# Effect of Fluorine Substitution on Phenol Acidities in the Gas Phase and in Aqueous Solution. A Computational Study Using Continuum Solvation Models

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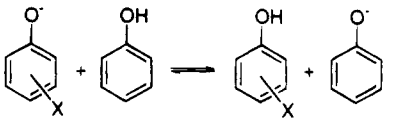
The effect of fluorine substitution on the gas and aqueous phase acidity of the monofluorophenols has been investigated with a combination of computational techniques. The effects of aqueous solvation were included using the SM2, SM3, and GB/SA continuum solvation models. These solvation models produce calculated free energies of hydration that are in good agreement with the available experimental data and appear to be quite useful for the prediction of the solvent effects on the relative acidities of the fluorophenols with respect to phenol. A thorough analysis of the charge distribution in the gas and aqueous phases provides insight into the nature of the experimentally observed solvent attenuation of substituent effects for these compounds. While fluorine substitution increases the hydrophobicity of the phenols and phenoxides, the perturbation of ring charge density imparted by fluorine substitution is quite similar in the gas and aqueous phases.

## Introduction

Despite the fact that naturally occurring organofluorine compounds are extremely rare,[1] fluorine and fluorinated groups are important substituents in bioorganic chemistry and often appear in drugs and other synthetic compounds which have biological activity. A comprehensive review of the synthesis of bioactive organofluorine compounds has recently appeared in the literature.[1] Fluorine substitution can lead to dramatic electronic effects which can impact the solubility, lipophilicity, reactivity, acidity, basicity, conformation, and other physicochemical properties of the parent compound with minimal steric consequence. This makes the fluorine substituent an effective tool for modifying the physiological properties of organic compounds.[2,3] Because of the important role molecular modeling plays in the design or discovery of compounds with specified activities or properties, it is important that computational techniques be able to adequately describe the effect of fluorine substitution on chemical properties. In biological systems two chemical properties that are of great interest are acidity and aqueous solvation. In the current study, we have investigated the ability of continuum solvation models to predict the effect of aqueous solvation on the acidity of a set of model organofluorine compounds, the mono fluorophenols.

*o*-, *m*-, and *p*-Fluorophenol are appropriate model compounds for this study because a great deal of experimental data exists.[4,5] These compounds allow for a study of the positional dependence of the fluorine substituent's effect on acidity and aqueous solvation. A great deal of work has been reported in the literature by Taft and Topsom and co-workers[4,6–11] which has identified several interesting trends in the effect of aqueous solvation on the acidity of phenols and other acids. In general, in aqueous solution the effects of substituents on acidity are attenuated compared to the gas phase. For *m*- and *p*-substituted phenols solvent attenuation factors of 5- to 7-fold on the $\Delta G$ of the reaction in Scheme 1 have been observed.[4]

**Scheme 1**




Using ab initio molecular orbital calculations with one to three water molecules hydrating protonation sites, Topsom and co-workers have studied the solvent effects on relative acidity for a variety of types of acids. They have found that local solvent effects alone can account for much of the solvent attenuation of substituent effects for small acids such as substituted acetic acids[12] and methylammonium ions.[13] This is not the case for larger acids such as phenols and pyridinium ions where it appears that a treatment of the bulk solvent is necessary.[11] In the current study, we examine how well implicit solvent models, which treat the bulk solvent as a dielectric continuum, describe these effects.

We are also interested in fluorinated phenols as model compounds for fluorinated derivatives of the amino acid

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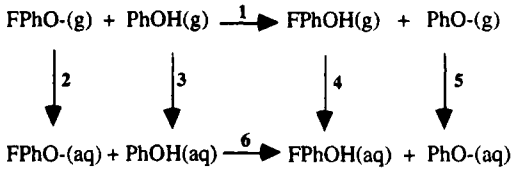
tyrosine. There has been considerable research dealing with the synthesis of fluorinated analogs of the naturally occurring α-amino acids.[14-18] These types of compounds are attractive because of the advantages of fluorine substitution described above. One can also take advantage of the $^{19}F$ NMR tag which facilitates studies of binding events, conformation, metabolism, and similar effects using individual fluoroamino acids or fluoroamino acids incorporated into oligopeptides. von Tersch and Phillips[19] have reported the synthesis of numerous fluorinated tyrosines using the enzyme tyrosine phenol-lyase (TPL). The fluorotyrosines were then used as substrates to investigate the mechanism of cleavage of the phenol side chain from tyrosine which is catalyzed by TPL. One of the factors which influences the activity of TPL is the $pK_a$ of the hydroxyl group of the tyrosine substrate. Introduction of fluorines in the ring positions can result in a tyrosine derivative which is predominantly the phenolate species under neutral pH conditions.[20]

In the current study we have applied a combination of computational techniques to examine the effects of fluorine substitution on the hydration free energy and gas and aqueous phase acidity of phenol. One of the goals of this work is to gain an understanding of how aqueous solvation impacts the electronic effects of the fluorine substituent. Also, we are interested in evaluating the performance of continuum hydration models for fluorinated compounds. In particular we have examined the GB/SA solvation model of Still et al.[21] and the SM2 and SM3 solvation models of Cramer and Truhlar.[22-25] These solvation models have proven to be very effective for the calculation of hydration free energies for diversified classes of organic compounds. Due to the unusual nature of the fluorine substituent, however, we felt it prudent to test the performance of these solvation models for the particular class of fluorophenols prior to applying them to more complicated fluorinated compounds such as fluorotyrosines. For example, the SM2 and SM3 solvation models have been thoroughly parameterized to reproduce hydration free energies for 150 neutral compounds and 28 ions.[26] The mean unsigned errors are only 0.7 and 2.6 kcal/mol across the entire sets of neutrals and ions, respectively. But, as would be expected, of the wide variety of compounds and ions used in this general parameterization of these models, only a small portion were fluorinated compounds. Fluoride ion itself was the only charged species considered. Nine of the neutral compounds used in the parameterization contained fluorine. Most of these were small fluoro- or chlorofluorocarbons with one to three carbons or small fluorinated alcohols.

