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Topological Modeling of Lipophilicity of Some Alkanes

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Abstract

In this work a study has been done to model the lipophilicity of few alkanes using topological indices. The result says that the indicator parameters play dominating role in predicting the activity of alkanes.

Key words: Topological modeling, QSPR, lipophilicity, log P, indicator parameters.

Introduction

Lipophilicity[1] in terms of log P is an important parameter in drug development. Log P has been modeled by Khadikar and Agrawal[2-4] for many compounds/drugs using topological indices. These indices include Randic connectivity, Kier & hall valence connectivity, Wiener index, Balaban & Balaban type indices. Sz index, Padmakar – Ivan index etc.[5-8]

It has also been shown that in case of derivatives the contribution of functional groups can be studied by adding indicator parameters which are termed as *de novo* constants[9-11]. These can be abbreviated as I_1, $I_{2...}$ etc. They are usually assigned a value of 1 for their presence and if the group is absent they are given value of zero. e.g. if in a series a functional group $-CH_3$ is present in few of the compounds then I_1 will be assigned value of 1 for the compound with $-CH-_3$ group and others will be given zero.

Methodology:

In fact Hansch[12-13] has suggested that the biological activity of a series of compounds can be modeled by using few independent parameters & the equation for this can be—

$$\mathbf{Y = m_1 x_1 + m_2 x_2 + ...+ m_i x_i + C} \quad (1)$$

Where, **Y** is biological activity & $\mathbf{x_1\ x_2\ ....x_i}$ are independent parameters **C** is intercept of the straight line. For obtaining the model one can use regression analysis[14] for which standard softwares are available.

Calculation of Xu and F :

Xu[15] index is a topological molecular descriptor based on adjacency and distance matrices. It was calculated using the following expression:

$$\mathbf{Xu=\sqrt{n.\log Li=\sqrt{n.\log \Sigma\delta i.\sigma j^2/\Sigma\delta i.\sigma j}}} \quad (2)$$

Where, 'n' is the number of atoms and 'L' represents the valence average topological distance calculated by vertex degree δ and vertex distance

degree σ of all the atoms. It was proposed as a particularly high discriminate molecular descriptor accounting for molecular size and branching.

For those properties where not only the "shape" but also the size of graph influences the property or activity, other Balaban index F[16] has been developed. It defines as:

$$F=J(R+1)=E\,S_{alledges}[di.\,dj]^{-½} \quad (3)$$

Where, J is Balaban index and R is cyclomatic number, this index is able to separate graph size, cyclicity and branching. For the calculation of Balaban index 'J' and cyclomatic number 'R' following expressions were used.

$$J=E/(R+1)=S_{alledges}[\,di.\,dj]^{-½} \quad (4)$$

Where, E is the number of bonds in a graph, R is the cyclomatic number.

$$R=E-N+1 \quad (5)$$

Where, E is number of edges in graph and N is number of vertices.

In the present paper we have taken 36 alkanes including cyclo compounds & -chloro, -nitro, -methyl derivatives. These alkanes and their derivatives are reported in Table- 1. This Table also includes their lipophilicity values which have been expressed in the form of logP. These compounds can be arranged in decreasing order of activity as below:

8>7>6>5>12>16>4>11>23>17>15>3>10>28>22>14>2>9>21>24>1>13>27>20>26>30>19>35>29>18>25>34>33>36>32>31.

