Frontier Electron Density Pattern of Dioxin Congeners

Yoshihiro Mizukami*
Faculty of Liberal Arts and Education, Shiga University, 2-5-1, Hiratsu, Otsu, Shiga 520-0862

(Received June 29, 2004; CL-040759)

Electron densities of highest occupied molecular orbitals (HOMO) of 75 congeners of chlorinated dibenzo-*p*-dioxins and a nonchlorinated dibenzo-*p*-dioxin were calculated. HOMO electron densities are localized mainly in out of plane π orbitals of the 12 carbons and 2 oxygens. These HOMO densities were used as variables in a multivariate statistical analysis. By principal component analysis, the 76 dioxins were classified according to their character. The most toxic dioxins have large negative values of the third principal component scores.

Dioxins are well known for their toxicity. In addition to being carcinogens and teratogens,[1,2] they damage the immune system and act as endocrine disrupters.[2,3] Typical acute toxic effects are chloracne, liver damage, and kidney dysfunction.[1] The World Health Organization (WHO) reported[4] the seven most toxic dioxin congeners, whose toxic equivalency factors[5] (TEFs) are listed in Table 1. Note that a systematic number, which correlates with the substitution pattern of congeners, suggested by Ballschmiter et al.[6] is used to identify 76 dioxin congeners.

Table 1. Toxic equivalency factors (TEFs) of dioxin congeners

No.	Structure	TEF[a]
48	2,3,7,8-T_4CDD	1
54	1,2,3,7,8-P_5CDD	1
66	1,2,3,4,7,8-H_6CDD	0.1
67	1,2,3,6,7,8-H_6CDD	0.1
70	1,2,3,7,8,9-H_6CDD	0.1
73	1,2,3,4,6,7,8-H_7CDD	0.01
75	1,2,3,4,6,7,8,9-O_8CDD	0.0001

[a]From Ref. 4.

In this study, we theoretically investigated the relationship between the toxicities and structures of the 75 congeners of polychlorinated dibenzo-*p*-dioxins (PCDDs) and the unsubstituted dibenzo-*p*-dioxin. We focused on the electron densities of frontier orbitals, especially HOMO, as frontier electrons are often responsible for the reactivity and properties of molecules.[7]

Figure 1 shows the skeleton of dibenzo-*p*-dioxin with the 12

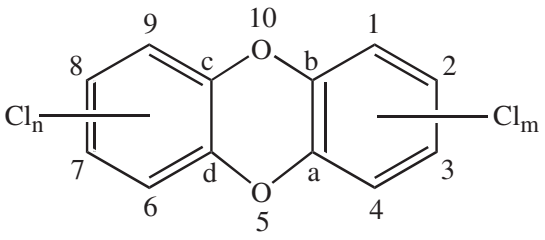

Figure 1. Structure and labeling of dibenzo-*p*-dioxin. $m, n =$ 1–4 for polychlorinated dibenzo-*p*-dioxins. $m, n = 0$ for unsubstituted dibenzo-*p*-dioxin.

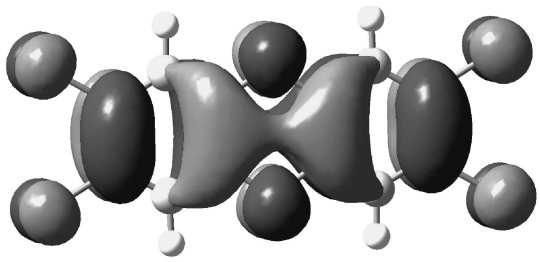

Figure 2. HOMO of 2,3,7,8-tetrachlorinated dibenzo-*p*-dioxin (2,3,7,8-T_4CDD) (#48).

