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Correlations and Predictions of pK_a Values of Fluorophenols and Bromophenols Using Hydrogen-Bonded Complexes with Ammonia

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Density functional theory calculations have been preformed on a series of the hydrogen-bonded fluorophenol−ammonia and bromophenol−ammonia complexes. Intermolecular and intramolecular properties, particularly those related to hydrogen bonding, have been carefully analyzed. Several properties, such as the bond length and stretching frequency of the hydroxyl group, the hydrogen bond length and binding energy, are shown to be highly correlated with each other and are linearly correlated with known experimental pK_a values of the halogenated phenols. The linear correlations have been used to predict the pK_a values of all fluorophenols and bromophenols in the series. The predicted pK_a values are shown to be consistent from different molecular properties and are in good agreement with available experimental values. This study suggests that calculated molecular properties of hydrogen-bonded complexes allow the effective and systematic prediction of pK_a values for a large range of organic acids using the established linear correlations.

1. Introduction

The acidity constant, commonly known as the pK_a value, of an organic pollutant is a fundamental physical−chemical property in assessing the environmental fate and biological activity of the compound. Halogenated phenols are present in the environment as a result of their agricultural and industrial uses, such as pesticides, preservatives, and precursors in the synthetic chemical industry.[1] They are toxic to both ecological and biological systems and tend to persist and accumulate in the environment.[2] The quantitative structure−activity relationship (QSAR) method has been employed to study the toxicities of substituted phenols, particularly halogenated phenols.[3−5] In the QSAR study, the acidity constant (pK_a) is used as a key molecular descriptor to evaluate the toxicity or bioactivity of different compounds in a series. Despite the importance of such a parameter, pK_a values have been reported only for a small fraction of halogenated phenols.[6,7] It would be valuable to develop an efficient theoretical method to systematically predict pK_a values for a large class of compounds.

The linear free-energy relationship was used to calculate pK_a values of substituted phenols.[8−10] Various molecular properties such as electrophilic superdelocalizability,[7] energy state difference,[11] bond orders, and partial atomic charges[12,13] from semiempirical quantum mechanical methods were explored to predict the pK_a values of substituted phenols and carboxylic acids. Other molecular properties such as the hydroxyl group C−O and O−H bond lengths and proton affinities, from density functional theory (DFT) calculations, were correlated with the pK_a values of substituted phenols.[14,15] Recently, atomic partial charges and electron charge densities from the atoms-in-molecules (AIM) theory were selected to study the substitutional effects on the acidity of phenol derivatives.[16] All these studies were attempted to adopt appropriate quantum mechanical descriptors that could correlate with the pK_a values of different compounds.

More recently, molecular properties resulting from hydrogen-bonding interactions of chlorophenols with a probe molecule, either water or ammonia, were explored for the prediction of pK_a values of chlorophenols.[17] Strong linear correlations were found between molecular properties, primarily associated with the acidic hydroxyl group, and experimental pK_a values of chlorophenols. Much weaker correlations were observed for monomeric chlorophenols or bromophenols.[18,19] In other words, the sensitivity of molecular properties to the acidity of a molecule is greatly enhanced in the presence of a probe molecule that accepts a proton from the acid molecule.

The pK_a value of an acid is ultimately determined by the difference in the free energy between the dissociated and undissociated forms of the acid in the aqueous medium, characterized by the dissociation of the OH covalent bond. As a result, the acidity of an acid is directly reflected in the OH bond strength, exhibited by the equilibrium OH bond length and stretching frequency. This explains the origin of correlations between the molecular properties (OH bond length and stretching frequency) and the acidity. The correlations can be enhanced by placing a base probe molecule to simulate the acid−base interaction in the aqueous phase, as the probe molecule pulls the proton away from the acid and weakens the OH bond. On the other hand, the acid−base interaction of the acid with the probe molecule may also reflect the acidity of the acid molecule, as demonstrated by strong correlations of the hydrogen bond length and binding energy with the acidity constant. Apparently, molecular properties responding to the presence of a given base would depend on the inherent acidity of the acid.

The above analysis is validated by the previous work on chlorophenols. It is highly desirable to apply the strategy and extend the work to much larger classes of molecules. The present study is focused on other two major series of halogenated phenols, fluorophenols and bromophenols. Note that no systematical study has been reported on the complexes of fluorophenols or bromophenols with ammonia except for the phenol−ammonia complex.[20−22] DFT calculations are performed to determine the molecular structures and properties of hydrogen-

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bonded complexes of all 19 fluorophenols and 19 bromophenols with ammonia. Correlations of molecular properties, particularly those associated with the acidic hydroxyl group, with available experimental pK_a values are explored. As shown in the study, strong linear correlations are established. The linear correlations are used to predict the pK_a values of other fluorophenols and bromophenols. The proposed method for the prediction of pK_a values is discussed and summarized.

