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Investigation on Aryl Hydrocarbon Receptor Binding Affinity QSAR Model of Polybrominated Diphenyl Ethers Based on Substituent Descriptors/Quantum Chemical Parameters

LONG JIANG, JINGYA WEN, YALING ZENG and YU LI*

Resources and Environmental Research Academy, North China Electric Power University, P.O. Box 58, Beijing 102206, P.R. China

*Corresponding author: Tel./Fax: + 86 10 61773886; E-mail: liyuxx8@hotmail.com

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In this paper, 21 quantum chemical parameters (charge parameters, energy parameters, polarization parameters) and 13 substituent descriptors (total number of substituents, substituents in different position, substituent positional relationship parameters, substituents difference between two rings) of 17 polybrominated diphenyl ethers were selected as the independent variables, the binding ability to aryl hydrocarbon receptor defined as dependent variable. Then, the QSAR model of polybrominated diphenyl ethers aryl hydrocarbon receptor binding affinities was established based on above-mentioned substituent descriptors/quantum chemical parameters to predict the binding affinities of unknown polybrominated diphenyl ethers, analyze the aryl hydrocarbon receptor binding mechanism from views of substituent pattern and quantum chemical parameters respectively, identify the aryl hydrocarbon receptor binding affinity level of each congener. The results showed that the aryl hydrocarbon receptor binding affinities of polybrominated diphenyl ethers were affected by Br substituent in each position significantly, not correlated with the total bromine and difference brominates type between two ring markedly. Among the quantum chemical parameters, qH^+, q^-, $\Delta\alpha$ and α_{xx} were the critical variables which effected the aryl hydrocarbon receptor binding affinity of polybrominated diphenyl ethers importantly, reflecting the binding affinity was main dominated by electrostatic force, polybrominated diphenyl ethers with symmetrical charge distribution, had small the molecular polarity and aryl hydrocarbon receptor binding affinity. The established QSAR model for polybrominated diphenyl ethers aryl hydrocarbon receptor binding affinity, with the simulation and prediction coefficients were 0.928 and 0.828, respectively, indicating good fitting and predicted ability, was to predict aryl hydrocarbon receptor binding affinities of other unknown polybrominated diphenyl ether congeners and identify binding level. The aryl hydrocarbon receptor binding affinities of polybrominated diphenyl ethers performed small relatively compared with dioxin, between them there were 13 congeners with medium aryl hydrocarbon receptor binding affinity, 188 congeners with low aryl hydrocarbon receptor binding affinity and only BDE-85 with high aryl hydrocarbon receptor binding affinity. This study may provide theoretical guidance to carry out more targeted control efforts for polybrominated diphenyl ethers' biological toxicity.

Keywords: Quantum chemical calculation, Substituent descriptors, Polybrominated diphenyl ethers, QSAR.

INTRODUCTION

Polybrominated diphenyl ethers (PBDEs) is an important class of flame retardant additives which have been widely synthesized and employed in household or industrial consumer products such as textiles, circuit board, plastics and electronic products[1-3]. There are 209 possible congeners depending on the number and substituent position of the Br atoms. Due to the non-covalently attachment to polymer, polybrominated diphenyl ethers could escape from the products easily into environment[4,5], meanwhile, the characteristics of persistence, bioaccumulation, long distance transportation *via* various approaches have make polybrominated diphenyl ethers are now ubiquitous in urban and rural environment, producing significant negative effect on environment and health of organisms. Currently, scientific studies have found that polybrominated diphenyl ethers are distributing in marine mammals, fish, birds, eggs and the different human organs such as breast, serum, adipose tissue and so on[6], even the remote arctic atmosphere has detected the emergence of polybrominated diphenyl ethers[7]. Recent toxicity data suggested that polybrominated diphenyl ethers might have endocrine disrupting effects similar to other halogenated organic compounds such as polychlorinated biphenyls (PCBs) and dioxins, which have gradually increased the concerns regarding health risks to man[8-10].

