HEURISTIC METHOD FOR PREDICTING THE TOXICITY OF POLYBROMINATED DIPHENYL ETHER (PBDE) CONGENERS BASED ON MOLECULAR DESCRIPTORS

Yawei Wang[1], An Li[2], Chunyan Zhao[3], Weiping Ma[3], Hanxia Liu[1], Guibin Jiang[1]

[1]Research Center For Eco-environmental Sciences, The Chinese Academy Of Sciences
[2]School of Public Health, University of Illinois at Chicago
[3]Department of Chemistry, Lanzhou University

Introduction

Polybrominateddiphenyl ethers have been extensively distributed as environmental contaminants due to their use as flame-retardants for various polymers (1). The levels of PBDEs in biota have shown a steady increase that parallels their historic rate of production. The weak to moderate binding affinity of PBDE congeners to the Ah receptor (AhR) and the weak induction of EROD (ethoxyresorufin-O-deethylase) activity suggest the possibility of dioxin-like behavior. It has been shown that PBDEs impact the same body systems as polychlorinated biphenyls (PCBs)[2,3] though they are thought to be less potent toxicants. But little is known about the toxicology of PBDEs, especially on a congener-specific basis. The structural similarities between PBDEs and PCBs suggest that PBDEs might activate the AhR signal transudation pathway. Relationships between descriptors of chemical substances and their activities/toxicity allure many workers to obtain reliable modes (quantitative structure activity relationships, QSAR) helpful to understand toxicological activities and to predict the toxicity of many new substances. In the QSAR studies, multiple linear regression (MLR) was used to investigate the effect of experimental physicochemical parameters of substituents in PCBs on the activities[4]. Here we report a QSAR model for all 209 PBDE congeners based on the toxicology index (AhR, p*I*) of 18 PBDEs using the heuristic method of CODESSA (Comprehensive Descriptors for Structural and Statistical Analysis) technique. The model was further used to investigate the relationships between the quantitative structure indices and toxicology index of PBDEs.

Materials and Methods

All 209 PBDE congeners along with biphenyl were included in the study. A toxicity data set of 18 PBDEs congeners was taken from the previous work by Chen et al[5]. The relative binding affinities (RBA) values (*I*), which were expressed as p*I* (-log*I*) for Ah receptor binding of individual PBDEs congeners, were in the μM range, indicating weaker affinity than the reference toxicant TCDD. Values of p*I* for these 18 PBDEs were binding affinities relative to TCDD; concentration of [^{3}H]-TCDD was 1.0 nM.

The structures of the compounds were drawn with the HyperChem Release 7.0 software and saved as the hin files for MOPAC[6], and then the hin files were transferred into software CODESSA[7] to calculate following descriptors: constitutional descriptors, topological descriptors, geometrical descriptors, electrostatic descriptors, and semi-empirical quantum chemical descriptors. Then we used heuristic method to build the regression equation. The obtained regression equation was used predict the p*I* values for the remaining 191 PBDEs, for which toxic indices are unavailable now.

Result and Discussion

By using the heuristic method, regression models were developed for 18 PBDEs. The heuristic correlations performed for the whole set provide the optimal equations for different numbers of descriptors in the range of 1-6. The result showed that the best model in all regression contains four parameters:

$$pI = -2.891E_R(C\text{-}C) + 3.072B + 0.00406DIP - 0.0334D + 50.051$$

$$R^2=0.903,\ R^2_{cv}=0.844,\ n=18,\ F=30.20,\ s^2=0.073$$

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; $E_R(C\text{-}C)$ is max resonance energy for a C-C bond,which is highly correlated with Max total interaction for a C-C bond ($E_{tot}(C\text{-}C)$) (correlation coefficient R is 0.911). B is Balaban index[8], DIP is 1X BETA polarizability (DIP), and D is ZX shadow. Positive values of the regression coefficients indicate that these descriptors account positively for the values of pI of PBDE congeners, whereas negative values indicate that these descriptors contribute negatively to values of pI of PBDE congeners. The experimental versus predicted pI values of PBDEs and the residuals of the best regression model are shown in Figure 1.

From the model, we found $E_{tot}(C\text{-}C)$ is most important to the activity pI (the estimated goodness of fit ratio, R^2, was 0.648; that is to say, 64.8% of the variance observed in the pI was explained by the E_{tot}(C-C)) (Figure 2). $E_{tot}(C\text{-}C)$ is related with electron-electron, nuclear-electron, and nuclear-nuclear interaction in the molecule, and further related with the conformational (rotational, inversional) changes, atomic reactivity in the molecule, and molecular electrostatic field. Therefore, these factors should be related to the toxicity of PBDEs. The results of previous experimental and theoretical studies have also indicated that the interaction between the halogenated aromatic compounds (HACs) and the AhRs is a charge transfer process and that toxins appear to act as electron acceptors in the charge transfer complex[9, 10]. Our work can also help to understand the HACs-AhR interaction[11,12].

Balaban index is a measure of molecular “centricity”, which describes the nonuniformity of mass distribution in a molecule. Value of the regression coefficient of Balaban index indicates the inferiority of cycle-symmetric structure to pI, and so superiority of cycle-symmetric to activities of PBDE congeners. ZX shadow, which codifies for the size of the molecules, could 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 pIdeclines as ZX shadow increases, therefore, an increase in ZX shadow leads to an increase in the activities of PBDEs.

Using the optimized four-descriptor model, the Ah receptor relative binding affinities (pI) of the remaining 191 PBDE congeners was predicted.

Conclusions

PBDEs contribute to the total “dioxin-like” activity of environmental samples, although their activity is much less than that of potent HACs such as PCDDs, PCDFs, and coplanar PCBs. In contrast to PCBs, AhR binding affinities of PBDEs could not be critically related to the planarity of the molecule, but the conformational (rotational, inversional) changes, atomic reactivity in the molecule, and molecular electrostatic field are important factors that influence the toxicity of PBDEs, possibly because the large size of the bromine atoms expands the Ah receptor's binding site.

