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Correlation of Octanol/Water Solubility Ratios and Partition Coefficients

Sirirat Pinsuwan, An Li, and Samuel H. Yalkowsky*

Department of Pharmaceutical Sciences, University of Arizona, Tucson, Arizona 85721

The octanol/water solubility ratio (S_o/S_w) was found to be highly correlated with the octanol/water partition coefficient (K_{ow}) of 82 pharmaceutically and environmentally relevant compounds. The solubility ratio gives comparable estimates to that of the group contribution ($\log P(\text{calcd})$) method for estimating the partition coefficient of the compounds used in this study.

Introduction

The partition coefficient between octanol and water (K_{ow}) is an important physicochemical parameter for characterizing the lipophilicity or hydrophobicity of a compound and it is used in many fields, especially in the environmental and pharmaceutical sciences.

The classical method for measuring K_{ow} is the flask-shaking method; however, this technique is not suitable for hydrophobic compounds with K_{ow} values of more than 10^5 . The generator-column method (1) and the slow-stirring method (2) were developed for measuring K_{ow} for highly hydrophobic compounds. Although these methods are somewhat more suitable for hydrophobic chemicals, they are laborious, time consuming, and subject to appreciable error.

In addition to determining K_{ow} by direct measurement, it can be estimated by using one of several estimation techniques. The most widely used estimation approach is the calculation based on group contributions. By this method, a K_{ow} value is reported as a calculated $\log P$, $\log P(\text{calcd})$, value (3). Although computer programs have simplified such computations, they can only be used for compounds for which all the structural parameters have been determined. Moreover, it is difficult to estimate $\log K_{ow}$ for molecules with interacting functional groups (4).

The K_{ow} has been correlated with other structural and physical properties of a chemical, such as water solubility, molecular connectivity indices, total surface area, and molar volume (5, 6). The existence of a relationship between partition coefficients and water solubilities has been discussed by many researchers. Yalkowsky et al. (13) assumed that the effect of octanol/water mutual saturation on the partition coefficient is small and could be ignored. If this is so, then K_{ow} may be set equal to the solubility ratio of solute in octanol and water (S_o/S_w). By this approach, the K_{ow} value of a compound is simply the ratio of its experimental octanol solubility and water solubility. In the present work, this relationship is examined more thoroughly by comparing the experimental K_{ow} values with those obtained from the solubility ratio.

Experimental Section

Materials. Gentisic acid and diphenylamine were obtained from Sigma Chemical Co. Hexamethylbenzene and bibenzyl were obtained from Eastman Kodak Co. *p*-Bromobenzoic acid, *o*-bromobenzoic acid, *m*-bromobenzoic acid, *p*-toluic acid, triphenylene, and 1,2,3-trichlorobenzene were obtained from Aldrich Chemical Co. 2-Propanol

(Baker analyzed) was used to dilute all of the solutions for UV measurement. All of the chemicals were used as received without further purification.

Octanol Solubility Measurement. The reported octanol solubilities of some of the organic chemicals were compiled from the literature. Only solubilities measured in the range of 15–30 °C were used. Solubilities of 10 other solid chemicals were directly determined in this laboratory by equilibrating an excess of solute with octanol in a sealed vial for 48–72 h at (25 ± 2) °C. Mixing was performed by using an end-over-end mechanical rotator. More solute was added if crystals were not observed. Saturation was assumed when crystals were observed in solvent, and the vial was rotated for an additional 24 h to assure that the equilibrium was in fact obtained. After equilibration, the samples were vacuum filtered through a 5.0 µm fritted-glass filter. Aliquots of the filtrate were appropriately diluted with 2-propanol, and their absorbance was measured using a UV spectrophotometer (Beckman, model DU-8). The entire procedure was carried out at least twice for each compound, and each analysis was also conducted in duplicate.

Water Solubilities and Partition Coefficients. The reported experimental values of water solubility and the logarithms of the partition coefficient ($\log K_{ow}$) were obtained from the AQUASOL dATABASE (17) and Day-Menus computer program (4) respectively. The average value was used if more than one datum was available for a compound. The calculated K_{ow} or $\log P(\text{calcd})$ based on the Hansch and Leo fragment method was also taken from the DayMenus VAX computer program (4).