Table1. List of 36 Alkanes along with theirbiological activity (log P)

S.No.	Name of compounds	Log p	S.No.	Name of compounds	Log p
1	n-Butane	2.81	19	1-Chloro Propane	1.994
2	n-Pentane	3.339	20	1-Chloro Butane	2.523
3	n-Hexane	3.868	21	1- Chloro Pentane	3.052
4	n-Heptane	4.397	22	1-Chloro Hexane	3.581
5	n-Octane	4.926	23	1-Chloro Heptane	4.11
6	n-Nonane	5.455	24	Carbon Tetra Chloride	2.875
7	n-Decane	5.984	25	1,2-Di chloro Ethane	1.458
8	n-Undecane	6.513	26	1,1,1-Tri Chloro Ethane	2.481
9	2-Methyl Butane	3.209	27	1,1,2,2-Tetra Chloro Ethane	2.644
10	2-Methyl Pentane	3.738	28	Penta Chloro Ethane	3.627
11	2-Methyl Hexane	4.267	29	1,2-DiBromo Ethane	1.738
12	2,2,4-Tri Methyl Pentane	4.536	30	Flouro Tri Chloro Methane	2.435
13	Cyclopentane	2.795	31	Nitro Methane	-0.284
14	Cyclo hexane	3.354	32	NitroEthane	0.245
15	Cyclo Heptane	3.913	33	1-Nitro Propane	0.774
16	Cyclo Octane	4.472	34	1-Nitro Butane	1.303
17	Adamantane	3.982	35	1-Nitro Pentane	1.832
18	1-Chloroethane	1.465	36	2-Nitro Propane	0.554

No one is to one correlation is seen in the activity and structure of the compounds. The structures of the molecules were drawn from Chem.Sketch software[17] which is freely available from ACD Labs. The molecules so drawn were used for the calculation of topological indices for which mol files are needed, therefore hydrogen depleted graphs were drawn and these mol files were used for the calculation of topological indices using DRAGON software.[18] More than 50 topological indices were calculated, but variable selection suggested that only $\mathbf{X}_u$ index is useful in modeling the log P of present set of compounds. We also calculated **F** index for these compounds. These calculated parameters are reported in Table-2.

The data was subjected to statistical analysis. We calculated correlation matrix of various parameters which are considered for modeling the log P of compounds used in the present study.

Table.2 Indicator parameters and calculated values of descriptors

Comp. No.	I_1	I_2	Xu	F
1	0	0	3.161	1.974
2	0	0	4.593	2.19
3	0	0	5.969	2.339
4	0	0	7.297	2.447
5	0	0	8.584	2.53
6	0	0	9.835	2.595
7	0	0	11.053	2.647
8	0	0	12.242	2.692
9	0	0	4.301	2.52
10	0	0	5.699	2.62
11	0	0	7.056	2.678
12	0	0	7.752	3.388
13	0	0	4.006	4.166
14	0	0	5.382	4.000
15	0	0	6.574	4.082
16	0	0	7.842	8.000
17	0	0	9.32	9.485
18	1	0	1.655	1.632
19	1	0	3.161	1.974
20	1	0	4.593	2.19
21	1	0	5.969	2.339
22	1	0	7.297	2.447
23	1	0	8.584	2.53
24	1	0	3.972	3.024
25	1	0	3.161	1.975
26	1	0	3.972	3.024
27	1	0	5.395	2.993
28	1	0	6.367	3.541
29	1	0	3.161	1.975
30	1	0	3.972	3.023
31	0	1	2.894	2.324
32	0	1	4.301	2.54
33	0	1	5.699	2.627
34	0	1	7.056	2.678
35	0	1	8.37	2.716
36	0	1	5.395	2.993

The derived correlation matrix is showing inter correlation among all the parameters is shown in the Table-3.

Table 3. Correlation Matrix showing inter-correlation among all the parameters

	I_1	I_2	X_u	F	Log p
I_1	1.0000				
I_2	-0.3362	1.0000			
X_u	-0.3979	-0.0687	1.0000		
F	-0.2369	-0.1876	0.3038	1.0000	
Log p	-0.2139	-0.6696	0.7475	0.2411	1.0000

A close look at this table gives following information.

1. No auto correlation exists with any of the independent parameters.
2. Log P shows strong correlation with $\mathbf{X_u}$ parameter.
3. Indicator parameter I_2 is also correlated with log P.
4. Therefore, the only mono-parametric model which is statistically acceptable may be $\mathbf{X_u}$.
5. Indicator parameter I_2 which accounts for the presence of—NO2, functional group may be a suitable parameter in multi-parametric analysis.

