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Estimation of Biological Action of Dioxins by Some Geometric Descriptors

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기하학적 변수에 의한 다이옥신의 독성 예측

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ABSTRACT

To effectively predict the lipophilicity, the aryl hydrocarbon receptor (AhR) affinity, and TEF (Toxic equivalency factor) of dioxins by geometrical descriptors, the multiple linear regression methods with the forward selection and backward elimination were employed with statistical validity. The lipophilicity, the Ah receptor binding affinity, and the toxic equivalency factor of dioxins could be predicted using some geometrical descriptors.

Key words : dioxin, QSAR, multiple regression, TEF, lipophilicity

INTRODUCTION

2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) is called simply dioxin, for this is regarded as the reference of halogenated aromatic hydrocarbons (HAH). The dioxin-related compounds, including the 75 chlorinated dibenzo-p-dioxin (CDD) congeners, the 135 polychlorinated dibenzofuran (CDF) congeners, and the 209 PCB congeners, have quite similar structure and represent similar physical and chemical properties, and then are treated as same family. Dioxins are produced as the undesired by-products during the manufacture of herbicide 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) which had used as a defoliant in Vietnam under the names of agent orange, or are currently released to the environment primarily through emissions from the incineration of municipal and chemical wastes and from the improper disposal of certain chlorinated chemical wastes. The routes of potential human exposure to dioxins may occur through consumption of meats and milk, inhalation, cigarette smoke, herbicide manufacture, and PCB-transformer fires.

Many studies have suggested that exposure to dioxin-like compounds is associated with serious health effects such as enzyme disorders, nervous system disorders, and cancer[1]. These compounds are not easily degraded in the environment and their distinct lipophilic character results in bioaccumulation in the food chain and very long half-life in the human tissue.

The toxic and biochemical effects associated with exposure to 2,3,7,8-TCDD are mediated via initial binding to the cytosolic aryl hydrocarbon (Ah) receptor protein. The AhR is a ubiquitous intracellular

receptor and transcriptional activator, and in the absence of ligand, this exists in the unbound form, presumably as the result of its tight association with the heat shock protein HSP 90 in the cytoplasm. The AhR is activated by a number of xenobiotic compounds such as wide spread environmental pollutants. TCDD is the prototypical agonist in the AhR activation[2]. Agonist binding initiates translocation of the receptor complex to the nucleus and concomitantly weakens the AhR-HSP90 association. Within the nucleus, HSP90 is displaced and the AhR dimerized with its partner, the AhR nuclear translocator protein (ARNT), resulting in a basic helix-loop-helix-PAS (bHLH-PAS) dimmer[3]. Binding of this AhR-ARNT heterodimer is capable of binding genomic enhancer elements, known as dioxin-responsive enhancers (DREs) and activating adjacent promoters[4]. This binding to specific cognate dioxin responsive DNA sequences results in the transcriptional activation of specific dioxin-inducible genes such as the drug metabolizing enzymes cytochromes P450 1A1 (aryl hydrocarbon hydoxylase), 1B1 and 1A2[5,6]. These drug metabolizing enzymes are both induced and metabolizing it, leading to highly reactive carcinogenic and mutagenic metabolites. The binding of dioxin to AhR mediates its toxicity and the activation of AhR results in numerous biological actions including altered metabolism and altered growth signaling pathways. The toxic potency of dioxins correlates broadly with their affinity for the Ah receptor, providing a link between toxicity and mechanism of action[7].

Because dioxin-like compounds are similar mode of action through an Ah receptor, these are usually assigned individual toxicity equivalence factor (TEF) values by international convention[8,9]. TEFs are estimates of exposure to dioxin-like compounds in terms of the 2,3,7,8-TCDD toxic equivalents (TEQ). 2,3,7,8-TCDD is assigned a TEF of 1 and generally accepted TEF values are shown in Table 1. Of the 419 dioxin, furan, and PCB congeners, only these 30 are considered to have dioxin like toxicity. The TEQ of a mixture is the summation of multiplying the concentration of individual congeners by their respective TEF. The actual binding affinities of dioxins to the Ah receptor by Safe *et al.*[10] are also reported in Table 1. The ED_{50} is defined as the concentration of the test chemical necessary to reduce specific binding of TCDD to 50% of the maximal value in the absence of the competitor.

