Rotational Barrier of the Polychlorinated Biphenyls as a Physico-Chemical Parameter for use in Modelling of QSARs and QSPRs.

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1. Introduction

A number of physical properties of the polychlorinated biphenyls (PCBs), such as octanol-water partition coefficients (Kow), Henry's law constant, and vapor pressure are often used to model environmental fate and transport. These physical properties as well as a number of biochemical activities, such as inhibition of intercellular communication,[1] and binding affinity to the cytosolic Ah-receptor,[2] are assumed to be related to the ability of the PCBs to become planar. The optimal conformation of the PCBs are however found with a dihedral angle around the inter-ring carbon-carbon bond of 40-80°. The activation energy to the planar transition state, i.e. the internal barrier of rotation (Erot), has recently been estimated by both empirical methods, such as photoelectron spectroscopy,[3] gas phase electron diffraction,[4] and X-ray diffraction,[5] and by semi-empirical methods, such as Austin Model 1 (AM1),[6] modified neglect of diatomic overlap (MNDO),[7] and intermediate neglect of diatomic overlap (INDO),[8] as well as an *ab initio* method.[9]

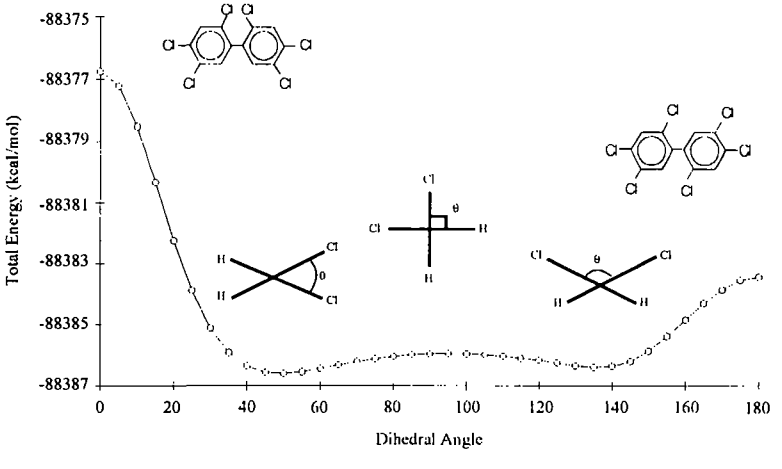

Figure 1. The total energy of PCB 153 (2,2',4,4',5,5') versus dihedral angle calculated every 5th degree. Illustrated are also the structural formulas of the two forced planar states, i.e. syn- (0°) and anti-form (180°), and the dihedral angles (θ) of the twisted conformation in syn- and anti-form and at 90°. The highest total energy of the forced planar states is found in the syn-form. The pre-set dihedral angle of 50° resulted in the lowest total energy for the shown PCB 153 (2,2',4,4',5,5').

In this study, the internal barriers of rotation were calculated by using the semi-empirical Austin Model 1 Hamiltonian for all 209 PCBs. Discussed are the importance of chlorine atoms in *ortho*-position, the buttressing effect and the use of Erot as a physico-chemical descriptor in modelling of quantitative structure-activity and structure-property relationships (QSARs/QSPRs).

2. Method

The Erot values of the 209 PCBs were calculated by using the AM1 Hamiltonian, included in the program package HyperChem™.[10] By comparing the semi-empirical methods AM1, MNDO and parametric method 3 (PM3), in calculating rotational barriers and preferred conformations of biphenyl, the AM1 Hamiltonian was found to be most accurate with results matching *ab initio* calculations and empirical observations.[11] The AM1 method is summing the electronic kinetic energies and the interaction energies of all electrons and atomic cores in the system in a total energy. The internal barrier of rotation was in this study defined as the difference in the total energy between a forced planar conformation and an optimised twisted structure. As seen in Figure 1, the PCBs were modelled in both syn- and anti-form, i.e. with the chlorine atoms in *ortho*-position on the same side and on the opposing sides, respectively. The anti-form of the forced planar state showed to be of lowest total energy and was hence used.

