Bull. Environ. Contam. Toxicol. (1997) 58:299-304

Environmental Contamination and Toxicology

Quantitative Structure-Activity Relationship Study for Toxicity of Organotin Compounds on Algae

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Received: 29 April 1996/Accepted: 10 September 1996

Organotin compounds $R_mSn X_{4-m}$(R are groups attached to Sn with C–Sn bonds, X with non C–Sn bonds) are a series of most extensively–used organometallic compounds. Recently, there have been many reports on the pollution of different organotins, including their degradation and methylation products, in different aquatic ecosystems worldwide, especially in harbors with heavy shipping traffic (Maguire 1991; Dai Shugui et al. 1993).

It has long been known that the toxicity of organotins varies greatly with their structures. Generally, triorganotins are much more toxic than the corresponding di– and mono–organotins. Within the unitary substituent series, organotins with different substitutent groups cause different levels of toxicity (Van Der Kerk and Kujjen 1954; Smith et al. 1979). However, attempts to set up quantitative structure activity relationship (QSAR) for organotins were initiated recently (Laughlin 1987; Nagase et al. 1991; Vighi and Calamari 1985). According to the results of the few studies published, the critical controlling factors of the toxicity of organotins are still a contention.

The inhibition effects of different kinds of organotins on the growth of two green algae *Scenedesmus obliquus* and *Platymonas sp.,* were studied in our laboratory earlier (Huang Guolan et al. 1996 *in press).* For both algae, the 96–hr EC_{50} values of the twelve R_mSnCl_{4-m} varied from 10 to 10^{-3} μmol/L, covering four orders of magnitude. In this paper, QSAR studies were carried out for these toxicity values using eight physicochemical and topological parameters as structural descriptors. To distinguish their structural features as organometallic compounds, two newly-corrected molecular connectivity indices (MCIs), radius–corrected MCI $^1\chi^r$ and bond–length–corrected MCI $^1\chi^b$, which have been proven to be more suitable for the structure expression of organometallic compounds than other MCIs (Kupchik 1986), were used in this study. The toxicity mechanism of organotins was proposed based on the QSAR equations.

MATERIALS AND METHODS

Eight structural parameters were used in this QSAR study. Simple MCI $^1\chi$ and valence MCI $^1\chi^v$: $^1\chi$ and $^1\chi^v$ values of organotins were calculated based on hydrogen–suppressed graphs as the following equations (Kier and Hall 1977).

$$^1\chi = \sum (\delta_i\delta_j)^{-\frac{1}{2}} \quad (1)$$

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$$^{1}\chi^{v} = \sum (\delta_i \delta_j)^{-\frac{1}{2}} \quad (2)$$

$$\delta^{v} = (Z^{v} - h)/(Z - Z^{v} - 1) \quad (3)$$

where δ is the delta value for each atom; it is equal to the number of non–hydrogen atoms attached to the atom studied. δ^{v} is the valence delta value. Z^{v}, Z and h are the number of valence electrons, atomic number, and the number of hydrogen atoms, respectively.

Radius–corrected MCI $^{1}\chi^{r}$ and bond–length–corrected MCI $^{1}\chi^{b}$: Valence MCI $^{1}\chi^{v}$ is a corrected pattern for $^{1}\chi$ to distinguish the contributions of heteroatoms and unsaturation to MCI. However, it has been proven to be not **valid for organometallic compounds. Two new MCIs, $^{1}\chi^{r}$ and $^{1}\chi^{b}$, were used** in this study and can be calculated as follows:

$$^{1}\chi^{r} = \sum (\delta_i \ \delta_j)^{-\frac{1}{2}} \quad (4)$$

$$\delta^{r} = r_c / r(Z^{v} - h) \quad (5)$$

$$^{1}\chi^{b} = \sum b(\delta_i \ \delta_j)^{-\frac{1}{2}} \quad (6)$$

where r_C and r are covalent radii of C atom and the atom studied, respectively. For Sn atom, $r_C/r = 0.77/1.40 = 0.55$. b is bond length ratio of the chemical bond studied to C–C bond. For C–Sn b = 2.17/1.54 = 1.41. The meaning of Z, Z^{v} and h is the same as described above.

Electronic parameters—Taft constant σ^{*} and ionization constant σ^{φ} derived from organophosphorus acids (Mastryukova and Kabachnik 1971): **σ^{*} and σ^{φ} values for organotins were the sum of those values of the** substituent groups attached to the Sn atom (Hansch and Leo 1979) .

Lipophilic parameters—total surface area of a molecule TSA and Hansch **constant $\prod$: TSA and $\prod$ values for organotins were the sum of those values** of the substituent groups attached to the Sn atom (Hansch and Leo 1979; Craig 1986).