**Scheme 2**




## Methods

Ab initio calculations were performed with the Gaussian 92[27] program on a Cray Y-MP supercomputer and an IBM RS6000-560 workstation. Geometry optimizations and frequency calculations were carried out with the HF/6-31+G(d) basis set. Single-point energies for the Hartree–Fock geometries were also obtained at the MP2/6-311+G(2d,p) level. This combination has been shown to provide accurate predictions of proton affinities of small organic compounds.[28] The inclusion of zero-point energy corrections and thermal enthalpy and entropy corrections using standard techniques[27] allowed for the calculation of $\Delta Gs$ for the reaction shown in Scheme 1. The experimental temperature of 380 K was used in the thermochemical corrections.[4]

Gas phase semiempirical geometry optimizations were carried out using the AM1[29] and PM3[30] Hamiltonians using the PRECISE keyword with the AMPAC2.1 program.[31] Aqueous phase AM1-SM2 and PM3-SM3 calculations were performed with AMSOL 3.5[32] running on a Cray X-MP. The geometry and electron density were allowed to fully relax in the SM2 and SM3 calculations. Free energies of hydration were calculated by subtracting the corresponding AM1 or PM3 gas phase heat of formation from the AM1-SM2 and PM3-SM3 energies as described previously in the literature.[24]

Molecular mechanics calculations were carried out with the MACROMODEL 3.5x[33] program using the OPLS* force field which is the MACROMODEL implementation of Jorgensen's OPLS force field.[34] The effect of aqueous solvation was included using the GB/SA[21] water model as incorporated in MACROMODEL3.5x. Two sets of molecular mechanics calculations were carried out. In the first (referred to as OPLS*-GB/SA), all parameters were the defaults for OPLS* contained in MACROMODEL 3.5x. In the second, the default electrostatic charges were replaced with those calculated from fits to the HF/6-31+G(d) electrostatic potential using the CHELPG[35] approach as incorporated into Gaussian 92. This set of calculations will be referred to a OPLS*(ESP)-GB/SA.

Three energetic terms will be discussed throughout this paper, $\Delta G_g$, $\Delta G_{aq}$, and $\Delta\Delta G$. $\Delta G_g$ is the gas phase relative acidity or the free energy change associated with process 1 in Scheme 2. $\Delta G_{aq}$ is the corresponding term in the aqueous phase (free energy change for process 6 in Scheme 2). $\Delta\Delta G$ is the solvent effect on the relative acidity and is defined as $\Delta\Delta G = \Delta G_{aq} - \Delta G_g$. Processes 2 through 5 in Scheme 2 are the hydration free energies ($\Delta G_{hyd}$) for the individual phenols or phenoxides. $\Delta\Delta G$ can be arrived at using the $\Delta G_{hyd}$s of the individual species as $\Delta\Delta G = \Delta G_{hyd}(4) + \Delta G_{hyd}(5) - [\Delta G_{hyd}(2)$

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**Table 1. Calculated and Experimental Gas Phase Acidity[a] of Fluorophenol Isomers Relative to Phenol**

| fluorphenol | AM1[b] | PM3[b] | HF[c] | MP2[d] | experiment[e] |
|---|---|---|---|---|---|
| ortho | 4.8 | 5.8 | 2.7 | 3.1 | 3.2 |
| meta | 6.4 | 7.6 | 7.0 | 5.9 | 5.3 |
| para | 5.9 | 5.9 | 2.5 | 2.8 | 2.3 |

[a] In kcal/mol. [b] $\Delta E$. [c] HF/6-31+G(d)//HF/6-31+G(d) calculated $\Delta G$. [d] MP2/6-311+G(2d,p)//HF/6-31+G(d) calculated $\Delta G$. [e] Reference 4.

$+ \Delta G_{hyd}(3)]$. $\Delta G_g$s were calculated with ab initio methods as described above and were approximated with the semiempirical methods as $\Delta E_g$s. $\Delta G_{aq}$s can be calculated directly for process 6 of Scheme 2 using AM1-SM2 and PM3-SM3. An alternative is to combine an experimental or ab initio $\Delta G_g$ with a value of $\Delta\Delta G$ that is calculated with the continuum solvation models to yield $\Delta G_{aq}$. The $\Delta G_{hyd}$ for any individual species can be calculated as the difference between the aqueous phase and gas phase energies using AM1-SM2, PM3-SM3, or OPLS*-GB/SA. These quantities can then be used to calculate the solvent effect as $\Delta\Delta G = \Delta G_{hyd}(4) + \Delta G_{hyd}(5) - [\Delta G_{hyd}(2) + \Delta G_{hyd}(3)]$.

## Results and Discussion

**Gas Phase Relative Acidities.** Experimental data for the gas phase acidities of the monofluorophenols relative to phenol ($\Delta G_g$) are available.[4] However, ab initio molecular orbital calculations of this quantity were carried out in this study for several reasons. Because the GB/SA solvation model is based on molecular mechanics force field calculations, it cannot be used to calculate free energy changes for reactions involving different chemical species.[36] To obtain GB/SA predictions of $\Delta G_{aq}$, one must add the GB/SA-calculated solvent effect ($\Delta\Delta G$) to gas phase data that is obtained via experiment or a quantum mechanical calculation. This approach can also be used to correct for any deficiencies in the AM1 or PM3 gas phase data that will affect the direct calculation of $\Delta G_{aq}$ with AM1-SM2 or PM3-SM3. The gas phase experimental data is available for the monofluorophenols, but we have also performed high level ab initio calculations in order to establish a protocol for making accurate predictions of aqueous phase free energy changes for related compounds for which the experimental data may be lacking. The SM2 and SM3 solvation models employ a semiempirical molecular orbital treatment of the solute allowing for the direct calculation of $\Delta G_{aq}$s for the relative acidity in aqueous solution. The accuracy of these calculations will depend on the underlying AM1 or PM3 treatment of the gas phase relative acidity. However, if the semiempirical treatment of the gas phase is inaccurate, it can be subtracted away yielding the SM2- and SM3-calculated solvent effect ($\Delta\Delta G$) which can be used to make predictions of the $\Delta G_{aq}$ in the same way as for GB/SA (via combination with ab initio values of $\Delta G_g$). The ab initio calculations of the gas phase relative acidity therefore allow for an assessment of the sources of error in the AM1-SM2 and PM3-SM3 $\Delta G_{aq}$s.