The existing researches showed that the biological toxicity of majority halogenated hydrocarbons (HAHs) are regulated by the aryl hydrocarbon receptor (AhR), a kind of inactive transcription factor belonging to the Basic Helix-Loop-Helix/Per Arnt-Sim protein, which usually combines with cytosolic chaperone[11,12]. Attacking to dioxins or other compounds, the aryl hydrocarbon receptor always could cause the dissociation

of molecular chaperones, where after the aryl hydrocarbon receptor transferred to the nucleus and changes the gene transcription, which would produce harm on organisms. The binding affinity of halogenated aromatic compounds to aryl hydrocarbon receptor (receptor binding affinities, RBA) had been widely characterized the degree of biological toxicity due to the positive correlation between them[13,14]. Compared to polychlorinated biphenyls and dioxins, the studies reported on RBA of polybrominated diphenyl ethers were relatively few and the binding mechanism was vague. The similar structure may imply the same aryl hydrocarbon receptor binding mechanism of polybrominated diphenyl ethers and polychlorinated biphenyls, such as the aryl hydrocarbon receptor signal transduction[15], but the RBA of PCBs were independent with molecular co-planarity[15,16], that was to say the known aryl hydrocarbon receptor binding affinity QSAR model of polychlorinated biphenyls could not be directly applied to polybrominated diphenyl ethers which molecular structure were non-planarity, so it was necessary to use the known aryl hydrocarbon receptor binding affinity values of polybrominated diphenyl ethers to explore the binding mechanism and establish the aryl hydrocarbon receptor binding affinity QSAR model to analysis the varying rules among 209 congeners comprehensively.

Generally, data on the aryl hydrocarbon receptor binding affinity of polybrominated diphenyl ethers were still limited, as well as the bioassay experiments were time-consuming and costly either *in vivo* or *in vitro*. The quantitative structure-activity relationships (QSAR) model and the quantum chemical calculation based on Gaussian software were two important ways to supplement the experimental missing values and explore the molecular interaction mechanism from molecular point of view. For the quantum chemical calculation, the density functional theory (DFT) was the most frequently used theoretical calculation method relied on Gaussian software which had been widely used in molecular structure optimization and spectra calculation, proving the strong feasibility in diphenyl ethers[17]. In addition, QSAR model could effectively reveal the relationship between the molecular activity with structure of persistent organic pollutants and predict the environmental effects of organic molecular which had not been detected. Some researches on aryl hydrocarbon receptor binding affinities of polybrominated diphenyl ethers have been carried out based on the same RBA data, various methods had been used to establish the aryl hydrocarbon receptor binding affinity QSAR model of polybrominated diphenyl ethers, such as the comparative molecular field method[18,19], support vector machines[20], multiple linear regression[21-25] and so on, but their emphasis was on the performance improving of model using different kinds of parameters and existed respective defects for their QSAR models: the selected topology parameter were too abstract to analysis binding mechanism inconveniently, the selected algorithm was opaque[18,19], not had validated the predictive performance[21, 23,24], no model scope characterization[22,25], lacked of mechanism analysis[20].

The purpose of this study was to research the aryl hydrocarbon receptor binding mechanism and RBA variation regulation of polybrominated diphenyl ethers based on QSAR model and quantum chemical calculation from views of substituent and quantization parameters, predict the other unknown aryl hydrocarbon receptor binding affinity values of polybrominated diphenyl ethers, seek the modified substituent type to increase/decrease aryl hydrocarbon receptor binding affinities of congeners and then grade the aryl hydrocarbon receptor binding affinity level of each congener. The research could provide the theoretical basis for the designation of new flame retardants and environmental behaviour regulation of polybrominated diphenyl ethers.

EXPERIMENTAL

Aryl hydrocarbon receptor binding affinity values of polybrominated diphenyl ethers: Experimental aryl hydrocarbon receptor binding affinity values of 18 polybrominated diphenyl ethers were referenced from the literature[16]. Chen *et al.*[16] had synthesized and tested the aryl hydrocarbon receptor binding affinities in rat hepatocytes of each congener. The binding affinities were calculated as the ratios of EC_{50} values for aryl hydrocarbon receptor binding of each congener to that of the reference compound namely TCDD in 1 nM. To facilitate the analysis, the ratios would be expressed as the negative of logarithm range, namely -logRBA, inversely proportional to aryl hydrocarbon receptor binding affinity, listed in Table-1.

Parameters for QSAR model establishing: Substituent descriptors for QSAR model were presented as follow: the total number of substituents (N_T), *ortho*-substituents number ($N_{2,6}$, N_2, N_6), *meta*-substituents numbers ($N_{3,5}$, N_3, N_5), *para*-substituents number (N_4), the pair number of *ortho*-substituents