Results and Discussion

The octanol (S_o) and water (S_w) solubilities of the compounds studied are listed in Table 1. From these values, the solubility ratio of solute in octanol and water (SR) can be calculated as

$$SR = S_o/S_w \quad (1)$$

or

$$\log SR = \log S_o - \log S_w \quad (2)$$

The values of $\log SR$ are also listed in Table 1 along with the observed partition coefficients and the difference between these two parameters. For most of the compounds studied, the solubility ratio does not differ greatly from the observed partition coefficient. The average absolute error is less than 0.3 log unit, corresponding to a factor of 2. This

* To whom correspondence should be addressed.

Table 1. Octanol/Water Solubility, Solubility Ratio, log *P*(calcd), and Partition Coefficient

chemical	ref ^b	log <i>S</i> _o ^a	log <i>S</i> _w ^a	log SR	log <i>P</i> (calcd)	log <i>K</i> _{ow}	difference	
							from log SR	from log <i>P</i> (calcd)
fumaric acid	7	-1.12	-1.279	0.159	-0.270	0.370	0.211	0.640
caffeine	7	-1.72	-0.876	-0.84	-0.100	-0.036	0.808	0.064
theophylline	7, 12	-1.99	-1.347	-0.64	-0.062	-0.028	0.615	0.034
anitpyrine	7	-0.19	-0.559	0.369	0.194	0.330	-0.039	0.136
cortisone	7	-1.97	-3.120	1.150	0.325	1.490	0.340	1.165
prednisolone	7	-1.62	-3.100	1.480	0.573	1.552	0.072	0.979
aminopyrine	7	0.00	-0.629	0.629	0.935	0.987	0.358	0.052
fenuron	13	-0.77	-1.647	0.879	0.977	0.960	0.081	-0.017
acetylsalicylic acid	7	-0.69	-1.614	0.924	1.104	1.185	0.261	0.081
acetanilide	7	-0.12	-1.310	1.190	1.161	1.187	-0.003	0.026
<i>p</i> -aminobenzoic acid	7	-0.80	-1.350	0.550	1.208	0.710	0.160	-0.498
phenol	7	0.94	-0.009	0.949	1.475	1.475	0.526	0.000
gentisic acid	<i>d</i>	-0.13	-1.759	1.629	1.639	1.610	-0.019	-0.029
metalaxyl	13	-0.33	-1.601	1.269	1.693	1.707	0.438	0.014
prostaglandin E2	7	-0.03	-2.460	2.430	1.773	2.255	-0.175	0.482
phenacetin	7	-0.84	-2.350	1.510	1.793	1.603	0.093	-0.190
metoxuron	13	-1.06	-2.581	1.523	1.795	1.570	0.047	-0.225
benzoic acid	7	-0.06	1.567	1.507	1.885	1.882	0.375	-0.003
monuron	13	-1.04	-2.997	1.954	1.992	1.960	0.006	-0.032
isazophos	13	0.50	-3.321	3.824	2.059	3.820	-0.004	1.761
salicylic acid	7	0.15	-1.733	1.883	2.187	2.195	0.312	0.008
<i>o</i> -bromobenzoic acid	<i>d</i>	-0.12	-2.276	2.158	2.196	2.200	0.042	0.004
<i>p</i> -toluic acid	7	-0.32	-2.562	2.241	2.384	2.323	0.082	-0.061
atrazine	8, 9, 11	-1.32	-3.868	2.544	2.604	2.576	0.032	-0.028
triazolam	7	-2.05	-4.090	2.040	2.651	2.420	0.380	-0.231
diuron	13	-1.14	-4.025	2.888	2.691	2.802	-0.086	0.111
ketoprofen	16	-0.10	-3.698	3.594	2.761	3.120	-0.474	0.359
naproxen	16	-0.89	-4.202	3.317	2.816	3.425	0.108	0.609
<i>p</i> -bromobenzoic acid	<i>d</i>	-1.11	-3.539	2.433	2.846	2.860	0.427	0.014
<i>m</i> -bromobenzoic acid	<i>d</i>	-0.07	-2.699	2.629	2.846	2.870	0.241	0.024
metolachlor	13	0.47	-2.729	3.202	2.950	3.310	0.108	0.360
2,4-dichlorophenol	11	0.36	-1.559	1.919	2.972	3.230	1.311	0.258
