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Research Article

STUDIES IN ESTIMATION OF LOGP VALUES FOR SUBSTITUTED AROMATIC COMPOUNDS AND COMPARISON WITH OTHER RESOURCES USING SIMPLE EXPEDIENT METHOD

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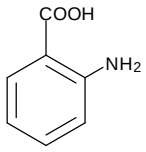
Abstract

The estimation of logP values has been considered for substituted aromatic compounds in present work by simple and expedient method to lead with structure-property relationships, showing that good enough results are achieved when resorting to a rudimentary form of information theory. A new factor "ortho factor" is derived to estimate the logP values for ortho substituted compounds. The logP values for a broad range of organic compounds are calculated and results are compared with others, arising from other methods. The agreement between the developed method and experimental value is found to be very good.

Key words: Partition coefficient, log P, QSAR, aromatic compounds

Graphical Abstract:



$\log P_{calculated} = 1.21$

$\log P_{experimental} = 1.21$

Deviation = 0.00

Introduction:

A fundamental idea in chemistry is that the structural characteristic of molecule is accountable for its properties[1]. The mathematical structure- property relationships quantify the correlation between the structures and the properties of molecule. The relationships are mathematical models that permit the

prediction of properties from structural parameters. The purpose of the present work is to investigate a very simple yet accurate method to deal withthe structure- activity (property) relationships, showing that good enough results can be obtained when using a somewhat rudimentary form of information theory. Molecular descriptors are the number and sort of atoms and the classical chemical bonds and functional groups. The molecular partition coefficient in 1-octanol/water system is the physical chemical property chosen to study through the present method for a wide range of organic molecules.

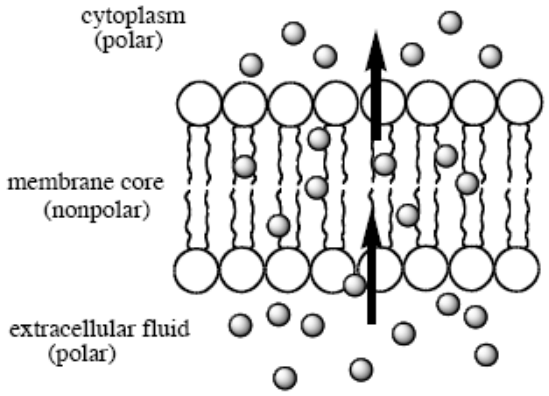


Figure 1: Direction of travel of drug/medicine

Drug molecules must cross a number of membranes before they can reach their target. During their journey across the body, they must dissolve in the aqueous environments of cytoplasm and extra cellular fluids as well as in the relatively non-polar environment of the cell membrane's interior (figure 1). Thus good drug must have reasonable partition between the two phases. The best way to estimate the ability of a compound to dissolve in both aqueous as well as non-polar environment is by measuring its partition coefficient. The so-called "logP" (i.e. the log of molecular partition coefficient in n-octanol/water system) is a very simple measure of a hydrophobic/ lyophilic character of given substance.

This parameter can be available from experimental determinations for extensive series of molecules using shake-flask method, reverse phase HPLC etc. , but there are cases where such values are still unknown as, for example, when molecules are completely new or/and when the experimental determination is rather difficult or subject to large uncertainties or time consuming and expensive. Consequently, several theoretical evaluation methods have been proposed for determining the logP values. Hansch and Leo[2] have given a somewhat complete updated review on measurement and

calculation methods of the hydrophobic parameter. Among the host of alternative methodologies to compute logP, that one based on fragment method was introduced by Rekker and coworkers[3,4] is closely related to our proposed method. A quite interesting way of calculating logP based on the idea of hydrophobic atomic contribution given by Ghose and Crippen[5] and later extensively used and modified. However, this approach has received criticism. A more detailed description of all these methods is beyond the scope of this paper. In addition a good number of software packages are also available to predict the logP values, but the problem with these packages, however, is that the results can differ widely (2 or more logP units) and differ from the experimental value[5].

2) Methodology:

More than two hundred molecules of relatively small size were randomly selected so as to cover the basic structures of organic compounds as much as possible and their experimental values were cited from the literature[5-8]. Aliphatic as well as aromatic molecules with diverse functional groups ranging from halogens, -OH, $-NH_2$, $-NO_2$, -CN, -X etc. were chosen to increase applicability of the method. The contribution factors for substituents were calculated by the method used by A. Leo[5] et *al*, however, by using more number of analyses. A comparison of contribution factors for few substituents is given in table 1.

Example:

$\log P_{\text{m-nitrobenzoic acid}} = 0.1313 \times 6 + 0.224 \times 4 + 0.08 \times 0.778 + 0.090 + 0.0962 = 1.926$ calcd

1.95 obsd

$\log P_{\text{p-nitrobenzoic acid}} = 0.1313 \times 6 + 0.224 \times 4 + 0.08 \times 0.708 + 0.090 + 0.0962 = 1.932$ calcd

1.96 obsd

$\log P_{\text{o-nitrobenzoic acid}} = 0.1313 \times 6 + 0.224 \times 4 + 0.090 + 0.0962 + -0.0869 + -0.4031 = 1.38$ calcd