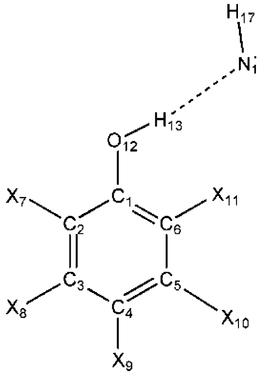
2. Method of Calculation

DFT with Becke's three parameter functional and Lee, Yang, and Parr's correlation functional (B3LYP) [23] was used to calculate the equilibrium geometries and harmonic frequencies of halogenated phenols and their complexes with ammonia. The 6-311++G(d,p) extended basis set of Pople and co-workers[24] for the first-row atoms and hydrogen, expanded by McGratch and Radom[25] to the third-row atoms, was employed in all calculations. It is known that the B3LYP method provides reliable structural and vibrational information for the hydrogen-bonded systems.[26−29] All calculations were carried out using the Gaussian 98 package.[30]

All 19 fluorophenols and 19 bromophenols are included, and they are monofluorophenols (FPs) and monobromophenols (BPs) (3 each), difluorophenols (DFPs) and dibromophenols (DBPs) (6), trifluorophenols (TFPs) and trichlorophenols (TBPs) (6), tetraflurophenols (TeFPs) and tetrabromophenols (TeBPs) (3), and pentafluorophenol (PFP) and pentabromophenol (PBP) (1). Each of the halogenated phenols forms a hydrogen-bonded complex with ammonia, with the latter being the hydrogen-bond acceptor from the hydroxyl group of the phenol. The equilibrium geometries of PBP and its complex with ammonia were not completely converged in full geometry optimization. As a result, the correlations of the molecular properties of the complex with the pK_a value of PBP turn out to be erratic and, therefore, are excluded from those of all other BP−NH_3 complexes and are not used in prediction.

In a previous study on chlorophenol complexes,[17] ammonia is demonstrated to be a better probing molecule than water in the formation of the hydrogen-bonded complex with a chlorophenol. The molecular properties are more responsive to the presence of ammonia (a stronger base), which induces larger measurable changes in the molecular properties. As a result, the use of hydrogen-bonded complexes with ammonia is expected to give more sensitive results. All halogenated phenol−ammonia complexes have C_s symmetry, and for asymmetric halogenated phenols, only anti conformers are considered (the hydroxyl hydrogen is away from the closest neighboring halogen).[17] The ammonia, as a probe molecule, is positioned with its lone pair pointing directly toward the hydroxyl hydrogen of the phenol, as shown in Figure 1. For an asymmetrically substituted halophenol monomer, the syn conformer, in which the OH group bends to the same side of halogen, is more stable due to intramolecular hydrogen bonds. However, when a probe molecule such as NH_3 or H_2O is introduced to accept a proton from the OH group, the anti conformer becomes more stable due to the stronger intermolecular hydrogen bond.

Molecular properties of the complexes with optimized geometries are examined to correlate with the pK_a values of halogenated phenols. They include the O−H bond lengths, r(O−H), the O−H stretching frequencies, ν(O−H), and the C−O bond lengths, r(C−O). Also included are the hydrogen bond length, r(OH···N), and the binding energy of the complexes, ΔE_{hb}, defined as a difference in total electronic energy between the complex and the comprising phenol and ammonia. The basis-set superposition error (BSSE) and the zero-point energy correction were not considered in the ΔE_{hb}.[17] The calculated molecular properties described above were plotted against the experimental pK_a values, and a least-squares linear regression was performed on each data set. The square of the correlation coefficient, R^2, and the standard deviation, SD, from the regression calculations were recorded. The linear equations were employed to predict the pK_a values for all halogenated phenols. Note that experimental pK_a values are only available for seven fluorophenols, ranging from 5.53 to 9.89, and seven bromophenols, from 6.08 to 9.37.[31, 32]



For FP-NH_3 complex, X = H, F, or both
For BP-NH_3 complex, X = H, Br, or both

Figure 1. Structure and atom-numbering scheme for the ammonia complex with fluorophenol or bromophenol.

TABLE 1: Selected Molecular Properties of Fluorophenol−Ammonia Complexes from B3LYP/6-311++G(p,d) Calculations

