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Relationships between aqueous acidities and computed surface-electrostatic potentials and local ionization energies of substituted phenols and benzoic acids

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Abstract Electrostatic potentials and average local ionization energies on the molecular surfaces of 19 phenols, 17 benzoic acids and their respective conjugate bases were computed at the HF/STO-5G(d)//B3LYP/6-311G(d,p) level. Good correlations were found between pK_a s and the $V_{S,max}$ values of the neutral acids and the $V_{S,min}$ and $\bar{I}_{S,min}$ of the conjugate bases for both sets of molecules. $V_{S,max}$ is the most positive value of the electrostatic potential on the molecular surface and is an indicator of the ease with which the phenols and benzoic acids lose their acidic hydrogens. $V_{S,min}$ and $\bar{I}_{S,min}$ are the minimum values of the electrostatic potential and the local ionization energy computed on the molecular surface; the $V_{S,min}$ and $\bar{I}_{S,min}$ of the conjugate bases of the phenoxides and benzoates are indicative, respectively, of the tendencies of electrophiles to *approach* the anions ($V_{S,min}$) and to *react* with the anions ($\bar{I}_{S,min}$) to reform the original acids. The correlations observed between the computed molecular surface quantities, taken as single parameters, and the experimental pK_a values ranged from $R=0.938$ to $R=0.970$ for the two classes of compounds.

Keywords Aqueous acidities · Substituted phenols · Substituted benzoic acids · Surface electrostatic potentials · Surface local ionization energies

Introduction

In earlier studies, we and others have shown that a variety of computed quantum chemical properties correlate well

with experimental pK_a s for sets of mono-, di- and tri-substituted anilines [1, 2, 3]. Our analyses involved computing the spatial and surface-electrostatic potential minima (V_{min} and $V_{S,min}$) and the surface-local ionization energy minima ($\bar{I}_{S,min}$) associated with the amine nitrogen of each aniline derivative and correlating these quantities with pK_a values [1, 3]. Seybold and coworkers have subsequently investigated how well the pK_a s for sets of substituted phenols [4] and benzoic acids [5] correlate with a variety of computed properties; these included atomic charges (by various definitions), HOMO energies and proton-transfer energies.

In this article we explore possible relationships between pK_a values of substituted phenols and benzoic acids and first, the computed surface electrostatic potentials of the neutral acids, and second, the surface average local ionization energies and electrostatic potentials of their anionic conjugate bases.

Methods and procedure

The geometries of 19 phenols and 17 benzoic acids and their conjugate bases (phenolates and benzoates) were optimized at the B3LYP/6-311G(d,p) level [4, 5]. These structures were then used to compute electrostatic potentials and average local ionization energies on the molecular surfaces at the HF/STO-5G(d) level. We have used this basis set extensively in studies of molecular reactive behavior [6, 7, 8, 9, 10, 11], and have shown that the trends obtained with a minimal basis set correlate well in most instances with those using larger basis sets [6, 7, 8, 9, 11]. Our molecular surfaces are defined as the 0.001 electrons/bohr³ contour of the electronic density $\rho(\mathbf{r})$.

Average local ionization energies

We have earlier defined, within the framework of Hartree–Fock theory, an average local ionization energy, $\bar{I}(\mathbf{r})$ [12], given by Eq. (1):

$$\bar{I}(\mathbf{r}) = \sum_i \frac{\rho_i(\mathbf{r})|\epsilon_i|}{\rho(\mathbf{r})} \quad (1)$$

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where $\rho_i(\mathbf{r})$ is the electronic density of the i th atomic or molecular orbital at the point \mathbf{r} , ϵ_i is the orbital energy, and $\rho(\mathbf{r})$ is the total electronic density function. Since the magnitudes of Hartree–Fock orbital energies are interpreted as approximations to the electronic ionization energies [13], $\bar{I}(\mathbf{r})$ can be interpreted as the average energy needed to remove an electron from the point \mathbf{r} in the space of an atom or molecule. Indeed, $\bar{I}(\mathbf{r})$ focuses upon a particular point in space rather than upon a particular molecular orbital.