Every chemical reaction including pharmacology, toxicology and carcinogenesis is dependent on molecular structure, electronic interaction and thermodynamic conditions of bonding molecules under specific environment. The biological function or properties of a molecule are dependent on the form or structure. Chemical reactivity may be defined as the ability of the molecular structure to take part in the electronic rearrangement processes during chemical interactions. The objective of quantitative structure-activity relationship (QSAR) is to find statistically significant parameters with biological activity from experiments or theory. The relationship between biological activity and molecular parameters is expressed in most general form:

$$\text{Biological activity} = f(\text{physicochemical and/or structural parameters})$$

A good model for a series of molecules may be used to predict similar properties of other molecules. Although this predictive element of QSAR is undoubtedly of exciting interest, the most useful tool is not proved. Hansch showed that for narcosis log P (octanol/water partition coefficient) has excellent correlation ($r = 0.97$, $n = 51$) with the molar concentration (C)[11]. The parameters widely used in QSAR studies include not only partition function coefficient but also geometrical and topological indices (molecular size, surface area, molar volume, molar refractivity), thermodynamic indices (solvation energy), and electronic indices (atomic partial charge, electron negativity, polarizability, dipole moment, electrostatic). Structure-property correlation studies are of interest to look for potential correlations between biological

Table 1. Toxic equivalency factors and observed AhR binding affinity of dioxin-like compounds

No.	Chemical name	No. of halogen	TEF[a]	log $(1/EC_{50})$[b]
1	Dibenzo-p-dioxin	0	0	
2	1-Chlorodibenzo-p-dioxin	1	0	4.000
3	2-Bromodibenzo-p-dioxin	1	0	6.530
4	2-Chlorodibenzo-p-dioxin	1	0	
5	2,3-Dichlorodibenzo-p-dioxi	2	0	
6	2,7-Dibromodibenzo-p-dioxin	2	0	7.810
7	2,7-Dichlorodibenzo-p-dioxin	2	0	
8	2,8-Dichlorodibenzo-p-dioxin	2	0	5.495
9	1,2,4-Trichlorodibenzo-p-dioxin	3	0	4.886
10	2,3,6-Trichlorodibenzo-p-dioxin	3	0	6.658
11	2,3,7-Tribromodibenzo-p-dioxin	3	0	8.932
12	2,3,7-Trichlorodibenzo-p-dioxi	3	0	7.149
13	1,2,3,4-Tetrachlorodibenzo-p-dioxin	4	0	5.886
14	1,2,3,7-Tetrachlorodibenzo-p-dioxin	4	0	
15	1,3,6,8-Tetrachlorodibenzo-p-dioxin	4	0	
16	1,3,7,8-Tetrabromodibenzo-p-dioxin	4	0	8.699
17	1,3,7,8-Tetrachlorodibenzo-p-dioxin	4	0	6.102
18	2,3,6,7-Tetrachlorodibenzo-p-dioxin	4	0	6.796
19	2,3,7,8-Tetrabromodibenzo-p-dioxin	4		8.824
20	2,3,7,8-Tetrachlorodibenzo-p-dioxin	4	1	8.000
21	2,3-Dibromo-7,8-dichlorodibenzo-p-dioxin	4		8.830
22	2,8-Dibromo-3,7-dichlorodibenzo-p-dioxin	4		9.350
23	2-Bromo-3,7,8-trichlorodibenzo-p-dioxin	4		7.939
24	1,2,3,4,7-Pentachlorodibenzo-p-dioxin	5	0	5.194
25	1,2,3,7,8-Pentabromodibenzo-p-dioxin	5		8.180
26	1,2,3,7,8-Pentachlorodibenzo-p-dioxin	5	0.5	7.102
27	1,2,4,7,8-Pentabromodibenzo-p-dioxin	5		7.770
28	1,2,4,7,8-Pentachlorodibenzo-p-dioxin	5	0	5.959
29	1,3,7,8,9-Pentabromodibenzo-p-dioxin	5		7.032
30	1,2,3,4,7,8-Hexachlorodibenzo-p-dioxin	6	0.1	6.553
31	1,2,3,4,6,7,8-Heptachlorodibenzo-p-dioxin	7	0.01	
32	1,2,3,4,6,7,8,9-Octachlorodibenzo-p-dioxin	8	0.001	5.000
33	Dibenzofuran	0	0	
34	2-Chlorodibenzofuran	1	0	3.553
35	3-Chlorodibenzofuran	1	0	4.377
36	4-Chlorodibenzofuran	1	0	3.000
37	2,3-Dichlorodibenzofuran	2	0	5.326
38	2,6-Dichlorodibenzofuran	2	0	3.609
39	2,8-Dichlorodibenzofuran	2	0	3.590
40	1,3,6-Trichlorodibenzofuran	3	0	5.357
41	1,3,8-Trichlorodibenzofuran	3	0	4.071
42	2,3,4-Trichlorodibenzofuran	3	0	4.721
43	2,3,8-Trichlorodibenzofuran	3	0	6.000
44	2,6,7-Trichlorodibenzofuran	3	0	6.347
45	1,2,3,6-Tetrachlorodibenzofuran	4	0	6.456
46	1,2,3,7-Tetrachlorodibenzofuran	4	0	6.959
47	1,2,4,8-Tetrachlorodibenzofuran	4	0	5.000
48	1,3,6,8-Tetrachlorodibenzofuran	4	0	6.658
49	2,3,4,6-Tetrachlorodibenzofuran	4	0	6.456
50	2,3,4,7-Tetrachlorodibenzofuran	4	0	7.602

