Journal of Environmental Sciences Vol.14, No.4, pp.552—557, 2002

ISSN 1001—0742
CN11—2629/X

Article ID: 1001-0742(2002)04-0552-06 **CLC number**: X131 **Document code**: A

Comparative study of four QSAR models of aromatic compounds to aquatic organisms

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Abstract: Quantitative structure-activity relationships (QSARs) were developed for 43 aromatic compounds toxicity to *Photobacterium phosphoreum* and *Daphnia magna* based on four methods: octanol/water partition coefficient, linear solvation energy relationship, molecular connectivity index and group contribution. Through the evaluation of four QSAR methods, LSER was proved to be the best. And it applied to the widest range of chemicals with the greatest accuracy.

Keywords: aromatic compounds; *Photobacterium phosphoreum*; *Daphnia magna*; QSAR models

Introduction

Quantitative structure-activity relationships (QSARs) can provide correlations between eco-toxicological properties and physico-chemical descriptors of a chemical. With the fast development of industry and agriculture, a huge number of chemicals were discharged into the ecological environment. Most of the chemicals present a direct or indirect toxic harm to human and other organisms. It is impossible to measure the toxicities of all the chemicals one by one because time and fund are limited. Therefore, it is especially important to establish and develop QSAR models of chemicals. We can estimate the toxicities of chemicals with the QSAR models based on their easily measured or calculated characteristics. And the application of QSAR models can provide scientific basis for the risk assessments of chemicals.

At present, there are four primary QSAR methods in common use (Blum, 1990; 1991; Zhao, 1997; Lyman, 1982): octanol/water partition coefficient ($\lg P$); linear solvation energy relationship (LSER); molecular connectivity index, and molecular group contribution (Free-Wilson).

Octanol/water partition coefficient is one of the most important physico-chemical descriptors in the toxicology study. It is equilibrium constant. And it is generally presented in logarithmic form ($\lg P$) in QSAR models because the logarithm is linear with the free energy. $\lg P$ describes the partition of a chemical between in organic solvent and in water. The lipophilic aptitude of a chemical increased with increasing $\lg P$. The linear relationship between $\lg P$ and the nonreactive toxicity of an organic chemical is very satisfactory (Blum, 1990).

LSER method was developed by Kamlet, Taft, and co-workers. It indicated that many properties of a chemical are determined by its interaction with diverse solvent. Within this approach there are three interdependent contributions: cavity, dipolarity/polarizability and hydrogen bonding terms. The model is as follows (Kamlet, 1987a; 1987b; 1988; James, 1991):

$$Z = Z_0 + mV_i/100 + s\pi^* + b\beta_m + a\alpha_m .$$

Where Z_0, m, b and a are constants; Z presents some property of a chemical related to its dissolution and partition; $V_i/100$ is the molecular cavity term. It measures the necessary free energy to separate the solvent molecules to provide a suitably sized cavity for the solute. π^* is the dipolarity/polarizability term. It measures the exoergic effects of solute-solvent dipole-dipole and dipole-induced dipole interactions. β_m and α_m are hydrogen bonding terms. Hydrogen bonding term measures the exoergic effects of complexation between solute and solvent. It is described as β_m when the solute is hydrogen bond

Foundation item: The Natural Science Foundation of Fujian Province (No. D9910016) and the Science Research Foundation of Huaqiao University

donor(HBD), whereas a_m when the solute is hydrogen bond acceptor(HBA).

Molecular connectivity index was posed and developed by Kier and Hall(Kier, 1976). There are zero-order index, first-order index, and so on. Molecular connectivity index is a topological parameter. It is a nonempiric value calculated based on molecular structure. So it can be applied to predict the effect of molecular structure on the toxicity of a chemical. The correlation between molecular structure and toxicity of an organic chemical is very satisfactory. The shortcoming of this method is that the molecular connectivity index has no straightforward physical meaning. However, it has been widely applied and developed in various study fields recently because of its simplicity, convenience, independence from experiments, and other merits.

