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Octanol/Water Partition Coefficients Expressed in Terms of Solute Molecular Surface Areas and Electrostatic Potentials

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For 70 molecules of various types and sizes, it is shown that their experimental octanol/water partition coefficients can be represented quantitatively in terms of the solute's molecular surface area in conjunction with two statistically-based quantities calculated from its surface electrostatic potential; the latter are the average deviation of the potential and its total variance. An *ab initio* SCF approach was used to compute STO-3G*-optimized geometries and STO-5G* electrostatic potentials.

Introduction

Quantitative structure activity relationships (QSAR) are widely used in modern drug design. In QSAR, biological activity is related to physicochemical parameters of the studied molecules.[1] Octanol/water partition coefficients are among the most frequently used parameters for this type of analysis. However, pharmacological and environmental research often concerns poorly characterized or not yet synthesized compounds for which partition coefficients are not known. Several methods for estimating them have therefore been proposed. A widely used approach is to add up empirically determined fragment contributions.[2-4] While this generally leads to very reliable results, it is limited by the availability of data and by the requirement that the parameterization has been conducted for the same fragment types as are in the molecules of interest.

Another approach has been to correlate partition coefficients with computed quantities, such as molecular surface area or volume, and semiempirically derived atomic charges.[5-8] A significant number of these parameters may be needed, since the charges have to be weighted differently depending upon the atom type and because additional empirical corrections are often necessary. An exception is the work of Famini *et al.*, in which only two parameters are employed.[8]

Kamlet and co-workers[9] have successfully used their linear solvation energy relationship (LSER) to correlate octanol/water partition coefficients P_{ow}:

$$\log P_{ow} = mV_I + s(\pi^* + d\delta) + b\beta_m + a\alpha_m + C \qquad (1)$$

P_{ow} is the ratio of the equilibrium concentration of a solute in octanol to that in water. V_I is the van der Waals volume of the solute molecule, π^* is a polarity/polarizability term, δ is a polarizability correction, α_m and β_m represent hydrogen-bond-donating and -accepting tendencies, respectively, and C is a constant. For 245 organic molecules of different types, eq 1 gave a correction coefficient of 0.996 and a standard deviation of 0.131. It should be noted that certain groups of compounds were eliminated from the correlation, e.g., pyridine and its derivatives, primary and secondary amines, and nitroalkanes. More recent work by Abraham has shown that these deficiencies can be corrected if a newly defined set of LSER parameters is used.[10] While this type of relationship may not always be practical for studies of novel drug molecules, since π^*, α_m, and β_m are estimated through elaborate experimental procedures, the results are still very encouraging.

This excellent correlation between partition coefficients and a limited number of quantities that were not explicitly designed for this purpose suggests that it may be possible to identify some fundamental molecular properties of a solute that determine its partitioning between water and octanol. V_I and β_m are found to be the dominant terms in eq 1, and since hydrogen bonding has been shown to be mainly electrostatic in nature,[11,12] it seems reasonable to use a molecule's electrostatic potential together with an estimate of its size as a starting point in a theoretical approach for predicting its partition coefficient. The electrostatic potential, $V(\mathbf{r})$, that surrounds a molecule is defined by eq 2:

$$V(\mathbf{r}) = \sum_A \frac{Z_A}{|\mathbf{R}_A - \mathbf{r}|} - \int \frac{\rho(\mathbf{r}')d\mathbf{r}'}{|\mathbf{r}' - \mathbf{r}|} \qquad (2)$$

Z_A is the charge on nucleus A, located at $\mathbf{R}_A$, and $\rho(\mathbf{r})$ is the electronic density function. $V(\mathbf{r})$ gives the interaction energy between a positive point charge of unitary magnitude located at $\mathbf{r}$ and the unperturbed charge distribution of the molecule. The electrostatic potential has been shown to be a very useful tool in the study of molecular reactivity, including hydrogen bonding and biological recognition interactions.[13-23] As an example, the hydrogen-bond-accepting ability of molecules has been shown to be quantitatively related to the magnitudes of the most

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negative electrostatic potentials, the spatial minima $V_{\min}$[16,17,19] and the surface minima $V_{S,\min}$,[20] while hydrogen-bond-donating abilities are related to the surface maxima, $V_{S,\max}$.[16,18,19]

