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Determination and Estimation of Aqueous Solubilities and *n*-Octanol/Water Partition Coefficients for Phenylacrylates

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With the development of industry, more and more chemicals, such as pesticides, detergents, plasticizers and some other industrial products, are being introduced into environment, and most of them are harmful to human. However, the environmental behaviors of xenobiotics are closely connected to their properties such as solubility (Sw), *n*-octanol/water partition coefficient (Kow), which are regarded as the main parameters controlling environmental fate (Thomsen, 1999).

Derivates of phenylacrylates, one kind of chemicals released into environment, were used widely as intermediary products to synthesize pesticides, drugs and spices. Their environmental behaviors and ecological effects are of interesting. However, there is no available data for these fate constants (Sw, Kow etc.). Hence, the purpose of this study is to determine the solubility (Sw) and *n*-octanol/water partition coefficient (Kow) of 11 ethyl 2-formamido-phenylacrylates, and develop simple robust predictive model on the basis of quantitative structure-property relationship (QSPR) techniques (e.g. linear solvation energy relationship (LSER)).

MATERIALS AND METHODS

A total of 11 ethyl 2-formamido-phenylacrylates was kindly presented by Professor Zhang Zheng. It was proved that there were no interference peaks by HPLC determination. Their chemical structures are shown in Table 1.

Sw values were determined with the traditional shake-flask method at 25±0.5℃, as described by the Organization for Economic Cooperation and Development's guidelines for testing of chemicals (OECD, 1987). A certain amount of double-distilled water with excess test compound was shaken for about 10 days to reach dissolving equilibrium completely. Each measure was done in triplicate bottles. The exact concentration of the water sample was determined with UV 2201 UV-VIS spectrophotometer (Shimadzu, Japan).

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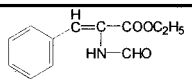
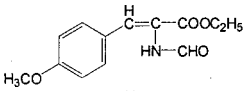
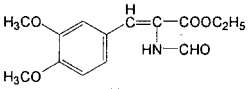
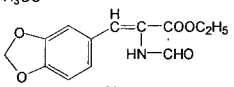
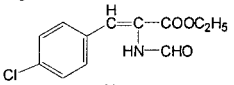
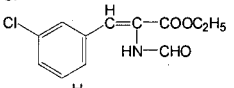
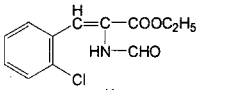
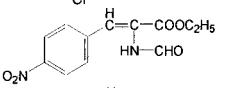
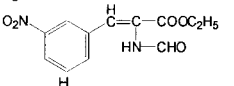
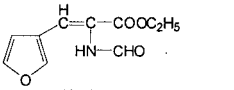
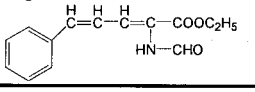
Table 1. The structures, some of linear solvation energy parameters and physiochemical properties of 11 test compounds

No.	Structures	λ_{max} (nm)	α_m	β_m	logKow			-logSw		
					Obs.	Fit.	Res.	Obs.	Fit.	Res.
1		278.2	0.50	1.43	2.48	2.43	0.04	2.89	2.95	0.06
2		309.6	0.50	1.65	2.22	2.25	-0.02	2.74	2.76	0.02
3		292.0	0.50	1.87	1.97	2.06	-0.09	2.41	2.57	0.16
4		288.1	0.50	2.45	1.66	1.58	0.08	2.14	2.08	-0.07
5		272.3	0.50	1.39	2.65	2.46	0.18	3.01	2.98	-0.03
6		323.9	0.50	1.39	2.51	2.46	0.05	3.11	2.98	-0.13
7		265.2	0.50	1.39	2.41	2.46	-0.06	3.00	2.98	-0.02
8		262.0	0.66	1.63	2.05	2.04	0.01	2.46	2.46	0.00
9		262.5	0.66	1.63	2.05	2.04	0.01	2.47	2.46	-0.01
10		312.7	0.50	1.64	2.08	2.26	-0.18	2.75	2.77	0.02
11		317.6	0.63	1.60	2.91	2.92	-0.01	3.35	3.37	0.02

Notes: logKow is logarithm of octanol/water partition coefficient, logSw is logarithm of aqueous solubility, α_m、β_m are linear solvation energy parameters, which represent the abilities of donating/accepting proton when the solute molecules combine and form hydrogen bond with solvent molecules, respectively.

