

QSPR models for the physicochemical properties of halogenated methyl-phenyl ethers

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Abstract

Halogenated methyl-phenyl ethers (anisoles) are ubiquitous organic compounds in the environment. In the present study, geometrical optimization and electrostatic potential calculations have been performed for 134 halogenated anisoles at the HF/6-31G* level of theory. A number of statistically based parameters have been obtained. Linear relationships between sub-cooled liquid vapor pressures ($\lg p_L$), *n*-octanol/water partition coefficient ($\lg K_{ow}$) and aqueous solubilities ($-\lg S_{w,L}$) of halogenated anisoles and the structural descriptors have been established by multiple regression method. The result shows that the quantities derived from electrostatic potential V_{min} , $V_{s,max}$, $\sum V_s^+$, $\sum V_s^-$, $V_{s,av}^-$ and v , together with the molecular volume (V_{mc}) and E_{HOMO} can be well used to express the quantitative structure–property relationships of halogenated anisoles, which proves the general applicability of this parameter set to a great extent. Good predictive capabilities have also been demonstrated. Based on these excellent equations, the predicted values have been presented for those halogenated anisoles whose experimentally determined physicochemical properties are unavailable.

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1. Introduction

Halogenated methyl-phenyl ethers (anisoles) are ubiquitous organic compounds in the environment. There are 134 possible congeners consisting of 19 chloroanisoles, 19 bromoanisoles and 96 bromo-chloroanisoles. Although they are not produced in industrial quantities, various members of the halogenated methyl-phenyl ethers have been detected in the air, water, sediments, food, marine algae and fish [1–8]. The musty odors of drinking water are among the major causes of complaints by consumers. Recently, much attention has been paid to the presence of halogenated anisoles which can be formed by biomethylation of the corresponding halophenols which are initially formed as drinking water disinfection byproducts by chlorination or chloramination practices. It is clear that very

low levels of haloanisoles can cause taste and odor episodes in treated water [9].

Physicochemical properties of an organic chemical compound play an important role in determining its distribution and fate in the environment. Vapor pressures (p_L), aqueous solubilities ($S_{w,L}$) and *n*-octanol/water partition coefficients (K_{ow}) are key physicochemical properties that can be used for assessing environmental partition and transport of organic substances. It has been shown in a recent study that they are linearly correlated to the gas-chromatographic relative retention time (RRT) for the halogenated methyl-phenyl ethers [10]. Ballschmiter et al. [1,10] measured systematically the RRT of about 60 possible halogenated anisoles in environmental samples by GC, then they further determined vapor pressures (p_L), water solubilities ($S_{w,L}$), and *n*-octanol/water partition coefficients (K_{ow}) by capillary HR-GC (high resolution gas chromatography) on a non-polar phase and by RP-HPLC (reversed phase high performance liquid chromatography) on a C_{18} phase with chlorobenzenes as reference standards. From these experimental data the Henry's law constants (H), and the

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gas/water (K_{gw}) and gas/*n*-octanol (K_{go}) partition coefficients were calculated.

Nonetheless, for the remaining halogenated anisoles, their physicochemical data are lacking. Due to not only the time consumption and high expense, but also the unavailability of chemical standards of many halogenated anisoles, it is nearly impossible to determine experimentally the physicochemical properties for all the halogenated anisoles. Therefore, alternative approaches are needed. Some previous studies showed that it was indeed feasible to predict the properties with quantitative structure–property relationship (QSPR) models for many organic compounds [11–18]. However, this kind of studies on halogenated anisoles is still limited [10].

The choice of appropriate structural parameters plays a pivotal role in the QSPR studies. It has been known that most of the physicochemical properties are associated with intermolecular non-covalent interaction, which is mostly electrostatic in nature, and the electrostatic potentials $V(r)$, especially those distributed on the molecular surface, can be well used to quantify the molecular interactions. In fact, the structural descriptors derived from the molecular electrostatic potentials $V(r)$ have been successfully applied in research of the quantitative structure–property relationships [19–24], and their application range is being increasingly extended [25–28]. In this paper, we report the quantitative structure–property relationships of the halogenated anisoles established by using the structural descriptors derived from the molecular surface electrostatic potentials $V_s(r)$. It serves on one hand to improve our understanding how the physicochemical properties change with the numbers and position of substituted halogen atoms, and to provide a new effective method for predicting physicochemical properties of the organic pollutants on the other hand.