Additional useful information can be extracted when the electrostatic potential is calculated on molecular surfaces and analyzed statistically.[24-27] A measure of local polarity, Π, has been defined by eq 3:[24]

$$\Pi = \frac{1}{A}\int_s |V(\mathbf{r}) - \bar{V}_s| \mathrm{d}S = \lim_{n\to\infty} \frac{1}{n}\sum_{i=1}^{n} |V(\mathbf{r}_i) - \bar{V}_s| \qquad (3)$$

$V(\mathbf{r}_i)$ is the potential at the ith point on the surface and $\bar{V}_s$ is its average value, $\bar{V}_s = \frac{1}{n}\sum_{i=1}^{n} V(\mathbf{r}_i)$. Π has been shown to correlate with the previously mentioned polarity/polarizability parameter π^* as well as with the dielectric constant.[24] As an indicator of the variability of the electrostatic potential over the molecular surface, the quantity σ_{tot}^2 has been introduced:[25]

$$\sigma_{\mathrm{tot}}^2 = \sigma_+^2 + \sigma_-^2 = \frac{1}{m}\sum_{i=1}^{m}[V^+(\mathbf{r}_i) - \bar{V}_s^+]^2 + \frac{1}{n}\sum_{j=1}^{n}[V^-(\mathbf{r}_j) - \bar{V}_s^-]^2 \qquad (4)$$

$V^+(\mathbf{r}_i)$ and $V^-(\mathbf{r}_j)$ are the positive and negative values of $V(\mathbf{r})$ on the surface, and $\bar{V}_s^+$ and $\bar{V}_s^-$ are their averages: $\bar{V}_s^+ = \frac{1}{m}\sum_{i=1}^{m} V^+(\mathbf{r}_i)$ and $\bar{V}_s^- = \frac{1}{n}\sum_{j=1}^{n} V^-(\mathbf{r}_j)$. As an example of an application of σ_{tot}^2, we have found good linear relationships between solubility in supercritical CO_2 and σ_{tot}^2 in conjunction with some measure of molecular size, i.e. surface area or volume.[26] For some properties, especially when they involve molecules interacting with their own kind (e.g., boiling points, critical temperatures, and critical pressures), it is helpful to introduce a balance parameter ν, defined by[27]

$$\nu = \frac{\sigma_+^2\sigma_-^2}{[\sigma_{\mathrm{tot}}^2]^2} \qquad (5)$$

In this work, we extend this analytical approach and investigate possible relationships between octanol/water partition coefficients, P_{ow}, and the quantities Π, σ_+^2, σ_-^2, σ_{tot}^2, ν, and surface area.

Methods

We have used an *ab initio* SCF approach to compute STO-5G* wavefunctions using STO-3G*-optimized geometries.[28] $V(\mathbf{r})$ was calculated rigorously from these wavefunctions on molecular surfaces defined, following Bader *et al.*,[29] by the 0.001 electrons/bohr^3 contour of the electron density. Π, σ_{tot}^2, and ν were obtained from $V(\mathbf{r})$ in accordance with eqs 3–5. The molecular surface area was computed from the number of surface points, using a 0.2 bohr square grid.

Results and Discussion

Table I lists the computed properties and experimental partition coefficients for 67 molecules of different types and sizes. The calculated data, for the most part, are taken from our earlier work.[27] ν was not found to significantly affect P_{ow} and is not included in Table I.

As shown in Table II, a fair correlation is obtained with the simple relationship

$$\log P_{\mathrm{ow}} = \alpha(\mathrm{area}) + \beta\sigma_{\mathrm{tot}}^2 + \gamma \qquad (6)$$

The correlation coefficient is 0.936, but the standard deviation is rather large, 0.552. Both are improved, to 0.946 and 0.513, by introducing Π:

$$\log P_{\mathrm{ow}} = \alpha(\mathrm{area}) + \beta\sigma_{\mathrm{tot}}^2 + \gamma\Pi + \delta \qquad (7)$$

From the signs of the coefficients α, β, and γ in eqs 6 and 7, given in Table II, we can conclude that partitioning into octanol is favored by large surface area, while high σ_{tot}^2 and Π values favor partitioning into water. It was further found advantageous to multiply Π by the area in eq 7, giving eq 8. The effect of this is to make the last term size dependent,

$$\log P_{\mathrm{ow}} = \alpha(\mathrm{area}) + \beta\sigma_{\mathrm{tot}}^2 + \gamma(\mathrm{area})\Pi + \delta \qquad (8)$$

whereas Π is defined to be size independent. The strength of the interaction with bulk water doubtless depends upon the extent of the interactive area, and eq 8 evidently takes better account of this than does eq 7. The correlation coefficient becomes 0.950, and the standard deviation is 0.493.