Additionally, a generator column method (Opperhuizen, 1986) was also used to determine the solubility of these compounds and compared with the results of shake-flask method. In short, a known excess amount of the test chemicals was dissolved in ether and then added to quartz-ball. The ether was evaporated under nitrogen so that the quartz-ball became coated with the test chemical. The coated quartz-ball was transferred to a generator column, a glass tube with a frit in it. Distilled water was pumped through the generator column and 30mL water

samples were collected in a 50mL glass tubes. The determination was repeated not until the concentration was stable.

Kow values were determined with the shake-flask method according to the standard procedure of OECD (1987). Octanol saturated by water was used as organic phase, and water saturated by octanol was used as aqueous phase. The volume ratio of organic phase to aqueous phase was 1:9 (mL). Octanol solutions of each compound of two different known concentrations were prepared. Three tubes were prepared for each concentration. Blanks were prepared in an identical manner, with the exception that no compounds were added. Compounds in organic phase was allowed to come to equilibrium with compounds in aqueous phase in the thermostatic oscillator at 25℃ for 24h. After equilibrium was achieved, the mixed solution was centrifuged, and the concentration of compounds in aqueous phase was measured with UV 2201 UV-VIS spectrophotometer. Kow values were calculated from the quotient of the volume-based octanol and water concentrations. The average reproducibility of each determination was better than 1.0% relative.

The linear solvation energy relationship concept is a general approach to describe solvation and partitioning or related properties in diverse media. It was developed by Kamlet, Taft, and co-workers (1988). Within this approach there are three contributions to the total solute-solvent interaction:

Total = cavity term + dipolarity/polarizability term + hydrogen bonding term

The *cavity term* measures the free energy or enthalpy input necessary to separate the solvent molecules, i.e., to overcome solvent-solvent cohesive interaction to provide a suitably sized cavity for solute. The *dipolarity/polarizability term* measures the effects of solute-solvent dipole-dipole and dipole-induced dipole interactions and usually is exoergic (release energy). The *hydrogen bonding term* measures the exoergic effects of complexation between hydrogen bond donor solvents and hydrogen bond acceptor solutes or vice verse.

Kamlet and Taft used the so-called 'solvatochromic parameter' to estimate the different interaction terms. These parameters are measured by different spectroscopic methods and are afflicted with bad availability and experimental errors. A theoretical approach with quantum chemical parameters and be independent of experiments, was introduced by Wilson and Famini (1991), which was called as 'Theoretical LSER' (TLSER). The *hydrogen bonding term* was separated into acidic and basic terms and each of them into a covalent and an electrostatic part. Subsequently, a handy estimation method "Rule of Thumb" was put forward by Hickey (1991). The parameters $V_{i/100}$, π^*, α_m and β_m were

corresponding to *cavity, dipolarity/polarizability and hydrogen bonding term*, respectively. Calculated α_m and β_m of test compounds are listed in Table 1.

The statistical analyses were done using STATGRAPHICS program (STSC,1985). The QSPRs were obtained with the stepwise procedure using forward selection. Correlations between the descriptors were checked and highly correlated parameters were eliminated. If a compound was an outlier (|studentized residuals|>2) in all cases, it was removed and the regressions were repeated.

RESULTS AND DISCUSSION

It was found that there was no significant discrepancy by comparing the solubility values determined with two different methods. Therefore, the present solubility was the average value of two methods. Generally, there is significant correlation between Kow and Sw (Dai,1998). The relationship obtained in present paper is shown as follow:

$$\log Sw = -0.5451(0.2071) - 0.9742(0.0902)\log Kow \quad (1)$$

$$n=11,\ R=-0.9635,\ SD=0.1015,\ F=116.6916,\ p=0.0000$$

where n represents the number of samples, R, the regression coefficient, SD, the standard deviation, F, the F-test value for analysis of variable, and p, the significance level. As shown in eq.1, $F=116.6916>F_{(1,9,0.01)}=10.65$, the correlation between Kow and Sw is significant, reasonable and reliable, which is similar to previous theoretical equations (Hansch,1968; Briggs,1981).