carbons and 2 oxygens. In our calculations, we fixed the length of all of the C–Cl bonds at 1.820 Å and that of all of the C–H at 1.071 Å. We performed ab initio MO calculations at the HF/3-21G level of theory using Gaussian 98,[8] partly modified, to estimate the HOMO electron densities. HOMO of 2,3,7,8-T_4CDD is shown in Figure 2. Note that the π-electron densities on the chlorine atoms are very small and that 93.8% of the HOMO densities are localized on the 12 carbons and 2 oxygens. The largest density, which is 0.235, is on the oxygen atoms. Since the 12 carbons and 2 oxygens are common to all 76 congeners, we used the HOMO densities on these atoms as variables in principal component analysis (PCA).[9] We used PCA to classify the 76 congeners according to their characterstics with respect to four principal components (Prin 1, 2, 3, 4) whose eigenvalues were greater than 1.0, and whose sum contribution is more than 98% of all of the principal components. We calculated the scores of the four principal components. Figure 3 is a plot of the scores of the first principal component (Prin 1) vs those of the third principal component (Prin 3), for all 76 congeners. Note that the seven most toxic dioxins have large negative values on the Prin 3 axis. Prin 3 has large coefficients (0.53, 0.50) with variables related to HOMO densities on the oxygen atoms, which correlates to the scores of Prin 3 ($r = 0.913$). The seven most toxic congeners have small electron densities on their oxygen atoms, all of which are included in the top 10 smallest density values as listed in Table 2.

From studies on dioxin's ability to induce microsomal aryl hydrocarbon hydroxylase (AHH) activity, it is known that toxic PCDDs have two common properties: (1) a planer structure; and (2) halogen atoms in at least three of the four lateral positions (positions 2, 3, 7, 8), i.e., positions furthest from the oxygens. Maximal toxicity appears when there are four halogen atoms, each in a lateral position.[10] Recent experiments have indicated that the Ah receptor mediates the biological effects of dioxins.[11] In light of this, we think that, since the most toxic PCDDs have relatively smaller electron density of the HOMOs over the oxygen atoms, the oxygens play an important role in the interactions with Ah receptor, and more importantly, in their toxicity. Murray et al.[12] speculate that, from their molecular electrostatic potential study of dioxins, that the weakening of the negative region above

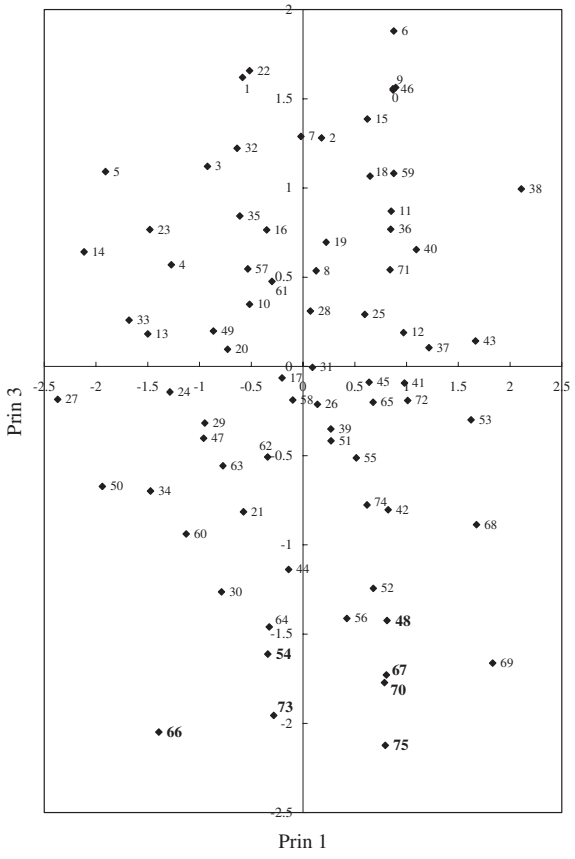

Figure 3. Principal component analysis of HOMO densities of 76 dioxins. Scores of the first principal component (Prin 1) vs the third principal component (Prin 3). The numbers refer to the dioxins as listed in Ref. 6. The seven most toxic dioxins are listed in Table 1.