1.46 obsd

Estimation of logP values for ortho substituted compounds is a difficult task since ortho substituents in reaction of aromatic compounds usually introduce polar and appreciable steric effects simultaneously. As

there is no general method of analysis of the resulting thermodynamic or kinetic data which will extract the separate polar and steric contributions to these composite structural effects[9] and therefore many time give predicted logP values far different from experimental values, hence a new quantity referred as 'Ortho factor' has been established and optimized to get best 'fit value' to estimate the values of ortho substituted compounds. The ortho factors were calculated with the assumption that after calculating the logP values by proposed formula, the difference between the experimental and calculated logP is because of ortho position of two groups with each other that is ortho factors are solely responsible for the deviation in the values. The calculation was first performed on symmetrically disubstituted aromatic molecules like o-dibromobenzene, catechol etc. The value obtained by the formula was then made 'best fit' of by using other o-disubtituted molecules with one substitutuents common to predict the logP values. The ortho factors were calculated by the formula:

$$\text{Ortho factor} = \frac{\text{Experimental logP} - \left(\begin{array}{l}\text{0.1313 x no. of aromatic carbons + 0.224 x no. of}\\ \text{aromatic hydrogens + 0.08 x } \sigma_{\text{position}} \text{ + Contribution}\\ \text{factors}\end{array}\right)}{2}$$

Example:

Ortho factor for –Br by using 0-dibromobenzene = 3.64 – 3.8658/2 = 0.1129

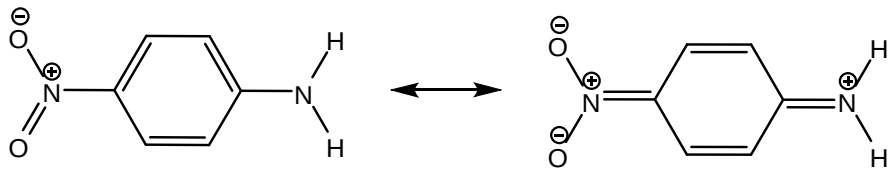
In order to minimize the errors 'Correction factors' were devised from analyzing the calculated and experimental logP values.

Correction factors:

Since the present fragment additive method is based on two-dimensional structure of molecule and do not consider other factors like polarity, steric factors etc., significant error in estimation may occur. Many other approaches have demonstrated that, in such cases, using correction factors is an efficient way to improve accuracy of logP estimation. We accept that finding and deciding correction factors is a tedious and time taking process. In fact, it is just as difficult as for either a 'Constructionist approach' or a 'Reductionist approach'. Some fragment additive methods, such as KOW-WIN[11], use large number of

correction factors. In our method, we have introduced and used few correction factors, which are general in nature. These are listed in Table 2.

Many researchers, including Hammett, have observed that for groups like –OH, -NH_2 etc which are strong electron donating and have high resonance effect, different σ constants should be used for electron withdrawing groups. For eg. The nitro group has a σ_p value of 0.778, but for p-nitrophenol or p-nitroaniline a value of 1.27 should be used. The probable reason might be the high resonance involved as in p-nitroaniline[10]. Consequently the probable reason for these correction factors might be the resonance, steric or other factors.



3) Results and Discussions:

The regression equation and calculated regression coefficients are as follows:

LogP = 0.1313 x N_C + 0.224 x N_H + 0.08 x $\sigma_{position}$ + Contribution factor + I_A x (Ortho factor O_Φ)

Where, N_C is number of carbon atoms in aromatic ring for aromatic molecule and for aliphatic molecule it is the number of carbon atoms in molecule,

N_H is number of hydrogen atoms in aromatic ring for aromatic molecule and for aliphatic molecule it is the number of hydrogen atoms in molecule,

I_A is 1 for ortho substituents and 0 (zero) for meta, para substituents.

The equation yield n = 156, r = 0.997, r^2 = 0.996, s.d. = 0.161, Q = 6.192. The standard deviation 0.161 log unit is within the experimental range that is generally considered to be 0.40 log units. All these results

demonstrate the acceptable predictive ability of our method for logP calculation. A high value for Pogliani quality factor[9] Q indicates high predictive power of the method.

The table 1 contains the fragment constants and ortho factors for various common groups along with their σ values. The experimental and calculated logP values for the different molecules are present in table 2, where one can verify the good agreement between both sort of results. The numerical data given in table 3 shows that the resulting predictions compare well with experimental logP values.

Comparison to other logP calculators available:

As mentioned in the introduction section, many approaches have already been developed for logP prediction. Some of them offer results comparable with experimental values. The estimated values were compared with various resources like ACD 11.0 freeware, Chem Draw Ultra 8.0 and KOW-WIN, which are well-established, commercially available procedures and frequently used by researchers to estimate logP values. The table 4 shows that the values calculated are in better agreement than some of the resources used for prediction of logP. To further check validity of our method, the results were checked and compared with above mentioned logP calculators by the method introduced by Mannhold[9].

The method and results were also evaluated as follows: the individual estimation errors are grouped using Mannhold's criteria[9]: errors less than +/- 0.50 are considered as acceptable; errors greater than +/- 0.50 and less than +/- 1.00 are considered as disputable; and errors exceeding +/- 1.00 are considered as unacceptable. The missing calculations are also counted. All these results indicate that the present method, if not the best, has quite satisfactory performance. The results are listed in table 5.