However, the basis of this estimation method is that the solute has similar physicochemical properties (e.g. the ability of forming hydrogen bond between solute and solvent) in different solvent systems. In fact, there are many factors affecting the properties of compounds, and it is difficult to provide accurate quantitative description only based on similar partitioning properties between different solvent systems. Fortunately, LSER technique can provide an effective approach to solve these problems, and the equations are shown as follows:

$$\log Kow = 4.3085(0.3307) - 0.8328(0.0805)\beta_m - 1.3734(0.4950)\alpha_m \quad (2)$$

$$n=11,\quad R^2_{adj}=0.9133,\quad SD=0.1047,\quad F=53.7004,\quad p=0.0000$$

$$\log Sw = -5.1680(0.2547) + 0.8540(0.0620)\,\beta_m + 2.0022(0.3812)\alpha_m \quad (3)$$

$$n=11,\quad R^2_{adj}=0.9497,\quad SD=0.0807,\quad F=95.4543,\quad p=0.0000$$

where R^2_{adj} is the multiple correlation coefficient adjusted by the degree of

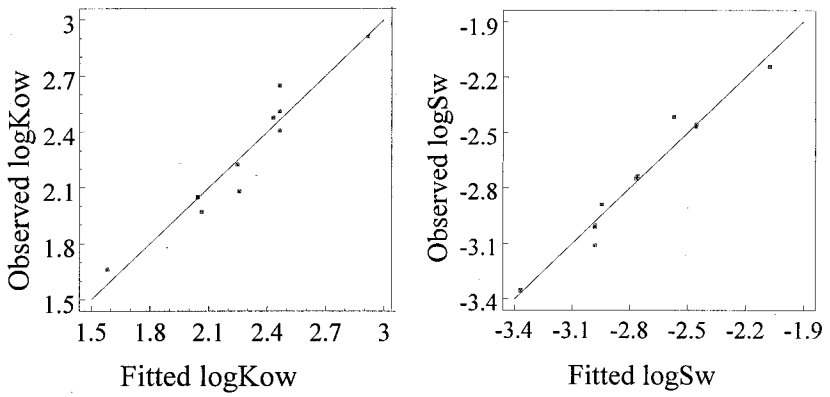


Figure 1. Plots of observed values *vs* fitted values of eqs. 2 and 3, respectively.

freedom. Considering the eqs. 2 and 3, linear solvation energy parameters α_m and β_m are positively correlated with logSw while negatively to logKow, which can be interpreted from the molecular structures of compounds. The introduction of electron-donating groups (such as $-OCH_3$, $-OCH_2-$) into benzene ring, would increase the electronic cloud density on ring, activate the benzene ring, and cause the high aqueous solubility. On the contrary, the electron-withdrawing group such as -Cl would decrease electron cloud density on phenyl ring, and lead to the low solubility. However, the introduction of $-NO_2$, electron-withdrawing group, increased the solubility, it might be understood that $-NO_2$ decreased the cloud density on phenyl ring, but it would form hydrogen bond with solvent water molecule and increase solubility. Therefore, the compound is much easier to partition to aqueous phase than to octanol phase due to the strong interaction between solute molecule and solvent water molecule. This result agrees with the negative correlation between logSw and logKow. The plots of fitted values against observed values based on eqs. 2 and 3 are shown in Figure 1.

To test the robustness of the obtained equations, a modified Jackknife test was used. In this study the test sample is a small one (n=11), so leave-one-out method was selected, about less than 10% observation was randomly deleted each time, and the regression was rerun for the rest 10 observations. The procedure was repeated 11 times, and the frequency distribution of multiple correlation coefficients of regressions is shown in Figure 2.