TABLE-1
VIP VALUES AND CORRELATION ANALYSIS OF ALL PARAMETERS

Variables	VIP	Correlation	Variables	VIP	Correlation	Variables	VIP	Correlation
TE	0.72	-	Qyz	0.91	-	N_6	0.95	+
E_{LUMO}	0.81	-	α	0.10	+	$N_{3,5}$	0.71	-
E_{HOMO}	0.69	-	Δα	1.80	-	N_3	1.88	-
ΔE	0.92	-	α_{xx}	1.12	-	N_5	1.75	+
qH^+	1.29	-	α_{yy}	0.86	+	N_4	1.50	-
q^-	1.31	-	α_{zz}	0.98	+	N_o	0.81	+
μ	0.71	-	α_{xy}	0.95	-	N_m	0.95	+
Qxx	0.66	-	α_{yz}	0.90	+	N_p	1.64	+
Qyy	0.80	-	α_{xz}	0.85	-	N_D	0.77	-
Qzz	0.80	-	N_T	0.72	+	$N_{2,4,6}$	1.25	+
Qxy	0.53	+	$N_{2,6}$	1.38	+	-	-	-
Qxz	0.69	-	N_2	1.36	+	-	-	-

(N_o), the pair number of *meta*-substituents (N_m), the pair number of *para*-substituents (N_P), the difference value of substituents between two rings (N_D), the sum of *ortho*-substituents and *para*-substituents (N_2, 4, 6). The atom mark numbers of polybrominated diphenyl ethers were shown in Fig. 1.

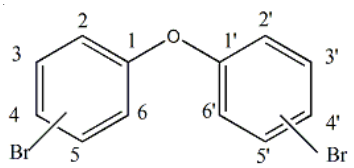

Fig. 1. Atom mark number and molecular geometry of polybrominated diphenyl ethers (PBDEs)

Quantum chemical parameters of polybrominated diphenyl ethers used to establish the QSAR model were obtained by the calculation of Gaussian 09 W package, usingwB3LYP method at the level of 6-31G(d) based on density functional theory (DFT), all the quantum chemical calculation tasks were set by Gauss view 5.0 software. The specific parameters including: the dipole moment (μ, Debye), Quadrupole moment (Q_{xx}, Q_{yy}, Q_{zz}, Q_{xy}, Q_{yz} and Q_{xz}), energy of the highest occupied molecular orbital (E_{HOMO}, eV), energy of the lowest unoccupied molecular orbital (E_{LUMO}, eV), E_{LUMO}-E_{HOMO} (ΔE, eV), Total energy (TE, eV), most negative atomic partial Mulliken charge in molecule (q^-, e), most positive partial Mulliken charge in molecule (q^+, e), the mean polarizability (α, 10^{-30esu}), the anisotropy polarisability (Δα, 10^{-30esu}) Approxpolarizability (α_{xx}, α_{yy}, α_{zz}, α_{xy}, α_{xz} and α_{yz}) which were six components reflecting perturbations of polarizability in different coordinates. Related to polarisability, the mean polarizability and the anisotropy polarisability were calculated derivatively as follows[26]:

$$\overline{\alpha} = (\alpha_{xx} + \alpha_{yy} + \alpha_{zz})/3,$$

$$\Delta\alpha = \sqrt{\frac{(\alpha_{xx} - \alpha_{yy})^2 + (\alpha_{xx} - \alpha_{zz})^2 + (\alpha_{yy} - \alpha_{zz})^2 + 6(\alpha_{xy} + \alpha_{yz} + \alpha_{xz})^2}{2}}$$

Establishing method of QSAR model: In this paper, the 21 quantum chemical parameters and 13 substituent descriptors of polybrominated diphenyl ethers were selected as the independent variables, the aryl hydrocarbon receptor binding ability defined as dependent variable. According to the sequence of aryl hydrocarbon receptor binding ability, the congeners were divided into model set and testing set by the fixed interval sampling method. Then the partial least square (PLS) was utilized to establish the aryl hydrocarbon receptor binding affinity QSAR model of polybrominated diphenyl ethers based on the above-mentioned substituents. In order to obtain the optimal model, the parameter of variable importance projection (VIP), measuring the ability of independent variables to explain the dependent variable, was used to eliminate the uncorrelated variable, when the VIP > 1, the relative independent variable could be identified as the decisive variable[27,28]. The all parameters QSAR model was established firstly to eliminate the parameter with the smaller VIP and then the rest parameters were used to form the QSAR model and so on until only two parameters were reserved. From the QSAR models established above, the optimal QSAR model was select give consideration to performance and parameters number included in the model.

Performance validation of QSAR model: Validity of QSAR model always needs to be evaluated from the views of fitness, robustness, predictability and application domain (AD)[29]. In this paper, the conventional square of correlation coefficient (R^2), the Fisher test value (F), the interpretation ability of model for original independent variables (R^2_x) and dependent variables (R^2_y) were used to test the fitness of the QSAR model; The robustness was evaluated during leave-one-out (LOO) cross validation[36], which finally gave the cross-validated correlation coefficient (q^2) and the prediction error sum of squares (PRESS); The correlation coefficient produced by testing set (R^2_{pre}) was used to test the predictability of model; For application domain, the ratio of congeners located in the effective domain based on Williams distribution map was employed to appraise[22].

