Estimating Lipophilicity Using the GB/SA Continuum Solvation Model: A Direct Method for Computing Partition Coefficients

Charles H. Reynolds

Computational Chemistry Group, Rohm and Haas Company, Spring House, Pennsylvania 19477

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The GB/SA continuum solvation model has been used in conjunction with the OPLS force field to estimate solute lipophilicity in a chloroform/water solvent system. A strong correlation is found ($r^2 = 0.92$) between $\Delta G_{aq} - \Delta G_{CHCl_3}$ and experimental chloroform/water log P for a set of 30 simple organic compounds. This correlation can be exploited to compute log P_{cw} or to provide a direct measure of ligand lipophilicity for use in deriving quantitative structure-activity relationships (QSAR). This method is simple and potentially more widely applicable than fragment or molecular property based methods for estimating lipophilicity. In addition, this general approach is likely to become more powerful in the future as new continuum solvation methods become available for aqueous and organic solvents.

INTRODUCTION

Lipophilicity often plays a significant role in determining the biological activity of organic ligands.[1,2] This can be due to hydrophobic interactions between receptor and ligand, transport across a membrane, or other pharmacokinetic considerations. Regardless of the exact mechanism, lipophilicity is commonly a leading term in biological quantitative structure-activity relationships (QSAR). In most cases lipophilicity is measured as the log of the equilibrium constant for partitioning a solute between aqueous and organic phases, log P. Because lipophilicity influences ligand transport and binding, and because of the practical value of log P in developing quantitative models for biological activity, there has been significant interest in methods for computing log P.[3-11]

The most common approach for estimating octanol/water log P (log P_{ow}) is to use either atomic or molecular fragment based group additivity. Specific values for the structural equivalents are determined using regression against a database of compounds with known partition constants. This approach has led to many successful models,[3-7] including CLOGP[8] and ALOGP.[4] The most serious limitations of this approach are reliance on experimental data, the cumbersome nature of defining and maintaining group contributions, and the lack of physical basis for some parameters. These limitations can lead to the frustrating situation where fragment contributions are unavailable for a compound of interest, or where the method suddenly breaks down with little hope of gaining any mechanistic insight into the failure. There have been attempts to derive models for log P which are based on molecular properties rather than structural fragments.[7,9-11] For example, Klopman[7,9] developed a method which includes partial charges computed using MINDO/3.[12] Bodor and co-workers have extended the use of molecular properties to compute log P_{ow} with their BLOGP method.[10] BLOGP applies a nonlinear empirical model based on AM1[13] computed properties such as partial charges, dipole moments, and molecular surface area. This method obviates the need to define molecular fragments and allows computation of log P_{ow} for different conformers of the same molecule. The most significant problems with BLOGP are that it is built on an empirical expression which contains many highly correlated terms and that it includes some terms for which no clear mechanistic justification exists. These factors call the statistical significance of the BLOGP model into question. Recently CoMFA has also been used to derive lipophilicities directly from solute steric and electronic fields.[11] For all their differences, these methods share the problems inherent in empirically derived models and may have limited validity outside their compound training sets.

The most theoretically satisfying method for computing partition constants would be direct simulation of a solute in water and organic solvent.[14-17] Once the free energy of solvation in aqueous and organic media have been determined, it is a simple matter to compute log P. This approach has been demonstrated with some success using molecular dynamics (MD)[14] and Monte Carlo (MC)[15-17] methods. The advantages of all atom simulations are their generality and theoretical rigor. The disadvantage of using all atom MD or MC simulations to compute log P is that both are computationally very demanding and, therefore, impractical for computing the number of partition coefficients needed for a typical QSAR study.