On the basis of above, the data was subjected to regression analysis & the models obtained are reported in Table 4. This table includes few statistical parameters which have been discussed in subsequent paragraphs.

Table 4.Regression Parameters and Quality of correlation of obtained Models

Model no.	Parameter Used	Ai (i=1….4)	B	Se	R^2	R^2A	F	Q
1	Xu	0.4792(±0.0730)	0.1842	0.4717	0.5587	0.5458	43.052	1.584
2	F	0.2894(±0.1997)	2.2405	0.6181	0.0581	0.304	2.099	0.389
3	Xu	0.5045(±0.0800)	-0.0827	0.5812	0.5670	0.5408	21.607	1.295
	I_1	0.3195(±0.4023)						
4	Xu	-0.2596(±0.1734)	0.7780	0.1770	0.9428	0.9393	271.718	5.485
	I_2	0.0268(±0.4518)						
5	F	-0.5354(±0.5525)	2.5668	0.7043	0.0842	0.0287	1.517	0.412
	I_1	0.2421(±0.2058)						
6	F	0.1437(±0.560)	3.0983	0.5045	0.4622	0.4299	14.178	1.347
	I_2	0.1437(±0.1560)						
7	Xu	0.4762(±0.778)	0.1500	0.5486	0.5590	0.5322	20.911	1.362
	F	0.0186(±0.186)						
8	F	-0.1636(±0.4935)	4.3615	0.4935	0.6670	0.6358	21.363	1.654
	I_1	-0.0459(±0.1318)						
	I_2	-3.5198(±0.4704)						
9	Xu	0.3974(±0.0215)	1.3887	0.1669	0.9713	0.9687	361.577	5.905
	I_1	-0.6472(±0.1145)						
	I_2	-0.8843(±0.1357)						
10	Xu	0.4999(±0.08366)	-0.1567	0.6698	0.5677	0.5272	14.010	1.124
	F	0.3222(±0.4119)						
	I_1	0.0344(±0.1477)						
11	Xu	0.4709(±0.0621)	1.0191	0.1917	0.9519	0.9474	210.928	0.783
	F	-0.1221(±0.0496)						
	I_2	-2.5064(±0.1640)						
12	Xu	-0.7676(±0.0703)	1.8570	0.1171	0.9901	0.9888	772.544	8.497
	F	-0.4153(±0.0839)						
	I_1	-0.4153(±0.0131)						
	I_2	-0.1796(±0.0235)						

Result and Discussion

The best mono parametric with $R^2 = 0.5587$ is with $\mathbf{X_u}$ and is as below:

$$\text{Log P} = 0.4792\ (\pm 0.0730)\ X_u + 0.1842 \quad (6)$$

n =36, Se = 0.4717, $R^2 = 0.5587$, $R^2A = 0.5458$, F = 43.052, Q = 1.584

Here & here onwards 'n' is total number of compounds, R^2 is variance square of correlation constant, R^2A is adjusted R^2, Se is standard error of estimation, F is Fischer's ratio & 'Q' is Pogliani's quality factor[19] which is a ratio R/Se.

When I_1 is added to X_u parameter we obtained a bi-parametric correlation with slightly improved statistical values. The model shows slight improvement in R^2 value which changes from 0.5587 to 0.5670. The model is as under—

$$\text{Log P} = 0.5045\ (\pm 0.0800)\ X_u + 0.3195\ (\pm 0.4023)\ I_1 - 0.0827 \quad (7)$$

n = 36, Se =0.5812, $R^2 = 0.5670$, $R^2A = 0.5408$, F =21.607, Q = 1.295

The decrease in R^2A from 0.5458 to 0.5408 clearly shows that the added parameter I_1 is not contributing in the model. In fact if the value of R^2A increases only the added parameter shows its contribution. Similarly the error in the coefficient of I_1 is also more than the coefficient. Hence, this bi-parametric model consisting of X_u & I_1 is not acceptable.