The gas phase relative acidities calculated with AM1, PM3, HF/6-31+G(d)//HF/6-31+G(d)(designated HF), and MP2/6-311+G(2d,p)//HF/6-31+G(d) (designated MP2) are presented in Table 1 along with the experimental values.[4] The largest deviation from experiment for the semiempirical calculations occurs with the para isomer. Both AM1 and PM3 predict a value of 5.9 kcal/mol which deviates significantly from the experimental value of 2.3 kca/mol. AM1 outperforms PM3 with an average deviation from experiment across all three isomers of 2.1 kcal/mol compared to 2.9 kcal/mol for PM3. In all cases the semiempirical calculations overestimate the effect of fluorine substitution on the relative acidity.

A significant improvement is seen in the ab initio calculations. In the HF calculations the largest deviation is 1.7 for the meta isomer, and it is significantly larger than the errors obtained for the ortho and para isomers (0.5 and 0.2 kcal/mol, respectively). The average error for the HF calculations is 0.8 kcal/mol. When the basis set is expanded and electron correlation included at the MP2 level, the average error across the three isomers drops to 0.3 kcal/mol. This is very near the experimental error which is estimated to be 0.2 kcal/mol.[4]

**Table 2. Calculated Free Energies of Hydration[a] ($\Delta G_{hyd}$) for Phenols and Phenoxides**

| | AM1-SM2 | PM3-SM3 | OPLS*-GB/SA | OPLS*(ESP)-GB/SA |
|---|---|---|---|---|
| PhOH | −5.7 | −5.4 | −6.4 | −7.1 |
| *o*-FPhOH | −4.8 | −4.8 | −4.7 | −4.6 |
| *m*-FPhOH | −4.9 | −4.9 | −6.1 | −6.4 |
| *p*-FPhOH | −5.0 | −5.4 | −6.3 | −6.8 |
| $PhO^-$ | −65.8 | −66.4 | −78.2 | −70.5 |
| *o*-$FPhO^-$ | −64.6 | −65.2 | −74.9 | −66.9 |
| *m*-$FPhO^-$ | −61.4 | −62.1 | −73.0 | −67.6 |
| *p*-$FPhO^-$ | −61.2 | −62.6 | −73.0 | −68.0 |

[a] In kcal/mol.

**Free Energies of Hydration.** Table 2 contains the calculated hydration free energies for all of the phenols and phenoxides. To the best of our knowledge, only the values for the parent phenol[37,38] and phenoxide[39] are known experimentally. For phenol this value is −6.6 kcal/mol. AM1-SM2 and PM3-SM3 underestimate the experimental value and both of the GB/SA values overestimate it. The best agreement is obtained using the GB/SA solvation model with the default OPLS* parameters which results in an error of only 0.2 kcal/mol. When ESP charges are used, which is the recommended procedure for use of GB/SA,[21,33] the error increases but is still only 0.5 kcal/mol. The AM1-SM2 and PM3-SM3 errors are larger but are still quite reasonable.

All of the calculated $\Delta G_{hyd}$s for the neutral phenols follow the same trends with respect to fluorine substitution. Introduction of fluorine on the ring reduces the magnitude of the solvation free energy, indicating that replacement of a hydrogen with a fluorine increases the hydrophobicity of the molecule. The reduction in $\Delta G_{hyd}$ is smallest for the para isomer due to the offsetting effect of a larger dipole moment. The calculated hydration free energies are very consistent across the four methods for the ortho isomer. For the meta and para isomers, GB/SA predicts larger hydration free energies than does AM1-SM2 or PM3-SM3.

The experimental hydration free energy for phenoxide is −72 kcal/mol.[39] All four calculated values are in good agreement with experiment given the magnitude of ionic hydration free energies and the difficulty in determining them experimentally. The best agreement is obtained

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**Table 3. Breakdown of AMSOL-Calculated Hydration Free Energies into $\Delta G_{ENP}$ and $\Delta G_{CDS}$ Terms[a]**

| | AM1-SM2 | | PM3-SM3 | |
|---|---|---|---|---|
| | $\Delta G_{ENP}$ | $\Delta G_{CDS}$ | $\Delta G_{ENP}$ | $\Delta G_{CDS}$ |
| PhOH | −2.4 | −3.3 | −2.7 | −2.7 |
| *o*-FPhOH | −2.5 | −2.3 | −2.8 | −1.9 |
| *m*-FPhOH | −2.4 | −2.5 | −2.9 | −2.0 |
| *p*-FPhOH | −2.5 | −2.5 | −3.4 | −2.0 |
| $PhO^-$ | −65.1 | −0.7 | −65.4 | −1.0 |
| *o*-$FPhO^-$ | −64.8 | 0.2 | −64.9 | −0.3 |
| *m*-$FPhO^-$ | −61.5 | 0.1 | −61.7 | −0.4 |
| *p*-$FPhO^-$ | −61.3 | 0.1 | −62.2 | −0.4 |

[a] In kcal/mol.

with OPLS*(ESP)-GB/SA. AM1-SM2, PM3-SM3, and OPLS*-GB/SA all deviate from experiment by roughly 6 kcal/mol. As for the neutrals, fluorine substitution diminishes the magnitude of the hydration free energy. In all cases the GB/SA hydration free energies of the phenoxide ions are larger than the AM1-SM2 or PM3-SM3 values.