In applying $\bar{I}(\mathbf{r})$ to predicting and interpreting chemical behavior, we have found it useful to plot $\bar{I}(\mathbf{r})$ on an appropriate molecular surface [6, 12, 14, 15, 16, 17, 18, 19, 20]. We call the pattern of $\bar{I}(\mathbf{r})$ on the molecular surface $\bar{I}_S(\mathbf{r})$. The minima of $\bar{I}_S(\mathbf{r})$, denoted $\bar{I}_{S,\min}$, are the positions on the surface at which are found, on the average, the least tightly bound, most reactive electrons.

In our first application of $\bar{I}_S(\mathbf{r})$, we showed, for a series of monosubstituted benzenes, that the $\bar{I}_{S,\min}$ corresponding to the ring carbons correctly predict each substituent's *ortho*-, *para*- or *meta*-directing tendencies as well as its ring-activating or -deactivating effects; this was evidenced by an excellent correlation with the corresponding Hammett constants [12]. We have also shown that the conjugate base $\bar{I}_{S,\min}$ of a variety of oxygen, carbon and nitrogen acids [14], of a series of azines and azoles [15] and for substituted anilines [1, 3] correlate well with their respective $\text{p}K_a$ values; the lower the $\bar{I}_{S,\min}$, the greater is the tendency for the base to react with H^+ , and the higher is the conjugate acid's $\text{p}K_a$.

In this work we are investigating the relationship between $\text{p}K_a$ and the conjugate base $\bar{I}_{S,\min}$ of a series of phenols and benzoic acids; we have accordingly computed $\bar{I}_S(\mathbf{r})$ on the surface of the corresponding phenolates and benzoates.

Molecular electrostatic potentials

The electrostatic potential $V(\mathbf{r})$ that is created in the space surrounding a molecule by its nuclei and electrons is given by Eq. (2):

$$V(\mathbf{r}) = \sum_A \frac{Z_A}{|R_A - \mathbf{r}|} - \int \frac{\rho(\mathbf{r}')d\mathbf{r}'}{|\mathbf{r}' - \mathbf{r}|} \quad (2)$$

where Z_A is the charge on nucleus A , located at R_A , and $\rho(\mathbf{r})$ is the electronic density. The sign of $V(\mathbf{r})$ at any point depends on whether the effects of the nuclei or the electrons are dominant there. The electrostatic potential has been applied to the interpretation of chemical reactive behavior since the 1970s [7, 8, 9, 10, 11, 21, 22, 23, 24].

It is important to mention that the electrostatic potential surrounding spherically symmetric, neutral atoms is positive everywhere; the localized positive charge of the nucleus causes the first term on the right-hand side of Eq. (2) to be the dominant one. However, when atoms combine to form molecules, regions of negative potential develop; these are usually in regions surrounding electronegative atoms, above and below multiple carbon–carbon bonds and aromatic rings, and along the outer edges of strained carbon–carbon bonds. Each such negative region has one or more spatial minima, V_{\min} , associated with it. These V_{\min} , as well as surface minima, $V_{S,\min}$, have served as a means for ranking sites for susceptibility toward electrophilic attack [7, 8, 9, 10, 11, 21, 22, 23, 24], and have been found to correlate with hydrogen bond basicity [10, 25] and, to a lesser extent, $\text{p}K_a$ [3, 11].

Gadre et al. have shown that positive regions of molecular electrostatic potentials have spatial maxima only at the positions of the nuclei [26]; these cannot be used as indicators of nucleophilic attack. However, when $V(\mathbf{r})$ is plotted on a molecular surface, surface maxima, $V_{S,\max}$, appear; these have been shown to correlate with hydrogen bond acidity [10, 11, 25] and sites for nucleophilic attack [8, 9].

Strategy

In this work, we will be focusing on the $V_{S,\max}$ values associated with the acidic hydrogens of the phenols and benzoic acids and the

$V_{S,\min}$ and $\bar{I}_{S,\min}$ values associated with the phenolate and benzoate oxygens. The $V_{S,\max}$ values associated with the phenolic hydrogens can be viewed as measures of how easily the hydrogens will be plucked off the acid by water to form H_3O^+ , while the $V_{S,\min}$ and $\bar{I}_{S,\min}$ values of the conjugate bases are indicative, respectively, of the tendencies for electrophiles such as H_3O^+ to *approach* the anions ($V_{S,\min}$) and to *react* with the anions ($\bar{I}_{S,\min}$) to reform the original acids. We will therefore be looking at factors that affect both sides of the reaction given in Eq. (3):



We have used the SAS program [27] to search for correlations between our computed quantities and the experimentally determined $\text{p}K_a$ s.

