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Relationship Between Specific Molecular Connectivity Indices and Teratogenicity, Carcinogenicity, and Mutagenicity of Chlorinated Benzenes and a Biphenyl

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The molecular connectivity value which is a measure of extent of molecular branching, increases with increasing molecular size. Therefore, to evaluate the structural information of molecular connectivity more pertinently, we introduced a concept of specific molecular connectivity which was the ratio of the molecular connectivity index to an information concerning the molecular size. Two specific molecular connectivity indices have been used in our studies: The zero-order specific molecular connectivity which is obtained by dividing the zero-order molecular connectivity index (Sabljić 1983) with the number of non-hydrogen atoms in a molecule, and the second-order specific molecular connectivity which is obtained by dividing the second-order molecular connectivity index (Kier and Hall 1977) with the number of molecular fragments consisting of three adjacent and consecutive non-hydrogen atoms. In this report we calculate the zero-order and second-order specific molecular connectivity values of various chlorinated benzenes and a polychlorinated biphenyl, and examine the relationships between these values and their mutagenic, carcinogenic and teratogenic potentials and toxic effects as reported in the literature.

MATERIALS AND METHODS

The zero-order molecular connectivity index, $^0\chi$, was calculated in the following fashion (Sabljić 1983). Each non-hydrogen atom in a molecule is described by its delta value, δ, which is equal to the number of adjacent non-hydrogen atoms. The index is then calculated for each compound according to the expression:

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$$^{0}\chi=\sum_{j=1}^{n}(\delta_j)^{-0.5}$$

where "n" is the number of non-hydrogen atoms in a molecule. The zero-order specific molecular connectivity index is expressed as $^{0}\chi/n$.

The second-order molecular connectivity index, $^{2}\chi$, refers to molecular fragments consisting of three adjacent and consecutive non-hydrogen atoms (i,j and k)(Kier and Hall 1977). The value of c_{ijk} is computed as the reciprocal square root of the product of the delta values, $(\delta_i \delta_j \delta_k)^{-0.5}$. These c_{ijk} values are then summed by considering all molecular fragments in the molecule. The summarizing expression becomes

$$^{2}\chi=\sum c_{ijk}=\sum_{s}(\delta_i \delta_j \delta_k)_s^{-0.5}$$

where "s" is the number of molecular fragments consisting of three adjacent and consecutive non-hydrogen atoms in a molecule. The second-order specific molecular connectivity index is expressed as $^{2}\chi/s$.

RESULTS AND DISCUSSION

We previously calculated the zero-order specific molecular connectivity values of representative pesticides and related compounds and found that carbaryl had very low value as compared with other pesticides (Murakami and Fukami 1985). Since there is increasing concern over the reported teratogenic effects of this compound in mammals (Fischbein 1976), we examined the relationships between the zero- and second-order specific molecular connectivity indices and mutagenicity, carcinogenicity and teratogenicity of carbaryl and other carbamate pesticides as reported in the literature (Woo 1983). It was demonstrated that carbaryl and benomyl had the lowest zero- and second-order specific molecular connectivity indices among the carbamates examined (Murakami and Fukami 1986). These two chemicals have positive evidence for teratogenicity (Woo 1983). In the present study the validity of this specific molecular connectivity-teratogenicity relationship found in carbamate pesticides is examined for organochlorine compounds.

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Table 1. Zero- and second-order specific molecular connectivity indices and the data on mutagenicity, carcinogenicity, teratogenicity and acute toxicity of chlorinated benzenes and a biphenyl[a]

Compound	$^0\chi$	$^0\chi/n$	$^2\chi$	$^2\chi/s$	Mutagenicity		Carcino-genicity		Terato-genicity		LD_{50}[c]
					Ames	Other tests[b]	Rat	Mouse	Rat	Mouse	(mg/kg)
Hexachlorobenzene	9.464	0.789	5.155	0.286	-	-	+	+		+	32
3,4,5,3',4',5'-Hexachlorobiphenyl	13.448	0.747	8.090	0.289					+	+	0.5[d]
Pentachlorobenzene	8.594	0.781	4.767	0.298					+		940
1,2,4-Trichlorobenzene	6.854	0.762	3.873	0.323					n.t.	n.t.	756
1,2-Dichlorobenzene	5.983	0.748	3.239	0.324	-	-,+	-	-			1516
1,4-Dichlorobenzene	5.983	0.748	3.365	0.337	-	n.t.	-	-			1625
Monochlorobenzene	5.113	0.730	2.743	0.343	-	-,+	+	-	n.t.	n.t.	2190

a Mutagenic, carcinogenic and teratogenic potencies: +, active; -, inactive; n.t., not tested. A blank space indicates that these activities have not been reported. Mutagenic, carcinogenic and teratogenic potencies and LD_{50} values are quoted from a recent review article (Lai 1984).

b The tests include mutagenicity assays using microbial and mammalian test systems and assays at the cellular and molecular levels except the Ames test (Lai 1984). The results obtained by using various methods are different in some cases.

c Per oral acute LD_{50} data for rats.

d Per oral acute LD_{50} data for guinea pigs.

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