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Novel Estimation of Lipophilic Behaviour of Polychlorinated Biphenyls

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Abstract—A novel method has been developed for the estimation of lipophilic behaviour of polychlorinated biphenyls (PCBs) using the recently introduced Padmakar–Ivan (PI) index. The results obtained are compared with the earlier reported Abraham method. The statistical analyses showed that the proposed method based on the PI index is quite useful. © 2002 Published by Elsevier Science Ltd.

Introduction

The octanol/water partition coefficient expressed as $\log P_{(oct)}$ (P = octanol/water partition coefficient) is an important property for pharmacology, toxicology and medicinal chemistry.[1,2] Log$P$ is used to model partitioning of chemicals between the lipophilic membrane and the relative hydrophobic cellular cytoplasmic material. $\text{Log}P_{(oct)}$ quantifies hydrophobicity of chemicals and is important both for the predicting pharmacokinetics and pharmacodynamics of drugs and toxicants.[1–3] Lipophilic is traditionally measured in the octanol/water system. $\text{Log}P_{(oct)}$ values have been shown to be generally satisfactory for modelling protein binding and lipophilic interactions with biological membranes consisting largely of protein, but for other types of membranes, alternative solvent systems might be more appropriate.[4] Several methods have been described in the literature for the estimation of the water–octanol partition coefficient, that is $\log P_{(oct)}$. Abraham et al.[5] have recently introduced a method for the estimation of $\log P_{(oct)}$ using descriptors designed to reflect the solution related process. They proposed the following equation for the estimation of $\log P_{(oct)}$:

$$\text{Log}P_{(oct)} = 0.088 - 0.562R_2 - 1.054\pi_2 r + 0.032\Sigma\alpha_2^H - 3.460\ \Sigma\beta_2^H + 3.814V_x \qquad (1)$$

In the aforementioned eq (1), the descriptors involved are defined as follows: R_2 is an excess molar refraction, $\pi_2 r$ is a combined dipolarity/polarizability descriptor. $\sum \alpha_2^H$ is the overall solute hydrogen bond acidity, $\sum \beta_2^H$ is the overall solute hydrogen bond basicity, V_x is McGowan's characteristic molecular volume ($\text{cm}^3\ \text{mol}^{-1}/100$).

The polychlorinated biphenyls (PCBs) are a set of 209 different isomeric compounds in which 1–10 chlorine atoms are attached to a biphenyl group (Fig. 1).[6,7] However, for the set of 16 PCBs (Table 1), the inherent toxicity, long experimental half-lives, and their tendency to bioaccumulate in adipose tissues have given rise to much concern about the possible hazards of PCBs to humans[8] and for their empirical modelling of an in-vitro activity.[9] Consequently, we have chosen these 16 PCBs for the present study. Another reason for choosing these PCBs is that they were used by Abraham et al.[5] and our main objective of the study is to compare our results with those obtained by Abraham et al.[5]

In the development of working models of the dynamics of PCBs in the ecosphere, reliable values of a number of their physicochemical properties are indispensible. In this regard, a knowledge of the partitioning behaviour

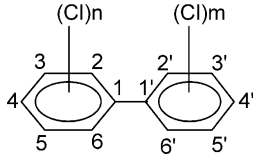

Figure 1. Structure of PCBs used in the present study.

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Table 1. PCBs, number of chlorine substitution (N), PI index and $\log P_{(oct)}$

