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# Effective Solvent Cavity for 1-Hydroxy-9,10-anthraquinone Derivatives in Methanol/Water, Using a Local QSAR Study Method

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**Abstract** The Onsager reaction field model was applied to 1-hydroxy-9,10-anthraquinone derivatives dissolved in binary solvent mixtures of methanol/water. Each solution was placed in a cavity surrounded by a continuous dielectric constant medium, and then the quantum chemical descriptors of the solute were calculated. Multiple linear regression was used to perform the QSPR model calculations in order to predict the acidity constants of the solutes. The resultant hexa-parametric model was able to predict the acidity constants within absolute average deviations less than 1.82 %. The proposed model suggests that the acidic property of the solute is controlled by solvation processes through coulombic interactions as well as orbital energies. It was found that the solvent lowered the excited orbital energy states of all 1-hydroxy-9,10-anthraquinone derivatives. The model proposes that an effective solvation cavity needs more methanol molecules than water in order to increase the solvation energy in the solution.

**Keywords** Reaction field model · Quantum chemical descriptors · Potential energy surface · Orbital energy · Acidity constant · Dielectric constant

## List of symbols

$N$	Number of components
$R^2$	Correlation coefficient
SE	Standard error of regression
$F$	Fisher's $F$ -ratio
$Q_{\text{LOO}}^2$	Correlation coefficients of leave-one-out cross-validations
$Q_{\text{LTO}}^2$	Correlation coefficients of leave-three-out cross-validations
$\text{p}K_{\text{a}}$	Acidity constant
AQ	Anthraquinone derivatives

## Subscripts

rms    Root mean square

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s	Surface potential
a	Acidity
LOO	Leave one out
LTO	Leave three out

### Superscripts

+	Positive potential energy surface value
–	Negative potential energy surface value

## 1 Introduction

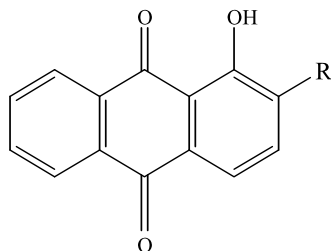
It is well known that the toxicity and pharmaceutical properties of an organic molecule depend on its acidic character [1, 2]. The acidity constants play fundamental roles in many analytical procedures such as acid–base titration, solvent extraction, complexometry, and ion transport. Therefore, knowledge of the acidic properties of chemical substances could help to elucidate their toxicities, pharmaceutical activities, and analytical roles. Some of the fundamental theories of classical physical organic chemistry are based on how an acid–base equilibrium is affected by changing the chemical structures of the molecules involved in the reaction [3]. Quantitative structure–activity/property relationship (QSAR/QSPR) techniques are promising computational tools for predicting acidity constants of new and even unsynthesized chemicals [4]. The QSPR techniques relate chemical properties of a class of compounds to their encoded molecular structure parameters that are called molecular descriptors [5, 6]. The chemical properties of interest can be boiling and melting points, acid–base behavior, chromatographic retention indices, partitioning phenomena, reaction kinetics and equilibria, and so on.

Molecular descriptors play fundamental roles in the QSAR/QSPR studies. Finding new molecular descriptors with higher correlation to activity/property is in the frontier of QSAR/QSPR research. In this regard, electronic descriptors obtained from quantum chemical calculations have found major popularity and there is a challenge in choosing between calculation complexity and accuracy in order to select the appropriate quantum chemical calculation methods, e.g. semi-empirical and *ab initio* [7].

Among the naturally occurring quinines, 1-hydroxy-9,10-anthraquinone derivatives have important application in industry and medicine [8]. Shamsipur et al. previously reported the  $pK_a$  values of several 2-substituted 1-hydroxy-9,10-anthraquinone derivatives (Fig. 1) in four different methanol–water mixtures [9–11]. Herein, we used these data for our QSPR study of acidity constants.

