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Estimation of Hydrophobicity Based on the Solvent-Accessible Surface Area of Molecules[1]

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A novel method of estimating Hansch's hydrophobic constant (log P) by making use of the solvent-accessible surface area (S_A) with correction for the hydrophilic effect of any polar moiety (S_H) is proposed. The correlation coefficient (r) between observed and estimated values of log P was 0.995 with 138 miscellaneous compounds. The method can reproduce the differences of log P among geometrical isomers. Such differences are not calculable by using other available methods. An application of S_A and S_H to the regression analysis of water-solubility data of 156 different organic liquids gave $r=0.981$. The proposed method may offer new insight into the physicochemical nature of hydrophobic phenomena.

Keywords——solvent-accessible surface area; Hansch's hydrophobic constant; partition coefficient; regression analysis; water-solubility

Hydrophobicity is the main factor governing the transport and distribution of drug molecules in biological systems, and is also an important property affecting drug-receptor interactions.[2] Thus, the use of log P (the logarithm of the octanol–water partition coefficient), as pioneered by Hansch and Fujita,[3] has become a standard method in quantitative structure–activity relationship studies. Hence, there is ever-increasing need for reliable estimation of log P for various chemicals for which experimental values are either not available or may be difficult to measure. For log P of these chemicals, empirical approximation has been done by use of the π-addition method[3,4] and the f-addition method,[5-7] but these have little physicochemical meaning.

Nemethy and Scheraga[8] have pointed out that a dominant energy source for hydrophobic behavior of a solute in water is the regularity of the cluster of water molecules in contact with the hydrophobic surface of the solute molecules. From this point of view, Watanabe and Mitsui[9] suggested that hydrophobicity of molecules might be estimated by using their solvent-accessible surface area[10] (S_A). This prompted us to carry out the present study; in this paper, we propose a method of estimating log P based on the total S_A of a molecule with a correction for any hydrophilic moiety, and demonstrate its application to the regression analysis of water-solubility data for 156 organic liquids.

Method

Solvent-Accessible Surface Area (S_A)——S_A was originally defined by Lee and Richards[10] as the area traced out by the center of a solvent molecule (assumed to be a sphere) as it is rolled over the van der Waals surface of the solute molecule. Most of the molecular coordinates were estimated as fully extended structures by using the MMI/MMPI program (QCPE No. 318). For structures of complex molecules, X-ray diffractional data[11] were employed. The values[12,13] in Å of van der Waals radii used were 1.7 for C, 1.1 for H, 1.5 for N, 1.4 for O, 1.8 for S, 1.4 for F, 1.8 for Cl, 1.9 for Br, and 2.1 for I. In most of the calculations, hydrogen atoms were not considered, as described later. The solvent radius was chosen to be 1.4 Å.[10] The spacing between sections of atomic spheres in the computation of S_A

was taken to be 0.1 Å. The calculation of S_A was performed by using the program ACCESS developed by Mitsui[9] on a HITAC M-280H computer in the Computer Center, University of Tokyo.

Regression Analysis——Correlations and regression equations were calculated using a Fortran program (written by us) on an OKITAC 50V/65 computer.

Results and Discussion

Neglect of Hydrogen Atoms in the Calculation of S_A

Since the three-dimensional coordinates of hydrogen atoms in molecules are usually not available from X-ray diffractional data, Lee and Richards[10] did not consider hydrogen atoms in their calculation of S_A. The validity of the neglect of hydrogen atoms in our S_A–$\log P$ correlation study was first investigated with apolar compounds.

Table I shows two kinds of S_A, *i.e.*, $S_{A\,\text{with H}}$ and $S_{A\,\text{without H}}$ calculated with and without consideration of hydrogen atoms, respectively, along with observed $\log P$ for aliphatic and aromatic hydrocarbons. The correlations are given by Eqs. 1—4. For aliphatic hydrocarbons:

$$\log P = 1.78(\pm 0.13) S_{A\,\text{with H}} - 0.36(\pm 0.12) DB - 1.26(\pm 0.28)$$

$$n=9 \quad r=0.997 \quad s=0.07 \quad F=585.4 \qquad (1)$$

$$\log P = 2.05(\pm 0.18) S_{A\,\text{without H}} - 0.45(\pm 0.15) DB - 1.29(\pm 0.35)$$