ammonia complex	r(C−O) (Å)	r(O−H) (Å)	ν(O−H) (cm^{-1})	−OHN (deg)	ΔE_{hb} (kcal mol^{-1})	r(OH···N) (Å)
2-FP	1.349	0.986	3363.0	168.2	−9.9	1.855
3-FP	1.352	0.986	3377.2	168.3	−9.7	1.863
4-FP	1.357	0.984	3402.4	168.5	−9.5	1.875
2,3-DFP	1.346	0.988	3325.2	168.1	−10.7	1.837
2,4-DFP	1.350	0.986	3367.9	168.0	−10.4	1.862
2,5-DFP	1.344	0.989	3311.3	169.0	−10.9	1.831
2,6-DFP	1.340	0.997	3178.1	167.8	−10.1	1.780
3,4-DFP	1.353	0.986	3366.0	168.4	−10.1	1.857
3,5-DFP	1.348	0.988	3324.5	169.9	−10.7	1.840
2,3,4-TFP	1.347	0.989	3313.2	168.6	−11.0	1.831
2,3,5-TFP	1.342	0.991	3270.5	169.4	−11.6	1.814
2,3,6-TFP	1.337	1.000	3121.0	167.6	−10.7	1.760
2,4,5-TFP	1.345	0.989	3304.2	169.0	−11.4	1.827
2,4,6-TFP	1.341	0.997	3165.0	167.5	−10.5	1.775
3,4,5-TFP	1.349	0.989	3319.4	169.8	−11.0	1.836
2,3,4,5-TeFP	1.343	0.991	3262.8	169.1	−11.9	1.811
2,3,4,6-TeFP	1.338	1.000	3106.4	167.8	−11.3	1.755
2,3,5,6-TeFP	1.334	1.003	3062.5	168.5	−11.7	1.742
PFP	1.336	1.003	3051.2	168.1	−12.1	1.738

3.Results and Discussion

3.1. Molecular Properties. Tables 1 and 2 list the O−H and C−O bond lengths, O−H harmonic stretching frequencies, hydrogen bond angles and lengths, and the binding energies of fluorophenol−ammonia and bromophenol−ammonia complexes, respectively. The complete geometric parameters of these complexes are available in Supporting Information of S-Tables 1 and 2, respectively.

It is clear from Table 1 that all fluorophenol complexes have nearly linear hydrogen bonds, with the bond angles typically around 169°. Similar observations exist for bromophenol complexes without di-ortho substitutions, as shown in Table 2. However, the hydrogen bonds of bromophenol complexes with di-ortho substitutions are severely bent, with the bond angles

TABLE 2: Selected Molecular Properties of Bromophenol−Ammonia Complexes from B3LYP/6-311++G(p,d) Calculations

ammonia complex	r(C−O) (Å)	r(O−H) (Å)	ν(O−H) (cm^{-1})	−OHN (deg)	ΔE_{hb} (kcal mol^{-1})	r(OH···N) (Å)
2-BP	1.346	0.987	3351.4	167.5	−10.0	1.851
3-BP	1.352	0.986	3370.7	168.9	−9.9	1.860
4-BP	1.353	0.986	3376.1	168.8	−9.8	1.864
2,3-DBP	1.344	0.988	3325.2	168.2	−10.5	1.843
2,4-DBP	1.344	0.989	3318.7	167.8	−10.7	1.837
2,5-DBP	1.342	0.990	3294.7	169.2	−11.1	1.825
2,6-DBP	1.335	0.992	3279.0	152.5	−7.4	1.843
3,4-DBP	1.350	0.987	3351.6	169.3	−10.4	1.856
3,5-DBP	1.348	0.989	3316.5	169.7	−10.9	1.837
2,3,4-TBP	1.342	0.990	3296.5	167.9	−11.0	1.829
2,3,5-TBP	1.341	0.991	3263.8	169.2	−11.5	1.816
2,3,6-TBP	1.333	0.994	3240.7	152.7	−7.7	1.829
2,4,5-TBP	1.341	0.991	3271.8	169.5	−11.5	1.816
2,4,6-TBP	1.333	0.994	3238.4	152.9	−8.0	1.826
3,4,5-TBP	1.347	0.990	3294.3	170.0	−11.2	1.828
2,3,4,5-TeBP	1.340	0.992	3249.8	169.2	−11.8	1.810
2,3,4,6-TeBP	1.332	0.995	3222.5	152.4	−8.1	1.821
2,3,5,6-TeBP	1.332	0.994	3241.5	150.6	−7.7	1.838
PBP	1.331	0.994	3243.2	149.5	−7.7	1.840

around 152°. In these cases, ammonia appears to be repelled by the bulky bromine atom at the ortho position. Such steric hindrance is obviously absent in the fluorophenol complexes. The severely bent hydrogen bonds in bromophenol complexes with di-ortho substitutions are expected to have considerable consequences on molecular properties of the complexes, as will be noted in the following paragraphs.

The position and the number of the substitutions at the phenol ring have systematic effects on the structure and properties of halogenated phenol complexes. The O−H bond length, r(O−H), increases progressively with the number of substitutions, from 0.984 to 1.003 Å in the fluorophenol complexes and from 0.986 to 0.994 Å in the bromophenol complexes. For a given number of halogen substitutions, r(O−H) decreases in the order of the ortho, meta, and para position. The inductive effect of the substituted halogen is responsible for the trends.