RESULTS AND DISCUSSION

Variable importance projection (VIP) analysis for each parameter: In contrast with other polybrominated diphenyl ethers, BDE-85 had a difference aryl hydrocarbon receptor binding machanism which resulted in the great deviation between the predicted -logRBA obtained by QSAR model and the experimental -logRBA, twice larger than other congeners. In order to guarantee the accuracy of QSAR model, BDE-85 was eliminated during the following process[23,25]. Due to the limited experimental samples, all the 17 congeners were used to analysis the VIP of each parameter. The average VIP value of chemical quantum parameter (0.90) was smaller than substituent descriptors (1.21), indicating the substituent descriptors had regulated the binding ability to aryl hydrocarbon receptor of polybrominated diphenyl ethers stronger than chemical quantum parameters.

According the VIP value and correlative analysis symbol of each substituent descriptor, the -logRBA was positive correlative with $N_{2(6)}$, N_6, N_5, N_p, $N_{2,4,6}$ significantly, namely negative correlative with aryl hydrocarbon receptor binding affinity. The Br atoms located on *meta*-position (5,5') and *ortho*-position (6,6') would weaken the aryl hydrocarbon receptor binding affinity of polybrominated diphenyl ethers. With the matching, the effect of Br on *ortho*-position (2,2'), *meta*-position (3,3') and *para*-position (4,4') would play the contrary the function, that is strengthen the aryl hydrocarbon receptor binding affinity. The total substituent numbers and the difference value of substituent between two rings were both not related to aryl hydrocarbon receptor binding affinity, thus the molecular symmetry of polybrominated diphenyl ethers didn't regulate the binding affinity.

Only four quantum chemical parameters of qH^+, q^-, Δα, α_{xx} were correlated with -logRBA significantly, both with negative correlation. Among them, qH^+, q^- were both the extreme positive/negative charge of atom in the molecule. The O atom always carried the most negative charge in all of congeners, decreasing the charge on O would increase the value of q^- and the negative charge on C and Br atoms in the benzene. The greater values of qH^+, q^- indicated the greater difference of charge distribution on the benzene, greater polarity of the

molecular, more susceptible to external electric field and greater binding ability to aryl hydrocarbon receptor, verifying the decisive effect of electrostatic interaction on the binding to aryl hydrocarbon receptor of polybrominated diphenyl ethers[20,30]. $\Delta\alpha$, namely the anisotropy polarizability, described the molecular modification performance in the external electric field, correlating with the volume, form and the atoms distribution in molecular. Increasing the volume of substituent increased the value of $\Delta\alpha$ and binding ability to aryl hydrocarbon receptor. α_{xx} reflected the polarization and dispersion forces between molecules and related to the force orientation. Hirokawa and his colleagues had found that α_{xx} played an important role in the binding of dioxin to aryl hydrocarbon receptor[31,32], manifesting the similar binding mechanism. Different with dioxin that possessed the coplanar structure, polybrominated diphenyl ethers' non-coplanar structure determined the effect of α_{xx} on aryl hydrocarbon receptor binding ability of polybrominated diphenyl ethers was weaker than dioxin.

Establishment of aryl hydrocarbon receptor binding affinity QSAR model for polybrominated diphenyl ethers: Seventeen samples were randomly divided into model set (14 species) and testing set (3 species, marked on relative experimental value with an asterisk "*", listed in Table-2). Using the modeling approach introduced above, the independent variables were screened constantly by VIP of each variable to obtain the optimal aryl hydrocarbon receptor binding affinity QSAR model based on substituent descriptors/quantum chemical parameters, presented as follow:

$$-\log RBA = 17.102 - 83.491\ qH^{+} + 0.724\ N_2, \quad 6 + 0.508\ N_5 + 0.307\ N_P \qquad (1)$$

For the performance validation of the established model, $R^2_x = 0.901$, $R^2_Y = 0.944$, $R^2 = 0.928$, $q^2 = 0.783$, PRESS = 1.421, F = 42.87 (sig. = 0.000), $R^2_{pre} = 0.828$, AD = 96.6 %, the QSAR model has shown good fitness and predictability. Comparison between predicted values and experimental values of -logRBA for polybrominated diphenyl ethers was present on Fig. 2, the points tended to cluster along the 45° tangent line and the conventional square of correlation coefficient for modeling phase and validation phases were 0.93 and 0.83, respectively. All these results indicated that the established QSAR model could be used to predict the unknown RBA of polybrominated diphenyl ethers (Table-2) which was difficult to determine experimentally. The great gap between the experimental and calculated -logRBA of BDE-85 had reflected the particularity of BDE-15 which was identical to previous study[23,25].

