

# Quantitative structure-activity relationships for studying alkyl (1-phenylsulfonyl) cycloalkane-carboxylates\*

He Yibing, Wang Liansheng\*\*

Department of Environmental Science and Engineering, Nanjing University, Nanjing 210093, China

**Abstract**—Octanol/water partition coefficients, adsorption coefficients for soils and sediments and acute toxicities to *Daphnia magna* of 28 alkyl (1-phenylsulfonyl) cycloalkane-carboxylates were measured. These properties were correlated by linear solvation energy relationship (LSER) and chromatographic retention data determined by reverse-phase high performance liquid chromatography (RP-HPLC). The accuracy and range of applicability of these two quantitative structure-activity relationship (QSAR) methods were compared in this paper.

**Keywords:** alkyl (1-phenylsulfonyl) cycloalkane-carboxylates; LSER; RP-HPLC.

## 1 Introduction

The unusual and diverse properties of sulphur atom have led to the development of a large variety of compounds containing sulphur atom in various oxidation states in recent years. These compounds are used more extensively as either synthesis intermediates in the manufacture of pesticides, herbicides and drug, or as floatation agents and extractant in the petrochemical and metallurgical industries (Han, 1992; Pandeya, 1985). Accompanying these new chemicals being introduced into the environment, pollution effects by this kind of compounds should be anticipated. It is widely recognized that knowledge on the environmental fate of pollutants is a basic need in the environmental risk assessment.

During the past decade, RP-HPLC has become a powerful tool for determination of the hydrophobic nature of organic compounds employed in studies of QSAR. It can give a simple and convenient way to study relationships between chromatographic retention data determined by RP-HPLC and physicochemical and biological properties of organic compounds (Carlson, 1975; Harnisch, 1983; Braumann, 1983; Jinno, 1994).

Linear solvation energy relationships (LSERs) developed by Kamlet and coworkers have successfully correlated many diverse chemical properties, including toxicity, that depend on solute-solvent interactions (Kamlet, 1985; 1986a; 1986b; 1987a; Blum, 1990; Taft, 1981). However, the absence of readily available methods to calculate the LSER variables has limit-

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\*\* To whom correspondence should be addressed

ed the utility of the LSER method. In 1991, Hickey and Passino-Reader (Hickey, 1991) developed a method to estimate LSER variable values quickly for vast array of possible organic compounds such as those found in the environment and facilitated widespread application of LSER.

In this paper, we report octanol/water partition coefficient and acute toxicity to *Daphnia magna* of 28 alkyl (1-phenylsulfonyl) cycloalkane-carboxylates and use two methods, RP-HPLC method and LSER method, to correlate and estimate these two properties of aromatic sulfones which are useful for understanding their environmental behavior.

## 2 Materials and methods

### 2.1 Instruments

The liquid chromatograph was a Shimadzu LC-3A HPLC, coupled with SPD-6AV UV-Vis spectrophotometric detector.

### 2.2 Reagents

Analytical grade solvents methanol and ethanol were redistilled before use. Octanol was of analytical grade. Water was doubly distilled in quartz vessel.

### 2.3 Samples

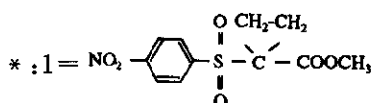
28 alkyl (1-phenylsulfonyl) cycloalkane-carboxylates were synthesized in our laboratory. Their purity were monitored by HPLC. The formulas are given in Table 1.