Table 1: Comparison of contribution factors for few substituents

Group	Contribution factor*		Fragment Constant#		Fragment constant**	
	f_ϕ	f_R	f_ϕ	f_R	f_ϕ	f_R
-COOH	0.0962	-1.0746	0.00	-1.00	-0.03	-1.09
-OH	-0.320	-1.6904	-0.37	-1.44	-0.40	-1.64
$-NO_2$	0.090	-1.1593	-0.09	-1.06	-0.02	-1.26
$-NH_2$	-1.000	-1.5304	-0.91	-1.38	-1.00	-1.54
$-CONH_2$	-0.9952	-2.1504	-1.26	-2.18	-1.26	-1.99
-S-	0.65	-0.9302	0.14	-0.51	0.03	-0.79
-CN	-0.320	-1.2305	-0.20	-1.13	-0.34	-1.28

* Present work # Nys & Rekker[3,4] ** A. Leo[5] *et al* method

Table 2: Fragment constants along with their σ values

a) Terminal fragments

Group	Contribution		Ortho factor	σ_{meta}^{10}	σ_{para}^{10}
	f_{ϕ}	f_R	O_{Φ}		
-COOH	0.0962	-1.0746	-0.4031	0.370	0.450
-OH	-0.320	-1.6904	-0.0819	0.121	-0.357
$-OCH_3$	0.225	-0.7905	-0.2669	0.115	-0.268
$-NO_2$	0.090	-1.1593	-0.0869	0.708	0.778
$-NH_2$	-1.000	-1.5304	0.2331	-0.160	-0.660
-F	0.330	-0.3805	0.0131	0.337	0.062
-Cl	0.942	0.0211	-0.0689	0.373	0.226
-Br	1.091	0.2990	-0.1129	0.391	0.232
-I	1.318	0.6100	0.0051	0.352	0.276
-CN	-0.320	-1.2305	-0.0269	0.678	0.660
$-CH_3$	0.650	0.8905	0.0681	-0.069	-0.170
$-COCH_3$	-0.320	-1.1305	-0.0819	0.376	0.502
$-CH_2-CH_3$	1.040	1.4401	-0.0219	-0.070	-0.150
$-CONH_2$	-0.9952	-2.1504	-0.7117	0.280	0.360
-CHO	-0.4172	-0.8501	-0.4247	0.360	0.220

-SH	0.6122	-0.1797	0.5482	0.250	0.150
$NHCONH_2$	-0.8138	-2.3340	-0.4031	0.180	
HCONH-	0.1262	-1.8070		0.250	
C_6H_5-	1.90	1.90		0.06	-0.01
-SCN	1.3722	1.38		0.63	0.52
-C-=CH	0.6222	0.0495		0.21	0.23
$-C=CH_2$	1.0422	0.8795		0.02	0.56
$-CF_3$	1.0621	1.4396		0.43	0.54
$-CSNH_2$	-0.4072	-1.9782			

b) Non-Terminal groups

Group	**Contribution**	
	f_ϕ	**f_R**
$-CH_2-$	0.5646	0.5496
-O-	0.380	-1.680
$-SO_2-$	-3.131	0.1083
-S-	0.65	-0.9302
-CH-		0.0900
-CO-	-0.52	-2.021
-NH-	-0.30	-2.14
-N<	-1.67	-2.90
-COO-	-0.21	-1.601
-CH=CH-	1.0122	0.8795
-CONH-	-1.5986	-1.690
-CON<	-2.782	-3.2212
-S-S-		-0.010

f_ϕ & O_Φ - a fragment attached to aromatic compound

Table 3: Correction factors

Sr. No.	Factor (In aromatic nuclei)	Contribution
1	-NO_2 with -$COCH_3$,o,m,p-NH_2, o,m,p-OH,	0.4975
2	-OH with m,p-NH_2, & m,p-OH	-0.2875
3	-CN with –NO_2	-0.3304
4	-CN with –NH_2 and o,m,p–OH	0.5833
5	-OH with -$COCH_3$,	-0.2684
6	-OH & –NH_2 ortho to -COOH	0.6000

Table 4: Experimental and Calculated logP values for the different molecules:

Sr. no.	Molecule	Experimental logP	Calculated logP	Deviation Δ
1.	Ph-H	2.13	2.13	0.00
2.	Ph-Cl	2.84	2.84	0.00
3.	Ph-F	2.27	2.23	0.04
4.	Ph-Br	2.99	2.99	0.00
5.	Ph-I	3.25	3.22	0.03
6.	Ph-NH_2	0.90	0.90	0.00
7.	Ph-OCH_3	2.11	2.13	-0.02

8.	Ph-$COCH_3$	1.58	1.58	0.00
9.	Ph-CH_3	2.69	2.55	0.14
10.	Ph-COOH	1.88	2.00	-0.12
11.	Ph-CH_2-CH_2-Ph	4.79	4.79	0.00
12.	1-Naphthol	2.85	2.78	0.07
13.	2-Naphthol	2.75	2.78	-0.03
14.	Ph-Ph	3.98	3.80	0.18
15.	Ph-O-Ph	4.21	4.18	0.03
16.	Ph-CN	1.56	1.58	-0.02
17.	Ph-$CONH_2$	0.65	0.90	-0.25
18.	Ph-OH	1.46	1.58	-0.12
19.	m-OH-Benzoic acid	1.50	1.48	0.02
20.	p-OH-Benzoic acid	1.41	1.43	-0.02
21.	o- OH-Benzoic acid	2.26	1.58	0.68
22.	m-NO_2-Benzoic acid	1.95	1.93	0.02
23.	p-NO_2-Benzoic acid	1.96	1.93	0.03
24.	o- NO_2-Benzoic acid	1.46	1.38	0.08
25.	m-OCH_3-Benzoic acid	2.02	2.01	0.01
26.	p-OCH_3-Benzoic acid	1.96	1.98	-0.02

