Universal Organic Solvent−Water Partition Coefficient Model

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A method that permits a semiquantitative estimate of the partitioning of any solute between any two media is presented. As an example, the organic solvent−water partition coefficients *P* are calculated. Program GSCAP is written as a version of Pascal's SCAP program. The only needed parameters are the dielectric constant and molecular volume of the organic solvent. The log *P* results are compared with the Pomona database. The average absolute deviation is 1.48 log units and the standard deviation is 1.66 log units.

1. INTRODUCTION

Free energy is the fundamental thermodynamic variable controlling equilibria, and free energy of solvation is the free energy difference between a molecule in the gas phase and in a solvent.[1] The free-energy of solvation of a solute *X* in solvent *Y* may be used to predict its vapor pressure over a dilute solution (Henry's law), and the free energy of solvation of *X* in *X* may be used to predict the vapor pressure of a pure liquid or of the solvent of a dilute solution (Raoult's law).[2]

Free energy of solvation may be considered as a special case of free energy of transfer in which one of the transfer media is an inert gas, usually called *air*, and the other is a liquid. By combining the free energy of transfer of solute *X* from air into solvent *Y* with the free energy of transfer of *X* from air into solvent *Z*, one can obtain the free energy of transfer of *X* from *Y* to *Z*, which allows one to calculate partition coefficients, i.e., the equilibrium distribution of a solute between immiscible liquid media, which are of critical importance in pharmaceutical[3] and environmental[4] applications or for extractions. Comparing the free energies of solvation of conformational or tautomeric isomers X_I and X_{II} of molecule *X* in various solvents allows one to predict solvent effects on conformational or tautomeric equilibria.[5]

Motivated by its widespread use as a bioavailability parameter in the drug industry, the partition coefficient for 1-octanol and water has received by far the most attention,[6] although Abraham, for example, has developed much broader relationships applicable to almost any solvent.

While much work has been done by many groups in developing models for water, as reviewed elsewhere,[7−9] much less effort has been devoted to developing models for nonaqueous solvents.[10−16] However, a large body of data is available for 1-octanol[17] and *n*-hexadecane.[18,19] A significant amount is also available for other alkanes, cyclohexane, benzene, toluene, xylenes, diethyl ether, chloroform, carbon tetrachloride, and chlorobenzene.[20] If one takes data from *all* organic solvents, a very large number of data are available. In this article, it is shown that it is possible to analyze these data as a whole and develop a model that encompasses a large number of solvents in a single framework.

Solvation energies for nonaqueous solvents are important for modeling a variety of phenomena in organic chemistry. In addition, in conjunction with an aqueous solvation model,[21] they can be used to predict partition coefficients of solutes between an organic phase and water,[22] and such partition coefficients are often used to provide some indication of how likely it is for the solute to penetrate a lipid bilayer, skin, brain, central nervous system, or other biophase or to bind to a nonpolar site in or on a protein.[23]

The present model is an extension of the solvent-dependent conformational analysis (SCAP) 1-octanol−water model[24,25] to organic solvents, and it uses extended versions of the functional forms developed in that work.[26] The method has been previously applied to the calculation of the partition coefficient of the stationary−mobile phase in size-exclusion chromatography.[27] In this work, the solubility in water and in a set of organic liquids and the organic solvent−water partition coefficients for a set of reference molecules have been calculated. The reference molecules are acetanilide derivatives and barbiturates. In addition, the effect of structural elements in the partition coefficients of a group of local anesthetics has been studied.

Section 2 presents the improvements in the solvation model from ref 26. In section 3, the results and their discussion are presented. For local anaesthetics, linear and nonlinear correlation models have been fitted. Section 4 summarizes our conclusions.

