STUDIES ON AROMATIC COMPOUNDS. REMARKABLE DIFFERENCE IN THE MOLECULAR ELECTROSTATIC POTENTIAL AND DIPOLE MOMENT OF TOXIC AND NON-TOXIC POLYCHLORINATED BIPHENYLS

Bernardo Herradón, * Antonio Chana, Miguel A. Concejero, Mercedes de Frutos, María J. González

Instituto de Química Orgánica General, C.S.I.C.,Juan de la Cierva 3, 28006 Madrid, Spain. *Fax: +34915644853. E-mail: herradon@iqog.csic.es

Introduction

Polychlorinated biphenyls (PCBs) are persistent environmental contaminants.[1] These chemicals are widely distributed in a variety of systems (food, water, atmosphere). In animals, these compounds accumulate in the adipose tissue, being difficult to metabolise and remove; causing long-term toxic effects.

Although the toxicity of PCBs has been claimed to be similar to the one reported for 2,3,7,8-tetrachlorodibenzo[1,4]dioxin [activation of the aryl hydrocarbon receptor (AhR)],[2] this assertion has not been unequivocally proved. Additionally, some PCBs have been reported to possess biological activities that are not linked to the activation of AhR.[3]

The limited structure-toxicity relationship studies[4] on PCBs have shown that the biological activity is highly dependent on the chlorination degree as well as on the substitution pattern. The congeners with 5 and 6 chlorine atoms are the most toxic, and the PCBs with *ortho*-substitution are less toxic than the analogues without *ortho*-substitution. Thus, the toxicity of the PCB congeners has been linked to the fact that the two aromatic rings become coplanar.

In connection with our current experimental[5] and computational[6] studies on aromatic compounds, we have been interested in chlorinated biphenyls. A significant structural difference between these compounds and the chlorinated dibenzo[1,4]dioxin is the conformational mobility. While the dibenzo[1,4]dioxin ring system is quite rigid, the biphenyl derivatives could exist in a variety of conformations that arise through rotation around the aryl-aryl bond.

Research on the bioactivity of chlorinated biphenyls requires a complete set of their physico-chemical properties. Although these data may be obtained experimentally; this approach is hampered by the high number of congeners (209), the elevated toxicity of some of them, and the unavailability of some compounds in a pure state. Therefore, a viable alternative is the computational one.

In this paper we report some details of a comprehensive computational study on all the chlorinated biphenyls (209 compounds).[7] We have performed *ab initio* calculations of the molecular electrostatic potential (MEP) and the dipole moment (m) as well as molecular dynamics simulations on all the chlorinated biphenyls. The main purpose of this research has been to investigate how the substitution pattern on this type of compounds influences the charge distribution on the molecule; an information that can be useful to understand the selective toxicity of the PCBs.

Methods

The calculations were performed in a Silicon Graphics O_2 R5000 computer, with Irix 6.5 operating system, and in a PC computer, working with two 867 MHz processors and running Linux operating

system. The starting geometry for the quantum-chemical calculation of each congener was generated through a conformational search (and further MM2 minimization) on each halogenated biphenyl, using the MM2 force field as implemented in *Sybyl* version 6.6 software. The molecular electrostatic potentials (MEPs) and dipole moments (m) of biphenyl and of all the chlorinated biphenyls (209 congeners) were computed in the vacuum. The calculations were carried out at the hybrid Hartree-Fock/density functional scheme HF/B3LYP[8] using 6-31G* as basis set, as implemented in the *Gaussian 98* program.[9] The molecular surface electrostatic potentials of the computed MEP were generated using the program *gopenmol*.[10] The surface electrostatic potentials (Figure 1) are plotted on an isoelectronic density surface of 0.05 *e*.bohr^{-3}. The plots show regions ranging from positive (red) to negative (blue) electrostatic potentials; the values of the electrostatic potentials (in stat *e*V) are indicated in the scale on the left to the plot. The molecular dynamics simulation were carried out using MMFF94 force field[11] as implemented in *Sybyl* version 6.6.

Results and Discussion

The molecular electrostatic potential [MEP, V(r)] at the point r is a measurement of the electrostatic interaction energy between a molecule and a test charge of magnitude *e* (that is a proton) placed at that point, supposing that the molecule is not polarized by the test charge.[12] The MEP can be calculated by the equation (1)

$$V(r) = \sum_A \frac{Z_A}{|R_A - r|} - \int \frac{\tilde{n}(r')}{|r - r'|} dr' \qquad (1),$$

where the first term is the contribution from the nuclear charges, which are considered to be point charges, and the second term arises from the electron density of the molecule. The MEP has been used as an indicator of the charge distribution in a molecule, where the regions with higher negative values of V(r) are richer in electron density. On basis to this characteristic, we reasoned that the comparison of the molecular electrostatic potentials of different chlorinated biphenyls can help to understand the selective toxicity of these chemicals.

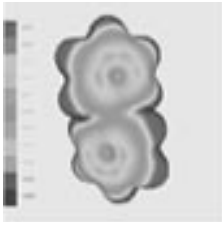
The dipole moment (m) is an indicator of the charge separation into the molecule. It is a vectorial electrostatic magnitude that depends on the conformation of the molecule. In the case of chlorinated biphenyls, the main individual contribution to the overall dipole moment is the polarized carbon-chlorine bond. Due to its conformational mobility, it is expected that the values of the dipole moment of a chlorinated biphenyl depends on the dihedral angle between the two aromatic rings. It is likely that the pernicious effect of a PCB is related to its capacity to accumulate in the adipose (low dielectric constant) tissue; the calculations have been carried out at the vacuum, what is a realistic situation.

