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Predicting Cosolvency. 1. Solubility Ratio and Solute log K_{ow}

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The solubility ratio of organic chemicals in an organic solvent and in water, σ, has been found to correlate with the logarithm of the octanol−water partition coefficient (log K_{ow}) of the solutes; i.e., log $\sigma = N + M$ log K_{ow}. A total of 607 sets of thousands of solubility data were extracted from literature sources. From this database, values of N and M are obtained for 15 completely water-miscible cosolvents which are often used in pharmaceutical and environmental activities. A linear free energy relationship between σ and log K_{ow} is theoretically derived. The deviation of the slope M from the theoretical value of unity seems to originate mainly from the differences in activity coefficients of solute in water-saturated octanol and in pure cosolvent. The effect of dissolved octanol in water in defining K_{ow} may also influence the slope of $\sigma \sim$ log K_{ow} regression.

Introduction

In the pharmaceutical industry, organic solvents such as ethanol, propylene glycol, and glycerin are often used to enhance the solubilization of drugs in aqueous vehicles. The ability of these cosolvents to increase the solubility of sparsely soluble organic solutes varies depending on the type and extent of their interactions with the solute. The ratio of solute solubilities in a specific organic solvent to that in pure water was defined as "cosolvency power" and given a symbol σ:[1,2]

$$\sigma = \log(S_c/S_w) \qquad (1)$$

where S's are the solubilities of solute in pure organic cosolvent (subscript c) and in pure water (subscript w). The values of σ can be positive, near-zero, or negative, depending on the relative polarity of water, solute, and cosolvent.

The term σ is the most important parameter in the widely recognized log-linear solubilization model.[1] It serves as the slope of the idealized (end-to-end) solubilization curve—the plot of solute solubility versus the volume fraction of the organic cosolvent in the solvent mixture. This log-linear model describes the increase in the solubility of an organic compound relative to its aqueous solubility as a function of cosolvent concentration:

$$\log S_m = \log S_w + f\sigma \qquad (2)$$

where S_m is the solute solubility in the water/cosolvent mixture with a solute-free cosolvent volume fraction f. With the aid of σ, the solubility of organic compounds in any mixed solvent can be predicted from the knowledge of its K_{ow} and water solubility S_w, for both of which large databases are available. The models developed for sorption of organic compounds on soils also depend on σ to account for the interactions between solute and mixed solvent.[2,6]

To predict σ, Yalkowsky and Roseman[1] proposed eq 3, which relates σ to the octanol−water partition coefficient, K_{ow}, of the solutes. While σ values are specific

$$\sigma = M \log K_{ow} + N \qquad (3)$$

for a specified solute/cosolvent/water system, the regression parameters M and N are specific for the cosolvent and independent of the solutes. The values of M and N have been reported for a few cosolvent/water systems.[1–5] Due to their universal nature with respect to solutes, M and N can be viewed as measures of cosolvent polarity.[1]

In many cosolvent applications such as drug formulation and environmental remediation, it is often practical to use only less than 50% of cosolvent in the aqueous solvent mixture. To more accurately predict the solute solubility at low cosolvent fractions, the end-to-half cosolvency power, $\sigma_{0.5}$, is defined by eq 4, where $S_{0.5}$ is

$$\sigma_{0.5} = (\log S_{0.5} - \log S_w)/0.5 \qquad (4)$$

the solubility of the organic compound in the solvent mixture with $f = 0.5$. The solute solubility can be estimated using eq 5 when the cosolvent in the solvent

$$\log S_m = \log S_w + f\sigma_{0.5} \qquad (5)$$

mixture is close to or lower than 50% volumetrically. Similar to the case of eq 3, cosolvent-specific $M_{0.5}$ and $N_{0.5}$ can be obtained by a linear regression of $\sigma_{0.5}$ against solute log K_{ow} (see eq 6).

$$\sigma_{0.5} = M_{0.5} \log K_{ow} + N_{0.5} \qquad (6)$$

In this paper, we report the values of M and N, as well as $M_{0.5}$ and $N_{0.5}$, for 15 cosolvents which are often used in pharmaceutical and environmental areas. A total of 607 solubilization curves composed of thousands of solubility data points were extracted from literature sources. For each data set, σ and $\sigma_{0.5}$ were calculated using eqs 1 and 4, respectively. Then, eqs 3 and 6 were established for each cosolvent. The linear free energy relationships between σ or $\sigma_{0.5}$ and solute K_{ow} were then derived. We will discuss the correlations of M and $M_{0.5}$

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with the structural and polarity properties of cosolvent in the following paper.