TABLE-2
PREDICTED -logRBA AND BINDING AFFINITY LEVEL OF 209 PBDES

No.	Pred.	Exp.[a]	Grade	No.	Pred.	Exp.[a]	Grade	No.	Pred.	Exp.[a]	Grade
1	4.760	ND	L	71	3.895	3.867	L	141	4.981	ND	L
2	3.383	ND	L	72	4.250	ND	L	142	7.169	ND	L
3	3.853	3.886	L	73	4.577	ND	L	143	4.737	ND	L
4	5.368	ND	L	74	3.282	ND	L	144	4.586	ND	L
5	4.401	ND	L	75	3.184	3.398	L	145	4.788	ND	L
6	4.471	ND	L	76	4.241	ND	L	146	4.694	ND	L
7	3.098	ND	L	77	2.487	2.658	M	147	4.741	ND	L
8	4.475	ND	L	78	2.529	ND	M	148	4.594	ND	L
9	3.819	ND	L	79	2.909	ND	L	149	5.025	ND	L
10	4.930	ND	L	80	3.331	ND	L	150[#]	5.602	ND	L
11	3.143	ND	L	81	2.582	ND	M	151	5.548	ND	L
12	3.374	ND	L	82	4.486	ND	L	152	5.695	ND	L
13	3.193	ND	L	83	4.511	ND	L	153	4.381	4.602*	L
14	2.972	ND	L	84	5.130	ND	L	154	4.846	4.638	L
15	3.730	3.420*	L	85	3.271	1.721	H	155	4.754	ND	L
16	5.042	ND	L	86	4.098	ND	L	156	3.171	ND	M
17	3.867	3.638	L	87	4.424	ND	L	157	3.496	ND	M
18	4.739	ND	L	88	3.846	ND	L	158	3.002	ND	L
19	5.607	ND	L	89	5.132	ND	L	159	3.610	ND	L
20	3.632	ND	L	90	4.041	ND	L	160	5.405	ND	L
21	3.809	ND	L	91	4.742	ND	L	161	3.478	ND	L
22	4.309	ND	L	92	5.204	ND	L	162	3.525	ND	L
23	3.609	ND	L	93	4.812	ND	L	163	3.960	ND	L
24	4.632	ND	L	94	5.085	ND	L	164	4.368	ND	L
25	2.909	ND	L	95	5.733	ND	L	165	4.439	ND	L
26	3.782	ND	L	96	6.208	ND	L	166	6.184	ND	L
27	4.474	ND	L	97	4.083	ND	L	167	3.904	ND	L
28	2.892	2.921	M	98	3.857	ND	L	168	3.817	ND	L
29	3.338	ND	L	99	4.033	3.854	L	169	3.575	ND	L
30	3.333	ND	L	100	3.860	4.114	L	170	4.199	ND	L
31	3.831	ND	L	101	4.865	ND	L	171	3.709	ND	L
32	4.751	ND	L	102	4.734	ND	L	172	4.199	ND	L
33	3.433	ND	L	103	4.676	ND	L	173	6.960	ND	L
34	3.908	ND	L	104[#]	4.860	ND	L	174	4.982	ND	L
35	2.595	ND	L	105	3.021	ND	M	175	4.515	ND	L
36	2.928	ND	L	106	3.170	ND	L	176	5.008	ND	L

