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Topological modeling of lipophilicity of some crown compounds

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Abstract

In the present paper a study on Benzo and di Benzo crown ethers has been done for the estimation of lipophilicity of these compounds. For this few topological parameters viz. Wiener and Balaban index along with MW gives best result. Proposed three-parametric model is capable of explaining the 97% of the variance.

Key words: Lipophilicity, log P, Topological modeling, Balaban index, Molecular Weight. QSAR

Introduction

Crown ethers are macro cyclic polyether that are characterized by having a different number of ethylene oxide unit, joined covalently in a macrocy clic ring so that in their simplest form they are cyclic oligomers of dioxane.[1]

It is well known that macro cyclic compounds have ability to surround or enclose many different cations[2]. Consequently, interest in the complexes of macro cyclic compounds has increased in recent years. Complexes of these crown-ligands with alkali and alkaline earth cations have been reported extensively, however, their complexes with transition and rare-earth cations are very scare. Complexes of multidentate macro cyclic ligands, viz., crown ethers and cryptande with lanthanide cations have, therefore, attracted considerable interest.[2-3]

Crown ether and related compounds become a central part of development in supra molecule (host/Guest) chemistry[4-6] many different modification of crown ethers, Such as changing ring size, the kinds of substituent's and the types donor atoms, have been madeto enhance their complexation properties.[7]

The partitioning of organic compounds acting as drugs between aqueous and lipophilic phase is of utmost importance for drug potency. Lipophilicity is an important endpoint used extensively in medicinal chemistry, drug design, pharmacy and environmental toxicity in predicting biological and hazardous effects of chemicals[8]. Consequently, the development of new methods for the quantitative estimation of the lipophilicity of organic molecules is extremely important. It is well known and well established that the useful measure of lipophilicity/ hydrophobicity of organic compounds acting as drugs is then passion coefficient between n-octanol and water[9-10]. No other physicochemical property has attracted as much interest in quantitative structure-activity relation (QSAR) studies as lipophilicity

(synonymously called hydrophobicity, any difference between both these terms is only a Semitic nemicity; the opposite of lipophilicity is hydrophobicity) generally expressed as log P.

Lipophilicity (Log P) is a physio-chemical property of principle importance in drug discovery and development.[11] Log P has been modeled by Khadikar and Agrawal[12-14] for many compounds using topological indices such as Randic connectivity, Kier & Hall valence connectivity, Wiener index, Balaban Index, Padmaker Ivan index[15-18] and many others.

They have successfully demonstrated that using topological indices one can develop excellent models which can predict log P value of different compounds. They developed the models and tested them also.

Methodology:

In Quantitative structure activity relationship (QSAR) studies the lipophilicity expressed as log P has a major role. C. Hansch[19-20] and coworkers have widely used lipophilicity (log P) in the field of chemical –biological interaction which can be modeled by using few independent parameters. We develop a mathematical model using multiple regression analysis[21].

$$\mathbf{Y = m_1x_1 + m_2x_2 + \ldots\ldots\ldots\ldots m_ix_i + c\ldots\ldots\ldots\ldots} \quad \mathbf{(1)}$$

Where

Y= biological activity and x_1, x_2, ...x_i are independent parameters**, C** is intercept.

It has been observed that since, the discovery of crown compound by Pederson they are widely used as membranes in medicinal chemistry. The membrane power of crown compounds is decided on the basis of Log P. Such Log P value for the crowns were quantitative calculated by using lipophilicity increments $\boldsymbol{\pi_x}$ by Hansch. However, not much work in QSAR has been done in modeling lipophilicity (Log P) of crown compounds.

The crown compounds used in the present study are reported in Table 1. The log P values for these compounds have been taken from literature. These values are also reported in this table. Topological parameters for these compounds have been calculated by the Dragon software.[22] before that we used Chem. Sketch software[23] to draw the molecular structures and then mole file were used for calculation of Topological indices depleting all the C-H bonds.

Parameters Used:

We have used following parameters for modeling log P of present set of crown ethers.

1. Wiener Index (W):
2. Balaban Index(J)
3. Zero order connectivity index (χ^0)
4. Molecular Weight (MW)

The calculation of these indices have been given in the literature[15].

Result and Discussion

These compounds can be arranged in increasingorder of lipophilicity (log P).