Out of five bi-parametric correlations one with X_u & I_2 gave best R^2 value equal to 0.9428. The increase is R^2 from 0.5587 to 0.9428 is due to the addition of an indicator parameter I_2. The adjusted R^2A value also shows dramatic improvement. The Q value shows a drastic increase which changes from 1.584 to 5.485. The obtained model is reported below:

$$\text{Log P} = -0.2596\ (\pm 0.1734)\ X_u + 0.0268\ (\pm 0.4518)\ I_2 + 0.7780 \quad (8)$$

n = 36, Se = 0.1770, $R^2 = 0.9428$, $R^2A = 0.9393$, F = 271.718, Q = 5.485

Unfortunately in this model the error in the coefficient of I_2 is more than the value of the coefficient which is statistically not acceptable.

To get a better model I_1, I_2 and X_u are taken together which resulted into a three-parametric model with $R^2 = 0.9713$. The derived model is as follows:

$$\text{Log P} = 0.3974(\pm 0.0215)\ X_u - 0.6472\ (\pm 0.1145)\ I_1 - 0.8843\ (\pm 0.1357)\ I_2 + 1.3887 \quad (9)$$

n = 36, Se = 0.1669, $R^2 = 0.9713$, $R^2A = 0.9687$, F = 361.577, Q = 5.905

In this model the R^2 changes from 0.9393 to 0.9687 which shows that the added I_1 parameter has its fair share in the model.

Through another three-parametric model (X_u, F, I_2) obtained is statistically significant but, it has lower R^2 value equal to 0.9519 than the three parametric model discussed above. Hence the model with X_u, F, I_2 is also discarded.

Finally, a four-parametric model with Xu, F, I_1 and I_2 as correlating parameter is obtained with $R^2 = 0.9901$. The model is discussed below:

$$\text{Log P} = -0.7676\ (\pm 0.0703)\ X_u - 0.4153\ (\pm 0.0839)\ F - 0.4153\ (\pm 0.0131)\ I_1 - 0.1796\ (\pm 0.0233)\ I_2 + 1.8570 \quad (10)$$

n = 36, Se = 0.1171, $R^2 = 0.9901$, $R^2A = 0.9888$, F = 772.544, Q = 8.497

For four -parametric model with X_u, F, I_1 and I_2, the R^2 value comes out to be 0.9901 as compared to three-parametric model with Xu, I_1, I_2(0.9713), which is certainly better. The change in R^2A from 0.9687 to 0.9888 clearly indicates that the added parameter F has significant role and its fair share in the model. The Q value also changes from 5.905 to 8.497 and is in favour of the above model.

Here the four parametric models with Xu, F, I_1 & I_2 is the best for modeling for log P value of the present set of the compounds.

To confirm above finding log P values have been estimated using the best four parametric model such values are reported in Table – 5. These values are in good agreement with the observed activities.

Table 5 Observed and Estimated values of log p for using model no. 12

Comp. No.	Observed log P	Estimated log P	Residual
1	2.810	2.815	-0.005
2	3.339	3.371	-0.032
3	3.868	3.916	-0.048
4	4.397	4.448	-0.051
5	4.926	4.967	-0.041
6	5.455	5.475	-0.020
7	5.984	5.972	0.012
8	6.513	6.457	0.056
9	3.209	3.190	0.019
10	3.738	3.753	-0.015
11	4.267	4.306	-0.039
12	4.536	4.468	0.068
13	2.795	2.772	0.023
14	3.354	3.374	-0.020
15	3.913	3.854	0.059
16	4.472	4.395	0.077
17	3.982	4.024	-0.042
18	1.465	1.383	0.082
19	1.994	2.109	-0.115
20	2.523	2.642	-0.119
21	3.052	3.175	-0.123
22	3.581	3.700	-0.119
23	4.110	4.215	-0.105
24	2.875	2.284	0.591
25	1.458	1.859	-0.401
26	2.481	2.384	0.097
27	2.644	2.787	-0.143
28	3.627	3.196	0.431
29	1.738	1.865	-0.127
30	2.435	2.384	0.051
31	-0.284	-0.341	0.057
32	0.245	0.204	0.041
33	0.774	0.824	-0.050
34	1.303	1.325	-0.022
35	1.832	1.832	0.000
36	0.554	0.580	-0.026

