

A New Group Contribution Approach to the Calculation of LogP

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Abstract: A new improved group contribution model that predicts the n-octanol/water partition coefficient (logP) is described. A combined parameter set that contains 153 basic parameters, 41 extended parameter and 14 molecular surface/property descriptors was generated from a training database of 8320 chemicals. The model achieved significant improvement after modifying the traditional group contribution equation by using a three dimensional steric hindrance modulator. The predictive ability of this model was accessed by calculating the logP values of a test set of 1667 ordinary organic chemicals and a set of 137 drug-like chemicals that were not included in the training database.

Keywords: n-octanol/water partition coefficient, group contribution, KlogP, calculation.

INTRODUCTION

The logarithm of the partition coefficient between n-octanol and water (logP) is commonly used to represent the lipophilicity of a molecule. In many quantitative structure-activity relationship (QSAR) studies (like biodegradation rate, soil sorption coefficient, bioconcentration factor and many pharmacological endpoints), logP has been used as a key parameter to estimate the biological activities of organic compounds. Experimental measurement of logP is reliable and accurate but it is prohibitive in most cases where a large number of molecules have to be tested in a short time. Furthermore, it is sometimes important to know the lipophilic properties of a compound before it is synthesized. Computation models which can give reliable estimation of the logP value for new compounds are therefore, important, particularly for pharmacological property prediction and drug design.

Methods for estimating logP values developed before the 1980s were reviewed by Lyman (1990) [1]. Since that time, many new methods have been proposed and the prediction accuracy and coverage have been significantly improved in these reports [2-11]. Methods for estimation logP can be divided into two classes. 1) The first type of methods is classified as 'substructure' approaches, in which the molecular structure is represented by atoms (atom contribution methods) [6] or fragments (group contribution methods) [2] and the LogP value is obtained by adding the contributions of each atom or fragment of the molecules. 2) The 'whole structure' approaches on the other hand, utilize descriptors like molecular lipophilicity potentials (MLP) [12], topological indices [13] and/or global molecular features [14] to calculate logP. Compared with the substructure approaches, less descriptors are needed in whole structure approaches. However, these kind of methods need experimental correction factors (like melting point or boiling point), or complex correction terms. Thus, the 'substructure

approaches' are more practical because they allow the calculation of logP directly from the chemical structure. On the negative side, however, substructural methods need a large and diverse training dataset in order to identify the contribution of the large number of possible structural fragments.

In the past ten years, many atom/group contribution approach models for estimation of logP values have been developed and implemented in computer programs. Current popular logP models include CLogP [2], KLogP [3], HLogP [4], ALogP [5], XLogP [6], Σf system [7], ACDLogP [8], SMILELOG [9], CHEMICALC [10] and LOGKOW [11]. Most of these models are currently available as commercial software packages. However, several limitations exist in most of the current atom/group contribution models. They can be summarized as follows: First, the correction factors used in these logP models are generally complex and difficult to relate to physicochemical mechanisms. Second, it is difficult to define correct descriptors. In other words, the descriptors generated from chemicals of the learning set work well with the learning set itself but fail to predict the logP value of 'unknown' chemicals. To overcome these problems, we have developed a new group contribution model for logP prediction based on our previous work [3]. This model requires significantly less parameters than most of the logP models mentioned above. Its predictive ability was verified by testing two 'unknown' test sets which contain 1663 ordinary organic chemicals and 137 drug-like chemicals. The major improvement of this model, compared to previous ones, is the use of a steric hindrance index to modify the traditional group contributions.

METHOD

Data Source

Originally a database of 11073 diverse compounds was compiled from various publications. The data used was all reported to have been obtained at 25°C. After removing mixtures and compounds that exist as gases under the selected experimental conditions, 9987 unique compounds

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were identified for the development and test of our new logP model. This database was split into two parts. 8320 compounds, which were randomly selected and used as a 'training set' for the development of the logP model and the remaining 1667 compounds were used as an unbiased test set. The whole training set is available upon request from the authors.

The molecular structure of each chemical was encoded using the SMILES code [15]. A program using the DREIDING force field [16] was utilized to simulate the molecular structure when the molecular properties were calculated.

Computational Model

Using the basic group contribution approach, the logP value of a chemical is calculated from an equation as:

$$\text{Log}P = C_0 + \sum_{i=1}^n C_i G_i \quad (1)$$

Where C_0 is a constant characteristic of the solvent, C_i is the number of occurrence of the i th group, which is a specific atom or fragment, in a molecule and G_i is the contribution coefficient of the i th group.