8>9>11>13>10>12>1>2>3>4>5>7>6

This means that di Benzo,18-crown-6 has highest lipophilicity (log P) while Benzo 30-crown-10 has lowest value of lipophilicity (log P), this sequence do not give any structure-activity relationship. No one correlation is seen in activity and structures of the compounds. The structures of the compounds were drawn from ACD labs chem. Sketch soft ware.[23] the calculated topological Parameters are reported in Table-2.

Table-1 Compounds used in the present study and lipophilicity in terms of Log P

Comp.No.	Name of Comp.	Logp
1	Bz,15-Crown-5	0.91
2	Bz, 18-crown-6	0.58
3	Bz,21-crown-7	0.57
4	Bz,24-crown-8	0.45
5	Bz,27-crown-9	0.23
6	Bz,30-crown-30	0.03
7	Bz,33-crown-11	0.09
8	Dbz,18-crown-6	2.20
9	Dbz,24-crown-8	2.11
10	Dbz,27-crown-9	1.63
11	Dbz,30-crown-10	1.80
12	Dbz33-crown-11	1.45
13	Dbz,21-crown-7	1.74

Bz-benzo; Dbz-di Benzo; Log P-lipophilicity;

Table-2 Lipophilicity (Log P) and calculated values of descriptors.

Compound No.	Log P	W	J	χ^0	MW
1	0.91	744	1.74	13.176	268.34
2	0.58	1171	1.685	15.297	312.4
3	0.57	1731	1.65	17.418	356.46
4	0.45	2458	1.615	19.539	400.52
5	0.23	3357	1.591	21.661	444.58
6	0.03	4465	1.567	23.782	488.64
7	0.09	5784	1.55	25.903	532.7
8	2.20	1797	1.438	17.866	360.44
9	2.11	3420	1.363	22.108	448.56
10	1.63	4497	1.341	24.23	492.62
11	1.80	5835	1.31	26.351	536.68
12	1.45	7368	1.292	28.472	580.74
13	1.74	2499	1.41	19.987	404.5

We have tried variable selection methodto get multi-parametric correlations and the results are reported in Table-3.

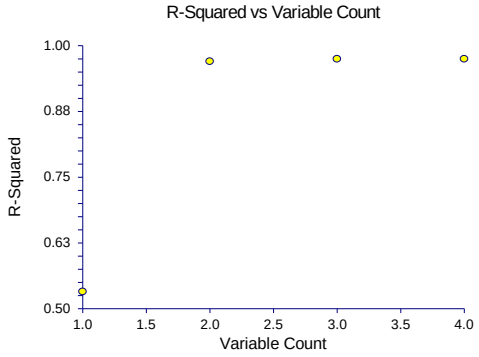
The Balaban index (J)[24] plays a dominating role in modeling of Log P of present set of compounds. Similarly MW. Also plays a dominating role in trimetric model using maximum R^2 method.

Table 3. Result of variable selection.

Selection Results Section with Variable Names

Model Size	R-Squared	R-Squared Change	Variable Names
1	0.532353	0.532353	J
2	0.970016	0.437663	χ^0,MW
3	0.974543	0.004527	W,J,MW
4	0.974590	0.000047	W, J, χ^0, MW

Plots Section



The above table shows that J, χ^0, and MW are excellent parameters for modeling Log P of present set of compounds. However the change in R^2 value is drastic from mono to bi-parametric correlation. We have also obtained correlation matrix which is reported in Table-4

Table 4.The correlation matrix.

	J	MW	log P
J	1.0000	-0.7184	-0.7296
MW	-0.7184	1.0000	0.0668
Log p	-0.7296	0.0668	1.0000

Correlation matrix shows that **J** and **MW** are highly correlated. Similarly **χ0** is also moderately correlated with log P, **J** and **MW**. log P shows strong correlation with **MW**.

The data was subjected to regression analysis and gave few statistically significant modelswhich are reported in Table 5.