Table 2. Top 10 of the dioxin congeners which have the smallest values of HOMO densities on oxygen atoms

No.	HOMO Densities on Oxygens
66	0.22643
75	0.22869
73	0.22887
70	0.23168
67	0.23171
54	0.23186
50	0.23195
60	0.23348
48	0.23486
63	0.23515

the oxygens may be a contributing factor to increasing activity. We are planning to perform a further study to evaluate the role of oxygens in dioxin's activity. A study, using a similar approach, on the toxicity of chlorinated dibenzofuran is reported elsewhere.[13]

In conclusion, 76 congeners of dioxins were classified by principal component analysis using HOMO densities as variables. The seven most toxic PCDDs all had a large negative score for the third principal component, which is related to the HOMO density on the oxygens. The most toxic dioxins have small electron densities over their oxygen atoms.

Calculations were partly performed on a workstation (Silicon Graphics O2) at the Center for Information Processing of Shiga University.

References and Notes

1 "Polychlorinated Dibenzo-*p*-dioxins and -furans(PCDDs/PCDFs): Sources and Environmental Impact, Epidemiology, Mechanisms of Action, Health Risk," ed. by S. Safe, O. Hutzinger, and T. A. Hill, Springer-Verlag, Berlin, Heidelberg (1990).
2 F. Ohtake, K. Takeyama, T. Matsumoto, H. Kitagawa, Y. Yamamoto, K. Nohara, C. Tohyama, A. Krust, J. Mimura, P. Chambon, J. Yanagisawa, Y. Fujii-Kuriyama, and S. Kato, *Nature*, **423**, 545 (2003).
3 "Generation at Risk: Reproductive Health and the Environment," ed. by T. Schettler, G. Solomon, M. Valenti, and A. Huddle, The MIT Press, Massachusetts (1999).
4 M. Van den Berg, L. Birnbaum, A. T. C. Bosveld, B. Brunstrom, P. Cook, M. Feeley, J. P. Giesy, A. Hanberg, R. Hasegawa, S. W. Kennedy, T. Kubiak, J. C. Larsen, F. X. R. van Leeuwen, A. K. D. Liem, C. Nolt, R. E. Peterson, L. Poellinger, S. Safe, D. Schrenk, D. Tillitt, M. Tysklind, M. Younes, F. Waern, and T. Zacharewski, *Environ. Health Perspect.*, **106**, 775 (1998).
5 The TEF concept is the most plausible and feasible approach for risk assessment of haloganated aromatic hydrocarbons with dioxin-like properties. TEF is unit to be used to evaluate the intensity of toxicity of dioxins based on the toxicity of 2,3,7,8-T_4CDD that is taken as 1 unit. Because of insufficient environmental and toxicological data, TEFs are only established for the 2,3,7,8-substituted PCDDs and PCDFs and the non- and mono- ortho-PCBs. We should also note that TEFs are relative potency of a compound relative to 2,3,7,8-T_4CDD to cause a particular toxic or biological effect, which is Ah receptor-mediated.
6 K. Ballshmiter, H. Buchert, R. Niemczyk, A. Munder, and M. Swerev, *Chemosphere*, **15**, 901 (1986).
7 "Frontier Orbitals and Reaction Paths: Selected Papers of Kenichi Fukui," ed. by K. Fukui and H. Fujimoto, World Scientific, Singapore (1997).
8 M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery, Jr., R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. M. Daniels, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, Q. Cui, K. Morokuma, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, C. Gonzalez, M. Challacombe, P. M. W. Gill, B. G. Johnson, W. Chen, M. W. Wong, J. L. Andres, M. Head-Gordon, E. S. Replogle, and J. A. Pople, "Gaussian 98," Gaussian, Inc., Pittsburgh, PA (2000).
9 "Multivariate Pattern Recognition in Chemometrics," ed. by R. G. Brereton, Elsevier, Amsterdam (1992).
10 J. P. Whitlock, Jr., *Chem. Res. Toxicol.*, **6**, 754 (1993).
11 K. Sogawa and Y. Fujii-Kuriyama, *J. Biochem.*, **122**, 1075 (1997).
12 J. S. Murray, B. A. Zilles, K. Jayasuriya, and P. Politzer, *J. Am. Chem. Soc.*, **108**, 915 (1986).
13 Y. Mizukami, *THEOCHEM*, **672**, 161 (2004).

Published on the web (Advance View) September 11, 2004; DOI 10.1246/cl.2004.1328