Quantitative structure–activity relationship for prediction of the toxicity of polybrominated diphenyl ether (PBDE) congeners

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Abstract

Levels of Polybrominated diphenyl ether (PBDEs) are increasing in the environment due to their use as flame retardants. The similarities of structure to polychlorinated biphenyl (PCB) congeners suggest that they may share similar toxicological properties, such as hepatic enzyme induction. In this work, quantitative structure–activity relationship (QSAR) models were constructed based on 406 descriptors for the logarithm of toxicology index (aryl hydrocarbon receptor relative binding affinities, AhR, *I*) of 18 PBDE congeners. The method used for building model is the Heuristic method, which is included in comprehensive descriptors for structural and statistical analysis (CODESSA) software. The best regression model involved four descriptors, which were related to the conformational changes, atomic reactivity, molecular electrostatic field, and non-uniformity of mass distribution in a molecule of PBDEs, etc. The high square of the correlation coefficient $R^2(0.903)$ showed the model was satisfactory.

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1. Introduction

Polybrominated diphenyl ethers (PBDEs) are widespread used in abundance as flame-retardants in polymers found in textiles and electrical appliances (Renner, 2000). The commercial PBDEs mixtures are produced with three degrees of bromination: deca-, consisting of 97–98% decabromodiphenyl ether (DeBDE); octa-, consisting of 10–12% hexabromodiphenyl ether (HxBDEs), 43–44% heptabromodiphenyl ether (HeptaBDE) and 31–35% octabromodiphenyl ether (OcBDEs); and penta-, consisting of 50–62% pentabromodiphenyl ether (PeBDEs) and 24–38% tetrabromodiphenyl ethers (TeBDEs) (Darnerud et al., 2001). The

global demand for PBDEs has been estimated to be close to 70 000 tones in 1999.

PBDEs have widely distributed in environmental matrix and other samples such as human milk, blood plasma, and adipose tissue (Norén and Meironyte, 2000; Booij et al., 2002; Hale et al., 2002; Song et al., 2004; Vives et al., 2004; Wolkers et al., 2004). Among the target PBDE congeners, BDE47 and 99 (2,2',4,4'-tetraBDE and 2,2',4,4',5-pentaBDE) are the most frequently encountered ones in the environment (Lindstrom et al., 1999).

PBDEs are concerned due to their persistence, bioaccumulation, and possible adverse effects in wildlife and humans (Tjärnlund et al., 1998; Sjödin et al., 1999). The toxicology of PBDEs is currently under investigation. But evidences emerge that PBDEs may be developmental neurotoxicants, and may cause neurochemical and hormonal deficits (Eriksson et al., 2001; Viberg et al., 2002; Zhou et al., 2002; Branchi et al., 2003). EU has banned

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the use in all applications of penta-BDE and octa-BDE in the EU market. However, limited toxicological data are obtained for only the most prevalent individual PBDE congeners (e.g. BDE-47, BDE-99, and BDE-100) (Chen et al., 2001; Rahman et al., 2001). Thus, there is a need for prediction tools to study PBDEs' properties including retention behavior, properties, and activity/toxicity for which analytical standards are currently difficult to obtain, but yet for which environmental data and toxicology indices are needed. Other works have been published to discuss retention mechanisms of PBDEs on capillary column by quantitative structure-gas chromatography retention time models (MLR) technique (Ikonomou and Rayne, 2002; Rayne and Ikonomou, 2003a,b). Wong et al. determined vapor pressures of 23 PBDEs by a function of temperature with a gas chromatographic retention time (Wong et al., 2001).

Here, based on the toxicology index (AhR, pI) of 18 PBDEs, we report a QSAR model for all 209 PBDE congeners by the Heuristic method of CODESSA (comprehensive descriptors for structural and statistical analysis) technique, to investigate the significant relationships between the quantitative structure parameters and toxicology index of PBDEs.