S. no.	PCBs	N	PI	Expt.	Log$P$ estimated from			
				$\log P_{(oct)}$	PI index		Abraham method	
					Est	Res	Est	Res
1	PCB	0	144	3.98	4.53	−0.55	4.22	−0.24
2	4C-PCB	1	170	4.61	4.83	−0.22	4.66	−0.05
3	2,2′DC-PCB	2	198	4.73	5.16	−0.43	5.10	−0.37
4	4,4′DC-PCB	2	198	5.58	5.16	0.42	5.10	0.48
5	2,4,5TRI-PCB	3	228	5.81	5.51	0.30	5.89	−0.08
6	2,2′,5TRI-PCB	3	228	5.60	5.51	0.09	5.70	−0.10
7	2,2′,5,5′TETR-PCB	4	260	6.09	5.88	0.21	6.32	−0.23
8	2,3,4,5TETR-PCB	4	264	6.41	5.92	0.49	6.57	−0.16
9	2,2′,4,5,5′PC-PCB	5	294	6.49	6.27	0.17	6.90	−0.46
10	2,3,4,5,6PC-PCB	5	294	6.52	6.27	0.25	7.06	−0.54
11	2,2′,4,4′,5,5′HEX-PCB	6	330	6.80	6.69	0.11	7.57	−0.77
12	3,3′,4,4′,5,5′HEX-PCB	6	330	7.55	6.69	0.86	7.20	0.35
13	2,2′,3,3′,4,4′,6HEPT-PCB	7	368	6.99	7.12	−0.13	7.86	−0.87
14	2,2′,3,3′,5,5′,6,6′OCT-C-PCB	8	408	7.15	7.59	−0.49	8.26	−1.11
15	2,2′,3,3′,4,5,5′,6,6′NANO C-PCB	9	450	8.16	8.08	0.08	8.74	−0.58
16	DECA C-PCB	10	494	8.26	8.59	−0.33	9.23	−0.97

D, di; TRI, tri, TETR, tetra; PC, penta; HEX, hexa; HEPT, hepta; OCT, octa.

of the PCBs in various media is of prime importance. Therefore, parameters such as their partition coefficient in an octanol/water system, distribution and solubility need to be known with high precision. The method is described here which enables accurate estimations of $\log P_{(0ct)}$. The method is based on the topological and graph-theoretical technique in that the recently introduced Padmakar–Ivan (PI) index is used.[10–12]

The calculation of the PI index is described in detail in our earlier publications[10–12,16–20] and, therefore, is not discussed here. However, we give the expression needed for the calculation of the PI index as follows:

$$\mathrm{PI} = \mathrm{PI(G)} = \sum_{e} [n_{eu}\ (e|G) + n_{ev}\ (e|G)] \qquad (2)$$

where $n_{eu}(e|G)$ is the number of edges lying closer to vertex u than the vertex v, of an edge $e = uv$. The meaning of n_{ev} is analogous.

The topological structure of the various PCB species (Table 1, Fig. 1), can be investigated and conveniently characterized for by means of the PI index. We have, therefore, adopted $\log P_{(oct)}$ values of PCBs (Table 1) and correlated them with the calculated PI index. The procedure for the calculation of the PI index is described in the Experimental. Regression analysis[14,15] has shown that the PI index is quite useful for the estimation of $\log P_{(oct)}$ of the PCBs under present study. The results are discussed below.

Results and Discussion

The set of 16 PCBs used in the present investigation are reported in Table 1. As stated earlier, we have chosen this set as the same was used by Abraham et al.[5] for proposing a method of the estimation of their $\log P_{(oct)}$ using solvacometric parameters. Table 1 also contains the calculated value of the PI index of PCBs. In addition, Table 1 gives comparison of our results ($\log P_{oct}$) with those of Abraham et al.[5]

At this stage, it worth mentioning that Abraham et al.[5] calculated $\log P_{(oct)}$ using the generalized eq (1), and that the parameters R, $\pi_2 r$, $\Sigma\alpha_2^H$, $\Sigma\beta_2^H$ and V_x corresponding to PCBs used in the present study are not given in ref 5 but are available from Abraham. Furthermore, in the present investigation we are mainly concern with final results, that is $\log P_{(oct)}$ obtained by Abraham et al.,[5] using these parameters.

A perusal of Table 1 shows that no degeneracy is present in the $\log P_{(oct)}$ of the PCBs used. However, little degeneracy is observed in PI index. This is obvious because the PI index belongs to first-generation topological index.[13] Balaban[13] has shown that first-generation topological indexes, in spite of their degeneracy are quite successful in developing quantitative structure–property–activity–toxicity (QSPR, QSAR, QSTR) relationships. This is found to be so in the present case also.