2. PARTITIONING OF ANY SOLUTE BETWEEN ANY TWO MEDIA

The basis for building a method that permits a semiquantitative estimate of the partitioning of any solute between any two media has been reported elsewhere.[26] A picture of the geometric descriptors of the solvation sphere is given in ref 25. The method is based on the model of Hopfinger.[28,29] The main improvement introduced with respect to ref 26 is the change in the standard Gibbs free energy parameter Δg_s° calculated using the generalized Born equation,[30]

$$\Delta g_s^\circ = \Delta g_o^\circ \frac{1 - 1/\epsilon_s}{1 - 1/\epsilon_o} = \Delta g_o^\circ \frac{\epsilon_o(\epsilon_s - 1)}{\epsilon_s(\epsilon_o - 1)} \qquad (1)$$

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Table 1. Free Energy of Solvation and Partition Coefficient Results for Reference Molecules

molecule	organic solvent	GSCAP	expt[a]
1,2-ethanediol	1-octanol	−1.22	−1.36
	hexadecane	−2.75	−4.76
	chloroform	−1.09	−2.43
p-dichlorobenzene	1-octanol	2.51	3.44
	hexadecane	0.44	3.43
	chloroform	2.41	3.89
thioanisole	1-octanol	4.22	2.74
	chloroform	4.17	2.38
	cyclohexane	2.55	2.15
methanol	1-octanol	−0.01	−0.77
	chloroform	0.34	−1.31
	cyclohexane	−0.52	−2.80
ethylenediamine	1-octanol	0.40	−2.04
methylamine	1-octanol	0.95	−0.57
	chloroform	1.21	−1.02
benzene	1-octanol	2.20	2.13
	chloroform	2.29	2.72
	cyclohexane	1.15	2.47
1-naphthol	1-octanol	2.20	2.84
	chloroform	2.11	1.82
	cyclohexane	0.28	0.54
caffeine	1-octanol	3.08	−0.07
	chloroform	2.73	1.30
anthracene	1-octanol	5.18	4.45
1-methylnaphthalene	1-octanol	5.53	3.87
acetanilide	1-octanol	2.07	1.16
	chloroform	2.01	0.80
	cyclohexane	0.08	−1.51
phenacetin	1-octanol	4.97	1.58
barbituric acid	1-octanol	−4.00	−1.47
	chloroform	−4.75	−2.10
5-allyl-5-phenylbarbituric acid	1-octanol	0.15	1.69
AAD[b]		1.48	
−SD[c]		1.66	

[a] Experiment data taken from ref 41. [b] AAD, average absolute deviation. [c] SD, standard deviation.

where the subscripts o and s stand for 1-octanol and for a general organic solvent, respectively, and ϵ_o and ϵ_s are the relative dielectric constants. Previous results for benzene suggested a variation of only 80% of that obtained by eq 1.[26] However, the calculation of more molecules has shown that it is a better rule to expand this variation up to 100%.

The only needed parameters are the Cartesian components of the solute molecule and the relative dielectric constant ϵ and molecular volume V_s of the organic solvent. The V_s values have been calculated with a new version of program TOPO,[31,32] which includes an actualized database of van der Waals radii.[33] Therefore, the V_s values are slightly different from those reported in ref 26. In the present work, the following values have been used: $\epsilon = 10.34$ (1-octanol), 2.023 (cyclohexane), 4.806 (chloroform), and 2.050 (hexadecane); $V_s = 155.0$ (1-octanol), 93.4 (cyclohexane), 72.1 (chloroform), and 258.6 Å^3 (hexadecane).

The 1-octanol−water partition coefficients log *P* have been compared with values calculated with a method developed by Kantola et al.[34] The method uses atomic charges,[35,36] which have been computed with program POLAR.[37−39] To compare our results with solvents other than 1-octanol, the method proposed by Leo et al.[40] has been used.

3. CALCULATION RESULTS AND DISCUSSION

The partition coefficients calculated for 15 reference molecules and 4 organic solvents included in the Pomona Medicinal Chemistry Database[41] have been reported in Table 1. Experimental data are available for 32 values of log *P*. The average absolute deviation (AAD) is 1.48 log units, and the standard deviation (SD) is 1.66 log units. The GSCAP results show that the molecules with positive log *P* values are treated with more accuracy than those with negative log *P* results are. In particular, AAD for the molecules with negative log *P* values is 1.87 log units and for those with positive log *P* results is 1.21 log units.

The GSCAP results in Table 1 are overestimated 0.55 log unit on average. However, this difference is greater for the molecules with negative log *P* values (1.07 log units) than for those with positive log *P* results (0.20 log unit).