The software CODESSA, developed by Katritzky group (Katritzky et al., 1995; Katritzky et al., 1995–1997), has been applied successfully in a variety of QSAR analyses (Oblak et al., 2000; Katritzky and Tatham, 2001). It can calculate a comprehensive set of descriptors: constitutional descriptors, topological descriptors, geometrical descriptors, electrostatic descriptors, and semi-empirical quantum chemical descriptors (in this work, 406 descriptors were calculated).

2. Materials and methods

A toxicity data set of 18 PBDEs congeners was taken from the previous work done by Chen et al. (2001). The relative binding affinities (RBA) values (I), which were expressed as $pI(-\log I)$ (Table 1) for Ah receptor binding of individual PBDEs congeners, were in the μM range, indicating weaker affinity than the reference toxicant TCDD. Values of these 18 PBDEs in Table 1 were binding affinities relative to TCDD; concentration of $[^3\text{H}]$ -TCDD was 1.0 nM.

2.1. Physicochemical property calculations

Firstly, 19 descriptors of PBDEs were calculated by HyperChem Release 7.0 software (HyperChem, 2002). Molecular geometries were optimized by the Polak Ribiere algorithm (Press et al., 1986) until rms gradient $0.01 \text{ kcal } \text{\AA}^{-1} \text{ mol}^{-1}$. The physicochemical quantities were obtained from the thermodynamically most stable configurations of the 209 PBDEs by semi-empirical parameterization method (PM3). Nineteen indices included molecular energies, heat of formation, frontier orbital energies, total dipole

moments, QSAR properties $\log P$, van der Waals volumes, and surface areas (Table 2).

2.2. Principal component analysis (PCA)

Principal component analysis (PCA) on the analytical data was executed to obtain a visual representation of the main characteristics. PCA is an unsupervised multivariate technique in which new variables (called principal components (PCs)) are calculated as linear combinations of the olds ones. When most of the variation is explained by the first two or three components, a two- or three-dimensional scattergram, plotting the values for the first two or three principal components of the data points can be obtained to give essential features of the multidimensional scatter (in this case, usually PC1 and PC2, which eigenvalues are >1 , are considered to represent the main examined objects and variables). The combined plot of scores and loadings allow us to recognize groups of samples with similar behavior and the existing correlation among the original variables. In this paper, PCA were performed with SPSS 12.0 for Windows Release 12.0.0 (4 Sep. 2003, SPSS Inc., 1989–2003).

2.3. Theory of CODESSA

The structures of PBDEs were drawn with HyperChem Release 7.0 software and saved as the hin files for MOPAC (Stewart, 1989), then the hin files were transferred into software CODESSA to calculate all kinds of descriptors. CODESSA includes two advanced procedures for systematic development of multi-linear QSAR/QSPR equations: (i) the Heuristic method, and (ii) the best multi-linear regression method. The heuristic method for descriptor selection proceeds with a preselection of descriptors by sequentially eliminating descriptors which do not match any of the following criteria: (i) the F -test greater than one unit; (ii) R^2 value less than a value defined at the start (default 0.01); (iii) the student's t -test less than that defined (default 0.1); and (iv) duplicate descriptors having a higher squared inter-correlation coefficient than a predetermined level (usually 0.8). The next step involves correlation of the given property with (i) the top descriptor in the above list with each of the remaining descriptors, and (ii) the next one with each of the remaining descriptors, etc. The best pairs, as evidenced by the highest F -values in the two-parameter correlations, are chosen and used for further inclusion of descriptors in a similar manner. The goodness of the correlation is tested by the correlation coefficient (R^2), the F -test (F), and the squared standard error (s^2). The stability of the correlations was tested against the cross-validated coefficient, R_{cv}^2 . The heuristic method's advantages are the high speed and no restrictions on the size of the data set. Besides, it will demonstrate which descriptors have bad or missing values, which descriptors are insignificant, and which descriptors are highly inter-correlated. So, in this paper, we selected the heuristic method to build the best QSAR models.

