

Water (2.3 M) dissolved in octanol (6) reduces solute solubility in octanol, while octanol (4.5×10^{-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^x
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_w*) and Octanol–Water Partition Coefficients (*PC*) of Tetra-, Penta-, and Hexachlorobenzenes

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

^a Reference 2. ^b Reference 3. ^c 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_w* 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*.

The third concern raised by Chiou *et al.* (1) is the lack of a correction for the mutual miscibility of water and octanol. They show three examples that indicate an error as high as 0.3–0.5 in $\log PC$ for very nonpolar solutes. This magnitude of error is not of particular concern. It is well within the error normally encountered in determining experimental values for both $\log S_w$ and $\log PC$ for hydrophobic compounds and certainly within the limitations of Eq. 2.

The conclusion of Chiou *et al.* (1) is that experimental values for $\log PC$ should be used to improve the reliability of the $\log S_w - \log PC$ correlation in the high $\log PC$ region. While this may be true, it is somewhat impractical. The value of Eq. 2 is that it provides a simple means of estimating $\log S_w$ from nothing more than a knowledge of the melting point of the solute and a group contribution

estimate of its partition coefficient. The measurement of accurate partition coefficients greater than 10,000 ($\log PC > 4$) is far more difficult and subject to error than the measurement of $\log S_w$.

(1) C. T. Chiou, D. W. Schmedding, and J. H. Block, *J. Pharm. Sci.*, **70**, 1176 (1981).

(2) S. H. Yalkowsky and S. C. Valvani, *ibid.*, **69**, 912 (1980).

(3) S. Banerjee, S. H. Yalkowsky, and S. C. Valvani, *Environ. Sci. Technol.*, **14**, 1227 (1980).

Samuel H. Yalkowsky^x

Shri C. Valvani

Pharmacy Research
The Upjohn Company
Kalamazoo, MI 49001

Received May 26, 1981.

Accepted for publication July 2, 1981.

BOOKS

REVIEWS

Controlled Release Technologies: Methods, Theory, and Applications. Edited by AGIS F. KYDONIEUS. CRC Press, 2000 N.W. 24th St., Boca Raton, FL 33431. 1980. Vol. I, 261 pp., and Vol. II, 273 pp. 17 × 26 cm. Price U.S. \$69.95 each (Foreign \$79.95).

Controlled Release Technologies is contained in two volumes, with a contributors list that reads like a “who’s who” in the field of controlled-release products. In the prefix, the editor indicates that “technologies described in these two volumes depend almost exclusively on the use of polymers and polymer technology” and that, although “applications, advantages and fundamental concepts of controlled release have been the subject of many symposia and several books dealing with formulations, all known delivery systems have not been assembled for consideration as they are in these volumes.” The editor is entirely correct on this point.

Volume I contains six chapters dealing with fundamental concepts of controlled release, monolithic polymer devices, monolithic elastomeric material, membrane systems, multilayered laminated structures, and controlled release from ultramicroporous triacetate. Volume II contains 13 chapters including topics on erodible matrixes and biodegradative controlled release of pesticides from polymeric substances, polymers containing pendent pesticide substituents, microencapsulation using coacervation phase separation techniques with pharmaceutical and agricultural applications, the Wurster process, microencapsulation using

physical methods, controlled-vapor release from hollow fibers, delivery of active agents by osmosis, starch and other polyols as encapsulating matrixes for pesticides, pine craft lignin as a pesticide delivery system, and other controlled-release technologies and applications.

Most chapters provide a brief description of the theory of preparing controlled-release devices but omit specific examples of formulations or preparation techniques which the “novice” could employ to make the products described. This may be because much of such information is proprietary, or it may be because the authors have assumed that the average reader will already have some knowledge in this area. Chapter 3 in Volume I is an exception in that many interesting product formulations have been presented. The volumes were published in 1980, and the editor’s introductory comments were signed and dated 1978. Thus, most chapters do not contain references more recent than 1976, but the literature prior to this time is well covered and a large number of excellent references are provided with each chapter.

In addition, Chapter 13 of Volume II, which deals with “other controlled release technologies and applications,” contains a series of tables listing U.S. patent numbers, companies holding the patents, titles of controlled-release systems, applications for the controlled-release systems, active agents involved, and the controlled-release method employed. These tables are quite informative.

The authors have done a good job of presenting polymeric controlled-release technology for drugs, insecticides, pesticides, herbicides, and antifouling formulations. Many chapters contain a brief mathematical description for active ingredient release theory followed by an