Table 1. Continued

No.	Chemical name	No. of halogen	TEF[a]	log (1/EC$_{50}$)[b]
51	2,3,4,8-Tetrachlorodibenzofuran	4	0	6.699
52	2,3,6,8-Tetrachlorodibenzofuran	4	0	6.658
53	2,3,7,8-Tetrachlorodibenzofuran	4	0.1	7.387
54	1,2,3,4,8-Pentachlorodibenzofuran	5	0	6.921
55	1,2,3,7,8-Pentachlorodibenzofuran	5	0.05	7.128
56	1,2,3,7,9-Pentachlorodibenzofuran	5	0	6.398
57	1,2,4,6,7-Pentachlorodibenzofuran	5	0	7.169
58	1,2,4,6,8-Pentachlorodibenzofuran	5	0	5.509
59	1,2,4,7,8-Pentachlorodibenzofuran	5	0	5.886
60	1,2,4,7,9-Pentachlorodibenzofuran	5	0	4.699
61	1,3,4,7,8-Pentachlorodibenzofuran	5	0	6.699
62	2,3,4,7,8-Pentachlorodibenzofuran	5	0.5	7.824
63	2,3,4,7,9-Pentachlorodibenzofuran	5	0	6.699
64	1,2,3,4,7,8-Hexachlorodibenzofuran	6	0.01	6.638
65	1,2,3,6,7,8-Hexachlorodibenzofuran	6	0.1	6.569
66	1,2,4,6,7,8-Hexachlorodibenzofuran	6	0	5.081
67	2,3,4,6,7,8-Hexachlorodibenzofuran	6	0.1	7.328
68	1,2,3,4,6,7,8-Heptachlorodibenzofuran	7	0.01	
69	1,2,3,4,7,8,9-Heptachlorodibenzofuran	7		
70	1,2,3,4,6,7,8,9-Octachlorodibenzofuran	8	0.001	

Source : [a]References [12] and [8], [b][10].

and physicochemical data, and to predict of biophysical and physicochemical properties.

The overall objective of this work is to develop effective geometrical descriptors to evaluate the toxicity of dioxins. The specific objectives are to create the efficient model for predicting the lipophilicity, the aryl hydrocarbon receptor (AhR) affinity, and TEF (Toxic equivalency factor) of dioxins using the multiple linear regression methods.

METHODS

The basic structure and numbering of CDD/F congeners is shown Fig. 1. Each hydrogen of the carbon positions numbered 1 to 4 and 6 to 9 can be substituted with halogen atoms. The chlorinated substituents of dioxins and furans are most of environmental interest. The physical and chemical properties of each congener vary according to the degree and position of chlorine substitution.