Due to the lack of available experimental data of log *P* for most organic solvents other than 1-octanol, in the rest of the work the calculated results have been compared with those calculated with the method of Leo et al.[40]

The solvation descriptors for another 10 reference molecules are reported in Table 2. The three organic solvent−water partition coefficients *P* show a variation of 7 orders of magnitude. The comparison with calculations carried out with program CDHI shows that GSCAP gives good log P_o results. Typical errors in absolute value are 0.8 log unit. The cyclohexane−water (ch) and chloroform−water (cf) partition coefficients show the same trend as P_o. When comparing the three organic solvents, the log *P* values are, in general, greater for polar 1-octanol and smaller for apolar cyclohex-

Table 2. Free Energy of Solvation and Partition Coefficient Results for Reference Molecules

molecule	$\Delta G_{solv,w}$[a]	$\Delta G_{solv,o}$[b]	$\Delta G_{solv,ch}$[c]	$\Delta G_{solv,cf}$[d]	log P_o (GSCAP)[e]	log P_o (CDHI)[f]	log P_{ch} (GSCAP)[g]	log P_{ch}[h]	log P_{cf} (GSCAP)[i]	log P_{cf}[h]
1,2-ethanediol	−24.63	−17.70	−11.08	−18.40	−1.22	−2.40	−2.38	−2.03	−1.09	−1.38
methanol	−11.02	−10.97	−8.08	−12.97	−0.01	−1.05	−0.52	−0.74	0.34	0.16
ethylenediamine	−14.63	−16.89	−11.58	−17.17	0.40	0.89	−0.54	−0.31	0.44	0.68
methylamine	−5.12	−10.55	−7.65	−12.04	0.95	0.78	0.44	0.28	1.21	1.39
benzene	−6.88	−19.38	−13.41	−19.92	2.20	2.29	1.15	1.60	2.29	2.97
1-naphthol	−21.08	−33.63	−22.69	−33.08	2.20	2.41	0.28	−0.35	2.11	1.14
caffeine	−31.39	−48.94	−32.53	−46.92	3.08	4.49	0.20	0.24	2.73	2.13
thioanisole	−0.05	−24.09	−14.59	−23.81	4.22	3.44	2.55	3.75	4.17	5.56
anthracene	−11.84	−41.35	−27.65	−39.84	5.18	4.48	2.78	1.66	4.92	4.49
1-methylnaphthalene	−4.48	−35.93	−24.31	−31.10	5.53	3.81	3.48	1.89	5.46	4.88

[a] Gibbs free energy of solvation in water (kJ·mol^{-1}). [b] Gibbs free energy of solvation in 1-octanol (kJ·mol^{-1}). [c] Gibbs free energy of solvation in cyclohexane (kJ·mol^{-1}). [d] Gibbs free energy of solvation in chloroform (kJ·mol^{-1}). [e] P_o is the 1-octanol−water partition coefficient. [f] CDHI, calculations carried out with a method developed by Kantola et al.[34] [g] P_{ch} is the cyclohexane−water partition coefficient. [h] Calculations carried out with a method developed by Leo et al.[40] [i] P_{cf} is the chloroform−water partition coefficient.

Table 3. Free Energy of Solvation and Partition Coefficient Results for Acetanilide Derivatives

molecule	$\Delta G_{solv,w}$[a]	$\Delta G_{solv,o}$[b]	$\Delta G_{solv,ch}$[c]	$\Delta G_{solv,cf}$[d]	log P_o (GSCAP)[e]	log P_o (CDHI)[f]	log P_{ch} (GSCAP)[g]	log P_{ch}[h]	log P_{cf} (GSCAP)[i]	log P_{cf}[h]
4′-aminoacetanilide	−31.04	−38.10	−25.63	−37.22	1.24	2.93	−0.95	−1.01	1.09	0.05
acetanilide	−23.31	−35.09	−23.77	−34.74	2.07	3.72	0.08	−0.45	2.01	0.99
4′-nitroacetanilide	−64.63	−76.76	−49.87	−69.70	2.13	1.89	−2.59	−0.40	0.89	1.06
4′-iodoacetanilide	−19.34	−33.83	−22.64	−32.75	2.54	3.07	0.58	−0.12	2.35	1.52
4′-bromoacetanilide	−19.34	−33.87	−22.67	−32.74	2.55	3.03	0.59	−0.12	2.35	1.53
diuron	−22.46	−48.80	−33.14	−48.69	4.63	3.64	1.88	1.28	4.61	3.87
phenacetin	−17.24	−45.52	−30.87	−45.39	4.97	3.45	2.40	1.51	4.95	4.25

