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Predicting the Relative Retention Time (RRT) of Polybrominated Diphenyl Ethers (PBDEs)

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Abstract: Using the molecular electronegativity distance vector descriptors derived directly from the molecular topological structures, the relative retention time (RRT) of polybrominated diphenyl ethers (PBDEs) were predicted. A four-variable regression model (M_{30}) with the correlation coefficient of 0.9816 and the root mean square errors of 0.061 was developed using a training set including 30 PBDEs. The correlation coefficient of 0.9841 and the root mean square errors of 0.054 between the values of *RRT* predicted by M_{30} and the RRT observed for 16 external PBDEs show a good predictive potential of M_{30}. The descriptors included in the M_{30} represent four interactions between four pairs of atom types, *i.e.*, atom –C= and –C=, –C= and >C=, >C= and >C=, –C= and –Br.

Keywords: Polybrominated diphenyl ethers (PBDEs), relative retention time (RRT), molecular electronegativity distance vector (MEDV).

Polybrominated diphenyl ethers (PBDEs) are used as flame retardants in many types of consumer products. Perhaps as a result of their widespread use and their lipophilicity, these compounds have become ubiquitous in the environment and in people[1]. Although other halogenated diaryl compounds have been observed in the environment over the last half-century (*e.g.* polychlorinated diphenyl ethers (PCDEs), polybrominated biphenyls (PBBs), polychlorinated naphthalenes (PCNs), polybrominated dibenzo-*p*-dioxins and dibenzofurans (PBDD/Fs)), the concentrations and/or toxicological importance of PBDEs are generally much less than PCBs and PCDD/Fs. Only PBDEs have recently been found at high concentrations (up to the mg/kg level in sediments and higher trophic level organisms such as marine mammals) that in some cases approach or even exceed that of PCBs and DDT[2]. Although the acute toxicity of PBDEs is thought to be low relative to PCDD/Fs and non-*ortho*-substituted PCBs, the chronic effects may result in endocrine disruption and immunosuppression. However, there is limited toxicological data for only the most prevalent individual PBDE congeners in environmental samples (*e.g.* 2,2′,4,4′-PBDE47; 2,2′,4,4′,5-PBDE99; and 2,2′,4,4′,6- PBDE100)[3]. Rayne *et al.*[2]

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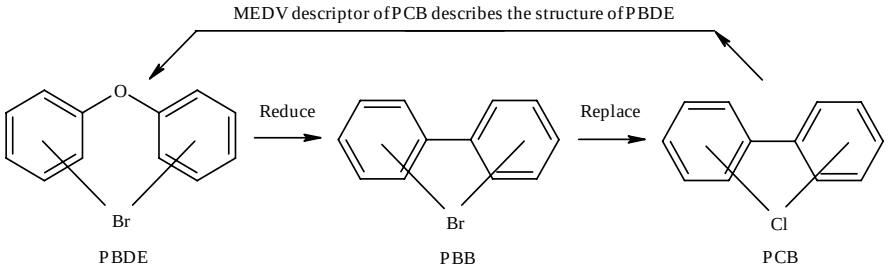
has demonstrated the necessity of identifying and monitoring concentrations of all PBDE congeners in environmental matrices.

In the present study, we investigated the possibility of predicting the gas chromatographic relative retention time (RRT) of PBDEs by using the molecular electronegativity distance vector[4-5] (MEDV) derived directly from their two-dimensional topological molecular structures and modified electrotopological state index. With the help of our program VSMP (variable selection and modeling based on the prediction)[6], a four-variable QSAR equation with high predictive power has been developed.

46 PBDEs (skeleton structure shown in **Figure 1**) and their RRT values observed are directly taken from the literature[2] (see supporting materials). From **Figure 1**, the unique structure difference between PBDE and PBB congener is that the former has an additional group (–O–). Replacing the Br atom in PBB with Cl, it converts to PCB. Furthermore, the structure of all PBDE, PBB, and PCB congeners changes with the number and location of halogen atoms. So, the changes in structure for PBDEs can be approximately described by the structural descriptors of PCBs. The original MEDV descriptors of PCBs are calculated according to the literature[6,7] and then used to characterize the structures of PBDEs. The results show that there are only 6 nonzero MEDV descriptors for all PBDEs under the study, because only exist three atomic types of nos. 2 (=C–), 3 (>C=), and 13 (–Cl) (see **Figure 1**) and so only 6 interactions between them (no considering the type –O–). The nonzero descriptors are $\boldsymbol{x}_{14}$ (interaction between atomic types of nos. 2 and 2), $\boldsymbol{x}_{15}$ (nos. 2 and 3), $\boldsymbol{x}_{25}$ (nos. 2 and 13), $\boldsymbol{x}_{26}$ (nos. 3 and 3), $\boldsymbol{x}_{36}$ (nos. 3 and 13), and $\boldsymbol{x}_{91}$ (nos. 13 and 13), respectively. The six descriptors can completely characterize the molecular structures of PBDEs.