2. Methods

The molecular structure in this article is halogenated methyl-phenyl ethers, in which there are few flexible bonds. As can be seen from our previous researches [24,28], conformational change about the kind of systems have no effect to the results. Therefore a conformational search of any kind was not performed. The initial geometries of each compound were optimized and frequency calculations were carried out with MOPAC 6.0 program implemented in VEGA package using AM1 method (keywords “PRECISE”, “GEO-OK”) [29]. Vibrational analyse showed that all of the species had no imaginary vibrational frequency, indicating the nature of the stationary point structures. Then the molecular geometries were reoptimized at the HF/6-31G* level with Gaussian98 software package [30]. Based on these optimized geometries, calculations of electronic density and electrostatic potentials with grid method were performed. The grid control option was set to “cube = 100”; therefore, for each molecule, there are about 100^3 points at which the values of electronic density and electrostatic potentials were computed.

Subsequently, a series of statistically based indices derived from these electrostatic potentials, mostly according to Politzer and co-workers [19], were obtained. The descriptors used in this paper include:

- (a) $V_{s,\text{max}}$, the maxima of electrostatic potentials on the surface.
- (b) $V_{s,\text{min}}$, the most negative electrostatic potentials $V(r)$ anywhere in the three-dimensional space around the molecule.
- (c) $\sum V_s^-$, defined as the sum of the surface minima values of the electrostatic potential. The sum started from the most negative potential on the molecular surface, and if two $V_{s,\text{min}}$ appeared within 2.1 Å of each other, only the minimum with the most negative potential was included in the sum. $V_{s,\text{av}}^-$ is its average.
- (d) For comparison, $\sum V_s^+$, defined as the sum of the surface maxima values of the electrostatic potential.
- (e) ν , the equilibrium parameter of electrostatic potentials on molecular surface. ν was defined as [19]:

$$\nu = \frac{\sigma_+^2 \sigma_-^2}{(\sigma_{\text{tot}}^2)^2} \quad (\text{i})$$

$$\sigma_{\text{tot}}^2 = \sigma_+^2 + \sigma_-^2$$

$$= \frac{1}{m} \sum_{i=1}^m |V^+(r_i) - \bar{V}_s^+|^2 + \frac{1}{n} \sum_{i=1}^n |V^-(r_i) - \bar{V}_s^-|^2 \quad (\text{ii})$$

where $V^+(r_i)$ and $V^-(r_i)$ are the positive and negative values, respectively, of the electrostatic potential at a point r_i on the molecular surface, and \bar{V}_s^+ and \bar{V}_s^- are their averages.

- (f) E_{HOMO} is the energy of the highest occupied molecular orbital.

Furthermore, because the physicochemical properties have close relation to the molecular weight, surface area (A_s) and volume (V_{mc}), these parameters were calculated with TSAR software package. Finally, correlation between the structural descriptors of halogenated anisoles and their physicochemical properties was established by multiple linear regression method.

3. Results and discussion

The experimentally determined physicochemical properties of halogenated anisoles were taken from previous publications [1,10], including sub-cooled liquid vapor pressures ($\lg p_L$), *n*-octanol/water partition coefficient ($\lg K_{\text{ow}}$) and water solubilities ($-\lg S_{\text{w,L}}$). These data, together with the chemical names and the predicted properties from QSPR models for all 134 halogenated anisoles, are collected in Table S1 of the supplementary materials. Table S2 of the supplementary materials lists the computed structural descriptors of each of the 134 halogenated anisoles.

Table 1 summarizes the correlations between the computed structural parameters and the physicochemical properties through linear regression analysis, where N represents the number of data points submitted to the regression, R is the

Table 1

Relationships between physicochemical properties of halogenated anisoles and the calculated descriptors

Equation nos.	<i>N</i>	<i>R</i>	S.D.	<i>F</i>
(1) $\lg p_L = 2.5964 - 0.0569V_{mc} + 0.0437 \sum V_s^- - 18.4854E_{HOMO}$	52	0.9473	0.3318	140.004
(1a) $\lg p_L = 1.4151 - 0.0591V_{mc} + 0.0437 \sum V_s^- - 22.9227E_{HOMO}$	42	0.9423	0.3540	105.72
(2) $\lg K_{ow} = 0.7719 + 0.0321V_{mc} + 0.5947V_{min} + 0.8219V_{s,max} - 0.0335 \sum V_s^+$	49	0.9779	0.1619	240.732
(2a) $\lg K_{ow} = 0.8361 + 0.0322V_{mc} + 0.5626V_{min} + 0.8769V_{s,max} - 0.0431 \sum V_s^+$	41	0.9789	0.1608	207.10
(3) $-\lg S_{w,L} = 2.2942 + 0.0355V_{mc} + 0.7838V_{min} - 4.3016\nu + 1.3970V_{s,av}^-$	27	0.9918	0.1303	360.321

correlation coefficient, S.D. the standard deviation and *F* is the overall statistical significance of the equation.