Acknowledgements

This work was jointly supported by the National Basic Research Program of China (2003CB415001) and the National Natural Science Foundation of China (20329701). The authors would like to thank Prof. Man-cang Liu and his group (Department of Chemistry, Lanzhou University, China) for helpful discussions.

Reference

1. WHO (**1994**), Environmental health criteria 162: Brominateddiphenyl ethers. World Health Organisation, Geneva, 31-34.

2. Eriksson, P.; Viberg, H.; Jakobsson, E.; Orn, U.; Fredriksson, A. (**2002**) A brominated flame retardant, 2, 2', 4, 4', 5-pentabromodiphenyl ether: uptake,retention, and induction of neurobehavioral alterations in mice during a critical phase of neonatal brain development. *Toxicol. Sci.* 67, 98-103.

3. Hallgren, S.; Darnerud, P.O. (**2002**) Polybrominateddiphenyl ethers (PBDEs), polychlorinated biphenyls (PCBs) and chlorinated paraffins (CPs) in rats-testing interactions and mechanisms for thyroid hormone effects. *Toxicology.* 177, 227-243.

4. Arulmozhiraja, S.; Morita, M. (**2004)** Structure-Activity Relationships for the Toxicity of Polychlorinated dibenzofurans: approach through density functional theory-based descriptors. *Chem. Res. Toxicol.* 17, 348-356.

5. Chen, G.S.; Konstantinov, A.D.; Chittim, B.G.; Joyce, E.M.; Bols, N.C.; Bunce, N.J. (**2001**) Synthesis of polybrominateddiphenyl ethers and their capacity to induce CYP1A by the Ah receptor mediated pathway. *Environ. Sci. Technol.* 35, 3749-3756.

6. Stewart, J.P.P. MOPAC, v.6.0. (1989) Quantum Chemistry Program Exchange, QCPE, No. 455; Indiana University: Bloomington, IN.

7. Katritzky, A.R.; Lobanov, V.S.; Karelson, M. (1995-1997) Comprehensive descriptors for structural and statistical analysis, Reference Manual, Version 2.13.

8. Balaban, A.T. (1982) Highly discriminating distance-based topological index. *Chem. Phys. Lett.* 89, 399-404.

9. Cheney, B.V., Tolly, T. (1979) Electronic factors affecting receptor binding of dibenzo-p-dioxins and dibenzofurans. *Int. J. Quantum Chem.* 16, 87-110.

10. Miller, G., Sontum, S., Crosby, D.G. (1977) Electron-acceptor properties of chlorinated dibenzo-p-dioxins. *Bull. Environ. Contam. Toxicol.* 18, 611-616.

11. Bonati, L.; Fraschini, E.; Lasagni, M.; Pitea, D. (1994) Toward a mechanistic understanding of PCDD biological activity based on molecular electrostatic potential modeling.*J. Mol. Struct. (THEOCHEM)* 303, 43-54.

12. Tuppurainen, K., Ruuskanen, J. (2000) Electronic eigenvalue (EEVA): a new QSAR/QSPR descriptor for electronic substituent effects based on molecular orbital energies. A QSAR approach to the Ah receptor binding affinity of polychlorinated biphenyls (PCBs), dibenzo-p-dioxins (PCDDs) and dibenzofurans (PCDFs). *Chemosphere* 41, 843-848.

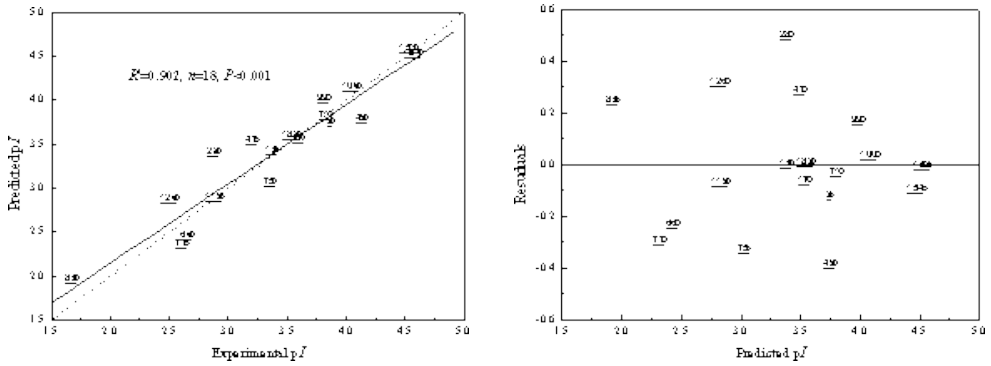

Figure 1. Predicted vs. actual Ah Receptor Relative Binding Affinities (RBA, pI) of PBDEs congeners and distribution of residuals over the range of predicted p*I* by the best regression model, which includes four descriptors.

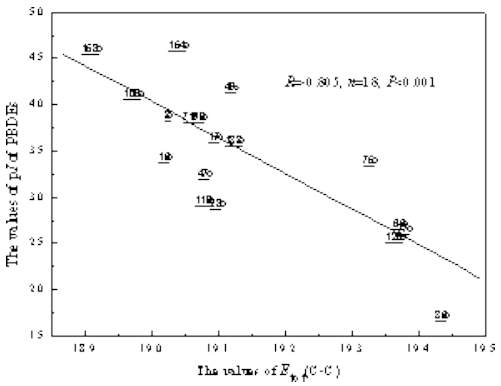

Figure 2. Relationship between E_{tot}(C-C) and the values of p*l* of 18 PBDEs.