Molecular group contribution method was established by Free and Wilson based on the relationship between substructure information and activity of a chemical(Lyman, 1982). The approach indicates that the toxic effect of a chemical on organism is the toxicity contribution additive of all different substituted groups, which are specially sited, in the chemical structure. The model is as follows:

$$\lg(1/c) = T_0 + \Sigma N_i T_i .$$

Where T_0 is the toxicity of the mother chemical. N_i is the number of each substituted group. T_i is the toxicity contribution of each substituted group. This approach is fit for the chemicals that have the same mother structure. Although this method cannot tell us the activity mechanism directly, it is often used to assess the toxicity preliminarily because it is so simple. Physico-chemical parameters need not to be calculated when the method is applied.

The purpose of this paper is to estimate the toxicities of 43 aromatic chemicals to *Photobacterium phosphoreum* and *Daphnia magna* by using the above four methods, and to compare and evaluate the accuracy and feasibility of these four QSAR methods.

1 Materials and methods

43 aromatic chemicals discussed in this paper were chlorobenzenes, toluenes, anilines, and phenols. Their QSAR descriptors are listed in Table 1. The observed toxicity data, presented as $-\lg EC_{50}$ for *Photobacterium phosphoreum* and $-\lg IC_{50}$ for *Daphnia magna*, are listed in Table 3. EC_{50}(mol/L) is the concentration causing a 50% inhibition of bioluminescence of *Photobacterium phosphoreum* after 15 minutes exposure. IC_{50}(mol/L) is the immobilization concentration for 50% of bioluminescence of *Daphnia magna* after 24 hours exposure.

Using above four QSAR methods($\lg P$, LSER, molecular connectivity index and molecular group contribution), the relationship between the physico-chemical parameters and toxicity was quantified by multiple linear regression. The relation equations obtained by the regression analysis are listed in Table 2. For each regression, the following descriptive information is provided here: number of observations used in analysis(n), adjusted correlation coefficient(r^2), and root mean square error(s). The predicted toxicities from the relation equations are listed in Table 3. All statistical analysis were performed using the Statgraphics program.

2 Results and discussion

2.1 Evaluation and comparison of four QSARs

2.1.1 Octanol/water partition

Good all-class chemical correlations were achieved for both organisms using $\lg P$. The QSAR equations of *Daphnia magna* were better than that of *Photobacterium phosphoreum*. The correlations were significantly better for sub-class chemicals. But unsuccessful correlations of toluenes were found for both organisms. And unsuccessful correlation of anilines was obtained for *Daphnia magna*. The chemical toxicity increased with increasing $\lg P$.