In a work by Shamsipur et al., a QSPR study based on topological and semi-empirical quantum descriptors with linear modeling was conducted on the acidity constant of 1-hydroxy-9,10-anthraquinone derivatives [12]. The correlation coefficient and root-mean-square error of their best QSPR model were 0.954 and 0.042, respectively. Hemmateenejad et al. developed the previous QSPR model by using a diverse set of modern quantum chemical descriptors and a genetic algorithm-based neural network to model nonlinear and complex relationships [13]. A three-layered, feed-forward ANN in conjunction with a genetic algorithm was used to model the nonlinear relationship between the selected descriptors and the acidity constants. The resulting model showed high prediction ability with the correlation coefficient and root-mean-square error of 0.993 and 0.008, respectively. However, it was found that in the presence of a solvent reaction field, the geometry, energy and charge distributions of solutes were all altered significantly [14]. Despite the high predictability of

**Fig. 1** Molecular structures of the anthraquinone derivatives where *m*-Me and *p*-Me stand for the *meta*- and *para*-position of the methyl group with respect to the –OH group, respectively



1	H	8	CH <sub>2</sub> Br
2	Me	9	CHBr <sub>2</sub>
3	Et	10	CHO
4	CH <sub>2</sub> OMe	11	CH <sub>2</sub> OH
5	CH <sub>2</sub> OEt	12	<i>m</i> -Me
6	CH <sub>2</sub> OPr	13	<i>p</i> -Me
7	CH <sub>2</sub> OBu		

the proposed models, the explicit effects of the solvent on acidity constant have been ignored since gaseous phase quantum descriptors were used to build the corresponding models [12, 13]. Therefore, it will be difficult to have any verification of the solvation mechanism and optimum media conditions using either of these proposed models.

In this article, a local QSPR study was conducted on the acidity constants of 1-hydroxy-9,10-anthraquinone derivatives by applying real quantum descriptors. In order to study the role of the solvent, quantum descriptors of any individual molecule were calculated in the solvent. Multiple linear regression (MLR) analysis was employed to obtain the structure–activity relationships between the acidity constants and molecular quantum descriptors.

## 2 Methods

### 2.1 Software

A Pentium IV personal computer with Windows XP operating system was used. All molecular structures (Z-matrix) were built and initially optimized in Hyperchem version 6.03 (Hypercube, Inc.). For full optimization of molecular structures and calculation of quantum chemical descriptors, Gaussian 98 software was used. Variable selections were performed with SPSS software version 11.5.0 (SPSS Inc., 2001) by employing the multiple linear regression method.

### 2.2 Quantum Chemical Computations

The electronic properties of several 2-substituted 1-hydroxy-9,10-anthraquinone derivatives (Fig. 1) were used in binary mixtures of methanol/water as solvents [9–11]. All molecular structures were built in Hyperchem Software for Structural Chemistry. Gaussian 98 was used to optimize the chemical structures in the solvent. The chemical structures were optimized with 6-31G basis set for all atoms at the HF level of theory. The idea that the effect of solvents on the energies of organic compounds is often reasonably related to the dielectric constant of the solvent, which has been applied quantitatively in some research [14, 15], was followed. In this manner the Onsager reaction field model, in which solute is placed in a cavity surrounded by a continuous dielectric constant medium, was applied [15].

**Table 1** Brief description of the calculated quantum chemical descriptors used in this study

Quantum descriptor	Definition
$Q_{\text{rms}}$	Root mean square of charges
SNC	Sum of negative charges
SPC	Sum of positive charges
$D_{\text{rms}}$	Root mean square of dipole moments
DM	Dipole moments
HOMO	Energy of highest occupied molecular orbital
LUMO	Energy of lowest unoccupied molecular orbital
EN	Electronegativity
HD	Hardness
SOF	Softness
EPH	Electrophilicity
MNC	Most negative charge
MPC	Most positive charge
HLG	Energy gap between HOMO and LUMO
DS	Square of dipole moment
HLG/HOMO	Ratio of HLG to HOMO
HLG/LUMO	Ratio of HLG to LUMO
LUMO/HOMO	Ratio of LUMO to HOMO
$V_s^+$	Positive potentials
$V_s^-$	Negative potentials
$\overline{V}_s^+$	Average of positive potentials
$\overline{V}_s^-$	Average of negative potentials
$n$	Number of negative potentials
$m$	Number of positive potentials