27.	o- OCH_3-Benzoic acid	1.59	1.34	0.25
28.	m-CH_3-Benzoic acid	2.37	2.42	-0.05
29.	p-CH_3-Benzoic acid	2.27	2.41	-0.14
30.	o-CH_3-Benzoic acid	2.46	2.10	0.36
31.	m-CN-Benzoic acid	1.48	1.48	0.00
32.	p-CN-Benzoic acid	1.56	1.51	0.05
33.	m-Cl-Benzoic acid	2.68	2.75	-0.07
34.	p-Cl-Benzoic acid	2.65	2.74	-0.09
35.	o-Cl-benzoic acid	2.05	2.25	-0.20
36.	m-F-Benzoic acid	2.15	2.14	0.01
37.	p- F-Benzoic acid	2.07	2.11	-0.04
38.	o- F-Benzoic acid	1.77	1.72	0.05
39.	m-Br-Benzoic acid	2.87	2.90	-0.03
40.	p-Br-Benzoic acid	2.86	2.89	-0.03
41.	o-Br-Benzoic acid	2.20	2.36	-0.16
42.	m-I-Benzoic acid	3.13	3.13	0.00
43.	p-I-Benzoic acid	3.02	3.12	-0.10
44.	o-I-Benzoic acid	2.40	2.70	-0.30
45.	m-NH_2-Benzoic acid	0.65	0.76	-0.11

46.	p-NH_2-Benzoic acid	0.83	0.73	0.10
47.	o- NH_2-Benzoic acid	1.21	1.21	0.00
48.	p-Et-Benzoic acid	2.89	2.88	0.01
49.	Phthalic acid	0.73	1.07	0.34
50.	Terephthalic acid	2.00	1.98	0.02
51.	p-$COCH_3$-Benzoic acid	1.61	1.50	0.11
52.	o- $COCH_3$-Benzoic acid	0.81	0.98	-0.17
53.	o-dibromobenzene	3.64	3.64	0.00
54.	m-OH-Benzamide	0.39	0.38	0.01
55.	p-OH-Benzamide	0.33	0.34	-0.01
56.	m-NH_2-Benzamide	-0.33	-0.33	0.00
57.	p-NH_2-Benzamide	-0.44	-0.37	0.07
58.	m-OCH_3-Benzamide	0.84	0.92	-0.08
59.	p-OCH_3-Benzamide	0.86	0.89	-0.03
60.	m-NO_2-Benzamide	0.77	0.83	-0.06
61.	p-NO_2-Benzamide	0.82	0.84	-0.02
62.	o- NO_2-Benzamide	-0.12	-0.02	0.10
63.	m-CN-Benzamide	0.52	0.42	0.10
64.	p-CN-Benzamide	0.48	0.42	0.06

65.	o-F-benzamide	0.59	0.32	0.27
66.	o-Cl-benzamide	0.64	0.85	-0.21
67.	o-Br-benzamide	0.77	0.95	-0.18
68.	o-Me-benzamide	0.76	0.70	0.05
69.	o-I-benzamide	0.93	1.30	-0.37
70.	Phthalimide	-1.73	-1.73	0.00
71.	o-difluorobenzene	2.37	2.37	0.00
72.	m-OH-methoxybenzene	1.58	1.60	-0.02
73.	p-OH-methoxybenzene	1.58	1.57	0.01
74.	o- OH-methoxybenzene	1.32	1.24	0.08
75.	m-NH_2-methoxybenzene	0.93	0.92	0.01
76.	m-OCH_3-methoxybenzene	2.21	2.14	0.07
77.	p-OCH_3-methoxybenzene	2.04	2.11	-0.07
78.	o-dimethoxybenzene	1.60	1.60	0.00
79.	m-NH_2-phenol	0.21	0.06	0.15
80.	p-NH_2-phenol	0.04	0.02	0.02
81.	o- NH_2-phenol	0.62	0.52	0.10
82.	o-F-phenol	1.71	1.63	0.08
83.	m-Cl-phenol	2.50	2.34	0.16

84.	p-Cl-phenol	2.39	2.34	0.05
85.	o- Cl-phenol	2.15	2.15	0.00
86.	p-Br-phenol	2.59	2.47	0.12
87.	o- Br-phenol	2.35	2.26	0.09
88.	o- I-phenol	2.65	2.61	0.04
89.	p-I-phenol	2.91	2.70	0.21
90.	o- CN-phenol	1.61	1.52	0.09
91.	p-CN-phenol	1.60	1.68	0.08
92.	m-OH-phenol	0.80	0.76	0.04
93.	p-OH-phenol	0.59	0.77	-0.18
94.	Catechol	0.88	0.88	0.00
95.	m-NO_2-phenol	2.00	2.01	-0.01
96.	p-NO_2-phenol	1.91	2.01	-0.10
97.	o- NO_2-phenol	1.79	1.78	0.01
98.	m-Br-phenol	2.63	2.49	0.14
99.	m-I-phenol	2.93	2.71	0.22
100.	m-CN-phenol	1.70	1.68	0.02
101.	m-NH_2-aniline	-0.33	-0.33	0.00
102.	p-NH_2-aniline	-0.30	-0.37	0.07

103.	o-aminoaniline	0.15	0.15	0.00
104.	m-CH_3-aniline	1.40	1.33	0.07
105.	p-CH_3-aniline	1.39	1.32	0.07
106.	m-NO_2-aniline	1.37	1.33	0.04
107.	p-NO_2-aniline	1.39	1.33	0.06
108.	o-NO_2-aniline	1.85	1.42	0.43
109.	m-Cl-aniline	1.88	1.66	0.22
110.	p-Cl-aniline	1.83	1.64	0.19
111.	m-Br-aniline	2.10	1.81	0.29
112.	p-Br-aniline	2.26	1.80	0.46
113.	m-I-aniline	2.86	2.03	0.83
114.	p-I-aniline	2.34	2.02	0.32
115.	m-CN-aniline	1.07	1.00	0.07
116.	o-diethylbenzene	3.72	3.72	0.00
117.	m-Cl-Toluene	3.28	3.30	-0.02
118.	p-Cl-Toluene	3.33	3.29	0.04
119.	m-Br-Toluene	3.41	3.45	-0.04
120.	p-Br-Toluene	3.42	3.44	-0.02
121.	p-NO_2-Toluene	2.37	2.48	-0.11