Theory

When an organic compound is placed in direct contact with a pure cosolvent, solutions of the organic substance in the cosolvent (subscript c) and of cosolvent in the organic solute (subscript s) are formed. For solutes with limited miscibility with the solvent, phase equilibrium is reached when the chemical potentials of the solute in both phases are equal; $\mu_s = \mu_c$. Therefore

$$\gamma_s x_s = \gamma_c x_c \tag{7}$$

where the γ's are the activity coefficients and the x's are the mole fractions of solute in phases designated by subscripts. All activity coefficients in this work are based on the reference states of the pure chemicals. As a first approximation, we assume that (1) the amount of pure cosolvent in the solute phase is negligible (i.e., $\gamma_s = x_s = 1$ and $x_c = 1/\gamma_c$) and (2) the mole fraction of the solute in the cosolvent phase is much smaller than that of the pure cosolvent, so that $x_c = S_c V_c$, where V is the molar volume of the pure solvent. Then, the molar solubilities of the solute in pure cosolvent and water are

$$\log S_c = -\log \gamma_c - \log V_c \tag{8}$$

and

$$\log S_w = -\log \gamma_w - \log V_w \tag{9}$$

respectively. The solubility ratio σ can thus be expressed as

$$\sigma = \log S_c - \log S_w = \log \gamma_w - \log \gamma_c - \log(V_w/V_c) \tag{10}$$

The octanol–water partition coefficient, K_{ow}, of a solute can be similarly derived:

$$\log K_{ow} = \log \gamma^\infty_{w^*} - \log \gamma^\infty_{o^*} + \log(V_{w^*}/V_{o^*}) \tag{11}$$

where the new subscripts w* and o* refer to the octanol-saturated water and the water-saturated octanol phases, respectively, in the biphasic partitioning system. The asterisk in the subscripts indicates the mutual saturation of the water and octanol. The superscript ∞ indicates infinite dilution with respect to the solute. In this paper, an activity coefficient without a superscript ∞ refers to a solute-saturated condition. The molar volumes of these phases are $V_{w^*} \approx V_w = 0.018$ L mol^{-1} and $V_{o^*} = 0.119$ L mol^{-1} based on a solubility of water in octanol of 2.3 mol L^{-1}.[7]

By combining eqs 10 and 11, we obtain

$$\sigma = \log K_{ow} + \log(\gamma^\infty_{o^*}/\gamma_c) + \log(\gamma_w/\gamma^\infty_{w^*}) + \log(V_{o^*}/V_c) \tag{12}$$

The second term on the right side of eq 12 compares the solute behaviors in water-saturated octanol under dilute conditions and in pure cosolvent at saturation. The magnitude of this ratio is likely to vary among solutes. The $\gamma_w/\gamma^\infty_{w^*}$ term reflects both the effect of dissolved octanol on the aqueous activity coefficient of the solute and the variation of activity coefficient with concentration. It also varies with solute hydrophobicity. The last term, $\log(V_{o^*}/V_c)$, is a constant specific for the

cosolvent. Since V_c of most solvents involved in this study is smaller than V_{o^*}, this molar volume ratio term is positive. Assuming the second and third terms have "ideal" values which are the same for all solutes, eq 12 will have a slope of 1 and a unique intercept. Further idealizing the situation by assuming both $\gamma^\infty_{o^*}/\gamma_c$ and $\gamma_w/\gamma^\infty_{w^*}$ equal unity would give eq 3 a slope of 1 and an intercept of $-(0.92 + \log V_c)$, where V_c is in L mol^{-1}.

Methods

Database. A database was established in our previous work, which contains experimental data for more than a thousand ternary systems composed of water, a cosolvent, and a solute. In this study, data for 15 cosolvents commonly used for pharmaceutical or environmental purposes are extracted from the database. A total of 607 different water/cosolvent/solute systems are included. All data used in this study were obtained at experimental temperatures ranging from 15 to 40 °C.