Quantum mechanical methods[13, 14] describe molecules in terms of explicit interactions between electrons and nuclei. In general, properties like molecular geometry, conformational energies, transition states and reaction paths can be calculated with high accuracy. Their disadvantages relative to molecular mechanics methods are the computational costs, time, and the limitation to the rather small molecules. In this work, to obtain the optimal structure of dioxins, the Parameterization Method Number 3 (PM3) method[15] was employed, which is one of the semiempirical methods used widely in quantum mechanics calculations.

Geometric descriptors are based on bond lengths, bond angles, and dihedral angles of molecules. The atoms are regarded as hard spheres, where the radius is the van der Waals radius. The van der Waals radius is defined in terms of the distance at which the repulsion between electron densities of two approximating atoms balances the attraction forces between them[16]. The van der Waals volume is represented by the volume contained by the surface of the intersection of all the van der Waals spheres in the molecule. The Connolly surface is the envelope traced out by

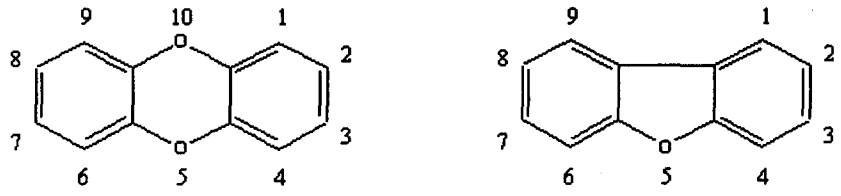

Fig. 1. The general formulas of dioxin and dioxin-like compounds

the point of contact of a defined probe sphere (representing a solvent) and a molecule of interest where they touch once, plus the van der Waals surface of the probe[17]. The solvent-accessible surface then describes the surface traced out by of a probe molecule, e.g., water. The Connolly Accessible Surface Area (CAA, Å^2) is the locus of the center of a probe sphere. The Connolly Molecular Surface Area (CMA, Å^2) is created when a probe sphere is rolled over the molecular shape. The Connolly Solvent-Excluded Volume (CSEV, Å^3) is the volume enclosed by the solvent-accessible surface. Ovality is the ratio of the molecular surface area to the minimum surface area. The minimum surface area is the surface area of a sphere having a volume equal to the Solvent-Excluded Volume of the molecule. The ovality property is computed from the Connolly Molecular Surface Area and Solvent-Excluded Volume properties.

Quantitative structure-activity relationships (QSAR) are mathematical relationships linking chemical structure and its activity in a quantitative manner for a series of compounds. The varieties of statistical methods are used to correlate any molecular property (intrinsic, chemical or biological) to any other property, using statistical regression or pattern recognition techniques. Methods which can be used in QSAR include various regression and pattern recognition techniques. Pearson's correlation coefficient (r) is a measure of linear correlation. Multiple R is the multiple regression analogue of the Pearson's correlation coefficient. R^2, called the coefficient of determination, is a measure of how much of the variation (dependent variable) is account for by knowing the information included in the regression equation. This coefficient, the square of r, is the percent of the variation that can be explained by the regression equation.

Most calculations were carried out on Windows NT 4.0 version in Pentium II-400 PC computer (256 M RAM). Molecular modeling were used for building of the starting compounds, and then energy minimization was performed using the semiempirical PM3 method implemented in Spartan Pro 1.01[18] and Hyperchem 5.01[19]. Geometric descriptors were estimated using Chem3D 4.5[20], MMP 3.0[21], Accumodel[22], Cache 3.11[23], Spartan Pro. The statistical analysis for valid data description was conducted with SPSS for Windows 9.0[24].