122.	m-NO_2-Toluene	2.45	2.48	-0.03
123.	o-NO_2-toluene	2.30	2.40	-0.10
124.	o-OH-toluene	1.95	2.00	-0.05
125.	m-Xylene	3.15	2.98	0.17
126.	p-Xylene	3.20	2.97	0.23
127.	o-xylene	3.12	3.12	0.00
128.	m-Cl-acetophenone	2.51	2.34	0.17
129.	p-Cl-acetophenone	2.32	2.32	0.00
130.	m-Br-acetophenone	2.47	2.49	-0.02
131.	p-Br-acetophenone	2.43	2.47	-0.04
132.	m-NO_2-acetophenone	1.42	1.48	-0.06
133.	p-NO_2-acetophenone	1.53	1.52	0.01
134.	p-CN-acetophenone	1.22	1.12	0.10
135.	p-OH-acetophenone	1.35	1.08	0.27
136.	p-dichlorobenzene	3.44	3.58	-0.14
137.	o-dichlorobenzene	3.43	3.43	0.00
138.	m-dinitrobenzene	1.49	1.92	-0.43
139.	p-dinitrobenzene	1.46	1.93	-0.47
140.	o-dinitrobenzene	1.69	1.69	0.00

141.	o-Cl-nitrobenzene	2.24	2.56	-0.32
142.	o-Br-nitrobenzene	2.52	2.66	-0.14
143.	o-F-nitrobenzene	2.01	2.02	-0.01
144.	o-OCH_3-nitrobenzene	1.73	1.64	-0.09
145.	Mesitylene	3.42	3.40	0.02
146.	m-OCH_3-p-CH_3-Benzoic acid	1.43	1.35	0.08
147.	m-NO_2-p-CH_3-phenol	2.18	2.42	-0.24
148.	p-NO_2-m-CH_3-phenol	2.48	2.43	0.05
149.	m-OH-p-NO_2-benzoic acid	1.98	1.89	0.09
150.	m-NH_2-acetophenone	0.83	0.85	-0.02
151.	p-NH_2-acetophenone	0.83	0.81	0.02
152.	m-NO_2-benzonitrile	1.17	1.18	-0.01
153.	p-NO_2-benzonitrile	1.19	1.18	0.01
154.	o-NO_2-benzonitrile	1.02	1.01	0.01
155.	o-cyanobenzonitrile	0.99	0.99	0.00
156.	o-NO_2-ethylbenzene	2.58	2.70	-0.12
157.	phthaladaldehyde	0.51	0.51	0.00
158.	Salicyaldehyde	0.31	0.21	0.10

Δ = experimental logP-Calculated logP Ph = C_6H_5-

Table 5: Comparison with other log P predicting resources

Molecule	LogP experimental	Log P Model	Log P ACD11.0 freeware	Log P ChemDraw Ultra 8.0	Log P KOW-WIN*
Ph-H	2.13	2.13	2.22	2.03	2.13
Ph-Cl	2.84	2.84	2.81	2.59	2.64
Ph-F	2.27	2.23	2.27	2.19	2.19
Ph-Br	2.99	2.99	2.99	2.86	2.88
Ph-I	3.25	3.22	3.25	3.39	3.16
Ph-NH_2	0.90	0.90	0.94	0.90	1.08
Ph-OCH_3	2.11	2.13	2.13	2.08	2.07
Ph-$COCH_3$	1.58	1.58	1.66	1.35	1.67
Ph-CH_3	2.69	2.55	2.68	2.52	2.54
Ph-COOH	1.88	2.00	1.89	1.86	1.87
Ph-CH_2-CH_2-Ph	4.79	4.79	4.70	4.81	4.79
1-Naphthol	2.85	2.78	2.71	2.64	2.99
2-Naphthol	2.75	2.78	2.71	2.87	2.99
Ph-Ph	3.98	3.80	3.98	3.71	3.76
Ph-O-Ph	4.21	4.18	4.21	4.20	4.05
Ph-CN	1.56	1.58	1.65	1.56	1.54

Ph-$CONH_2$	0.65	0.90	0.74	0.65	0.74
Ph-OH	1.46	1.58	1.48	1.64	1.51
m-OH-Benzoic acid	1.50	1.48	1.50	1.49	1.39
p-OH-Benzoic acid	1.41	1.43	1.42	1.45	1.39
o-OH-Benzoic acid	2.26	1.58	2.06	2.27	2.24
m-NO_2-Benzoic acid	1.95	1.93	1.82	1.18	1.69
p-NO_2-Benzoic acid	1.96	1.93	1.89	1.18	1.69
o-NO_2-Benzoic acid	1.46	1.21	1.56	1.18	1.35
m-OCH_3-Benzoic acid	2.02	2.01	2.02	1.46	1.96
p-OCH_3-Benzoic acid	1.96	1.98	1.96	2.14	1.96
o-OCH_3-Benzoic acid	1.59	1.34	1.49	1.46	1.61
m-CH_3-Benzoic acid	2.37	2.42	2.35	2.08	2.42
p-CH_3-Benzoic acid	2.27	2.41	2.35	2.32	2.42
o-CH_3-Benzoic acid	2.46	1.92	2.35	2.08	2.08
m-CN-Benzoic acid	1.48	1.48	1.48	1.62	1.42
p-CN-Benzoic acid	1.56	1.51	1.56	1.62	1.42
m-Cl-Benzoic acid	2.68	2.75	2.90	2.15	2.52
p-Cl-Benzoic acid	2.65	2.74	2.65	2.66	2.52
o-Cl-Benzoic acid	2.05	2.08	2.04	2.01	2.18

