ELECTRONIC ELASTISITY AS A NEW DETERMINANT OF PCDD CONGENERS' TOXICITY

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Introduction

The predominant origin of dibenzo-p-dioxins and polychlorinated dibenzofurans (PCDD/F) are combustion and thermal processes[1-8]. Extreme toxicity of these widespread environmental contaminants strongly depends on the degree and position of chlorination[1]. The superposition of thermodynamic stability and kinetically limited reactivity of PCDD isomers, can be used to generate a qualitative description of typical PCDD congener patterns in the effluent from combustion systems[5,6]. To our knowledge, why 2,3,7,8 TCDD is the most toxic congener has yet to be demonstrated or related to the nature of the intermolecular binding.

It has been previously established, that the cytosolic aryl hydrocarbon receptor (AhR) is the regulator of the biochemical and toxicological actions of these structurally diverse chemicals[8-12]. Activation of the intracellular AhR-protein is initiated by its specific binding to dioxin substrates. The composition and overall molecular structure of the nuclear and cytosolic Ah receptor complexes have not been delineated. Little is known about the actual nature of the receptor sites, active centers, or nature of functional groups[12].

Although all the types of molecular interactions may occur in the mechanism of binding of dioxins to receptors, it is unclear which step is rate determining. It is usually supposed that planarity and existence of hydrophobic lateral substituents are essential determinants for the effective recognition of agonists. Some interaction models have been proposed to explain experimental results of competitive bindings of PCDD/F, PCBs and polycyclic aromatic hydrocarbons[9-10]. Proposed conceptual models include some types of interactions of dioxins with the Ah-receptor[9-11]. However, these models can only account for differences due to number and kinds of halogens but not positions of halogens or conformation of the molecule[9]. Attempted to generalize and explain the structure-activity relationships and to elucidate the binding interactions and mechanisms for halogenated aromatic hydrocarbons, broad ranges of types of intermolecular forces have been evaluated[11]. These efforts also have furnished much valuable data; while at the same time, many controversial interpretations have been suggested. Comparative analysis was made between limited representatives of different classes of compounds, using a number of arbitrarily selected parameters.

Traditionally used static reactivity indexes, such as partial atomic charges and HOMO-LUMO energies of congeners reported in the literature[11] are not directly applicable to the origin of the hyper toxicity of PCDD/F congeners with the 2,3,7,8-chlorination pattern – rather, there is an implicit and complex dependence based on general expressions of receptor-substrate interaction energies. Thus, development of structure-activity relationships and correlations of molecular electronic properties with biological activity would be more accurate if the models used in this development only considered isoelectronic systems with equal quantities of substituents (viz., number of electrons). Besides, the

accessibility to active centers also can play a basic role. At the present many charged and neutral, large molecules have been found, which are able to pass through cellular membranes. Certainly, an alternative, nonspecific mechanism of a passing can be exist, which connect with local converted breakdown of membranes in places of a sorption of molecules[13]. Binding molecules to a diaphragm leads to a local fall of a surface tension of a membrane, and in many cases to appearance of a local electric field in membrane. Energetic barrier for formation a pore in a diaphragm in this place is reduced, and the probability of formation a pore is increases.

In this manuscript, we report the systematic examination and quantum mechanical calculation of the long-range molecular characteristics and electrical responces of title compounds. Proceeding from above-stated we estimate the specific, relative, response of dioxin substrates to the external perturbation (influencing by receptors or some kinds of electrical forces) by the means of linear (a) and non-linear, viz. hyper-, (b and g) polarizabilities of molecules. Specific changes of the calculated parameters may be interpreted as a fluctuation from the average value and identified as a measure of electronic elasticity and the flexibility of conjugated heteroaromatic congeners.

Methods and Materials

The SCF-MO calculations were performed using the MNDO formalism and the PM3 set of parameters[14] at the restricted Hartree-Fock (RHF) level as available in the MOPAC and Spartan suite of programs. The detailed methodology of calculations has been described elsewhere[11.] Noting that polarizabilities of molecules have been calculated within the framework of finite field theory [15].