37	2.642	ND	M	107	3.789	ND	L	177	4.690	ND	L
38	2.551	ND	L	108	3.606	ND	L	178	5.427	ND	L
39	2.969	ND	L	109#	3.099	ND	L	179	5.927	ND	L
40	4.961	ND	L	110	4.128	ND	L	180	4.340	ND	L
41	4.614	ND	L	111	4.290	ND	L	181	5.411	ND	L
42	3.774	ND	L	112	4.051	ND	L	182	4.665	ND	L
43	4.524	ND	L	113	4.811	ND	L	183	4.508	4.602	L
44	4.470	ND	L	114	3.222	ND	L	184	4.673	ND	L
45	5.287	ND	L	115	3.088	ND	L	185	6.786	ND	L
46	5.706	ND	L	116#	7.259	ND	L	186	7.365	ND	L
47	3.511	3.252*	L	117	4.041	ND	L	187	5.420	ND	L
48	4.166	ND	L	118	3.187	ND	L	188	5.590	ND	L
49	4.118	4.174	L	119	3.097	2.959	M	189	3.633	ND	L
50	3.946	ND	L	120	3.115	ND	L	190	4.847	ND	L
51	4.424	ND	L	121	3.566	ND	L	191	3.423	ND	L
52	5.268	ND	L	122	3.539	ND	L	192	5.025	ND	L
53	5.421	ND	L	123	3.010	ND	M	193	4.385	ND	L
54#	6.372	ND	L	124	4.034	ND	L	194	4.602	ND	L
55	3.518	ND	L	125	4.130	ND	L	195	6.078	ND	L
56	3.345	ND	M	126	2.545	2.569	M	196	4.689	ND	L
57	3.564	ND	L	127	2.981	ND	L	197	4.931	ND	L
58#	4.593	ND	L	128	4.143	ND	M	198	6.212	ND	L
59	4.478	ND	L	129	4.158	ND	L	199#	5.105	ND	L
60	3.647	ND	M	130	4.435	ND	L	200	7.097	ND	L
61	3.196	ND	L	131	3.799	ND	L	201	6.256	ND	L
62	3.225	ND	L	132	5.069	ND	L	202	6.675	ND	L
63	3.620	ND	L	133	4.965	ND	L	203	5.742	ND	L
64	4.471	ND	L	134	4.727	ND	L	204	5.804	ND	L
65	4.178	ND	L	135	5.313	ND	L	205	5.817	ND	L
66	2.719	2.699	M	136	6.384	ND	L	206	5.997	ND	L
67	3.242	ND	L	137	3.987	ND	L	207	5.713	ND	L
68	3.070	ND	L	138	4.014	ND	L	208	6.646	ND	L
69	4.171	ND	L	139	3.763	ND	L	209	7.112	ND	L
70	3.472	ND	L	140	4.057	ND	M	-	-	-	-

[a]Experimental-logRBA were cited from literature 16, [#]Predicted-logRBA of relative PBDE congener was outlines

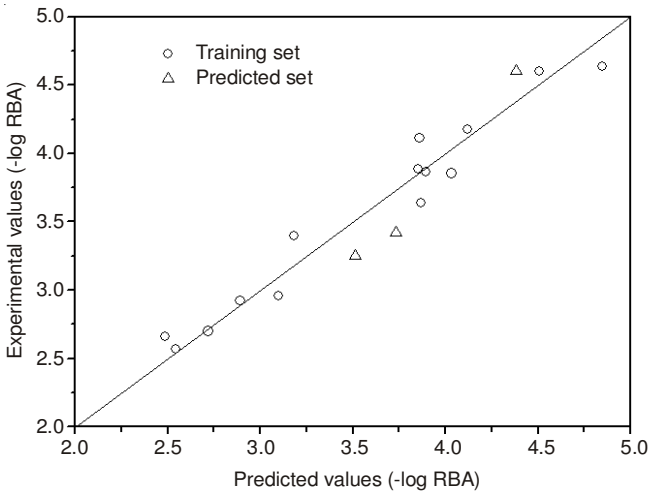

Fig. 2. Comparison between predicted -logRBA and experimental -logRBA of polybrominated diphenyl ethers (PBDEs)

From the eqn. 1, the standard regression coefficients of four detective parameters were 0.885, 1.103, 0.356 and 0.280, respectively, with the same magnitude showing the small difference in effecting the affinity of polybrominated diphenyl ethers binding to aryl hydrocarbon receptor. Not only the selected parameters number ratio for substituent descriptors/quantum chemical parameters in QSAR model (3:1), but also the standardized regression coefficients weight ratio (1.739:0.885), the substituent descriptors both played a more important role in binding affinity of polybrominated diphenyl ethers to aryl hydrocarbon receptor.

Comparison with existing QSAR models: Table-3 had listed a variety of evaluation indicators of the previous aryl hydrocarbon receptor binding affinity QSAR model of polybrominated diphenyl ethers based on the same RBA data source. The comparison shown that the established 3D-QSAR model of Wang *et al.*[18] and Gu *et al.*[19] could provide a more perfect exposition for binding mechanism, but could not guarantee the predictive performance because of lacking testing set; Zheng *et al.*[20] had established the QSAR model by support vector machine (SVM) which could not format the specific regression model, not conducive to analysis the binding mechanism; three QSAR models cited from literatures 21, 23 and 24 were both established base on multiple linear regression model (MLR) to analysis binding mechanism from different kinds of parameters, but all not had set the testing set to validate the predictive performance of QSAR model. Among them, only Papa *et al.*[22] had taken the AD of model into account, the predictive -logRBA of 40 PBDE congeners were identified as outlines with great deviation, much higher than our study (7 outlines marked out with "#" in Table-3), meaning not well applicability in PBDE homologues. Compared with previous QSAR models, the model in this paper was mainly established by substituent descriptors which were conducive to regulate