A graph has been drawn using observed and estimated log P values which are demonstrated in Figure – 1. The predictive power of the model comes out to be 0.990, which shows that this model explains 99% variance of the data used in the present study.

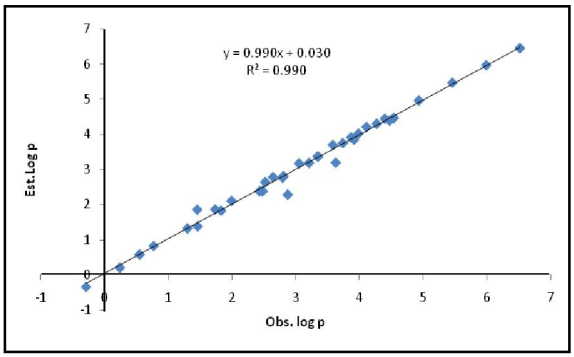

Fig. 1 Correlation between observed and estimated log P using model no. 12

The model was tested by evaluating cross validated parameters. These parameters for different models are reported in Table – 6. The lowest PRESS/ SSY value 0.279 for the four parametric model and higher R^2cv value which is 0.9874 confirms the finding for the four-parametric model with Xu, F, I_1 and I_2.The PSE value for this model is 0.173 which is lowest and S_{PRESS} which comes out to be 0.1868 further verifies our result.

The four-parametric model is free from any of the defect. For this we have performed Ridge analysis. The Ridge trace is reported in Figure – 2. All the parameters are with the permissible limits.

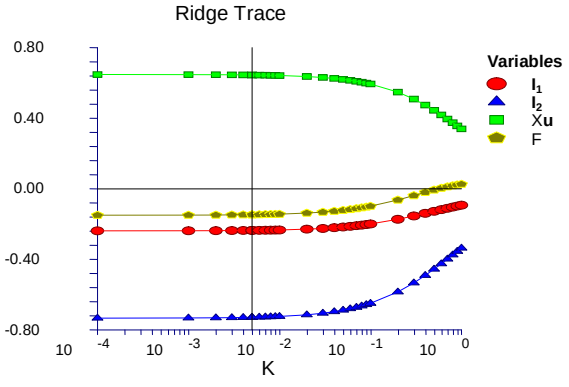

Fig. 2. Ridge Trace for Best four parametric Model no. 12

Table 6. Cross Validated parameters for various models.

Model no.	ParameterUsed	PRESS/SSY	R2 cv	S_{PRESS}	PSE
1	Xu	1.726	0.5148	1.217	1.176
2	F	2.203	0.000	1.752	1.706
3	Xu,I_1	1.371	0.5001	1.142	1.094
4	Xu,I_2	0.484	0.9342	0.414	0.394
5	F,I_1	2.227	0.000	1.770	1.694
6	F,I_2	1.564	0.3556	1.297	1.242
7	Xu, F	1.630	0.3797	1.273	1.218
8	F,I_1,I_2	1.223	0.6008	1.037	0.977
9	Xu,I_1,I_2	0.460	0.9655	0.307	0.289
10	Xu,F,I_1	1.594	0.3325	1.317	1.242
11	Xu,F,I_2	0.507	0.9285	0.439	0.413
12	Xu,F,I_1,I_2	0.279	0.9874	0.1868	0.173