$$n=9 \quad r=0.996 \quad s=0.09 \quad F=406.3 \qquad (2)$$

For aromatic hydrocarbons:

$$\log P = 1.89(\pm 0.16) S_{A\,\text{with H}} - 2.27(\pm 0.52)$$

$$n=12 \quad r=0.992 \quad s=0.10 \quad F=658.7 \qquad (3)$$

TABLE I. Two Kinds of S_A and $\log P$ for Apolar Molecules

	$S_{A\,\text{with H}}$[a] (10^2 Å^2)	$S_{A\,\text{without H}}$[b] (10^2 Å^2)	$\log P$[c] Obsd
Methane	1.344	1.183	1.09
Ethane	1.699	1.487	1.81
Propane	2.008	1.748	2.36
Butane	2.302	2.021	2.89
Isobutane	2.259	1.976	2.76
Hexane	2.905	2.545	3.82
Ethylene	1.594	1.455	1.13
1-Butene	2.221	1.977	2.40
Isobutylene	2.206	1.972	2.34
Benzene	2.331	2.098	2.13
Toluene	2.584	2.366	2.69
m-Xylene	2.875	2.629	3.20
p-Xylene	2.923	2.621	3.15
Fluorene	3.454	3.198	4.18
Biphenyl	3.398	3.147	4.09
Naphthalene	3.007	2.716	3.37
Anthracene	3.596	3.304	4.45
Phenanthrene	3.528	3.299	4.46
Ethylbenzene	2.905	2.612	3.15
Propylbenzene	3.036	2.812	3.68
Pyrene	3.708	3.411	4.88

a) Calculated with consideration of hydrogen atoms. *b*) Calculated without consideration of hydrogen atoms. *c*) Refs. 4 and 7.

$$\log P = 1.94(\pm 0.14) S_{\mathrm{A\,without\,H}} - 1.92(\pm 0.41)$$

$$n = 12 \quad r = 0.995 \quad s = 0.09 \quad F = 933.2 \qquad (4)$$

In these equations, n is the number of data points, r is the correlation coefficient, s is the standard deviation of errors, and F is the F statistics for the correlation. The figures in parentheses are the 95% confidence limits. DB in Eqs. 1 and 2 is the number of isolated double bonds, being tentatively introduced to take account of the effect of their polarity.

In Eqs. 1—4, no significant difference between $S_{\mathrm{A\,with\,H}}$ and $S_{\mathrm{A\,without\,H}}$ is apparent in the correlation with $\log P$. Consequently, hydrogen atoms were neglected in all subsequent calculations of S_{A}.

Hydrophobic Effect of a Polar Moiety

In Eqs. 1 and 2, the parameter DB was tentatively introduced to correct for the hydrophilic effect of isolated double bonds. Polar molecules such as alcohols, carboxylic acids, amines, amides, nitro compounds, *etc.* are expected to require greater correction for the effect of their polar moieties in the correlation of S_{A} with $\log P$. Lee and Richards$^{10)}$ computed the percentage contribution made to total S_{A} by polar atoms (nitrogen and oxygen) to elucidate the folding trends of protein molecules. However, such a simple approach to the effect of polarity seemed inappropriate for the estimation of $\log P$. Accordingly, correction values, S_{H}, compiled in Table II were evaluated for a wide variety of polar groups or moieties separately by the least-squares technique using the data of total S_{A} and observed $\log P$ of 138 miscellaneous compounds listed in Table III.

TABLE II. Hydrophilic Effect of Polar Moieties, S_{H}

	Aliphatic			Aromatic		
	S_{H}	S.D.	$n^{a)}$	S_{H}	S.D.	$n^{a)}$
$-\overset{\vert}{C}=$	0.25	0.03	5			
$-C\equiv$	0.63	0.06	2			
Conjugated moiety				0.68	0.06	64
C(–F)				0.24	0.03	2
$C(-Cl_{1-4})$	1.13	0.07	8			
C(–Cl)				0.16	0.02	5
C(–Br)	0.94	0.10	3	0.01	0.05	3
C(–I)	0.74	0.11	2	0.03	—	1
–CHO				1.25	0.23	2
$\rangle$CO (ketones)	2.59	0.10	3	1.66	0.11	3
–COOH	2.26	0.05	7	1.28	0.11	2
–COO– (esters)	2.65	0.12	2			
$-CONH_2$	3.51	—	1	2.51	0.01	3
–CONH–	3.95	—	1			
–CN	2.34	0.11	2	1.40	—	1
$-NH_2$	2.20	0.09	3	1.72	0.06	5
–NH–	2.15	0.07	4	1.40	0.11	2
				0.59$^{b)}$	—	1
$-\overset{\vert}{N}-$	2.46	0.09	3	1.03	0.11	2
–N=				0.45	—	1
$-NO_2$	2.26	0.09	4	1.21	0.04	7
–OH	2.16	0.05	14	0.97	0.05	8
–O– (ethers)	2.22	0.10	3	0.98	—	1