Some alkylamines have been used as cosolvents in the environmental cleanup of heavily contaminated soils and sediments.[8,9] However, the behavior of alkylamines as cosolvents has never been investigated in detail, and few solubility data were found. To fill this gap, the solubilities of four organic chemicals having wide ranges of hydrophobicities in mixtures of water and n-butylamine were experimentally determined in this study. Phenanthrene was purchased from Aldrich Chemical Co. (Milwaukee, WI) and has a reported purity of 98%. Naphthalene (Certified grade), n-butylamine (98.9%), and methanol (HPLC grade) were obtained from Fisher Scientific Co. (Pittsburgh, PA), and benzocaine (>99%) and hydantoin (>99%) were purchased from Sigma Chemical Co. (St. Louis, MO). All chemicals were used as received. Milli-Q water was used in all experiments. The experimental procedures were similar to those described in our previously published work.[10]

For data collected from the literature, different expressions for solvent composition have been converted to volume fraction of cosolvent and the units of solute solubility to moles per liter. In cases where the density of a saturated solution was needed for conversion but was not available, the density of the solute-free solvent mixture was used to convert the solubility values to molarity. The density of a solute-free solvent mixture at any composition was calculated through a polynomial regression equation of experimental density data[11] against the volume fraction of the cosolvent in the mixture.

Calculations of σ and $\sigma_{0.5}$. Values of σ were obtained by using eq 1. In cases where S_w was not provided in the originally reported data set, its value was obtained from the AQUASOL dATAbASE.[12] Some solubility data were reported up to a volume fraction of cosolvent less than unity; thus the value of S_c was missing. If the highest volume fraction of cosolvent was greater than 0.7, the solubility value at the highest volume fraction of cosolvent was linearly converted to S_c using eq 13, where f_h is the highest cosolvent volume

$$S_c = S_w + (S_h - S_w)/f_h \tag{13}$$

fraction in the data set. When $S_{0.5}$ was not provided in the original data set, it was calculated by linear conversion using all available solubility data obtained in the range $0.4 \leq f \leq 0.6$, where f is the volume fraction of the cosolvent.

**Table 1. Solubility of Selected Solutes in Water/
n-Butylamine Systems at 25 °C (log M ± Standard
Deviation of Duplicates)**

			solute	
f	phenanthrene	naphthalene	benzocaine	hydantoin
0	-5.11 ± 0.01	-3.51 ± 0.04	-2.14 ± 0.00	-0.41 ± 0.00
0.1	-3.71 ± 0.02	-2.85 ± 0.03	-1.28 ± 0.00	1.01 ± 0.00
0.2	-2.18 ± 0.01	-1.63 ± 0.03	-0.79 ± 0.01	1.21 ± 0.00
0.4	-1.39 ± 0.01	-0.97 ± 0.01	-0.28 ± 0.00	1.26 ± 0.02
0.6	-0.89 ± 0.02	-0.52 ± 0.02	-0.08 ± 0.00	1.21 ± 0.02
0.8	-0.38 ± 0.05	-0.12 ± 0.03	-0.74 ± 0.01	0.82 ± 0.02
1.0	0.06 ± 0.03	0.01 ± 0.03	0.90 ± 0.00	0.48 ± 0.01
σ	5.17	3.52	3.04	0.89
$\sigma_{0.5}$	7.93	5.53	3.92	3.30
log K_{ow}	4.49	3.32	1.92	-1.69

Calculation of Solute log K_{ow}. The log K_{ow} values
of solutes were calculated by the ClogP subroutine of
the DayMenus computer program.[13] Only the chemical
structure was required as input.

Regression Analysis. All regression analyses were
performed by the Regression Analysis Tool of Microsoft
Excel at the 95% confidence level.

