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Original Scientific Paper

Predicting the Acidities of Substituted Phenols Using Electrostatic Potential at Nuclei*

Maria Dimitrova and Boris Galabov**

Department of Chemistry, University of Sofia, Sofia 1164, Bulgaria

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Abstract. The experimental gas-phase acidities of a series of substituted phenols at the *meta*- and *para*-positions are interpreted in terms of electronic parameters characterizing the hydroxyl functionality. It is found that the acidities are linearly related to the theoretically derived electrostatic potentials at the atoms of the OH group. The NBO atomic charges at the same atoms correlate reasonably well with acidities.

Keywords: substituted phenols, acidities, electrostatic potential, NBO charges

INTRODUCTION

With the advancements in electronic structure theory it became possible to analyze the origin of various chemical processes and phenomena. Acidities and basicities of molecules have always been of principal interest because of their critical role in chemical interactions. The aim of this study is to examine the application of quantities reflecting the electronic structure of molecules at the equilibrium geometry in understanding the variations of acidities of a series of 39 substituted phenols at *meta* and *para* positions. The interplay between experiment and theory has been of crucial importance in structuring our understanding of chemical properties. With the development of experimental techniques for quantitative studies of proton transfer reactions, such as ion cyclotron resonance (FT-ICR) and high-pressure mass spectrometry (HPMS), the acid and base strengths of isolated molecules could be determined. It was, therefore, of interest to assess how theoretically derived electronic parameters would correlate with the acidic properties of a representative series of phenols. The experimental gas-phase acidities of phenols used in the present research were taken from the study of Fujio *et al.*¹

A number of quantities defined in relation to the molecular electrostatic potential (MESP) were successfully applied in examining various molecular properties.²⁻⁴ Minima and maxima of MESP at the Van der Waals surface of molecules were shown to be useful in

understanding chemical reactivity and intermolecular interactions.²⁻¹¹ Relationships between acidities and basicities of organic molecules and electronic parameters derived from the molecular surface electrostatic potential were examined in a series of studies of Gross *et al.*^{12,13} Busch and Knapp¹⁴ reported theoretical predictions of pK_a values of 26 organic molecules including several phenols by applying density functional theory (DFT) with the Becke(1/2)¹⁵ and B3LYP^{16,17} functionals. Good agreement with the experimental pK_a values was obtained. In recent studies Vianello and Maksić^{18,19} applied theoretical computations in rationalizing the acidities of substituted phenols and benzoic acids. These authors used a triadic formula, which aids to discriminate between initial, intermediate and final state effects in analyzing the deprotonation process. The theoretically estimated acidities were found to be in very good agreement with the experimental values. An excellent review on the subject by Maksić and Vianello²⁰ is also available. Chattaraj and co-workers²¹ applied the group philicity approach in predicting the pK_a values of 31 variously substituted carboxylic acids, 9 substituted phenols, and a number of anilines and alcohols. The group philicity (ω_g^a) was defined earlier by the same authors²² by localizing the electrophilicity index of Parr²³ into the functions group domain.²⁴ The direct plots between theoretically calculated group philicities and experimental pK_a values yielded rather poor correlations. However, by applying polynomial regression analysis satisfactory correlations between group philicities and pK_a values were obtained.

* Dedicated to Professor Zvonimir Maksić on the occasion of his 70th birthday.

** Author to whom correspondence should be addressed. (E-mail: Galabov@chem.uni-sofia.bg)

In the present study we explore the application of the electrostatic potential at nuclei (EPN)² and natural bond orbital atomic charges^{25,26} in understanding the variations of acidities of substituted phenols.

Theoretical Background

The molecular electrostatic potential (MESP) is a rigorously defined quantity that can be determined from the wave function by the expression²⁻⁴

$$V(\mathbf{r}) = \sum_{A \neq Y} \frac{Z_A}{|\mathbf{R}_A - \mathbf{r}|} - \int \frac{\rho(\mathbf{r}')}{|\mathbf{r} - \mathbf{r}'|} d\mathbf{r}' \quad (1)$$