Another direct approach is to compute the free energy change for transferring a solute from aqueous to organic solution using a continuum solvation model, such as the molecular mechanics based GB/SA model[18] or the quantum mechanical SM2 model.[19] These methods are simpler and much more efficient than MD and MC simulations using explicit solvent and show promise for giving reasonable estimates of solution free energies.[20,21] The GB/SA method has also been parameterized to model one organic solvent, chloroform. This means that one can calculate the free energy associated with taking a compound from the gas phase to either water or chloroform. Using a simple thermochemical cycle this provides the free energy change from chloroform to water. The purpose of this paper is to demonstrate that chloroform/water log P coefficients (log P_{cw}) can be reliably estimated by computing this free energy change using the GB/SA solvation model.

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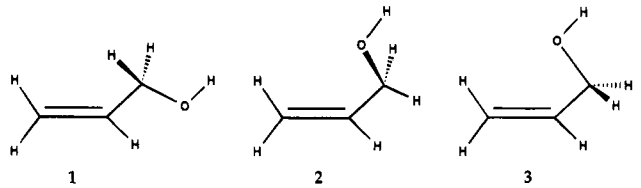
Table 1. Conformational Dependence of Total E and ΔG_{aq} for Allyl Alcohol

compound	total E, kcal/mol	deviation from av	ΔG_{aq}, kcal/mol	deviation from av
1	−6.24	2.56	−5.14	0.09
2	−9.61	−0.80	−5.43	−0.20
3	−10.57	−1.76	−5.13	0.10
av	−8.81		−5.23	

PROCEDURE

All calculations were carried out using the OPLS[22] all atom force field as implemented in MacroModel.[23] Extended nonbond cutoffs of 8 and 20 Å were used for the van der Waals and electrostatic interactions, respectively. The free energies of solution (gas → solution) were determined using GB/SA. The solvation free energy term (ΔG_{sol}) is added to the force field potential energy to obtain a total energy for the molecule in solution. For each compound, the total energy was minimized, and the solvation free energy contribution was extracted. In most cases the molecules were simply minimized starting with a staggered all-anti conformation. In some cases limited bond rotations were examined to assure that the starting conformation was reasonable, but the potential surface was not surveyed in any systematic way. The same conformation was used to compute free energies of solution in water (ΔG_{aq}) and chloroform (ΔG_{CHCl_3}) in order to minimize any conformational effects on the relative solubilities. All compounds with acidic or basic functionality were studied in their neutral form and compared to buffered experiments which purport to measure the neutral log P.

The solvation free energies were used rather than total energies because the solvation term is less sensitive to conformational effects than total energy. This can be illustrated with allyl alcohol in water. Rotation about the single C−C bond leads to three conformers (**1**−**3**). The total energies for these conformers vary from −6.24 to −9.81 kcal/mol, but the aqueous solvation term varies only from −5.13 to −5.43 kcal/mol (Table 1). The observed invariance of ΔG_{sol} with conformation is reasonable for the simple compounds in this study, most of which only contain a single polar group. But this is less likely to hold true for larger multifunctional compounds.[24] Since the conformational space is not being sampled, as would be the case in MD or MC simulations, it seems reasonable to use the less sensitive solvation free energies for comparison rather than the OPLS-GB/SA total energies.



1 2 3

The log P for any water-organic solvent interface is related to the free energies of solution, ΔG_{aq} and ΔG_{org}, by the following relationship

$$\log P_{org\text{-}aq} = M^*\Delta\Delta G; \quad \text{where } M \text{ is a constant} \qquad (1)$$

$$\Delta\Delta G = \Delta G_{aq} - \Delta G_{org} \qquad (2)$$

Therefore, if the OPLS GB/SA calculated solvation energies are sufficiently reproducible (a systematic error is acceptable), it should be possible to relate the difference in solvation energies $\Delta\Delta G$ directly to log P. If the solvation free energies are quantitative, not just correlated, then the constant in eq 1 should be $1/2.30RT$ (R = gas constant; T = 298 K).