Table 1 Chemicals and QSAR parameters

Chemical	lg$p$[1]	LSER[2]				$^1\chi^{V3}$
		V_i/100	π^*	β_m	α_m	
Hexachlorobenzene	6.53	1.031	0.74	0.04	0	4.90
1,2,4,5-tetrachlorobenzene	5.05	0.851	0.69	0.04	0	3.92
1,2,4-trichlorobenzene	4.27	0.761	0.74	0.07	0	3.44
1,2,3-trichlorobenzene	4.27	0.761	0.84	0.04	0	3.44
1,4-dichlorobenzene	3.59	0.671	0.64	0.07	0	2.95
1,3-dichlorobenzene	3.38	0.671	0.69	0.07	0	2.95
1,2-dichlorobenzene	3.55	0.671	0.79	0.07	0	2.95
Chlorobenzene	2.81	0.581	0.69	0.11	0	2.78
1,4-dibromobenzene	4.07	0.753	0.59	0.06	0.20	3.78
1,3-dibromobenzene	3.75	0.753	0.84	0.06	0.20	3.78
Bromobenzene	2.99	0.622	0.79	0.06	0.12	2.89
1-chloro-4-bromobenzene	3.83	0.712	0.64	0.07	0.10	3.37
2,4,5-trichlorotoluene	4.93	0.859	0.53	0.09	0	3.85
2,5-dichlorotoluene	4.04	0.769	0.60	0.11	0	3.08
4-chlorotoluene	3.31	0.679	0.66	0.11	0	2.89
p-xylene	3.09	0.687	0.51	0.17	0	2.82
m-xylene	3.09	0.687	0.51	0.16	0	2.83
o-xylene	3.09	0.687	0.51	0.16	0	2.41
Toluene	2.59	0.589	0.55	0.15	0	3.30
p-xylene chloride	2.65	0.867	1.25	0.47	0.12	3.54
4-chloro-benzyl chloride	3.07	0.769	1.04	0.26	0.06	2.91
Benzene	2.13	0.491	0.59	0.14	0	2.00
2,4,6-trichloroaniline	3.04	0.841	1.08	0.40	0.26	3.64
2,6-dichloroaniline	2.75	0.751	0.96	0.44	0.26	2.83
2,4-dichloroaniline	2.75	0.751	0.96	0.44	0.26	3.16
3,4-dichloroaniline	2.55	0.751	0.96	0.44	0.26	3.16
3-chloro-4-fluoroaniline	2.04	0.791	0.87	0.43	0.34	2.78
4-chloroaniline	1.90	0.661	0.84	0.48	0.26	2.68
4-bromoaniline	2.05	0.702	0.92	0.44	0.36	3.09
2-chloro-4-nitroaniline	1.58	0.801	1.26	0.68	0.42	3.13
2,4-dinitroaniline	2.38	0.851	1.56	0.92	0.58	3.10
4-nitroaniline	1.39	0.711	1.14	0.72	0.42	2.65
3-nitroaniline	1.37	0.711	1.14	0.72	0.42	2.65
Diphenylamine	3.92	1.062	1.31	0.58	0.17	4.32
Aniline	0.93	0.571	0.72	0.52	0.26	2.20
Pentachlorophenol	5.04	0.986	0.87	0.23	0.60	3.56
2,4-dichlorophenol	2.90	0.716	0.96	0.29	0.60	3.09
4-chlorophenol	2.39	0.626	0.84	0.33	0.60	2.61
2-chlorophenol	2.18	0.626	0.84	0.33	0.60	2.62
4-nitrophenol	1.92	0.676	1.21	0.53	0.90	2.58
2-methyphenol	1.37	0.634	0.68	0.38	0.60	2.55
Resorcinol	0.80	0.581	0.74	0.60	1.20	2.27
Phenol	1.46	0.536	0.72	0.37	0.60	2.13

1. lg$p$ values is obtained from literature(Zhao, 1995); 2. LSER parameters are calculated on the basis of rules from literature(James, 1991); 3. $^1\chi^v$ is calculated on the basis of rules from literature(Kier, 1976)

2.1.2 Linear solvation energy relationship

Satisfactory all-class chemical correlations were achieved for both organisms. Relation equations were better for sub-class chemicals (anilines excluded). As the intrinsic molecular volume (V_i) increased, aqueous solubility decreased and toxicity increased. The only parameter which runs counter to the trend expected on the basic of aqueous solubility is the dipolarity/polarizability term(π^*). As π^* increased,

aqueous solubility and toxicity increased. This is true for the correlations determined here as well as previous study results (Kamlet, 1987a). Kamlet *et al*. hypothesized that this effect may relate to the mechanism of nonreactive toxicity. The effects of hydrogen bond terms (α_m and β_m) are various for different chemicals (Table 2). In these as well as previous study LSER toxicity correlations (Blum, 1991), the most influential terms are intrinsic molecular volume (V_i) and hydrogen bond acceptor basicity (β_m), with dipolarity/polarizability term (π^*) and hydrogen bond donor acidity (α_m) being relatively less important.