3,4-dichloronitrobenzene	11	-0.08	-3.201	3.121	3.134	3.055	-0.066	-0.079
dieldrin	11	-0.97	-6.248	5.278	3.176	5.109	-0.169	1.933
endrin	11	-0.94	-6.174	5.234	3.176	5.200	-0.034	2.024
naphthalene	10, 11, 16	-0.15	-3.620	3.469	3.316	3.335	-0.134	0.019
2,4,6-trichlorophenol	11	0.22	-2.341	2.561	3.391	3.791	1.230	0.400
testosterone	7	-0.49	-3.972	3.482	3.409	3.190	-0.292	-0.219
desoxycorticosterone	7	-0.71	-3.450	2.740	3.440	2.827	0.087	-0.613
2,3,4-trichloronitrobenzene	11	-0.29	-3.939	3.649	3.522	3.575	-0.074	0.053
1,4-dichlorobenzene	8, 9, 11	0.20	-3.329	3.532	3.568	3.439	-0.093	-0.129
diphenylamine	<i>d</i>	0.03	-3.504	3.539	3.620	3.440	-0.099	-0.180
ibuprofen	7, 16	0.18	-3.760	3.940	3.679	3.492	-0.448	-0.187
lindane	11	-0.74	-4.464	3.724	3.752	3.517	-0.207	-0.235
flurbiprofen	7	-0.20	-3.740	3.540	3.754	3.010	-0.530	-0.744
acenaphthene	10	-0.59	-4.615	4.023	3.770	3.955	-0.068	0.185
1,4-dibromobenzene	11	-0.30	-4.072	3.772	3.868	3.790	0.018	-0.078
fluorene	7, 10	-0.62	-4.885	4.265	3.925	4.197	-0.068	0.272
methyltestosterone	7	-0.45	-3.990	3.540	3.928	3.360	-0.180	-0.568
progesterone	7	-0.71	-4.449	3.739	3.965	3.652	-0.087	-0.313
terbutryne	13	-0.27	-3.711	3.442	3.975	3.730	0.288	-0.245
2,3,5,6-tetrachloronitrobenzene	11	-0.68	-5.097	4.417	4.033	3.890	-0.527	-0.143
1,2,3-trichlorobenzene	<i>d</i> , 9, 11	0.18	-4.089	4.266	4.041	4.070	-0.196	0.029
1,3,5-trichlorobenzene	11	-0.16	-4.575	4.415	4.281	4.203	-0.212	-0.078
pentachlorophenol	11	-0.11	-4.279	4.169	4.354	5.070	0.901	0.716
1-methylfluorene	10	-0.56	-5.218	4.662	4.242	4.970	0.308	0.546
profluralin	13	-0.20	-6.541	6.343	4.464	6.340	-0.003	1.876
phenanthrene	10, 11, 16	-0.45	-5.219	4.767	4.490	4.523	-0.244	0.033
anthracene	8, 10, 16	-1.91	-6.107	4.202	4.490	4.556	0.354	0.066
bibenzyl	<i>d</i>	-0.35	-4.627	4.277	4.588	4.437	0.160	-0.151
hexachloroethane	11	-0.28	4.488	4.208	4.610	4.000	-0.208	-0.610
mirex	11	-0.51	-6.783	6.273	4.650	5.280	-0.993	0.630
1,2,4,5-tetrachlorobenzene	9, 11	-0.92	-5.316	4.396	4.754	4.626	0.230	-0.128
1,2,3,5-tetrachlorobenzene	9	0.15	-4.732	4.882	4.754	4.630	-0.252	-0.124
fluorodifen	13	-1.52	-5.215	3.695	4.788	3.550	-0.145	-1.238
hexamethylbenzene	<i>d</i>	-0.89	-5.227	4.337	4.836	4.686	0.349	-0.150
heptachlor	11	-0.63	-6.317	5.687	4.925	5.425	-0.262	0.500
fluoranthene	10	-0.76	-5.915	5.152	4.950	5.070	-0.082	0.120
pyrene	10, 11	-0.90	-6.235	5.333	4.950	5.082	-0.251	0.132
fenchlorphos	13	-0.16	-5.729	5.564	4.972	4.775	-0.789	-0.197
pentachlorobenzene	<i>d</i> , 11	-0.56	-5.493	4.933	5.227	5.213	0.280	-0.014
triphenylene	<i>d</i>	-1.77	-6.602	4.832	5.664	5.490	0.658	-0.174
chrysene	10, 11	-2.60	-7.857	5.253	5.664	5.730	0.477	0.066
hexachlorobenzene	8, 9, 11, 14	-1.86	-7.685	5.829	5.700	5.665	-0.164	-0.035
perylene	10	-2.52	-8.798	6.281	6.124	5.460	-0.821	-0.664
benzo[<i>a</i>]pyrene	11	-1.60	-8.699	7.099	6.124	6.205	-0.894	0.081