RESULTS AND DISCUSSION

The eight parameters and 96–hr EC_{50} values for the twelve organotins are listed in Table 1. Simple linear correlation relationships were analyzed in the relationship between each structural parameter as an independent variable **and lnT ($\ln T = \ln 1/EC_{50}$) as a dependent variable (Table 2). Of the eight parameters, $\prod$, TSA and $^{1}\chi^{v}$, which represent the lipophilicity of organotins,** have good correlation with the lnT. Hence, the toxicity of organotins is determined mainly by the lipophilicity of the compound. This conclusion is in accordance with that of Laughlin (1987) who used zoeae of the mud crab, *Rhithropanopeus harrisi,* as the toxicity test animal. The two newly–introduced **MCIs, $^{1}\chi^{b}$ and $^{1}\chi^{r}$, are better corrected with the toxicity than $^{1}\chi$ and $^{1}\chi^{v}$. Therefore, the application of the two newly–corrected MCIs, $^{1}\chi^{b}$ and especially $^{1}\chi^{r}$, to the QSAR studies of organotins was successful. Electronic parameters σ^{*} and σ^{φ} were poorly corrected with the toxicity. However, the conclusion that σ^{*} and σ^{φ} had no relationship to the toxicity of organotins** can not be achieved just on this point. The different influences of lipophilicity and electronic property of organotins on their toxicity should be further studied. To illustrate this, QSAR studies were made within the unitary substituent series (R_3Sn, R_2Sn, RSn individually, Table 3).

Table 1. 96-hr EC_{50} values on the two algae and structural parameters of the twelve organotins (R_mSnCl_{4-m}).

Compound	96 hr EC_{50} μmol / L		TSA	∏	$^1\chi$	$^1\chi^v$	$^1\chi^b$	$^1\chi^r$	σ^φ	σ^*
	S. obliquus	*Platymonas sp.*								
Me_3SnCl	4.03×10^{-1}	8.26×10^{-1}	143.4	2.39	2.000	13.865	2.890	2.392	−1.15	2.96
Pr_3SnCl	1.94×10^{-2}	1.04×10^{-2}	268.5	5.36	5.182	14.539	5.892	5.341	−2.61	2.62
Bu_3SnCl	4.89×10^{-3}	2.61×10^{-3}	331.5	7.10	6.682	16.039	7.392	6.841	−2.73	2.57
$Cy_2MeSnCl$	7.09×10^{-2}	6.32×10^{-2}	313.8	6.29	7.210	16.663	7.927	7.375	−2.41	2.66
Ph_3SnCl	2.21×10^{-2}	5.31×10^{-3}	322.2	6.59	9.826	14.566	9.623	7.032	−0.51	4.76
Me_2SnCl_2	6.67	8.33	138.2	2.54	2.000	14.314	2.961	1.926	−0.06	5.92
Et_2SnCl_2	1.61	5.26	183.7	3.46	3.121	13.763	3.963	2.946	−0.34	5.72
Bu_2SnCl_2	2.64×10^{-1}	2.53×10^{-1}	263.7	5.68	5.121	15.763	5.963	4.946	−0.58	5.66
Ph_2SnCl_2	4.15×10^{-1}	2.10×10^{-1}	257.5	5.34	7.210	14.781	7.450	5.074	0.90	7.12
$MeSnCl_3$	1.33	1.79	133.2	2.69	2.000	14.763	3.033	1.541	1.83	8.88
$BuSnCl_3$	3.36×10^{-1}	3.23×10^{-1}	195.9	4.26	3.561	15.487	4.533	3.051	1.57	8.75
$PhSnCl_3$	7.20×10^{-1}	4.46×10^{-1}	192.8	4.09	4.605	14.996	5.277	3.115	2.31	9.48

Table 2. Simple linear regression equations and correlation coefficients between ln T (T= $1/EC_{50}$) and each structural parameter for the twelve organotins.

Structural parameter	lnT = a + b(parameter)					
	S. obliquus			*Platymonas sp.*		
	a	b	r	a	b	r
$\prod$	−3.55	1.08	0.85	−4.92	1.40	0.88
TSA	−4.15	0.03	0.86	−5.66	0.03	0.88
$^1\chi^r$	−2.17	0.85	0.84	−3.10	1.09	0.86
$^1\chi^v$	−15.22	1.12	0.47	−19.35	1.40	0.47
$^1\chi^b$	−2.46	0.70	0.74	−3.81	0.96	0.81
$^1\chi$	−1.47	0.60	0.72	−2.50	0.83	0.79
σ^*	4.29	−0.50	0.62	4.64	−0.55	0.54
$\sigma^\#$	1.21	−0.80	0.66	1.28	−0.88	0.58

Table 3. Correlation coefficient values(r) of the simple linear regression equations between lnT (T = 1 / EC_{50}) and each structural parameter for unitary and mixed substituent organotins.