m-F-Benzoic acid	2.15	2.14	2.16	1.75	2.07
p-F-Benzoic acid	2.07	2.11	2.07	1.75	2.07
o-F-Benzoic acid	1.77	1.55	1.86	1.75	1.73
m-Br-Benzoic acid	2.87	2.90	2.71	2.42	2.76
p-Br-Benzoic acid	2.86	2.89	2.86	2.42	2.76
o-Br-Benzoic acid	2.20	2.19	2.15	2.45	2.42
m-I-Benzoic acid	3.13	3.13	3.11	2.95	3.04
p-I-Benzoic acid	3.02	3.12	3.02	2.95	3.04
o-I-Benzoic acid	2.40	2.53	2.16	2.42	2.70
m-NH_2-Benzoic acid	0.65	0.76	0.78	0.18	0.96
p-NH_2-Benzoic acid	0.83	0.73	0.83	0.78	0.96
o-NH_2-Benzoic acid	1.21	1.21	1.21	0.79	1.36
p-Et-Benzoic acid	2.89	2.88	2.89	2.50	2.91
Phthalic acid	0.73	1.07	0.81	1.15	1.07
Terephthalic acid	2.00	1.98	2.00	1.15	1.76
p-$COCH_3$-Benzoic acid	1.61	1.50	1.61	0.90	1.55
o-$COCH_3$-Benzoic acid	0.81	0.98	0.81	0.90	1.21
m-OH-Benzamide	0.39	0.38	0.39	0.55	0.26
p-OH-Benzamide	0.33	0.34	0.25	0.55	0.33

m-NH_2-Benzamide	-0.33	-0.33	0.33	0.14	-0.18
p-NH_2-Benzamide	-0.44	-0.37	0.09	-0.19	-0.18
m-OCH_3-Benzamide	0.84	0.92	0.85	0.90	0.82
p-OCH_3-Benzamide	0.86	0.89	0.81	0.81	0.82
m-NO_2-Benzamide	0.77	0.83	0.68	0.54	0.56
p-NO_2-Benzamide	0.82	0.84	0.82	0.54	0.56
o-NO_2-Benzamide	-0.12	-0.02	0.17	0.54	-0.18
m-CN-Benzamide	0.52	0.42	0.52	0.97	0.29
p-CN-Benzamide	0.48	0.42	0.48	0.97	0.29
m-OH-methoxybenzene	1.58	1.60	1.52	1.54	1.59
p-OH-methoxybenzene	1.58	1.57	0.80	1.44	1.59
o-OH-methoxybenzene	1.32	1.24	1.19	1.33	1.34
m-NH_2-methoxybenzene	0.93	0.92	0.83	0.93	1.16
m-OCH_3-methoxybenzene	2.21	2.14	1.93	1.78	2.15
p-OCH_3-methoxybenzene	2.04	2.11	2.10	1.78	2.15
m-NH_2-phenol	0.21	0.06	0.34	0.20	0.24
p-NH_2-phenol	0.04	0.02	-0.29	0.84	0.24
o-NH_2-phenol	0.62	0.52	0.48	0.58	0.60
m-Cl-phenol	2.50	2.34	2.40	2.50	2.15

p-Cl-phenol	2.39	2.34	2.43	2.43	2.15
o-Cl-phenol	2.15	2.15	2.04	2.16	2.16
p-Br-phenol	2.59	2.47	2.49	2.57	2.40
o-Br-phenol	2.35	2.26	2.47	2.34	2.40
p-I-phenol	2.91	2.70	2.91	2.89	2.68
o-I-phenol	2.65	2.61	2.65	2.65	2.68
o-F-phenol	1.71	1.63	1.71	1.68	1.71
p-CN-phenol	1.60	1.68	1.60	1.63	1.61
o-CN-phenol	1.61	1.52	1.61	1.6	1.61
m-OH-phenol	0.80	0.76	0.76	0.80	1.03
p-OH-phenol	0.59	0.77	0.64	0.56	1.03
Catechol	0.88	0.88	0.88	0.91	1.03
m-NO_2-phenol	2.00	2.01	1.93	1.44	1.91
p-NO_2-phenol	1.91	2.01	1.57	1.44	1.91
o-NO_2-phenol	1.79	1.78	1.71	1.44	1.91
m-Br-phenol	2.63	2.49	2.63	2.47	2.40
m-I-phenol	2.93	2.71	2.93	2.97	2.68
m-CN-phenol	1.70	1.68	1.70	1.68	1.61
m-NH_2-aniline	-0.33	-0.33	-0.31	0.43	-0.39