The OH stretching frequency, ν(O−H), decreases with the number of halogen substitutions, from 3402.4 to 3051.2 cm^{-1} in the fluorophenol complexes and from 3376.1 to 3243.2 cm$^{-1\ 1}$ in the bromophenol complexes. The reduction in ν(O−H) indicates the weakening of the OH bond and so is the lengthening of the OH bond. Figure 2 plots the values of ν(O−H) vs r(O−H). For the fluorophenol complexes, as shown in the upper panel of Figure 2, the ν(O−H) values are linearly correlated with r(O−H) ($R^2 = 0.9996$). For the bromophenol complexes, two separate linear correlations are evident, one with di-ortho substitutions and the other without, as shown in the lower panel of Figure 2. The reduction in the OH stretching frequencies for the bromophenol complexes with di-ortho substitutions is clearly a consequence of the severely bent hydrogen bond resulting from the steric interference of ortho bromine atom.

In contrast to the OH bond length, the C−O bond length, r(C−O), decreases with the number of halogen substitutions, from 1.357 to 1.336 Å in the fluorophenol complexes and from 1.353 to 1.331 Å in the bromophenol complexes. There are strong linear correlations between r(C−O) and r(O−H) for fluorophenol complexes ($R^2 = 0.870$) and bromophenol complexes ($R^2 = 0.932$). Multiple halogen substitutions enhance the overall electron-withdrawing power and strengthen the C−O bonding character by shifting electron density away from antibonding orbitals of the CO group. As a result, the reduction in r(C−O) with the increasing number of halogen substitutions is consistent with the lengthening of the O−H bond length.

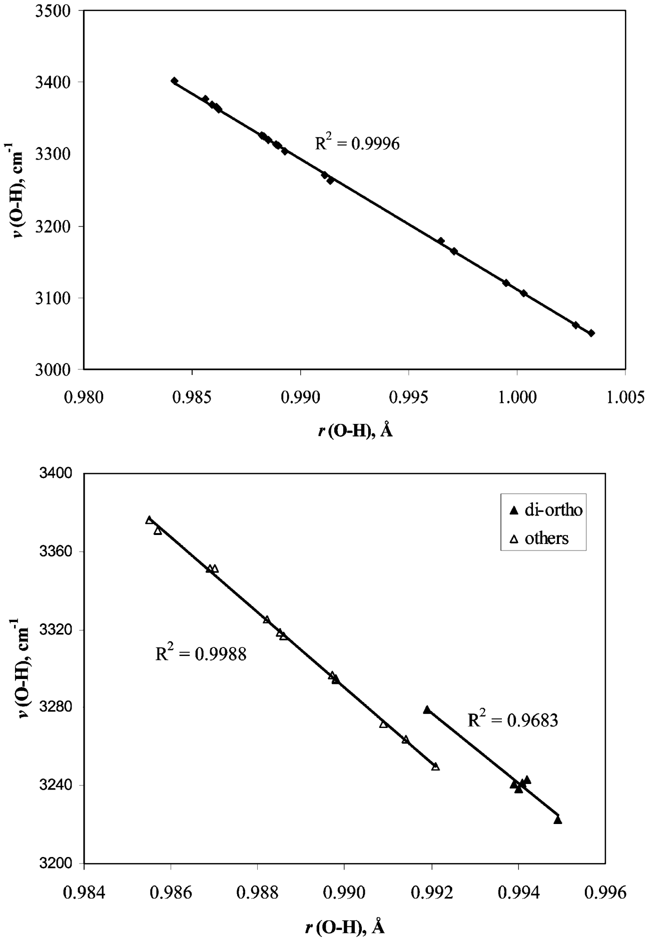


Figure 2. Correlation between O−H stretching frequency (cm^{-1}) and the O−H bond length (Å) for halogenated phenol−ammonia complexes. The upper panel is for the fluorophenol−ammonia complexes, and the lower panel is for the bromophenol−ammonia complexes.

Intermolecular properties, such as the hydrogen bond length, r(OH···N), and binding energy, ΔE_{hb}, are also systematically dependent on the number and positions of halogen substitutions and are strongly correlated with the O−H bond length and OH stretching frequency. Figure 3 shows the correlation between r(OH···N) and r(O−H) for fluorophenol complexes (upper panel) and bromophenol complexes (lower panel). As expected, two separate correlations are shown for bromophenol complexes as a result of the steric effect of ortho bromine atom. Figure 4 shows the correlation between ΔE_{hb} and r(O−H) for fluorophenol complexes (upper panel) and bromophenol complexes (lower panel). It is interesting to note that the correlations for both complex series with di-ortho substitutions are separated from the other complexes. For bromophenol complexes, the separate correlations are understandable based on the noted steric effect of ortho bromine atom. It is somewhat puzzling to observe the separate correlation for fluorophenol complexes with di-ortho substitutions from the remaining complexes. Intramolecular hydrogen bonding is known to exist in all ortho-substituted phenols, and it is particularly important for ortho fluorophenols.[33−36] The same hydroxyl group is competed for intramolecular hydrogen bonding (with ortho halogen) and intermolecular hydrogen bonding (with ammonia). Such a competition would unavoidably diminish the strength of intermolecular hydrogen bonding, or the binding energies.

