Bull. Environ. Contam. Toxicol. (2000) 65:190–199
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DOI: 10.1007/s001280000114

Bulletin of Environmental Contamination and Toxicology

Prediction of Octanol/Water Partitioning Coefficient and Sediment Sorption Coefficient for Benzaldehydes by Various Molecular Descriptors

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Received: 5 November 1999/Accepted: 12 May 2000

Substituted benzaldehyde compounds are used extensively as intermediates to synthesize medicines (e.g. chloramphenicol, ephedrin, ampicillin, diphenylhydantoin and other products), dyes and pesticides (e.g. Monsanto's herbicide Lasso and other agricultural chemicals). They have also been observed as ozonolysis by-products of water disinfection (Koga 1991), as products of incomplete oxidation and combustion (Manaha 1990), and as products of metabolism (Que 1993). Benzaldehyde and its derivatives are being introduced into the environment. Their environmental behavior and ecological effects should be estimated. However, few published data are available for their environmental behavior.

The soil/sediment sorption coefficient (Koc) and the octanol/water partition coefficient (Kow) are of critical importance for evaluating organic compounds fate and potential exposure to environment and, consequently, for the whole process of environmental risk assessment. Because the experimental determination of Kow and Koc values of organic compounds is often difficult and expensive, alternative methods of estimation are frequently employed. During the past two decades the study of quantitative structure-activity relationships (QSARs) has been developed in pharmacology and drug design. Now QSARs are used increasingly to screen and predict toxicity and the fate of chemicals released into the environment. The essential assumption for QSARs studies is that biological, chemical, and physical properties of compounds depend on their structures. The QSAR models are usually developed for a group of compounds with similar structure. The commonly used methods in QSARs studies are Hansch's method, Linear Solvation Energy Relationship (LSER) method, Molecular Connectivity Indices (MCIs) method, and quantum chemical descriptors. Molecular connectivity is a method describing molecular structure based solely on bonding and branching patterns rather than physical or chemical characteristics. A large number of studies have demonstrated that many physicochemical and biological properties, such as water solubility, Kow, Koc, and biological activity correlate with the connectivity index (Blum and Speece 1990). Quantum chemical parameters derived from molecular orbital calculations have the advantage of not being class dependent as is often the case with group theoretical, topological or topographical variables (where many correlations using these types of descriptors are usually limited to a single type of compound, such as aliphatic alcohols). MO

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derived descriptors are also readily computed, and can be selected in such a way as to assure (or nearly assure) orthogonality of the parameter space (Famini and Wilson 1997). Because of their advantages, they are widely used in the QSAR studies (Nevalainen 1994).

Many models based on molecular properties such as molecular volume, dipole moment, hydrogen bond acceptor basicity, hydrogen bond donor acidity (Hickey and Passino-reader 1990) have been reported to predict Kow and Koc of chemicals. Molecular connectivity models have been shown to outperform traditional empirical models based on physicochemical properties in predicting Kow and Koc (Meylan 1992). However, information on QSAR models based on quantum chemistry descriptors to predict Kow and Koc is limited (Reddy and Locke 1994). In this study, Kow and Koc of 14 substituted benzaldehydes were determined. The model based on quantum chemistry descriptors and MCIs were developed to predict the Kow and Koc the studied chemicals. Furthermore, the factors determining these properties are discussed and compared.

MATERIALS AND METHODS

14 substituted benzaldehydes were synthesized in School of Chemistry and Chemical Engineering of Nanjing University. Purities were monitored by HPLC to assure that no interference peak would be occurred. The chemicals are listed in Table 1.

