

Table IV—Day-To-Day Variability Data

Day	Concentration of Platinum, ng/ml	Average Absorbance	
		Serum	Ultrafiltrate
1	50	0.081	0.079
	100	0.160	0.160
	250	0.390	0.389
2	50	0.073	0.064
	100	0.151	0.140
	250	0.349	0.324
3	50	0.075	0.071
	100	0.148	0.140
	250	0.369	0.352

Table I contains the absorbance data obtained for a typical standard curve of platinum in serum and in ultrafiltrate; the relationship of platinum to absorbance was linear in the 0–250-ng/ml range. Table II contains the recovery data for serum and ultrafiltrate with known amounts of standard platinum as compared to similarly treated pure solutions of platinum in distilled, deionized water. The recoveries ranged from 79.4 to 92.2%. This result demonstrates that a standard curve of platinum cannot be prepared from distilled, deionized water. Recoveries of platinum from serum and ultrafiltrates using the respective matrix to prepare the standard curve are shown in Table III.

The day-to-day variability data in Table IV indicate that a standard working curve must be run each time for significant results. Placement of a standard at the end of each sample run is used to monitor the drift

in instrument conditions during the run. The sampler trays^a hold 30 polyethylene cups, giving a maximum run of four standards and 24 samples. The pyrolytic-coated graphite furnaces were replaced routinely at ~200 injections. Studies were not run to determine the maximum number of injections possible with these furnaces. It was necessary to optimize the optical alignment and the furnace alignment each day before beginning a run.

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Solubility and Partitioning IV: Aqueous Solubility and Octanol-Water Partition Coefficients of Liquid Nonelectrolytes

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Abstract □ The aqueous solubility and octanol-water partition coefficient of over 100 nonelectrolyte organic liquid solutes are related by the simple equation $\log S_w = -1.016 \log PC + 0.515$, where S_w is the molar solubility of liquid solutes in water and PC is the experimental partition coefficient of the solutes in the octanol-water system. The liquids studied represent a wide variety of organic compounds including aliphatic and aromatic hydrocarbons, alcohols, esters, ethers, aldehydes, and ketones. This finding is in agreement with that reported by Hansch and coworkers. However, these results are significant because only the experimental values for the aqueous solubilities and octanol-water partition coefficients are included, as opposed to the calculated partition coefficients used by Hansch. This relationship is extremely useful in understanding the overall solubility and partitioning phenomenon for organic liquids and provides a basis for studying crystalline solids and gases.

Keyphrases □ Aqueous solubility—aliphatic and aromatic hydrocarbons, liquid nonelectrolytes, experimental values compared with calculated values □ Partitioning—octanol-water partition coefficients, experimental values compared with calculated values, aliphatic and aromatic hydrocarbons, liquid nonelectrolytes □ Hydrocarbons, aliphatic and aromatic—aqueous solubility and partition coefficients obtained experimentally compared with calculated values □ Liquid nonelectrolytes—aliphatic and aromatic hydrocarbons, aqueous solubility and partition coefficients obtained experimentally compared with calculated values

The aqueous solubility and partition coefficient of a drug are key parameters in determining its biological activity. The partition coefficient frequently is used in quantitative structure-activity studies. Its usefulness in the assessment of transport properties of drugs through

biological membranes, extraction of solutes in aqueous-organic liquid systems, measurement of equilibria, and design of controlled-release drug delivery systems is well documented (1–4).

The aqueous solubility of a drug influences the dissolution rate and thus the rate and extent of absorption through biological membranes. The efficiency or biological performance of drugs from these formulations depends on the release and transfer of drug molecules to the systemic circulation. The release and transport of drugs are determined by solubility and the partition coefficient. The combined effects of aqueous solubility and the membrane-water partition coefficient on absorption were quantitatively described by Yalkowsky and coworkers (5–8).