Mono-parametric Model:

Out of three mono-parametric models, one with **J** (Balaban index) gives maximum $\mathbf{R^2}$ value which is 0.5324. The valve of adjusted $\mathbf{R^2_A}$ comes out to be 0.4898. The model is as under:

log P = -3.7625 (±1.0633)J+6.7164 (2)

n=13, **Se**=1.6068, $\mathbf{R^2}$= 0.05324, $\mathbf{R^2A}$=0.4898,**F**=12.522, **Q**=0.45410

here and here after, n is total no of compounds, R^2 is variance (square of correlation constant), R^2_A is adjusted R^2, Se is standard error of estimation, F is Fischer's ratio and 'Q' is Pogliani's quality factor[25] which is the ratio of R/Se.

Bi-parametric Model:

Table-5.Regression Parameters and quality of correlations of obtained Models.

Model No.	Parameters Used	Ai=(1----3)	B	Se	R^2	R^2 Adj.	F	Q=R/Se
1	W	0.0000±0.0001	0.9865	0.4678	0.0030	0.0000	0.033	0.11708
2	MW	0.0006(±0.0025)	0.8163	1.1241	0.0045	0.0000	0.049	0.05967
3	J	-3.7625(±1.0633)	6.7164	1.6068	0.5324	0.4898	12.522	0.45410
4	W	-0.0003(±0.0001)	12.2649	1.2042	0.8995	0.8794	34.858	0.78759
	J	-6.7018(±0.7096)						
5	J	-7.2886(±0.4435)	15.4801	0.9197	0.9645	0.9573	135.64	1.06783
	MW	-0.0080(±0.0007)						
6	W	0.0002(±0.0001)	16.8537	1.0963	0.9745	0.9661	114.846	0.90045
	J	-7.4068(±0.4006)						
	MW	-0.0123(±0.0024						

When **MW** is added to mono-parametric model discussed above, a bi-parametric model is obtained. A drastic improvement in $\mathbf{R^2}$ is observed. The $\mathbf{R^2}$ value changes from **0.5323** to **0.9645.** The adjusted R^2 **(R^2A)** also changes from 0.4898 to 0.9573 which clearly indicates that the addition of **MW** is significant and it has itsand fair sharein the model. The model is as given below:

Log P = -7.2886(±0.4435)J -0.0080(±0.0007)MW +15.4801 (3)

n=13, Se=0.09197, R^2=0.9645, R^2_A=0.9573, F=135.654, Q= 1.06783

Tri-parametric Model:

Finally a tri parametric model is obtained when Wiener index W is added to the above model. For this model a slight improvement in R^2 value is observed. The value changes from 0.9645 to 0.9745 and R^2_A also increases from 0.9573 to 0.9661. Hence, Addition of MW is significant and has fair share in the model. The model is discussed below:

log P = 0.0002(±0.0001)W -7.4068(±0.4006)J -0.0123 (±0.0024) MW+16.8537 (4)

n=13, se=1.0963, R^2=0.9745, R^2A =0.9661, F=114.846, Q=0.90045

A perusal of equation 4 *i.e.* the model 6 and its comparison with equation 2 clearly shows that the Q value in the latter has decreased. Therefore, though the R^2 value of tri-parametric model is more than what we have in bi-parametric model, it cannot be accepted as best model. The cross validated R^2 value also confirms this finding, which has been discussed below.

Therefore the tri-parametric model is the best among all the discussed models for estimation of Log P value of present set of compounds.

To confirm above finding,Log P values have been estimated using best Tri-parametric model and calculated values are shown in Table 6.

Table 6. Observed and estimated log P values of compounds using model no. 6

Comp. no.	Observed Log P	Estimated Log P	Residual
1	0.91	0.801	0.109
2	0.58	0.749	-0.169
3	0.57	0.576	-0.006
4	0.45	0.436	0.014
5	0.23	0.249	-0.019
6	0.03	0.103	-0.073
7	0.09	-0.052	0.142
8	2.2	2.11	0.09
9	2.11	1.901	0.209
10	1.63	1.735	-0.105
11	1.8	1.687	0.113
12	1.45	1.582	-0.132
13	1.74	1.913	-0.173

These values are in good agreement with the observed activities. Such correlation is obtained by plotting a graph between observed and estimated log P which is demonstrated in Fig. 1. The predictive power of model comes out to be 0.974, which shows that model explain more than 97% variance of the data used in the present study.

The above bi-parametric model is also tested by evaluating cross validation parameters reported in Table-5. The lowest PRESS/SSY value 0.22519 for the bi-parametric model and higher R^2cv value 0.9334 confirms above findings. The PSE value0.1954 for this model is lowest and S_{PRESS} comes out to be 0.2226, further verifies our result.