RESULTS AND DISCUSSION

The size of a molecule is most basic in a ligand binding. As represented in Table 2, the lengths of the longest axis (X) of dioxin molecules are in the range of 11.2 A (dibenzofuran) to 14.6 A (1,3,7,8,9-pentadibromodibenzo-p-dioxin). For the bromine atom is larger than other atoms including chlorine, the size and the surface area of the bromine-containing dioxin molecules are appeared to be larger. All dioxins except bromine-containing compounds satisfy the size condition to be AhR ligands, suggested by Waller and McKinney[25], which is 12-14 A in length and 5 A in depth. Regardless types of the basis set used in this work, all dioxins display fairly planar structures, and from this fact it may be considered that the ligands of the highest binding affinity with the Ah

Table 2. Geometric (size) descriptors of dioxins

No.	X	Y	Z	SA	V_m	VDWA	CAA	CMA	CSEV	ovality
1	11.4	7.3	3.4	212.2	202.4	95.1	356.1	174.2	137.4	1.353
2	11.7	8.5	3.5	228.8	220.0	105.4	378.1	188.3	151.4	1.370
3	13.2	8.2	3.9	235.6	226.6	110.5	387.8	194.0	157.2	1.377
4	12.8	7.9	3.5	230.3	220.4	105.6	379.7	188.8	151.6	1.374
5	12.4	7.4	3.5	245.9	237.5	114.7	398.8	201.7	165.2	1.385
6	14.7	8.4	3.9	259.1	250.6	125.9	422.3	215.6	178.3	1.407
7	13.9	8.2	3.5	248.4	238.3	116.1	402.9	203.3	165.6	1.394
8	13.5	7.4	3.5	248.4	238.3	116.3	402.9	203.4	165.6	1.394
9	12.7	9.5	3.5	260.9	254.6	123.9	418.8	215.1	179.1	1.400
10	12.7	8.4	3.5	262.5	255.1	124.7	420.4	215.6	179.2	1.403
11	14.5	7.8	3.9	276.8	271.9	138.8	441.7	229.2	194.7	1.411
12	13.7	7.7	3.5	263.9	255.5	125.3	422.0	216.2	179.3	1.406
13	12.4	9.6	3.5	274.0	271.0	131.2	435.7	228.1	194.3	1.406
14	13.9	8.4	3.5	278.0	272.2	133.5	442.0	230.4	194.6	1.418
15	13.5	9.7	3.5	283.8	274.5	135.9	452.1	234.3	196.1	1.435
16	14.3	8.9	3.9	298.0	295.2	153.7	469.8	248.2	414.5	1.433
17	13.5	8.5	3.5	280.5	273.0	135.1	443.4	230.0	193.1	1.423
18	13.9	8.4	3.5	278.0	272.2	133.7	439.6	228.5	192.9	1.416
19	14.4	7.4	3.9	294.4	293.2	151.7	464.2	244.8	212.5	1.421
20	13.5	7.4	3.5	279.5	272.6	134.3	445.6	231.5	195.1	1.423
21	13.9	7.4	3.9	287.0	282.9	143.0	452.7	236.9	202.7	1.420
22	14.3	7.4	3.9	280.0	283.7	143.2	453.9	237.7	203.4	1.421
23	14.1	7.7	3.9	283.7	278.2	138.8	447.5	233.4	198.2	1.420
24	13.7	9.6	3.5	292.1	289.0	141.6	457.0	240.8	206.4	1.430
25	14.6	8.9	3.9	313.6	316.0	163.6	490.4	264.1	234.4	1.436
26	13.7	8.5	3.5	293.6	289.4	142.6	458.7	241.4	206.6	1.429
27	14.6	10.3	3.9	316.2	317.6	165.5	492.3	264.9	233.7	1.443
28	13.7	9.6	3.5	294.6	289.7	143.5	461.1	242.4	206.8	1.434
29	14.6	9.3	3.9	317.2	318.0	164.0	486.1	264.1	235.7	1.431
30	13.5	9.6	3.5	307.6	306.1	150.6	476.0	253.6	220.0	1.439
31	13.7	9.6	3.5	321.7	322.9	158.9	490.0	266.2	234.8	1.447
32	13.5	9.6	3.5	335.7	339.6	166.4	503.7	278.8	249.6	1.454
33	11.2	7.2	3.4	203.5	192.3	90.6	341.3	166.8	131.2	1.336
34	12.0	8.1	3.5	221.6	210.3	101.3	364.6	181.3	145.3	1.356
35	12.3	8.0	3.5	221.5	210.2	101.2	364.5	181.2	145.3	1.356
36	10.9	8.5	3.5	220.9	210.1	101.0	363.8	181.1	145.4	1.354
37	12.3	7.6	3.5	230.1	227.4	110.5	383.5	194.1	159.0	1.368
38	12.0	8.8	3.5	239.0	228.1	111.4	387.0	195.6	159.5	1.375
39	11.9	7.5	3.5	239.6	228.2	111.9	387.8	195.8	159.4	1.377
40	12.1	8.5	3.5	252.5	245.2	119.6	402.8	207.1	173.2	1.378
41	13.1	9.0	3.5	253.2	245.3	119.8	403.5	207.3	173.2	1.380
42	12.4	8.7	3.5	252.0	244.5	118.9	402.0	206.8	172.7	1.379
43	12.9	7.9	3.5	255.1	245.3	121.3	406.8	208.6	173.0	1.389
44	13.2	8.4	3.5	254.6	254.3	120.4	406.1	207.5	173.2	1.388
45	12.0	8.5	3.5	265.5	261.6	127.1	417.8	218.4	186.5	1.383
46	13.4	8.5	3.5	266.1	261.7	127.4	418.4	218.5	186.4	1.385
47	11.9	9.2	3.5	268.1	262.4	128.7	421.9	220.0	186.9	1.392
48	12.8	9.5	3.5	270.6	263.1	129.7	425.9	221.6	187.3	1.400
49	12.3	8.7	3.5	269.5	262.2	129.2	424.4	221.1	186.9	1.399
50	13.5	8.6	3.5	270.1	262.4	129.3	425.1	221.3	186.8	1.400