Results

Phenols and phenolates

In Table 1 are listed the experimentally determined $\text{p}K_a$ s [28] and computed $V_{S,\max}$ values of 19 neutral phenols and the $V_{S,\min}$ and $\bar{I}_{S,\min}$ values of their conjugate bases. The trends shown in Table 1 are as follows: $\text{p}K_a$ values increase as the phenol $V_{S,\max}$, phenolate $V_{S,\min}$, and phenolate $\bar{I}_{S,\min}$ values decrease. It is therefore not surprising that linear correlations between $\text{p}K_a$ and each of these quantities exists. These are given below in Eqs. (4), (5) and (6).

$$\text{p}K_a = -0.1909(\pm 0.0180)(V_{S,\max}) + 16.81(\pm 0.71) \\ n = 19, R = 0.932, s = 0.314, F = 112 \quad (4)$$

$$\text{p}K_a = -0.1240(\pm 0.0111)(V_{S,\min}) - 8.806(\pm 1.631) \\ n = 19, R = 0.938, s = 0.300, F = 124 \quad (5)$$

$$\text{p}K_a = -1.431(\pm 0.124)(\bar{I}_{S,\min}) + 20.73(\pm 0.99) \\ n = 19, R = 0.941, s = 0.292, F = 132 \quad (6)$$

The correlation coefficients, R , are 0.932, 0.938 and 0.941, respectively; the corresponding standard deviations, s , are 0.314, 0.300 and 0.292. The best single-variable relationship, between $\text{p}K_a$ and the phenolate $\bar{I}_{S,\min}$, is shown in Fig. 1.

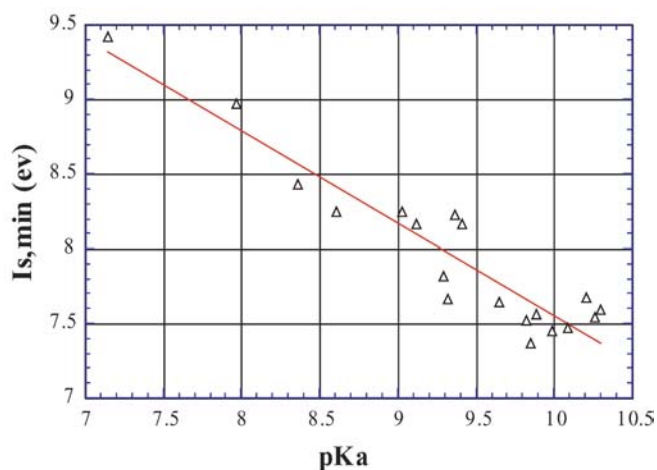
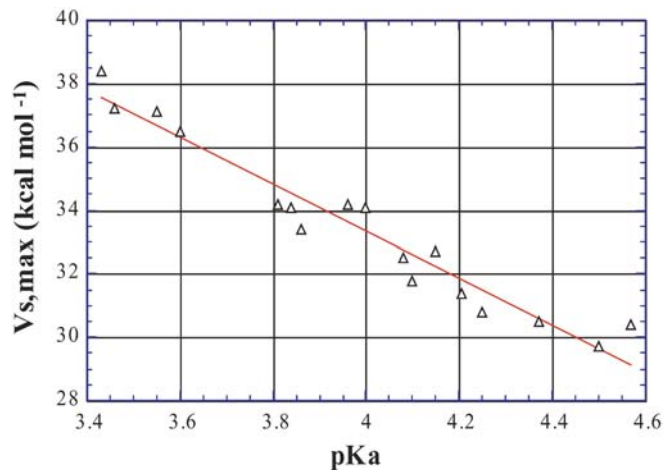
Combining the phenolate $\bar{I}_{S,\min}$ and the phenol $V_{S,\max}$ into a two-variable correlation results in an increase of the linear correlation coefficient to 0.953; the standard deviation decreases to 0.271. This relationship is given in Eq. (7).

$$\text{p}K_a = -0.8456(\pm 0.3222)(\bar{I}_{S,\min}) \\ -0.08445(\pm 0.04342)(V_{S,\max}) + 19.38(\pm 1.15) \\ n = 19, R = 0.953, s = 0.271, F = 78 \text{aligned} \quad (7)$$

If all three variables are included in the correlation, the correlation coefficient increases only insignificantly to 0.957.