Sediment taken from Yangtze River near Nanjing City (sampling site, N: 32°13′13.5′′, E: 118°50′44.3″) was used in this study. Sediment was air-dried, grounded to sieve through 80 mesh, and stored in the laboratory in a dry place at ambient temperature. The organic carbon content was 1.57%, which is determined by the Walkley-Blank method, and the pH was 6.75. Sorption on sediment was determined by batch method based on the OECD guidelines (OECD 1981) for testing of chemicals. Concentrations of the test chemicals ranged from 1-20μg/mL for lower solubility chemicals or 10-100μg /mL for higher solubility chemicals. The batch equilibrium experiments were performed at 25±0.5°C. Sediment-free tubes containing only the initial solutions were used as blank references to check for sorption onto glass or caps. There were 7-9 points in each isotherm. The octanol/water partition coefficients were determined using shake flask method at 25±0.5°C based on the OECD guidelines (OECD 1981). The equilibrium concentrations for samples in the water phase were determined by UV/Visible spectrophotometry; the sediment values were calculated by the difference. All measurement was carried out in duplicate.

Molecular geometry was optimized and parameters were calculated using the semi-empirical orbital MOPAC6.0 procedures (Stewart 1990) according to methods AM1, PM3, (Dewar 1985; Stewart 1990). MOPAC was used to determine the individual structural parameters influencing Kow and Koc, including the dipole moment (μ), the energy of the highest occupied molecular orbital (E_{homo}), the energy of the lowest unoccupied molecular orbital (E_{lumo}), the most positive net atomic charges on hydrogen (qH^{+}), the largest negative atomic charge on an atom (q^-), and the total energy (TE). Molecular connectivity index was calculated using program developed by our laboratory (designed with FORTRAN language) according to the method described by Kier and Hall (1976). The parameters included in the regression equation were listed in Tables 2 and 3.

The regression analysis was performed using the "Statgraphics" program (STSC Inc 1985). All multiple linear regressions reported in this paper adhere to two conditions. First, this cross correlation of descriptors is minimized, as determined by the variance inflation factor (VIF). The VIF is defined as $1/(1-r^2)$, where r is the correlation coefficient of the subject independent variable against all other independent variables in the regression. A value of 1.0 indicates no correlation, with values under 5.0 being acceptable. Values over 10.0 indicate an unstable regression that should be reexamined. Second, all independent variables in the regressions have a significance of at least 95% (Based on Student's 2-tail t-score).

RESULT AND DISCUSSION

The sorption isotherms for all the samples were analyzed using the Freundlich equation, $C_s=K_fC_e^N$, where C_S was the amounts of benzaldehyde sorbed (μmol kg^{-1}) and C_e is the solution concentration ((μmol L^{-1}). K_f and N are empirical constants, where K_f is the Freundlich coefficient (L kg^{-1}) and the exponent N is a dimensionless parameter commonly less than unity. Nonlinear regression techniques used to derive K_f and N minimized the weighted residual sum of square. Consequently, the sorption partition coefficient K_f is normalized for organic carbon to yield an organic-carbon-partition coefficient, Koc (Table 1).

In order to describe the relationship between the Koc of tested chemicals and the calculated quantum chemical parameters, a multiparameter regression analysis was performed. The obtained QSRR equations are presented as follow:

AM1:

$\log Koc=5.99-1.02\mu-9.24qH^{+}+0.49q^{-}$

$n=14, R^2(adj.)=0.8636, SE=0.129, F=28.48, p=0.0000$ (1)

$\log Koc=5.52-0.92\mu-7.45qH^{+}-0.67{}^3\chi_{pc}+0.26{}^2\chi^v_p$

$n=14, R^2(adj.)=0.9126, SE=0.104, F=34.94, p=0.0000$ (2)

PM3:

$\log Koc=5.48-1.19\mu-8.36qH^{+}+1.08q^{-}$

$n=14, R^2(adj.)=0.8167, SE=0.155, F=18.83, p=0.0002$ (3)

$\log Koc=5.28-0.89\mu-5.80qH^{+}-1.26{}^3\chi_{pc}+0.28{}^2\chi^v_p$

$n=14, R^2(adj.)=0.9223, SE=0.098, F=39.60, p=0.0000$ (4)

Where n is the number of observations, R is the correlation coefficient adjusted by degree of freedom, SE is the standard error of estimates, n is the number of chemicals, F is the *F*-test value, p is the significance level of the whole equation.