In order to reach the assumed optimum geometry of each congener, viz. the lowest total energy, a number of structural parameters must be pre-set. All binding lengths and the aromatic angles were initially set by the used software.[10] The dihedral angles were set to (I) 44°,[4] (II) 57°,[9] and (III) 74°,[5] for (I) non-*ortho* substituted PCBs, (II) mono-*ortho* and 2,6-di-*ortho* substituted PCBs, and (III) 2,2'-di-, tri- and tetra-*ortho* substituted congeners. The pre-set conformation of the congeners was optimized by using the Polak-Ribiere algorithm. The optimisation procedure was performed with the following limits; maximum number of cycles 330, criterion of root-mean-square gradient 0.5 kcal/mol, maximum number of iterations 50, and limit of convergence 0.5 kcal/mol.

3. Results and Discussion

The internal barrier of rotation for the 209 PCBs varied between 2.0 and 115.5 kcal/mol, see Table 1. The most significant structural characteristics of the PCBs influencing the results was the number of chlorine atoms in *ortho* position. The following Erot values were obtained; non-*ortho* chlorinated congeners 2.0-2.3 kcal/mol, mono-*ortho* PCBs 6.8-8.3 kcal/mol, di-*ortho* PCBs 14.4-20.2 kcal/mol, tri-*ortho* PCBs 42.2-53.6 kcal/mol and the tetra-*ortho* PCBs 89.2 to 115.5 kcal/mol.

Table 1. Internal barriers of rotation for the PCBs shown as the average±standard deviation.

Type of PCBs	Erot (kcal/mol)
non-*ortho*	2.13±0.1
mono-*ortho*	7.49±0.5
di-*ortho*	16.9±1.6
tri-*ortho*	47.3±3.3
tetra-*ortho*	101±8.0

Illustrated in Figure 2 is another important structural feature of the PCBs which influences the Erot values. Substitution of chlorine atoms in *meta* positions is known to enhance the racemization barriers of optically active biphenyls by the so-called buttressing effect.[12] The buttressing effect is explained by

a greater steric hindrance in the planar transition state owing to the *meta* substituent which is hindering an outward bending of the chlorine atoms in *ortho* position. As seen in Figure 2, the Erot values of the di-*ortho* substituted PCBs increased by approximately 1.5 kcal/mol per added vicinal *meta* substituent. The buttressing effect increased by each buttressing chlorine atom and was most significant for tetra-*ortho* PCBs, viz. at about 7 kcal/mol per *meta* substituent.

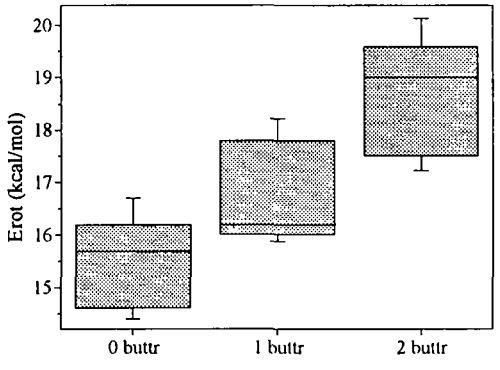

Figure 2. The buttressing effect of each added chlorine atom in vicinal *meta* position for di-*ortho* PCBs. The Box and Whisker plots show the median, lower and upper quartiles, and the 95% confidence limits.

3.1 Erot for use in QSPRs

The environmental fate of the PCBs can be modelled by parameters, such as bioconcentration and bioaccumulation factors, aqueous solubility and binding affinity to aerosol particles. These properties are often estimated from physico-chemical variables, e.g. retention characteristics, vapor pressure, Henry's law constant, and log Kow, which are related to number of chlorine atoms and their specific positions. In order to validate the capacity of the internal barrier of rotation as a structural describing parameter, suitable for usage in structure-property relationships, following plots seen in Figure 3 were obtained. Seen in Figure 3 is the vapor pressures (logP) of some penta chlorinated PCBs, determined by Foreman and Bidleman,[13] and the distribution coefficient in soil for PCB 87 (2,2',3,4,5'), PCB 95 (2,2',3,5',6), PCB 97 (2,2',3',4,5), PCB 101 (2,2',4,5,5'), PCB 105 (2,3,3',4,4'), PCB 110 (2,3,3',4',6), and PCB 118 (2,3',4,4',5), determined by Paya-Perez, Riaz, and Larsen,[14] plotted versus Erot. The soil-sorption, expressed as the distribution coefficient Kd, was clearly stronger for the less *ortho* substituted congeners of the same degree of chlorination. Also the vapor pressure, estimated based on retention characteristics, showed an *ortho*-effect. In conclusion both properties of the PCBs are related to the internal barrier of rotation.