Table 1

Experimental, predicted activities (pI), and residual values of PBDEs by CODESSA

No.	Br sites	Pred.	Exp.	Diff.
1	2	3.767		
2	3	3.478		
3	4	3.766	3.886	−0.120
4	2,2'	3.641		
5	2,3	3.308		
6	2,3'	3.096		
7	2,4	3.888		
8	2,4'	3.327		
9	2,5	4.582		
10	2,6	3.561		
11	3,3'	2.830		
12	3,4	2.820		
13	3,4'	2.888		
14	3,5	4.142		
15	4,4'	3.429	3.420	0.009
16	2,2',3	3.247		
17	2,2',4	3.577	3.638	−0.061
18	2,2',5	4.190		
19	2,2',6	4.025		
20	2,3,3'	2.856		
21	2,3,4	3.449		
22	2,3,4'	2.875		
23	2,3,5	4.361		
24	2,3,6	3.307		
25	2,3',4	3.009		
26	2,3',5	3.313		
27	2,3',6	3.121		
28	2,4,4'	3.423	2.921	0.502
29	2,4,5	4.790		
30	2,4,6	4.283		
31	2,4',5	3.432		
32	2,4',6	2.947		
33	2,3',4'	2.553		
34	2,3',5'	3.900		
35	3,3',4	2.300		
36	3,3',5	3.470		
37	3,4,4'	2.557		
38	3,4,5	3.153		
39	3,4',5	3.977		
40	2,2',3,3'	2.988		
41	2,2',3,4	3.140		
42	2,2',3,4'	3.038		
43	2,2',3,5	4.110		
44	2,2',3,5'	3.491		
45	2,2',3,6	3.766		
46	2,2',3,6'	2.759		
47	2,2',4,4'	3.541	3.252	0.289
48	2,2',4,5	4.174		
49	2,2',4,5'	3.794	4.174	−0.380
50	2,2',4,6	3.728		
51	2,2',4,6'	3.934		
52	2,2',5,5'	4.502		
53	2,2',5,6'	4.645		
54	2,2',6,6'	4.051		
55	2,3,3',4	1.778		
56	2,3,3',4'	2.224		
57	2,3,3',5	3.454		
58	2,3,3',5'	3.413		
59	2,3,3',6	3.384		
60	2,3,4,4'	1.976		
61	2,3,4,5	4.074		
62	2,3,4,6	3.534		
63	2,3,4',5	3.426		

Table 1 (continued)