Table 2 Summary of QSAR equations

Method	Chemical class	*Photobacterium phosphoreum*	*Daphnia magna*
LgP	All classes	(1) $2.80 + 0.47\lg P$, $n = 43$, $s = 0.45$, $r^2 = 0.62$	(2) $2.89 + 0.51\lg p$, $n = 43$, $s = 0.37$, $r^2 = 0.75$
	Chlorobenzenes	(3) $1.96 + 0.66\lg p$, $n = 12$, $s = 0.23$, $r^2 = 0.90$	(4) $2.45 + 0.62\lg p$, $n = 12$, $s = 0.17$, $r^2 = 0.94$
	Toluenes	Unsuccessful	Unsuccessful
	Anilines	(5) $2.91 + 0.48\lg p$, $n = 13$, $s = 0.25$, $r^2 = 0.78$	Unsuccessful
	Phenols	(6) $2.82 + 0.59\lg p$, $n = 8$, $s = 0.18$, $r^2 = 0.96$	(7) $2.57 + 0.73\lg p$, $n = 8$, $s = 0.22$, $r^2 = 0.96$
LSER	All classes	(8) $0.91 + 4.13V_i/100 + 1.04\pi^* - 2.21\beta_m + 0.28\alpha_m$, $n = 43$, $s = 0.37$, $r^2 = 0.74$	(9) $1.02 + 4.09V_i/100 + 1.33\pi^* - 2.82\beta_m + 0.56\alpha_m$, $n = 43$, $s = 0.37$, $r^2 = 0.85$
	Chlorobenzenes	(10) $-0.29 + 6.19V_i/100 + 0.15\pi^* + 3.89\beta_m + 0.06\alpha_m$ $n = 12$ $s = 0.22$ $r^2 = 0.90$	(11) $1.29 + 5.07V_i/100 + 0.03\pi - 1.45\beta_m - 0.26\alpha_m$, $n = 12$, $s = 0.22$, $r^2 = 0.90$
	Toluenes	(12) $3.39 + 3.21V_i/100 - 0.80\pi^* - 9.56\beta_m + 40.44\alpha_m$, $n = 10$, $s = 0.19$, $r^2 = 0.95$	(13) $0.96 + 4.79V_i/100 + 0.66\pi - 4.07\beta_m + 7.85\alpha_m$, $n = 9$, $s = 0.07$, $r^2 = 0.88$
	Anilines	Unsuccessful	(14) $3.24 - 0.49V_i/100 + 3.52\pi - 3.64\beta_m - 0.96\alpha_m$, $n = 13$, $s = 0.27$, $r^2 = 0.64$
	Phenols	(15) $2.51 + 3.05v_i/100 + 1.02\pi^* - 3.32\beta_m - 0.03\alpha_m$, $n = 8$, $s = 0.24$, $r^2 = 0.91$	(16) $0.41 + 5.37V_i/100 + 0.99\pi - 3.11\beta_m + 0.76\alpha_m$, $n = 8$, $s = 0.09$, $r^2 = 0.99$
$^1X^V$	All classes	(17) $0.99 + 1.05\ ^1X^V$, $n = 43$, $s = 0.39$, $r^2 = 0.72$	(18) $1.25 + 1.03\ ^1X^V$, $n = 43$, $s = 0.39$, $r^2 = 0.72$
	Chlorobenzenes	(19) $1.15 + 1.02\ ^1X^V$, $n = 12$, $s = 0.21$, $r^2 = 0.88$	(20) $1.77 + 0.93\ ^1X^V$, $n = 10$, $s = 0.24$, $r^2 = 0.87$
	Toluenes	(21) $0.39 + 1.26\ ^1X^V$, $n = 10$, $s = 0.45$, $r^2 = 0.71$	(22) $1.47 + 0.94\ ^1X^V$, $n = 10$, $s = 0.31$, $r^2 = 0.74$
	Anilines	(23) $1.58 + 0.79\ ^1X^V$, $n = 13$, $s = 0.20$, $r^2 = 0.82$	(24) $1.99 + 0.71\ ^1X^V$, $n = 13$, $s = 0.28$, $r^2 = 0.66$
	Phenols	(25) $-0.04 + 1.57\ ^1X^V$, $n = 8$, $s = 0.36$, $r^2 = 0.82$	(26) $-1.30 + 2.06\ ^1X^V$, $n = 8$, $s = 0.28$, $r^2 = 0.93$
Free-wilson	All classes	(27) $3.26 + 0.50Cl + 0.73Br + 0.33CH_3 + 0.38NO_2 - 0.42F - 0.06NH_2 + 0.06OH$, $n = 42$, $s = 0.33$, $r^2 = 0.79$	(28) $3.54 + 0.50Cl + 0.77Br + 0.21CH_3 + 0.64NO_2 - 0.05F - 0.31NH_2 - 0.02OH$, $n = 42$, $s = 0.24$, $r^2 = 0.89$

2.1.3 Molecular connectivity index

First-order index ($^1X^V$) was used in QSAR equations in this paper. It mainly presented the branch situation of intrinsic molecular. The all-class chemical correlations were better than those of LgP, whereas worse than those of LSER. The sub-class correlations of chlorobenzenes and phenols were improved for both organisms. But the anilines equation for *Daphnia magna* was still unsatisfactory. As for toluenes, the sub-class correlations were not improved at all. The toxicity increased with increasing $^1X^V$.