a) Number of compounds used for the determination of S_{H}. *b*) For Ar_2NH.

Table III. S_A, ΣS_H, and log P for 138 Miscellaneous Compounds

Compound	S_A	ΣS_H	log P		Compound	S_A	ΣS_H	log P	
			Obsd[a]	Calcd[b]				Obsd[a]	Calcd[b]
Methane	1.183	0	1.09	1.19	*o*-Methylbenzaldehyde	2.675	1.93	2.26	2.09
Ethane	1.483	0	1.81	1.77	2-Butanone	2.118	2.59	0.29	0.37
Propane	1.748	0	2.36	2.26	2-Hexanone	2.650	2.59	1.38	1.39
Butane	2.021	0	2.89	2.79	Cyclohexanone	2.294	2.59	0.81	0.71
Isobutane	1.976	0	2.76	2.69	Acetophenone	2.659	2.34	1.68	1.65
Hexane	2.545	0	3.82	3.78	Propiophenone	2.947	2.34	2.19	2.20
Cyclopentane	2.019	0	3.00	2.78	Benzophenone	3.428	2.34	3.18	3.11
Ethylene	1.455	0.50	1.13	1.20	Formic acid	1.451	2.26	−0.54	−0.56
1-Butene	1.977	0.50	2.40	2.20	Acetic acid	1.736	2.26	−0.17	−0.02
Isobutylene	1.972	0.50	2.34	2.19	Propionic acid	1.970	2.26	0.33	0.42
Cyclohexene	2.172	0.50	2.86	2.57	Butyric acid	2.242	2.26	0.79	0.94
1,5-Hexadiene	2.496	1.00	2.45	2.68	Succinic acid	2.471	4.52	−0.59	−0.89
Acetylene	1.417	1.26	0.37	0.37	Adipic acid	2.965	4.52	0.08	0.05
1-Pentyne	2.256	1.26	1.98	1.97	Azelaic acid	3.802	4.52	1.57	1.64
Benzene	2.098	0.68	2.13	2.25	Benzoic acid	2.556	1.96	1.87	1.84
Toluene	2.366	0.68	2.69	2.76	*p*-Toluic acid	2.797	1.96	2.27	2.29
Ethylbenzene	2.612	0.68	3.15	3.24	Methyl acetate	2.043	2.65	0.18	0.17
Propylbenzene	2.812	0.68	3.68	3.60	Ethyl acetate	2.338	2.65	0.73	0.73
Isopropylbenzene	2.783	0.68	3.66	3.55	Butyramide	2.296	3.51	−0.21	−0.22
o-Xylene	2.571	0.68	3.12	3.14	*N*-Methylacetamide	2.083	3.95	−1.05	−1.05
m-Xylene	2.629	0.68	3.20	3.26	Benzamide	2.576	3.19	0.65	0.64
p-Xylene	2.621	0.68	3.15	3.24	Acetanilide	2.863	3.19	1.17	1.19
Biphenyl	3.147	0.68	4.09	4.24	Propionanilide	3.091	3.19	1.61	1.62
Fluorene	3.198	0.68	4.18	4.34	Acetonitrile	1.601	2.34	−0.34	−0.36
Naphthalene	2.716	0.68	3.37	3.42	Propionitrile	1.875	2.34	0.16	0.16
Anthracene	3.304	0.68	4.45	4.54	Benzonitrile	2.475	2.08	1.56	1.55
Phenanthrene	3.299	0.68	4.46	4.53	Methylamine	1.395	2.20	−0.57	−0.61
Pyrene	3.411	0.68	4.88	4.74	Butylamine	2.204	2.20	0.88	0.93
Methyl chloride	1.578	1.13	0.91	0.81	Amphetamine	2.989	2.88	1.76	1.74
Ethyl chloride	1.850	1.13	1.43	1.33	Diethylamine	2.141	2.15	0.57	0.86
Butyl chloride	2.379	1.13	2.39	2.33	Dipropylamine	2.561	2.15	1.73	1.66
Methylene chloride	1.914	1.13	1.25	1.45	Methylbutylamine	2.503	2.15	1.33	1.55
Chloroform	2.240	1.13	1.97	2.07	Piperazine	2.078	4.30	−1.17	−1.41
Carbon tetrachloride	2.482	1.13	2.62	2.53	Trimethylamine	1.929	2.46	0.27	0.15
Ethylidene chloride	2.145	1.13	1.79	1.89	Triethylamine	2.629	2.46	1.44	1.48
1,1,1-Trichloroethane	2.413	1.13	2.49	2.39	Tripropylamine	3.407	2.46	2.79	2.95
Methyl bromide	1.647	0.94	1.19	1.13	Aniline	2.263	2.40	0.90	0.84
Ethyl bromide	1.907	0.94	1.61	1.62	*m*-Toluidine	2.534	2.40	1.40	1.35
Propyl bromide	2.177	0.94	2.10	2.14	*p*-Toluidine	2.538	2.40	1.39	1.36
Methyl iodide	1.794	0.74	1.69	1.61	1-Naphthylamine	2.843	2.40	2.25	1.94
Ethyl iodide	2.036	0.74	2.00	2.07	Benzidine	3.528	4.12	1.34	1.52
Fluorobenzene	2.248	0.92	2.27	2.29	*N*-Ethylaniline	2.756	2.08	2.26	2.10
Hexafluorobenzene	2.830	2.12	2.22	2.20	*N*-Propylaniline	3.017	2.08	2.45	2.59
Chlorobenzene	2.451	0.84	2.84	2.76	Diphenylamine	3.341	1.95	3.34	3.33
o-Dichlorobenzene	2.701	1.00	3.38	3.07	*N*, *N*-Dimethylaniline	2.741	1.71	2.31	2.44
m-Dichlorobenzene	2.788	1.00	3.38	3.24	*N*, *N*-Diethylaniline	3.130	1.71	3.31	3.18
p-Dichlorobenzene	2.777	1.00	3.39	3.22	Azobenzene	3.403	1.58	3.82	3.83
Hexachlorobenzene	3.692	1.64	4.13	4.31	Nitromethane	1.757	2.26	0.08	0.02
Bromobenzene	2.511	0.69	2.99	3.02	Nitroethane	1.987	2.26	0.18	0.46
o-Dibromobenzene	2.805	0.70	3.64	3.57	Nitrobutane	2.473	2.26	1.47	1.38
m-Dibromobenzene	2.919	0.70	3.75	3.79	Nitropentane	2.738	2.26	2.01	1.88
Iodobenzene	2.644	0.71	3.25	3.24	Nitrobenzene	2.556	1.89	1.85	1.91
Benzaldehyde	2.436	1.93	1.48	1.64	*o*-Nitrotoluene	2.698	1.89	2.30	2.18