Table 1. The compounds and the observed and fitted Koc and residual.

			logKoc				
No.	Compounds	logKf	Obs.	Fit. (equ.2)	Diff.	Fit. (equ.4)	Diff.
1	3,4-dihydroxybenzaldehyde	1.635	3.439	3.402	0.037	3.350	0.089
2	4-hydroxybenzaldehyde	1.295	3.099	3.170	-0.071	3.205	-0.106
3	3-methoxy-4-hydroxybenzaldehyde	1.633	3.438	3.525	-0.087	3.485	-0.047
4	3-ethoxy-4-hydroxybenzaldehyde	1.288	3.092	3.020	0.072	3.056	0.036
5	p-methylsulfonylbenzaldehyde	1.633	3.438	3.450	-0.012	3.408	0.030
6	2,5-dimethoxybenzaldehyde	1.661	3.465	3.414	0.051	3.465	0.000
7	5-bromo-2-hydroxybenzaldehyde	1.465	3.269	3.236	0.033	3.251	0.018
8	3,4,5-trimethoxybenzaldehyde	1.531	3.335	3.505	-0.170	3.505	-0.170
9	4-chloro-benzaldehyde	2.129	3.933	3.785	0.148	3.797	0.136
10	3-chloro-benzaldehyde	2.040	3.844	3.923	-0.079	3.903	-0.059
11	4-bromo-benzaldehyde	2.136	3.940	3.944	-0.004	3.960	-0.020
12	4-N,N-dimethyl benzaldehyde	1.273	3.077	3.077	0.000	3.093	-0.016
13	p-nitro-acetophenone	0.907	2.711	2.751	-0.040	2.704	0.007
14	3,4-dichlorobenzaldehyde	1.763	3.568	3.447	0.121	3.466	0.102

Table 2. Quantum chemical descriptors using AM1method and molecular connectivity indices for 14 studied chemicals.

	Quantum structure descriptors					MCIs			
No.	μ	qH^+	$-q^-$	$-TE\times10^3$	$-EE\times10^3$	$^2\chi^v_p$	$^3\chi_{pc}$	$^4\chi_{pc}$	$^3\chi^v_{pc}$
1	0.378	0.242	0.293	1.940	8.028	1.866	0.676	1.574	0.225
2	0.866	0.224	0.295	1.619	6.493	1.709	0.493	0.901	0.171
3	0.420	0.241	0.296	2.095	9.451	2.278	0.606	1.514	0.220
4	0.932	0.237	0.293	2.251	10.968	2.049	0.606	1.465	0.220
5	1.504	0.164	0.946	2.289	10.834	2.962	0.348	1.130	0.198
6	1.204	0.163	0.302	2.250	10.885	2.226	0.537	1.485	0.210
7	0.204	0.225	0.282	1.959	7.857	2.735	0.691	1.418	0.475
8	1.110	0.163	0.289	2.726	14.514	2.577	0.674	1.915	0.265
9	0.822	0.160	0.285	1.659	6.384	2.105	0.493	0.901	0.285
10	0.685	0.159	0.283	1.659	6.397	2.108	0.493	0.837	0.285
11	0.785	0.160	0.282	1.638	6.314	2.583	0.493	0.901	0.423
12	1.643	0.152	0.300	1.830	9.040	2.604	0.704	1.533	0.394
13	1.649	0.177	0.354	2.285	10.393	1.974	0.667	1.609	0.260
14	1.088	0.174	0.278	2.019	7.790	2.604	0.676	1.574	0.423

Equations (1) and (3) were quite good with large correlation coefficients and small SE values. This indicated that Koc can be predicted by models based on quantum chemical descriptors. It has been suggested that an adequate model should include as many descriptors as possible to increase the probability of good characterization of compounds. Therefore, 8 molecular connectivity indices were