Table 1 Experimental pK_a values^a and computed surface properties for phenols

Molecule	pK_a	$V_{S,max}$ (kcal mol ⁻¹)	Conjugate base $V_{S,min}$ (kcal mol ⁻¹)	Conjugate base $\bar{I}_{S,min}$ (eV)
<i>p</i> -Nitrophenol	7.15	47.7	-129.8	9.42
<i>p</i> -Cyanophenol	7.97	45.6	-134.8	8.97
<i>m</i> -Nitrophenol	8.36	44.3	-140.9	8.43
<i>m</i> -Cyanophenol	8.61	43.8	-142.3	8.25
<i>m</i> -Bromophenol	9.03	40.4	-143.6	8.25
<i>m</i> -Chlorophenol	9.12	40.2	-144.6	8.16
<i>m</i> -Fluorophenol	9.29	39.4	-148.8	7.82
<i>m</i> -Hydroxyphenol	9.32	37.0	-149.9	7.66
<i>p</i> -Bromophenol	9.37	41.3	-142.9	8.23
<i>p</i> -Chlorophenol	9.41	41.1	-143.6	8.16
<i>m</i> -Methoxyphenol	9.65	35.9	-150.1	7.64
<i>m</i> -Aminophenol	9.82	33.9	-151.9	7.52
<i>p</i> -Hydroxyphenol	9.85	35.8	-152.4	7.37
<i>p</i> -Fluorophenol	9.89	38.9	-150.2	7.56
Phenol	9.99	36.4	-152.5	7.45
<i>m</i> -Methylphenol	10.09	35.5	-152.3	7.47
<i>p</i> -Methoxyphenol	10.21	35.7	-149.4	7.67
<i>p</i> -Methylphenyl	10.26	35.4	-151.4	7.54
<i>p</i> -Aminophenol	10.30	33.9	-150.8	7.59

^a pK_a values taken from [28]**Fig. 1** Correlation between pK_a and the computed $\bar{I}_{S,min}$ of the anionic conjugate bases of the phenols listed in Table 1. The linear correlation coefficient is 0.941**Fig. 2** Correlation between pK_a and the computed $V_{S,max}$ of the benzoic acids listed in Table 2. The linear correlation coefficient is 0.970

Benzoic acids and benzoates

In Table 2 are listed the pK_a s [28] and computed $V_{S,max}$ values of 17 neutral benzoic acids and the $V_{S,min}$ and $\bar{I}_{S,min}$ values of their conjugate bases. The trends shown in Table 2 are the same as those in Table 1: pK_a values increase as the benzoic acid $V_{S,max}$, benzoate $V_{S,min}$, and benzoate $\bar{I}_{S,min}$ values decrease. The corresponding correlations are given in Eqs. (8), (9) and (10).

$$pK_a = -0.1278(\pm 0.0081)(V_{S,max}) + 8.265(\pm 0.273)$$

$$n = 17, R = 0.970, s = 0.085, F = 247 \quad (8)$$

$$pK_a = -0.09092(\pm 0.00836)(V_{S,min}) - 10.77(\pm 1.36)$$

$$n = 17, R = 0.942, s = 0.120, F = 119 \quad (9)$$

$$pK_a = -1.455(\pm 0.135)(\bar{I}_{S,min}) + 14.26(\pm 0.95)$$

$$n = 17, R = 0.941, s = 0.120, F = 117 \text{aligned} \quad (10)$$

The correlation coefficients are 0.970, 0.942 and 0.941, respectively; the corresponding standard deviations are 0.085, 0.120 and 0.120. The best single-variable relationship for this set of molecules is between pK_a and the benzoic acid $V_{S,max}$ values; this relationship is shown in Fig. 2.