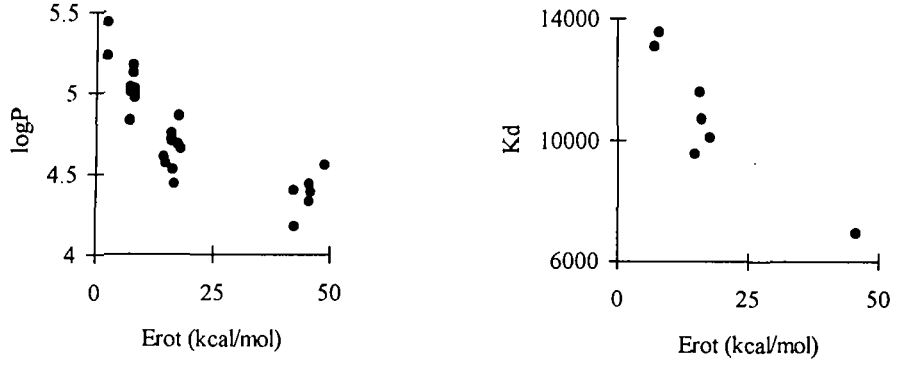

Figure 3. Vapor pressure (logP) and distribution coefficient (Kd) in soil versus Erot for some penta chlorinated biphenyls.

3.2 Erot for use in QSARs

Crucial in modelling of structure-activity relationships is the capability of the included physico-chemical parameters to describe finer structural dependent characteristics of the compounds. A number of biochemical activities of the PCBs, such as inhibition of cell-cell communication,[1] binding affinity to the cytosolic Ah-receptor,[2] and decreased dopamine contents,[15] are thought to be dependent on the number of chlorine atoms in *ortho* position. The biochemical processes underlying a toxicological response are complex and thus a large number of structural properties are probably required to model such systems. However, as shown in Figure 4, a correlation was found by plotting the inhibition of intercellular communication for some tetra-chlorobiphenyls versus Erot.

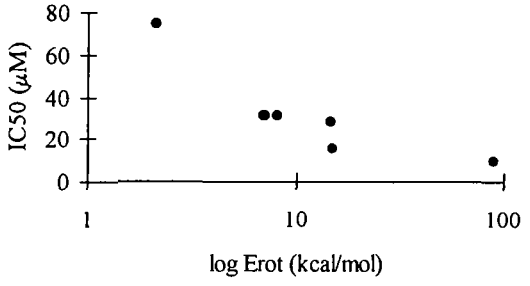

Figure 4. Inhibition of cell-cell communication in a rat liver WB cell culture, expressed as the concentration (μM) causing 50% induction of each individual congener, versus log Erot.

4. Conclusion

The internal barriers of rotation have been calculated for all 209 PCBs. The most important structural characteristics of the PCBs, reflected in the Erot values, was the number of chlorine atoms in *ortho* position. Erot is also influenced by vicinal *meta* and *ortho* substituents, which are causing the so-called buttressing effect. The internal barrier of rotation reflects important structural characteristics of the PCBs and provides a physico-chemical parameter for usage in structure-activity and structure-property relationships. However, the physical and biochemical processes are complex and a few physico-chemical properties are unlikely to be sufficient in more general models. By including all 209 congeners, Erot is suited for future multivariate approaches in modelling of environmental as well as biochemical characteristics.

5. Acknowledgement

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6. References

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