In Table 3, the AM1-SM2 and PM3-SM3 hydration free energies are broken down into the $\Delta G_{ENP}$ and $\Delta G_{CDS}$ components. These terms have been well described in the literature.[23,24] In short, the former represents the solute electronic (E) and nuclear (N) contributions to the solvation free energy as well as the polarization (P) contribution which arises from the interaction of the network of atom-centered charges with the surrounding dielectric medium. The $\Delta G_{CDS}$ term represents all other contributions to the solvation free energy which pertain to the first hydration shell. This includes the free energy associated with cavity formation (C), dispersive (D) solute−solvent interactions, and any other structural (S) rearrangements of the solvent due to the presence of the solute. It should be noted that the SM2 and SM3 solvation models were parameterized against experimental intact hydration free energies as opposed to individual $\Delta G_{ENP}$ and $\Delta G_{CDS}$ terms. However, Cramer and Truhlar have reported[24] that they were able to largely separate the optimization of the parameters which contribute predominantly to the $G_{ENP}$ term from that of the solvent-accessible surface tensions ($\sigma_k$s) which contribute mainly to the $G_{CDS}$ term.

For the neutral phenols, the $\Delta G_{ENP}$ and $\Delta G_{CDS}$ terms are both negative as calculated with AM1-SM2 and PM3-SM3, indicating a hydrophilic contribution to the total hydration free energy. Breaking down the hydration free energy into these terms clearly illustrates the effect of fluorine substitution on the interactions with solvent. Introduction of fluorine increases the hydrophobicity of the phenols or phenoxides that can be traced predominantly to changes in $\Delta G_{CDS}$. The results indicate that favorable first-shell solute−solvent interactions are diminished, but the electrostatic $\Delta G_{ENP}$ term either remains unchanged or becomes slightly more negative (more favorable interaction with solvent) upon fluorine substitution. Much of the change in the total solvation free energy caused by fluorine substitution can be traced to the $\Delta G_{CDS}$ term which becomes more hydrophobic in all cases. This is consistent with the general observation in drug design that introduction of fluorine increases the lipophilicity of a bioactive compound and improves its distribution throughout an organism.[1-3] Given the electronegativity of fluorine, it is perhaps surprising that the short-range first-hydration shell effects contribute more to the changes in solvation free energy than do the longer-range electrostatic interactions that might arise from changes in charge density.

**Table 4. Calculated Partial Atomic Charges for Phenol**

| atom | 6-31+G(d) ESP | AM1 | SM2 | PM3 | SM3 |
|---|---|---|---|---|---|
| C1 | 0.57 | 0.08 | 0.05 | 0.10 | 0.08 |
| C2 | −0.32 | −0.16 | −0.18 | −0.14 | −0.18 |
| C3 | −0.42 | −0.21 | −0.22 | −0.20 | −0.21 |
| O4 | −0.71 | −0.25 | −0.27 | −0.23 | −0.25 |
| C5 | −0.01 | −0.09 | −0.10 | −0.06 | −0.08 |
| C6 | 0.04 | −0.09 | −0.10 | −0.06 | −0.08 |
| H7 | 0.17 | 0.15 | 0.16 | 0.12 | 0.14 |
| H8 | 0.15 | 0.13 | 0.15 | 0.11 | 0.14 |
| H9 | 0.46 | 0.22 | 0.23 | 0.19 | 0.22 |
| C10 | −0.24 | −0.17 | −0.18 | −0.14 | −0.17 |
| H11 | 0.10 | 0.13 | 0.16 | 0.10 | 0.13 |
| H12 | 0.09 | 0.13 | 0.15 | 0.10 | 0.13 |
| H13 | 0.12 | 0.13 | 0.15 | 0.11 | 0.13 |

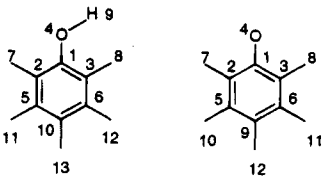


**Figure 1.** Numbering scheme for phenol (left) and phenoxide (right) charges given in Tables 4−11.

**Analysis of Partial Atomic Charges.** The partial atomic charges were calculated for all phenols and phenoxides using a variety of techniques and are presented in Tables 4−11. The numbering schemes are shown in Figure 1. Gas phase charges derived from fits to the 6-31+G(d) electrostatic potential were calculated and will be referred to as ESP charges. Gas phase charges were also calculated using the AM1 and PM3 Hamiltonians with the standard methods in AMPAC2.1.[31] In addition to gas phase charges, aqueous phase charges were calculated using the SM2 and SM3 solvation models in AMSOL for the phenols and phenoxides. The SM2 and SM3 solvation models offer the advantage over the molecular mechanics-based GB/SA that the effect of the solvent continuum on solute charge density is accounted for in the calculation. A comparison of the gas phase and aqueous phase charges reveals any solvent-induced redistribution of charge. In this section, we will first discuss the effect of fluorine substitution on the charges in the gas phase for the phenols and phenoxides. We will then turn our attention to the effect of fluorine substitution on aqueous phase charges.

There are well-established trends regarding substituent effects in electrophilic aromatic substitution reactions which reveal something of the nature of substituent effects on benzene rings.[40] There are two types of effects, resonance and induction, which must be considered. The halogens are generally considered to be deactivating through induction (due to their electronegativity) but *o*- and *p*-directing through resonance (due to the presence of unshared electrons). One would expect an increase in charge due to resonance effects at the carbons ortho and para to the fluoro substituent in phenol. Upon comparison of the ab initio ESP charges for the fluorinated phenols with those of phenol itself, the expected trends are uncovered. Similar qualitative trends were seen in an earlier study using HF/STO-3G calculations.[41]

(40) March, J. *Advanced Organic Chemistry*, 3rd ed.; John Wiley and Sons: New York, 1985.
(41) Pross, A.; Radom, L.; Taft, R. W. *J. Org. Chem.* **1980**, *45*, 818.