Table 1 Molecular formulas for 28 alkyl (1-phenylsulfonyl) cycloalkane-carboxylates

No.	Compound
1	4-NO <sub>2</sub> -ph-SO <sub>2</sub> -C(CH <sub>2</sub> ) <sub>2</sub> -CO <sub>2</sub> -CH <sub>3</sub>
2	4-NO <sub>2</sub> -ph-SO <sub>2</sub> -C(CH <sub>2</sub> ) <sub>2</sub> -CO <sub>2</sub> -CH(CH <sub>3</sub> ) <sub>2</sub>
3	4-NO <sub>2</sub> -ph-SO <sub>2</sub> -C(CH <sub>2</sub> ) <sub>3</sub> -CO <sub>2</sub> -CH(CH <sub>3</sub> ) <sub>2</sub>
4	4-NO <sub>2</sub> -ph-SO <sub>2</sub> -C(CH <sub>2</sub> ) <sub>5</sub> -CO <sub>2</sub> -CH(CH <sub>3</sub> ) <sub>2</sub>
5	4-NO <sub>2</sub> -ph-SO <sub>2</sub> -C(CH <sub>2</sub> ) <sub>6</sub> -CO <sub>2</sub> -CH(CH <sub>3</sub> ) <sub>2</sub>
6	4-Br-ph-SO <sub>2</sub> -C(CH <sub>2</sub> ) <sub>2</sub> -CO <sub>2</sub> -CH <sub>3</sub>
7	4-Br-ph-SO <sub>2</sub> -C(CH <sub>2</sub> ) <sub>3</sub> -CO <sub>2</sub> -CH <sub>3</sub>
8	4-Br-ph-SO <sub>2</sub> -C(CH <sub>2</sub> ) <sub>4</sub> -CO <sub>2</sub> -CH <sub>3</sub>
9	4-Br-ph-SO <sub>2</sub> -C(CH <sub>2</sub> ) <sub>5</sub> -CO <sub>2</sub> -CH <sub>3</sub>
10	4-Cl-ph-SO <sub>2</sub> -C(CH <sub>2</sub> ) <sub>2</sub> -CO <sub>2</sub> -CH <sub>3</sub>
11	4-Cl-ph-SO <sub>2</sub> -C(CH <sub>2</sub> ) <sub>3</sub> -CO <sub>2</sub> -CH <sub>3</sub>
12	4-Cl-ph-SO <sub>2</sub> -C(CH <sub>2</sub> ) <sub>2</sub> -CO <sub>2</sub> -CH(CH <sub>3</sub> ) <sub>2</sub>
13	4-Cl-ph-SO <sub>2</sub> -C(CH <sub>2</sub> ) <sub>2</sub> -CO <sub>2</sub> -C(CH <sub>3</sub> ) <sub>3</sub>
14	4-Cl-ph-SO <sub>2</sub> -C(CH <sub>2</sub> ) <sub>4</sub> -CO <sub>2</sub> -CH(CH <sub>3</sub> ) <sub>2</sub>
15	4-Cl-ph-SO <sub>2</sub> -C(CH <sub>2</sub> ) <sub>5</sub> -CO <sub>2</sub> -CH(CH <sub>3</sub> ) <sub>2</sub>
16	4-Cl-ph-SO <sub>2</sub> -C(CH <sub>2</sub> ) <sub>6</sub> -CO <sub>2</sub> -CH(CH <sub>3</sub> ) <sub>2</sub>
17	4-CH <sub>3</sub> -ph-SO <sub>2</sub> -C(CH <sub>2</sub> ) <sub>2</sub> -CO <sub>2</sub> -CH(CH <sub>3</sub> ) <sub>2</sub>

Table 1 (continued)