RESULTS AND DISCUSSION

The OPLS GB/SA computed $\Delta\Delta G$ values for 30 simple organic compounds are reported in Table 2 along with experimental[1] chloroform/water partition coefficients. The theoretically computed chloroform/water log P (M in eq 1 = $1/2.30RT$) is reported in Table 2 and plotted against experimental log P_{cw} in Figure 1. The correlation is excellent with $r^2 = 0.92$ for 30 compounds, but instead of a theoretical slope of 1.0 the slope for this correlation is 0.732. This indicates a systematic error between predicted and observed log P_{cw}. The regression equation[25] is given in eq 3.

$$\log P_{cw} = 0.0550 + 0.732^*(\Delta\Delta G/2.30RT) \qquad (3)$$

The deviation from unit slope in Figure 1 is due to GB/SA overestimating the hydrophilicity of low log P_{cw} compounds and the lipophilicity of high log P_{cw} compounds. It might not be surprising that errors are larger for more strongly lipophilic or hydrophilic compounds since the energy differences are larger. These compounds also exert a much greater influence on the slope in Figure 1 relative to compounds with log P_{cw} near zero. One advantage of using OPLS-GB/SA to compute log P over less theoretical approaches is that it is possible to delve deeper into the reasons for errors in computed log P. For example, the computed amide log P_{cw} values are much too negative and make a large contribution to the deviation from unit slope found in Figure 1. Negative errors in log P can arise either from overestimating the solubility of these compounds in water or underestimating their solubility in chloroform. In this case it is quite possible that the water solubilities are too negative given that the GB/SA solvation free energy for acetamide is −0.8 kcal/mol more negative than experiment. This is enough to cut the error in the computed log P_{cw} for acetamide in half.

Similarly, at the other extreme benzene and substituted benzenes exhibit computed log P_{cw} values which are systematically too positive relative to experiment. Comparison of GB/SA and experimental free energies of aqueous solvation show that the error for benzene is either −0.1 or +1.8 kcal/mol depending on which of two independent experimental values[18] is chosen. Comparison of the computed and experimental log P_{cw} suggests that the latter value may be correct.

Since the primary practical use of this approach is to derive a relative measure of lipophilicity for QSAR studies, it makes sense to examine the direct correlation between $\Delta\Delta G$ and experimental log P_{cw}. The $\Delta\Delta G$ values are plotted against log P_{cw} in Figure 2. The regression equation for this correlation (eq 4) has an intercept near zero and r^2 of 0.92, consistent with eqs 1 and 3.

$$\log P_{cw} = 0.0550 + 0.537^*\Delta\Delta G \qquad (4)$$

This correlation holds over a span of seven log units. The errors between predicted (using the regression model) and observed log P_{cw} are centered around zero and have a

Table 2. Log P_{cw} and Computed $\Delta\Delta G$ of Solvation (kcal/mol) for Some Simple Organic Compounds