Results and Discussion

SCF-MO computations have been performed for all of the tetra-, penta-, hexa-, hepta-, and octa-chlorinated derivatives of dibenzo-*p*-dioxin and, for comparison, the non-toxic 2,3,7,8-tetrafluoro-dibenzo-*p*-dioxin (TFDD) and non-chlorinated dibenzo-p-dioxin (DD). Qualitative relationships were developed between empirical, international-toxic equivalence factors (I-TEF) for PCDD congeners and parameterized electrical susceptibilities, their relative (specific) polarizabilities α,ß,γ and mean values of second hyperpolarizabilities. It must be emphasized that the toxicity factor, I-TEF, is a complicated empirical parameter and cannot be simply defined by a single determinant of intracellular interaction.

As expected, the calculated permanent dipole moments, m, for PCDDs are not large. In congeners with higher symmetry, dipole moments, as well as the first hyperpolarizability (ß) are very small. In the more asymmetric congeners with the higher dipole moments, the vector component of b along m increases. Within a homologue class, the congeners with the highest linear polarizability, a, are also the congeners with non-zero I-TEFs. It is notable that a correlates with the second hyperpolarizability,g, but not the first hyperpolarizability, ß.

There is also a noticeable correlation between α and γ with heat of formation. These correlations are of some direct interest, since they are simply related to the co-ordination ability of molecules. It should be noted also that the calculated by PM3 heat of formation for non-chlorinated dibenzo-p-dioxin is in consistent with recent experimental and estimation data[16,17].

Although the calculated values of α and γ correlate with I-TEFs for congeners within homologue classes, they do not correlate across homologue classes. For this reason, it is difficult to understand the role of polarizability in correlation expressions developed by McKinney and others for structurally diverse compounds [9-10]. To correct for this effect, it is necessary to devise a parameter that correctly expresses the fluctuation in the polarizability across and within homologue classes. The following simple relations allow the fluctuation in the linear and second hyperpolarizability to be applied to all congeners regardless of which homologue class they belong:

$$A_n(\alpha) = \alpha_n - [\ \alpha_{DD} + n(\alpha_{OCDD} - \alpha_{DD})/8\ ] \quad (1)$$

$$A_n(\gamma) = \gamma_n - [\ \gamma_{DD} + n(\gamma_{OCDD} - \gamma_{DD})/8\ ] \quad (2)$$

where α_n and γ_n are the total polarizability and second hyperpolarizability, respectively, of a given congener with *n* chlorine substituents, and α_{DD}, γ_{DD}, α_{OCDD}, γ_{OCDD}, are the same parameters for the non-chlorinated dibenzo-*p*-dioxin (DD) and perchlorinated octachlorodibenzo-*p*-dioxin (OCDD). As shown in figure 1, the resultant values of $A_n(\alpha)$ and $A_n(\gamma)$ correlate with the I-TEFs of DD and PCDD congeners with non-zero I-TEF values. Obviously, this phenomenon is related to the secondary effects of polarizabilities (it is not the result of non-linearities of α).

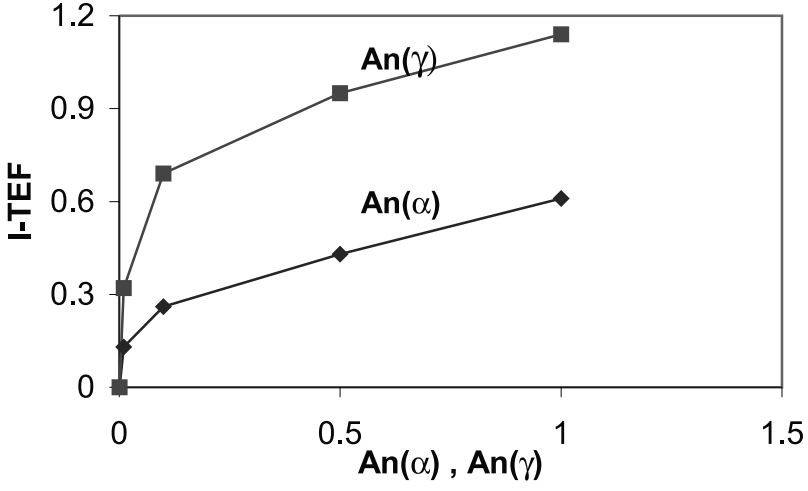

Figure 1. Plots of I-TEF vs. $A_n(\alpha)$ *and* $A_n(\gamma)$ *for PCDD* (from *tetra-* through *octa-* congeners*)* with non-zero I-TEFs