No.	Compound
18	4-CH <sub>3</sub> -ph-SO <sub>2</sub> -C(CH <sub>2</sub> ) <sub>3</sub> -CO <sub>2</sub> -CH(CH <sub>3</sub> ) <sub>2</sub>
19	4-CH <sub>3</sub> -ph-SO <sub>2</sub> -C(CH <sub>2</sub> ) <sub>2</sub> -CO <sub>2</sub> -CH <sub>3</sub>
20	4-CH <sub>3</sub> -ph-SO <sub>2</sub> -C(CH <sub>2</sub> ) <sub>2</sub> -CO <sub>2</sub> -CH <sub>2</sub> CH <sub>3</sub>
21	4-CH <sub>3</sub> -ph-SO <sub>2</sub> -C(CH <sub>2</sub> ) <sub>3</sub> -CO <sub>2</sub> -CH <sub>2</sub> CH <sub>3</sub>
22	4-CH <sub>3</sub> -ph-SO <sub>2</sub> -C(CH <sub>2</sub> ) <sub>4</sub> -CO <sub>2</sub> -CH(CH <sub>3</sub> ) <sub>2</sub>
23	4-CH <sub>3</sub> -ph-SO <sub>2</sub> -C(CH <sub>2</sub> ) <sub>5</sub> -CO <sub>2</sub> -CH(CH <sub>3</sub> ) <sub>2</sub>
24	4-CH <sub>3</sub> -ph-SO <sub>2</sub> -C(CH <sub>2</sub> ) <sub>5</sub> -CO <sub>2</sub> -CH <sub>3</sub>
25	ph-SO <sub>2</sub> -C(CH <sub>2</sub> ) <sub>2</sub> -CO <sub>2</sub> -CH <sub>3</sub>
26	ph-SO <sub>2</sub> -C(CH <sub>2</sub> ) <sub>3</sub> -CO <sub>2</sub> -CH <sub>3</sub>
27	ph-SO <sub>2</sub> -C(CH <sub>2</sub> ) <sub>4</sub> -CO <sub>2</sub> -CH <sub>3</sub>
28	ph-SO <sub>2</sub> -C(CH <sub>2</sub> ) <sub>5</sub> -CO <sub>2</sub> -CH <sub>3</sub>



### 2.3 Determination of partition coefficients

The octanol/water partition coefficients were determined by shake-flask as described by OECD (the Organization for Economic Cooperation and Development) guideline for testing of chemicals (OECD, 1981) at 25°C followed by centrifuging and were quantitatively measured with a UV-spectrophotometer against water blank.

### 2.4 Determination of adsorption coefficients for soils and sediments

The sediment was sampled in Xuanwu Lake. The content of organic carbon is 1.71%, and pH is 7.56. The adsorption coefficients for soils and sediments was determined according to OECD guideline for testing of chemicals (OECD, 1981) at 25°C. Samples were quantitatively measured by HPLC against blank. The adsorption isotherms were linear, and  $K_{oc}$  were calculated as a function of the organic carbon content of the sediment,  $K_{oc} = (K \times 100) / \% \text{ organic carbon}$ .

### 2.5 Determination of capacity factor by HPLC

A Nucleosil C18 column, 15 cm × 4.6 mm (made by Dalian Institute of Chemical Physics, Chinese Academy of Sciences), was used with flow rate of 1.0 ml/min at ambient temperature (20 ± 2°C). The detector was set at 254 nm (NO<sub>2</sub> alkyl (1-phenylsulfonyl) cycloalkane-carboxylates) and 230 nm (others compounds). The mobile phase consisted of different volume fractions of methanol in water (100:0, 95:5, 90:10, 85:15, 80:20, 75:25, 70:30), respectively. The column dead time ( $t_0$ ) was determined by the injection of NaNO<sub>3</sub> dissolved in methanol, and the capacity factor  $K'$  [ $k' = (t_R - t_0) / t_0$ ] of these compounds were measured.  $t_R$  is retention time. Table 2 collects the data from regression analysis of the relationship between  $\log k'$  and the volume fraction of methanol ( $\varphi_{CH_3OH} = 0$ ) in the mobile phase.