Table 1 (Continued)

chemical	ref ^b	log S_o^a	log S_w^a	log SR	log $P(\text{calcd})$	log K_{ow}	difference	
							from log SR	from log $P(\text{calcd})$
biphenyl	7, 10	-0.13	-4.139	4.009	4.030	3.905	-0.104	-0.125
2,3,4,5-tetrachlorobiphenyl	9	-0.85	-7.261	6.411	6.272	6.242	-0.169	-0.030
2,2',5,5'-tetrachlorobiphenyl	9	-0.63	-6.443	5.813	6.382	5.195	-0.618	-1.187
<i>p,p'</i> -DDT	8, 9, 11, 13, 14	-0.98	-7.512	6.535	6.613	6.083	-0.452	-0.530
coronene	8, 10	-2.37	-8.829	6.463	7.044	6.050	-0.413	-0.994
dicachlorobiphenyl	9	-2.77	-10.684	7.914	9.200	8.257	0.343	-0.943
av absolute error ^c :							0.299	0.400

^a Molar solubility. ^b References for octanol solubility. ^c In log unit. ^d Determined in this study.

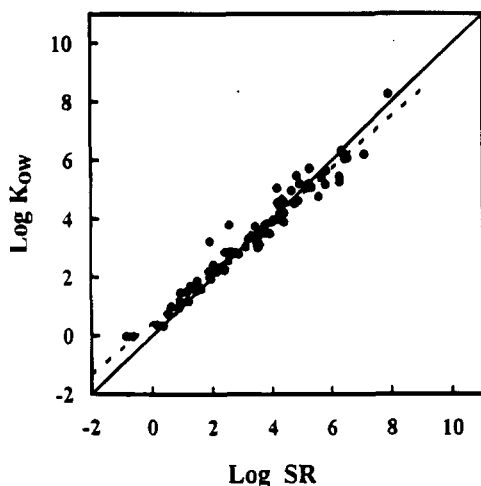


Figure 1. Relationship between the partition coefficient and solubility ratio. Key: (---) regression line described by eq 3, (—) theoretical line.

shows that the solubility ratio gives good estimates of the partition coefficient for the solutes used in this study.

The largest errors are observed for three chlorinated phenols: 2,4-dichlorophenol, 2,4,6-trichlorophenol, and pentachlorophenol. Ma et al. (18) showed that the chlorinated phenols tend to dissociate in neutral aqueous solution because of their low pK_a values. They point out that accurate determination of the solubility and the partition coefficient of these compounds require control of pH.

A plot of the observed log K_{ow} versus log SR for the data from Table 1 is presented in Figure 1. The regression line is described by

$$\log K_{ow} = (0.88 \pm 0.02) \log SR + (0.41 \pm 0.08) \quad (3)$$

$$r^2 = 0.96, \quad S_{yx} = 0.35, \quad n = 84$$

This equation demonstrates a statistically significant relationship between log K_{ow} and log SR. The theoretical basis for a linear relationship between log K_{ow} and log SR has been developed by Yalkowsky et al. (13). They assumed that the effect of octanol-water mutual saturation on the partition coefficient was small and K_{ow} is equal to the solubility ratio. From our data, although the results for the solubility ratios are in good agreement with the values for K_{ow} , the slope of the regression is lower than the theoretical (or perfect fit) value of unity and the intercept has a positive value of 0.4. By examining the data from Figure 1, this deviation seems mainly caused by the relatively polar compounds with low K_{ow} and high water solubility. This may suggest that, in K_{ow} measurements, the water dissolved in the octanol phase could result in a higher solubility of these polar solutes in the water-saturated octanol phase than that in "dry" octanol. On the