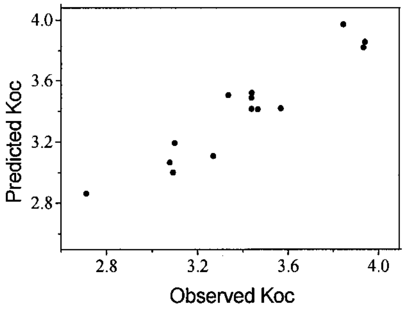

Figure 1. Plot of observed logKoc vs. predicted logKoc using equation 2

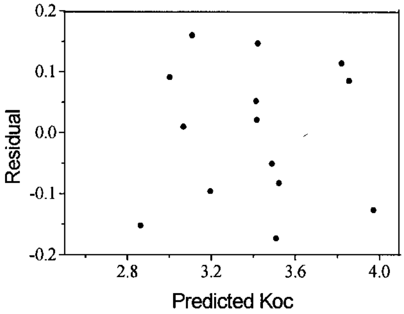

Figure 2. Pattern of distribution of residuals for vs. predicted Koc

used in this study. Equations (2) and (4) were obtained by stepwise regression analysis. Comparing equation (2) and (4) with equation (1) and (3), we find that the correlation coefficient is significantly improved and the standard error of estimation is reduced through introducing MCIs into equations. This indicated that manifold parameters method is more effective than one kind of descriptors for predicting Koc for studied compounds. The predicted values and the residuals for the studies of compounds are shown in Table 1. The predicted Koc (using equation 2) were well fitted with observed Koc (Figs. 1 and 2).

Table 3. Quantum chemical descriptors using PM3 method and molecular connectivity indices for 14 studied chemicals.

	Quantum structure descriptors					MCIs		
No.	α	μ	qH^+	$-q^-$	-HOF	$^2\chi^v_p$	$^3\chi^v_p$	$^3\chi_{pc}$
1	69.625	0.405	0.213	0.323	99.617	1.866	1.136	0.676
2	64.686	0.857	0.201	0.333	56.415	1.709	1.029	0.493
3	78.472	0.489	0,212	0.324	92.311	2.278	1.420	0.606
4	85.025	0.909	0.211	0.322	98.138	2.049	1.340	0.606
5	90.261	1.706	0.128	0.834	74.016	2.962	1.726	0.348
6	87.85	1.101	0.134	0.329	84.239	2.226	1.560	0.537
7	76.676	0.193	0.142	0.311	47.413	2.735	1.609	0.691
8	99.654	0.962	0.136	0.315	118.334	2.577	1.823	0.674
9	69.43	0.823	0.123	0.313	17.142	2.105	1.258	0.493
10	68.235	0.710	0.122	0.311	16.993	2.108	1.219	0.493
11	71.421	0.759	0.128	0.311	2.552	2.583	1.534	0.493
12	88.586	1.485	0.121	0.326	13.786	2.604	1.546	0.704
13	80.41	1.674	0.137	0.596	25.017	1.974	1.199	0.667
14	79.147	0.982	0.140	0.309	22.297	2.604	1.817	0.676

$^tx_p^v$ represents *t*th order valence path index (t=0-4), $^tx_{pc}^v$ represents *t*th order valence path-cluster index (*t*=3-5).

According to the principles of statistics, a regression equation is of no relevance when the explanatory variables applied were mutually interrelated by simple or multiple regression. However, as it was shown that the correlation coefficients of the independent variables and the VIF values (Tables 4 and 5), the two obtained equations are of significance that can be used to explain the mechanisms of sorption for the studied compounds.

Table 4. Correlation coefficient matrix for significant independent variables and the variance inflation factors (VIF) for equation (2).

	Correlation matrix				R^2(adj.)	(VIF)
	μ	qH^+	$^3\chi_{pc}$	$^2\chi^v_p$		
μ	1.000				0.2477	1.33
qH^+	0.5290	1.000			0.2714	1.37
$^3\chi_{pc}$	-0.2303	-0.3505	1.000		0.0974	1.11
$^2\chi^v_p$	-0.1886	0.2500	-0.0248	1.000	0.0181	1.02

Table 5. Correlation coefficient matrix for significant independent variables and the variance inflation factors (VIF) for equation (4).