No.	Br sites	Pred.	Exp.	Diff.
64	2,3,4',6	2.506		
65	2,3,5,6	4.606		
66	2,3',4,4'	2.472	2.699	−0.227
67	2,3',4,5	3.519		
68	2,3',4,5'	3.528		
69	2,3',4,6	3.197		
70	2,3',4',5	2.660		
71	2,3',4',6	3.843	3.867	−0.024
72	2,3',5,5'	4.003		
73	2,3',5',6	3.840		
74	2,4,4',5	4.048		
75	2,4,4',6	3.071	3.398	−0.327
76	2,3',4',5'	3.721		
77	3,3',4,4'	2.365	2.658	−0.293
78	3,3',4,5	3.451		
79	3,3',4,5'	2.621		
80	3,3',5,5'	3.653		
81	3,4,4',5	3.153		
82	2,2',3,3',4	1.725		
83	2,2',3,3',5	3.495		
84	2,2',3,3',6	2.447		
85	2,2',3,4,4'	1.970	1.721	0.249
86	2,2',3,4,5	3.394		
87	2,2',3,4,5'	2.287		
88	2,2',3,4,6	2.864		
89	2,2',3,4,6'	2.679		
90	2,2',3,4',5	3.566		
91	2,2',3,4',6	2.650		
92	2,2',3,5,5'	4.229		
93	2,2',3,5,6	3.832		
94	2,2',3,5,6'	4.155		
95	2,2',3,5',6	3.355		
96	2,2',3,6,6'	3.510		
97	2,2',3,4',5'	3.523		
98	2,2',3,4',6'	2.810		
99	2,2',4,4',5	4.027	3.854	0.173
100	2,2',4,4',6	4.153	4.114	0.039
101	2,2',4,5,5'	4.283		
102	2,2',4,5,6'	2.852		
103	2,2',4,5',6	3.929		
104	2,2',4,6,6'	4.028		
105	2,3,3',4,4'	1.774		
106	2,3,3',4,5	2.988		
107	2,3,3',4',5	2.591		
108	2,3,3',4,5'	2.194		
109	2,3,3',4,6	3.074		
110	2,3,3',4',6	2.308		
111	2,3,3',5,5'	3.794		
112	2,3,3',5,6	3.257		
113	2,3,3',5',6	3.317		
114	2,3,4,4',5	3.469		
115	2,3,4,4',6	2.650		
116	2,3,4,5,6	4.653		
117	2,3,4',5,6	2.878		
118	2,3',4,4',5	2.796		
119	2,3',4,4',6	2.895	2.959	−0.064
120	2,3',4,5,5'	3.957		
121	2,3',4,5',6	3.954		
122	2,3,3',4',5'	2.341		
123	2,3',4,4',5'	2.600		
124	2,3',4',5,5'	3.685		
125	2,3',4',5',6	2.914		
126	3,3',4,4',5	2.890	2.569	0.321
127	3,3',4,5,5'	3.712		

(continued on next page)

Table 1 (continued)

No.	Br sites	Pred.	Exp.	Diff.
128	2,2',3,3',4,4'	2.789		
129	2,2',3,3',4,5	2.866		
130	2,2',3,3',4,5'	2.161		
131	2,2',3,3',4,6	2.949		
132	2,2',3,3',4,6'	2.838		
133	2,2',3,3',5,5'	3.858		
134	2,2',3,3',5,6	2.996		
135	2,2',3,3',5,6'	3.298		
136	2,2',3,3',6,6'	3.366		
137	2,2',3,4,4',5	3.134		
138	2,2',3,4,4',5'	2.362		
139	2,2',3,4,4',6	2.993		
140	2,2',3,4,4',6'	2.480		
141	2,2',3,4,5,5'	2.816		
142	2,2',3,4,5,6	3.954		
143	2,2',3,4,5,6'	2.654		
144	2,2',3,4,5',6	3.649		
145	2,2',3,4,6,6'	2.193		
146	2,2',3,4',5,5'	4.509		
147	2,2',3,4',5,6	4.373		
148	2,2',3,4',5,6'	3.659		
149	2,2',3,4',5',6	3.262		
150	2,2',3,4',6,6'	3.787		
151	2,2',3,5,5',6	3.990		
152	2,2',3,5,6,6'	4.257		
153	2,2',4,4',5,5'	4.598	4.602	−0.004
154	2,2',4,4',5,6'	4.544	4.638	−0.094
155	2,2',4,4',6,6'	3.888		
156	2,3,3',4,4',5	2.829		
157	2,3,3',4,4',5'	2.256		
158	2,3,3',4,4',6	2.425		
159	2,3,3',4,5,5'	3.069		
160	2,3,3',4,5,6	4.153		
161	2,3,3',4,5',6	3.749		
162	2,3,3',4',5,5'	2.648		
163	2,3,3',4',5,6	2.674		
164	2,3,3',4',5',6	2.450		
165	2,3,3',5,5',6	3.736		
166	2,3,4,4',5,6	3.408		
167	2,3',4,4',5,5'	2.951		
168	2,3',4,4',5',6	2.678		
169	3,3',4,4',5,5'	3.463		
170	2,2',3,3',4,4',5	2.310		
171	2,2',3,3',4,4',6	2.388		
172	2,2',3,3',4,5,5'	3.162		
173	2,2',3,3',4,5,6	2.927		
174	2,2',3,3',4,5,6'	3.431		
175	2,2',3,3',4,5',6	1.694		
176	2,2',3,3',4,6,6'	2.202		
177	2,2',3,3',4,5',6'	2.255		
178	2,2',3,3',5,5',6	3.570		
179	2,2',3,3',5,6,6'	3.685		
180	2,2',3,4,4',5,5'	3.463		
181	2,2',3,4,4',5,6	2.370		
182	2,2',3,4,4',5,6'	2.320		
183	2,2',3,4,4',5',6	3.613	3.602	0.011
184	2,2',3,4,4',6,6'	3.089		
185	2,2',3,3,5,5',6	2.630		
186	2,2',3,4,5,6,6'	3.881		
187	2,2',3,4',5,5',6	4.576		
188	2,2',3,4',5,6,6'	4.017		
189	2,3,3',4,4',5,5'	4.525		
190	2,3,3',4,4',5,6	3.094		
191	2,3,3',4,4',5',6	2.715		
192	2,3,3',4,5,5',6	4.155		