In this equation Z_A is the charge on nucleus A with radius vector \mathbf{R}_A , $\rho(\mathbf{r})$ is the electronic density of the molecule, \mathbf{r} is a point around the molecule and \mathbf{r}' is a dummy integration variable. Eq. (1) is written in atomic units and contains a summation over all atomic nuclei, treated as positive point charges, as well as integration over the continuous distribution of the electronic charge. MESP is an experimental observable.²⁻⁵ The electrostatic potential at nuclei is an alternative quantity, which is also rigorously defined from the molecular wave function. The electrostatic potential at a particular nucleus (Y) positioned at \mathbf{R}_Y is defined by Eq. (2), where the singular term $\mathbf{R}_A = \mathbf{R}_Y$ has been excluded.^{2,27}

$$V_Y \equiv V(\mathbf{R}_Y) = \sum_{A \neq Y} \frac{Z_A}{|\mathbf{R}_Y - \mathbf{R}_A|} - \int \frac{\rho(\mathbf{r}')}{|\mathbf{R}_Y - \mathbf{r}'|} d\mathbf{r}' \quad (2)$$

V_Y measures the electrostatic potential at the position of atom Y due to all electrons and the rest of nuclei. Thus, the variations of electron densities induced by substitution or other influences at a particular reaction center are accurately reflected in changes of the EPN values. Furthermore, V_Y by definition is a local molecular property associated with particular atomic centers. In a series of studies from this laboratory²⁸⁻³² it was shown that EPN can be employed as a reactivity index, defining quantitatively the reactivity of molecules in chemical interactions and hydrogen bonding. Recent studies on other systems confirmed these findings.³³⁻³⁵

The natural bond orbital atomic charges^{25,26} were also evaluated. The NBO scheme is a superior tool for population analyses. As known, the atomic charges are model-dependent quantities and not physical observables.

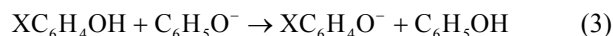
COMPUTATIONAL METHODS

All computations were carried out using the GAUSSIAN 98 program package. The geometries of the studied phenols were optimized by DFT computa-

tions employing the B3LYP hybrid functional^{16,17} and 6-31+G(2d,2p) basis set.^{36,37} Harmonic vibrational frequencies were calculated at the same level of theory to verify that all optimized structures are true minima in the potential energy surfaces. Preliminary HF/3-21G computations were carried out for molecules, where more than one conformer is possible. The lowest energy conformers were selected for the further studies. The optimized structures at the B3LYP/6-31+G(2d,2p) level of theory were used to determine EPN values and NBO atomic partial charges for the atoms of the hydroxyl functionality. As already discussed Busch and Knapp¹⁴ showed the B3LYP method with mid-size basis set can provide reliable estimates of the pK_a values for a number of organic molecules.

RESULTS AND DISCUSSION

In the present study we analyzed experimental and theoretical data for a series of phenols substituted at meta and para positions. The derivatives studied are listed in Table 1. As mentioned, the experimental gas-phase acidities, $\Delta G_{\text{acid}}^\circ$, considered were taken from the study of Fujio *et al.*¹ These authors measured the relative gas-phase acidities ($\delta\Delta G_{\text{acid}}$) of substituted phenols using ion cyclotron resonance (ICR) mass spectrometry for the reaction:



The determination of absolute acidities by Fujio *et al.*¹ is based on the usual definition as the standard Gibbs' free energy for the reaction:



Details on the approach used in determining the respective enthalpy, $\Delta H_{\text{acid}}^\circ$, and entropy, $\Delta S_{\text{acid}}^\circ$, changes for reaction (4) can be found in Ref. 1. The method for calculation of $\Delta H_{\text{acid}}^\circ$ involves a thermochemical cycle that employs information for the ionization potential of hydrogen, the bond strength of A-H and the electron affinity of the radical A. $\Delta S_{\text{acid}}^\circ$ is estimated by using statistical mechanics. By using HF and HCl as anchor points the absolute acidity of phenol is calculated to be $343 \pm 2 \text{ kcal mol}^{-1}$.

The experimental values of Fujio *et al.*¹ are shown in the second column of Table 1. Ortho derivatives were not considered in the present work since entropy related effects in the above reaction can obscure the effects of changing electronic structure in the different phenols.