**Table 5. Calculated Partial Atomic Charges for *o*-Fluorophenol**

| atom | 6-31+G(d) ESP | AM1 | SM2 | PM3 | SM3 |
|---|---|---|---|---|---|
| C1 | 0.38 | 0.05 | 0.03 | 0.08 | 0.07 |
| C2 | −0.26 | −0.14 | −0.15 | −0.12 | −0.14 |
| C3 | 0.18 | 0.00 | −0.03 | −0.03 | −0.08 |
| O4 | −0.66 | −0.24 | −0.26 | −0.22 | −0.23 |
| C5 | −0.12 | −0.11 | −0.10 | −0.07 | −0.07 |
| C6 | −0.19 | −0.12 | −0.13 | −0.09 | −0.11 |
| H7 | 0.18 | 0.16 | 0.17 | 0.12 | 0.15 |
| F8 | −0.25 | −0.11 | −0.13 | −0.09 | −0.11 |
| H9 | 0.46 | 0.22 | 0.23 | 0.20 | 0.23 |
| C10 | −0.15 | −0.14 | −0.14 | −0.12 | −0.13 |
| H11 | 0.13 | 0.14 | 0.17 | 0.11 | 0.14 |
| H12 | 0.17 | 0.15 | 0.17 | 0.12 | 0.14 |
| H13 | 0.13 | 0.14 | 0.17 | 0.11 | 0.14 |

**Table 6. Calculated Partial Atomic Charges for *m*-Fluorophenol**

| atom | 6-31+G(d) ESP | AM1 | SM2 | PM3 | SM3 |
|---|---|---|---|---|---|
| C1 | 0.63 | 0.11 | 0.09 | 0.13 | 0.13 |
| C2 | −0.40 | −0.17 | −0.18 | −0.16 | −0.18 |
| C3 | −0.60 | −0.26 | −0.26 | −0.23 | −0.25 |
| O4 | −0.70 | −0.25 | −0.25 | −0.22 | −0.23 |
| C5 | 0.03 | −0.07 | −0.07 | −0.04 | −0.04 |
| C6 | 0.57 | 0.13 | 0.09 | 0.11 | 0.06 |
| H7 | 0.19 | 0.16 | 0.17 | 0.13 | 0.15 |
| H8 | 0.22 | 0.15 | 0.16 | 0.13 | 0.15 |
| H9 | 0.46 | 0.21 | 0.23 | 0.19 | 0.24 |
| C10 | −0.42 | −0.20 | −0.20 | −0.18 | −0.20 |
| H11 | 0.12 | 0.14 | 0.17 | 0.10 | 0.14 |
| F12 | −0.28 | −0.10 | −0.12 | −0.09 | −0.11 |
| H13 | 0.18 | 0.15 | 0.17 | 0.13 | 0.14 |

**Table 7. Calculated Partial Atomic Charges for *p*-Fluorophenol**

| atom | 6-31+G(d) ESP | AM1 | SM2 | PM3 | SM3 |
|---|---|---|---|---|---|
| C1 | 0.47 | 0.07 | 0.06 | 0.09 | 0.09 |
| C2 | −0.24 | −0.13 | −0.14 | −0.12 | −0.14 |
| C3 | −0.34 | −0.19 | −0.19 | −0.17 | −0.17 |
| O4 | −0.69 | −0.25 | −0.26 | −0.22 | −0.24 |
| C5 | −0.24 | −0.13 | −0.13 | −0.09 | −0.10 |
| C6 | −0.19 | −0.13 | −0.13 | −0.09 | −0.10 |
| H7 | 0.18 | 0.16 | 0.17 | 0.12 | 0.15 |
| H8 | 0.16 | 0.14 | 0.16 | 0.11 | 0.15 |
| H9 | 0.46 | 0.22 | 0.23 | 0.20 | 0.23 |
| C10 | 0.37 | 0.05 | 0.02 | 0.02 | −0.04 |
| H11 | 0.17 | 0.15 | 0.17 | 0.12 | 0.14 |
| H12 | 0.17 | 0.15 | 0.17 | 0.12 | 0.14 |
| F13 | −0.28 | −0.11 | −0.13 | −0.09 | −0.11 |

Substitution of fluorine on the ring results in a shifting of charge away from the ipso carbon to the fluorine, a moderate reduction in the charge on the carbon meta to the fluorine, and an increase in the charge on the carbons ortho and para to the fluorine substituent. The first two of these are inductive effects and the third a resonance effect. Specifically, for *o*- and *m*-fluorophenol (Tables 5 and 6), the charges at the carbons ortho to the fluorine have gained roughly 0.18 negative charge compared to the corresponding atoms in phenol. For *p*-fluorophenol (Table 7), the increase is greater with C5 and C6, becoming roughly 0.24 more negative than in phenol. Fluorine substitution also causes a depletion of charge at carbons meta to the fluorine ranging from 0.06 to 0.10 electron for the fluorophenols. The carbon bearing the fluorine substituent is most positively charged for *m*-fluorophenol. This is to be expected because the depletion of electron density through induction from the fluorine is partially offset by the resonance effect of the hydroxyl substituent for *o*- and *p*-fluorophenol but not for *m*-fluorophenol. The charge on the acidic proton is not affected by fluorine substitution, and the charge on the oxygen is only slightly perturbed by fluorine substitution, with the greatest change occurring for *o*-fluorophenol ($q_O$ = 0.71, −0.66, −0.70, −0.69 for phenol and *o*-, *m*-, and *p*-fluorophenol, respectively).