**Table 2** Regression analysis of the relationship between  $\log k'$  and the volume fraction of methanol in mobile phase:  
 $\log k' = \log k_w - s \varphi_{\text{CH}_3\text{OH}}$

Compound	$\log k_w$	$-s$	$r$	$sd$	$n$
1	1.059(0.068)	1.636(0.079)	-0.9942	0.021	7
2	1.746(0.044)	2.293(0.052)	-0.9987	0.014	7
3	2.082(0.139)	2.614(0.162)	-0.9906	0.043	7
4	3.167(0.194)	3.650(0.227)	-0.9905	0.060	7
5	3.548(0.199)	3.597(0.232)	-0.9915	0.061	7
6	1.548(0.089)	1.643(0.104)	-0.9902	0.027	7
7	1.692(0.098)	1.786(0.114)	-0.9899	0.030	7
8	2.121(0.117)	2.193(0.137)	-0.9904	0.036	7
9	2.553(0.140)	2.600(0.170)	-0.9901	0.044	7
10	1.228(0.070)	1.307(0.082)	-0.9904	0.022	7
11	1.403(0.078)	1.486(0.091)	-0.9908	0.024	7
12	1.860(0.095)	1.936(0.111)	-0.9919	0.029	7
13	2.190(0.115)	2.264(0.134)	-0.9914	0.035	7
14	2.613(0.121)	2.657(0.141)	-0.9930	0.037	7
15	3.005(0.141)	3.014(0.165)	-0.9926	0.043	7
16	3.549(0.130)	3.543(0.152)	-0.9954	0.040	7
17	1.599(0.091)	1.693(0.107)	-0.9902	0.028	7
18	1.808(0.099)	1.879(0.115)	-0.9907	0.031	7
19	1.019(0.054)	1.114(0.063)	-0.9922	0.017	7
20	1.309(0.073)	1.407(0.085)	-0.9910	0.023	7
21	1.468(0.085)	1.557(0.099)	-0.9900	0.026	7
22	2.240(0.095)	2.293(0.111)	-0.9942	0.029	7
23	2.672(0.130)	2.700(0.152)	-0.9922	0.040	7
24	1.903(0.087)	1.950(0.101)	-0.9933	0.027	7
25	0.660(0.037)	0.779(0.043)	-0.9924	0.011	7
26	0.849(0.051)	0.957(0.060)	-0.9905	0.016	7
27	1.128(0.063)	1.207(0.073)	-0.9909	0.019	7
28	1.524(0.079)	1.586(0.092)	-0.9917	0.024	7

## 2.6 Determination of toxicity to *Daphnia magna*

These compounds were diluted with experiment water (dissolved oxygen concentration =  $8.2 \pm 0.5$  mg/L; pH =  $7.5 \pm 0.3$ ; hardness =  $115 \pm 8.0$  mg/L expressed as  $\text{CaCO}_3$ ). Acetone was used as dispersant-solvent for chemicals slightly soluble in water. The volume of acetone never exceeded 0.1 ml/L of experiment water. The *Daphnia magna* used in the experiments obtained from local waterbodies, about 3 years prior to the experiment, and cultured in 15L glass carboy containing 10L of nutrient media. The green algae (*Selenastrum*

capricornutum) was served as food source for *Daphnia magna*. *Daphnia magna* cultured at laboratory exposure chambers consisted of 250 ml glass beaker that contained 200 ml test solution. The concentration range of alkyl (1-phenylsulfonyl) cycloalkane-carboxylates in which effects were likely to occur was determined from range-finding tests. 10 *Daphnia magna* (< 24h old) were randomly assigned to each of three replicates test vessels at each exposure level, and the test chambers were covered with loosely fitting lids to retard evaporation and renewed water every 24h (Francis, 1986). There were also three replicates of the controls without chemical. Test were performed in darkness at 22°C. Mortality was determined by probing for movement at the end of 48h. Toxicity values ( $LC_{50}$ ) were determined by probit regression analyses (Exner, 1988) and control mortality was less than 10% for all analyses. The level of statistical significance employed in all cases was  $P < 0.05$ . The results of  $\log Kow$ ,  $\log Koc$  and  $\log 1/LC_{50}$  are given in Table 3.