Results

Experimental Data. The experimental solubilities
of four solutes in n-butylamine/water systems are
presented in Table 1, along with the estimated log K_{ow}
values of the solutes. If the solubility is plotted against
cosolvent volume fractions, the resulting solubilization
curves for the four solutes appear to be convex to some
extent, i.e., positively deviated from the ideal end-to-
end straight lines represented by eq 2. For all but
hydantoin, solute solubilities increase as the volume
percentage of n-butylamine increases, typical of solu-
bilization of hydrophobic organic compounds by water-
miscible cosolvents. A parabolic curve of log solubility

versus n-butylamine volume fraction was observed for
hydantoin solute, with the highest solubility occurring
at 40% n-butylamine. Similar parabolic curves were
also observed for caffeine, theophylline, and phenyl-
alanine, with cosolvents ethanol and propylene glycol.[1]

σ and log K_{ow} Correlations. Regression analyses
of σ or $\sigma_{0.5}$ against solute log K_{ow} for each cosolvent are
summarized in Table 2. Figure 1 illustrates the results,
with the regression equation shown by straight lines.
These plots are drawn with the same axis scales for
direct comparison. For the ethanol system, the values
of M and N as well as the regression coefficients are
very similar to our previously published results.[10] The
greatly increased number of data points is due mainly
to additional data and the use of σ from each individual
data set in this study, while in the previous study an
averaged σ was used for the same solute when more
than one data set was found in the database.

For most water/cosolvent systems, the regression line
of $\sigma_{0.5}$ is above that of σ, indicating that for most organic
solutes, $\log(S_{0.5}/S_w)$ is more than half of $\log(S_c/S_w)$. This
implies that most solubilization curves are positively
deviated from the idealized linear model. For 1-butyl-
amine, 1-propanol, and 2-propanol, the distances be-
tween the two regression lines are larger than those for
the other cosolvents (see Figure 1). This indicates that
they are more efficient in enhancing solute solubility
at low fractional compositions. In most pharmaceutical
and engineering applications, cosolvent concentration
has to be restricted. For relatively polar cosolvents such
as methanol, glycerol, and ethylene glycol, regressions
of σ and $\sigma_{0.5}$ versus solute log K_{ow} are very close to each
other.

Accuracy of the M and N Values. The constants
M and N are empirically obtained. Their reliability
mainly depends on the number of the data sets used in

Table 2. Summary of Regression Results for the Relationship between σ or $\sigma_{0.5}$ and Solute log K_{ow}