This paper is part of a series dealing with the relationship between solubility and partitioning and deals exclusively with liquid nonelectrolyte solutes in water and octanol-water partitioning systems. In subsequent contributions, nonelectrolyte crystalline solids as well as weak acids and bases will be investigated.

There is a direct quantitative relationship between aqueous solubility and partitioning. However, due to a lack of reliable solubility and partitioning data, attempts to quantitate this relationship have met with only limited success (9).

This report demonstrates that there is a simple, nearly

quantitative relationship between aqueous solubility and the partition coefficient for nonionizable liquids and that significant deviation from this relationship is justifiable reason to question the accuracy of the data.

EXPERIMENTAL

Solutes—Several nonelectrolyte solutes, which are liquids at room temperature ($mp \leq 25^\circ$) and for which aqueous solubility data (between 20 and 40°) as well as experimental partition coefficient data in octa-

Table I—Observed Aqueous Solubility, Octanol-Water Partition Coefficient (PC), and Aqueous Solubility Predicted by Eq. 3 for Liquid Nonelectrolytes

Solute	Experimental Log PC	Observed Log Molar Solubility	Observed Log Solubility Average	Log Solubility Predicted by Eq. 3	Solute	Experimental Log PC	Observed Log Molar Solubility	Observed Log Solubility Average	Log Solubility Predicted by Eq. 3
Carbon tetra-chloride	2.83	-1.99	-2.22	-2.36	Methyl ethyl ketone	0.35	0.58	0.52	0.16
		-2.24					0.55		
		-2.28					0.52		
		-2.28					0.58		
Chloroform	1.96	-2.30	-1.12	-1.48			0.55		
		-0.95					0.52		
		-1.19					0.27		
		-1.16					0.57		
		-1.16					0.58		
Methylene chloride	1.25	-0.40	-0.65	-0.75	Propyl formate	0.83	-0.50	-0.52	-0.33
		-0.81					-0.51		
		-0.63					-0.54		
		-0.81					-0.90		
Methyl iodide	1.69	-1.01	-1.01	-1.20	Vinyl ethyl ether	1.04	-0.90	-0.90	-0.55
		-1.02					-0.02		
		0.22					-0.04		
		0.19					-0.06		
Nitromethane	-0.34	0.19	0.20	0.86	Ethyl acetate	0.70	-0.08	-0.06	-0.19
		0.19					-0.10		
Trichloroethylene	2.29	-2.12	-2.20	-1.82			-0.14		
Ethylidene chloride	1.79	-1.26	-1.27	-1.30			-0.05		
		-1.29					-0.05		
Ethylene dichloride	1.48	-1.04	-1.05	-0.99			-0.01		
		-1.06					-0.08		
		-1.06					-2.14		
		-1.04					-2.10		
Ethyl bromide	1.61	-1.06	-1.07	-1.12	<i>n</i> -Butyl chloride	2.64	-2.10	-2.12	-2.16
		-1.08					-1.46		
		-1.08					-1.46		
Ethyl chloride	1.43	-0.93	-1.02	-0.94	1-Nitrobutane	1.47	-1.46	-1.46	-0.98
		-1.05					-2.19		
		-1.03					-2.19		
		-1.05					-2.19		
Ethyl iodide	2.00	-1.59	-1.60	-1.52	<i>n</i> -Butyl nitrate	2.15	0.01	-2.19	-1.67
		-1.60					-0.03		
Nitroethane	0.18	-0.44	-0.29	0.33	<i>n</i> -Butyl alcohol	0.89	-0.05	-0.01	-0.38
		-0.22					0.00		
		-0.22					0.02		
		0.14					0.00		
Acrylonitrile	-0.92	0.17	0.15	1.45			0.02		
		0.14					-0.02		
Propionitrile	0.10	0.33	0.33	0.41			-0.04		
		0.32					-0.05		
Methyl acetate	0.18	0.52	0.45	0.33			0.03		
		-0.18					-0.02		
		0.63					-0.05		
		0.65					-0.03		
1,3-Dichloropropane	2.00	-1.60	-1.60	-1.52			0.00		
		-1.60					0.00		
		-1.62					0.03		
		-1.69					0.08		
Propyl bromide	2.10	-1.69	-1.71	-1.62			0.02		
		-1.73					-0.02		
1-Nitropropane	0.87	-0.80	-0.80	-0.37			-0.05		
		-0.80					-0.02		
Propyl chloride	2.04	-1.46	-1.46	-1.55	<i>sec</i> -Butyl alcohol	0.61	0.38	0.39	-0.10
		-1.46					0.35		
Isopropyl chloride	1.90	-1.40	-1.40	-1.41			0.40		
		-1.40					0.52		
Methylal	0.00	0.64	0.64	0.52			0.23		
Furan	1.34	-0.83	-0.83	-0.84			0.48		
Thiophene	1.81	-1.45	-1.45	-1.33	Isobutyl alcohol	0.75	0.07	0.06	-0.25
		-1.45					0.08		
1,3-Butadiene	1.99	-1.86	-1.86	-1.51			0.08		
		-1.86					0.13		
2-Bromobutyric acid	1.42	-0.40	-0.40	-0.92			0.04		
		-0.40					0.02		
		-0.40					0.01		