A close look of Table 1 also shows that $\log P_{(oct)}$ of PCBs goes on increasing with increase in chlorine substituent as well as with increase in the magnitude of the PI index. This indicates that $\log P_{(oct)}$ of PCBs is linearly correlated with the PI index. The regression analysis of the data gave the following expression for estimating $\log P_{(oct)}$ (which conforms to linear equation: $Y = AX + B$, where, $Y = \log P$, $X =$ PI index, and A and B are regression parameters).

$$\log P(\mathrm{oct}) = 0.0116\ (\pm 0.0002)\mathrm{PI} + 2.8617 \qquad (3)$$

The statistical parameters are given in Table 2.

Using the model expressed by eq (3), we have estimated $\log P_{(oct)}$ of PCBs and compared them with the experimental $\log P_{(oct)}$ value (Table 1).

Table 2. Statistical parameters for the proposed models

No.	Model	S_x	S_y	Intercept	Slope	R
1	Based on PI index	99.3793	1.2217	2.8617	0.0116	0.9464
2	Based on Abraham method	1.1677	1.4771	−1.1305	1.2481	0.9868
3	Predictive correlation based on PI index	1.2217	1.1677	0.5279	0.9074	0.9493
4	Predictive correlation based on Abraham PI model	1.2217	1.4452	−0.5621	1.1373	0.9614

Sx, standard deviation of the accumulated X-values. Sy, standard deviation of the accumulated Y-values.

When the estimated $\log P_{(oct)}$ is plotted against the experimental $\log P_{(oct)}$, it is immediately apparent that the intercept and slope of the line of the best fit with value of 0.5279 and 0.9074 are significantly different from their ideal value of 0.00 and 1.00, respectively, of the intercept and slope. This may be attributed to the observed degeneracy of the PI index. The magnitude of correlation coefficient ($r = 0.9464$) indicates that the PI index can be successfully used for the estimation of $\log P_{(oct)}$ of PCBs under present investigation. The $\log P_{(oct)}$ estimated by Abraham et al.[5] employing eq (1) is also given in Table 1. It will be interesting to compare the predictive potential of our model based on the PI index with that of Abraham et al.,[5] based on solvacometric parameters. Therefore, we have also obtained correlation coefficient of the Abraham model[5] for comparison and we found it to be 0.9868. This shows that the Abraham model[5] is slightly better than our model based on the PI index. However, our method based on the PI index will be more useful when solvent parameters (R_2, π_2^H, $\sum \alpha_2^H$, $\sum \beta_2^H$ and V_x) are not available or could not be calculated.

In order to confirm our results, we have correlated $\log P_{(oct)}$ values obtained by us with those obtained by Abraham.[5] The observed predictive correlation coefficient of the order of 0.9614 compared to 0.9493 confirms that both the methods have similar correlation potential.

Conclusion

The aforementioned results and discussion led us to conclude that the predictive potential of our model based on the PI index is similar to that of the model proposed by Abraham, which gives slightly better results. Our method is useful when the solvent parameters are not available.

Experimental

Log *P*

The log*P* values for the set of PCBs were used as reported by Abraham et al.[5] and are given in Table 1.

Calculation of the PI index

The PI index of PCBs used in the present investigation were calculated using the methods described earlier.[8–10] This recently introduced PI index is calculated using the following expression:

$$PI = PI(G) = \sum_e [n_{eu}\ (e|G) + n_{ev}\ (e|G)\ ] \quad (4)$$

where n_{eu} are the number of edges nearer to a vertex u of a graph G, while the meaning of n_{ev} is analogous. The edges equidistant from the vertices u and v of an edge e = uv are not counted. The values of the PI index calculated for the set of PCBs under the present investigation are given in Table 1.

Statistical analysis

The statistical analysis of the data was made by regression analysis using the method of least-squares.[14,15] Various regression parameters so calculated for the various systems (models) are shown in Table 2. The regression program as provided by Prof. Lukovits was used for this purpose.

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