| cosolvent	no.	N	M	R^2	SE	log K_{ow} range
			$\sigma = M \log K_{ow} + N$			
methanol	79	0.36 ± 0.07	0.89 ± 0.02	0.96	0.63	$-4.53-7.31$
ethanol	197	0.30 ± 0.04	0.95 ± 0.02	0.95	0.61	$-4.90-8.23$
1-propanol	17	0.01 ± 0.13	1.09 ± 0.05	0.97	0.55	$-3.73-7.31$
2-propanol	20	-0.50 ± 0.18	1.11 ± 0.07	0.94	0.67	$-3.73-4.49$
acetone	22	-0.10 ± 0.24	1.14 ± 0.07	0.92	0.55	$-1.38-5.66$
acetonitrile	10	-0.49 ± 0.42	1.16 ± 0.16	0.86	0.65	$-0.06-4.49$
dioxane	23	0.40 ± 0.16	1.08 ± 0.07	0.91	0.71	$-4.90-4.49$
DMA	11	0.75 ± 0.30	0.96 ± 0.12	0.87	0.30	$0.66-4.49$
DMF	11	0.92 ± 0.41	0.83 ± 0.17	0.73	0.41	$0.66-3.32$
DMSO	12	0.95 ± 0.43	0.79 ± 0.17	0.68	0.42	$0.66-4.49$
glycerol	21	0.28 ± 0.15	0.35 ± 0.05	0.72	0.35	$-3.28-4.75$
ethylene glycol	13	0.37 ± 0.13	0.68 ± 0.05	0.95	0.20	$-3.73-4.04$
propylene glycol	62	0.37 ± 0.11	0.78 ± 0.04	0.89	0.43	$-7.91-7.21$
PEG400	10	0.68 ± 0.43	0.88 ± 0.16	0.79	0.67	$-0.10-4.18$
butylamine	4	1.86 ± 0.30	0.64 ± 0.10	0.96	0.46	$-1.69-4.49$
			$\sigma_{0.5} = M_{0.5} \log K_{ow} + N_{0.5}$			
methanol	87	0.70 ± 0.07	0.73 ± 0.02	0.92	0.67	$-4.53-7.31$
ethanol	191	1.14 ± 0.05	0.81 ± 0.02	0.91	0.71	$-4.90-8.23$
1-propanol	20	1.76 ± 0.09	1.03 ± 0.04	0.97	0.41	$-3.73-7.31$
2-propanol	22	1.00 ± 0.09	0.96 ± 0.03	0.98	0.35	$-3.73-4.49$
acetone	28	0.21 ± 0.48	1.25 ± 0.15	0.72	0.92	$-1.38-5.66$
acetonitrile	16	0.44 ± 0.79	1.04 ± 0.30	0.46	1.25	$-0.06-4.49$
dioxane	31	1.54 ± 0.21	0.99 ± 0.08	0.85	1.15	$-4.90-4.49$
DMA	13	1.28 ± 0.68	0.89 ± 0.26	0.51	0.93	$0.66-4.49$
DMF	12	1.70 ± 0.59	0.65 ± 0.25	0.40	0.69	$0.66-3.32$
DMSO	16	0.78 ± 0.55	0.72 ± 0.21	0.45	0.75	$0.66-4.49$
glycerol	23	0.14 ± 0.13	0.38 ± 0.05	0.77	0.34	$-3.28-4.75$
ethylene glycol	14	0.28 ± 0.32	0.52 ± 0.13	0.59	0.55	$-3.73-4.04$
propylene glycol	86	0.87 ± 0.08	0.55 ± 0.03	0.85	0.55	$-7.91-7.21$
PEG400	14	1.27 ± 0.56	0.78 ± 0.21	0.54	0.93	$-0.10-4.18$
butylamine	4	3.83 ± 0.85	0.67 ± 0.28	0.74	1.28	$-1.69-4.49$
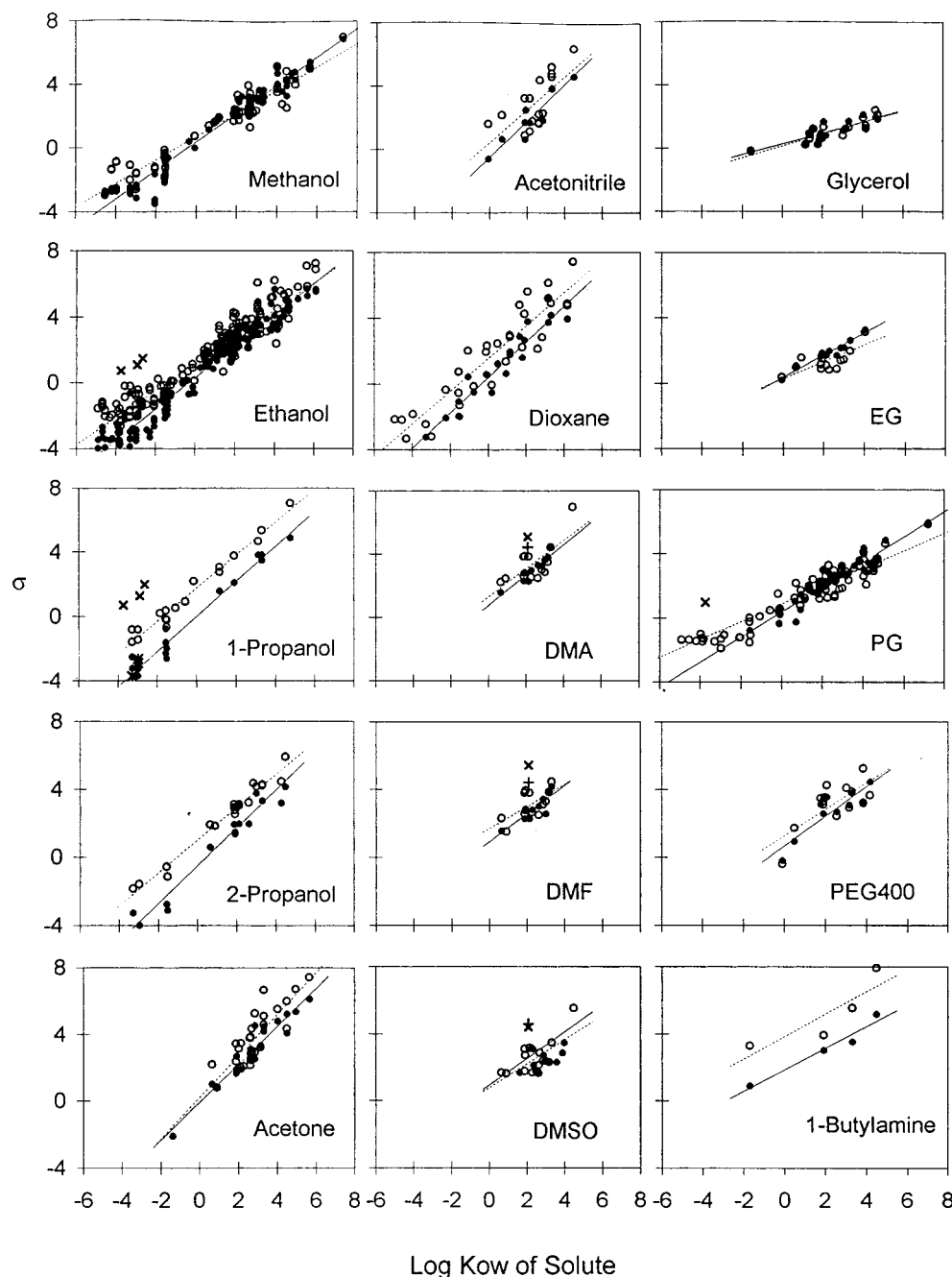
Figure 1. Regression of the solubility ratios σ (filled circles) and $\sigma_{0.5}$ (empty circles) against solute log K_{ow}. Outlier symbols: + for σ, × for $\sigma_{0.5}$. Outliers are not included in the regression.