The average value of the dielectric constants of the solvent mixture was used as an input in order to account for the solvent effects on the molecular structures. No molecular symmetry constraint was applied; rather, full optimization of all bond lengths and angles was carried out at the HF/6-31G level. In a separate calculation, the density functional B3LYP/6-31G option of Gaussian 98 was run to optimize the molecular geometry and compute the electrostatic potential  $V(r)$ , on the molecular surfaces [16]. The calculated electronic descriptors for each molecule are summarized in Table 1.

Hardness HD, softness SOF, electronegativity EN, and electrophilicity EPH are the important electronic features used to describe stability, reactivity, chemical potential and other related properties of the molecules. Hardness has been used to understand chemical reactivities and stabilities of molecules [17]. Electronegativity was introduced by Pauling as a power of an atom in a molecule to attract electrons toward itself. Softness is a molecular property that measures the extent of chemical reactivity. Electrophilicity was proposed by Parr et al. [17] as a measure of energy lowering due to maximal electron flow between donor and acceptor. Taking into account the ionization potential ( $I$ ) =  $-E_{\text{HOMO}}$  and the electron affinity ( $A$ ) =  $-E_{\text{LUMO}}$ , the quantum chemical indices of HD, SOF, EN, and EPH can be calculated as  $\text{HD} = (I - A)/2 = (E_{\text{LUMO}} - E_{\text{HOMO}})/2$ ,  $\text{EN} = (I + A)/2 = -(E_{\text{LUMO}} + E_{\text{HOMO}})/2$ ,  $\text{SOF} = 1/\text{HD}$ , and  $\text{EPH} = (-\text{EN})^2/(2\text{HD})$  [18, 19]. Quantitative analysis of the electrostatic potential energy surface  $V_s(r)$  is often focused on locating and ranking the most negative potentials,  $V_s^-(r_k)$ , in the region surrounding a molecule; the more negative potentials,

$V_s^-(r_k)$  are viewed as indicating that the sites are most reactive toward electrophiles. The  $V_s^-(r_k)$  values are usually associated with the lone pairs of the more electronegative atoms such as N, O, F, Cl, S, and Br, and unsaturated aromatic and strained carbon–carbon bonds. The electrostatic potential computed at the molecular surface has been shown to provide an effective basis for correlating and predicting properties that reflect molecular interactions [20–22]. Bulat et al. proposed that among several quantities that help to characterize the detailed features of the electrostatic potential on a molecular surface, positive  $V_s^+(r_j)$ , negative  $V_s^-(r_k)$ , electrostatic potential extremes, their overall average value  $\bar{V}_s(r)$ , and its positive and negative averages  $\bar{V}_s^+$  and  $\bar{V}_s^-$  are of concern [23]. Using the method of Bulat et al., these quantities were computed by appropriate summations over a finely spaced grid covering the entire molecular surface:  $\bar{V}_s = \sum_{i=1}^t \frac{V_s(r_i)}{t}$ ,  $\bar{V}_s^+ = \sum_{j=1}^m \frac{V_s^+(r_j)}{m}$ ,  $\bar{V}_s^- = \sum_{k=1}^n \frac{V_s^-(r_k)}{n}$  where  $t$  is the total number of points on the potential energy surface grid, and  $m$  and  $n$  are the numbers of points at which  $V_s(r)$  is positive and negative, respectively.

The calculated descriptors can be classified into four different electronic categories including local charges, dipoles, orbital energies and electrostatic surface potential. For each molecule in the solvent, 24 electronic descriptors (Table 1) were calculated. In addition, the solvent composition (volume-% of methanol in water), VP, was used. Therefore, the descriptor data matrix of each molecule in a particular solvent was composed of 25 columns.