Molecular volume (V_{mc}) and molecular surface area (A_s) are measurement of the molecular size. They are highly correlated with each other. The correlation coefficient amounts to as high as 0.9841 for the present compound set of 134 halogenated anisoles. Our results show that the V_{mc} term were introduced in Eqs. (1–3), and less satisfactory correlations were yielded when using A_s term as an alternative. Generally speaking, for the compounds with similar structure, the larger the molecular volume is, the stronger the intermolecular dispersion force will be. In addition, molecular volume is often viewed as a cavity term in linear solvation energy relationship (LSER) which is a measure of the energy needed to overcome the cohesive forces in order to form a cavity for the solute, and the larger molecules would tend to be excluded from the more polar solvent (e.g. water).

As can be seen in Table 1, the V_{mc} term is negatively correlated with $\lg p_L$ in Eq. (1), which indicates that the larger the molecule is, the stronger the intermolecular dispersion force is, lower the volatility or liquid vapor pressure is. Similarly, it is quite reasonable that the V_{mc} term was introduced in the QSPR equations of $\lg K_{ow}$ and $\lg S_{w,L}$, because the larger halogenated anisole molecule would yield stronger dispersion-type interaction with the *n*-octanol molecule (i.e. the $\lg K_{ow}$ value becomes larger) or the more weak interaction with the water molecule (lowering the water solubility).

E_{HOMO} , an electron-donor parameter, is defined as the energy of the highest occupied molecular orbital. The inclusion of E_{HOMO} in the model (1) indicates that there is probably electron-transfer process in the interaction between molecules. The parameter has a negative sign, which means that the larger E_{HOMO} , the lower the p_L value. That E_{LUMO} is not included in the equation probably means that the chemicals are electron-donor, showing halogenated anisole compounds have the ability to provide π -electron and yield π – π electron interaction each other.

The other six parameters introduced are all related with the molecular surface electrostatic potentials. V_{min} and $V_{s,max}$ are defined by Politzer and co-workers [19] as the spatial minima and surface maxima of the electrostatic potential, respectively. The former measures the hydrogen bond-accepting tendency or hydrogen bond basicity of a molecule, whereas the latter measures the hydrogen bond-donating tendency or hydrogen bond acidity of a molecule [19,31,32]. It has been found that the V_{min} gave a slightly better correlation than the $V_{s,min}$, a quite similar quantity just defined as the surface minima of the

molecular electrostatic potential. In Eq. (2), the sign of the V_{min} term is positive, which means that the increase of hydrogen bond basicity of a solute would favor its partition in water. The same conclusion can be found in many other literatures [24,33]. Similarly, it is quite reasonable that the V_{min} term was introduced in the QSPR equations of $\lg S_{w,L}$, which is negatively correlation, i.e., the stronger hydrogen bond basicity of a solute, the larger its water solubility. Several researchers have shown that the hydrogen bond acidity makes no significant contribution to the K_{ow} for their data set [33,34]. However, the $V_{s,max}$ term in Eq. (2) reveals that the hydrogen bond acidity is statistically significant and gives a positive contribution to $\lg K_{ow}$. This finding is in accordance with the one of our previous research which obtained the $\lg P$ for a data set of 103 disubstituted benzenes [24], and Kamlet et al. who correlated the $\lg P$ for a data set of 245 organic compounds [35].

$\sum V_s^-$ is defined as sum of independently negative electrostatic potentials on the molecular surface. It is noteworthy that the sum started from the most negative potential on the molecular surface, and if two $V_{s,min}$ appeared within 2.1 Å of each other, only the minimum with the most negative potential was included in the sum. In other words, the distance between two minimum electrostatic potentials introduced in $\sum V_s^-$, 2.1 Å, is an empirical cutoff value. This value is just the arithmetic mean value between the van der Waals radius of a water molecule (1.4 Å) and the diameter of the water molecule (2.8 Å). As demonstrated in our prior publications [24,27] and the present study, the statistical quality has been considerably improved when $\sum V_s^-$, as a variable, is introduced in QSPR/QSAR models. In addition, we also find that $\sum V_s^-$ correlates better to Π ($r = 0.8705$), another descriptor derived from electrostatic potential, which has been proven to be a good descriptor reflecting non-specific intermolecular interactions [23,36]. Therefore, $\sum V_s^-$ reflects non-specific intermolecular interactions to a certain extent. $\sum V_s^+$ is the sum of independently positive electrostatic potentials on the molecular surface, a descriptor quite similar to $\sum V_s^-$. The quality has improved when it is presented in Eq. (2).