TABLE-3
COMPARISON WITH EXISTING QSAR MODELS

Equations	Train/Test	R^2	q^2	R^2_{pre}	F	AD	Method	Ref.
NE	18/0	0.995	0.580	-	376.27	-	CoMFA	18
NE	18/0	0.987	0.870	-	134.21	-	CoMFA	19
NE	15/3	0.892	0.896	0.985	-	-	SVM (3-fold)	20
$-\log RBA = -0.049-19.374\sigma^2_{tot} + 0.107\ N_v + 9.443\ \overline{V}_s^- - 2.214V_{s,min}$	18/0	0.641	-	-	5.97	-	MLR	21
-logRBA = -11.33 + 0.92L1v-11.56 Mor22u	10/8	0.900	0.790	0.730	-	79.1 %	MLR	22
$-\log RBA = 8.541-0.02\Delta\alpha-3.544SIC + 0.014\alpha_{xy}$	17/0	0.864	0.774	-	28.60	-	MLR	23
$-\log RBA = 50.05-2.89E_R(C\text{-}C) + 3.072B + 0.00406DIP-0.0334D$	18/0	0.903	0.844	-	30.20	-	CODESSA	24
$-\log RBA = 17.102-83.491qH^+ + 0.724N_{2,6} + 0.508N_5 + 0.307N_P$	14/3	0.928	0.783	0.828	42.87	96.3 %	PLS	This paper

NE: No equation established

the binding ability to aryl hydrocarbon receptor of polybrominated diphenyl ethers and had comprehensively considered the transparency of the algorithm, fitness, predictive performance, AD of the model would more suitable for research on polybrominated diphenyl ethers.

Fig. 3 had shown the comparison between the predicted -log RBA obtained by previous QSAR models in literatures with the model in this paper, the points located on both sides of the slope of diagonal line for literature 18 (Fig. 3a) and 22 (Fig. 3b), with the standard deviation (SD) in the range of 0.01-0.49, 0-0.61, respectively, manifesting the well consistent. For literature 23 (Fig. 3c), there were some outliers: BDE-142, BDE-150, BDE-166, BDE-198, the respective predicted -logRBA were slightly lower than our paper, with the SD interval of 0.02-1.22.

Aryl hydrocarbon receptor binding affinity level identifying of polybrominated diphenyl ethers: Papa *et al.*[22] had divided the aryl hydrocarbon receptor binding ability of organic compounds into three levels: RBA > 0.01, the high binding affinity (H); 0.01 > RBA > 0.001, the medium binding affinity (M), RBA < 0.001, the low binding affinity (L). When converted into -logRBA, the relative level standards were as follow: -logRBA < 2, high binding affinity; 2 < -logRBA < 3, medium binding affinity, 3 < -logRBA, low binding affinity. The predicted -logRBA of polybrominated diphenyl ethers were all graded by using the above standards (Table-2). Among them, only BDE-85 had the high aryl hydrocarbon receptor binding affinity, 13 homologues had medium level and the rest 195 homologues with low biological toxicity, 50-100 times smaller than dioxins generally[16].

Table-4 listed the substituent position and type of 13 homologues with medium aryl hydrocarbon receptor binding affinity and the specific atom mark number were shown in Fig. 1. From Table-4 we could see, substituent mainly distributed on the *meta*-position (3,3') and *para*-position (4,4') can strengthen the aryl hydrocarbon receptor binding ability of

