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Quantitative Structure-Toxicity Relationship of Chlorinated Compounds: A Molecular Connectivity Investigation

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An estimated 70 000 chemical compounds are currently in common use and their number grows by about 1000 each year. Because potential risk is present for each synthesized chemical, their toxicity testing is required. In addition, water is polluted by chlorinated compounds from industrial discharges, from agricultural use of pesticides, and from water chlorination in large cooling systems (e.g. nuclear reactors). Almost all these compounds are highly toxic (MÜLLER 1976) and some of them are known or suspected carcinogens (TOMATIS et al. 1978). Because of their widespread use, persistence, concentration in food chains, and toxicological properties, they constitute a major group of potential environmental hazards to living species, including man. Thus, there is a need for a simple and accurate method for the preliminary estimation and ranking of the potentially hazardous chemicals, which will enable us to create an adequate priority list for testing them. Several physico-chemical properties have been found to correlate satisfactory with various acute toxicity parameters and thus far the octanol/water partition coefficient is the most successful (KÖNEMANN 1981).

Here, an alternative approach for toxicity prediction of chlorinated compounds will be presented. Its simple applicability and purely nonempirical nature make this method preferable to physico-chemical properties, which necessitate experimental determinations and/or reference tables. The method is known as molecular connectivity. It is based on molecular topology. Several extensive reviews (BALABAN et al. 1980, SABLJIĆ & TRINAJSTIĆ 1981, TRINAJSTIĆ 1982) on the theory and calculation of topological indices, as well as their application in structure-property and structure--activity relationships, have been published recently, which can be consulted for a detail description. Molecular connectivity indices have been found to correlate with toxic effects of alcohols and their derivatives (KIER & HALL 1982) and with the toxicity of selected nitrogenous heterocyclic compounds (SCHULTZ et al. 1982). This work presents our continuous interest in the fate and behaviour of chlorinated compounds in the environment and in the applicability of the topological indices in ecotoxicological studies (SABLJIC & PROTIC 1982). The acute toxicity data used in this study are from the work of HEITMULLER et al. (1981). These data were obtained under uniform conditions, using methods recommended by the U.S. EPA.

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In addition, the number of studied compounds and their structural variety alow us to make a meaningful quantitative structure-activity relationship (QSAR) study.

TOXICITY DATA AND METHOD OF CALCULATION

Marine toxicity tests (HEITMULLER et al. 1981) were conducted with sheepshead minnows, Cyprinodon variegatus. Mortality was recorded at 24, 48, 72, and 96 hours and their LC_{50}'s were calculated. In addition, the highest concentration of the studied chemicals which had no apparent effect on sheepshead minnows was measured. The toxicity parameters used in our QSAR study are defined as the negative logarithms of the LC_{50}'s or the concentration that produced no effect on the tested population of sheepshead minnows.

The zero-order molecular connectivity index, $^{0}\chi$, was introduced by RANDIĆ (1975). It is calculated in the following fashion. 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 than calculated for each compound according to the expression:

$$^{0}\chi = \sum_{i=1}^{n}(\delta_i)^{-0.5}$$

where "n" is the number of non-hydrogen atoms in a molecule.

Regression analyses were performed using a statistical analysis system (SAS). To test the quality of the regression equations, the following statistical parametres were used: correlation coefficient (r), the standard error of the estimate (s), and the amount of explained variance (EV). All calculations were carried out on a DECsystem10 computer at the National Institutes of Health.

RESULTS AND DISCUSSION

The chlorinated compounds examined in the present QSAR study are shown in Table 1 together with their toxicity parameters and zero-order molecular connectivity indices.