Combining the benzoic acid $V_{S,max}$ values and either the benzoate $V_{S,min}$ or $\bar{I}_{S,min}$ leads to two-parameter correlations with linear correlation coefficient of 0.973. If all three variables are included, the linear correlation coefficient is 0.974. However, the coefficients of both the benzoate $V_{S,min}$ and $\bar{I}_{S,min}$ in these relationships are positive, rather than negative, as in their single-variable re-

Table 2 Experimental pK_a values^a and computed surface properties for benzoic acids

Molecule	pK_a	$V_{S,max}$ (kcal mol ⁻¹)	Conjugate base $V_{S,min}$ (kcal mol ⁻¹)	Conjugate base ⁻ $\bar{I}_{S,min}$ (eV)
<i>p</i> -Nitrobenzoic acid	3.43	38.4	-155.8	7.48
<i>m</i> -Nitrobenzoic acid	3.46	37.2	-157.5	7.38
<i>p</i> -Cyanobenzoic acid	3.55	37.1	-157.3	7.37
<i>m</i> -Cyanobenzoic acid	3.60	36.5	-158.7	7.29
<i>m</i> -Bromobenzoic acid	3.81	34.2	-160.3	7.20
<i>m</i> -Chlorobenzoic acid	3.84	34.1	-160.9	7.16
<i>m</i> -Fluorobenzoic acid	3.86	33.4	-163.3	7.01
<i>p</i> -Bromobenzoic acid	3.96	34.2	-160.7	7.17
<i>p</i> -Chlorobenzoic acid	4.00	34.1	-161.1	7.14
<i>m</i> -Hydroxybenzoic acid	4.08	32.5	-164.1	6.94
<i>m</i> -Methoxybenzoic acid	4.10	31.8	-164.6	6.91
<i>p</i> -Fluorobenzoic acid	4.15	32.7	-164.1	6.95
Benzoic acid	4.204	31.4	-166.2	6.83
<i>m</i> -Methylbenzoic acid	4.25	30.8	-166.4	6.82
<i>p</i> -Methylbenzoic acid	4.37	30.5	-166.4	6.82
<i>p</i> -Methoxybenzoic acid	4.50	29.7	-166.2	6.83
<i>p</i> -Hydroxybenzoic acid	4.57	30.4	-166.1	6.83

^a pK_a values taken from [28]

relationships with pK_a and do not make physical sense. This suggests that only the single-variable relationships are physically meaningful for the benzoic acid pK_a s.

Discussion and summary

In discussing our correlations between pK_a and the computed quantities for the phenols and phenolates, it is important to point out that the phenolic and benzoic acid $V_{S,max}$ values and the phenolate and benzoate $V_{S,min}$ or $\bar{I}_{S,min}$ values all yield good single-variable correlations, separately. In other words, one can either find a correlation looking at the neutral acid form's $V_{S,max}$ values or the conjugate base's $V_{S,min}$ or $\bar{I}_{S,min}$ values. The more positive is the $V_{S,max}$ value of the neutral acid, the more acidic is the molecule, for both the phenols and the benzoic acids. Likewise, when looking at the properties of the conjugate bases, we find that acidity increases as $\bar{I}_{S,min}$ and $V_{S,min}$ values increase. When the $\bar{I}_{S,min}$ values are low, there is a greater tendency for a proton to transfer back to form the neutral acid, leading to a lower acidity and a higher pK_a . When the $V_{S,min}$ values are more negative, the anionic conjugate base is more attractive to the approach of an electrophile, and the acidity is lower. That both $\bar{I}_{S,min}$ and $V_{S,min}$ values yield good correlations with pK_a is not surprising, since these quantities correlate well with one another for these systems ($R=0.997$ for the phenolates and $R=0.999$ for the benzoates). This was also found to be true for substituted anilines [1, 3]. However, it is important to recognize that $\bar{I}_{S,min}$ and $V_{S,min}$ values corresponding to different atoms in general do *not* correlate [17, 19, 29]. For example, in the DNA base guanine, the $V_{S,min}$ associated with the carbonyl oxygen and N₃ have values of -63 and -18 kcal mol⁻¹, respectively, while the $\bar{I}_{S,min}$ of these atoms are 13.83 and 13.13 eV [29]. Clearly, the atom with the more negative $V_{S,min}$ does not have the lower $\bar{I}_{S,min}$ value.