**Table 8. Calculated Partial Atomic Charges for Phenoxide Ion**

| atom | 6-31+G(d) ESP | AM1 | SM2 | PM3 | SM3 |
|---|---|---|---|---|---|
| C1 | 0.91 | 0.27 | 0.18 | 0.35 | 0.24 |
| C2 | −0.52 | −0.34 | −0.35 | −0.36 | −0.36 |
| C3 | −0.52 | −0.34 | −0.35 | −0.36 | −0.36 |
| O4 | −0.94 | −0.53 | −0.72 | −0.57 | −0.76 |
| C5 | 0.05 | −0.06 | −0.07 | −0.02 | −0.04 |
| C6 | 0.05 | −0.06 | −0.07 | −0.02 | −0.04 |
| H7 | 0.11 | 0.09 | 0.12 | 0.08 | 0.11 |
| H8 | 0.11 | 0.09 | 0.12 | 0.08 | 0.11 |
| C9 | −0.40 | −0.34 | −0.29 | −0.36 | −0.28 |
| H10 | 0.04 | 0.07 | 0.14 | 0.05 | 0.12 |
| H11 | 0.04 | 0.07 | 0.14 | 0.05 | 0.12 |
| H12 | 0.07 | 0.08 | 0.15 | 0.08 | 0.14 |

**Table 9. Calculated Partial Atomic Charges for *o*-Fluorophenoxide Ion**

| atom | 6-31+G(d) ESP | AM1 | SM2 | PM3 | SM3 |
|---|---|---|---|---|---|
| C1 | 0.67 | 0.27 | 0.16 | 0.35 | 0.24 |
| C2 | −0.47 | −0.34 | −0.30 | −0.35 | −0.32 |
| C3 | 0.11 | −0.14 | −0.19 | −0.20 | −0.25 |
| O4 | −0.86 | −0.50 | −0.70 | −0.54 | −0.73 |
| C5 | −0.01 | −0.07 | −0.07 | −0.03 | −0.03 |
| C6 | −0.15 | −0.10 | −0.09 | −0.06 | −0.06 |
| H7 | 0.12 | 0.10 | 0.14 | 0.09 | 0.11 |
| F8 | −0.31 | −0.15 | −0.16 | −0.13 | −0.14 |
| C9 | −0.38 | −0.32 | −0.26 | −0.33 | −0.26 |
| H10 | 0.07 | 0.07 | 0.16 | 0.05 | 0.14 |
| H11 | 0.11 | 0.09 | 0.15 | 0.07 | 0.14 |
| H12 | 0.10 | 0.09 | 0.16 | 0.08 | 0.16 |

**Table 10. Calculated Partial Atomic Charges for *m*-Fluorophenoxide Ion**

| atom | 6-31+G(d) ESP | AM1 | SM2 | PM3 | SM3 |
|---|---|---|---|---|---|
| C1 | 0.95 | 0.29 | 0.21 | 0.36 | 0.28 |
| C2 | −0.60 | −0.34 | −0.34 | −0.36 | −0.35 |
| C3 | −0.73 | −0.37 | −0.39 | −0.39 | −0.40 |
| O4 | −0.92 | −0.52 | −0.68 | −0.56 | −0.73 |
| C5 | 0.10 | −0.05 | −0.05 | 0.00 | 0.01 |
| C6 | 0.61 | 0.14 | 0.11 | 0.13 | 0.10 |
| H7 | 0.13 | 0.10 | 0.14 | 0.09 | 0.12 |
| H8 | 0.19 | 0.11 | 0.14 | 0.11 | 0.12 |
| C9 | −0.59 | −0.36 | −0.31 | −0.38 | −0.32 |
| H10 | 0.06 | 0.07 | 0.15 | 0.05 | 0.14 |
| F11 | −0.35 | −0.17 | −0.14 | −0.15 | −0.11 |
| H12 | 0.15 | 0.10 | 0.16 | 0.10 | 0.16 |

The AM1 and PM3 gas phase charges show the same qualitative trends as the ab initio ESP charges, but the magnitudes are much smaller. AM1 and PM3 both indicate that fluorine substitution results in increases in charge density at positions ortho and para to the fluorine (0.02 to 0.05 electron). There is also a slight depletion of charge from positions meta to the fluorine (0.02 to 0.03 electron). As was seen with the ab initio ESP charges, the fluorine-bearing carbon is most depleted of charge in the case of *m*-fluorophenol.

The ab initio ESP charges for the phenoxides (Tables 8−11) indicate that fluorine substitution has an effect on the ring carbon charges that is very similar to that of the neutral phenols, both qualitatively and quantitatively. The increase in charge at positions ortho and para to the fluorine ranges from 0.19 to 0.24, which is only slightly greater than was seen in the neutral phenols. The same is true for the gas phase semiempirical phe-

**Table 11. Calculated Partial Atomic Charges for *p*-Fluorophenoxide Ion**

| atom | 6-31+G(d) ESP | AM1 | SM2 | PM3 | SM3 |
|---|---|---|---|---|---|
| C1 | 0.78 | 0.27 | 0.21 | 0.35 | 0.24 |
| C2 | −0.43 | −0.33 | −0.33 | −0.34 | −0.32 |
| C3 | −0.43 | −0.33 | −0.33 | −0.34 | −0.32 |
| O4 | −0.92 | −0.52 | −0.67 | −0.56 | −0.73 |
| C5 | −0.19 | −0.08 | −0.09 | −0.04 | −0.05 |
| C6 | −0.19 | −0.08 | −0.09 | −0.04 | −0.05 |
| H7 | 0.12 | 0.10 | 0.14 | 0.09 | 0.12 |
| H8 | 0.12 | 0.10 | 0.14 | 0.09 | 0.12 |
| C9 | 0.25 | −0.14 | −0.13 | −0.21 | −0.17 |
| H10 | 0.12 | 0.09 | 0.15 | 0.07 | 0.14 |
| H11 | 0.12 | 0.09 | 0.15 | 0.07 | 0.14 |
| F12 | −0.35 | −0.17 | −0.15 | −0.14 | −0.12 |

noxide charges. Very slight increases in charge ortho and para to the fluorine, accompanied by slight decreases meta to the fluorine, are seen in the phenoxide AM1 and PM3 charges.