Single variable regression equations were calculated for zero-, first-, and second-order molecular connectivity indices. The best one-variable equations were obtained for the zero-order molecular connectivity index, $^{0}\chi$,

$$\log(1/C)(\text{no effect}) = 0.52(\pm 0.04)\cdot {}^{0}\chi - 1.75(\pm 0.28) \qquad (1)$$

N = 19 r = 0.94 s = 0.34 EV = 0.88

$$\log(1/C)(96h) = 0.50(\pm 0.05)\cdot {}^{0}\chi - 1.90(\pm 0.33) \qquad (2)$$

N = 19 r = 0.92 s = 0.37 EV = 0.84

$$\log(1/C)(72h) = 0.51(\pm 0.06)\cdot {}^{0}\chi - 1.98(\pm 0.35) \qquad (3)$$

N = 16 r = 0.93 s = 0.37 EV = 0.86

where N is a number of chlorinated compounds used in the regression analysis. Equations 1, 2 and 3 account for 88%, 84% and 86% of the variation in toxicity data, respectively. The 95% confidence intervals are shown in parentheses. Valence zero-, first-, and second-order molecular connectivity indices were also tested in one-variable equations, but were found to be less successful.

Table 1. Toxicity parameters and zero-order molecular connectivity indices

Compound	log(1/C)[a] no effect	log(1/C)[a] 96 h	log(1/C)[a] 72 h	$^0\chi$
Chlorobenzene	1.26	1.05	-	5.11
1,2-Dichlorobenzene	-	1.18	1.18	5.98
1,3-Dichlorobenzene	1.54	1.28	1.26	5.98
1,4-Dichlorobenzene	1.42	1.30	1.30	5.98
1,2,4-Trichlorobenzene	1.08	0.94	< 0.59	6.85
1,2,3,5-Tetrachlorobenzene	2.33	1.77	1.66	7.72
1,2,4,5-Tetrachlorobenzene	2.86	2.43	2.43	7.72
Pentachlorobenzene	2.92	2.50	1.40-1.89	8.59
1,2-Dichloroethane	-0.12	b	b	3.41
1,1,1-Trichloroethane	0.49	0.27	0.27	4.50
1,1,2,2-Tetrachloroethane	>1.28	1.15	1.11	5.15
Pentachloroethane	0.83	0.24	0.23	6.08
Hexachloroethane	2.37	2.00	1.99	7.00
1,3-Dichloropropane	0.43	0.11	0.11	4.12
Dichloromethane	-0.18	-0.59	-0.63	2.71
1-Chloronaphthalene	2.13	1.83	1.83	7.68
4-Chlorophenol	1.60	1.38	1.38	5.98
2,4,5-Trichlorophenol	2.30	2.07	2.07	7.72
2,3,5,6-Tetrachlorophenol	2.37	2.09	2.06	8.59
1,1-Dichloroethylene	0.08	-0.41	-0.41	3.58
Tetrachloroethylene	0.76	0.50-0.76	-	5.15

[a] Concentration in mmol/l; [b] (-0.37)-(-0.12)

It is not surprising that the derived equations do not account for more than 84-88% of the variation in toxicity data since accuracy of those data is low. The purity of the chemicals tested ranged down to 80%, which also influenced the quality of the toxicity data. In addition, the range of experimental data is only 3.2 logarithmic units. Both of these factors tend to make better correlations difficult to obtain.

Several chlorinated compounds were chosen to test the predictive ability of the above equations. Their toxicity data have been determined only semiquantitatively, thus they could not have been included in regression analyses. The results of the test are presented in Table 2. The molecular connectivity method was very accurate in predicting the toxicity data, especially when we remember the low precision of the measured values.

The present results and the results of other investigators

working in the field of quantitative structure-toxicity relationships are encuraging and may be a useful beginning of the development of a general theoretical method for predicting acute toxicity parameters. Our future plans are to examine various classes of organic pesticides using different topological indices as structural descriptors.

Table 2. Comparison of observed and calculated toxicity parameters for chlorinated compounds

Compound	$\log(1/C)_{obs}$	$\log(1/C)_{calc}$	test
1,1,2,2-Tetrachloroethane	> 1.28	0.93	no effect
1,2-Dichloroethane	(-0.37)-(-0.12)	-0.19	96 h
Tetrachloroethylene	0.50 - 0.76	0.67	96 h
1,2,4-Trichlorobenzene	< 0.59	1.50	72 h
Pentachlorobenzene	1.40 - 1.89	2.40	72 h
1,2-Dichloroethane	(-0.37)-(-0.12)	-0.24	72 h

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