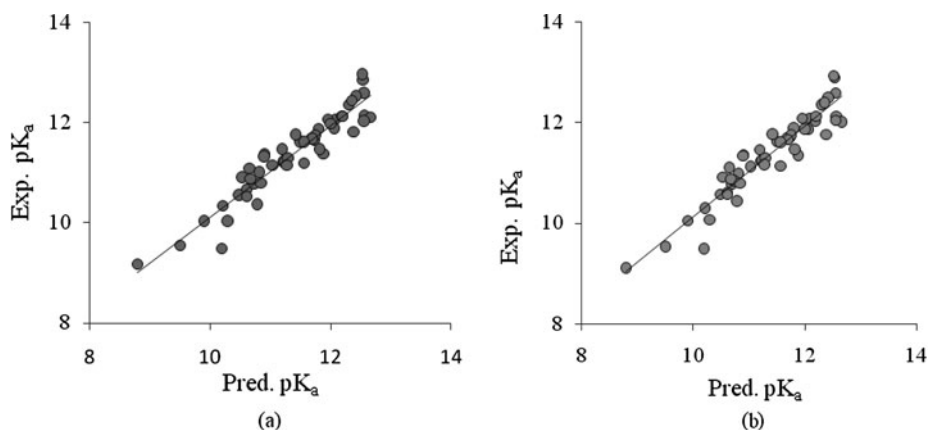
### 3 Results and Discussion

The chemical structures of thirteen 1-hydroxy-9,10-anthraquinone derivatives (Fig. 1) in four different methanol/water solvent mixtures (52 entries in overall) were optimized and their corresponding quantum descriptors were calculated. Since each 1-hydroxy-9,10-anthraquinone derivative in the four different methanol/water solvent mixtures show different electronic energy distributions, our one time regression model was composed of a data matrix of  $52 \times 25$ . In this work, the most important variables are selected by a stepwise selection procedure, which combines the forward selection and backward elimination approaches. This procedure considers first the descriptive variable most highly correlated with the response. If the inclusion of this variable results in a significant improvement of the regression model, evaluated with an overall  $F$ -test, it is retained and the selection continues. In a next step the variable that gives the largest significant decrease of the regression sum of squares, evaluated with a partial  $F$ -test, is added. After each forward selection step a backward elimination step is performed. At this stage a partial  $F$ -test for the variables, already in the equation, is carried out. If a variable is no longer contributing significantly to the regression model, it is removed. The procedure stops when no more variables fulfill the requirements needed to be removed or entered. After this selection procedure classical MLR can be applied on the retained variables to build a predictive model.

When stepwise variable selection-based MLR analysis was employed to obtain the structure–reactivity relationships, the following hexa-parametric model was obtained;

$$\begin{aligned} pK_a = & 11.34(\pm 0.51) + 0.045(\pm 0.004)VP - 0.156(\pm 0.016)DS \\ & - 4.523 \times 10^{-6}(\pm 7.96 \times 10^{-7})n \\ N = & 52, \quad R^2 = 0.898, \quad SE = 0.298, \quad F = 65.8, \\ Q_{\text{LOO}}^2 = & 0.893, \quad Q_{\text{LTO}}^2 = 0.895 \end{aligned} \quad (1)$$

The values in parentheses represent the standard deviation of the coefficients. The symbols  $N$ ,  $R^2$ ,  $SE$  and  $F$  are the number of components in different solvents, correlation coefficient,



**Fig. 2** (a) Leave-one-out and (b) leave-three-out cross-validation predicted values of the acidity constants of different 1-hydroxy-9,10-anthraquinone derivatives in four different methanol/water mixtures

cient, standard error of regression and Fisher's  $F$ -ratio, respectively. The correlation coefficients of leave-one-out and leave-three-out cross-validations are denoted by  $Q_{\text{LOO}}^2$  and  $Q_{\text{LTO}}^2$ , respectively. The  $R^2$  value of 0.898 indicates that the resultant equation can explain about 89.8 % of the variance in the  $\text{p}K_{\text{a}}$  data of the 1-hydroxy-9,10-anthraquinone derivatives in the solvent mixtures, whereas the high value of cross-validated correlation coefficients and also their closeness to each other explain the predictive power and stability of the proposed model (Fig. 2). The widely used approach to establish the robustness of the resulting models is called  $Y$ -randomization. The values of  $\text{p}K_{\text{a}}$  were randomly attributed to the molecules and the MLR modeling was repeated with the randomized data. The randomization was repeated one hundred times and the maximum values obtained for the  $R^2$  and RMS are 0.33 and 0.11, respectively. The statistical qualities of these models are much lower than the original one. Therefore, it can be concluded that our model is reasonable and had not been obtained by chance.