Table 1 (continued)

No.	Br sites	Pred.	Exp.	Diff.
193	2,3,3',4',5,5',6	4.293		
194	2,2',3,3',4,4',5,5'	3.305		
195	2,2',3,3',4,4',5,6	3.638		
196	2,2',3,3',4,4',5,6'	3.567		
197	2,2',3,3',4,4',6,6'	3.409		
198	2,2',3,3',4,5,5',6	4.941		
199	2,2',3,3',4,5,5',6'	3.364		
200	2,2',3,3',4,5,6,6'	2.175		
201	2,2',3,3',4,5',6,6'	2.337		
202	2,2',3,3',5,5',6,6'	3.868		
203	2,2',3,4,4',5,5',6	4.965		
204	2,2',3,4,4',5,6,6'	2.497		
205	2,3,3',4,4',5,5',6	3.477		
206	2,2',3,3',4,4',5,5',6	3.787		
207	2,2',3,3',4,4',5,6,6'	2.390		
208	2,2',3,3',4,5,5',6,6'	2.613		
209	Deca-	4.306		

3. Results and discussion

3.1. Results of PCA using physicochemical properties calculated by PM3

Result of PCA gives three significant PCs (eigenvalues >1), which explains 92.4% of the variation in the data (75.3%, 11.6%, and 5.5%, respectively). Parameters influencing PC1 are surface area (Grid) (SAG), surface area (Approx.) (SAA), core–core interaction (CCIA), log *P*, binding energy (BE), polarizability (*P*), refractivity (*R*), van der waals volume (*V*), heat of formation (HOF), E_{LUMO} , E_{HOMO} , hydration energy (HE), electronic energy (EE), etc. PC2 is positive by Q_{min} and ΔE , negative by Q_{max} , E_{HOMO} , and HOF. PC3 is positively determined by dipole moment (DIP) and negatively by Q_{min} . As shown in Fig. 1, nine clusters of PBDE congeners can be observed in the score plot of PC1 and PC2, corresponding to the different degrees of bromination, from mono- (left) to deca-BDE (right). There are some crosses in tetra-BDE, penta-BDE, and hexa-BDE groups. For example, hexa-BDE166 falls together in penta-BDE group. This is similar to the results of the previous works for 154 PCBs (Andersson et al., 1996) and PBDEs (Harju et al., 2002). In PC2, the degree of ortho-bromination separates the congeners. Congeners having one ortho-bromination have higher scores, such as BDE27, 75, 116, 191, etc. The non-ortho and two ortho-bromination with lower are found in the opposite area, such as BDE54, 104, etc.