(continued)

Table I—Continued

Solute	Experimental Log PC	Observed Log Molar Solubility	Observed Log Solubility Average	Log Solubility Predicted by Eq. 3	Solute	Experimental Log PC	Observed Log Molar Solubility	Observed Log Solubility Average	Log Solubility Predicted by Eq. 3									
Diethyl ether	0.83	-0.09	-0.06	-0.32	Nitrobenzene	1.87	-2.19	-2.07	-1.38									
		-0.03																
		-0.09																
		-0.01																
		-0.03																
		-0.09																
		-0.14																
		-0.06																
		-0.14																
		-0.09																
		-0.03																
		-0.09																
		-0.01																
1-Butane-thiol	2.28	-2.08	-2.08	-1.80	Benzene	2.01	-1.66	-1.66	-1.53									
		-0.63																
		-0.77																
		-0.60																
		-0.62																
		-0.60																
		-0.57																
		-0.62																
		-0.67																
		-0.57																
		-0.60																
		-0.64																
		-0.64																
Ethyl sulfide	1.95	-1.47	-1.46	-1.46	Aniline	0.93	-0.39	-0.15	-0.43									
		-1.46																
		-2.09					1,4-Cyclohexadiene			2.30	0.10							
		-0.77									-2.06	-1.97	-1.82					
		-0.60									-1.93							
		-0.62									-1.92							
		-0.67									0.07			0.07	-0.75			
		-0.57									-2.59							
		-0.60									-2.44							
		-0.51									-2.43							
		-0.20									-2.80							
		-0.23									-2.80							
		-0.27									-2.69					-2.69	-1.97	
-0.28	-2.45																	
-0.22	-2.45																	
-0.21	-2.69																	
-0.16	-2.45																	
-0.20	-2.45																	
-0.24	-2.45																	
-0.26	-2.45																	
-0.37	-2.45																	
-0.40	-2.45																	
-0.43	-2.45																	
-0.44	-2.45																	
-0.44	-2.45																	
3-Pentanol	1.21	-0.20	-0.23	-0.71	1,5-Hexadiene	2.45	-2.69	-2.69	-1.97									
		-0.23																
		-0.27																
		-0.28																
		-0.22																
		-0.21																
		-0.16					Phenylhydrazine			1.25	0.07	0.07	-0.75					
		-0.20																
		-0.24																
		-0.26																
		-0.37												Cyclohexene	2.86	-2.59	-2.61	-2.39
		-0.40														-2.44		
		-0.43														-2.43		
-0.44	-2.80																	
-0.44	-2.80																	
-0.44	-2.69	-2.69	-1.97															
-0.44	-2.45																	
-0.44	-2.45																	
-0.44	-2.45																	
-0.44	-2.45																	
-0.44	-2.45																	
-0.44	-2.45																	
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-0.44	-2.45																	