It can be seen from Eq. 1 that the selected molecular structural parameters cover all four different electronic classes of the suggested descriptors including local charges, dipoles, orbital energies and electrostatic surface potential.

This model was used to calculate the acidity constants of 1-hydroxy-9,10-anthraquinone derivatives in the same methanol/water mixtures with four different volume-% of methanol. Results are shown in Table 2.

Concerning the model Eq. 1, the positive sign of volume-% of methanol, VP, in the mixed solvent shows the importance role of the volume-% of methanol not only in constructing the solvent (methanol/water) cavity in the solvation process, but also in the other solute–solvent interactions such as dipolarity or hydrogen bonding. The significance of dipolar coulombic interactions between the solute and solvent is reflected in the selected dipole moment, DS, and most negative charge, MNC. This can be ascribed to the coulombic nature of strong solute–solvent interactions like halogen and hydrogen bonding. Considering the negative value of MNC, its positive sign in Eq. 1 implies that an increase of negative charge stabilizes the anion and decreases the values of  $\text{p}K_{\text{a}}$ . The other two correlating parameters are  $n$  and  $\overline{V}_{\text{s}}^-$ , the number of negative electrostatic potential energy and average of negative electrostatic potential energy surfaces, respectively. This reveals that the more negative potentials, indicating the sites most reactive toward electrophiles, should be more involved through its

**Table 2** Experimental (Exp.) and leave-one-out cross-validation predicted (Pred.) values of the acidity constant of different 1-hydroxy-9,10-anthraquinone derivatives in four different methanol/water mixtures. The last column is the percent relative error (%-RE) of the predicted values with respect to the experimental values

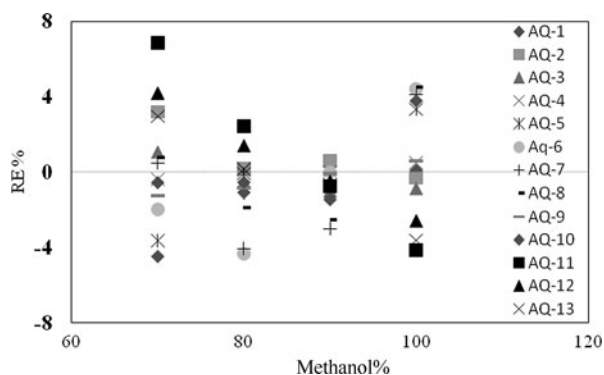
AQ	$pK_a$											
	100 % methanol			90 % methanol			80 % methanol			70 % methanol		
	Expt.	Pred.	%-RE	Expt.	Pred.	%-RE	Expt.	Pred.	%-RE	Expt.	Pred.	%-RE
1	12.08	12.07	0.08	11.50	11.62	-1.04	11.03	11.15	-1.09	10.61	10.67	-0.57
2	12.55	12.59	-0.32	12.20	12.13	0.57	11.70	11.68	0.17	11.56	11.19	3.20
3	12.42	12.53	-0.89	11.95	12.07	-1.00	11.56	11.62	-0.52	11.27	11.15	1.06
4	12.19	12.13	0.49	11.68	11.68	0.00	11.23	11.22	0.09	10.73	10.77	-0.37
5	12.56	12.14	3.34	11.80	11.88	-0.68	11.29	11.30	-0.09	10.53	10.91	-3.61
6	12.66	12.1	4.42	11.75	11.75	0.00	10.90	11.37	-4.31	10.67	10.88	-1.97
7	12.55	12.03	4.14	11.42	11.76	-2.98	10.89	11.33	-4.04	10.84	10.79	0.46
8	12.38	11.82	4.52	11.19	11.47	-2.50	10.81	11.01	-1.85	10.61	10.53	0.75
9	11.73	11.66	0.6	11.21	11.22	-0.09	10.69	10.78	-0.84	10.21	10.34	-1.27
10	10.78	10.37	3.80	9.90	10.04	-1.41	9.50	9.55	-0.53	8.79	9.18	-4.44
11	10.65	11.09	-4.13	10.48	10.56	-0.76	10.29	10.04	2.43	10.19	9.49	6.87
12	12.53	12.85	-2.55	12.30	12.36	-0.49	12.06	11.89	1.41	11.88	11.38	4.21
13	12.52	12.97	-3.59	12.35	12.44	-0.73	12.00	11.98	0.17	11.82	11.47	2.96

