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Frontier density pattern of dibenzofurans: a relation between structures and toxicity

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Abstract

Electron densities of highest occupied molecular orbitals (HOMO) of 135 congeners of chlorinated dibenzofurans and a nonchlorinated dibenzofuran are calculated. Electron densities of HOMO are localized mainly on out of plane π orbitals of 12 carbons and an oxygen in dibenzofuran structure. Multivariate statistical analysis with principal component analysis is performed for HOMO densities of 136 congeners of dibenzofurans to extract the pattern of HOMO density distributions. It was found that all of the most toxic dibenzofurans are involved in the group that has large negative values of the third principal component score.

Keywords: Dibenzofurans; Frontier density; Multivariate statistical analysis; Toxicity

1. Introduction

Polychlorinated dibenzofurans (PCDFs) are dioxin-like compounds. Dioxins are known as most dangerous compounds. Dibenzofurans show similar toxicity with dioxins. Typical toxic effects are liver damage, chloracne, kidney abnormalities, carcinogenicity and teratogenicity [1]. In 1968 an outbreak known as 'Yusho' occurred in Japan [2]. Yusho was an accident where PCBs contaminated rice oil, which had been consumed by customers. This contamination included 1000 ppm of PCBs and 5 ppm of dibenzofurans. About 2000 people became ill. Not only PCBs but also dibenzofurans are thought to be the causes of the disease. Recently, it has been confirmed that dioxin-like compound is a cancer hazard. It is doubt that exposure to dioxin-like compound, which acts as endocrine disrupter, can cause severe reproductive and developmental problems [3].

In this work, we have studied a relation between toxicity and structure of dibenzofurans by theoretical calculations. Ab initio MO calculations are performed to obtain the electron densities of frontier orbitals, especially, highest occupied molecular orbitals (HOMO) of 136 congeners of dibenzofurans. These HOMO densities are used to perform multivariate statistical analysis to extract the character of dibenzofurans by principal component analysis. In this paper, a systematic number, which correlates with the substitution pattern of congeners, suggested by Ballschmiter et al. [4] is used to identify 136 congeners of dibenzofurans.

2. Methods

Ab initio MO calculations for 135 congeners of chlorinated dibenzofurans and a nonchlorinated dibenzofuran are performed. Fig. 1 shows the frame of the dibenzofuran with the labels. The full-optimized structure of nonchlorinated dibenzofuran is used as dibenzofuran skeleton. For chlorinated dibenzofurans, chlorine atoms are appropriately substituted to dibenzofuran skeleton, where C–Cl distance and C–H distance are fixed to be 1.778 and 1.083 A, respectively. The basis sets are STO-3G. GAUSSIAN 98 program systems [5] are used to obtain the molecular orbitals and electron densities. The program is partly modified to obtain the electron densities of HOMO on each atom. Fig. 2 shows a typical electron density distribution of HOMO of 2,3,4,7,8-pentachlorinated dibenzofuran (P_5CDF). All of these densities are mainly localized on out of plane π orbitals of 12 carbons and an oxygen of

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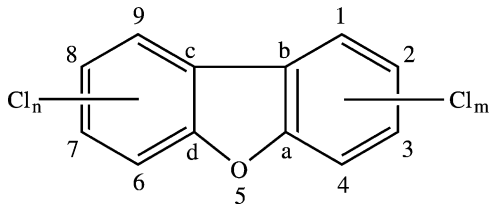
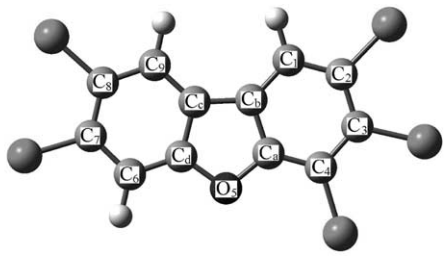


Fig. 1. Structure and labeling of a dibenzofuran molecule. m, $n = 1-4$ for polychlorinated dibenzofuran. m, $n = 0$ for nonchlorinated dibenzofuran.

dibenzofuran skeleton. The skeleton is common for all of 136 congeners of dibenzofurans. So HOMO densities on the 12 carbons and an oxygen can be used as variables for multivariate statistical analysis. However, care is needed to adopt the alignment of the dibenzofuran molecule. For example, 2,3,4,7,8-P_5CDF is the same with 2,3,6,7,8-P_5CDF if we adopt the different alignment rule. For HOMO densities, this means that 13 variables (C_1, C_2, C_3, C_4, C_a, C_b, C_c, C_d, C_6, C_7, C_8, C_9, O_5) are possible to have two different data sets for one dibenzofuran molecule. In multivariate statistical analysis, in order to exclude the arbitrariness from the alignment rule, we use 7 variables ($X_1, X_2, X_3, X_4, X_a, X_b, X_5$) as shown in Fig. 2. Considering the symmetry, 2,3,4,7,8-P_5CDF can have two data sets for variables X_1-X_5. The first is HOMO densities on C_1, C_2, C_3, C_4, C_a, C_b, O_5 and the second is those on C_9, C_8, C_7, C_6, C_d, C_c, O_5. Values of two data sets (#114-1, #114-2) for 2,3,4,7,8- P_5CDF are also shown in Fig. 2. Each of 136 congeners of dibenzofurans has two data sets like 2,3,4,7,8-P_5CDF has. So, there are 272 (136×2) samples. 272 samples $\times$ 7 variables are used to perform principal component analysis (PCA). PCA is one of the useful methods of multivariate statistical analysis to analyze large number of data [6]. A correlation matrix is diagonalized to obtain eigenvalues and eigenvectors in PCA. Several large eigenvalues and their eigenvectors called principal components are used to analyze data. The score of the main principal components are used to extract the character of each dibenzofuran. Each dibenzofuran has two scores for each principal component. We sum these two scores to obtain total score. Each dibenzofuran has one total score for each principal component that is used in further discussion.