the regression and the accuracy of the original solubility data. For each cosolvent system, solubility data were collected from 2 (1-butylamine) to 36 (ethanol) literature sources with a wide range of experimental reliability. Many solutes have more than one solubilization data set in the same cosolvent/water system from different literature sources. These data sets are used as individual sets. As shown in Figure 1, only 3 of the 512 and 10 of the 577 data sets are excluded from the regressions for σ and $\sigma_{0.5}$, respectively, based on their outliner behavior.

The quality of the correlation of σ with log K_{ow} is much better than that of $\sigma_{0.5}$, as can be seen by comparing the corresponding R^2 values in Table 2 for each cosolvent. This is partially because experimental values of $\sigma_{0.5}$ were missing in many of the original studies and had to be estimated by extrapolation from data at

cosolvent fractions near 0.5, such as 0.4 and 0.6, in obtaining $M_{0.5}$ and $N_{0.5}$, while less estimated values were involved in obtaining M and N. More important might be the complexity of interactions among molecules of solute, cosolvent, and water in the ternary solutions. Solubility of organic compounds is more difficult to predict in solvent mixtures than in a pure solvent, due to more types of molecular interactions involved.

It is observed that the regression parameters M and N depend, to some degree, on the range of solute log K_{ow}. Morris et al.[5] obtained N and M values for cosolvents with an average of 10 solute compounds for each cosolvent system, with all of the solutes having log K_{ow} values greater than zero. Their values of N are generally higher than those obtained in this study, while the opposite is mostly true for values of M. This is believed to be due to the range of solutes used in the

regression. When the solutes are grouped according to their log K_{ow} values, regression of σ against log K_{ow} results in lower M and higher N than the regression over all solutes. For instance, for solutes with log K_{ow} ≤ 0, $0.01-2.99$, and ≥ 3, the $\sigma \sim$ log K_{ow} regressions for solvent ethanol have slopes of 0.84, 0.79, and 0.69, respectively, and the corresponding intercepts increase accordingly. The slope of the overall regression, however, is 0.95. Among the 15 water/cosolvent systems studied, DMA, DMF, and DMSO systems have very limited numbers of data sets. The solute log K_{ow} values are in a range $0.6-4.5$. This relatively narrow range may affect the reliability of the regression parameters and needs to be expanded when more data are available.