Finally, we tested the possibility that eq 8 could be improved by using σ_-^2 in place of σ_{tot}^2 (eq 9); this would give

$$\log P_{\mathrm{ow}} = \alpha(\mathrm{area}) + \beta\sigma_-^2 + \gamma(\mathrm{area})\Pi + \delta \qquad (9)$$

greater emphasis to the negative portions of the molecular surface, consistent with the conclusions of Famini *et al.*[8] and Kamlet *et al.*[9] that the dominating factors in determining P_{ow} are size and hydrogen bond accepting ability. Equation 9 does have a somewhat better correlation coefficient and standard deviation, 0.961 and 0.437, than eq 8 (Table II).

The log P_{ow} values obtained with eq 9 are listed in Table I. They are in generally good agreement with the experimental data, but there are a few notable discrepancies. By far the worst are ethylene glycol, $HOCH_2CH_2OH$, *N,N*-dimethylformamide, $(CH_3)_2NCHO$, and *N,N*-dimethylacetamide, $(CH_3)_2NCOCH_3$. (If these three

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Table I. Experimental Octanol/Water Partition Coefficients and Calculated Properties

	log P_{ow}[a] (expl)	log P_{ow} (eq 9)	log P_{ow} (eq 10)	surface area	Π	σ_+^2	σ_-^2	σ_{tot}^2	N
H_2O	-1.38	-1.66	-1.78	38.8	21.60	85.3	172.8	258.1	2
$HOCH_2CH_2OH$	-1.34[b]	-0.20	-1.84	96.4	13.52	68.5	157.2	225.7	4
$(CH_3)_2SO$	-1.35	-1.20	-1.44	107.8	15.39	24.3	271.7	296.0	2
$(CH_3)_2NCHO$	-1.01	0.31	-0.59	112.2	11.07	18.6	158.8	177.4	3
$(CH_3)_2NCOCH_3$	-0.77	0.70	-0.26	130.8	10.08	17.3	169.6	186.9	3
CH_3OH	-0.70	-0.96	-1.08	64.7	12.79	49.6	181.5	231.0	2
CH_3NO_2	-0.34	-0.23	0.01	81.2	19.90	34.4	81.7	116.0	1
CH_3CN	-0.34	-0.90	-0.27	75.9	17.12	23.6	167.8	191.4	1
CH_3CH_2OH	-0.31	-0.34	-0.46	87.1	10.05	45.1	182.4	227.5	2
CH_2OCH_2	-0.30	-0.13	-0.23	75.3	10.33	11.6	130.0	141.5	2
CH_3COOH	-0.24	0.08	-0.05	86.4	12.89	41.2	112.1	153.3	2
CH_3COCH_3	-0.24	0.18	0.06	99.4	9.40	15.9	159.8	175.7	2
$CH_3CH_2NH_2$	-0.13	-0.96	0.14	92.2	9.84	27.5	264.3	291.9	1
$CH_3CHOHCH_3$	0.05	0.19	0.06	107.0	8.70	35.5	184.2	219.7	2
$(CH_3)_2O$	0.10	-0.11	-0.21	87.3	9.12	9.0	164.8	173.7	2
CH_3COOCH_3	0.18	0.62	0.49	109.3	10.03	9.7	129.2	138.9	2
CH_2F_2	0.20	0.43	0.48	60.7	12.55	24.4	22.0	46.4	1
$(CH_3)_3COH$	0.36	0.68	0.55	123.5	7.69	31.1	182.7	213.8	2
C_2H_2	0.37	0.61	0.67	59.8	9.01	36.3	20.5	56.7	1
CF_3CH_2OH	0.37	0.64	0.50	96.2	15.20	85.0	50.2	135.2	2
$(CH_2)_4O$	0.46	0.43	0.31	111.3	7.80	6.3	180.0	186.4	2
CH_3F	0.51	0.25	0.45	58.2	9.78	12.3	51.8	64.4	1
CHF_3	0.64	0.61	0.62	63.0	11.74	58.2	11.6	69.8	1
pyridine	0.65	0.02	0.89	110.4	8.55	18.5	212.3	230.8	1