	C_1	C_2	C_3	C_4	C_a	C_b	O_5
HOMO densities	0.135	0.015	0.232	0.070	0.094	0.137	0.022

	C_c	C_d	C_6	C_7	C_8	C_9
HOMO densities	0.279	0.230	0.006	0.268	0.154	0.015

	Variable						
Sample	X_1	X_2	X_3	X_4	X_a	X_b	X_5
#114-1	C_1 0.135	C_2 0.015	C_3 0.232	C_4 0.070	C_a 0.094	C_b 0.137	O_5 0.022
#114-2	C_9 0.015	C_8 0.154	C_7 0.268	C_6 0.006	C_d 0.230	C_c 0.279	O_5 0.022

Fig. 2. HOMO densities of 2,3,4,7,8-pentachlorinated dibenzofuran (P_5CDF) (#114) on carbons and an oxygen. Variables and data sets for multivariate statistical analysis are also shown.

3. Results and discussion

Toxicity of dibenzofurans. To estimate the toxicity of dibenzofurans, toxic equivalency factors (TEFs) are useful. TEF is unit to evaluate the intensity of toxicity of dioxin-like compounds based on the toxicity of the most toxic dioxin, 2,3,7,8-T_4CDD, that is taken as 1 unit. Recent TEFs of dibenzofurans for mammals, fish and birds published by World Health Organization (WHO) [7] are summarized in Table 1. These 10 dibenzofurans are thought to be most toxic. One of the most plausible mechanism of the toxic action of dioxins is caused by binding with the Ah (Dioxin) receptor [8]. We should 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 mediated by Ah receptor.

Principal component analysis. Correlation matrix of seven variables in PCA is shown in Table 2. We can see large correlations (>0.8) of X_1-X_4 (0.851), X_1-X_a (-0.914), X_3-X_5 (-0.952) and X_4-X_b (-0.849). As variables X_1-X_5 relate to HOMO densities of dibenzofurans, it means that dibenzofuran which has a large HOMO density on C_1 (C_9) atom tends to have large HOMO

Table 1
Toxic equivalency factors (TEFs) of dibenzofuran congeners

No.	Structure	TEF[a]
114	2,3,4,7,8-P_5CDF	0.5
83	2,3,7,8-T_4CDF	0.1
118	1,2,3,4,7,8-H_6CDF	0.1
121	1,2,3,6,7,8-H_6CDF	0.1
124	1,2,3,7,8,9-H_6CDF	0.1
130	2,3,4,6,7,8-H_6CDF	0.1
94	1,2,3,7,8-P_5CDF	0.05
131	1,2,3,4,6,7,8-H_7CDF	0.01
134	1,2,3,4,7,8,9-H_7CDF	0.01
135	1,2,3,4,6,7,8,9-O_8CDF	0.001

[a] From Ref. [7].

Table 2
Correlation matrix of seven variables in principal component analysis

	X_1	X_2	X_3	X_4	X_a	X_b	X_5
X_1	1.000						
X_2	−0.664	1.000					
X_3	−0.136	−0.436	1.000				
X_4	0.851	−0.230	−0.577	1.000			
X_a	−0.914	0.724	0.244	−0.792	1.000		
X_b	−0.669	0.169	0.767	−0.849	0.740	1.000	
X_5	0.115	0.556	−0.952	0.587	−0.143	−0.689	1.000

densities on C_4 (C_6) and small HOMO densities on C_a (C_d) and C_b (C_c), vice versa. Eigenvalues and coefficients of each principal component are shown in Table 3. There are three principal components whose eigenvalues are larger than 0.1. Cumulative from the first to the third principal components is 0.986. We use the first three principal components (PC1, PC2 and PC3) as main principal components to analyze the data. We can see that variables X_1, X_4, X_a and X_b contribute much to characterize PC1 and variables X_2, X_3 and X_5 characterize PC2. As for PC3, variables X_1, X_2 and X_4 have large coefficients of 0.443, 0.407 and 0.537, respectively.