Considering the structures of tested compounds and the frequency distribution of multiple correlation coefficients, it can be seen that the distribution of structural fragment would affect the robustness of model to a great extent. In addition, some useful information can be extracted from the frequency distribution of residuals that came from the difference of observed values and the predicted values of

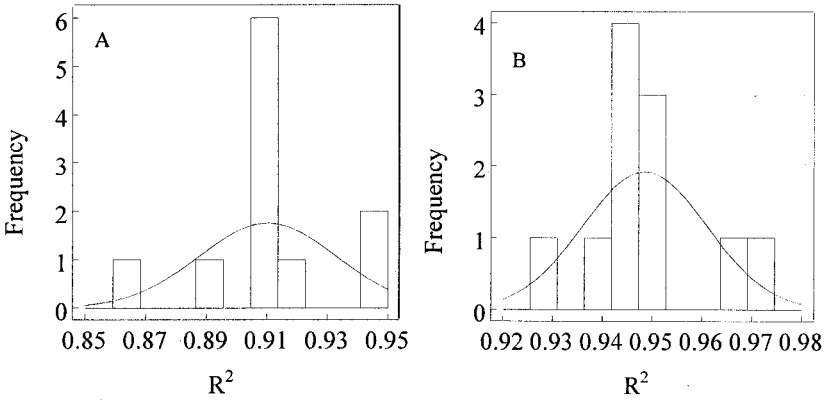


Figure 2. The frequency distribution of correlation coefficients of eqs. 2 (A) and 3 (B) by using leave-one-out method

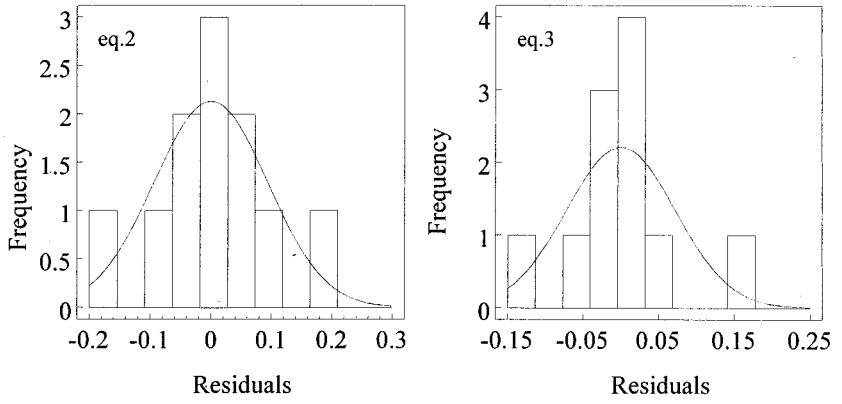


Figure 3. The frequency distribution of residuals from eqs.2 and 3, respectively.

model (Figure 3). It is necessary to test the distribution of residuals for evaluating model. Once more, because there were only 11 members (less than 50), the K-S method was used to test, and the results showed that the frequency distribution of logKow and logSw conformed to the normal function X-N(-4.6428×10^{-16}, 0.0110^2) and X-N(1.0093×10^{-15}, 0.0065^2), respectively. The skewness coefficients were 0.0704 (eq.2) and 0.4596 (eq.3), less than the critical value 0.93 (p=0.95, n=11); and their kurtosis coefficients were 1.7115 and 0.159, which were ranging between the critical values 1.60 and 4.00 (p=0.95 n=11). Therefore, it can be concluded that the obtained models are so robust that are suitable to predict the logKow and logSw values of new chemicals.

The presently determined physicochemical data form a consistent dataset, which is reflected in high correlations with simple molecular descriptors α_m and β_m. The

developed models are so robust that are suitable to predict the physicochemical properties of a new chemical with similar structure. The linear solvation energy parameters, which are derived from quantum chemical calculations, proved to be suitable to describe the physicochemical properties. Moreover, these parameters have clear physicochemical sense and the calculation is simple.

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