CH_3CHF_2	0.75	0.99	1.06	85.8	10.36	17.4	30.9	48.3	1
$CH_3(CH_2)_3OH$	0.88	0.95	0.83	127.9	7.54	35.0	165.9	201.0	2
$(CH_3CH_2)_2O$	0.89	1.46	1.36	131.4	6.68	8.0	129.8	137.8	2
$C_6H_5NH_2$	0.93	1.44	1.77	129.5	9.28	50.4	95.5	145.8	1
$HCCCH_3$	0.94	1.14	1.22	83.3	8.08	13.9	27.0	40.9	1
CH_4	1.09	0.94	0.97	55.5	3.15	5.4	3.5	8.9	1
C_2H_4	1.14	1.21	1.25	68.9	4.06	7.2	8.3	15.5	1
CF_4	1.18	0.93	0.92	65.5	8.32	66.9	2.9	69.8	1
1,3,5-$C_6H_3(NO_2)_3$	1.18	1.58	1.46	183.0	18.70	105.3	47.4	152.7	1
1,4-$C_6H_4(NH_2)NO_2$	1.39	0.88	1.27	152.0	14.69	85.5	133.9	219.4	1
CH_3CH_2Cl	1.43	1.30	1.37	94.2	9.00	14.3	28.4	42.7	1
1,3-$C_6H_4(NO_2)_2$	1.49	1.60	1.34	160.4	17.08	35.3	67.9	103.2	1
C_6H_5OH	1.49	1.30	1.50	124.7	8.63	63.8	73.7	137.4	2
C_6H_5CN	1.56	0.75	1.42	135.6	9.98	18.4	176.9	195.3	1
1,4-$C_6H_4(CN)OH$	1.63	0.80	1.34	144.6	12.44	81.6	159.0	240.5	1
C_3H_6	1.72	1.78	1.82	90.2	3.83	5.5	9.5	15.1	1
C_2H_6	1.81	1.62	1.63	77.5	2.42	3.4	0.6	4.0	1
$C_6H_5NO_2$	1.85	1.30	1.61	142.8	12.13	16.7	105.2	121.9	1
1,4-$C_6H_4(NO_2)OH$	1.92	1.03	1.32	145.9	14.41	83.9	110.0	193.9	1
C_6H_5COOH	1.95	1.76	1.64	143.3	8.24	41.0	106.8	147.9	2
C_2F_6	2.00	1.62	1.58	98.6	8.58	71.5	2.2	73.7	1
$C_6H_5OCH_3$	2.08	2.30	2.20	144.2	7.43	15.9	61.3	77.2	2
C_6H_6	2.13	2.35	2.37	115.3	4.83	7.1	9.2	16.3	1
indole	2.14	2.66	2.66	149.1	8.39	76.0	20.7	96.6	1
C_6F_6	2.22	2.19	2.11	132.0	10.35	39.1	6.1	45.3	1
C_6H_5F	2.27	2.12	2.24	117.7	5.56	12.0	32.9	45.0	1
C_3H_8	2.36	2.20	2.22	98.5	2.38	3.1	0.8	3.9	1
1,3-C_6H_4ClOH	2.49	1.12	2.02	139.7	8.61	80.1	53.6	133.7	2
C_6H_5Cl	2.49	2.49	2.55	132.2	6.30	14.4	22.9	37.4	1
CCl_4	2.72	2.50	2.48	120.3	5.22	28.8	2.5	31.3	1
$C_6H_5CH_3$	2.74	2.89	2.91	136.0	4.63	6.8	11.1	17.9	1
$(CH_3)_3CH$	2.76	2.69	2.70	116.7	2.52	3.1	1.0	4.1	1
1,4-$C_6H_4ClOCH_3$	2.82[c]	2.69	2.57	160.8	8.32	26.0	47.8	73.8	2
2-naphthol	2.87	2.83	2.71	169.8	8.14	56.5	57.4	113.9	2
$CH_3(CH_2)_2CH_3$	2.89	2.76	2.78	118.8	2.37	2.9	0.8	3.7	1
C_6H_5Br	2.99	2.69	2.73	137.0	5.94	13.4	18.8	32.2	1
$C(CH_3)_4$	3.11	3.10	3.10	132.4	2.76	3.1	1.1	4.2	1
naphthalene	3.36	3.47	3.46	159.9	5.12	8.1	7.8	15.9	1
1,4-$C_6H_4Cl_2$	3.38	3.02	3.00	148.5	6.24	18.1	10.1	28.3	1
$CH_3(CH_2)_3CH_3$	3.39	3.35	3.36	139.7	2.35	2.8	0.9	3.6	1
c-C_6H_{12}	3.44	3.29	3.30	136.8	2.16	2.5	0.7	3.2	1
$CH_3(CH_2)_4CH_3$	3.90[c]	3.90	3.91	159.6	2.33	2.7	0.9	3.6	1
anthracene	4.45	4.65	4.61	207.1	5.30	8.8	6.8	15.6	1
phenanthrene	4.53	4.54	4.51	203.0	5.28	9.7	7.1	16.8	1
$C_6(CH_3)_6$	5.11[c]	5.20	5.24	221.9	3.89	3.8	15.9	19.7	1
$CH_3(CH_2)_6CH_3$	5.18[c]	5.04	5.05	200.6	2.32	2.6	1.0	3.6	1