An illustrative selection of results, along with data on the toxicity, for biphenyl and different chlorinated derivatives are presented in Figure 1. Although space limitations hamper a detailed analysis of results, some conclusions are the following:

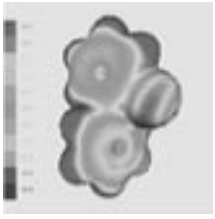
a) We have found that the most toxic congeners possess relatively low electron density on the aromatic rings along with regions of relatively high electron density on the chlorine atoms.

b) The main effect of *ortho*-chlorination is to increase the electron density on the vicinal ring; and the lower toxicity of these congeners can be due to the relatively high density of this ring. Additionally, molecular dynamics simulations have shown that the conformational mobility of the *ortho*-chlorinated congeners is lower than the non-*ortho* substituted biphenyls.[7]

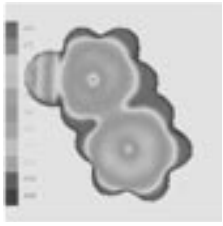
c) All the most toxic compounds have low dipole moments. On basis to the conditions of the calculations (vacuum), the conformers with low polarity are energetically favoured. We have found that the congeners with chlorine substitutions at the *meta*- and *para*- positions of the aromatic rings tends to adopt a coplanar conformation that, indeed, are the ones with the lower dipole moment.



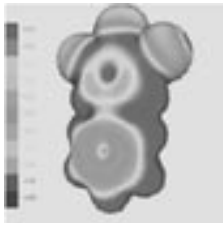
Biphenyl
μ = 0.0 D



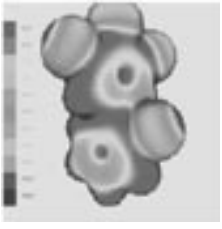
2-Cl-biphenyl
PCB # 1
μ = 1.66 D



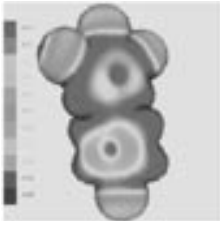
3-Cl-biphenyl
PCB # 2
μ = 2.11 D



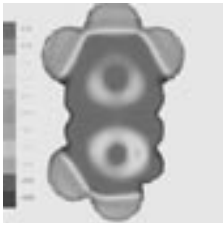
3,4,5-$(Cl)_3$-biphenyl
PCB # 38
μ = 3.80 D



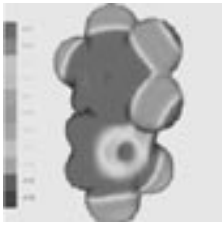
3,3',4,4',5-$(Cl)_5$-biphenyl
PCB # 126
μ = 1.60 D
lg (TEF) = -1.0



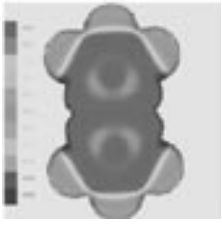
2',3,4,5-$(Cl)_4$-biphenyl
PCB # 76
μ = 4.41 D



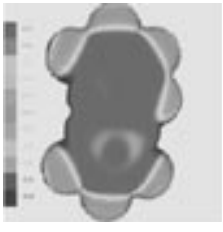
3,4,4',5-$(Cl)_4$-biphenyl
PCB # 81
μ = 1.63 D
lg (TEF) = -4.0



2,3,3',4,4',5-$(Cl)_6$-biphenyl
PCB # 156
μ = 1.94 D
lg (TEF) = -3.3



3,3',4,4',5,5'-$(Cl)_6$-biphenyl
PCB # 169
μ = 0.0 D
lg (TEF) = -2.0



2,3,3',4,4',5,5'-$(Cl)_7$-biphenyl
PCB # 189
μ = 0.9 D
lg (TEF) = -4.0

Figure 1. Representation of the molecular surface electrostatic potential (MEP) of biphenyl and some chlorinated biphenyls. The computed dipole moment (m) corresponds to the indicated conformer. The values of toxic equivalency factor (TEF) are relative to 2,3,7,8-tetrachlorodibenzo[1,4]dioxin [log (TEF) = 0].

Acknowledgements

Financial support from the Spanish Ministry of Science and Technology (Project BQU2001-2270) and Madrid Autonomous Community (Project 08.5/0056/2000-2) is gratefully acknowledged.

References

1. Safe, S. (1990) Crit. Rev. Toxicol. 21, 1.
2. Hahn, M.E. (1998) Comp. Biochem. Physiol. Part C 121, 23..
3. Olivero, J.; Ganey, P.E. (2001) Biochem. Pharmacol. 62, 1125.
4. So, S.-S.; Karplus, M. (1997) J. Med. Chem. 40, 4360; and references cited therein.
5. Heaton, N.J.; Bello, P.; Herradón, B.; del Campo, A.; Jiménez-Barbero, J. (1998) J. Am. Chem. Soc. 120, 9632.
6. Bello, P.; Chana, A.; Heaton, N.J.; Maestro, M.A.; Mahía, J.; Herradón, B. (2001) J. Mol. Struct. 569, 71.
7. Chana, A. Progressing Ph. D. thesis.
8. Becke, A. (1988) Phys. Rev. A 38, 3098.
9. Gaussian 98, Revision A.3, Gaussian Inc., Pittsburgh PA, 1998.
10. Bergman, D.L.; Laaksonen, L.; Laaksonen, A. (1997) J. Mol. Graph. 15, 301.
11. Halgren, T. A. (1996) J Comp Chem 17, 490.
12. Murray, J.S.; Sen, K. (eds.) (1996) Molecular Electrostatic Potentials. Concepts and Applications; Elsevier. ISBN 0-444-82353-0.