The training set of 8320 chemicals with experimental logP values were fitted with the parameter sets described in the next section. It gave a new logP model (Model 1) with the statistical result as $R^2 = 0.915$ and $\sigma = 0.49$ (Table 1).

Table 1. Comparison Between the Results Obtained for the Group Contribution Methods with and Without Using the Steric Factor

Model	R^2	σ	F
Model 1	0.915	0.49	487
Model 2	0.922	0.46	531

Steric hindrance plays an important role in determining the logP value of a molecule. For example, the logP value of 2,4-di-*t*-butylphenol is larger than that of its isomer 2,6-di-*t*-butylphenol. In traditional group contribution models, the difference was normally accounted for by including an extra correction factor which is normally another substructural descriptor. Thus, it normally needs a very large number of similar correction factors to account for such differences of logP values induced by steric.

To solve this problem, we introduced a steric index H_i originally proposed by Cherkasov [17] and modified the equation 1 as:

$$\text{Log}P = C_0 + \sum_{i=1}^n C_i (1 - H_i) G_i \quad (2)$$

In this equation, the parameter H represents the steric hindrance of the i th atom by other atoms in a molecule and can be calculated using the following equation:

$$H_i = \sum_{j \neq i}^n \frac{R_j^2}{A \cdot r_{ij}^2} \quad (3)$$

Where A is a constant; R_j is the atomic radius of the j th atom and r_{ij} is the distance between the i th and j th atoms [17].

Thus, the H value of the i th atom will range from a minimum value as 0 to a maximum as 1 and proportional to its shielding by all other atoms of the molecule. As a result, a functional group with large substituents nearby will not contribute much to the estimated logP value. Using this equation, a new model (Model 2) was developed based on the same training set and parameters. It provided a small but significant improvement in accuracy (Table 1).

RESULTS AND DISCUSSION

Parameter Selection

The key in the development of the new logP model resides in the selection of reliable parameters. Based on the diversity of the atoms and the environment of atoms inside the molecule, 153 basic parameters were selected. Every non-hydrogen atom in a molecular structure is used as a 'center' for a basic parameter. Specific functional groups like carbonyl ($>C=O$), nitro ($-NO_2$), and so on are also treated as centers of parameters. The bonds connected with these centers are also described, like cyclic ($-CH<$), aliphatic ($-CH<$), nitro group binding with aromatic ring or binding with aliphatic atom, and so on. Moreover, for atoms in a ring, more parameter diversity is used based on the variety of the environments of center atoms. First, the types of ring structures are classified as 3-member, 4-member and normal ring structure. Second, the atoms included in more than one ring are distinguished from the atoms included in one ring. For example, the logP value of dodecahydro-phenalene (CAS 2935-07-1) is calculated to be the result of the contributions of nine $-CH_2-$ in a ring, three $-CH<$ in two rings and one $-CH<$ in three rings (Fig. (1)). Third, if any center atom has a lone electron pair, i.e. the oxygen atom of a carbonyl group, it is necessary to account for it whether there is resonance effect between this atom and its neighbors. Because of this rule, the carbonyl group in 3-Penten-2-one (CAS 625-33-2) is represented a different parameter than the carbonyl group in 2-Pentenone (CAS 107-87-9). The details of some basic parameters used in our final logP model are listed in Table 2.

Num.	Description	Ring	Ring type	Aromaticity
9	-CH ₂ -	1	Normal	-
3	-CH-	2	Normal	-
1	-CH-	3	Normal	-

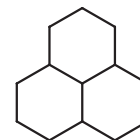


Fig. (1). The basic parameters identified from the molecular structure of dodecahydro-phenalene.

In addition, a set of 14 surface areas and molecular volume descriptors were used. These include total Van der Waals volume, polar surface areas, hydrophobic surface areas,

