Quantitative Structure-Activity Relationship of Alkyl Ethers Using a Set of Novel Topological Parameters

B.K. MISHRA*, M. KUANAR, J. PRADHAN AND R.N. MOHARANA[1]
Centre of Studies in Surface Science and Technology,
Department of Chemistry, Sambalpur University, Jyoti Vihar - 768 019
[1]The Pharmaceutical College, Barapali - 768 029

Accepted 27 December 1999
Revised 16 October 1999
Received 13 May 1999

Two novel topological parameters, V_c and V_{bc}, have been derived for 28 alkyl ether by considering connectivity of constituent atoms and their valence electrons. These two parameters have been used separately to correlate the anesthetic potency of the alkyl ethers and also their octanol-water partition coefficient. To optimize the relationship, parabolic equations have been proposed for anesthetic activities and partition coefficient values.

In the molecular designing for biological activity, it is observed that anesthetics are structurally nonspecific[1], i.e. they have no definite pattern of chemical structure. However, drug designers are making several attempts to obtain suitable regression model for optimizing prediction of anesthetic activity. The pioneering work in this area is by Glave and Hansch[2], who used octanol-water partition coefficient (P) on the anesthetic potency (C) of a series of aliphatic ethers[3] (Eq. 1).

$$\text{Log } 1/C = (1.038 \pm 0.19) \log P - (0.221 \pm 0.07) (\log P)^2 + (2.161 \pm 0.12) \quad (1)$$

Partition coefficient values are found to correlate well with various molecular descriptors including topological descriptors. The topological parameters, in general, concern with the shape and size of the molecule and thus it can explain the diffusion of the molecules in lipid membrane. Di Paolo[4] has related the anesthetic potency with Kier's molecular connectivity index[5] with a significant correlation. In the present communication attempts have been made to correlate the anesthetic potency of 28 aliphatic ethers with novel connectivity parameters.

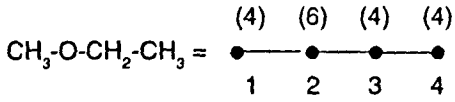
The anesthetic activities of the aliphatic ethers in mice as log 1/C (C is the effective concentration of the ether) have been collected from literature (Table 1)[3]. The topological parameter, valence connectivity index (V_c), has been obtained as the sum over all the atomic parameters calculated as given below.

*For correspondence

$$V_c = \Sigma a_i \quad (2)$$

$$\text{Atomic parameter } ai = \sum_{i=1}^{m} \sum_{J=1}^{n} (\pi V_j)^{-1/2} \quad (3)$$

where V_i is the valence of atoms, n is the total number of atoms connected to the concerned atom with various path length and m is the number of possible fragments with concerned atom in the terminal position.



$$a_1 = (4)^{-1/2} + (4x6)^{-1/2} + (4x6x4)^{-1/2} + (4x6x4x4)^{-1/2}$$

$$a_2 = (6)^{-1/2} + (6x4)^{-1/2} + (6x4)^{-1/2} + (4x6x4)^{-1/2}$$

$$a_3 = (4)^{-1/2} + (4x6)^{-1/2} + (4x6x4)^{-1/2} + (4x4)^{-1/2}$$

$$a_4 = (4)^{-1/2} + (4x4)^{-1/2} + (4x4x6)^{-1/2} + (4x4x6x4)^{-1/2}$$

$$V_c = a_1 + a_2 + a_3 + a_4 = 3.735$$

With analogy to Kier's connectivity index[5], valence bond connectivity index, V_{bc}, can be calculated as,

$$V_{bc} = (a_1 \times a_2)^{-1/2} + (a_2 \times a_3)^{-1/2} + (a_3 \times a_4)^{-1/2} = 3.166$$

The parameters for all the 28 ethers were calculated and are given in Table - 1. The regression models are derived by using multiple regression analysis.

The topological parameters derived from the simple algebraic operations of the number of vertices and edges can not distinguish the alkane isomers due to their

TABLE 1 : THE TOPOLOGICAL PARAMETERS (V_c, V_{bc}), OBSERVED AND PREDICTED ANESTHETIC POTENCY (LOG 1/C) AND PARTITION COEFFICIENT (LOG P) VALUES OF SOME ALKYL ETHERS

Sl. No	Alkyl ether	V_c	V_{bc}	Log 1/C (Obs)	Log 1/C[a] (Calc)	Log P (Obs)	Log P[b] (Calc)
1	Dimethyl ether	2.429	2.465	1.85	1.85	-0.23	0.22
2	Methyl ethyl ether	3.735	3.166	2.22	2.30	0.27	0.42
3	Divinyl ether	6.092	3.280	2.80	2.92	—	0.47
4	Ethyl vinyl ether	5.592	4.358	2.82	2.81	1.04	1.12
5	Methyl cyclopropyl ether	6.194	3.920	2.85	2.94	0.48	0.81
6	Methyl *iso*propyl ether	5.288	1.633	2.70	2.74	0.57	0.18
7	Diethyl ether	5.092	3.854	2.75	2.69	0.77	0.77
8	Methyl propyl ether	5.138	3.827	2.90	2.70	0.77	0.76
9	Ethyl cyclopropyl ether	7.628	4.602	3.10	3.19	0.98	1.32
10	Ethyl *iso*propyl ether	6.699	4.317	3.00	3.04	1.07	1.09
11	Methyl *t*-butyl ether	7.097	3.960	3.00	3.11	0.80	0.84
12	Methyl *sec*butyl ether	6.819	4.225	3.04	3.06	1.04	1.02
13	Methyl *iso*butyl ether	6.791	4.271	3.00	3.06	1.08	1.06
14	Ethyl propyl ether	6.521	4.514	3.10	3.01	1.27	1.25
15	Methyl butyl ether	6.589	4.482	3.15	3.02	1.27	1.22
16	Di*isopropyl* ether	8.358	4.768	3.15	3.28	1.63	1.47
17	Ethyl *tert.* butyl ether	8.557	4.633	3.15	3.30	1.56	1.35
18	Ethyl *sec*butyl ether	8.253	4.902	3.22	3.27	1.80	1.59
19	Ethyl *iso*butyl ether	8.199	4.960	3.22	3.26	1.83	1.65
20	Propyl *isopropyl* ether	8.204	4.929	3.26	3.26	1.83	1.62
21	Methyl amyl ether	8.065	5.139	3.40	3.25	2.03	1.83
22	Dipropyl ether	7.962	5.177	3.40	3.23	2.03	1.87
23	Ethyl butyl ether	7.985	5.171	3.30	3.24	2.03	1.86
24	Ethyl *tert* amyl ether	10.13	5.377	3.40	3.40	2.08	2.08
25	Ethyl *isoamyl* ether	9.699	5.619	3.45	3.38	2.35	2.36
26	Ethyl amyl ether	9.467	5.830	3.45	3.37	2.53	2.61
27	Di *sec.* butyl ether	11.53	5.953	3.45	3.39	2.57	2.77
28	Di*isobutyl* ether	11.36	6.080	3.30	3.39	3.64	2.93