	Correlation matrix				R^2(adj.)	(VIF)
	μ	qH^+	$^3\chi_{pc}$	$^2\chi^v_p$		
μ	1.000				0.1834	1.22
qH^+	0.4588	1.000			0.1458	1.17
$^3\chi_{pc}$	-0.0209	-0.2719	1.000		0.0000	1.00
$^2\chi^v_p$	-0.2028	0.2419	-0.0627	1.000	0.0000	1.00

Student *t*-values for partial correlation coefficients in equation 4 are -10.69, -6.64, -4.73 and 3.24 for μ, qH^+、 $^3\chi_{pc}$ and $^2\chi^v_p$, respectively. This indicates that the dipole moment (μ) descriptor is the most significant factor for Koc. The parameter μ has a negative sign, which means that the larger μ, the lesser in the tendency to partition or adsorb into the sediment as well as into aqueous media (Famini and Wilson 1997). This is reasonable since a larger dipole would imply greater dipole-dipole and dipole-induced dipole interactions with the polar water molecules. The most positive net atomic charges on hydrogen (qH^+) descriptor are related to the ability of the solutes to participate in hydrogen-bonding interactions with solvent molecules. As may be concluded from the partial correlation coefficients, this kind of interaction is less important for Koc. The parameter qH^+ has also a negative sign, which means that the larger qH^+ term, the easier the molecules is to form hydrogen-bonding with aqueous media, so the lesser solutes is partition or adsorb in sediment. It can be seen from equations (1) and (3) that an increase in solute electrostatic (q^-) basicity increases the adsorption on the sediment. This may by due to the hydrogen bonding interactions between the solutes and the sediment phase, with the compound molecules provide electrons and organic substance molecules in the sediment accept electrons, or the electrostatic interactions between the positive charge of the sediment particles and the negative charge on oxygen atoms (q^-) in the solutes.

There were enormous reports correlating the sediment sorption coefficients to octanol/water partition coefficients. For nonpolar chemicals, sorption to the organic matter of the sediment could be regarded as a distribution process between a polar aqueous phase and a nonpolar organic phase (Hamaker and Thompsom 1972; Karichkoff et al. 1979). However, logKoc correlated to $\log K_{OW}$ poorly for substituted benzaldehydes tested. This showed that there must be other mechanisms of benzaldehydes sorption on natural sediment except of partition, such as physical adsorption and chemosorption. These tested chemicals contained polar functional groups such as -OH and -CHO, so they could be sorbed by both organic and inorganic sediment components (Sanchez-Martin 1991). Some research indicated that, for polar organic compounds, hydrogen bonding and electron donor-acceptor processes involving free radicals had a prominent role in polar organic compounds-humic interaction (Sanchez-Martin 1991). It is mentioned above that sorption is influenced by μ, qH^+, and q^- for substituted benzaldehydes in our study. This further showed that chemosorption and physical adsorption might be the fundamental process for polar compound sorption on natural sediment other than lipophilic partitioning.

In order to describe the relationship between the Kow of tested chemicals and the calculated structure descriptors, a multiparameter regression analysis was performed. The obtained QSRR equations are presented as follow:

AM1:

$$\log Kow=3.02-5.01qH^{+}+2.14q^{-}+3.68\,{}^{3}\chi^{v}_{pc}-0.48\,{}^{4}\chi_{pc}$$

$$n=14,\ R^{2}(adj.)=0.9179,\ SE=0.188,\ F=37.33,\ p=0.0000 \qquad (5)$$

PM3:

$$\log Kow=2.51-5.61qH^{+}+2.38q^{-}+3.55\,{}^{3}\chi^{v}_{pc}$$

$$n=14,\ R^{2}(adj.)=0.8317,\ SE=0.27,\ F=22.41,\ p=0.0001 \qquad (6)$$

The F and p values of equations (5) and (6) show that the equations are significant. It may be concluded from equations (5) and (6) that AM1 method is more effective than PM3 method in predicting Kow for studied compounds. The calculated and residual values of Kow based on equations (5) and (6) are listed in Table 6. It can be seen from Table 6 that the experimental values of Kow were close to the predicted. The average errors of estimated logKow were 0.11, 0.14 log units, respectively. The correlation coefficients of the independent variables and the VIF values show that the obtained equations are of significance that can be used to explain the mechanisms of partition for the studied compounds (Table 7 and 8).

