy  
Oregon State University  
Corvallis, OR 97331

Received February 23, 1981.

Accepted for publication May 21, 1981.

Supported by U.S. Public Health Grants ES-00210 and ES-02400 and Environmental Protection Agency Grant CR-808046 from the EPA Environmental Research Laboratory, Corvallis, OR.

## Correlation of Water Solubility with Octanol–Water Partition Coefficient: A Response

**Keyphrases** □ Solubility—water, correlation with octanol–water partition coefficient, response □ Partition coefficient—octanol–water, correlation with water solubility, response □ Melting-point effect—correlation between water solubility and octanol–water partition coefficient, response

### To the Editor:

The preceding paper (1) raised three concerns about our recent paper (2) which we shall now attempt to alleviate.

The first concern of Chiou *et al.* (1) is that Eqs. 32–36 of Ref. 2 do not have slopes of unity and intercepts of zero. The reason for this apparent discrepancy was mentioned

**Table I—Aqueous Molar Solubility (*S<sub>w</sub>*) and Octanol–Water Partition Coefficients (*PC*) of Tetra-, Penta-, and Hexachlorobenzenes**

Compound	Melting point	Experimental log <i>PC</i>	log <i>S<sub>w</sub></i>	
			Observed <sup>a</sup>	Pre-dicted by Eq. 2
1,2,3,5-Tetrachlorobenzene	54°	4.46 <sup>b</sup>	–4.79	–4.46
Pentachlorobenzene	86°	4.94 <sup>b</sup>	–5.65	–5.35
Hexachlorobenzene	230°	5.50 <sup>c</sup>	–7.76	–7.67

<sup>a</sup> Reference 2. <sup>b</sup> Reference 3. <sup>c</sup> Reference 1.

briefly in the paragraph preceding Eq. 37 of Ref. 2 but will be discussed more completely here.

Equation 30 of Ref. 2 was developed on the basis of the theoretical relationships between solubility, partition coefficient, melting point, and entropy of fusion. Solubility data for five classes of compounds were compared to the predictions based on:

$$\log S_w \cong -\log PC - 0.01MP + 1.05 \quad (\text{Eq. 1})$$

Only if this theoretical equation perfectly predicted all of the solubilities would the slope be unity and the intercept zero.

In most cases, the slopes were not significantly different from unity; however, the intercepts tended to be slightly negative rather than zero. This trend shows a systematic overestimation of solubility by a factor of ~3. This finding indicated that while the theoretical equation was not perfect, it did provide a basis for assessing the role of the partition coefficient and the melting point in controlling aqueous solubility.

Each of the five classes of compounds represents a fairly small data set (in most cases covering only a few orders of magnitude in solubility). The slopes and intercepts are thus more subject to errors in the log *S<sub>w</sub>* measurements and/or the log *PC* estimation than is the whole data set, which covers almost nine orders of magnitude. The empirical equation for rigid molecules (Eq. 39 of Ref. 2) is:

$$\log S_w = -1.05 \log PC - 0.012MP + 0.87 \quad (\text{Eq. 2})$$

When Eq. 2 is used to estimate solubilities, it gives a slope and intercept of unity and zero, respectively. This final equation rather than the ones based on the smaller data sets should be used to estimate aqueous solubilities.

Second, Chiou *et al.* (1) point out that log *PC* calculations tend to be imprecise for low solubility compounds and seem surprised that the calculated values work better for estimating aqueous solubility than their own experimentally determined values. The reason for this situation is again statistical. For the reasons already described, it is best to use Eq. 2 to estimate solubility. When this is done, the experimental log *PC* values of Chiou *et al.* (1) will yield calculated solubilities that are in excellent agreement with the observed values as shown in Table I.

The regression equations were obtained by correlating aqueous solubility with melting points and calculated values of log *PC*. If experimental log *PC* values were available, the regression coefficient of log *PC* as well as the intercept probably would be somewhat altered. Thus, systematic errors in estimating log *PC* are compensated for by the choice of the coefficient of log *PC*.