compound	ΔG_{aq}	ΔG_{CHCl_3}	$\Delta\Delta G$	log P_{theor}[a]	log P_{obs}[b]	error$_{theor}$	log P_{reg}[c]	error$_{reg}$
benzene	−0.64	−6.51	5.87	4.30	2.80	1.50	3.20	0.40
methanol	−5.74	−3.75	−1.99	−1.46	−1.31	−0.15	−1.01	0.30
methylamine	−4.24	−3.48	−0.76	−0.56	−0.73	0.17	−0.35	0.38
acetone	−2.24	−4.41	2.17	1.59	0.72	0.87	1.22	0.50
pentanol	−4.24	−5.75	1.51	1.11	1.05	0.06	0.87	−0.18
diethylamine	−1.31	−5.11	3.80	2.79	0.85	1.94	2.09	1.24
acetic acid	−5.88	−3.93	−1.95	−1.43	−1.52	0.09	−0.99	0.53
hexanol	−4.03	−6.26	2.23	1.64	1.69	−0.05	1.25	−0.44
ethylbenzene	0.55	−6.96	7.51	5.51	3.68	1.83	4.08	0.40
toluene	0.30	−6.51	6.81	4.99	3.41	1.58	3.71	0.30
acetophenone	−2.60	−7.37	4.77	3.50	2.79	0.71	2.61	−0.18
p-toluic acid	−5.14	−7.03	1.89	1.38	1.81	−0.42	1.07	−0.74
1-napthol	−5.64	−8.79	3.15	2.31	1.82	0.49	1.75	−0.07
ethanol	−4.95	−4.26	−0.69	−0.50	−0.85	0.34	−0.32	0.53
butyric acid	−5.04	−4.91	−0.13	−0.10	−0.27	0.18	−0.01	0.26
iso-butyl alcohol	−3.80	−5.13	1.33	0.98	0.34	0.64	0.77	0.43
m-chlorophenol	−5.83	−7.06	1.23	0.90	1.02	−0.12	0.71	−0.31
pyridine	−4.11	−6.91	2.80	2.05	1.43	0.62	1.56	0.13
hexanoic acid	−4.60	−5.92	1.32	0.97	0.95	0.02	0.76	−0.19
benzonitrile	−3.09	−7.25	4.16	3.05	2.71	0.34	2.29	−0.42
chlorobenzene	−0.70	−6.66	5.96	4.37	3.46	0.91	3.25	−0.21
bromobenzene	−0.86	−6.70	5.84	4.28	3.61	0.67	3.19	−0.42
phenol	−5.65	−7.00	1.35	0.99	0.30	0.69	0.78	0.48
propionamide	−9.75	−6.01	−3.74	−2.74	−1.40	−1.34	−1.95	−0.55
acetamide	−10.46	−5.53	−4.93	−3.61	−2.00	−1.62	−2.59	−0.59
p-hexylpyridine	−1.92	−9.26	7.34	5.38	5.00	0.38	3.99	−1.01
allyl alcohol	−5.43	−5.54	0.11	0.08	−0.51	0.59	0.11	0.62
p-bromophenol	−6.12	−7.23	1.11	0.81	1.07	−0.26	0.65	−0.42
p-chlorophenol	−5.97	−7.17	1.20	0.88	0.97	−0.09	0.70	−0.27
acetaldehyde	−4.34	−3.50	−0.84	−0.62	0.11	−0.73	−0.40	−0.51

[a] Theoretical calculation of log P_{cw} using eq 1 and $M = 1/2.30RT$. [b] Experimental log P_{cw} values were taken from a compilation by Hansch and Leo;[1] where more than one comparable value is given the mean is reported in Table 2. [c] Estimated from regression equation for $\Delta\Delta G$.

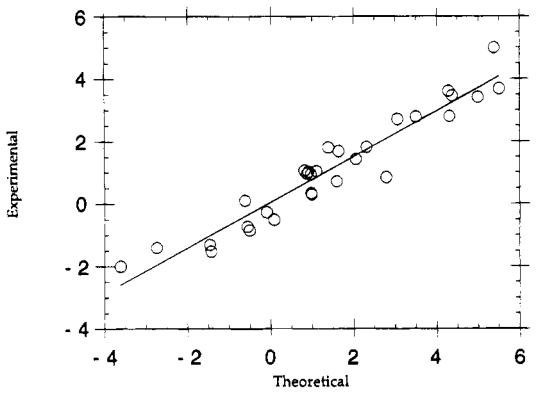


Figure 1. Comparison of theoretically computed log P_{cw} and experimental[1] log P_{cw}.

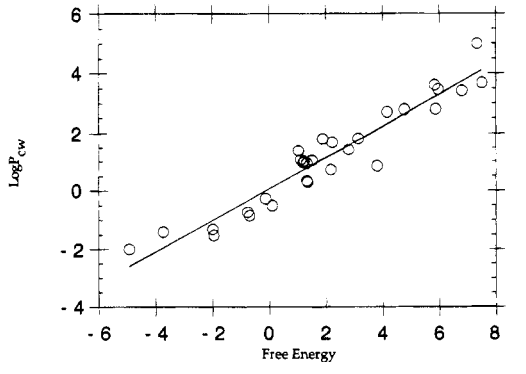


Figure 2. Regression of $\Delta\Delta G$ against experimental[1] log P_{cw}.