Table 2. Continued

No.	X	Y	Z	SA	V_m	VDWA	CAA	CMA	CSEV	ovality
51	13.1	8.8	3.5	270.1	262.4	129.7	425.2	221.3	186.8	1.400
52	12.5	8.7	3.5	272.5	263.1	130.9	429.2	222.9	187.2	1.408
53	13.5	7.5	3.5	270.6	262.4	130.0	425.7	221.4	186.7	1.401
54	13.0	9.2	3.5	281.1	278.8	135.9	436.9	231.3	200.2	1.397
55	13.5	8.4	3.5	281.7	278.8	136.7	437.5	231.4	200.1	1.399
56	13.4	8.8	3.5	277.4	277.2	133.4	430.7	228.8	199.2	1.387
57	13.2	9.6	3.5	283.0	279.4	137.3	440.3	232.7	200.7	1.404
58	11.9	9.6	3.5	285.5	280.1	138.7	444.4	234.3	201.1	1.412
59	12.7	9.4	3.5	283.6	279.5	137.8	440.9	232.8	200.6	1.405
60	13.0	9.9	3.5	279.2	277.8	134.8	434.0	230.2	199.7	1.393
61	13.3	9.1	3.5	283.5	279.5	137.9	440.8	232.8	200.6	1.405
62	13.5	8.7	3.5	285.6	279.5	138.6	444.1	234.1	200.5	1.413
63	13.5	9.3	3.5	283.6	279.5	137.3	440.9	232.8	200.6	1.405
64	13.5	9.4	3.5	296.6	295.9	144.8	455.9	244.1	213.8	1.411
65	13.4	8.8	3.5	296.6	295.9	145.1	455.9	244.1	213.9	1.411
66	13.0	9.6	3.5	298.5	296.5	146.2	459.2	245.5	214.3	1.418
67	13.5	8.6	3.5	300.5	296.6	147.1	462.4	246.8	214.2	1.426
68	13.5	9.5	3.5	311.5	312.9	153.4	474.2	256.8	227.6	1.424
69	13.4	9.3	3.5	305.1	310.4	149.1	463.7	252.5	226.1	1.407
70	13.5	9.5	3.5	319.9	327.5	157.4	482.0	265.2	239.9	1.420

Abbreviations: SA, surface area; V_m, molar volume; VDWA, van der Waals area; CAA, Connolly accessible area; CMA, Connolly molecular area; CSEV, Connolly solvent-excluded volume.