Table 2

The variance inflation factor (VIF) of each descriptor and the cross-validated correlation coefficient (R_{cv})

Models	VIF	R_{cv}
1	$V_{mc}(2.154)$; $\sum V_s^-(1.376)$; $E_{HOMO}(2.425)$	0.9214
2	$V_{mc}(2.089)$; $V_{min}(2.083)$; $V_{s,max}(2.099)$; $\sum V_s^+(2.059)$	0.9690
3	$V_{mc}(2.167)$; $V_{min}(3.111)$; $\nu(1.983)$; $V_{s,av}^-(1.955)$	0.9867

$V_{s,av}^-$, which is defined as the average of $\sum V_s^-$ mentioned above, is another descriptor introduced in Eq. (3) besides V_{min} . Though the physical meaning of $V_{s,av}^-$ is still not very explicit now, its entering in the correlation implies that the negative electrostatic potentials of halogenated anisoles play a significant role in the physicochemical properties of halogenated anisoles. Also included in Eq. (3) is ν . ν is the balance parameter of electrostatic potentials on molecular surface. The quality of Eq. (3) is considerably improved by introducing ν as a variable. In the equation, ν is positively correlated with $\lg S_{w,L}$, indicating that the larger ν value is, the better the balance between positive and negative electrostatic potentials is, and the larger water solubility is.

As there is more than one variable presented in the correlations, it is necessary to examine the stability of our regression. Upon investigating the collinearity of variables in Eqs. (1)–(3), we obtain the variance inflation factor (VIF) for each descriptor which is summarized in Table 2. As one can see, the VIF values are all less than 3.0 except that of V_{mc} is somewhat large (3.111) in Eq. (3), indicating the stability of the equations constructed (according to statistics principle, a value of 1.0 is indicative of no correlation, while a value of under 10.0 is statistically satisfactory).

To test the predictive power of the QSPR models, a leave-one-out cross-validate analysis has been made for each model. The results are satisfactory for the physicochemical properties of halogenated anisoles. The cross-validated correlation coefficients (R_{cv}) are all larger than 0.94, which shows high predictive capability of these models (see Table 2), especially Eq. (3) (the R_{cv} reached to 0.9918). The plots of predicted versus observed results for Eq. (3) is shown in Fig. 1, from which good fits are seen. Table S1 of the supplementary materials presents the predicted values for all 134 halogenated anisoles including those whose experimentally determined physicochemical properties are unavailable. For p_L and K_{ow} , considering that the data are plentiful and the cross-validation could be made by leaving out more samples, we randomly split these data into training and test sets to evaluate further the

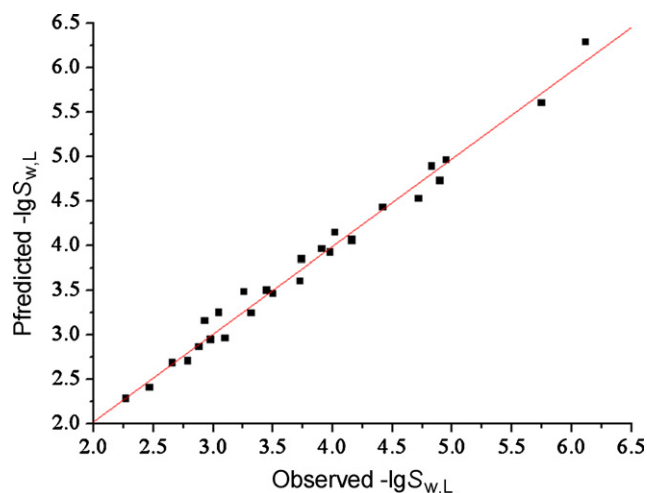


Fig. 1. Relationship between predicted and observed aqueous solubilities ($-\lg S_{w,L}$).