In summary, the systematic trends in molecular properties have been found with the number and positions of halogen substitutions. Strong and consistent linear correlations have been

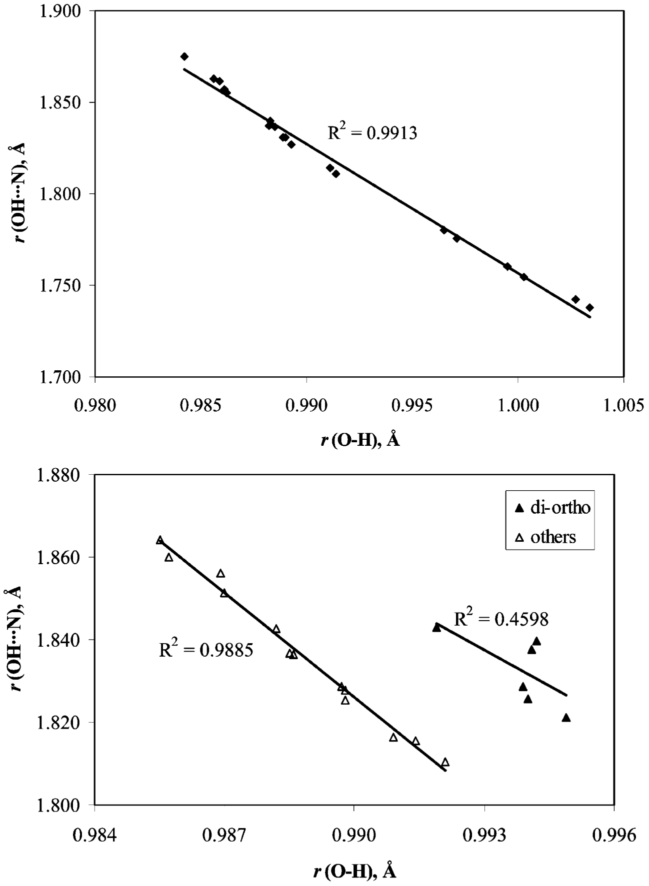


Figure 3. Correlation between the hydrogen bond length (Å) and the O−H bond length (Å) for halogenated phenol−ammonia complexes. The upper panel is for the fluorophenol−ammonia complexes, and the lower panel is for the bromophenol−ammonia complexes.

determined between different molecular properties of the halogenated phenol complexes.

3.2. Linear Correlations with the Experimental pK_a Values. It is well known that the acidity constant and other physical and chemical properties of a halogenated phenol depend on the number and positions of halogen substitutions. Overall, the acidity increases with the number of substitutions, and for a given number of substitutions, it decreases in the order of the ortho, meta, and para position of substitution. On the other hand, the acidity of a halogenated phenol would be reflected in the structure and interaction in the hydrogen-bonded complexes with a proton acceptor such as ammonia. A strong acid forms a strong hydrogen bond with ammonia, giving a large binding energy and a short hydrogen bond distance. A strong hydrogen bond also weakens the OH covalent bond, resulting in an increase in the bond length and a decrease in the stretching frequency. Consequently it is apparent that the acidity constants of halogenated phenols can be correlated with the molecular properties of the corresponding hydrogen bonded complexes.

The available experimental pK_a values for seven fluorophenols and eight bromophenols are listed in Tables 4 and 5. These experimental pK_a values are correlated with the molecular properties discussed above and least-squares linear regressions are performed. The resulting regression equations are given in Table 3, along with the R^2 and SD values. As a representation, Figure 5 shows the strong linear correlations of r(C−O) with the corresponding pK_a values of fluorophenols and bromophenols. Similarly, Figure 6 gives the correlations of r(O−H) with pK_a values of the halogen-substituted phenols.