Discussion

Dominating Effect of log K_{ow}. Although most terms on the right side of eq 12 cannot be kept constant when we "change" from one solute to another, the relative magnitudes of these changes are not generally comparable. For the solutes used in this work, log K_{ow} covers more than 11 orders of magnitude for some solvent systems. Much narrower ranges can be expected for changes of both $\gamma^{\infty}_{o*}/\gamma_c$ and $\gamma_w/\gamma^{\infty}_{w*}$. In addition, the two γ terms may cancel each other to some degree for many solutes, further reducing their effects on the correlation between σ and log K_{ow}. Therefore, although the $\gamma^{\infty}_{o*}/\gamma_c$ and $\gamma_w/\gamma^{\infty}_{w*}$ terms in eq 12 influence the regression parameters M and N, as will be discussed below, their effects are secondary to the effect of K_{ow} in determining the solubility ratio σ. The results of this study clearly demonstrate the predominant role of solute hydrophobicity in solubilization by organic cosolvents.

Effect of $\gamma^{\infty}_{o*}/\gamma_c$. The slopes of eq 3, M, are close to 1 for the less polar cosolvents (see Table 2). The deviations from the ideal slope of 1 seem to originate mainly from the differences in the extent of interactions of solute in water-saturated octanol (γ^{∞}_{o*}) and in the pure cosolvent (γ_c).

The variation of $\gamma^{\infty}_{o*}/\gamma_c$ with solute log K_{ow} is not easy to determine. We may recognize that, for hydrophobic solutes with no polar functional groups, $\gamma^{\infty}_{o*}/\gamma_c$ tends to be much less than unity with glycols, close to unity with alcohols, and greater than unity with aprotic cosolvents. For such solutes, when log K_{ow} increases, both γ^{∞}_{o*} and γ_c will increase. But γ_c increases more rapidly than γ^{∞}_{o*} with glycol cosolvents, both increase at comparable rates with alcohol cosolvents, and γ_c increases more slowly than γ^{∞}_{o*} with aprotic cosolvents. These trends seem to be true even if we extend the range of solutes to all those covered in this study. Generally speaking, however, both γ^{∞}_{o*} and γ_c are likely to depend on the solute chemical structure in a complicated pattern. As a result, $\gamma^{\infty}_{o*}/\gamma_c$ varies in a yet unpredictable manner with the chemical structures (functional groups) and polarity of both solutes and cosolvents, as well as the solubility level of solute in cosolvent.

Nevertheless, $\gamma^{\infty}_{o*}/\gamma_c$ seems to be the major influencing factor in eq 12 causing the slope of the $\sigma \sim$ log K_{ow} correlation to deviate from unity. The values of M are close to 1 for alcohols and less than 1 for glycols (see Table 2). For aprotic cosolvents DMA, DMF, and DMSO, the M's reported in Table 2 may be lower than what they should be, due to the relatively narrow range of the solute log K_{ow} values used to derive the correlation parameters, as discussed in the previous section.

Effect of $\gamma_w/\gamma^{\infty}_{w*}$. The term $\gamma_w/\gamma^{\infty}_{w*}$, which is the ratio of the activity coefficient of an organic solute in pure water at saturation to that in octanol-saturated water at infinite dilution, may also influence the slope of the $\sigma \sim$ log K_{ow} regression. For organic solutes that are only sparsely soluble in water, this ratio tends to be slightly over 1 since dissolved octanol lowers the activity coefficient of the solute in water. Chiou et al.[14] reported a similarly defined ratio of activity coefficients γ_w/γ_{w*}, where γ_{w*} is the activity coefficient of solute in octanol-saturated water at saturation, of 2.6 for DDT and 1.8 for hexachlorobenzene. Since γ^{∞}_{w*} (at infinite dilution) tends to be higher than γ_{w*} (at saturation), $\gamma_w/\gamma^{\infty}_{w*}$ should be lower than γ_w/γ_{w*} (i.e., $\gamma_w/\gamma^{\infty}_{w*} < 2.6$ for DDT and $\gamma_w/\gamma^{\infty}_{w*} < 1.8$ for hexachlorobenzene).