TABLE III. (continued).

Compound	S_A	ΣS_H	log P		Compound	S_A	ΣS_H	log P	
			Obsd[a]	Calcd[b]				Obsd[a]	Calcd[b]
m-Nitrotoluene	2.788	1.89	2.45	2.35	Octanol	3.212	2.16	3.15	2.88
p-Nitrotoluene	2.785	1.89	2.37	2.34	Ethylene glycol	1.771	4.32	−1.93	−2.02
m-Dinitrobenzene	3.052	3.10	1.49	1.64	2,3-Butanediol	2.248	4.32	−0.92	−1.11
p-Dinitrobenzene	3.043	3.10	1.49	1.62	Phenol	2.242	1.65	1.48	1.55
1,3,5-Trinitrobenzene	3.365	4.31	1.18	1.02	*o*-Cresol	2.486	1.65	1.95	2.01
Methanol	1.362	2.16	−0.64	−0.63	*m*-Cresol	2.508	1.65	1.95	2.06
Ethanol	1.638	2.16	−0.30	−0.11	*p*-Cresol	2.512	1.65	1.95	2.06
Propanol	1.900	2.16	0.30	0.39	1-Naphthol	2.831	1.65	2.98	2.67
Isopropanol	1.884	2.16	0.05	0.36	2-Naphthol	2.866	1.65	2.84	2.74
Butanol	2.163	2.16	0.88	0.89	*o*-Dihydroxybenzene	2.370	2.62	0.88	0.82
Isobutanol	2.132	2.16	0.76	0.83	*m*-Dihydroxybenzene	2.395	2.62	0.80	0.87
Pentanol	2.449	2.16	1.40	1.43	Dimethyl ether	1.683	2.22	0.10	−0.08
Isopentanol	2.380	2.16	1.16	1.30	Diethyl ether	2.237	2.22	0.77	0.97
3-Pentanol	2.376	2.16	1.21	1.29	Dipropyl ether	2.771	2.22	2.03	1.98
Hexanol	2.691	2.16	2.03	1.89	Anisole	2.542	1.66	2.11	2.13
Cyclohexanol	2.323	2.16	1.23	1.19					