2.1.4 Molecular group contribution

Two satisfactory equations (Eqs. (27)-(28)) were obtained by this method. Benzene was considered as mother structure here. The toxicity sequence of different groups for *Photobacterium phosphoreum* was: -Br > -Cl > $-NO_2$ > $-CH_3$ > -OH > $-NH_2$ > -F, whereas -Br > $-NO_2$ > -Cl > $-CH_3$ > -OH > -F > $-NH_2$ for *Daphnia magna*. This result may relate to the different mechanisms of diverse organisms (Jaworska, 1994).

Comparing above four QSAR methods, LSER method is more relatively satisfactory. The QSAR

correlations with different methods are various for different chemicals and different organisms. So applicable QSAR equations should be identified from Table 2 when the toxicity of some specific chemical is to be estimated. And the estimation result will be more reliable.

Table 3 Measured and predicted toxicity values

Chemical	$-\lg EC_{50}$					$-\lg IC_{50}$				
	Obs*	$\lg P$	LSER	$^1\chi^V$	Free-wilson	Obs*	$\lg P$	LSER	$^1\chi^V$	Free-wilson
Hexachlorobenzene	6.31	6.27	6.36	6.15	6.26	\	6.50	6.48	6.33	6.54
1,2,4,5-tetrachlorobenzene	5.51	5.29	5.24	5.15	5.26	\	5.58	5.57	5.42	5.54
1,2,4-trichlorobenzene	4.50	4.78	4.80	4.66	4.76	4.70	5.10	5.07	4.97	5.04
1,2,3-trichlorobenzene	4.53	4.78	4.70	4.66	4.76	5.13	5.10	5.12	4.97	5.04
1,4-dichlorobenzene	4.39	4.33	4.23	4.16	4.26	4.58	4.68	4.68	4.51	4.54
1,3-dichlorobenzene	4.24	4.19	4.24	4.16	4.26	4.41	4.55	4.61	4.51	4.54
1,2-dichlorobenzene	4.38	4.30	4.25	4.17	4.26	4.83	4.65	4.68	4.52	4.54
Chlorobenzene	3.86	3.81	3.84	3.68	3.76	4.26	4.19	4.10	4.08	4.04
1,4-dibromobenzene	4.54	4.65	4.74	5.01	4.72	5.00	4.97	4.99	5.29	5.08
1,3-dibromobenzene	4.99	4.44	4.74	5.01	4.72	4.94	4.78	5.00	5.29	5.08
Bromobenzene	3.78	3.93	3.92	4.10	3.99	4.40	4.30	4.35	4.46	4.31
1-chloro-4-bromobenzene	4.50	4.49	4.49	4.59	4.49	4.86	4.82	4.79	4.90	4.81
2,4,5-trichlorotoluene	4.86	5.12	4.86	5.03	5.09	4.99	5.40	5.05	5.09	5.25
2,5-dichlorotoluene	4.38	4.70	4.33	4.22	4.59	4.76	4.95	4.78	4.37	4.75
4-chlorotoluene	3.88	4.36	3.99	4.02	4.09	\	4.58	4.20	4.19	4.25
p-xylene	3.68	4.25	3.54	3.95	3.92	3.79	4.47	3.84	4.12	3.96
m-xylene	3.65	4.25	3.53	3.96	3.92	3.74	4.47	3.75	4.13	3.96
o-xylene	\	4.25	3.53	3.52	3.92	4.08	4.47	3.75	3.74	3.96
Toluene	3.08	4.02	3.41	4.46	3.59	3.57	4.21	3.68	4.57	3.75
p-xylene chloride	5.50	4.05	5.53	4.71	4.92	5.05	4.24	4.94	4.80	4.96
4-chloro-benzyl chloride	5.01	4.24	4.97	4.05	4.59	4.56	4.20	4.75	4.21	4.75
Benzene	3.34	3.80	3.16	3.09	3.26	3.54	3.98	3.44	3.35	3.54
2,4,6-trichloroaniline	4.51	4.37	4.61	4.46	4.70	4.20	4.44	4.45	5.00	4.73