[a,b] Predicted values are obtained by using equations 6 and 11 respectively.

degeneracy. The mathematical basis of this degeneracy is proposed to be the use of the exponent -(1/2) for the generation of connectivity parameters[6]. However, the parameters V_c and V_{bc} are found to be nondegenerate and thus are capable of identifying each isomer from one another. The generation method of the parameters indicates that each atomic parameter takes care of the contribution of the other atoms (except hydrogen) of the molecule. The summation of the atomic parameters is considered as the valence molecular connectivity descriptor (V_c) and the summation of the bond parameters obtained from the inverse square root of the product of connecting atomic parameters as the valence bond connectivity parameter (V_{bc}). Both the values increase with increasing chain length, as well as, with increasing branching.

The log 1/C values are found to correlate well with the V_c and V_{bc} parameters of the alkyl ethers (Eqs. 4 and 5). However, the parabolic equation (Eq. 6) obtained by using V_c is found to be more significant that the single parameter linear equation. The parabolic equation (Eq. 7) due to V_{bc} does not experience any improvement from the linear equation (Eq. 5). The predicted values of log 1/C using equation - 6 are found to match well with the observed values (Table 1).

$$\text{Log } 1/C = (1.9067\pm0.1213) + (0.1560\pm0.0163)\ V_c \quad (4)$$
$$n = 28,\ R = 0.887,\ F = 96.06$$

$$\text{Log } 1/C = (0.6757\pm0.1724) + (0.3072\pm0.0376)V_{bc} \quad (5)$$
$$n = 28,\ R = 0.849,\ F = 66.86$$

$$\text{Log } 1/C = (0.8025\pm0.1652) + (0.4863\pm0.0457)V_c - (0.0227\pm0.003)\ V_c^2 \quad (6)$$
$$n = 28,\ R = 0.966,\ F = 173.6$$

$$\text{Log } 1/C = (1.8949\pm0.4370) + (0.1913\pm0.0215)V_{bc} + (0.0143\pm0.0261)\ V_{bc}^2 \quad (7)$$
$$n = 28,\ R = 0.851,\ F = 32.68$$

Generally, the magnitude of the log P value of a compound determines the ease of transport of the compound through the cell membrane, thus, leading to many related events. Many attempts have been made to use various topological parameters to correlate the log P values with the topological parameters[7]. In the present study, the log P values were subjected to multiple regression analysis by using V_c and V_{bc} separately as independent variables. Equations 8 and 9 are obtained with significant correlation coefficient.

$$\text{Log } P = -(1.0339\pm0.2006) + (0.3311\pm0.0262)\ V_c \quad (8)$$
$$n = 27,\ R = 0.93,\ F = 160.1$$

$$\text{Log } P = -(1.6698\pm0.2866) + (0.681\pm0.0619)\ V_{bc} \quad (9)$$
$$n = 27,\ R = 0.91,\ F = 121.0$$

$$\text{Log } P = -(1.1475\pm0.4798) + (0.3652\pm0.1331)\ V_c - (0.0024\pm0.0090)\ V_c^2 \quad (10)$$
$$n = 27,\ R = 0.93,\ F = 77.11$$

$$\text{Log } P = (0.7415\pm0.4535) + (0.6015\pm0.2232)\ V_{bc} + (0.1582\pm0.0271)\ V_{bc}^2 \quad (11)$$
$$n = 27,\ R = 0.964,\ F = 157.8$$

A parabolic relationship analogous to Glave and Hansch model (Eq.1) was attempted and no improvement is observed when V_c^2 was added to Eq. 8 (Eq.10). The 't' value for the second parameter was found to be insignificant (t = 0.26). However, a significant improvement is observed when V_{bc} and V_{bc}^2 were taken as independent variables (Eq. 11). The log P values of the alkyl ethers have been predicted by using equation 11 and are reported in Table 1. The values are found to match well with the observed values.

The new parameters are able to explain the anesthetic potency as well as the log P values of the alkyl ethers successfully. These parameters may find wide applications in predicting other physico-chemical properties of various organic compounds. The work in this area is under progress.

ACKNOWLEDGMENTS

The author (BKM) thanks University Grants Commission, New Delhi, for the financial help through the UGC Research Award - 1999. The author (MK) thanks CSIR New Delhi for providing Extended Senior Research Fellowship.

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