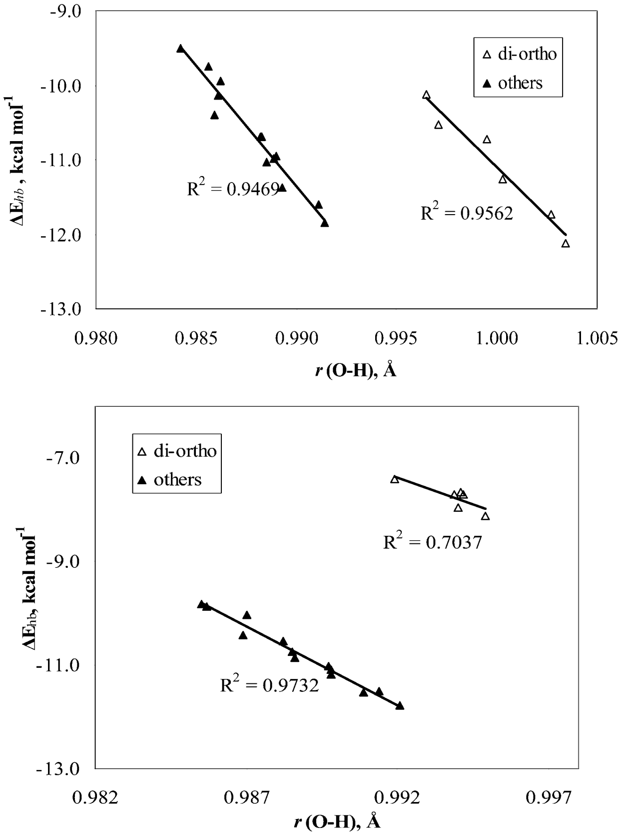


Figure 4. Correlation between the binding energy (kcal mol^{-1}) and the O−H bond length length (Å) and for halogenated phenol−ammonia complexes. The upper panel is for the fluorophenol−ammonia complexes, and the lower panel is for the bromophenol−ammonia complexes.

TABLE 3: Linear Correlations of Available Experimental pK_a Values with Different Molecular Properties of Fluorophenol−Ammonia Complexes and Bromophenol−Ammonia Complexes along with R^2 and SD Values

parameter (x)	N^a	eq	R^2	SD
		FP−NH$_3$ Complexes		
r(C−O)	8	pK_a = 186.61x − 243.12	0.965	0.34
r(O−H)	8	pK_a = −195.23x + 201.66	0.950	0.41
ν(O−H)	8	pK_a = 0.0107x − 26.892	0.954	0.39
r(OH···N)	8	pK_a = 27.05x − 41.173	0.952	0.40
ΔE_{hb}	3 (di-ortho)	pK_a = 0.9768x + 17.384	0.999	0.06
	5 (others)	pK_a = 1.1501x + 20.540	0.855	0.28
		BP−NH$_3$ Complexes		
r(C−O)	8	pK_a = 159.18x − 206.06	0.975	0.23
r(O−H)	8	pK_a = −379.67x + 383.33	0.987	0.16
ν(O−H)	2 (di-ortho)	pK_a = 0.0145x − 40.98	1	
	6 (others)	pK_a = 0.0217x − 63.947	0.963	0.18
r(OH···N)	2 (di-ortho)	pK_a = 33.714x − 55.469	1	
	6 (others)	pK_a = 44.827x − 74.398	0.968	0.17
ΔE_{hb}	2 (di-ortho)	pK_a = 0.9833x + 13.947	1	
	6 (others)	pK_a = 1.1678x + 20.522	0.908	0.28

[a] The number of compounds used in correlations, including phenol.

It is clear from Table 3 that strong linear correlations are obtained for the pK_a values of fluorophenols and bromophenols with the molecular parameters r(C−O), r(O−H), ν(O−H), r(OH···N), and ΔE_{hb}, respectively. The consistent and strong correlations of the pK_a values are inherited from strong internal correlations of molecular properties of hydrogen-bonded complexes discussed previously. As shown by the regression equations, the pK_a of a fluorophenol decreases with r(O−H) and ΔE_{hb} and increases with r(C−O), ν(O−H), and r(OH···

TABLE 4: Predicted pK_a Values for Fluorophenols from Linear Correlations

		predicted pK_a values				
compound	pK_a exp	r(O−H)	ν(O−H)	r(OH···N)	avg	SD
phenol	9.99	9.65	9.66	9.81	9.71	0.09
2-FP	8.73	9.12	9.09	9.00	9.07	0.06
3-FP	9.29	9.24	9.24	9.21	9.23	0.02
4-FP	9.89	9.51	9.51	9.55	9.52	0.02
2,3-DFP		8.73	8.69	8.52	8.65	0.11
2,4-DFP	8.58	9.18	9.14	9.18	9.17	0.02
2,5-DFP		8.58	8.54	8.34	8.49	0.12
2,6-DFP	7.51	7.11	7.11	6.98	7.07	0.08
3,4-DFP		9.14	9.12	9.06	9.11	0.04
3,5-DFP		8.71	8.68	8.59	8.66	0.07
2,3,4-TFP		8.60	8.56	8.35	8.50	0.13
2,3,5-TFP		8.17	8.10	7.89	8.05	0.14
2,3,6-TFP		6.53	6.50	6.44	6.49	0.04
2,4,5-TFP		8.52	8.46	8.24	8.41	0.14
2,4,6-TFP		7.00	6.97	6.85	6.94	0.08
3,4,5-TFP		8.68	8.63	8.50	8.60	0.09
2,3,4,5-TeFP		8.11	8.02	7.81	7.98	0.16
2,3,4,6-TeFP		6.37	6.35	6.29	6.34	0.04
2,3,5,6-TeFP	6.00	5.90	5.88	5.96	5.91	0.04
PFP	5.53	5.77	5.76	5.83	5.79	0.04

[a] pK_a values from ref 31.