Organism	Compound	Number	Correlation coefficient r				
			$\prod$	TSA	$^1\chi^r$	σ^*	$\sigma^\#$
S. obliquus	R_3Sn	unitary 5	0.86	0.82	0.71	0.01	0.44
	R_2Sn	unitary 4	0.99	0.99	0.98	0.28	0.03
	RSn	unitary 3	0.88	0.86	0.81	0.23	0.40
	R_3Sn+ R_2Sn+RSn	mixed 12	0.85	0.86	0.84	0.62	0.66
Platymonas sp.	R_3Sn	unitary 5	0.88	0.86	0.76	0.21	0.27
	R_2Sn	unitary 4	0.98	0.97	0.98	0.50	0.34
	RSn	unitary 3	0.93	0.91	0.87	0.12	0.30
	R_3Sn+ R_2Sn+RSn	mixed 12	0.88	0.88	0.86	0.54	0.58

It can be seen that, for both algae, lipophilic parameters always had better correlation with the toxicity for the unitary substituent series than that for the mixed substituent series (R_3Sn+R_2Sn+RSn, together), whereas the opposite held true for electronic parameters. Hence, electronic properties may be related to the difference of the toxicity between the different substituent series. Multiparametric correlation studies are necessary. Triparametric approaches have been studied, and found to be not reasonable because of the colinearity between the parameters of lipophilicity and MCIs. The results of some diparametric approaches are shown in Table 4.

Table 4. Diparametric regression equations between lnT (T= 1 / EC_{50}) and structural parameters for the twelve organotins.

Organism	Equation	a	b_1	b_2	r	F
S. obliquus	$lnT = a+b_1\prod+b_2\sigma^*$	−1.28	0.91	−0.26	0.89	17.91
	$lnT = a+b_1TSA+b_2\sigma^*$	−2.28	0.02	−0.19	0.88	16.04
	$lnT = a+b_1\ ^1\chi^r+b_2\sigma^*$	−0.79	0.73	−0.16	0.86	12.39
Platymonas sp.	$lnT = a+b_1\prod+b_2\sigma^*$	−3.09	1.26	−0.21	0.90	18.51
	$lnT = a+b_1TSA+b_2\sigma^*$	−4.57	0.03	−0.11	0.89	17.03
	$lnT = a+b_1\ ^1\chi^r+b_2\sigma^*$	−2.60	1.05	−0.06	0.86	13.26

The correlation relationship between lnT and the two independent variables $\prod$ and σ^* was the best of the diparametric approaches (equations 7 and 8). For the two algae, both the correlation equations and the coefficients before each parameter were significant in statistic tests ($F_{0.05} = 4.256$; $t_{0.10} = 1.383$).

Scenedesmus obliquus:

$$lnT = -1.284 + 0.905\prod - 0.260\sigma^* \quad (7)$$
$$r = 0.8940 \quad F = 17.913 \quad t(\prod) = 4.320 \quad t(\sigma^*) = 1.940$$

Platymonas sp.:

$$lnT = -3.902 + 1.256\prod - 0.212\sigma^* \quad (8)$$
$$r = 0.8968 \quad F = 18.511 \quad t(\prod) = 4.859 \quad t(\sigma^*) = 2.278$$

According to the t values of the $\prod$ and σ^*, the toxicity of organotins is controlled mainly by $\prod$, lipophilicity of the compound, and to a small extent by σ^*, electronic property. The toxicity of organotins increases with $\prod$ value. The larger $\prod$ is, the more lipophilic the compound is, and the easier it is for the compound to concentrate from a polar aquatic environment into algae, hence the more toxic the compound is. On the contary, the toxicity of organotins decreases with the increasing σ^*. Taft constant σ^* is a constant to measure the polarizing effect of a substituent group on a reaction center. Groups with small σ^* have a tendency to give electrons to the reaction center, and decrease the positive charge of the center. In hard and soft acids and bases principle (Pearson 1968 a, b), metals react as electron–pair acceptors (Lewis acids) with electron–pair donors (Lewis bases). Metals with low polarizability, low electronegativity, large positive charge density belong to hard acids, whereas the opposite holds true for soft acids. As a general rule it was found that hard acceptors prefer to bind to hard donors and soft acceptors prefer to bind to soft donors to form stable compounds. According to this, it is not difficult to reach the conclusion (Forstner and Wittmann 1979) that metals such as Na, K, Mg and Ca which belong to hard acids only form stable bonds to hard bases such as H_2O, OH^-, and Cl^-, and to be stable in natural environment and less toxic. Metals such as Hg, As and Pb which belong to soft acids form stable bonds to soft bases such as –SH group, which is amongst many active sites of proteins and enzymes, and to be highly toxic. Sn^{4+} is situated between the typical hard acids and typical soft acids. Hence, groups which tend to turn Sn 'softer' will increase its toxicity. It has been concluded above that groups with small σ^* have a tendency to give electrons to the centric Sn atom, and decrease the positive charge density of the Sn atom, and accordingly, turn Sn to be a 'softer' acid. This is why the toxicity of organotins decreases with the increasing σ^*.

Acknowledgment. This study was supported by the National Nature Science Foundation of China. Grant No. 29290600

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