[a] Gibbs free energy of solvation in water (kJ·mol^{-1}). [b] Gibbs free energy of solvation in 1-octanol (kJ·mol^{-1}). [c] Gibbs free energy of solvation in cyclohexane (kJ·mol^{-1}). [d] Gibbs free energy of solvation in chloroform (kJ·mol^{-1}). [e] P_o is the 1-octanol−water partition coefficient. [f] Calculations carried out with a method by Kantola et al.[34] [g] P_{ch} is the cyclohexane−water partition coefficient. [h] Calculations carried out with a method by Leo et al.[40] [i] P_{cf} is the chloroform−water partition coefficient.

Table 4. Free Energy of Solvation and Partition Coefficient Results for Barbituric Acid Derivatives

molecule	$\Delta G_{solv,w}$[a]	$\Delta G_{solv,o}$[b]	$\Delta G_{solv,ch}$[c]	$\Delta G_{solv,cf}$[d]	log P_o (GSCAP)[e]	log P_o (CDHI)[f]	log P_{ch} (GSCAP)[g]	log P_{ch}[h]	log P_{cf} (GSCAP)[i]	log P_{cf}[h]
barbitutric acid	-58.65	−35.90	−22.97	−31.58	−4.00	−3.25	−6.27	−4.98	−4.75	−4.93
cyclopropane-1′,5-spirobarbituric acid	-53.68	−42.62	−27.26	−37.39	−1.94	−2.64	−4.64	−3.15	−2.86	−3.53
5-allyl-5-phenylbarbituric acid	-57.87	−58.74	−37.81	−52.46	0.15	−1.65	−3.52	−1.74	−0.95	−1.17
5,5-diphenylbarbituric acid	-63.12	−64.83	−42.18	−59.34	0.30	−1.42	−3.68	−1.64	−0.66	−1.01

[a] Gibbs free energy of solvation in water (kJ·mol^{-1}). [b] Gibbs free energy of solvation in 1-octanol (kJ·mol^{-1}). [c] Gibbs free energy of solvation in cyclohexane (kJ·mol^{-1}). [d] Gibbs free energy of solvation in chloroform (kJ·mol^{-1}). [e] P_o is the 1-octanol−water partition coefficient. [f] Calculations carried out with a method by Kantola et al.[34] [g] P_{ch} is the cyclohexane−water partition coefficient. [h] Calculations carried out with a method by Leo et al.[40] [i] P_{cf} is the chloroform−water partition coefficient.

ane, presenting chloroform an intermediate trend. Typical errors in absolute value are 0.5 log unit.

The solvation descriptors for seven acetanilide derivatives are reported in Table 3. The three organic solvent−water partition coefficients P show a variation of 4 orders of magnitude. The comparison with calculations carried out with program CDHI shows that GSCAP gives good log P_o results. Typical errors in absolute value are 1.0 log unit. In particular, the homologous series of 4′-substituted acetanilides shows that the amino (NH_2) substituent decreases the 1-octanol−water partition coefficient P_o of acetanilide, while the nitro (NO_2), I, and Br substituents increase P_o. The corresponding calculated results indicate a difference of 1 order of magnitude in P_o for the 4′-substituted acetanilides. For log P_{ch} and log P_{cf}, typical errors in absolute value are 0.8 log unit.

The solvation descriptors for four barbituric acid derivatives are reported in Table 4. The three organic solvent−water partition coefficients P show a variation of 4 orders of magnitude. The comparison with calculations carried out with program CDHI shows that GSCAP gives good log P_o results. Typical errors in absolute value are 1.2 log units. For log P_{ch} and log P_{cf}, typical errors in absolute value are 1.0 log unit.