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-0.44	-2.45																	
-0.44	-2.45																	
2,2-Dimethyl-1-propanol	1.34	-0.37	-0.42	-0.84	Cyclohexanone	0.81	-0.61	-0.33	-0.30									
		-0.40																
		-0.43																
		-0.44																
		-0.44																
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2-Methyl-1-butanol	1.29	-0.44	-0.48	-0.79	Cyclohexane	3.44	-3.18	-3.07	-2.98									
		-0.47																
		-0.49																
		-0.53																
		-0.52																
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Isopentyl alcohol	1.29	-0.52	-0.52	-0.79	Methyl butyl ketone	1.38	-0.76	-0.83	-0.89									
		-0.52																
		0.20					0.20			-0.39	-0.39	-0.85						
		-0.17											-0.78					
		-0.17											-0.78					
		-0.17											-0.78					
		-0.17											-0.78					
		-0.17											-0.78					
		-0.17											-0.78					
		-0.17											-0.78					
		-0.17											-0.78					
		-0.17											-0.78					
		-0.17											-0.78					
-0.17	-0.78																	
-0.17	-0.78																	
tert-Pentyl alcohol	0.89	0.20	0.20	-0.39	o-Dichlorobenzene	3.38	-3.01	-3.13	-2.92									
		-0.17																
		-0.17																
		-0.17																
		-0.17																
		-0.17																
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		-0.17																
Ethyl methylal	0.84	-0.17	-0.17	-0.34	m-Dichlorobenzene	3.38	-3.08	-3.08	-2.92									
		-0.17																
		-0.17																
		-0.17																
		-0.17																
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		-0.17																
		-0.17																
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		-0.17																
o-Dichlorobenzene	3.38	-3.01	-3.13	-2.92	Bromobenzene	2.99	-2.58	-2.39	-2.52									
		-3.26																
		-3.08																
		-2.58																
		-2.50																
		-2.10																
		-2.35					-2.26			-2.37	-2.37	Cyclohexanol	1.23	0.07	-0.30	-0.73		
		-2.36																
		-2.36																
		-2.36																
		-2.36																
		-1.80																
		-2.32																
-1.79	-1.79	-1.79	-1.79	n-Caproic acid	1.90	-1.08		-1.07	-1.41									
-1.80																		
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Fluorobenzene	2.27	-1.79	-1.79	-1.79	Iodobenzene	3.25	-3.05	-2.87	-2.79									
		-1.80																
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		-1.80																
Iodobenzene	3.25	-3.05	-2.87	-2.79			-2.78											
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Table I—Continued