**Table 3** The experimental and estimated  $\log Kow$ ,  $\log Koc$  and  $\log 1/LC_{50}$  for this kind of compounds

Compound	$\log Kow$			$\log Koc$			$\log 1/LC_{50}$		
	exptl.	calcd.	diff.	exptl.	calcd.	diff.	exptl.	calcd.	diff.
1	1.33	1.41	-0.08	2.02	2.01	0.01		3.16	
2	2.05	1.94	0.11	2.42	2.39	0.03	3.60	3.48	0.12
3	2.36	2.21	0.15	0.59	2.57	0.02	3.70	3.64	0.06
4	2.84	3.06	-0.22		3.17		3.97	4.14	-0.17
5	3.41	3.42	-0.01		3.38			4.34	
6	2.32	2.30	0.02	2.18	2.28	-0.10	3.54	3.59	-0.05
7	2.45	2.40	0.05	2.39	2.36	0.03	3.70	3.66	0.04
8	2.73	2.74	-0.01	2.60	2.60	0.00	3.83	3.86	-0.03
9	2.94	3.09	-0.15	2.81	2.83	-0.02		4.06	
10	2.03	2.08	-0.05	2.05	2.11	-0.06	3.43	3.46	-0.03
11	2.28	2.20	0.08	2.07	2.20	-0.13	3.59	3.54	0.05
12	2.64	2.55	0.09	2.37	2.45	-0.08	3.67	3.74	-0.07
13	2.68	2.79	-0.11	2.54	2.63	-0.09	3.78	3.89	-0.11
14	3.16	3.13	0.03		2.87		3.97	4.09	-0.12
15	3.49	3.46	0.03		3.08		4.16	4.28	-0.12
16	3.83	3.87	-0.04		3.38			4.53	
17	2.52	2.33	0.19	2.39	2.31	0.08	3.72	3.62	0.10
18	2.78	2.51	0.27	2.55	2.42	0.13	3.96	3.72	0.24
19	1.77	1.91	-0.14	1.89	1.99	-0.10	3.21	3.36	-0.15
20	2.23	2.12	0.11	2.14	2.15	-0.01	3.49	3.49	0.00
21	2.31	2.24	0.07	2.26	2.24	0.02	3.75	3.56	0.19
22	2.88	2.85	0.03	2.62	2.66	-0.04	4.11	3.92	0.19
23	3.21	3.19	0.02		2.90		4.25	4.12	0.13

Table 3 (continued)

Compound	logKow			logKoc			log1/LC <sub>50</sub>		
	exptl.	calcd.	diff.	exptl.	calcd.	diff.	exptl.	calcd.	diff.
24	2.54	2.61	-0.07	2.58	2.48	0.10		3.77	
25	1.43	1.62	-0.19	1.80	1.80	0.00	3.03	3.19	-0.16
26	1.63	1.77	-0.14	1.91	1.90	0.01	3.18	3.28	-0.10
27	1.98	2.01	-0.03	2.13	2.05	0.08	3.39	3.41	-0.02
28	2.30	2.31	-0.01	2.40	2.27	0.13		3.60	

### 3 Results and discussion

In RP-HPLC, the mobile phase effects can be separated from stationary phase effects by using the linear relationship between the retention values and the composition of the mobile phase. The linear approximation of the relationship between the logarithm of the capacity factors ( $\log k'$ ) and the composition of the mobile phase ( $\varphi$ ) can be described by (Snyder, 1979),

$$\log k' = \log k_w - S\varphi_{\text{CH}_3\text{OH}}, \quad (1)$$

where  $k'$  is the capacity factor,  $\varphi_{\text{CH}_3\text{OH}}$  is the volume fraction of methanol in binary mobile phase,  $k_w$  represents the  $k'$  value for a compound if pure water is used as eluent ( $\varphi_{\text{CH}_3\text{OH}}=0$ ), and  $s$  is slope of the regression curve. Table 2 collects the data from regression analysis of the relationship between  $\log k'$  and  $\varphi_{\text{CH}_3\text{OH}}$ .