Table 2. List of Basic Parameter Set

N	Description *	Ring	Ring type	Aromaticity	Resonance effect	Freq. of use
1	-CH ₃ or CH ₄	-	-	-	-	10463
2	-CH ₂ -	-	-	-	-	9278
3	-CH<	-	-	-	-	1584
4	>C<	-	-	-	-	635
5	=CH ₂	-	-	-	-	119
6	=CH-	-	-	-	-	194
7	=C<	-	-	-	-	162
8	CH\$C-	-	-	-	Yes	1
9	-C\$C-	-	-	-	Yes	44
10	CH\$C- or -C\$C-	-	-	-	No	40
11	-CH ₂ -	1	Normal	-	No	4516
12	-CH ₂ -	1	3-member	-	-	165
13	-CH ₂ -	1	4-member	-	-	54
14	-CH<	1	Normal	-	-	2073
15	-CH<	1	3-member	-	-	86
16	-CH<	1	4-member	-	-	75
17	>C<	1	Normal	-	-	376
18	>C<	1	3-member	-	-	35
19	>C<	1	4-member	-	-	5
20	=CH-	1	Normal	-	-	133
21	-N<	2	4-member	-	No	41
22	=CH-	1	4-member	-	-	2
23	-CH=	1	Normal	Yes	-	29534
24	-OH	-	-	-	No	1635
25	-CH ₂ -OH or -C(OH)-	-	-	-	-	878
26	-C-OH	-	-	-	-	67
27	Ph-OH	-	-	-	-	781
28	-OH	-	-	-	Yes	1573
29	-O-	1	Normal	-	No	421
30	-O-	-	-	-	No	761
31	-CH=O	-	-	-	No	18
32	Ph-C(=O)OH	-	-	-	-	207
33	-C(=O)OH	-	-	-	-	726
34	-C(=O)O-	-	-	-	-	1458
35	-C(=O)O-	1	Normal	-	-	109
36	-C(=O)NH ₂	-	-	-	-	353
37	-C(=O)NH-	-	-	-	-	1649
38	-C(=O)N<	-	-	-	-	510
39	-C(=O)N=	-	-	-	-	7
40	-C(=O)-	-	-	-	No	133
41	-C(=O)-	1	Normal	-	No	39
42	-N=O	-	-	-	Yes	154
43	-S=O	-	-	-	No	25
44	-CH ₂ -NH ₂	-	-	-	-	100
45	-CH-NH ₂ or C-NH ₂	-	-	-	-	101
46	Ph-NH ₂	-	-	-	-	866
47	-NH ₂	-	-	-	No	420

(Table 2). contd....

N	Description *	Ring	Ring type	Aromaticity	Resonance effect	Freq. of use
48	-NH-	-	-	-	No	221
49	-N-	-	-	-	No	216
50	-NH-	1	Normal	-	No	83
51	-N<	1	Normal	-	No	236
52	Ph-N\$C	-	-	-	-	148
53	-N\$C	-	-	-	-	88
54	=N-	-	-	-	Yes	578
55	=N-	1	Normal	-	No	1
56	Ph-NO ₂	-	-	-	-	1538
57	-NO ₂	-	-	-	-	1678
58	-SH	-	-	-	No	7
59	-S-	-	-	-	No	127
60	-S-	1	Normal	-	No	57
61	-P<	-	-	-	Yes/No	3
62	-P<	1	Normal	-	Yes/No	1
63	-SO ₂ -	-	-	-	-	992
64	-SO ₂ -	1	Normal	-	-	300
65	P=O	-	-	-	No	115
66	P=O	1	Normal	-	No	10
67	=C<	1	Normal	-	No	77
68	S=C<	1	Normal	-	Yes	23
69	-CH<	3	Normal	-	-	80
70	-CH<	2	Normal	-	-	642
71	-F	-	-	-	No	940
72	Ph-F	-	-	-	-	328
73	-Cl	-	-	-	No	566
74	Ph-Cl	-	-	-	-	1905
75	Ph-Br	-	-	-	-	338
76	-Br	-	-	-	No	94
77	Ph-I	-	-	-	-	127
78	-I	-	-	-	No	18
79	-O-	1	3-member	-	No	31
80	-O-	1	4-member	-	No	4
81	-NH _n -C(=N)-NH _n -	-	-	-	-	79
82	-NH _n -C(=N)-NH _n -	1	Normal	-	-	2
83	-NH-	1	3-member	1	-	10
84	P(=O)OH	-	-	-	-	8
85	-N<	1	3-member	-	-	30
86	-NH _n -C(=S)-NH _n -	-	-	-	-	60
87	-NH-	1	Normal	Yes	-	392
88	=N-	1	Normal	Yes	-	2876
89	=C<	1	Normal	-	Yes	1865
90	=C<	2	Normal	-	Yes	150
91	P=S	-	-	-	No	82
92	-N=N-	-	-	-	-	136
93	-S-	1	Normal	Yes	-	274
94	-O-	1	Normal	Yes	-	296

(Table 2). contd.....