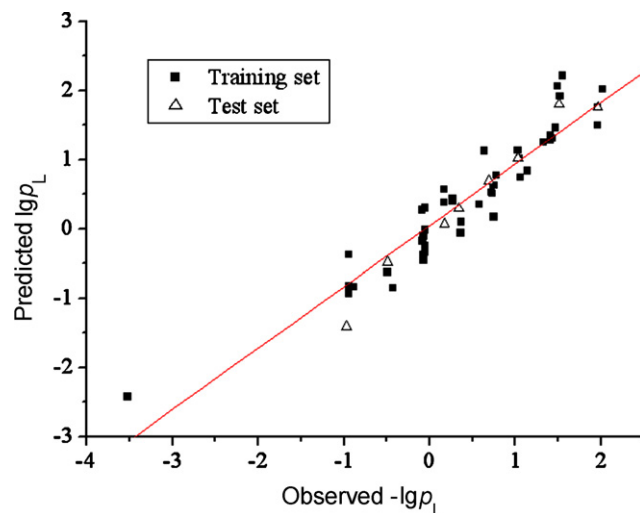


Fig. 2. Relationship between predicted and observed vapor pressures ($\lg p_L$) for training and test sets.

predictive power of the model (the test sets marked by asterisk in Table S1 of the supplementary materials). By using stepwise linear regression analysis, the relationship has been established for the training set (Eqs. (1a) and (2a) in Table 1). As one can see, the correlations established for the training set do not differ significantly from that for the whole data set (Eqs. (1) and (2)), implying the robustness of our QSPR models. Using Eqs. (1a) and (2a), we predict $\lg p_L$ and $\lg K_{ow}$ of the halogenated anisoles in both the training and test sets, respectively. Figs. 2 and 3 show the relationships between the observed and predicted results from which good agreement has been noted without obvious exceptions. Hence, these models obtained can be used to predict the p_L , K_{ow} and $S_{w,L}$ values of other halogenated anisoles, and the predicted results list in Table S1 of the supplementary materials.

Although Pfeifer et al. [10] also calculated the Henry's law constants (H), and the gas/water (K_{gw}) and gas/*n*-octanol (K_{go}) partition coefficients based on p_L , K_{ow} and $S_{w,L}$,

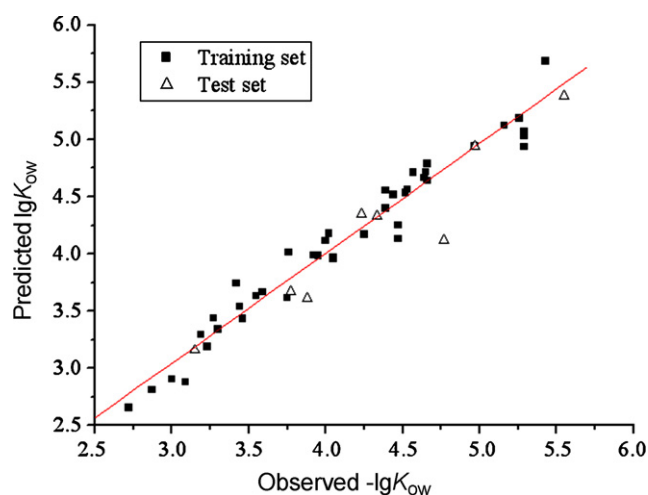


Fig. 3. Relationship between predicted and observed *n*-octanol/water partition coefficients ($\lg K_{ow}$) for training and test sets.

because of errors of the two starting values, the uncertainty of H , K_{gw} and K_{go} may be even higher. Indeed, the QSPR model fitting results for H , K_{gw} and K_{go} are not as significant as those for p_{L} , K_{ow} and $S_{\text{w,L}}$, thus those results are not presented in this paper.

4. Conclusions

Quantitative structure–property relationships for sub-cooled liquid vapor pressures ($\lg p_{\text{L}}$), n -octanol/water partition coefficient ($\lg K_{\text{ow}}$) and water solubilities ($-\lg S_{\text{w,L}}$) of halogenated anisoles have been established. It has been shown that the structural descriptors derived from molecular electrostatic potentials together with molecular volume and the energy of the highest occupied molecular orbital can be well used to express the quantitative structure–property relationships of halogenated anisoles. This, together with our previous QSPR studies on polychlorinated biphenyls, polycyclic aromatic hydrocarbons demonstrates and polybrominated biphenyl ethers [26–28], to a certain extent, demonstrates that the parameter set derived from electrostatic potentials on molecular surface has general applicability in property prediction of organic pollutants.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jmgm.2007.09.004.

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