Table 2 shows that the above-stated relationship has produced good linear regression lines for all investigated compounds.

#### 3.1 Correlation studies

To perform the liquid chromatographic determination of  $K_{ow}$ , the HPLC capacity factors of all investigated substances were correlated with the corresponding octanol/water partition coefficients which were determined by shake-flask method. As can be seen from Eq. (2), good linear relationship between  $\log K_{ow}$  and  $\log k'$  was obtained at the methanol-water eluent of composition 60:40 (v:v; extrapolated).

$$\log K_{ow} = 1.265(0.051) + 1.843(0.069)\log k' (60\%), \quad (2)$$

$$n = 28 \quad r = 0.982 \quad sd = 0.116$$

In this and all the regression equations that follow,  $n$  is the number of data points in the regression,  $r$  is the correlation coefficient and  $sd$  is the standard deviation. As described above, we obtain Eq. (3) for  $\log K_{oc}$ - $\log k'$  and Eq. (4) for  $\log LC_{50}$ - $\log k'$ .

$$\log K_{oc} = 1.434(0.057) + 0.548(0.034)\log k_w, \quad (3)$$

$$n = 22 \quad r = 0.963 \quad sd = 0.077$$

$$\log 1/LC_{50} = 2.949(0.073) + 0.887(0.083)\log k' (50\%). \quad (4)$$

$$n = 22 \quad r = 0.923 \quad sd = 0.126$$

#### 3.2 Calculation of $\log K_{ow}$ , $\log K_{oc}$ and $\log 1/LC_{50}$ values

The above equations can be used to calculate  $\log K_{ow}$ ,  $\log K_{oc}$  and  $\log 1/LC_{50}$  for all investigated substances. Table 3 lists the estimated  $\log K_{ow}$ ,  $\log K_{oc}$  and  $\log 1/LC_{50}$  values which were derived from RP-HPLC method. The estimated values of these compounds studied in this paper are in good agreement with our experimental values. Thus, these relationships provided a rapid and simple way to predict these three properties of compounds of this class. It can be seen that increasing  $\log k'$  leads to increasing  $K_{ow}$ ,  $K_{oc}$  and toxicity.

### 3.3 Linear solvation energy relationships (LSER)

According to linear solvation energy relationships (LSERs; Kamlet, 1986a; 1985; 1987b; Taft, 1981), the solvation process essentially consists of three energy dependent steps: a cavity must be formed in the solvent into which the solute can enter; a single solute molecule must be separated from the bulk liquid solute and deposited in that cavity, and attractive forces must exist between solvent and solute.

Thus, many solvent-dependent properties, represented by the term  $XYZ$ , depend on linear combination of energy contribution of three types of terms: cavity term, dipole term and hydrogen bonding terms, characterized by  $mV_1/100, \pi^*, \alpha_m, \beta_m$ . We obtain,

$$XYZ = XYZ_0 + mV_1/100 + s\pi^* + a\alpha_m + b\beta_m. \quad (5)$$

The  $mV_1/100$  term measures the endoergic process of separating the solvent molecules to provide a suitably sized cavity for the solute.  $V_1$  is intrinsic molecular volume of the solute.  $V_1$  is scaled by 1/100 so that it should be comparable to other three variables. The  $s\pi^*$  term measures the (usually) exoergic effects of solute-solvent dipole-dipole, dipole-induced dipole and dispersion interactions.  $a\alpha_m$  and  $b\beta_m$  terms measure exoergic effects of hydrogen bonding interactions;  $\alpha_m$  and  $\beta_m$  are the solvatochromic parameters that measure hydrogen bond donor (HBD) acidity and hydrogen bond acceptor (HBA) basicity, respectively. For non-self-associating compounds,  $\alpha_m = \alpha$ ,  $\beta_m = \beta$ . The term in  $\alpha_m$  drops out of Eq. (5) for the alkyl (1-phenylsulfonyl) cycloalkane-carboxylates are not hydrogen bond donors (Kamlet, 1986a). The alkyl (1-phenylsulfonyl) cycloalkane-carboxylate follow nonreactive toxicity mechanism because of their hydrolyzing very slowly at pH=7 and 25°C (Han, 1992; Kamlet, 1987a).