N	Description *	Ring	Ring type	Aromaticity	Resonance effect	Freq. of use
95	-c =	1	Normal	Yes	-	15706
96	-c =	2	Normal	Yes	-	3696
97	-c =	3	Normal	Yes	-	49
98	-CH<	2	3-member	-	-	40
99	-CH<	2	4-member	-	-	43
100	>C<	2	Normal	-	-	400
101	>C<	2	3-member	-	-	4
102	-C(=O)-NH-	1	Normal	-	-	447
103	>C<	3	Normal	-	-	48
104	-C(=O)-N<	1	Normal	-	-	284
105	-C(=O)-N<	2	Normal	-	-	11
106	-N<	2	Normal	-	-	17
107	-C(=O)-N<	2	Normal	Yes	-	23
108	-C(=O)-	1	Normal	Yes	-	469
109	=CH2	-	-	-	Yes	104
110	=CH-	-	-	-	Yes	652
111	=C<	-	-	-	Yes	4699
112	-O-	1	Normal	-	Yes	283
113	-O-	-	-	-	Yes	3193
114	-CH=O	-	-	-	Yes	103
115	=CH-	1	Normal	-	Yes	465
116	-C(=O)-	-	-	-	Yes	4276
117	-C(=O)-	1	Normal	-	Yes	1076
118	-N=O	-	-	-	Yes	154
119	NH=	-	-	-	Yes	72
120	-NH ₂	-	-	-	Yes	1436
121	-NH-	-	-	-	Yes	2125
122	-N-	-	-	-	Yes	764
123	-NH-	1	Normal	-	Yes	560
124	-N<	1	Normal	-	Yes	457
125	-N=	1	Normal	-	Yes	361
126	-SH	-	-	-	Yes	10
127	-S-	-	-	-	Yes	280
128	-S-	1	Normal	-	Yes	101
129	-C(=S)-	-	-	-	Yes	52
130	-SO ₃ H	-	-	-	-	18
131	-S(=O)(=O)N _n	-	-	-	-	476
132	Ph-O-Ph	-	-	-	-	148
133	>[N+]-O-	-	-	-	-	7
134	-N<	1	Normal	Yes	-	621
135	>C< or >CH-	3	3 or 4-member	-	-	3
136	-S-S-	-	-	-	-	4
137	-C(=O)-	1	4-member	-	Yes	58
138	-NH _n -C(=S)-NH _n -	1	Normal	-	-	17
139	-NH-	1	4-member	-	Yes	11
140	-N<	1	3-member	-	Yes	19
141	-N<	1	4-member	-	Yes	7
142	-N=O	1	Normal	Yes	-	70
143	-NSC	-	-	-	Yes	285
144	Ph-S-Ph	-	-	-	-	18

(Table 2). contd....

N	Description*	Ring	Ring type	Aromaticity	Resonance effect	Freq. of use
145	-F	-	-	-	Yes	331
146	-Cl	-	-	-	Yes	1982
147	-Br	-	-	-	Yes	360
148	-I	-	-	-	Yes	127
149	N _n -C(=O)-N _n	-	-	-	-	582
150	N _n -C(=O)-N _n	1	Normal	-	-	181
151	Ph-C(=O)-NH ₂	-	-	-	-	135
152	Ph-C(=O)NH-	-	-	-	-	245
153	Ph-C(=O)N<	-	-	-	-	52

* 'n' ranges from 0 to 2.

positively and negatively charged surface areas. Partial charges on atoms were calculated using Gasteiger method [18] and used in conjunction with the surface area calculations. We have developed an algorithm for calculating the surface areas from the 2D structure of the molecules. It sums up individual atomic contributions to surface area by looking up in a table of values which was initially built by studying a large number of organic molecules. The algorithm was validated by comparing calculated surface areas from 2D structure with the surface areas calculated using Connolly's algorithm using the same structures but complete with 3D coordinates. We have used the Tinker molecular modeling software* for calculating Connolly's surface area and volume. A squared correlation coefficient (r^2) of 0.99 was obtained between the two sets of surface areas. Similar algorithm was used to calculate molecular volumes.