a) Refs. 4 and 7. *b*) Using Eq. 6.

As shown in Table II, the standard deviation (S.D.) of S_H for each moiety is farily small. This indicates that the S_H value is nearly constant for homologous compounds bearing the same hydrophilic moiety, and therefore that the use of the S_H parameter may be reasonable. The sum of S_H in the molecule, ΣS_H, for the 138 compounds is also listed in Table III.

The correlations of $\log P$ with S_A and with S_A and ΣS_H are given by Eqs. 5 and 6, respectively.

$$\log P = 1.53(\pm 0.33)S_A - 1.98(\pm 0.84)$$

$$n=138 \quad r=0.614 \quad s=1.04 \quad F=82.3 \qquad (5)$$

$$\log P = 1.90(\pm 0.04)S_A - 1.00(\pm 0.02)\Sigma S_H - 1.06(\pm 0.10)$$

$$n=138 \quad r=0.995 \quad s=0.13 \quad F=7284.5 \qquad (6)$$

The regression coefficient ($r=0.995$) in Eq. 6 is excellent. The colinearity of S_A with ΣS_H was very low ($r^2=0.034$). Since S_A is the total surface area and not the hydrophobic area, the S_H parameter is considered to imply both a correction for hydrophilic surface area and the effect of hydration of any polar moiety.

Estimation of log *P* by Using S_A and S_H

Equation 6 indicates that $\log P$ of a wide variety of compounds can be calculated from their S_A and S_H values. The values of $\log P$ calculated for the 138 compounds are listed in Table III. It is clear that differences in hydrophobicity among geometrical isomers can be estimated by use of the present method. For example, the values of log P estimated are 3.14 (obsd. 3.12) for *o*-xylene, 3.26 (obsd. 3.20) for *m*-xylene, and 3.24 (obsd. 3.15) for *p*-xylene. Neither the π-addition method nor the *f*-addition method can reproduce such differences in $\log P$ among isomers.

Table IV shows the results of our estimation of $\log P$ for $C_6H_5(CH_2)_{1-3}X$, where X= OH, COOH, NH_2, and CN, along with those[5)] calculated using the π- and *f*-addition methods. For these compounds, the folded structures[4)] proposed on the basis of calculations by the π-addition method were ruled out by Nys and Rekker[5)] using the *f*-addition method.

Table IV. Observed and Calculated log P of $C_6H_5(CH_2)_nX$

Compound	Obsd log P[a]	Calcd log P		
		This method[b]	π-Addition[c]	f-Addition[c]
$C_6H_5CH_2OH$	0.87	0.87	1.47	0.98
$C_6H_5CH_2CH_2OH$	1.36	1.36	1.97	1.51
$C_6H_5CH_2CH_2CH_2OH$	1.88	1.85	2.47	2.04
$C_6H_5CH_2COOH$	1.41	1.30	1.96	1.42
$C_6H_5CH_2CH_2COOH$	1.84	1.99	2.46	1.95
$C_6H_5CH_2CH_2CH_2COOH$	2.42	2.50	2.96	2.47
$C_6H_5CH_2NH_2$	1.09	0.89	1.44	1.04
$C_6H_5CH_2CH_2NH_2$	1.41	1.37	1.94	1.57
$C_6H_5CH_2CH_2CH_2NH_2$	1.83	1.87	2.44	2.10
$C_6H_5CH_2CN$	1.56	1.19	1.79	1.29
$C_6H_5CH_2CH_2CN$	1.70	1.69	2.29	1.82
$C_6H_5CH_2CH_2CH_2CN$	2.21	2.20	2.79	2.35
Sum of squared errors	—	0.22	3.57	0.28

a) Ref. 7. *b*) Using Eq. 6. *c*) Ref. 5.