The calculated LSER variable values of 28 alkyl (1-phenylsulfonyl) cycloalkane-carboxylates are shown in Table 4.

We applied the LSER of Eq. (4) in order to correlate  $\log K_{ow}$ ,  $\log K_{oc}$  and  $\log 1/LC_{50}$  and to obtain quantitative information on the factors affecting them. The multiple linear regression equations for 28 alkyl (1-phenylsulfonyl) cycloalkane-carboxylates are given by Eqs. (6)-(8),

$$\log K_{ow} = 2.576(1.229) + 3.206(0.126)V_1/100 - 1.064(0.510)\pi^* - 2.584(0.252)\beta$$

$$n = 28 \quad r = 0.980 \quad sd = 0.119 \quad (6)$$

$$\log K_{oc} = 1.786(0.856) + 2.119(0.130)V_1/100 - 0.906(0.361)\pi^* - 0.605(0.197)\beta$$

$$n = 22 \quad r = 0.962 \quad sd = 0.075 \quad (7)$$

$$\log 1/LC_{50} = 1.177(1.048) + 1.880(0.127)V_1/100 + 0.299(0.443)\pi^* - 0.893(0.242)\beta$$

$$n = 22 \quad r = 0.955 \quad sd = 0.094 \quad (8)$$

**Table 4** The solvatochromic parameters and estimated logKow, logKoc and log1/LC<sub>50</sub> for 28 alkyl (1-phenylsulfonyl) cycloalkane-carboxylates

Compound	V <sub>1</sub> /100	π*	β	logKow		logKoc		log1/LC <sub>50</sub>	
				calcd.	diff.	calcd.	diff.	calcd.	diff.
1	1.326	2.02	1.26	1.42	-0.09	2.00	0.02	3.16	
2	1.526	2.02	1.26	2.06	-0.01	2.43	-0.01	3.54	0.06
3	1.610	2.03	1.26	2.32	0.04	2.60	-0.01	3.70	0.00
4	1.806	2.04	1.26	2.94	-0.10	3.00		4.06	-0.09
5	1.904	2.04	1.26	3.25	0.16	3.21		4.25	
6	1.317	2.08	0.97	2.08	0.24	2.11	0.07	3.42	0.12
7	1.415	2.09	0.97	2.38	0.07	2.30	0.09	3.60	0.10
8	1.513	2.10	0.97	2.68	0.05	2.50	0.10	3.79	0.04
9	1.611	2.10	0.97	3.00	-0.06	2.71	0.10	3.97	
10	1.276	2.07	0.96	1.98	0.05	2.03	0.02	3.35	0.08
11	1.374	2.08	0.96	2.29	-0.01	2.23	-0.16	3.54	0.05
12	1.462	2.07	0.96	2.58	0.06	2.43	-0.06	3.70	-0.03
13	1.560	2.07	0.96	2.89	-0.21	2.64	-0.10	3.89	-0.11
14	1.658	2.09	0.96	3.19	-0.03	2.83		4.07	-0.10
15	1.756	2.09	0.96	3.50	-0.01	3.03		4.26	-0.10
16	1.854	2.09	0.96	3.81	0.02	3.24		4.40	
17	1.470	2.16	1.03	2.33	0.19	2.32	0.07	3.65	0.07
18	1.568	2.17	1.03	2.63	0.15	2.52	0.03	3.84	0.12
19	1.284	2.16	1.03	1.73	0.04	1.93	-0.04	3.30	-0.09
20	1.382	2.16	1.03	2.05	0.18	2.14	0.00	3.49	0.00
21	1.480	2.17	1.03	2.35	-0.04	2.33	-0.07	3.67	0.08
22	1.666	2.18	1.03	2.93	-0.05	2.72	-0.10	4.02	0.09
23	1.764	2.18	1.03	3.25	-0.04	2.93		4.20	0.05
24	1.578	2.18	1.03	2.65	-0.11	2.53	0.05	3.85	
25	1.186	2.12	1.01	1.51	-0.08	1.77	0.03	3.14	-0.11
26	1.281	2.13	1.01	1.81	-0.18	1.96	-0.05	3.31	-0.13
27	1.376	2.14	1.01	2.10	-0.12	2.15	-0.02	3.49	-0.10
28	1.471	2.14	1.01	2.40	-0.10	2.35	-0.05	3.67	