The cross validated R^2cv value for the three-parametric correlation is lower than the bi-parametric model hence that model cannot be accepted as best model.

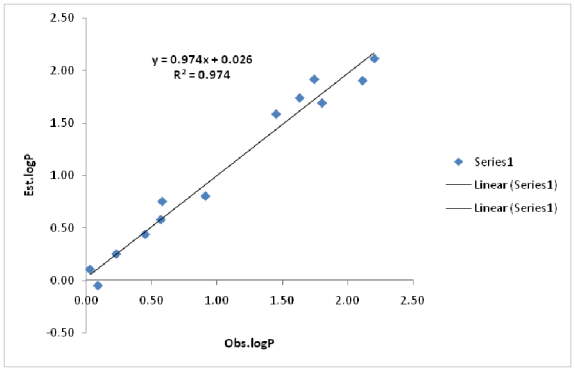


Fig.1 correlation between observed and estimate Log P using model 6.

Table 7. Cross Validated parameters for the obtained models.

Model No	Parameters Used	PRESS/SSY	R^2cv	S_{PRESS}	PSE
1.	J	0.74027	0.3611	0.1811	0.19835
2.	J,MW	0.22519	0.9334	0.2226	0.1954
3.	W,J,MW	0.23594	0.9313	0.2383	0.1666

In order to test whether the model is free from the defect of collinearity, we have calculated **VIF**, **λi**, condition number **(k)**, tolerance **(T)** for all independent parameters used in proposed models recorded in Table-8. It is clear bi-parametric model is free from defect of collinearity.

The **VIF** for the proposed model also rejects the tri-parametric model as some of the parameters exceed the limited values. The ridge traces are recorded in fig. 2 and fig.3.

Table 8. Ridge regression parameters for the best models

Model No	Parameters Used	VIF	T	λi	k
1.	J	0.9901	1.0000	1.00000	1.00
2.	J	2.0031	0.4840	1.71833	1.00
	MW	2.0031	0.4840	0.28166	6.10
3.	W	16.2530	0.0319	2.59491	1.00
	J	2.0138	0.4722	0.38633	6.72
	MW	17.6608	0.0352	0.01875	135.36

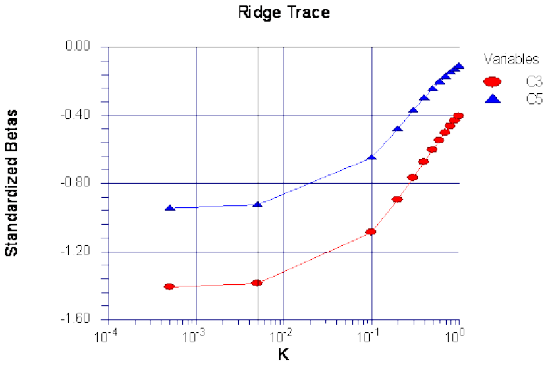


Fig. 2. Ridge Trace for Best bi parametric model no. 5

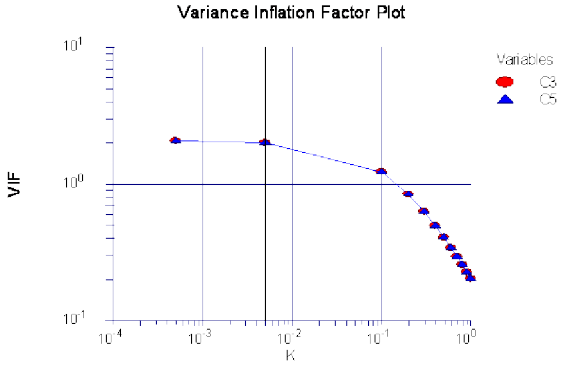


Fig. 3. VIF plot for bi parametric Model no. 5

Conclusions

1. The result and discussion made above indicates that the balaban index (J) alone is not capable of modeling lipophilicity of the bz, dbz, crown compounds used in the present study.
2. The bi-parametric model comprising of J and MW is best for modeling the Log P value of present set of crown ethers.
3. The coefficient of J and Mw are negative suggesting that these parameters have retarding effect towards exhibition of Log P. Hence the new compounds with low value of J and MW will favor the activity Log P.

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