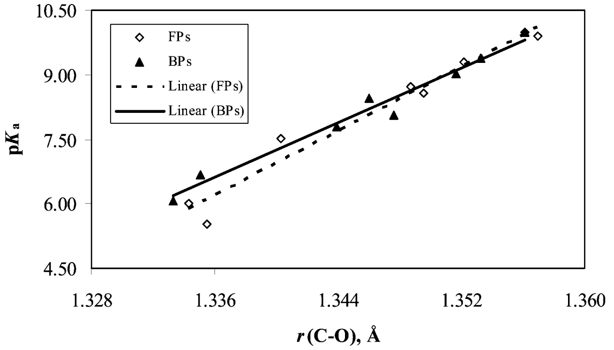


Figure 5. Correlation of the C−O bond lengths (Å) of halogenated phenol−ammonia complexes with the acidity (pK_a) values of corresponding phenol compounds in aqueous solution.

N). Not surprisingly, the correlations of pK_a with some properties are divided into two separate groups, one for substituted phenols with di-ortho substitutions and the other without. Note that only two data sets are used to generate the regression equations for di-ortho fluorophenols or bromophenols because of the limited availability of experimental pK_a values.

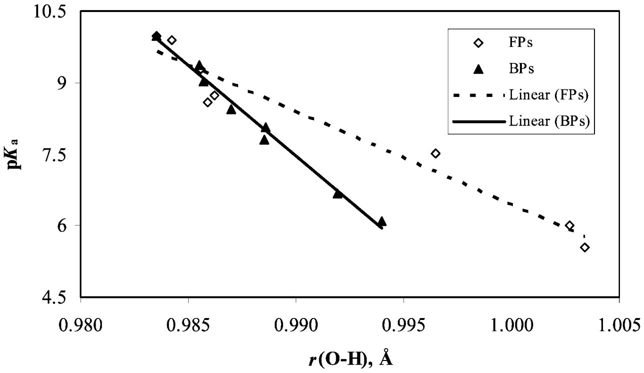


Figure 6. Correlation between the O−H bond length (Å) of halogenated phenol−ammonia complexes with the acidity (pK_a) values of corresponding phenol compounds in aqueous solution.

3.3. Prediction of pK_a Values for Fluorophenols and Bromophenols. The pK_a values of all fluorophenols and bromophenols are generated from the regression equations given in Table 3. Tables 4 and 5 list the predicted pK_a values of fluorophenols and bromophenols, respectively, from the regression equations for different properties, along with the average pK_a values, the corresponding standard deviations, and the available experimental values.

Consistent pK_a values for both fluorophenols and bromophenols are predicted from the regression equations using different molecular properties, as evidenced by small standard deviations for the average pK_a values, 0.04−0.16 for fluorophenols and 0.03−0.27 for bromophenols. Even the predicted pK_a values from the regression equations based on two data points are in good agreement with those from multiple data equations. For example, the pK_a values of 2,3,6-TBP from the two data-point regressions of ν(OH), r(OH···N), and ΔE_{hb}, 6.01, 6.19, and 6.38, respectively, are very consistent with 6.13 and 5.98 from the eight data-point regressions of r(C−O) and r(O−H).

Table 6 compares predicted pK_a values of phenol, fluorophenols, chlorophenols, and bromophenols with the available theoretical results from literature. Shown in the table are the average values of prediction using multiple molecular parameters as well as those using only the O−H bond length, r(O−H).

TABLE 5: Predicted pK_a Values for Bromophenols from Linear Correlations

		predicted pK_a values						
compound	pK_a exp	r(C−O)	r(O−H)	ν(O−H)	r(OH···N)	ΔE_{hb}	avg	SD
phenol	9.99[a]	9.80	9.92	10.18	10.09	10.01	10.0	0.15
2-BP	8.45[a]	8.20	8.60	8.78	8.59	8.82	8.60	0.25
3-BP	9.03[a]	9.10	9.09	9.20	8.98	9.00	9.07	0.09
4-BP	9.37[a]	9.36	9.17	9.31	9.17	9.05	9.21	0.12
2,3-DBP		7.89	8.14	8.21	8.21	8.21	8.13	0.14
2,4-DBP	7.79[a]	7.86	8.03	8.07	7.94	7.98	7.98	0.08
2,5-DBP		7.56	7.53	7.55	7.43	7.57	7.53	0.06
2,6-DBP	6.67[a]	6.46	6.74	6.57	6.67	6.67	6.62	0.11
3,4-DBP		8.83	8.63	8.78	8.80	8.36	8.68	0.19
3,5-DBP	8.06[a]	8.45	7.99	8.02	7.93	7.84	8.05	0.24
2,3,4-TBP		7.62	7.57	7.59	7.58	7.66	7.61	0.04
2,3,5-TBP		7.32	6.93	6.88	6.99	7.08	7.04	0.17
2,3,6-TBP		6.13	5.98	6.01	6.19	6.38	6.14	0.16
2,4,5-TBP		7.32	7.11	7.05	7.03	7.05	7.11	0.12
2,4,6-TBP	6.08[b]	6.17	5.94	5.98	6.08	6.08	6.05	0.09
3,4,5-TBP		8.32[c]	7.53	7.54	7.54	7.48	7.52	0.03
2,3,4,5-TeBP		7.19	6.66	6.57	6.75	6.77	6.79	0.24
2,3,4,6-TeBP		5.95	5.60	5.75	5.93	5.98	5.84	0.16
2,3,5,6-TeBP		5.92	5.90	6.02	6.48	6.38	6.14	0.27

[a] pK_a values from ref 31. [b] Reference 32. [c] Value excluded from the calculation of pK_a average and standard deviation.