In Eq. (8), the coefficient for π\* is statistically zero and not significant at the 0.95 confidence level. Thus, log1/LC<sub>50</sub> values were regressed using a two-parameters equation which includes V<sub>1</sub> and β. The resulting LSER equation is given as follows.

$$\log 1/LC_{50} = 1.866(0.240) + 1.883(0.125)V_1/100 - 0.954(0.222)\beta$$

$$n = 22 \quad r = 0.957 \quad sd = 0.093 \quad (9)$$

It can be seen in Eqs. (6)–(9) that logKow, logKoc and log1/LC<sub>50</sub> are correlated well



with the solvatochromic parameters. The following information may be deduced from Eqs. (6)–(9): (a) Since water is a more cohesive solvent than 1-octanol, alkane and lipid or protein components of the organism, increasing  $V_1$  leads to increasing  $\log K_{ow}$ ,  $\log K_{oc}$  and  $\log 1/LC_{50}$  (a positive sign of the coefficient). (b) Because water is a stronger HBD acid than 1-octanol, alkane and any components of the organism, increasing chemical basicity should, and does lead to decreasing these three properties. (c) Increasing dipolarity and polarizability ( $\pi^*$ ) leads to increasing water solubility, which in turn decrease  $\log K_{ow}$  and  $\log K_{oc}$ . However, as polarity increases, aqueous solubility and toxicity increases. This is true for the correlations determined here as well as other toxicity correlations with solvatochromic parameters (Blum, 1991). Dipolarity/polarizability plays not very important role in Eq. (8) and is dropped out of in Eq. (9).

It also can be seen from Table 3 and Table 4 that with molecular volume increasing,  $\log K_{ow}$ ,  $\log K_{oc}$  and  $\log 1/LC_{50}$  increase. The order of  $K_{ow}$  for the same substituted group on benzene is: heptacyclic compound > hexacyclic compound > pentacyclic compound > tetracyclic compound > tricyclic compound, and *t*-butyl acetate > *i*-propyl acetate > ethyl acetate > methyl acetate. The order of  $\log K_{oc}$  and  $\log 1/LC_{50}$  are the same as that of  $\log K_{ow}$ .

### 3.4 Evaluation and comparison of RP-HPLC and LSER method

The RP-HPLC equations have simple, logical interpretations. As capacity factor increases, octanol/water coefficient and toxicity increase. The LSER equations can not only correlate and predict but also provide quantitative analysis of the factors determining the properties studied; as the intrinsic molar volume increases,  $K_{ow}$ ,  $K_{oc}$  and toxicity increase; as the hydrogen bond acceptor basicity increases,  $K_{ow}$ ,  $K_{oc}$  and toxicity decrease; as polarity increases,  $K_{ow}$  and  $K_{oc}$  decrease and toxicity increases. The accuracy of predicted values for  $\log K_{ow}$  and  $\log 1/LC_{50}$  by RP-HPLC models are comparable to those by the LSER while range of applicability is less broad than LSER models since capacity factors determined by RP-HPLC are not as easily obtained as solvatochromic parameters.

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