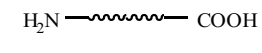
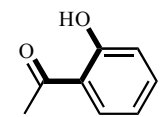
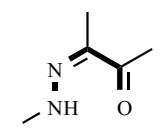
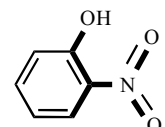
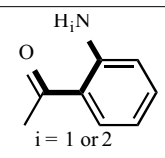
It is widely accepted that in some molecules, the interactions between functional groups may affect their lipophilicity. For this reason, correction factors are needed for most logP models. While basic parameters are used to describe the diversity of the heavy atoms and functional groups, correction factors were used to account for internal hydrogen bonds, tautomerization effect and other effects between diverse functional groups. In our study, an artificial intelligent program MCASE was used to help find the fragments which were used as correction factors in our study. The algorithm used in the Multiple Computer Automated

Structure Evaluation (MCASE) program was previously described by Klopman [19]. This program was used to identify the fragments which are responsible for the observed differences between the experimental and predicted logP values obtained only from the basic parameter set. From this analysis, 41 substructures which were statistical significant and/or had relative physicochemical mechanism basis were identified and used as correction factors in our final logP model (Table 3).

The first correction factor listed in Table 3 represents the substructure of amino acid type compounds. The simultaneous presence of -COOH and -NH₂ groups in this substructure makes this kind of molecules exist in a zwitterionic form instead of the neutral forms. This transformation lowers the logP values of the molecules that contain them.

In salicylic acid, the interaction between -COOH and -OH groups was found to have an effect on its logP value. This effect is due to the intramolecular hydrogen bond formed between ortho >C=O and -OH groups. The second correction factor in Table 3 was used to account for this effect in our model. Correction factors 3, 4 and 5 reflect other substructures that are able to form intramolecular hydrogen bonds and their effects on logP values (Table 3).

Table 3. Examples of Correction Factors

No.	Fragments	Type	Coeff.	Freq. of use
1		Zwitterionic forms	-0.59	84
2		Internal hydrogen bond	1.507	98
3		Internal hydrogen bond	2.187	35
4		Internal hydrogen bond	0.664	42
5		Internal hydrogen bond	1.28	50

Compared to most of the current available group contribution logP models which contain hundreds of correction factors [8, 11], only 41 correction factors were utilized in our model and similar prediction rate was archived for similar size of training database. It is due to both the high quality of our basic parameter set and the inclusion of the steric modulator. To use additional correction factors in our model resulted in more accurate results, but lower *F* statistic values. It indicates that the additional correction factors may not be reliable and may possibly damage our final logP model.

*<http://dasher.wustl.edu/tinker/>

Table 4. Statistical Results for LogP Prediction of 'Unknown' Chemicals Using ClogP, Previous KlogP, Model 1 and Model 2 in this Study

Model	Normal Chemicals*		Drugs**	
	R ²	σ	R ²	σ
ClogP	0.87	0.79	0.82	0.86
Previous KlogP	0.86	0.74	0.64	1.12
Model 1	0.88	0.69	0.74	1.08
Model 2	0.89	0.65	0.83	0.78

*The total number of ordinary organic chemicals is 1667.

**The total number of drug-like chemicals is 137.

Prediction of the Unknown Test Set

A good logP model must provide accurate logP predictions for chemicals not included in its training set. In our study, the first unbiased test set was that containing the 1667 compounds which were randomly excluded from the training database. Using our new logP model (Model 2) to predict this test set, the overall correlation (R²) is 0.89 and standard deviation (σ) is 0.65 (Table 4). The results obtained from previous KlogP model, including Model 1 and another popular group contribution logP model (ClogP*), were also listed (Table 4). As can be seen, our new model gives the best prediction for this test set as compared to the other three models.

We recently collected 137 drugs and drug-like chemicals whose experimental logP values was known but not available when we started this study. None of these compounds are included in either the training set or the first test set mentioned above. Thus, this set represents a second unbiased test of the prediction ability of our logP model. Using Model 2, the overall correlation (R²) is 0.83 and standard deviation (σ) is 0.78 (Table 4). The results were also compared with those obtained from ClogP, previous KlogP model and Model 1 (Table 4). Our new model again gives the best correlation (R²) and the lowest standard error (σ) for these drug-like chemicals.

Compared to the result obtained from Model 1, the clear improvement achieved by Model 2 indicates the importance of including the steric index as a general modulator for all the substructural parameters in the model. It also shows that there is still room, and hope, for improving the predictions of other physicochemical properties and biological activities using the group contribution approach.

CONCLUSION

A modified group contribution approach was used to correlate the logP value of 8320 organic chemicals. The

model was significantly improved after using steric effect as a general modulator for all the substructural parameters. The prediction ability of this model was verified by calculating the logP values of two 'unknown' test set. The new model presents higher prediction rate for both normal organic and drug-like compounds compared to ClogP and our previous KlogP model.

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*The ClogP values were calculated by using ChemOffice Ultra® (version 7.0).