Principal component scores. To investigate the character of each congener of dibenzofurans we have calculated principal component scores for three main principal components. Principal component score is inner product between the coefficients of the principal component and the standardized data set of each sample. In our method each dibenzofuran congener has two scores for each principal component. We sum these two scores to obtain total scores. Plots of total scores of 136 dibenzofurans for the first principal component (PC1) vs. those for the third principal component (PC3) are shown in Fig. 3 with the positions of the most toxic dibenzofurans (#114, #83 #118, #121, #124, #130, #94, #131, #134 and #135). In this graph, all of the most toxic dibenzofurans have large negative values for PC3 axes forming a group. 1,3,4,7,8-P_5CDF (#108) is also included in the group of toxic dibenzofurans though it is thought to be less toxic as its TEF value is zero. In Table 4, top 15 dibenzofurans of the lowest total scores of the third principal component are shown. All of the most toxic 10 dibenzofurans

Table 3
Eigenvalues and coefficients of the principal component transformation

	PC1	PC2	PC3
Eigenvalue	4.127	2.512	0.265
X_1	−0.408	−0.317	0.443
X_2	0.146	0.586	0.407
X_3	0.323	−0.456	0.370
X_4	−0.471	−0.002	0.537
X_a	0.422	0.302	0.231
X_b	0.468	−0.103	0.390
X_5	−0.298	0.496	0.084

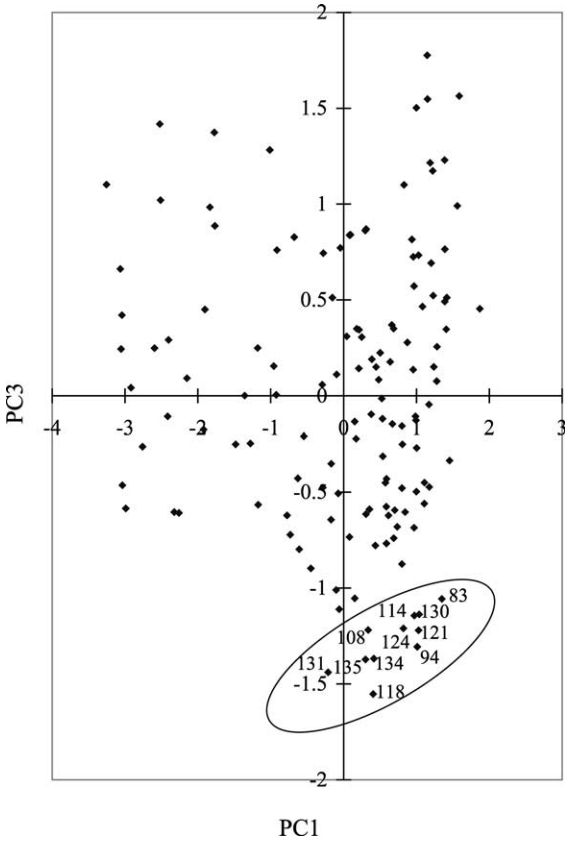


Fig. 3. Principal component analysis on HOMO densities of dibenzofurans. Projection of the total scores on the plane of the first principal component (PC1) vs. the third principal component (PC3). Several dibenzofurans are identified by the numbering in Table 1.

are rank within top 12. 'Non-toxic' 1,3,4,7,8-P_5CDF (#108) is the seventh in the rank. To understand the mechanism of toxic action of dioxin-like compound, analysis of the induction of microsomal aryl hydrocarbon hydroxylase

Table 4
Top 15 of the dibenzofuran congeners which have the lowest values of total scores of the third principal components

Rank	Congener no.	Total scores of PC3
No.1	118	−1.552
No.2	131	−1.439
No.3	135	−1.372
No.4	134	−1.367
No.5	94	−1.306
No.6	121	−1.220
No.7	108	−1.218
No.8	124	−1.210
No.9	114	−1.143
No.10	130	−1.137
No.11	128	−1.110
No.12	83	−1.056
No.13	122	−1.053
No.14	132	−1.010
No.15	100	−0.897

(AHH) activity by dioxin-like compound is useful. From the structure activity relationship, dioxin congeners, which induce AHH activity have two common properties: (1) planer structure; (2) halogen atoms occupy in at least three of the four lateral positions (positions 2, 3, 7, 8). For maximal potency, four halogen atoms in lateral positions [8,9]. For dibenzofurans there is no criteria suggested such as those for toxic dioxins. However, 1,3,4,7,8-P_5CDF (#108) satisfies those properties which toxic dioxins have. Considering 1,3,4,7,8-P_5CDF (#108) is included in the group of most toxic dibenzofurans from our results, we may conclude that 1,3,4,7,8-P_5CDF (#108) could be potentially toxic.

4. Conclusions

136 congeners of dibenzofurans are classified by principal component analysis using HOMO densities as variables. All of the most toxic dibenzofurans are included in the group that has large negative value of the total score for the third principal components. From this criteria, 1,3,4,7,8-P_5CDF are predicted to be potentially toxic. We think such a quantum chemometrical approach is useful to study toxicity of dioxin-like compounds theoretically.

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