3.2. Modeling quantitative structural–activity relationships by heuristic method of CODESSA

By using the Heuristic method, regression models were developed for 18 PBDE congeners. The heuristic correlations performed for the whole set provided the optimal equations for different numbers of descriptors in the range of 1–6. To avoid the over-parameterization of the model, an increase of the R^2 value of less than 0.02 was chosen

Table 2
Calculated physicochemical parameters with abbreviations

Physicochemical properties	Abbreviation	Methods	Unit
Total energy	TE	PM3	kcal/mol
Binding energy	BE	PM3	kcal/mol
Isolated atomic energy	IAE	PM3	kcal/mol
Electronic energy	EE	PM3	kcal/mol
Core–core interaction	CCIA	PM3	kcal/mol
Heat of formation	HOF	PM3	kcal/mol
The net charge of the most negative atom	Q_{MIN}	PM3	–
The net charge of the most positive atom	Q_{MAX}	PM3	–
Total dipole moment	DIP	PM3	Debye
Energy of the highest occupied molecular orbitals	E_{HOMO}	PM3	eV
Energy of the lowest unoccupied molecular orbitals	E_{LUMO}	PM3	eV
LUMO–HOMO energy gap (hardness)	ΔE	PM3	eV
Surface area (Approx.)	SAA	QSAR	$\text{\AA}^2$
Surface area (Grid)	SAG	QSAR	$\text{\AA}^2$
van der Waals volume	V	QSAR	$\text{\AA}^3$
Hydration energy	HE	QSAR	kcal/mol
$\log P$	$\log P$	QSAR	–
Refractivity	R	QSAR	–
Polarizability	P	QSAR	–

Fig. 1. PCA score plots of the first three principal components PCs (above), and corresponding loading plots (below) using the physicochemical properties calculated by PM3.

as the breakpoint criterion. From the viewpoint of statistics, the number of samples should be 4–5 times of that

of variables for linear regression. Plotting of R^2 and R^2_{cv} values against the number of descriptors (Fig. 2), which

Fig. 2. Correlation coefficients (R^2 , R_{cv}^2) versus number of descriptors.

provide guidance regarding the number of descriptors to retain in the models, suggested that the best model contained four parameters. The experimental pI versus predicted pI of PBDEs and the residuals of the best regression model (Table 1) indicated that the best regression model (containing four descriptors) was very satisfactory. The descriptors involved in these correlations and the regression coefficients were listed in Table 3.

From Table 3 and Fig. 3 (relationship between $E_{tot}(C-C)$ and pI), we can see that Max total interaction for a C–C bond ($E_{tot}(C-C)$) (Strouf, 1986) (the first regression model, which contains one descriptor) is most important to the activity index pI . This descriptor is defined as follows:

$$E_{tot}(C-C) = E_c(C-C) + E_{exc}(C-C) \quad (1)$$

where $E_c(C-C)$ is maximum coulomb interaction energy between two given atomic species (C, here are carbon