In order to elucidate the intramolecular factors determining the variation of acidities upon substitution we

Table 1. B3LYP/6-31+G(2d,2p) *ab initio* calculated atomic electrostatic potential values and NBO atomic charges at the sites of hydrogen and oxygen atom of the hydroxyl group in substituted phenols, and experimental gas-phase acidities $-\Delta G_{\text{acid}}^{\circ}$ ^(a)

	Substituents in the phenols studied	$\frac{\Delta G_{\text{acid}}^{\circ}}{\text{kcal mol}^{-1}}$	$\frac{V_{\text{H}}}{\text{a. u.}}$	$\frac{V_{\text{O}}}{\text{a. u.}}$	$\frac{Q_{\text{H}}^{\text{NBO}}}{e}$	$\frac{Q_{\text{O}}^{\text{NBO}}}{e}$
1.	<i>p</i> -NH ₂	346.3	-0.982	-22.306	0.510	-0.718
2.	<i>p</i> -NMe ₂	345.1	-0.985	-22.309	0.509	-0.711
3.	<i>m</i> -NH ₂	344.4	-0.978	-22.301	0.510	-0.709
4.	<i>m</i> -NMe ₂	344.2	-0.982	-22.306	0.509	-0.711
5.	<i>p</i> -OCH ₃	344.2	-0.978	-22.302	0.511	-0.715
6.	<i>p</i> -CH ₃	344.1	-0.976	-22.300	0.511	-0.712
7.	<i>p</i> -OH	343.8	-0.976	-22.300	0.511	-0.715
8.	<i>p</i> -CH ₂ CH ₃	343.6	-0.977	-22.301	0.511	-0.713
9.	<i>m</i> -CH ₃	343.4	-0.975	-22.299	0.511	-0.710
10.	<i>p</i> -CH(CH ₃) ₂	343.1	-0.976	-22.300	0.511	-0.712
11.	<i>m</i> -CH ₃ CH ₂	343.1	-0.975	-22.299	0.511	-0.710
12.	-H	343	-0.973	-22.296	0.512	-0.710
13.	<i>m</i> -CH(CH ₃) ₂	342.9	-0.976	-22.299	0.511	-0.710
14.	<i>m</i> -OCH ₃	341.9	-0.975	-22.299	0.512	-0.709
15.	<i>p</i> -F	340.7	-0.967	-22.291	0.513	-0.710
16.	<i>m</i> -OH	340.6	-0.973	-22.296	0.513	-0.707
17.	<i>m</i> -CO ₂ Et	337.9	-0.966	-22.290	0.514	-0.708
18.	<i>m</i> -OCOCH ₃	337.9	-0.965	-22.289	0.514	-0.708
19.	<i>m</i> -F	337.7	-0.963	-22.287	0.515	-0.704
20.	<i>p</i> -Cl	337.1	-0.963	-22.287	0.514	-0.707
21.	<i>m</i> -COCH ₃	336.5	-0.966	-22.289	0.517	-0.707
22.	<i>m</i> -Cl	335.9	-0.962	-22.286	0.515	-0.704
23.	<i>m</i> -SOCH ₃	335.2	-0.964	-22.287	0.518	-0.704
24.	<i>m</i> -CHO	334.5	-0.960	-22.284	0.517	-0.705
25.	<i>m</i> -CF ₃	333.4	-0.957	-22.281	0.516	-0.703
26.	<i>p</i> -SOCH ₃	331.6	-0.960	-22.283	0.515	-0.704
27.	<i>p</i> -OCOCH ₃	331.3	-0.960	-22.283	0.515	-0.700
28.	<i>p</i> -CF ₃	331.1	-0.955	-22.278	0.516	-0.700
29.	<i>m</i> -SO ₂ CH ₃	330.2	-0.955	-22.278	0.518	-0.702
30.	<i>m</i> -CN	330	-0.951	-22.275	0.517	-0.701
31.	<i>p</i> -COCH ₃	329.7	-0.957	-22.280	0.515	-0.698
32.	<i>m</i> -NO ₂	328.6	-0.949	-22.273	0.519	-0.700
33.	3,5-di-Cl	328.6	-0.952	-22.276	0.517	-0.698
34.	<i>p</i> -CHO	327.2	-0.952	-22.275	0.517	-0.696
35.	<i>p</i> -CN	326.4	-0.947	-22.270	0.517	-0.696
36.	<i>p</i> -SO ₂ CH ₃	325.4	-0.950	-22.273	0.517	-0.697
37.	3,4,5-tri-Cl	325.1	-0.948	-22.272	0.518	-0.697
38.	3-CH ₃ ,4-NO ₂	323.8	-0.946	-22.268	0.518	-0.692
39.	<i>p</i> -NO ₂	322.1	-0.943	-22.265	0.519	-0.692
	Correlation coefficients (<i>r</i>)		0.980	0.982	0.920	0.965

^(a) From Ref. 1.

evaluated theoretically two quantities that describe the electronic structure of the hydroxyl group in isolated molecules: the electrostatic potential at nuclei values (EPN) at the hydroxyl oxygen and hydrogen as well as the natural bond orbital charges at these atoms. The computational results are given in Table 1. The electronic parameters obtained were then correlated with the experimental acidities. The obtained linear regression correlation coefficients for the dependencies between acidities and electronic parameters are given in the last row of Table 1.