As stated above, it is possible to obtain information about the effect of aqueous solvation on the distribution of charge by comparing the SM2 and SM3 aqueous phase charges with the corresponding AM1 and PM3 gas phase charges. Such an analysis has revealed quite dramatic solvent-induced charge redistribution effects for 4-pyridone[24] and the nucleic acid base thymine.[42] For all of the neutral phenols the O—H bond is slightly more polarized in water with $\Delta q$'s ($\Delta q = q_O - q_H$) increasing by 0.02−0.03 electron for AM1-SM2 and 0.02 to 0.06 electron for PM3-SM3. The opposite trend is seen for the C—F bonds where aqueous solvation causes a slight decrease in the charge difference across the bond. Upon aqueous solvation, the fluoro substituents become slightly more negatively charged as do the carbons to which they are attached, and the net effect is a decrease in C—F bond polarity in the aqueous phase. In general, the effect of fluorine substitution on the other ring carbon charges is unchanged by aqueous solvation. Comparison of the SM2 charges of the fluorophenols with those of phenol indicates slight increases in charge at positions ortho and para to the fluorine substituent, and the magnitudes of this difference are very similar to the gas phase AM1 values. The only noticeable effect of aqueous solvation on the perturbation of charge density caused by the fluorine is a slight enhancement, in some cases, of the depletion of charge from carbons meta to the fluorine. The overall results, for both SM2 and SM3, indicate that aqueous solvation has little impact on the resonance effects of the fluoro substituent and only a very slight impact on the inductive effects of the fluoro substituent. While the charges on many atoms change in going from the gas to the aqueous phase, the charge differences due to fluorine substitution are, in general, very similar in the gas and aqueous phases. This is consistent with the fact that the differences in hydration free energies caused by fluorine substitution can be mostly attributed to cavitation and other first-shell effects ($\Delta G_{CDS}$).

**Aqueous Phase Relative Acidity.** The aqueous phase acidity of the fluorophenols relative phenol ($\Delta G_{aq}$, process 6 of Scheme 2) can be calculated directly with AM1-SM2 and PM3-SM3. The results of these calculations are shown in Table 12. As stated above, the aqueous relative acidity cannot be calculated directly with the molecular mechanics-based GB/SA technique. An evaluation of the solvent effect on this reaction ($\Delta\Delta G$) is possible however with all of the solvation models in this study and these data are presented in Table 13.

**Table 12. Calculated and Experimental Aqueous Phase Acidity[a] of Fluorophenol Isomers Relative to Phenol**

| fluorophenol | AM1−SM2 | PM3-SM3 | experiment |
|---|---|---|---|
| ortho | 4.5 | 5.2 | 1.6[b] |
| meta | 2.8 | 2.8 | 1.1[c] |
| para | 1.9 | 2.1 | 0.1[c] |

[a] In kcal/mol. [b] Reference 5. [c] Reference 2.

**Table 13. Calculated and Experimental Aqueous Solvent Effects on Acidity[a] of Fluorophenol Isomers Relative to Phenol**

| fluorphenol | SM2 | SM3 | GB/SA[b] | GB/SA (ESP)[c] | experiment[d] |
|---|---|---|---|---|---|
| ortho | −0.3 | −0.6 | −1.5 | −1.1 | −1.6 |
| meta | −3.6 | −3.9 | −5.9 | −2.3 | −4.2 |
| para | −4.0 | −3.9 | −5.2 | −2.2 | −2.2 |
| error[e] | 1.2 | 1.0 | 1.6 | 0.8 | |

[a] In kcal/mol, $\Delta\Delta G = \Delta G_{aq} - \Delta G_g$ for the reaction in Scheme 1. [b] Calculated using the default OPLS* force field parameters in MACROMODEL 3.5×. [c] The OPLS* charges were replaced with charges derived from fits to the HF/6-31+G(d)//HF6-31+G(d) electrostatic potential. [d] References 4, 5, and 11. [e] Average deviation (in kcal/mol) from experiment across the three isomers.

The average deviation from experiment for the $\Delta G_{aq}$ using the AM1-SM2 and PM3-SM3 methods is 2.1 and 2.4 kcal/mol, respectively. For both techniques, the largest error is seen for the ortho isomer where the calculated values differ from experiment by 2.9 kcal/mol for AM1-SM2 and by 3.6 kcal/mol for PM3-SM3. Much of this error, however, is due to the underlying AM1 and PM3 treatments of the gas phase. The average deviation in gas phase acidities is 2.1 kcal/mol with AM1 and 2.5 kcal/mol with PM3. The semiempirical gas phase results can be subtracted, leaving just the solvent effect on the reaction. The errors in this $\Delta\Delta G$ are much smaller. For SM2, the average error drops to 1.2 kcal/mol. For SM3, the average error in $\Delta\Delta G$ is only 1.0 kcal/mol. These errors are only slightly larger than the errors seen in hydration free energies for a set of 150 neutral compounds that was used in the original parameterization of SM2 and SM3 (0.7 and 0.9 kcal/mol, respectively).[24] For a set of 28 ions, the average errors in hydration free energy are 2.6 and 3.5 kcal/mol for SM2 and SM3, respectively.[24] The solvation models appear, therefore, to perform well for fluorophenols even though this particular functionality was not included in the original parameterization scheme.

For both of these solvation models, the largest error in $\Delta\Delta G$ occurs for the para isomer. The experimental data indicate that the largest solvent effect exists for the meta isomer with a $\Delta\Delta G$ of −4.2 kcal/mol. The ortho and meta isomers show solvent effects much smaller than the para and similar to each other with values of −1.6 and −2.2 kcal/mol. SM2 and SM3 predict the solvent effects to be similar for *m*- and *p*- and much smaller for *o*-fluorophenol.