Table 3
Regression models built by using heuristic method

Model	Descriptor	Abbreviation	Coefficient	t-test
$R^2 = 0.648$ $F = 29.50$ $s^2 = 0.2156$	Intercept		77.572	5.683
	Max total interaction for a C–C bond ^a	$E_{tot}(C-C)$	–3.871	–5.431
<i>One parameter</i>				
$R^2 = 0.767$ $F = 24.68$ $s^2 = 0.1524$	Intercept		70.040	6.726
	Max resonance energy for a C–C bond ^a	$E_R(C-C)$	–3.798	–6.498
	FNSA-2 fractional PNSA (PNSA-2/TMSA) [Zefirov's PC] ^b	FNSA-2	–4.076	–2.937
<i>Two parameters</i>				
$R^2 = 0.849$ $F = 26.29$ $s^2 = 0.106$	Intercept		55.785	5.530
	Max resonance energy for a C–C bond	$E_R(C-C)$	–3.080	–5.583
	FNSA-2 fractional PNSA (PNSA-2/TMSA) [Zefirov's PC]	FNSA-2	–6.626	–4.482
<i>Three parameters</i>				
$R^2 = 0.903$ $F = 30.20$ $s^2 = 0.073$	Principal moment of inertia B/# of atoms ^a	P	6759.600	2.864
	Intercept		50.051	5.880
	Max resonance energy for a C–C bond	$E_R(C-C)$	–2.891	–5.813
	Balaban index ^c	B	3.072	3.789
<i>Four parameters</i>				
$R^2 = 0.9263$ $F = 30.15$ $s^2 = 0.06$	1X BETA polarizability (DIP) ^a	DIP	0.004	4.213
	ZX shadow ^d	S_{ZX}	–0.033	–3.288
	Intercept		73.645	6.329
	Max resonance energy for a C–C bond	$E_R(C-C)$	–3.193	–6.629
	Balaban index	B	4.576	5.030
<i>Five parameters</i>				
$R^2 = 0.958$ $F = 42.01$ $s^2 = 0.037$	1X BETA polarizability (DIP)	DIP	0.002	3.294
	Min atomic orbital electronic population ^a	OEP _{min}	–28.967	–3.470
	Principal moment of inertia B/# of atoms	P	4596.000	2.710
	Intercept		117.960	5.649
	Max resonance energy for a C–C bond	$E_R(C-C)$	–3.347	–6.203
	FNSA-2 fractional PNSA (PNSA-2/TMSA) [Zefirov's PC]	FNSA-2	–9.710	–8.531
<i>Six parameters</i>				
	Principal moment of inertia B/# of atoms	P	8372.400	5.528
	Avg electroph. react. index for a C atom ^a	RI _{avg}	110.880	3.491
	Max total interaction for a C–O bond ^a	$E_{tot}(C-O)$	–2.336	–4.007
	Min exchange energy for a C–C bond ^a	EE _{min} (C–C)	–3.351	–3.422

^a Topological descriptor.

^b Geometrical descriptor.

^c Electrostatic descriptor.

^d Quantum-chemical descriptor.

Fig. 3. Relationship between $E_{\text{tot}}(\text{C-C})$ and the values of pI of 18 PBDEs.

atoms) in the molecule, $E_{\text{exc}}(\text{C-C})$ is maximum electronic exchange energy between two given atomic species (here are carbon atoms) in the molecule. $E_{\text{c}}(\text{C-C})$ is defined as

$$E_{\text{c}}(\text{C-C}) = E_{\text{ee}}(\text{C-C}) + E_{\text{ne}}(\text{C-C}) + E_{\text{nn}}(\text{C-C}) \quad (2)$$

where $E_{\text{ee}}(\text{C-C})$ is maximum electronic repulsion energy between two given atomic species (atom carbon) in the molecule; $E_{\text{ne}}(\text{C-C})$ is maximum nuclear-electron attraction energy between two given atomic species (atom carbon) in the molecule, and $E_{\text{nn}}(\text{C-C})$ is maximum nuclear repulsion energy between two given atomic species (atom carbon) in the molecule, calculated as follows:

$$E_{\text{ee}}(\text{C-C}) = \sum_{\mu \in \text{C}} \sum_{\sigma \in \text{C}} P_{\mu\nu} P_{\lambda\sigma} \langle \mu\nu | \lambda\sigma \rangle \quad (3)$$

$$E_{\text{ne}}(\text{C-C}) = \sum_{\mu \in \text{C}} P_{\mu\nu} \langle \mu | Z_{\text{C}} / R_{\text{IC}} | \nu \rangle \quad (4)$$

$$E_{\text{nn}}(\text{C-C}) = Z_{\text{C}} Z_{\text{C}} / R_{\text{C-C}} \quad (5)$$

$$E_{\text{exc}}(\text{C-C}) = \sum_{\mu, \nu \in \text{C}} \sum_{\sigma \in \text{C}} P_{\mu\nu} \langle \mu\nu | \mu\nu \rangle \quad (6)$$