Figure 1 PBDE reduced to PBB and replaced to PCB.



To develop a stable and predicable quantitative structure-RRT relationship (QSRR) between the MEDV descriptors and RRTs of 46 PBDE congeners, 30 PBDEs is extracted from a pool of 46 PBDEs to construct a training set and the remaining 16 PBDEs form a testing set. The training set is used to develop a QSRR model (M_{30}) using the VSMP program developed in house and the M_{30} is then employed to predict the RRTs of PBDEs in the testing set. The VSMP results show that the best QSRR model including four MEDV descriptors, $\boldsymbol{x}_{14}$, $\boldsymbol{x}_{15}$, $\boldsymbol{x}_{25}$, and $\boldsymbol{x}_{26}$, has a good calibration statistics of r=0.9816 and *RMSE*= 0.061 and a model stability of q= 0.9729 and RMSV= 0.074. The best model is as follows.

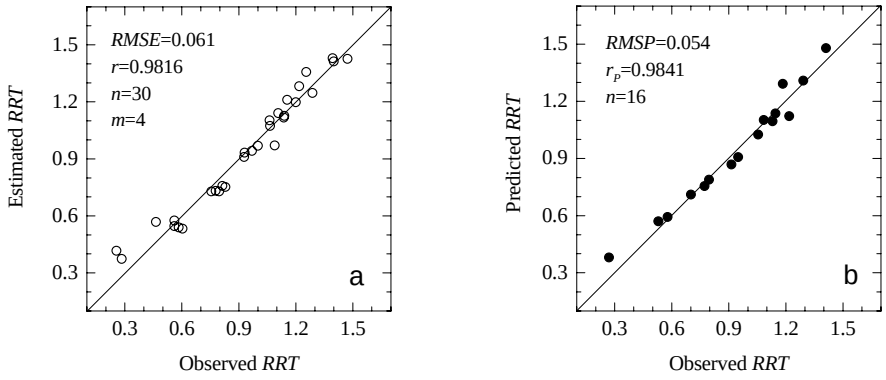
$$RRT = -(2.75615 \pm 0.81185) + (0.02837 \pm 0.00964)\cdot \boldsymbol{x}_{14} + (0.06983 \pm 0.01453)\cdot \boldsymbol{x}_{15} + (0.02207 \pm 0.00742)\cdot \boldsymbol{x}_{25} + (0.11334 \pm 0.02191)\cdot \boldsymbol{x}_{26} \quad (1)$$

n = 30, m = 4, r=0.9816, *RMSE*= 0.061, F= 165.12 (Estimation)

n = 30, m = 4, q= 0.9729, *RMSV*= 0.074 (LOO validation)

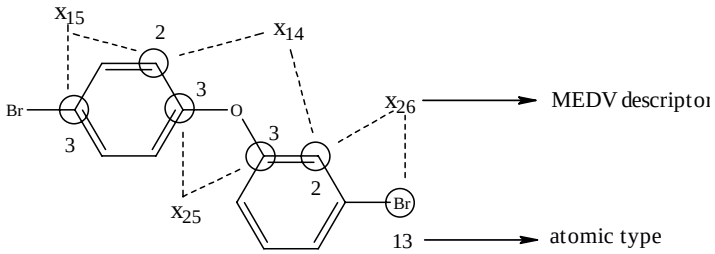
where n and m are the number of samples and the optimal MEDV descriptors, respectively. The r, *RMSE* and F are the correlation coefficient, the root mean square error, and Fisher's statistic in modeling, respectively. The value after the symbol "±" in eq. 1 is the standard derivation related to the regression coefficient. To test the stability of M_{30}, a leave–one–out (LOO) cross validation procedure is performed. The q and *RMSV* refer to the correlation coefficient and the root mean square error in the LOO validation procedure. A good QSRR model should have not only an excellent estimation ability for the internal example but also a good predictive power for the external example. The results of predicting the RRTs of 16 PBDEs in testing set by model M_{30} show a high predictive power for the external congeners. The correlation coefficient and the root mean square error between RRTs predicted by M_{30} and ones observed are 0.9841 and 0.054, respectively. The values of RRTs estimated and predicted (with symbol "*") by eq. 1 and observed experimentally are all listed in **Table 1** of supporting material together with the values of four optimal MEDV descriptors. The relationship graph between RRT estimated (a) and predicted (b) versus observed is shown in **Figure 2**.