Table.7 Ridge Regression Parameters for the obtained model

Model no.	Parameter Used	VIF	T	i	K
1	Xu	0.9901	1.0000	1.000	1.00
2	F	0.9901	1.0000	1.000	1.00
3	Xu	1.1719	0.8417	1.3979	1.00
	I_1	1.1719	0.8417	0.6020	2.32
4	Xu	0.9947	0.9953	1.0686	1.00
	I_2	0.9947	0.9953	0.9313	1.15
5	F	1.0477	0.9439	1.2369	1.00
	I_1	1.0477	0.9439	0.7630	1.62
6	F	1.0255	0.9648	1.876	1.00
	I_2	1.0255	0.9648	0.8123	1.46
7	Xu	1.0477	0.9439	1.2369	1.00
	F	1.0477	0.9439	0.7630	1.62
8	F	1.1424	0.8633	1.3420	1.00
	I_1	1.2404	0.9737	1.1705	1.15
	I_2	1.2140	0.8113	0.4874	2.75
9	Xu	1.2373	0.7954	1.4883	1.00
	I_1	1.3850	0.7089	1.0676	1.39
	I_2	1.1755	0.8382	0.4439	3.35
10	Xu	1.2394	0.7952	1.6305	1.00
	F	1.1080	0.8972	0.7772	2.10
	I_1	1.1929	0.8262	0.5922	2.75
11	Xu	1.0887	0.9076	1.3902	1.00
	F	1.1224	0.8798	0.9390	1.48
	I_2	1.0256	0.9646	0.6706	2.07
12	Xu	1.2783	0.7699	1.6374	1.00
	F	1.1803	0.8356	1.2682	1.29
	I_1	1.2522	0.7855	0.6715	2.44
	I_2	1.4564	0.6733	0.4226	3.87

The VIF plots(Figure-3) also shows that all the parameters arebelow 10 hence, the used parameters in the four-parametric model is free from the defect of the colearinity or chance.

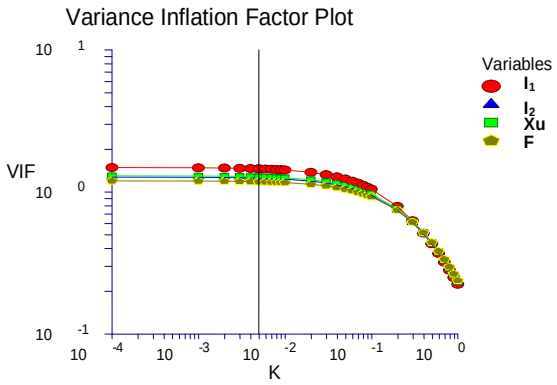

Fig. 3: VIF plot for best four parametric model

The calculated ridge parameters are reported in Table -7. The VIF value for Xu parameter in all the models reported are less than 10. Similar T is also with theLimit of one. The value of li and k are in favour of proposed model hence the four parametric models is acceptable on the basis of ridge analysis.

Conclusion

$$\text{Log P} = -0.7676\,(0.0703)\,X_u - 0.4153\,(\pm 0.0839)\,F - 0.4153\,(\pm 0.0131)\,I_1 - 0.1796\,(\pm 0.0235)\,I_2 + 1.8570$$

On the basis of our study following conclusion may be drawn:

1. Topological indices Xu and F are capable of modelling Log P value of alkanes along with indicator parameters.
2. The indicator parameters are important for prediction of biological activity.
3. Indicator parameter I_2 is very effective in modelling the activity of presence set of alkanes.
4. The four parametric models with Xu, F, I_1 & I_2 is the best model which is statistically significant for predicting and estimating lipophilicity (Log P) of presence set of compounds.
5. The best parametric models proposed in free from any defect.
6. Xu, F alone are not capable of modeling the lipophilicity, therefore use of indicator parameters are essential in the study.
7. The coefficients of all the four parameters are negative suggesting that their lesser value will favour the activity (log P).

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