standard deviation of 0.50. This is good agreement and is consistent with the errors in GB/SA aqueous solvation energies reported for 20 neutral compounds by Still et al.[18] The largest error in the regression model is for diethylamine. Examination of the computed solvation free energies shows that the aqueous solubility of diethylamine is predicted to be more positive than one might expect based on other amines ($\Delta G_{aq} = -1.31$ kcal/mol). However, the AM1-SM2 calculated[26] ΔG_{aq} for diethylamine is only 0.65 kcal/mol more negative at −1.96 kcal/mol. The chloroform solvation energy offers another potential source of error, and the large error for log P_{cw} may simply be due to addition of smaller errors. Finally, it is conceivable that the experimental log P_{cw} is low because of the strong basicity of diethylamine. Any significant concentration of protonated amine would make the observed log P_{cw} lower.

This thermodynamic approach for estimating lipophilicity has significant advantages. It is relatively general since it can be applied to any molecule for which OPLS parameters are available.[27] Indeed given the dominant role of atomic charges in solvation, it can most likely be applied to any compound where high quality atomic charges (e.g., HF/6-31G* ESP) are available.[28] Thus in contrast to fragment and molecular property based approaches it is possible to estimate log P for classes of compounds where no previous experimental log P data is available. The GB/SA solvation energy approach is a significant simplification over schemes such as BLOGP or earlier property based methods which rely on complicated regression equations. It may also be more general since it does not depend on a series of strictly empirically derived parameters, some of which are not clearly related to solubility. The accuracy of the procedure outlined in this paper is ultimately limited by the accuracy of the underlying solvation model. Since GB/SA can be tested against experimental or theoretical free energies of solvation,

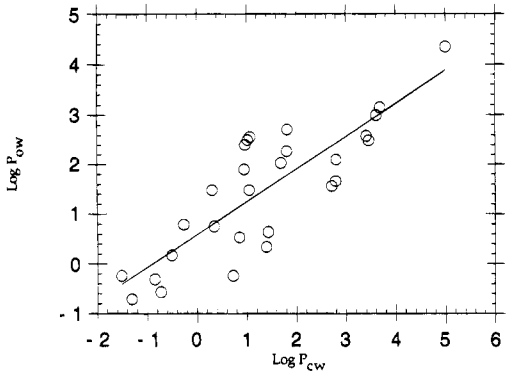


Figure 3. Plot of experimental[1] log P_{cw} and log P_{ow}. Acetamide, propionamide, and acetaldehyde are not included in this plot.

it should often be possible to obtain an independent estimate of the reliability of this approach for a given class of chemistry. Finally, computing free energy differences using GB/SA provides mechanistic insight into log P which is unavailable from fragment based methods. This can be helpful for understanding the structural, electronic, or other features of a molecule which give rise to a specific log P.

Of course, it is impossible to compare the GB/SA $\Delta\Delta G$ directly with CLOGP or BLOGP because these methods compute ocatanol/water partition coefficients (log P_{ow}), not chloroform/water. Indeed, most work on organic/water partitioning has centered on the octanol/water system. This is primarily due to evidence[1,2] that octanol/water is a particularly good solvent system for modeling lipid bilayers. It is also due to other practical considerations such as the favorable solubility of most organic compounds in octanol and the ease with which it can be handled in the lab. These factors have made log P_{ow} the standard for measuring solute lipophilicity. Nevertheless, it has been shown that for most solutes organic/water partition coefficients tend to show parallel behavior.[2,29] The most significant deviations in log P for octanol and solvents which lack a polar group, such as chloroform, are typically found for solutes which have good hydrogen bond acceptors or donors.