Student *t*-values for partial correlation coefficients in equation (5) are –3.11, 6.47, 6.17 and –3.08, for qH^+, q^-, ${}^{3}\chi^{v}_{pc}$, and ${}^{4}\chi_{pc}$; –2.26, 4.24, and 4.13 for qH^+, q^-, and ${}^{3}\chi^{v}_{pc}$ in equation (6), respectively. This indicates that the largest negative atomic charge on an atom (q^-) descriptor is the most significant factor for Kow. The largest negative atomic charge on an atom (q^-) descriptor is related to the ability of the solutes to participate in hydrogen-bonding interactions with solvent molecules. As may be concluded from the sign and magnitude of the partial correlation coefficients that an increasing in solute electrostatic (q^-) basicity decrease the distribution into octanol. This implied a difference in the acidity between octanol and water acidity. Further, electrostatic basicities favor solvation into the aqueous layer, so decreasing the distribution into octanol. The $^3\chi^v_{pc}$ term had a positive sign, which means that the larger $^3\chi^v_{pc}$ term, that is, the more branching pattern in molecular, the larger logKow values. The qH^+ determines logKow for test compounds, and is related the ability of the solutes to participate in hydrogen-bonding interactions with the water molecules. Its participation in the correlation equation is even less than the $^3\chi^v_{pc}$ term, this indicates that this kind of interaction is rather less importance for Kow.

Table 6. Experimental and calculated logKow for tested compounds.

No.			logKow		
	Obs.	Fit. (equ.5)	Diff.	Fit. (equ.6)	Diff.
1	1.09	1.244	-0.154	1.344	-0.254
2	1.36	1.458	-0.098	1.195	0.165
3	1.21	1.253	-0.043	1.329	-0.119
4	1.58	1.301	0.279	1.344	0.236
5	0.35	0.353	0.000	0.511	-0.158
6	1.91	1.608	0.302	1.719	0.191
7	2.32	2.357	-0.037	2.325	-0.005
8	1.39	1.632	-0.242	1.940	-0.550
9	2.10	2.215	-0.115	2.084	0.016
10	2.26	2.259	0.001	2.093	0.167
11	2.75	2.731	0.022	2.554	0.199
12	2.24	2.319	-0.083	2.453	-0.217
13	1.54	1.554	-0.014	1.248	0.292
14	2.53	2.346	0.1840	2.492	0.038

Table 7. Correlation coefficient matrix for independent variables and the variance inflation factors (VIF) for equation (5).

	Correlation matrix				R^2(adj.)	(VIF)
	qH^+	q^-	$^3\chi^v_{pc}$	$^4\chi_{pc}$		
qH^+	1.000				0.000	1.00
q^-	0.287	1.000			0.000	1.00
$^3\chi^v_{pc}$	0.346	0.373	1.000		0.096	1.10
$^4\chi_{pc}$	-0.155	0.090	-0.040	1.000	0.052	1.05

Table 8. Correlation coefficient matrix for significant independent variables and the variance inflation factors (VIF) for equation (6).

	Correlation matrix			R^2(adj.)	(VIF)
	qH^+	q^-	$^3\chi^v_{pc}$		
qH^+	1.000			0.000	1.00
q^-	-0.365	1.000		0.023	1.02
$^3\chi^v_{pc}$	0.342	-0.412	1.000	0.014	1.01

In summary, sorption behavior of 14 substituted benzaldehydes on natural sediment has been reported. The results showed that chemosorption and physical adsorption might be the fundamental process for benzaldehydes sorption on natural sediment other than lipophilic partitioning. The information presented in this study shows that these models based on quantum chemistry descriptors can predict not only Kow but also Koc. PM3 method is more accurate than AM1 method in predicting Koc, and AM1 method is more accurate than PM3 method in predicting Kow for studied compounds. Compared with empirical descriptors, the quantum chemistry descriptors have following advantages: the structure descriptors can be easily and precisely obtained by computation instead of experimentation, the quantum parameters have clear "chemical sense". These models can provide a useful starting point for predicting the potential environmental contaminant of new compounds.

Acknowledgments. This research was financed by the National Natural Science Fund of P. R. China.

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