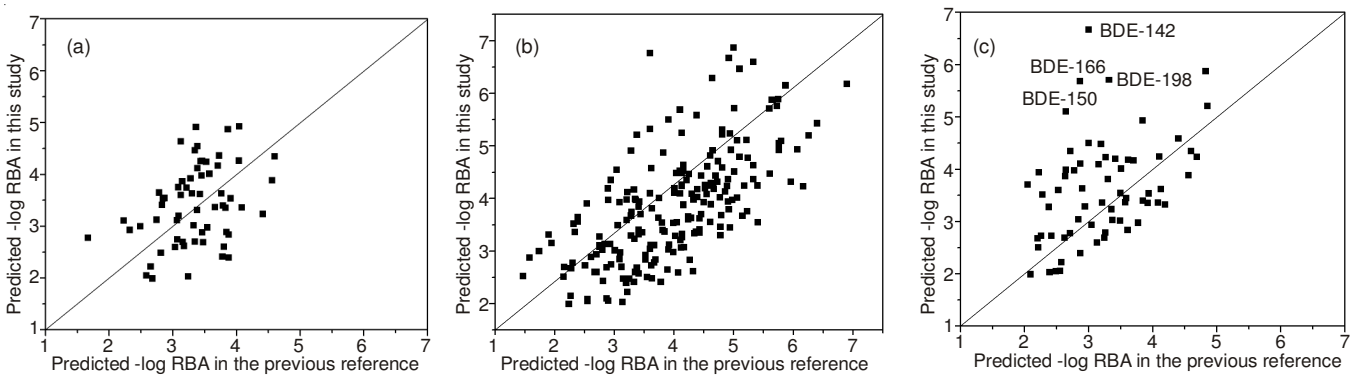

Fig. 3. Comparison of -logRBA prediction of PBDEs between the QSAR of this study and the previous models: (a) cited from Ref. 18, (b) cited from Ref. 22, and (c) cited from Ref. 23

TABLE-4
SUBSTITUENT PATTERN OF 13 PBDES WITH MEDIUM AHR BINDING AFFINITY

No.	-logRBA	Substituent pattern	No.	-logRBA	Substituent pattern
14	2.972	3, 5	39	2.969	3, 4′, 5
25	2.909	2, 3′, 4	66	2.719	2, 3′, 4, 4′
28	2.892	2, 4, 4′	77	2.487	3, 3′, 4, 4′
35	2.595	3, 3′, 4	81	2.582	3, 4, 4′, 5
36	2.928	3, 3′, 5	119	2.959	2, 3′, 4, 4′, 6
37	2.642	3, 4, 4′	126	2.545	3, 3′, 4, 4′, 5
38	2.551	3, 4, 5	-	-	-

polybrominated diphenyl ethers, consistent with the conclusion obtained above and validating the greater effect and stronger regulation for substituent descriptors than quantum chemical parameters. Among 13 congeners, BDE-77 and BDE-126 had the strongest binding ability to aryl hydrocarbon receptor, at the same time, *meta*-position (3,3') and *para*-position (4,4') of them both had been substituted by Br atoms. With a more substituent of BDE-126 in *meta*-position (5) caused the slightly lower binding ability than BDE-77, the same conclusion also had been obtained by previous research: PCB-66 and PCB-126 possessed the great binding ability between PCBs[22].

Conclusion

Seventeen polybrominated diphenyl ethers with known experimental aryl hydrocarbon receptor binding affinity were used to established the aryl hydrocarbon receptor binding affinity QSAR model of polybrominated diphenyl ethers based on substituent descriptors/quantum chemical parameters, predicted the other unknown aryl hydrocarbon receptor binding affinity values of polybrominated diphenyl ethers and graded the binding affinity of each congener. For the substituent descriptors, the aryl hydrocarbon receptor binding affinity of polybrominated diphenyl ethers was mainly regulated by the substitutional position and type in respective benzene, positive correlated with *ortho*-position (2,2'), *meta*-position (3,3'), *para*-position (4,4'), negative with *meta*-position (5,5'), *ortho*-position (6,6') and uncorrelated with total Br numbers and difference brominated type between two ring. For the quantum chemical parameters, qH^+, q^-, $\Delta\alpha$ and α_{xx} were the critical variables which effected the aryl hydrocarbon receptor binding ability of polybrominated diphenyl ethers importantly, reflecting the binding ability was main dominated by electrostatic force, meanwhile, the increasing the symmetrical of charge distribution would decrease the molecular polarity and aryl hydrocarbon receptor binding affinity of polybrominated diphenyl ethers. The established aryl hydrocarbon receptor binding affinity QSAR model of polybrominated diphenyl ethers had well fitting and predicted ability, with the simulation and prediction coefficients of were 0.928 and 0.828, respectively. Not only the selected parameters number ratio for substituent descriptors/quantum chemical parameters in QSAR model (3:1), but also the standardized regression coefficients weight ratio (1.739:0.885), both manifested the substituent descriptors had played a more important role in binding affinity of polybrominated diphenyl ethers to aryl hydrocarbon receptor. The aryl hydrocarbon receptor binding affinities of polybrominated diphenyl ethers performed small relatively compared with dioxins, between them there were 13 congeners with moderate aryl hydrocarbon receptor binding affinity, 188 congeners with low aryl hydrocarbon receptor binding affinity and only BDE-85 with high aryl hydrocarbon receptor binding affinity.

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