p-NH_2-aniline	-0.30	-0.37	-0.68	0.43	-0.39
o-aminoaniline	0.15	0.15	0.05	0.15	0.16
m-CH_3-aniline	1.40	1.33	1.40	1.42	1.62
p-CH_3-aniline	1.39	1.32	1.40	1.43	1.62
m-NO_2-aniline	1.37	1.33	1.37	1.01	1.47
p-NO_2-aniline	1.39	1.33	1.39	1.01	1.47
o-NO_2-aniline	1.85	1.42	1.83	1.01	2.02
m-Cl-aniline	1.88	1.66	1.81	1.89	1.72
p-Cl-aniline	1.83	1.64	1.76	1.79	1.72
m-Br-aniline	2.10	1.81	2.10	2.06	1.97
p-Br-aniline	2.26	1.80	2.05	2.11	1.97
m-I-aniline	2.86	2.03	2.74	2.59	2.24
p-I-aniline	2.34	2.02	2.34	2.59	2.24
m-CN-aniline	1.07	1.00	1.07	1.26	1.17
m-Cl-Toluene	3.28	3.30	3.27	3.08	3.18
p-Cl-Toluene	3.33	3.29	3.27	3.08	3.18
m-Br-Toluene	3.41	3.45	3.45	3.35	3.43
p-Br-Toluene	3.42	3.44	3.45	3.35	3.43
m-NO_2-Toluene	2.45	2.48	2.41	2.24	2.36

p-NO_2-Toluene	2.37	2.48	2.41	2.24	2.36
o-NO_2-toluene	2.30	2.40	2.41	2.24	2.36
m-Xylene	3.15	2.98	3.14	3.01	3.09
p-Xylene	3.20	2.97	3.14	3.01	3.09
o-xylene	3.12	3.12	3.14	3.01	3.09
m-Cl-acetophenone	2.51	2.34	2.51	1.90	2.32
p-Cl-acetophenone	2.32	2.32	2.35	2.32	2.32
m-Br-acetophenone	2.47	2.49	2.58	2.18	2.56
p-Br-acetophenone	2.43	2.47	2.43	2.51	2.56
m-NO_2-acetophenone	1.42	1.48	1.49	1.28	1.49
p-NO_2-acetophenone	1.53	1.52	1.42	1.28	1.49
p-CN-acetophenone	1.22	1.12	1.22	1.38	1.22
p-OH-acetophenone	1.35	1.08	1.42	1.40	1.19
p-dichlorobenzene	3.44	3.58	3.34	3.15	3.28
m-dinitrobenzene	1.49	1.92	1.62	1.79	1.63
p-dinitrobenzene	1.46	1.93	1.37	1.79	1.63
o-dinitrobenzene	1.69	1.69	1.84	1.79	1.63
Mesitylene	3.42	3.40	3.60	3.50	3.63
m-OCH_3-p-CH_3-Benzoic acid	1.43	1.35	1.33	1.35	1.22

m-NO_2-p-CH_3-phenol	2.18	2.42	2.39	1.85	2.46
p-NO_2-m-CH_3-phenol	2.48	2.43	2.03	1.85	2.46
m-OH-p-NO_2-benzoic acid	1.98	1.89	1.84	0.79	2.64
m-NH_2-acetophenone	0.83	0.85	0.69	0.54	0.76
p-NH_2-acetophenone	0.83	0.81	0.41	0.54	0.76
m-NO_2-benzonitrile	1.17	1.18	1.17	1.33	1.36
p-NO_2-benzonitrile	1.19	1.18	1.19	1.33	1.36
o-NO_2-benzonitrile	1.02	1.01	1.33	1.33	1.36
o-Cl-nitrobenzene	2.24	2.56	2.34	2.44	2.46
o-Br-nitrobenzene	2.52	2.66	2.52	2.71	2.70
o-F-nitrobenzene	2.01	2.02	1.69	1.96	2.01
o-OCH_3-nitrobenzene	1.73	1.64	1.73	1.96	1.89
o-NO_2-ethylbenzene	2.58	2.70	2.94	2.70	2.85
o-OH-toluene	1.95	2.00	1.94	2.13	2.06
o-F-benzamide	0.59	0.32	0.64	1.10	0.20
o-Cl-benzamide	0.64	0.85	0.93	1.50	0.65
o-Br-benzamide	0.77	0.95	0.73	1.77	0.89
o-Me-benzamide	0.76	0.70	1.20	1.43	0.55
o-I-benzamide	0.93	1.30	0.93	2.30	1.17

o-dichlorobenzene	3.43	3.43	3.28	3.15	3.28
o-dibromobenzene	3.64	3.64	3.63	3.35	3.77
o-difluorobenzene	2.37	2.37	2.23	2.35	2.39
o-dimethoxybenzene	1.60	1.60	1.96	1.79	1.64
o-cyanobenzonitrile	0.99	0.99	1.07	2.10	1.09
o-diethylbenzene	3.72	3.72	4.20	3.84	4.07
Phthalimide	-1.73	-1.73	-1.73	-0.15	-1.99

* Data collected via internet (the website www. syrres.com/esc/est_kowdemo.htm accessed on 04/10/2008)

Ph = C_6H_5-

A remarkable percentage of acceptable plus very small number of disputable and unacceptable values indicates the high performance of presented model. Finally, graphs were plotted between the experimental and calculated logP values for all the logP calculators for comparison as shown in figure 2. In general, for all the calculators there is a straight-line relation signifying excellent agreement between experimental and calculated values. This confirms the validity and usefulness of the present model and has comparable utility with other logP calculators, which use a large no. of variables to predict the logP values whereas the present model use few variables.

Figure 3 present a scatter diagram, in which horizontal co-ordinate is the correlation coefficient while the vertical co-ordinate is the acceptable percentage. According to fig. 3, the 16 procedures can be roughly divided into two categories. The first occupy the upper right corner with acceptable percentage of 77 to 91% while the correlation coefficient are generally higher than 0.95.