So, it can be concluded that the polarizabilities and hyperpolarizabilities of PCDD congeners correlate with their toxicities (as represented by their I-TEF values) within isoelectronic series that contain the common 2,3,7,8-chlorine substitution pattern and any additional chlorine. However, enlargement of systems due to the addition of new halogen atom substituents, increases the system's polarizabilities, leading to drastic reductions of the bulk toxicities of non- isomeric congeners. Apparently, the direct relation between total values of polarizabilities and toxicities of structurally diverse compounds is not as obvious as previously presented in literature.

However, it is possible to derive a simple and universal relationship using specific fluctuations of a and g from average values of target compounds. Novel parameters, $A_n(\alpha)$ and $A_n(\gamma)$, are identified as a measure of elasticity of PCDD congeners and strongly correlate with inter-group toxicities. It seems clear that this phenomenon is a secondary effect of first (α) and third order (γ) polarizabilities and needs further clarification. Secondary effects of dipole and second order polarizabilities and the formation of these complexes may also be constrained by accessibility to active centers and the local arrangement of interacting systems. Our approach could, in principle, be applicable to different

complexation problems and other classes of compounds (PCDFs, PCBs, PAHs, etc) for which the toxicity parameters are well defined.

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References

1. Barnes, D.G. (1991) Sci. Total Environment 104, 73
2. Olie, K., Vermeulen, P.L., Hutzinger, O. (1977) Chemosphere 6, 455
3. Tsang, W. (1994) Khim. Fiz. 13,17 (In Russian).
4. Dellinger, B. and Taylor, P.H. (1997) Hazardous Waste Incineration, Pershing, D.W. and Sarofim, A.F., eds., John Wiley, New York
5.Tuppurainen, K., Halonen, I., Ruokojarvi,P., Tarhanen, J.,Ruuskanen, J. (1998) Chemosphere, 36, 7
6. Wehrmeier, A., Lenoir, D., Schramm, K.-W., Zimmermann, R., Hahn, K., Henkelmann, B., Kettrup, A. (1998) Chemosphere 36, 2775
7. Khachatryan, L., Dellinger, B., Burcat, A., Asatryan, R. (2001) A reaction kinetic model of the gas phase, surface initiated formation of PCDD/F. In: 5th Int'l Conf. on Chemical Kinetics, NIST, Gaithersburg, MD, USA, Abstracts, 246.
8. Dioxins– supertoxicants of XXI century. VINITI, 1997, 1-2; 1998, 3-4, Moscow (In Russian).
9. Long , G., McKinney, J.D., Pederson,L. (1987) Quant. Struct.- Act. Relat. 6, 1-7.
10. McKinney, J.D., Darden, T., Lyerly, M.A., Pederson, L.G. (1985) Quant. Struct.– Act. Relat., 4, 166
11. Asatryan R.S., Mailyan N.Sh., Khachatryan L., Dellinger B. (2002) Chemosphere, in press
12. Kobayashi, S., Kitadi, M., Sameshima, K., Ishii, Y., Tanaka, A. (1999) J. Mol. Struct. 475, 203
13. Putvinskii, A.B., Chernomordik, L.V. (1981) Electrical breakdown of membrane and the cell's pathology. In: Biomembranes: Structure, functions and medical aspects, Riga, Zinatie, 278.
14. Stewart, J.J.P. (1989) J. Comput. Chemistry 10, 209; 221
15. Kurtz, H.A., Stewart, J.J.P., Dieter, K.M. (1990) J. Comput. Chemistry 11, 82
16. Dorofeeva, O.V., Iorish, V.S., Moiseeva, N.F. (1999) J. Chem. Eng. Data, 44, 516
17. Pimenova, S.M., Melkhanova, S.V., Kolesov, V.P., Demyanov, P.I., Fedotov, A.N., Vorobieva, V.P. The Standard Molar Enthalpy of Dibenzo-*p*-Dioxin. (in press).