Solute	Experimental Log PC	Observed Log Molar Solubility	Observed Log Solubility Average	Log Solubility Predicted by Eq. 3	Solute	Experimental Log PC	Observed Log Molar Solubility	Observed Log Solubility Average	Log Solubility Predicted by Eq. 3
2,2-Dimethylbutane	3.82	-3.67 -3.56 -3.61	-3.61	-3.37	<i>o</i> -Xylene	2.95	-2.72 -2.78 -2.79	-2.76	-2.48
2,3-Dimethylbutane	3.85	-3.58 -3.65	-3.62	-3.40			-2.70 -2.80		
1-Hexanol	2.03	-1.24 -1.27 -1.29 -1.21 -1.22 -1.22 -1.26 -1.26 -1.25 -1.16 -1.23 -1.23 -1.24 -1.25	-1.24	-1.55	<i>m</i> -Xylene	3.20	-2.79 -2.73 -2.86 -2.82 -2.90	-2.82	-2.74
					<i>p</i> -Xylene	3.15	-2.72 -2.73 -2.76 -2.83	-2.77	-2.69
					Ethylbenzene	3.15	-2.80 -2.71 -2.84 -2.82 -2.82 -2.78 -2.91 -2.79	-2.81	-2.69
3,3-Dimethyl-2-butanol	1.48	-0.59 -0.62 -0.66 -0.72	-0.65	-0.99			-2.85 -2.79 -0.70		
Propyl ether	2.03	-1.32 -1.28 -1.61 -1.53 -1.61 -1.61	-1.49	-1.55	2-Phenylethanol	1.36	-0.79	-0.74	-0.87
Acetal	0.84	-0.37	-0.37	-0.34	<i>o</i> -Methylbenzyl alcohol	1.59	-0.39	-0.39	-1.10
<i>n</i> -Dipropylamine	1.70	-0.54	-0.54	-1.21	<i>p</i> -Methylbenzyl alcohol	1.59	-1.20	-1.20	-1.10
Triethylamine	1.45	-0.83	-0.83	-0.96	2-Phenoxyethanol	1.16	-0.71 -0.71	-0.71	-0.67
Benzotri-fluoride	2.79	-2.51	-2.51	-2.32	Phenetole	2.51	-2.08	-2.08	-2.04
Benzaldehyde	1.48	-1.18 -1.21 -1.40 -1.21 -1.49 -1.48 -1.43 -1.21 -1.51 -1.51 -1.57	-1.37	-0.99	Octanol	3.15	-2.49 -2.42 -2.39 -2.35 -2.35 -2.34	-2.39	-2.68
<i>o</i> -Chlorotoluene	3.42	-2.53	-2.53	-2.96	2-Ethylhexylamine	2.82	-1.71	-1.71	-2.35
<i>p</i> -Chlorotoluene	3.33	-2.53	-2.53	-2.87	<i>n</i> -Dibutylamine	2.75	-1.44	-1.44	-2.28
<i>o</i> -Nitrotoluene	2.30	-2.32	-2.32	-1.82	Quinoline	2.03	-0.33	-0.33	-1.55
<i>m</i> -Nitrotoluene	2.43	-2.44	-2.44	-1.96	Cinnamaldehyde	1.90	-1.97	-1.97	-1.42
Toluene	2.58	-2.22 -2.27 -2.27 -2.28 -2.42 -2.24 -2.17 -2.24 -2.25 -2.17 -2.14 -2.21	-2.24	-2.11	Ethylbenzoate	2.64	-2.08 -2.32 -2.27	-2.22	-2.17
					<i>n</i> -Propylbenzene	3.63	-3.34 -3.30 -3.00 -3.00 -3.08	-3.14	-3.17
					Cumene	3.66	-3.22 -3.38 -3.36 -3.26 -3.39 -2.85 -3.17 -3.17 -3.14	-3.21	-3.20
					Mesitylene	3.42	-3.09 -3.40	-3.24	-2.96
Benzyl alcohol	1.02	-0.47 -0.43	-0.45	-0.52	3-Phenylpropanol	1.88	-1.38	-1.38	-1.39
Ethynylbenzene	2.53	-2.35	-2.35	-2.06	Ethyl cinnamate	2.99	-3.00	-3.00	-2.52
Styrene	2.95	-2.54	-2.54	-2.48	Phenyl ether	4.28	-2.60	-2.60	-3.83
Methyl benzoate	2.12	-1.95 -1.73 -1.75	-1.81	-1.64	1-Dodecanol	5.13	-5.04 -4.81 -4.71 -4.64	-4.80	-4.70
Acetophenone	1.66	-1.33 -1.28	-1.31	-1.17			-4.08 -4.06	-4.07	-3.70
Phenethyl alcohol	1.36	-0.88	-0.88	-0.87	Diphenylmethane	4.14	-4.08	-4.07	-3.70
					Tributylin	2.54	-3.48	-3.48	-2.06

nol-water partition systems are available, were included. A total of 111 compounds were studied.

Solubility—The aqueous solubility data in the desired temperature range were obtained from a compilation of data gathered from several literature sources. All available aqueous solubility values for each compound are listed in Table I. Also shown in Table I are the average of solubility values used for statistical analysis.