2,6-dichloroaniline	4.16	4.23	4.11	3.82	4.20	\	4.29	4.48	4.16	4.23
2,4-dichloroaniline	4.09	4.23	4.11	4.08	4.20	\	4.29	4.40	4.50	4.23
3,4-dichloroaniline	4.20	4.13	4.11	4.08	4.20	4.26	4.19	4.40	4.50	4.23
3-chloro-4-fluoroaniline	3.28	3.89	5.09	3.78	3.28	3.69	3.93	3.57	4.11	3.68
4-chloroaniline	3.57	3.85	3.53	3.70	3.70	3.85	3.86	3.88	4.01	3.45
4-bromoaniline	3.92	3.89	3.89	4.02	3.93	4.35	3.94	4.19	4.43	4.00
2-chloro-4-nitroaniline	3.99	3.67	4.14	4.05	4.08	4.37	3.70	4.40	4.47	4.37
2,4-dinitroaniline	4.16	4.05	4.17	4.03	3.96	4.72	4.10	4.41	4.44	4.51
4-nitroaniline	3.70	3.58	3.56	3.67	3.58	3.40	3.60	3.88	3.98	3.87
3-nitroaniline	3.77	3.57	3.56	3.67	3.58	3.83	3.59	3.88	3.98	3.87
Diphenylamine	4.88	4.79	5.42	4.99	\	\	4.89	4.31	5.70	\
Aniline	3.28	3.36	2.94	3.32	3.20	3.58	3.36	3.35	3.52	3.23
Pentachlorophenol	5.69	5.79	5.67	5.55	5.82	6.33	6.25	6.31	6.03	6.02
2,4-dichlorophenol	4.45	4.53	4.74	4.81	4.32	4.70	4.69	4.76	5.07	4.52
4-chlorophenol	4.48	4.23	4.05	4.06	3.82	4.13	4.31	4.03	4.08	4.02
2-chlorophenol	4.14	4.11	4.05	4.07	3.82	3.95	4.16	4.03	4.10	4.02
4-nitrophenol	4.05	3.95	4.06	4.01	3.70	4.28	3.97	4.27	4.01	4.16
2-methyphenol	3.75	3.63	3.91	3.96	3.70	3.71	3.57	3.76	3.95	3.73
Resorcinol	3.00	3.29	3.06	3.52	3.38	3.30	3.15	3.31	3.38	3.50
Phenol	3.64	3.68	3.30	3.68	3.32	3.36	3.64	3.31	3.09	3.52

Note: * The observed values are obtained from the literature(Zhao, 1995)

2.2 Comparison of QSARs of chemical class

The results in Table 2 and Table 3 clearly show that the correlations for chlorobenzenes and phenols with the first three methods are all relatively satisfactory ($r^2 = 0.82$—0.99), whereas relatively worse for anilines and toluenes. No correlations are obtained for toluenes for both organisms by using $\lg P$. The reason may be that chlorine atoms, which existed in given chemicals, affect the toxicity mechanisms (Stefan, 1995). So all-class equations (Eqs. (1)-(2)) should be applied to toluenes.

3 Conclusions

Quantitative structure-activity relationships were developed for 43 aromatic compounds toxicities to *Photobacterium phosphoreum* and *Daphnia magna* based on four methods: $\lg P$, LSER, $^1X^V$ and Free-wilson. And the sub-class chemicals were studied respectively. LSER QSAR was proved to be the best. And it applied to the widest range of chemicals with the greatest accuracy. $\lg P$ and Free-wilson methods are often used to estimate the toxicity preliminarily because they are both simple and feasible.

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(Received for review July 23, 2001. Accepted January 10, 2002)