It can be seen that the EPN values provide a reliable prediction of acidities of the O–H functionality and the influence of various substituents in the aromatic ring. Electron-donating substituents, such as NMe_2 , NH_2 , OCH_3 , OH , lead to increased negative charge at the hydroxyl oxygen and hydrogen, which is reflected in higher negative EPN values for these atoms. This result is in accord with the findings of Politzer³⁸ regarding the effect of increased negative charge on the V_A values. Small variations of EPN reflect quite precisely the influence of the substituent, thus providing a quantitative measure of their effect. The NMe_2 group, which is known to possess strong electron-donating properties, leads to highest negative V_O and V_H values. In accord with the resonance mechanism of this effect the substituents at para position has stronger influence than at meta position. At the opposite end the highest effect is exerted by nitro group at para position. This group has strong electron-withdrawing properties and leads to significantly reduced negative charge at the atoms of the hydroxyl functionality. The obtained linear regression correlation coefficient for the relationship between $\Delta G^\circ_{\text{acid}}$ and V_O is $r = 0.982$. The equations obtained is as follows:

$$\Delta G^\circ_{\text{acid}} = -584.7(\pm 18.5)V_O - 12696.1(\pm 413.1) \quad (5)$$

$n = 39$, $r = 0.982$, Fischer criterion $F = 995.30$

The linear plot between EPN and $\Delta G^\circ_{\text{acid}}$ values is illustrated in Figure 1. Considering the large number of compounds, the usual experimental uncertainties as well as the approximate nature of the wave functions employed, the obtained relationship can be considered quite satisfactory.

The NBO atomic charges obtained at the same level of theory predict also correctly the trend of changes the $\Delta G^\circ_{\text{acid}}$ values. The respective correlation coefficient for the dependence between $\Delta G^\circ_{\text{acid}}$ and q_O is, however, considerably lower, $r = 0.964$. Nonetheless, we see that both quantities, V_O and q_O , describe well the changing electronic structure of the reaction center in the studied phenols. It appears that these theoretical parameters can be successfully employed in characterizing acidities, especially in series of related molecules.

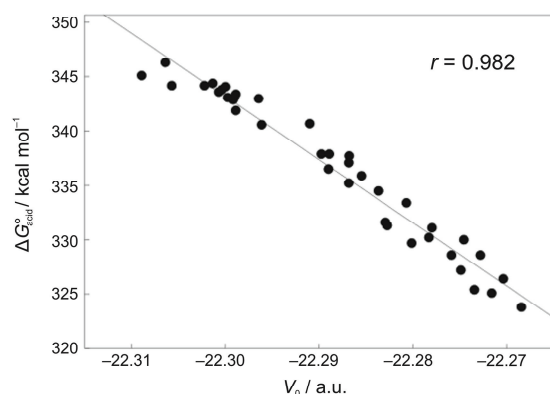


Figure 1. Dependence between atomic electrostatic potential values V_O and experimental gas-phase acidities $\Delta G^\circ_{\text{acid}}$.

CONCLUSION

The results obtained show that the gas phase acidities of series of 39 substituted phenols are linearly related to the theoretically derived electrostatic potentials at the atoms of the hydroxyl functionality. NBO atomic charges at the hydroxyl oxygen atoms correlate also reasonably with the experimental acidities. These electronic parameters can, therefore, be used in characterizing and predicting the acidity properties of phenols.

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SAŽETAK

Predviđanje kiselosti supstituiranih fenola korištenjem elektrostatskih potencijala na jezgri

Maria Dimitrova i Boris Galabov

Department of Chemistry, University of Sofia, Sofia 1164, Bulgaria

Eksperimentalne kiselosti u plinskoj fazi serije fenola supstituiranih u *meta*- i *para*-položajima interpretirane su pomoću elektronskih parametara koji karakteriziraju hidroksilnu funkcionalnu skupinu. Pronađeno je kako je kiselost linearno povezana sa teorijski dobivenim elektrostatskim potencijalima na atomima OH skupine. NBO atomski naboji na istim atomima dobro koreliraju s kiselošću tih spojeva.