Partition Coefficients—Although partition coefficients are reported for nearly 100 oil-water partitioning systems, almost one-quarter of the compiled data refer to the octanol-water system (10). Therefore, the octanol-water partitioning system was chosen. The experimental partition coefficients for all the compounds were obtained from Ref. 10. In cases where multiple partition coefficients were reported for a compound, the values were averaged. Only a few obvious outliers were omitted in the averaging of partition coefficients.

Calculations and Treatment of Data—All reported aqueous solubilities were converted to gram (grams per liter) or molar (moles per liter) units with appropriate use of the solute molecular weight. Approximate mole fractional solubilities (X) were calculated from molar solubilities (S_w) by:

$$X = \frac{S_w}{S_w + \frac{1000 - (\text{mol. wt.}) S_w}{18}} \quad (\text{Eq. 1})$$

This approximation assumes a density of unity and equivalent molar and partial molal volumes for all compounds, an approximation that is not strictly valid but that introduces no systematic error in the calculations.

The mole fractional partition coefficients (PC_x) were calculated from the reported octanol-water partition coefficients (PC) by:

$$PC_x = PC \frac{M_w}{M_o} \quad (\text{Eq. 2})$$

where M_w and M_o are the molarities of pure water (55.5) and pure octanol (6.35), respectively.

Statistical Analysis—The statistical data analysis was performed using standard statistical analysis procedures.

RESULTS

The molar aqueous solubility (S_w) and the octanol-water partition coefficient (PC) are related by:

$$\log S_w = -1.016 \log PC + 0.515 \quad (\text{Eq. 3})$$

$n = 111 \quad r = 0.931 \quad s = 0.421$

where n is the number of observations, r is the correlation coefficient, and s is the standard deviation.

The aqueous solubility and octanol-water partition coefficients used for Eq. 3 are presented in Table I. Figure 1 is a graphical representation of the observed and predicted solubilities based on Eq. 3.

If aqueous solubility is expressed as grams per liter (S_g) instead of moles per liter, the following relationship is obtained:

$$\log S_g = -0.95 \log PC + 2.40 \quad (\text{Eq. 4})$$

$n = 111 \quad r = 0.916 \quad s = 0.438$

For mole fractional units, the expression is:

$$\log X = -1.026 \log PC_x - 0.23 \quad (\text{Eq. 5})$$

$n = 111 \quad r = 0.931 \quad s = 0.427$

where X is the mole fractional aqueous solubility and PC_x is the octanol-water partition coefficient in mole fractional units.

DISCUSSION

Thermodynamically, the partition coefficient is defined as an equilibrium constant relating the activity of the solute in two immiscible phases at equilibrium (11):

$$PC = \frac{\alpha_o}{\alpha_w} \quad (\text{Eq. 6})$$

where α_o and α_w are the activities of the solute in oil and water, respectively. An alternative form of Eq. 6 is:

$$PC = \frac{\gamma_o C_o}{\gamma_w C_w} \quad (\text{Eq. 7})$$

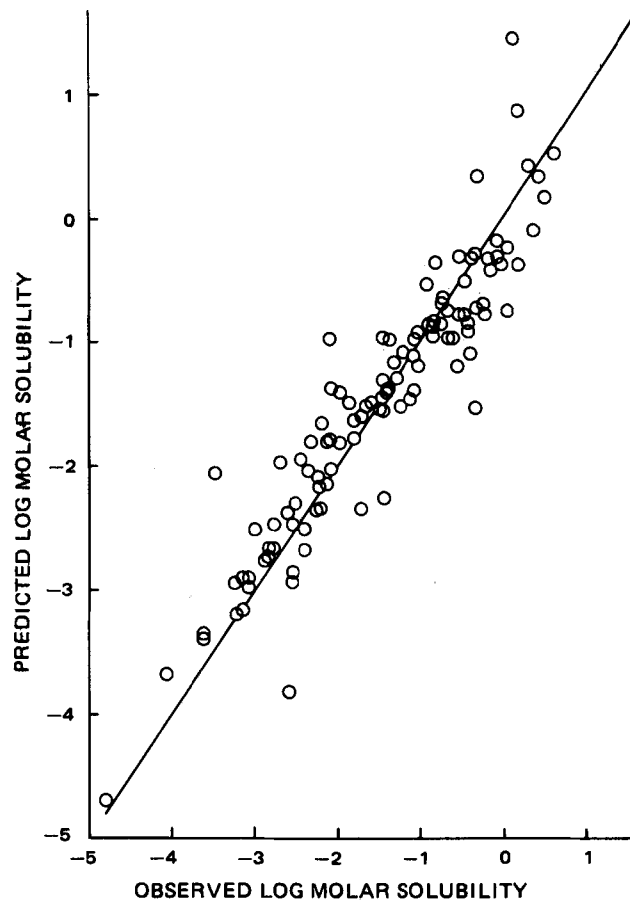


Figure 1—Observed molar aqueous solubility versus molar solubility predicted by Eq. 3.

where the activity is replaced by a product of the activity coefficient (γ) and the concentration (C) of the solute. In dilute solutions, the activity coefficients can be approximated by unity. Therefore, Eq. 7 reduces to:

$$PC = \frac{C_o}{C_w} \quad (\text{Eq. 8})$$

For most liquid solutes, the concentrations at saturation are equal to the solubilities in oil and water phases, respectively. Therefore:

$$PC = \frac{S_o}{S_w} \quad (\text{Eq. 9})$$

The logarithmic form of Eq. 9 is:

$$\log S_w = -\log PC + \log S_o \quad (\text{Eq. 10})$$

Although partitioning was restricted to octanol-water systems in the present study, it is applicable to most solvent systems. The major difference may be in the coefficient values of some equations.

If the solubilities of liquid solutes in octanol are comparable, the $\log S_o$ term in Eq. 10 will nearly be constant. In fact, almost all liquids included in this study are completely miscible with octanol. Therefore, their solubilities in octanol are equal to their molarities in the pure state or, on a mole fractional scale, they are equal to unity.

This finding suggests that octanol behaves as a nearly ideal (in thermodynamic sense) solvent for the liquid solutes considered. The reason for this excellent solvency of octanol for organic liquids is that its polarity is in the middle of the range where most organic liquids are found. If the solubility parameter (δ) is used as a measure of solvent polarity, octanol has a δ value of 10.3 (12). The lowest normally encountered δ value for pure hydrocarbons is about 7. Most nonionizable compounds have solubility parameters between 7 and 15. The exceptions are water and some polyhydroxy alcohols; ethylene glycol, glycerol, and propylene glycol have δ values greater than 15. Methanol and ethanol have δ values of 14.5 and 13, respectively.

The results obtained from this study are in excellent agreement with Eq. 10. The coefficients of $\log PC$ for Eqs. 3-5 are almost identical and

very close to -1 as predicted by Eq. 10. This finding is noteworthy since the data used for these analyses cover a wide variety of organic nonelectrolyte liquids and span over five orders of magnitude. Furthermore, the aqueous solubility and partition coefficient data were taken from the work of many independent investigators who used various experimental techniques and compounds of various degrees of purity. Moreover, the aqueous solubility data cover a temperature range of $20-40^{\circ}$.

Along with the variation in the solubility and partition coefficients, a slight deviation in log PC may be attributed to the nonideal behavior of liquid solutes. The assumption of dilute solutions and activity coefficients being unity may not be completely valid. In fact, the data include several compounds with aqueous solubilities greater than $1.0 M$. Mutual solubility and self-association of low molecular weight solutes may contribute to the deviation observed.