Experimental log P_{ow} and log P_{cw} values[1] are plotted against each other for the 30 compounds in Table 2 (Figure 3). The trends are the same, i.e., the compounds which are more soluble in chloroform are also more soluble in octanol, but there is significant scatter in the plot. Thus, although log P_{ow} and log P_{cw} are correlated, the correlation is weaker than one might hope ($r^2 = 0.70$). This means in broad terms that the chloroform/water log P is a reasonable indicator of lipophilicity, but use of log P_{cw} may lead to a different QSAR equation than log P_{ow}. It also means that the computed $\Delta\Delta G$ for chloroform/water is a relatively imprecise predictor of log P_{ow}. Consistent with earlier comparisons between octanol and chloroform based partition coefficients, some of the largest deviations in Figure 3 are found for fatty alcohols and acids such as *p*-chlorophenol and hexanoic acid.

The method outlined in this paper provides a simple alternative for estimating the lipophilicity of organic solutes for use in QSAR studies. The calculated chloroform/water $\Delta\Delta G$ can be used to fill gaps in the log P_{cw} scale or used directly as a measure of ligand lipophilicity. Since $\Delta\Delta G$ correlates well with log P_{cw}, there is no need to convert these numbers to a log P scale. The advantage of using $\Delta\Delta G$ directly is that one can quickly compute a relative lipophilicity for any compound which can be modeled using OPLS. Using the free energy difference negates the need for regression over large numbers of dissimilar compounds to generate a global equation for log P or to derive more accurate equations for specific homologous series. The accuracy of $\Delta\Delta G$ in determining relative lipophilicity depends on the performance of OPLS and GB/SA for any given series of compounds. For a series of related analogs where reliable OPLS charges are available, accuracy is likely to be quite good.

Table 3. Comparison of QSAR using log P_{ow} and $\Delta\Delta G$

compd	ΔG_{aq}	ΔG_{CHCl_3}	$\Delta\Delta G$	log P_{ow}[a]	pC[a]
pentanol	−4.23	−5.75	1.51	1.40	0.53
heptanol	−3.82	−6.78	2.96	2.53	1.59
octanol	−3.61	−7.29	3.68	3.03	2.18
nonanol	−3.40	−7.81	4.41	3.53	2.76
decanol	−3.20	−8.32	5.12	4.03	3.09

[a] Taken from Hansch and Dunn.[30]

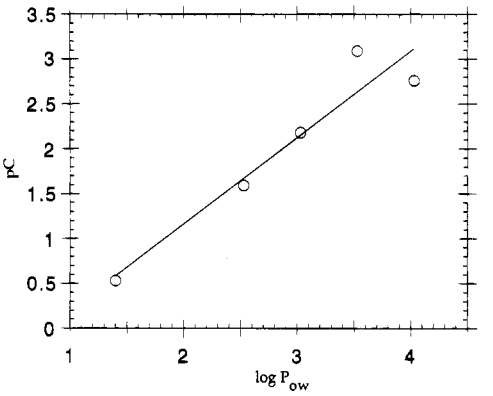


Figure 4. Correlation of alcohol partitioning into red blood cells[30] with log P_{ow}.

In order to illustrate use of the computed free energy changes as a measure of lipophilicity, a simple QSAR equation was computed for penetration of ghost red blood cells by five alcohols.[30] In each case diffusion into the cell membrane was measured by determining the alcohol concentration of the aqueous phase (C). This is a classical example where log P_{ow} has been shown to give excellent results. The experimental pC (−log C) values[30] are given in Table 3 along with log P_{ow} and computed $\Delta\Delta G$. Regression of log P_{ow} against pC gives a structure−activity equation (eq 5) with $r^2 = 0.92$ (Figure 4).

$$pC = -0.765 + 0.962*\log P_{ow} \quad (5)$$

A similar equation can be derived using the OPLS GB/SA computed free energy differences for these five compounds. This equation (eq 6) has a smaller slope, as we would expect given eq 3, but the correlation is equally good with $r^2 = 0.91$ (Figure 5).