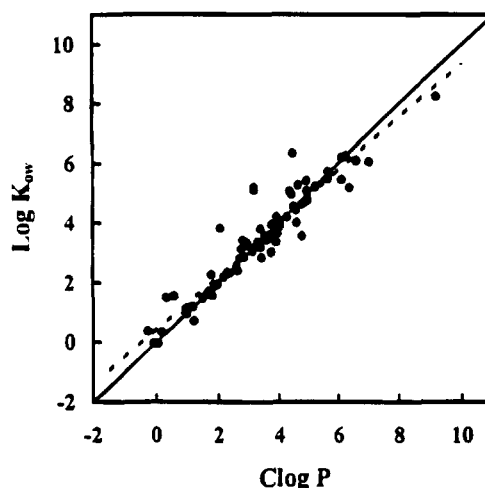


Figure 2. Relationship between the partition coefficient and log $P(\text{calcd})$. Key: (---) regression line described by eq 4, (—) theoretical line.

other hand, data for compounds with log K_{ow} higher than 5 show some scatter in Figure 1 due probably to the experimental difficulties in both water solubility and K_{ow} determinations. The slightly systematic difference between log SR and log K_{ow} suggests that the effects of mutual saturation depend upon the polarity of the solutes.

The calculated partition coefficients (log $P(\text{calcd})$) of the solutes studied and the difference from the observed K_{ow} are also listed in Table 1 for comparison. The log $P(\text{calcd})$ values are estimated from computerized calculations based on the group contribution method, described by Hansch and Leo (4). When log $P(\text{calcd})$ is used to estimate the partition coefficient, the average absolute estimation errors are increased to 0.4 log unit. This error is higher than that obtained from the solubility ratio approach discussed above. The relationship between log $P(\text{calcd})$ and log K_{ow} is illustrated in Figure 2. Regression analysis yields

$$\log K_{ow} = (0.89 \pm 0.03) \log P(\text{calcd}) + (0.43 \pm 0.13) \quad (4)$$

$$r^2 = 0.89, \quad S_{yx} = 0.56, \quad n = 84$$

As the results indicate, the partition coefficients of the compounds used in this study are not very well correlated with log $P(\text{calcd})$. The largest deviations are found for endrin and dieldrin. These deviations may be due to the different substitution patterns and proximity effects that occur in the compounds with interacting functional groups (6). Also, like the chlorinated phenols, the values for these compounds are prone to experimental error.

Notice that eq 3 is very similar to eq 4 in terms of the slope and the intercept of the regression equations in estimating the partition coefficients of the compounds studied. Therefore, it is not surprising that log SR and

$\log P(\text{calcd})$ are highly correlated. The result of the regression analysis is given by the following equation:

$$\log \text{SR} = (0.97 \pm 0.04) \log P(\text{calcd}) + (0.13 \pm 0.15) \quad (5)$$

$$r^2 = 0.88, \quad S_{yx} = 0.60, \quad n = 84$$

As can be seen from eq 5, the coefficient of $\log P(\text{calcd})$ (0.97 ± 0.04) and the intercept (0.13 ± 0.15) are close to the theoretical value of 1 and 0, respectively. However, the regression coefficient (r^2) suggests that the solubility ratios of the compounds studied are not perfectly correlated with $\log P(\text{calcd})$. In addition, the average absolute estimation errors are greater than 0.4 log unit. These results therefore, show that the solubility ratio is different from $\log P(\text{calcd})$ for many compounds. Overall, the solubility ratio gives at least as good an estimate as the group contribution methods for estimating the partition coefficient of the compounds used in this study.

In conclusion, the octanol/water solubility ratio can be used as the estimate of the partition coefficient for 82 compounds used in this study. This approach assumes that K_{ow} is equal to the solubility ratio of the solute in octanol and in water. The solubility ratio method has been shown to be simple and easy to use since only the experimental data of octanol and water solubility are required, while the group contribution method requires all the fragmentation or structure parameters of the molecule. However, the latter method can be used for compounds for which the S_o and S_w experimental data are not available. The results of this study are also useful where the solubility of a chemical in octanol is needed but no experimental data are available. Because there are large compilations of the experimental data of water solubility and octanol/water partition coefficient, the solubility in octanol may be obtained from these data by applying eq 1 or 2.

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