A set of five structural elements of 14 local anesthetics[42] included in Table 5 was described by Corriou et al.[43] The structural elements are as follows: lipophilic portion L, hydrophilic portion H, intermediate chain C, number of nitrogen atoms N, and number of oxygen atoms O. The corresponding indexes are set to either 1 or 0 depending on their similarity to a reference anesthetic. In this work, procaine was selected as reference. For procaine, the lipophilic portion is a phenyl radical, the hydrophilic portion is an amine, the intermediate chain is an ester, and there are

Table 5. Structural Elements for Local Anaesthetics

molecule	L[a]	H[b]	C[c]	N[d]	O[e]	log P_o[f]
benoxinate	1	1	1	1	0	11.5
benzocaine	1	0	1	0	1	2.00
bupivacaine	1	1	0	1	0	11.9
2-chloroprocaine	1	1	1	1	1	5.97
cocaine	1	1	1	0	0	6.34
dibucaine	0	1	0	0	1	12.6
dyclonine	1	1	0	0	1	13.6
lidocaine	1	1	0	1	0	10.3
phenytoin	1	0	0	1	1	1.41
prilocaine	1	1	0	1	0	8.01
procaine	1	1	1	1	1	6.27
(R)-propanolol	0	1	0	0	1	8.82
(S)-propanolol	0	1	0	0	1	8.64
tetracaine	1	1	1	1	1	9.40

[a] L, lipophilic portion. [b] H, hydrophilic portion. [c] C, intermediate chain. [d] N, number of nitrogen atoms. [e] O, number of oxygen atoms. [f] P_o is the 1-octanol−water partition coefficient.

two nitrogen atoms and two oxygens. Obviously the indexes associated to procaine are $L = H = C = N = O = 1$. The value $O = 1$ has been associated with benoxinate since there are three oxygens in this case. The indexes $H = 0$ and $N = 0$ are associated with benzocaine since the hydrophilic portion is not an amine and there is one nitrogen in this case.

The 1-octanol−water partition coefficient for the local anesthetics in Table 5 have been calculated and linear and nonlinear correlation models have been fitted. The best linear correlation model for log P_o is obtained as

$$\log P_o = 9.41 - 2.50C \qquad (2)$$

where index C has been described above. The mean absolute percentage error (MAPE) is 30.55% and the approximation error variance (AEV) is 0.878 57. The best nonlinear model is obtained as

$$\log P_o = 1.71 + 8.85\mathrm{H} - 2.66HC \qquad (3)$$

where the *H* and *C* indexes have been described above. In this case, the MAPE decreases to 20.29% and AEV to 0.299 34.

4. CONCLUSIONS

A method that permits a semiquantitative estimate of the partioning of any solute between any two media is presented. The model is based on the modification of a previously established model known as SCAP and proposed by Hopfinger.[28,29] The hallmark of the model is that it has been designed for all organic solvents without previous fitting parametrization. It is based in the division of ΔG°_{solv} in order to obtain a system of increments by atoms or by groups. As an example, the organic solvent−water partition coefficients *P* are calculated. From the preceding results the following conclusions can be drawn.

1. The comparison of the GSCAP results with the Pomona database[41] show an AAD of 1.48 log units and a SD of 1.66 log units. The results of the present work clearly indicate that it may become necessary to recalibrate the GSCAP method with experimental data on different solvents.

2. Program GSCAP has been written as a version of Pascal's SCAP program implementing the modeling of the solubility in any organic solvent and the calculations of organic solvent−water log *P*. The only needed parameters are the dielectric constant and molecular volume of the organic solvent of interest. No fitted parameters are included in the model.

3. The method differentiates the log *P* values of acetanilide derivatives and barbituric acid derivatives and shows a gradual variation in the homologous series of 4′-substituted acetanilides.

4. The correlation models between log P_o and structural elements make clear the existence of a homogeneous general scheme in local anesthetics. These correlations point also to the ability to predict and tailor drug properties. The latter is nontrivial in pharmacology.

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