TABLE 6: Comparisons of pK_a Values of Halogenated Phenols from Different Methods

		this work		other theoretical work from literature[a]			
compound	pK_a exp	avg	r(O−H)	a	b	c	d
Phenol	9.99	10.00	9.92	10.00	9.93	9.74	9.88
3-FP	9.29	9.23	9.24		9.05		9.33
4-FP	9.89	9.52	9.51		9.26		9.90
2-CP	8.52	8.46	8.61	9.16		8.29	7.66
3-CP	8.79	8.92	8.90	9.32	9.15	8.92	9.29
4-CP	9.37	9.13	9.08	9.50	9.15	9.44	9.84
2,3-DCP	7.71	7.90	8.04	8.68		7.54	
2,4-DCP	7.90	7.94	8.11	7.28		7.86	
2,5-DCP	7.30	7.35	7.50	8.45		7.38	
2,6-DCP	6.78	6.49	6.53	7.03		6.82	
3,4-DCP	8.62	8.43	8.43	8.68	8.63	8.56	
3,5-DCP	8.25	7.87	7.86	8.56	8.53	7.97	
2,3,4-TCP	6.94	7.53	7.71	8.54		7.16	
2,3,5-TCP	7.23	6.79	6.96	7.90			
2,3,6-TCP	5.80	5.65	5.56	6.63			
2,4,5-TCP	6.72	6.90	7.14	6.48		6.94	
2,4,6-TCP	5.99	5.78	5.67	6.51		6.31	
3,4,5-TCP	7.84	7.39	7.57	8.01			
2,3,4,6-TeCP	5.22	5.11	5.09			5.61	
2,3,5,6-TeCP	5.03	5.05	5.09	6.16			
PCP	4.74	4.84	4.70	5.72		4.89	
2-BP	8.45	8.60	8.60	9.43			
3-BP	9.03	9.07	9.09	9.75	9.15		
4-BP	9.37	9.21	9.17	9.64	8.94		
2,4-DBP	7.79	7.98	8.03	8.95			
2,6-DBP	6.67	6.62	6.74	6.43			
3,5-DBP	8.06	8.05	7.99		8.48		
SD		0.23	0.28	0.56	0.34	0.17	0.36

[a] Experimental and predicted pK_a values for chlorophenols (CPs), dichlorophenols (DCPs), trichlorophenols (TCPs), tetrachlorophenols (TeCPs), and pentachlorophenol (PCP) are taken from ref 17. Predicted pK_a values from other theoretical work: (a) ref 13, (b) ref 7, (c) ref 9, and (d) ref 10. SD values are calculated in reference to experimental values.

Note also that the pK_a values of chlorophenols are taken from the previous study.[17] The literature values are based on correlations using (column a) AM1 partial charges of the hydroxyl oxygen,[13] (column b) electrophilic superdelocalizability derived from AM1 molecular orbitals,[7] (column c) free energies in the gas phase and solution phase calculated using semiempirical and ab initio methods,[9] and (column d) free energies calculated using density functional and ab initio methods.[10] SD values, calculated in reference to experimental values, are given for the different theoretical methods. The relatively small SD values of the present work, 0.23 and 0.28 pH units, for a large set of compounds clearly show that the method proposed in this study is capable of predicting reliable and consistent pK_a values.

4. Conclusions

The method for the prediction of pK_a values using ammonia as a probe molecule has been applied to two classes of halogenated phenols, fluorophenols and bromophenols. The method is efficient and straightforward, and the results are reliable and consistent. A range of calculated molecular properties for the hydrogen-bonded complexes with ammonia, primarily involving the acidic hydroxyl group, can be independently used to predict consistent results of nearly equal accuracy. All of the molecular properties are shown to have simple linear correlations with the pK_a values, allowing reliable prediction from as little information as pK_a values of two compounds in a series. Nevertheless, two of the properties, the O−H bond length and OH stretching frequency, stand out to be the best descriptors. There are, however, special considerations arising from steric hindrance and intramolecular hydrogen bonding in unique molecular structure and environment.

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Supporting Information Available: S-Table 1 and S-Table 2 contain the optimized geometrical parameters of all 19 fluorophenol−ammonia complexes and 19 bromophenol−ammonia complexes calculated at the B3YLP/6-311++G(d,p) level of theory, respectively. This material is available free of charge via the Internet at http://pubs.acs.org.

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