Table 6: Comparison [a] of 4 logP calculators

Calculator	Acceptable[b]	Disputable[c]	Unacceptable[d]	Uncalculated	< logP[e]	> logP[e]
Model	98.72	1.28	00	00	48.71	36.53
ACD11.0 freeware	98.07	1.93	00	00	37.82	31.41
Chem Draw Ultra 8.0	86.54	10.90	2.56	00	54.48	39.10
KOW-WIN	98.72	1.28	00	00	47.43	44.23

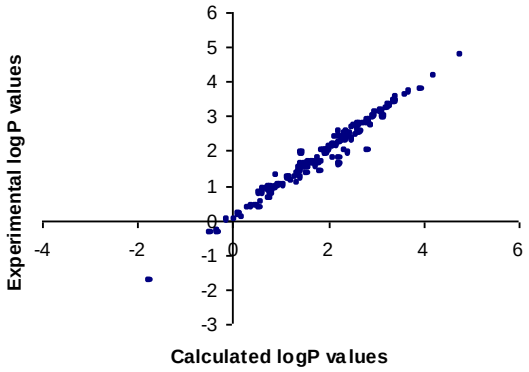
a Figures are in percentage for all the molecules (n = 111)

b Percentage of acceptable results (error < +/- 0.50)

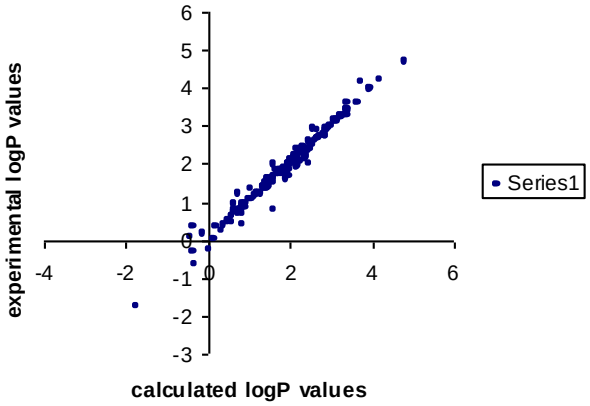
c Percentage of disputable results (error > +/- 0.50 and < +/- 1.00)

d Percentage of unacceptable results (error > +/- 1.00)

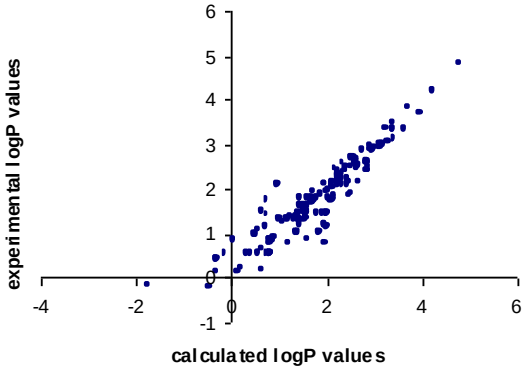
e Experimental logP



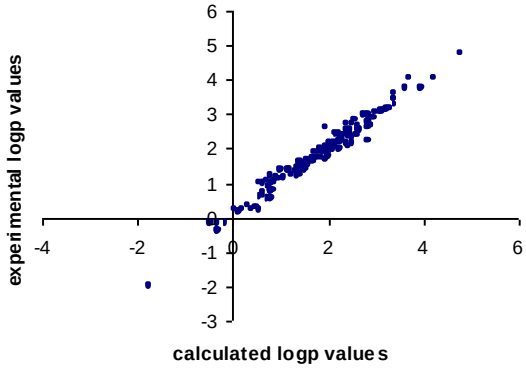
a) For model



b) For ACD 11.0 Freeware



c) For Chem Draw 8.0



d) For KOW-WIN

Figure 2: Correlation between the experimental and the calculated logP values for n = 156 for all the logP calculators.

Most members in this class are fragmental methods. All the other procedures fall into second category. They have low acceptable percentage (<70%)[11].

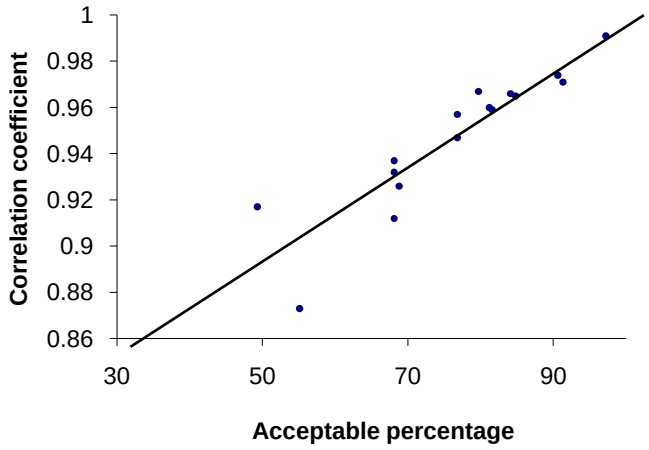


Figure 3: Scattering graph of 16 logP calculation procedures being compared

Conclusions: We have presented ample results to predict logP values in QSAR/QSPR calculated on the basis of presented simple fragmentation method. The quite valuable results for the various molecules make it evident the suitability degree of this rather simple equation. The new scheme is quite systematic and easier to understand.

We deem that before to state more definitive conclusions, it is obligatory to make additional research in order to study other physical-chemical properties and biological activities for quite different molecules. Work on this field is presently being made in our laboratory and further progresses are under developments, more results will be given elsewhere in the forthcoming future.

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