Table 3. The correlation coefficients among geometrical descriptors

	X	Y	Z	SA	V_m	VDWA	CAA	CMA	CSEV	ovality
Y	−0.10									
Z	0.64	−0.20								
SA	0.66	0.45	0.27							
V_m	0.66	0.45	0.28	1.00						
VDWA	0.71	0.40	0.40	0.99	0.99					
CAA	0.71	0.40	0.36	0.99	0.99	0.99				
CMA	0.67	0.44	0.32	1.00	1.00	0.99	1.00			
CSEV	0.53	0.31	0.38	0.71	0.71	0.74	0.72	0.72		
Ovality	0.73	0.30	0.36	0.93	0.91	0.92	0.96	0.93	0.68	
EC_{50}	0.79	−0.20	0.60	0.55	0.55	0.61	0.61	0.57	0.49	0.61

receptor have planar structures [26].

In Table 3, the correlation coefficients among geometrical descriptors are represented to grasp out the relationships of each descriptor. The surface area (SA) has high correlation with molar volume (V_m, r = 1.00), van der Waals area (VDWA, r = 0.99), Connolly accessible area (CAA, r = 0.99), Connolly molecular area (CMA, r = 1.00), Connolly solvent-excluded vol-ume (CSEV, r = 0.71), and ovality (r = 0.93). The AhR binding affinity also is in relatively high correlation with the length of ligand molecule (r = 0.79), comparable to VDWA, CAA, and ovality (the same as r = 0.61). From these correlations, it is inferred that the size effect of dioxins plays a critical role in binding with the Ah receptor.

The lipophilicity of dioxins is depicted in terms of geometrical and topological descriptors using a multiple regression equation by the backward elimina-

tion procedure

$\text{Log } P = 13.200 + 0.417*X - 5.370*Z + 0.025*V_m$

($R = 0.810$, $R^2 = 0.657$, and adjusted $R^2 = 0.612$)

It is well known that there exist strong relationships among water solubilities or partition coefficients and various size parameters of hydrophobic solutes[27]. Cramer[28] points out that the hydration of hydrophobic solutes as well as their solvation in octanol are obviously more complex processes than are reflected by the partition coefficient.

A highly significant linear relationship between EC_{50} and some geometrical and topological descriptors is presented as the results of multiple backward regression

$EC_{50} = 78.178 + 0.540*X - 0.647*Y + 0.306*CAA - 0.327*CMA - 93.957*\text{ovality}$

($R = 0.872$, $R^2 = 0.760$, and adjusted $R^2 = 0.737$)

The following equation may be used to predict the TEF value for other dioxins. This multiple regression was created according to the backward elimination procedure.

$TEF = -1.045 - 0.047*X - 0.125*Y - 0.019*VDWA + 0.012*CAA$

($R = 0.521$, $R^2 = 0.271$, and adjusted $R^2 = 0.220$)

CONCLUSIONS

To get the optimal geometries of dioxins, geometry optimization for dioxins were performed using semi-empirical method by PM3, and this calculation results were in accord with the crystallographic data.

The efficient models for predicting the lipophilicity, the AhR affinity, and TEF (Toxic equivalency factor) of dioxins could be presented using some geometrical and tolpological descriptors. The lipophilicity of dioxins could be estimated using a multiple regression equation by the backward elimination procedure; $\text{Log } P = +13.200 + 0.417*X - 5.370*Z + 0.025*V_m$ ($R = +0.810$, $R^2 = 0.657$, and adjusted $R^2 = 0.612$). A highly significant linear relationship between EC_{50} and some geometrical and topological descriptors is presented as the results of multiple backward regression; $EC_{50} = 78.178 + 0.540*X - 0.647*Y + 0.306*CAA - 0.327*CMA - 93.957*\text{ovality}$ ($R = 0.872$, $R^2 = 0.760$, and adjusted $R^2 = 0.737$). To predict the TEF value for dioxins, the following multiple regression was created using the backward elimination procedure. $TEF = -1.045 - 0.047*X - 0.125*Y - 0.019*VDWA + 0.012*CAA$ ($R = 0.521$, $R^2 = 0.271$, and adjusted $R^2 = 0.220$).

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