Table V. Regression Equations for Water Solubility of Organic Liquids

$$\log(1/S)^{a)} = k_1 S_A + k_2 \Sigma S_H + k_0$$

Type of compd.	k_1	k_2	k_0	n[b]	r[c]
Alkanes	2.22	[d]	−1.68	16	0.949
Alkenes	2.26	−1.16	−1.81	12	0.987
Alkynes	2.41	−0.93	−2.58	7	0.999
Aromatics	2.40	−0.91	−2.77	16	0.988
Alkyl halides	2.34	−1.13	−2.30	20	0.946
Ketones	2.38	[d]	−5.44	13	0.986
Esters	1.91	[d]	−4.20	18	0.989
Alcohols	2.21	−0.75	−3.23	41	0.969
Ethers	2.21	[d]	−4.72	12	0.926
All compds.	2.23	−1.31	−1.80	156[e]	0.981

a) S: water solubility in molar concentration. *b*) Number of compounds. *c*) Correlation coefficient. *d*) Not significant at $p \leqq 0.05$. *e*) Including one nitrile.

As shown in Table IV, our calculation using S_A and S_H is in good agreement with the experimental values, as well as the result of calculation by the f-addition method.

Application of S_A and S_H to Regression Analysis of Water Solubility Data

The usefulness of S_A and S_H in studies of hydrophobic phenomena was tested with the water-solubility data[14] for 156 miscellaneous organic liquids by the use of multiple regression analysis. The set of compounds includes 16 alkanes, 12 alkenes, 7 alkynes, 16 aromatics, 20 alkyl halides, 13 ketones, 18 esters, 41 alcohols, 12 ethers, and one nitrile. The regression equations obtained for each type of compound and for all the compounds are shown in Table V. The detailed figures for individual compounds are omitted because of limited space. No compound was excluded from the original set of data[14] in the derivation of the equations.

The correlation calculated with all compounds is given by Eq. 7, where S is the water-solubility in molar concentration.

$$\log(1/S)=2.23(\pm 0.11)S_A-1.31(\pm 0.05)\Sigma S_H-1.80(\pm 0.27)$$

$$n=156 \quad r=0.981 \quad s=0.26 \quad F=1963.3 \qquad (7)$$

The correlation in Eq. 7 is superior to those of the original study[14] (Eq. 8) and our previous study[12] (Eq. 9).

$$\log(1/S)=1.34(\pm 0.07)\log P-0.98(\pm 0.15)$$

$$n=156 \quad r=0.935 \quad s=0.47 \qquad (8)$$

$$\log(1/S)=3.73(\pm 0.26)V_W-4.10(\pm 0.22)V_H-0.72(\pm 0.26)$$

$$n=156 \quad r=0.960 \quad s=0.37 \qquad (9)$$

In Eq. 9, V_W is the van der Waals volume and V_H is the hydrophilic effect.

The ratio of the coefficients for S_A and ΣS_H in Eq. 7 is -1.70, which is a little greater than that (-1.90) in Eq. 6. This suggests that the contribution of the hydrophilic effect of polar moieties is slightly greater in the aqueous dissolution process than in the octanol–water partition process.

Conclusion

A new method for estimating log P by the use of S_A and S_H is proposed. The correlation between observed and estimated values of log P is excellent with 138 miscellaneous compounds. Moreover, the differences in log P among geometrical isomers can be estimated by the present method.

To enhance the usefulness of the present method, S_H values for moieties not included in Table III, especially for heterocyclic moieties, must be determined. In addition to this, some correction for electronic effects on S_H should be introduced for more accurate estimation of log P. Although the present method is still imperfect as mentioned above, it seems to be a promising approach for estimating log P. Furthermore, the present method may offer some insight into the physicochemical nature of hydrophobic phenomena such as drug–biopolymer interactions.

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