For hydrophilic organic chemicals, however, we would expect $\gamma_w/\gamma^{\infty}_{w*}$ to be lower than 1. In this case, it is the effect of concentration on the activity coefficient that makes $\gamma_w < \gamma^{\infty}_{w*} \approx \gamma^{\infty}_w$. When the concentration of solutes in water increases, their activity coefficients will decrease due to interactions between solute molecules. More hydrophilic compounds have higher aqueous solubilities; thus their activity coefficients in water are expected to change significantly from infinite dilution to saturation, and $\gamma^{\infty}_w/\gamma^{\infty}_{w*}$ will be closer to unity than $\gamma_w/\gamma^{\infty}_{w*}$. Therefore, the overall effect of $\gamma_w/\gamma^{\infty}_{w*}$ on the $\sigma \sim$ log K_{ow} regression tends to be positive on the slope M and negative on the intercept N. However, from the results of this study, this effect may be less significant than the influence of $\gamma^{\infty}_{o*}/\gamma_c$ discussed above.

The Intercept N. The intercept of the $\sigma \sim$ log K_{ow} regression is affected by all of the last three terms on the right side of eq 12. Since both $\gamma^{\infty}_{o*}/\gamma_c$ and $\gamma_w/\gamma^{\infty}_{w*}$ are not ideal and cannot be predicted at present, it is not possible to estimate the intercept N. The 95% confidence intervals of N are in general larger than those of M, indicating higher uncertainty of N. Weak correlations ($R^2 = 0.3$) were found between M and N. The difference between N values and the last term of eq 12, $-(0.92 + \log V_c)$, ranges from -0.7 (2-propanol) to 1.8 (n-butylamine), with those for monoalcohols, acetone, and acetonitrile being negative and those for polyalcohols and aprotic cosolvents being positive. As discussed under Results, values of N seem to be affected by the range of the solutes used in the regression. There is no evidence that N is dependent on cosolvent properties.

Limitations of the $\sigma \sim$ log K_{ow} Linear Relationship. Strictly speaking, the relationship between σ and log K_{ow} may not be linear as expressed by eq 3, due to the possible dependence of $\gamma^{\infty}_{o*}/\gamma_c$ and $\gamma_w/\gamma^{\infty}_{w*}$ on solute K_{ow}. The quality of linear free energy relationships depends generally on whether the solutes used in establishing the relationship have the same types of interactions with the two nonaqueous solvents.[15] In this sense, $\sigma \sim$ log K_{ow} regression for cosolvent alcohols should have a better quality than others since these solvents mostly resemble octanol. The structural dissimilarities among solutes will be relatively similarly reflected in their activity coefficients in octanol (γ^{∞}_{o*}) and in cosolvent alcohol (γ_c). This will result in more linear $\sigma \sim$ log K_{ow} relationships. Glycols, however, can provide one or two more sites of specific interactions than octanol for solutes capable of hydrogen bonding. The $\gamma^{\infty}_{o*}/\gamma_c$ ratios of these solutes will then be different from those of solutes without hydrogen-bonding groups. In other words, inclusion of solutes with functional

groups that can form hydrogen bonds with solvent molecules will increase the scattering of the $\sigma \sim \log K_{ow}$ regression when the cosolvent is different from octanol in hydrogen-bonding properties. This is manifested by the lower R^2 values with nonalcohol cosolvents (see Table 2).

Although more scattered for aprotics and glycols than alcohols, the overall regressions are basically linear. The observed linearity of the $\sigma \sim \log K_{ow}$ correlation (Figure 1) indicates that the variations in $\log(\gamma^\infty_{o*}/\gamma_c)$ and $\log(\gamma_w/\gamma^\infty_{w*})$ are much less than those in $\log K_{ow}$. This is because the predominant type of intermolecular interaction between solutes and both octanol in the partitioning process and polar solvent in the dissolution process is the so-called "hydrophobic interaction". Even in the polar organic solvents such as those investigated here, the effect of hydrophobic interaction may outweigh those of other interactions such as hydrogen bonding for a majority of the organic compounds. Thus, K_{ow}, as the index for solute hydrophobicity, predominates σ.

Acknowledgment

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