positive end. This indicates the significant interaction of lone pairs of the more electronegative atoms, such as O and Br, and unsaturated aromatic and strained carbon-carbon bonds with the hydrogens of water and methanol molecules. The negative sign of the energy gap between the highest occupied and the lowest unoccupied molecular orbital, HLG/LUMO, may be attributed to the fact that the solvation process prefers a low energy gap to stabilize the resulting ions by delocalizing charges among the ground and virtual molecular states. Then, using the proposed model, the acidity constants were predicted and shown in Table 2.

The leave-one-out cross-validation model can reproduce the acidity constants of 1-hydroxy-9,10-anthraquinone derivatives in the four different methanol/water solvent mixtures within an absolute average deviation of less than 1.82 % (Table 2). The relative errors of the calculated acidity constants of thirteen different 1-hydroxy-9,10-anthraquinones against the percent of methanol in solvent mixture are compared in Fig. 3. As is shown in this figure, the relative errors decrease as the percent of methanol increases in the methanol/water mixtures. In other words, the acidity constant values are better fitted to the proposed model for the solvent mixtures containing less water molecules. This fact can be explained in that water increases the average negative charge density in the solvent cavity, which leads to a low solubility for 1-hydroxy-9,10-anthraquinone derivatives with lone electron pairs on electronegative atoms such as O and Br as well as unsaturated aromatic and strained carbon-carbon bonds. This finding has been confirmed by *ab initio* calculations and Monte-Carlo simulation, and also in a study by Hemmateenejad on properties of the solute in methanol/water association [24, 25] in which they found more a higher negative charge on water than on methanol. A closer look at Fig. 3 reveals that the acidity constant of one of the 1-hydroxy-9,10-anthraquinone derivatives, encoded as AQ-11 ( $R = CH_2OH$ ), comes into closer agreement with experimental data as the percent of methanol in the solvent mixture increases. Such behavior is expected for solutes with an alcoholic nature that show a higher solubility in an alcohol-rich solvent. As a result, the proposed model can provide a good



**Fig. 3** Relative errors of acidity constants versus volume-% methanol in solvent mixture for thirteen 1-hydroxy-9,10-anthraquinone derivatives



prediction of the acidity constants of 1-hydroxy-9,10-anthraquinone derivatives as well as the solute–solvent interaction mechanism. The predictability of the model can be attributed to the descriptors with most of them evaluated in the solvent.

## 4 Conclusions

A variety of quantum chemical descriptors including electrical charges, dipoles and orbital energies in the solvent, and the electrostatic potential energy surface for the whole molecule of 1-hydroxy-9,10-anthraquinone derivatives, were calculated. Using the multiple linear regression method, a model was established to predict the acidity constant of 1-hydroxy-9,10-anthraquinone derivatives within average absolute errors of less than 1.82 %. It was found that the acidity is controlled by a solvation processes through coulombic interactions as well as the lower excited state orbital energies of 1-hydroxy-9,10-anthraquinone derivatives. Also, it seems that an effective solvation cavity needs more contribution from methanol molecules than water in order to increase the solvation energy in the solution.

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