The GB/SA-calculated hydration free energies were used to compute the aqueous solvent effect on the relative acidity. Using the default OPLS* force field parameters, the average deviation from experiment for $\Delta\Delta G$ is 1.6 kcal/mol. Qualitatively, the results are similar to those obtained with SM2 and SM3, although the overall error is slightly larger. As with the AMSOL solvation models, GB/SA predicts the smallest solvent effect for the ortho isomer and larger solvent effects for the meta and para

(42) Cramer, C. J.; Truhlar, D. G. *Chem. Phys. Lett.* **1992**, *198*, 74.

isomers. Excellent agreement with experiment is obtained for the ortho isomer, but a significant error of 3.0 kcal/mol is seen for the para isomer.

The GB/SA-OPLS* results are significantly improved if the default charges are replaced with HF/6-31+G(d) ESP charges. The average deviation from experiment decreases from 1.6 to 0.8 kcal/mol when the ESP charges are used. The most dramatic effect of the charge replacement is seen for the para isomer where the calculated $\Delta\Delta G$ decreases from −5.2 to −2.2 kcal/mol.

The use of HF/6-31+G(d) ESP charges in conjunction with the GB/SA solvation model and the OPLS* force field results in the best overall agreement with experiment in terms of $\Delta\Delta G$. This is also the most costly of the methods studied in this work due to the need to carry out the ab initio calculations on each of the species involved in the equilibria. It is interesting to note that all of the continuum solvation models in this study underestimate the difference in solvent effect for the meta and para isomers. Even the GB/SA-OPLS*(ESP) results, which provide excellent agreement with experiment for the para isomer, predict only a 0.1 kcal/mol difference in $\Delta\Delta G$ for *m*- and *p*-fluorophenol. Experimentally, the solvent effect on this equilibrium is 2.0 kcal/mol greater for the para isomer than the meta.

One of the motivations for this work is to establish a computational protocol that will enable the a priori prediction of the aqueous phase acidities of fluorinated tyrosine analogues relative to the parent tyrosine. Such a protocol could presumably be extended to other fluorinated bioactive compounds. We are therefore interested in comparing the predicted aqueous phase relative acidities based on the computational methods with the experimental data. This will allow for an assessment of the impact of the approximations used on the accuracy of the predictions. The most straightforward calculation of the aqueous phase relative acidity is that obtained directly from SM2 and/or SM3 calculations of the $\Delta G_{aq}$ for process 6 of Scheme 2. As stated above, this provides a reasonable estimate of the relative acidities. The greatest shortcoming of this approach is that the underlying gas phase relative acidities are those of the semiempirical methods which showed sizeable errors when compared to experiment (Table 1). Better predictions of relative acidity can be obtained by adding the solvent effect as calculated with GB/SA, SM2, or SM3 to the gas phase ab initio data. Replacing the semiempirical gas phase data with HF/6-31+G(d)//HF/6-31+G(d) $\Delta G_g$s results in a significant improvement. Even better agreement with experimental relative acidities can be obtained if the system size allows for the calculation of $\Delta G_g$ at the MP2/6-311+G(2d,p)//HF/6-31+G(d) level.

## Summary

The SM2 and SM3 aqueous solvation models of the AMSOL program and the GB/SA aqueous solvation model in the program MACROMODEL have been used to investigate the effect of aqueous solvation on the relative acidity of fluorophenols. The SM2, SM3, and GB/SA solvation models produce calculated solvent effects ($\Delta\Delta$G's) for the reaction in Scheme 1 that are, on average across the three isomers, within ca. 1 kcal/mol of experimental values. Combining these calculated solvent effects with high level ab initio calculated gas phase relative acidities leads to predictions of the aqueous phase relative acidity of the monofluorophenols that are, on average, within slightly over 1 kcal/mol of the experimental values.

A thorough analysis of the calculated charge distribution of the parent phenol and phenoxide and their fluorinated derivatives has been carried out in the gas phase and in aqueous solution. This indicates that the effect of fluorine substitution on the charge density is not greatly perturbed by the presence of an aqueous medium. It is well known that an aqueous medium acts to attenuate the effects of fluorine substituent on phenol acidity. The results reported here suggest that this attenuation cannot be traced to the atomic charges. The difference in charge distribution that is caused by fluorine substitution is very similar in the gas and aqueous phases. Fluorine substitution does introduce a hydrophobic shift in the hydration free energies of phenol and phenolate, and the balance between the solvent effect on these two species determines the solvent attenuation of the substituent effect. A breakdown of the SM2 and SM3 calculated hydration free energies indicates that this effect is most pronounced in the $\Delta G_{CDS}$ term which accounts for cavitation and other first-shell hydration effects.

The errors seen in this study are comparable to the errors that have been reported in the literature for acid−base equilibria in similar systems.[22] This would indicate that these solvation models have been adequately parameterized for the particular class of compounds under investigation in this work. There is the general tendency, however, for the difference in solvent effect for *m*- and *p*-fluorophenol to be underestimated by the continuum hydration models. Taft and co-workers have found that local hydration effects alone cannot account for the solvent attenuation effects for *m*- and *p*-fluorophenol and have suggested that the bulk properties of the solvent continuum need to be included in the calculations to fully account for these effects.[11] In this work, the bulk properties of the solvent have been modeled as a dielectric continuum and some discrepancies with the experimental data still exist. The fact that neither of two vastly different approaches to modeling solvent effects can fully account for the impact of the surrounding aqueous medium on the effect of fluoro substitution indicates the degree of difficulty associated with modeling relative or absolute acidities in aqueous solution. It also suggests that an approach that makes use of explicit water molecules to model the local solvent effects and an accurate continuum model to account for longer-range effects may be useful for these types of systems.

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**Supplementary Material Available:** MP2/6-311+G(d2,p)//HF/6-31+G(d) total energies and HF/6-31+G(d)//HF/6-31+G(d) total energies, structures, and thermochemical data for all compounds (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.