[a] Experimental values taken from ref 3 unless otherwise noted. [b] Reference 31. [c] Reference 9.

molecules were omitted, the correlation coefficient for eq 9 would be 0.976 and the standard deviation would be 0.329). For all three molecules, our results underestimate the tendency for partitioning into water. In the case of ethylene glycol, a possible reason is suggested by noting that although it has twice as many hydroxyl oxygens as

Table II. Relationships between Experimental Octanol/Water Partition Coefficients and Calculated Quantities for the 70 Molecules from Table I

equation	correln coeff	std devn
$\log P_{ow} = 0.0243(\text{area}) - 0.0109\sigma_{tot}^2 - 0.2611$	0.936	0.552
$\log P_{ow} = 0.0233(\text{area}) - 0.00869\sigma_{tot}^2 - 0.0644\Pi + 0.188$	0.946	0.513
$\log P_{ow} = 0.0285(\text{area}) - 0.00848\sigma_{tot}^2 - 0.000603(\text{area})\Pi - 0.415$	0.950	0.493
$\log P_{ow} = 0.0298(\text{area}) - 0.00912\sigma_-^2 - 0.000849(\text{area})\Pi - 0.529$	0.961	0.437
$\log P_{ow} = 0.0300(\text{area}) - 0.00472\text{N}\sigma_-^2 - 0.000963(\text{area})\Pi - 0.504$	0.985	0.277

methanol, its σ_-^2 is actually smaller (Table I), reflecting the fact that the electrostatic potential is more negative around the oxygen in methanol than around those in ethylene glycol.

This example shows that σ_-^2 alone may not give a complete picture of the solute's capability for interacting with electrophilic portions of the solvent molecules. This problem is expected to be most significant in relation to any nitrogens and oxygens that are present in the solute molecule, since the minima V_{min} associated with their lone pairs are typically the most negative that are observed in molecular electrostatic potentials. It seemed possible, therefore, that the problems encountered for ethylene glycol, *N,N*-dimethylformamide, *N,N*-dimethylacetamide and some of the other molecules could be achieved by explicitly taking account of the number of nitrogen and oxygen lone pairs in each molecule. This was done by introducing the factor N, as shown in eq 10

$$\log P_{ow} = \alpha(\text{area}) + \beta N\sigma_-^2 + \gamma(\text{area})\Pi + \delta \qquad (10)$$

where $N = n_N + 2n_O$, n_N and n_O being the numbers of nitrogen and oxygen atoms in the molecule. (Oxygens normally have two lone pairs.) When there are two oxygens on the same carbon, we used $N = 2$, since steric factors are likely to preclude interactions at all the V_{min}. We have found in another study that the partitioning of nitro derivatives depends primarily upon the regions of positive electrostatic potential;[30] accordingly, we have used $N = 1$ for these, regardless of any other substituent that may be present, and for cyano derivatives as well since CN is also strongly electron withdrawing. If the molecule has no nitrogens or oxygens, N must be set equal to 1 in order to retain the σ_-^2 term in eq 10.

The effect of introducing N is striking. The correlation coefficient for eq 10 is 0.985, and the standard deviation is 0.277! Both of these are markedly better than for eq 9. Thus, eq 10 is a very good relationship between the octanol/water partition coefficient and calculated molecular surface properties; on the other hand, the factor N has introduced an element of arbitrariness that was not present in eqs 6–9 nor in our earlier applications of the statistically-based quantities obtained from molecular surface electrostatic potentials.[24–27] Accordingly, we view N as a temporary palliative which is suggestive of the direction to take in our continuing effort to develop effective computational means for treating molecular interactions.

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