The Molecular Electrostatic Potential as a Guide in Understanding the Biological Mechanism of Polychlorodibenzo-p-Dioxin Action at the Molecular Level

Laura Bonati, Elena Fraschini, Marina Lasagni and Demetrio Pitea

Dipartimento di Chimica Fisica ed Elettrochimica, Università degli Studi di Milano, V. Golgi 19, 20133 Milano, Italy

PCDDs, PolyChlorinated Dibenzo-p-Dioxins constitute a group of chemicals that have been shown to occur everywhere in the environment. They have been identified[1] in emissions from MSW, hazardous waste, and industrial incinerators, as contaminants in commercial and technical products and in exhaust gases from cars. Their persistency and accumulation in biological systems contribute to the widespread environmental and toxicological problems associated with them.

Toxic and biological effects[2] produced by these compounds are species- and tissue-dependent; most appear to be mediated by binding to the Ah receptor, the intracellular receptor of Polycyclic Aromatic Hydrocarbons (PAH). QSAR studies[2] on the highly-specific noncovalent binding with this receptor have indicated that structural and electronic requirements for the ligand are planar, polarizable aromatic skeletons and hydrophobic lateral substituents. Theoretical studies have suggested that ligand-receptor interactions are guided by dispersion[3] or by electrostatic[4] forces.

The knowledge of the recognition process with the target cellular receptor at the molecular level plays a key role in gaining insight into the biological mechanism of the PCDD action. As the receptor molecular structure is not known we have used an indirect method which compares known active and inactive ligand properties.

Molecular Electrostatic Potential (MEP), the potential created in the space around the molecule by its nuclei and electrons, has proven to be an effective means to analize biological recognition processes[5].

This paper reports a study of the relationships between MEP distributions of some PCDDs and their Ah receptor binding affinities.

To study the electronic effects of different substitution patterns the following isomers of TetraChloroDibenzo-p-Dioxins (TCDD) have been chosen: 2,3,7,8–, 2,3,6,7–, 1,3,7,8–, 1,2,3,4– and 1,4,6,9–TCDD. To study the effects of the degree of chlorination the analysis has been extended to 1,2,3,7,8–PeCDD, 1,2,3,6,7,8–HxCDD and OCDD.

These molecules have been selected for two other reasons. Their binding affinities and activities show a broad range of values, from the most active 2,3,7,8–TCDD to the inactive OCDD. Moreover a homogeneous set of measurements[6] is available, the exception being 1,4,6,9–TCDD. This molecule has been considered as it lacks substituents in the lateral positions.

On the basis of a previous analysis[7,8] calculation of the MEP distributions were

made with the HF–SCF method at the 3–21G level. The comparison of MEP patterns is performed on a plane parallel to the molecular plane and on a three dimensional lattice around the molecule.

For the active PCDDs the electronic distribution is strongly polarized toward the outer regions of the aromatic rings and thus causes the presence of accessible positive regions of MEP above the molecular plane.

This result suggests that an effective molecular recognition process requires the electrostatic interaction between the PCDD aromatic region and an electron donor site of the receptor. Moreover, for the TCDD isomers the electrostatic "accessibility" to the electrophilic planar region decreases with the same trend as for the binding affinities.

With respect to some TCDD isomers, 1,2,3,7,8–PeCDD and 1,2,3,6,7,8–HxCDD show higher values of affinity; this could be attributed to the effect of four chlorine atoms in the 2,3,7,8 positions which seems to overcome the decreased "accessibility" of the electrophilic aromatic region.

REFERENCES

1) Rappe C., *et al.*, *Waste Manag. & Res.*, **5**, 225-237 (1987)
2) Goldstein J. A., Safe S., in "*Halogenated Biphenyls, Terphenyls, Naphthalenes, Dibenzodioxins and Related Products*", Kimbrough and Jensen (Eds.), Elsevier Science Publishers (1989)
3) McKinney J. D., *Environ. Health Perspect.*, **82**, 323-336 (1989)
4) Politzer P., *Toxicol. Lett.*, **43**, 257-276 (1988)
5) Politzer P., Truhlar D.G. (Eds.), "*Chemical Applications of Atomic and Molecular Electrostatic Potentials*", Plenum Press (1981)
6) Mason G., Farrell K., Keys B., Piskorska-Pliszczynska J., Safe L., Safe S., *Toxicology*, **41**, 21-31 (1986)
7) Bonati L., Fraschini E., Lasagni M., Pitea D., *J. Chim. Phys.*, **88**, 2631-2638 (1991)
8) Bonati L., Cosentino U., Fraschini E., Moro G., Pitea D., *J. Comput. Chem.*, in press