If the aqueous solubilities and octanol-water partition coefficients are expressed in mole fraction units and if it is assumed that the solutes are completely miscible with octanol, then log S_o in Eq. 10 is expected to be zero. Examination of Eq. 5, which relates the mole fractional aqueous solubilities and partition coefficients, reveals that the intercept is indeed close to zero.

The significance of the intercept can be further explained as follows. If it is assumed that the solutes are miscible with octanol and that the average density of liquid solutes is ~ 1 g/ml, then the solubility of liquid solutes in octanol can be approximated with their densities. Upon substitution of the average density value in Eq. 10, an intercept value of 3.0 is expected. The intercept value obtained (2.54) from Eq. 4 is in reasonable agreement with the value expected from Eq. 10. The assumption of miscibility and the use of average density were verified in great detail by Roseman¹.

These results, although in qualitative agreement with those of Hansch *et al.* (9), differ significantly in the coefficient of log PC . The relationship between molal aqueous solubility and partition coefficients of several liquid nonelectrolytes was reported in their work (9):

$$\log S = -1.339 \log PC + 0.978 \quad (\text{Eq. 11})$$
$$n = 156 \quad r = 0.935 \quad s = 0.472$$

Almost all of the partition coefficients used in Eq. 11 were calculated from the group contribution approach. Only 22 of 156 partition coefficients reported were experimentally determined. The coefficient of log PC in Eq. 11 is significantly different from -1 , the value expected from Eq. 10. The deviation may be attributed to a systematic error in the cal-

culated partition coefficients for hydrocarbons². The significance of the results reported in this study can be illustrated by the following:

1. Only experimentally determined partition coefficients and solubility values were used.

2. A greater number of experimentally measured partition coefficients are available now than were available in 1968.

3. More solubility values were used.

4. Since no calculated values were used, systematic errors in values for a series of compounds are not likely.

Furthermore, these results are supported by the equality of partition coefficients and solubility ratios observed by Roseman¹ for various drugs in several oil-water systems. This relationship is important in understanding the solubility and partitioning phenomena of liquids and will provide a basis for crystalline solids and gaseous compounds.

These equations can be helpful in assessing the reliability of reported values for aqueous solubility estimation. These equations were employed to verify the solubility or partition coefficients of a few compounds that showed a great difference between the calculated and observed values, and this study will be the subject of a separate report.

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High-Performance Liquid Chromatographic Assay for Fenopropfen in Human Plasma

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Abstract □ A high-performance liquid chromatographic method is described for the quantitation of fenopropfen, *dl*-2-(3-phenoxyphenyl)propionic acid, in human plasma. The proteins in plasma were precipitated by the addition of hydrochloric acid. Fenopropfen and the internal standard, *dl*-2-(4-phenoxyphenyl)valeric acid, were extracted into butyl chloride and then back-extracted into sodium hydroxide. The aqueous solution was injected onto a reversed-phase alkylphenyl column, and the compounds were eluted using a mobile phase of acetonitrile-water-acetic acid (50:50:2 v/v/v). At a flow rate of 1 ml/min, the retention times of fenopropfen and the internal standard were 8 and 12 min, respectively.

The absorbance was monitored at 272 nm. The method requires 1.0 ml of plasma and is sensitive to 0.5 $\mu\text{g/ml}$. This procedure has been used for routine assay of multiple samples from bioavailability and compliance studies.

Keyphrases □ Fenopropfen—high-performance liquid chromatographic analysis, human plasma □ High-performance liquid chromatography—assay, fenopropfen, human plasma □ Anti-inflammatory agents—fenopropfen, high-performance liquid chromatographic analysis, human plasma

The pharmacological and toxicological properties of fenopropfen [*dl*-2-(3-phenoxyphenyl)propionic acid, I] have been studied extensively and were reviewed recently (1-3). Compound I was shown to be absorbed readily after oral

administration. It is extensively metabolized to I glucuronide and to *dl*-2-[3-(4-hydroxyphenoxy)phenyl]propionic acid (II) glucuronide, both of which are excreted rapidly in the urine (4, 5).