Figure 2 Plot of *RRT* values calculated by model M_{30} *vs* observed.



Obviously, the gas chromatographic relative retention time (*RRT*) of PBDE is closely related to the molecular structure. To explain the effect of each atomic type on the *RRT* of PBDE, the standard regression coefficients (b_0) of four MEDV descriptors are also calculated by our VSMP program and the b_0 values of four descriptors, $\boldsymbol{x}_{14}$, $\boldsymbol{x}_{15}$, $\boldsymbol{x}_{25}$, and $\boldsymbol{x}_{26}$, are 1.382, 1.617, 0.380, and 3.149, respectively. So, the most important descriptor affecting the *RRT* is the 26th MEDV descriptor ($\boldsymbol{x}_{26}$) implying an interaction between the atomic type 2 (–C=) and 13 (–Br). That is, the number and location of bromine atoms in PBDE molecule dominate the partition process of PBDE in the mobile and stationary phase. The second important descriptors are $\boldsymbol{x}_{15}$ and $\boldsymbol{x}_{14}$, which reflects

Figure 3 The atomic types and MEDV descriptors for 3,4′-PBDE13 compound.



the necessity of the interactions between atom segment –C= and >C= ($\boldsymbol{x}_{15}$) and –C= and –C= ($\boldsymbol{x}_{14}$) (see **Figure 3** in detail).

The results in **Figure 2** show that the model M_{30} from 30 compounds in the training set has not only a good estimation ability but also a good predictive potential. To realize the prediction of the gas chromatographic RRTs for all 209 PBDEs, it is essential to model the whole set including 46 PBDE congeners. Using the optimal four MEDV descriptors by VSMP program, a novel QSRR model between the MEDV descriptors and RRTs values of 46 PBDEs has been developed by multiple linear regression. The model and its some statistics are as follow.

$$\begin{aligned} RRT = &-(3.01842 \pm 0.59814) + (0.03213 \pm 0.00727)\cdot\boldsymbol{x}_{14} + (0.07156 \pm 0.01031)\cdot\boldsymbol{x}_{15} \\ &+ (0.02880 \pm 0.00626)\cdot\boldsymbol{x}_{25} + (0.12016 \pm 0.01602)\cdot\boldsymbol{x}_{26} \end{aligned} \quad (2)$$

$n = 46$, $m = 4$, r=0.9829, $RMSE$= 0.058, F= 291.33 (Estimation)

$n = 46$, $m = 4$, q= 0.9786, $RMSV$= 0.064 (LOO validation)

Comparing the regression coefficients and relative statistics such as r, $RMSE$, q, and $RMSV$ in eq. 1 with ones in eq. 2, there is no significant difference between two equations.

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References

1. R. A. Hites, *Environ. Sci. Technol.*, **2004**, *38*, 945.
2. S. Rayne, M. G. Ikonomou, *J. Chromatogr. A*, **200**3, *1016*, 235.
3. F. Rahman, K. H. Langford, M. D. Scrimshaw, J. N. Lester, *Sci. Total. Environ.*, **2001**, *275*, 1.
4. S. S. Liu, C. Z. Cao, Z. L. Li, *J. Chem. Inf. Comput. Sci.*, **1998**, *38*, 387.
5. S. S. Liu, C. S. Yin, S. X. Cai, Z. L. Li, *J. Chem. Inf. Comput. Sci.*, **2001**, *41*, 321.
6. S. S. Liu, H. L. Liu, C. S. Yin, L. S. Wang, *J. Chem. Inf. Comput. Sci.*, **2003**, *43*, 964.
7. S. S. Liu, S. H. Cui, L. S. Wang, *Chin. Chem. Lett.*, **2004**, *15*, 467.

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