where $P_{\mu\nu}$ and $P_{\lambda\sigma}$ are the density matrix elements and $\langle \mu\nu | \lambda\sigma \rangle$ are the electron repulsion integrals on the atomic basis; Z_{C} and Z_{C} are the nuclear (core) charges of atom carbon, respectively, and $R_{\text{C-C}}$ is the distance between them; $\langle \mu | Z_{\text{C}} / R_{\text{IC}} | \nu \rangle$ denote the nuclear-electron attraction integrals on the given atomic basis; $E_{\text{ee}}(\text{C-C})$, describes the electron repulsion driven processes in the molecule; $E_{\text{ne}}(\text{C-C})$, describes the nuclear-electron attraction driven processes in the molecule; $E_{\text{nn}}(\text{C-C})$, describes the nuclear repulsion driven processes in the molecule. These three factors may be related to the conformational (rotational, inversional) changes or atomic reactivity in the molecule; $E_{\text{exc}}(\text{C-C})$, reflects the change in the Fermi correlation energy between the two electrons localized on atom carbon, respectively. It can be of importance in determining the conformational changes of the molecule and its spin properties.

So, $E_{\text{tot}}(\text{C-C})$ is related to electron-electron, nuclear-electron, and nuclear-nuclear interaction in the molecule, and further related to the conformational (rotational, inversional) changes, atomic reactivity in the molecule, and molecular electrostatic field. The highest coefficient of pI and $E_{\text{tot}}(\text{C-C})$ suggest that conformation, atomic reactivity, and molecular electrostatic field should act an important role that influences the toxicity of PBDEs. The results of previous experimental and theoretical studies have also indicated that the interaction between the halogenated aromatic hydrocarbons (HAHs) and the AhR is a charge transfer type and that toxins appear to act as electron acceptors in the charge transfer complex (Poland et al., 1976; Miller et al., 1977; Cheney and Tolly, 1979; Bonati et al., 1994, 1995; Tuppurainen and Ruuskanen, 2000).

For 18 PBDE congeners, the best regression model can be described as follows:

$$\begin{aligned} pI = & -2.891E_{\text{R}}(\text{C-C}) + 3.072B + 0.00406\text{DIP} \\ & - 0.0334D + 50.051 \\ R^2 = & 0.903, R_{\text{cv}}^2 = 0.844, n = 18, \\ F = & 30.20, s^2 = 0.073 \end{aligned} \quad (7)$$

where R is the correlation coefficient, F is the value of the Fisher test, s is the standard deviation of the fit, R_{cv} is the cross-validated correlation coefficient, and n is the number of PBDE congeners; $E_{\text{R}}(\text{C-C})$ is max resonance energy for a C-C bond, which is highly correlated with $E_{\text{tot}}(\text{C-C})$ (correlation coefficient R is 0.911). They also represent the kinetic energy and electronuclear attraction energy associated with a charge distribution that lies between two atoms.

B is Balaban index (Balaban, 1982). Balaban index is a measure of molecular “centricity”, which describes the non-uniformity of mass distribution in a molecule. The value of the regression coefficient of Balaban index indicates the inferiority of cycle-symmetric structure to pI , and superiority of cycle-symmetric structure to activities of PBDE congeners. DIP is 1X BETA polarizability (DIP), and D is ZX shadow. ZX shadow (Rohrbaugh and Jurs, 1987), which codifies the size of the molecules, can be explained as the influence of steric factors on probability of forming a binding complex. The negative value of the respective correlation coefficient for ZX shadow indicates that the value pI declines as ZX shadow increases. So, an increase in this descriptor leads to an increase in the activities of PBDEs.

Using the best regression model, the Ah receptor relative binding affinities (RBA, pI) of the remaining 191 PBDE congeners are predicted and list in Table 1.

3.3. Results of PCA using molecular descriptors selected by regression models

PCA was used for further study the relationship between descriptors and pI based on 11 descriptors included in six regression models. The first three significant PCs

toxicology of PBDEs, especially congener-specific data. It is possible that QSAR models could be expanded to obtain predicted toxicity data and to explain toxicology behavior of PBDEs.

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