For the phenols, a slight improvement is found in going from single-variable correlations (Eqs. 4, 5 and 6) to the dual-variable correlation shown in Eq. (7). The $\bar{I}_{S,min}$ and $V_{S,max}$ terms in Eq. (7) reflect factors affecting both sides of the proton transfer reaction shown in Eq. (3). In the case of the benzoic acids, however, we find no physically meaningful improvement in going from the best single-variable correlation involving the benzoic acid $V_{S,max}$ term to a dual-parameter correlation.

It is interesting to discuss the results of Gross and Seybold for phenols [4] and Hollingsworth et al. for benzoic acids [5] in relation to our results. They investigated the possible relationships of pK_a to atomic charges defined by a variety of procedures, as in an earlier study of substituted anilines [3]. Gross and Seybold found good correlations between the pK_a s of the 19 phenols in Table 1 and the natural charges of the phenolic hydrogens and the phenoxide oxygens, with corresponding correlation coefficients of 0.941 and 0.954 [4]. For the benzoic acids, Hollingsworth et al. found excellent correlations between pK_a and the Lowdin charges of the acidic hydrogens, the CO₂H groups as a whole and the CO₂⁻ groups as a whole, and with the natural charges of the CO₂H groups [5]; the correlation coefficients are 0.981, 0.989, 0.985, and 0.984, respectively. On the other hand, some definitions of charge gave poor correlations, or were satisfactory for one set of molecules but not another; for example, the correlations between pK_a of the phenols and the Merz–Sing–Kollman electrostatic charges of the acidic hydrogens and anionic oxygens had correlation coefficients of 0.587 and 0.832, respectively [4].

Our relationships between pK_a and the computed $V_{S,max}$ and $V_{S,min}$ are similar in concept to those of Gross and Seybold, and Hollingsworth et al., in that $V_{S,max}$ is telling how positive is the electrostatic potential of the hydrogen, and $V_{S,min}$ is telling us how negative is the electrostatic potential of the oxygen. However, in contrast to atomic charges, the electrostatic potential is a real

physical property, which can be obtained experimentally as well as computationally, and thus is physically more meaningful.

As has been shown by Seybold et al., no one definition of atomic charge was found to give uniformly good results. This reflects the fact that atomic charge is a defined quantity, not a physical observable.

We have shown in the present work that the electrostatic potentials and local ionization energies on the molecular surfaces of the phenols, benzoic acids and their conjugate bases correlate well with pK_a , for each series taken separately. The fact that our correlations do not take into account the nature of the solvent suggests that the role of water is fairly constant within each group of compounds. Within each series, the $V_{S,max}$ values of the acids are good indicators of the ease of proton loss, while the $V_{S,min}$ values of the conjugate bases reflect the tendencies of electrophiles to approach the anions to reform the acids. The surface local ionization energy, on the other hand, is a property that allows one to predict the sites of the most reactive electrons, and hence the sites most amenable to electrophilic attack. Thus, the $\bar{I}_{S,min}$ values of the phenoxides and benzoates are indicative of the tendencies for electrophiles to react with the anions to reform the acids. It is noteworthy that we find no significant improvement in going from single-variable to higher-variable correlations.

As has just been discussed, we have found good relationships between pK_a and our computed $V_{S,max}$, $V_{S,min}$ and $\bar{I}_{S,min}$ values, for each series of compounds taken separately. However, we are not able to represent all of them by the same correlation. This is due to certain seemingly anomalous features that can be seen in Tables 1 and 2: (a) the phenols have greater $V_{S,max}$ values than the more acidic benzoic acids; and (b) the more basic phenolates have higher $\bar{I}_{S,min}$ and less negative $V_{S,min}$ than the benzoates. We can explain the higher $V_{S,max}$ values of the phenols by noting that the benzoic acid hydrogen is in very close proximity to the carbonyl oxygen of the carboxylic acid group, which reduces the magnitude of the $V_{S,max}$ associated with the former; this effect has been noted earlier [30, 31]. Basically, we believe that the inability of a single correlation to encompass all of these compounds reflects the key structural difference between them: the benzoates have two equivalent oxygens (in contrast to the phenolates' one) that affects the surface properties and interactive behavior.

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