$$pC = -0.439 + 0.698*\Delta\Delta G \quad (6)$$

This general approach is likely to become even more powerful in the future as new continuum solvation models become available for organic solvents. In particular, new molecular orbital based solvation models for organic media such as chloroform or octanol could dramatically improve the state-of-the-art for estimating log P. For example, an organic SM2 model[31] would extend this direct procedure for

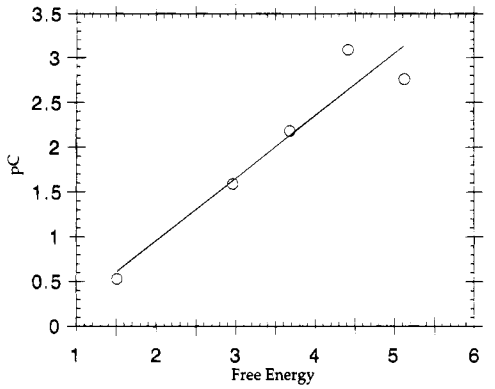


Figure 5. Correlation of alcohol partitioning into red blood cells[30] with computed $\Delta\Delta G$.

estimating lipophilicities to almost any organic ligand. Two AM1 calculations are all that would be required. This avoids the need for specialized group equivalents and would provide a simple and general lipophilicity estimate for use in conventional and 3-D QSAR. Given the success of methods like GB/SA and AM1-SM2, it seems likely that additional continuum models for organic solvents will be forthcoming in the near future.

CONCLUSION

The difference in OPLS-GB/SA computed solvation free energies for a solute in chloroform and water correlates very well with experimental chloroform/water partition coefficients. This correlation can be exploited to estimate experimental chloroform/water log *P* values, or the GB/SA $\Delta\Delta G$ can be used directly as a measure of lipophilicity in QSAR studies. In addition this work shows that future continuum models for organic solvents may provide a powerful new approach for estimating lipophilicity that is less empirical and, therefore, potentially more generally applicable than fragment or molecular property based methods.

REFERENCES AND NOTES

(1) Hansch, C.; Leo, A. J. Substituent Constants for Correlation Analysis in Chemistry and Biology; Wiley: New York, 1979.
(2) Martin, Y. C. Quantitative Drug Design: A Critical Introduction, Marcel Dekker, Inc.: 1978.
(3) Leo, A. Calculating Log P_{oct} from Structure. *Chem. Rev.* **1993**, *30*, 1283−1306.
(4) Ghose, A. K.; Crippen, G. M. Atomic Physicochemical Parameters for Three-Dimensional Structure-Directed Quantitative Structure-Activity Relationships I. Partition Coefficients as a Measure of Hydrophobicity. *J. Comput. Chem.* **1986**, *7*, 565−577.
(5) Klopman, G.; Li, J.-Y.; Wang, S.; Dimayuga, M. Computer Automated log *P* Calculations Based on an Extended Group Contribution Approach. *J. Chem. Inf. Comput. Sci.* **1994**, *34*, 752−781 and references therein.
(6) Rekker, R. F.; Mannhold, R. Calculation of Drug Lipophilicity; VCH: New York, 1992.
(7) Klopman, G.; Iroff, L. Calculation of Partition Coefficients by the Charge Density Method. *J. Comput. Chem.* **1981**, *2*, 157−160.
(8) Leo, A. J. CLOGP, Daylight Chemical Information Systems.
(9) Klopman, G.; Namboodiri, K.; Schochet, M. Simple Method of Computing the Partition Coefficient, *J. Comput. Chem.* **1985**, *6*, 28−38.
(10) Bodor, N.; Gabanyi, Z.; Wong, C.-K. A New Method for the Estimation of Partition Coefficient. *J. Am. Chem. Soc.* **1989**, *111*, 3783−3786.
(11) Waller, C. L. A Three-Dimensional Technique for the Calculation of Octanol-Water Partition Coefficients. *Quant. Struct.-Act. Relat.* **1994**, *13*, 172−176.
(12) Bingham, R. C.; Dewar, M. J. S.; Lo, D. H. Ground States of Molecules. XXV. MINDO/3. An Improved Version of the MINDO Semiempirical SCF-MO Method. *J. Am. Chem. Soc.* **1975**, *97*, 1285−1293.
(13) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. AM1: A New General Purpose Quantum Mechanical Molecular Model. *J. Am. Chem. Soc.* **1985**, *107*, 3902−3909.
(14) Essex, J. W.; Reynolds, C. A.; Richards, W. G. Theoretical Determination of Partition Coefficients. *J. Am. Chem. Soc.* **1992**, *114*, 3634−3639.
(15) Dunn, W. J., III; Nagy, P. I. Relative Log P and Solution Structure for Small Organic Solutes in the Chloroform/Water System Using Monte Carlo Methods. *J. Comput. Chem.* **1992**, *13*, 468−477.
(16) Dunn, W. J., III; Nagy, P. I.; Collantes, E. R. A Computer-Assisted Method for Estimation of the Partition Coefficient. Monte Carlo Simulations of the Chloroform/Water log *P* for Methylamine, Methanol, and Acetonitrile. *J. Am. Chem. Soc.* **1991**, *113*, 7898−7902.
(17) Jorgensen, W. L.; Briggs, J. M.; Contreras, M. L. Relative Partition Coefficients for Organic Solutes from Fluid Simulations. *J. Phys. Chem.* **1990**, *94*, 1683−1686.
(18) Still, W. C.; Tempczyk, A.; Hawley, R. C.; Hendrickson, T. Semianalytical Treatment of Solvation for Molecular Mechanics and Dynamics. *J. Am. Chem. Soc.* **1990**, *112*, 6127−6129.
(19) Cramer, C. J.; Truhlar, D. G. AM1-SM2 and PM3-SM3 Parameterized SCF Solvation Models for Free Energies in Aqueous Solution. *J. Comput.-Aided Mol. Design* **1992**, *6*, 629−666 and references therein.
(20) Brown, F. K.; Charifson, P.; Unwalla, R. The Role of Water in Drug Design. 205th American Chemical Society National Meeting, March 28−April 2, 1993.
(21) Jorgensen, W. L.; Nguyen, T. B. Monte Carlo Simulations of the Hydration of Substituted Benzenes with OPLS Potential Functions. *J. Comput. Chem.* **1993**, *14*, 195−205.
(22) Jorgensen, W. L.; Tirado-Rives, J. The OPLS Potential Functions for Proteins. Energy Minimizations for Crystals of Cyclic Peptides and Crambin. *J. Am. Chem. Soc.* **1988**, *110*, 1657−1666.
(23) MacroModel version 4.5, Copyright Columbia University.
(24) Richards, N. G.; Williams, P. B.; Tute, M. S. Empirical Methods for Computing Molecular Partition Coefficients: II. Inclusion of Conformational Flexibility within Fragment-Based Approaches. *Int. J. Quantum Chem.* **1992**, *44*, 219−233.
(25) KaleidaGraph, Synergy Software, 2457 Perkiomen Ave., Reading, PA 19606.
(26) AMPAC 5.0, Copyright 1994 Semichem, 7128 Summit, Shawnee, KS 66216.
(27) Given the similarity of OPLS and AMBER force fields, comparable results would probably be obtained using AMBER-GB/SA.
(28) McDonald, D. Q., personal communication; MacroModel 5.0 Technical Manual.
(29) See Chapter 4 in ref 2.
(30) Hansch, C.; Dunn, W. J., III. Linear Relationships Between Lipophilic Character and Biological Activity of Drugs. *J. Pharm. Sci.*, **1972**, *61*, 1−19.
(31) Giesen, D. J.; Storer, J. W.; Cramer, C. J.; Truhlar, D. G. General Semiempirical Quantum Mechanical Solvation Model for Nonpolar Solvation Free Energies. *n*-Hexadecane. *J. Am. Chem. Soc.* **1995**, *117*, 1057−1068.

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