A Computational Study of Charge Delocalization and Ring Fluoro Substituent Effects in 4-Fluoromethylphenoxides

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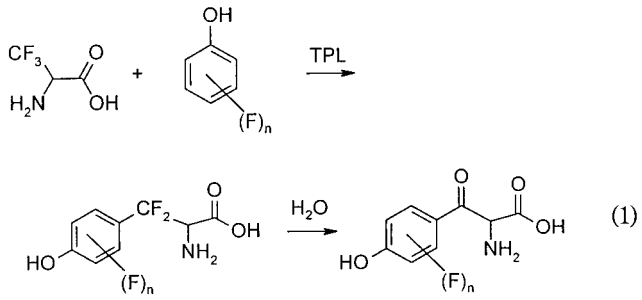
The degree of charge delocalization in 4-fluoromethylphenoxide anions has been investigated with ab initio molecular orbital calculations at the Hartree−Fock and MP2 levels and with the B3LYP density functional using the 6-31+G(d) and 6-311+G(2d,p) basis sets. The effect of aqueous solvation on the rotational profiles has been investigated using the AM1−SM2 solvation model. These anions serve as model systems for fluorinated tyrosine derivatives, which have been used as substrates for the enzyme tyrosine phenol-lyase. The importance of the double-bond/no-bond resonance structure has been assessed through an analysis of conformational profiles, geometries and charge distribution. The effect of ring fluorination on the degree of charge delocalization was investigated to aid in the interpretation of previous experimental mechanistic studies of the tyrosine phenol-lyase enzyme. Calculations were also carried out on benzyl fluoride, and the inclusion of diffuse functions was found to result in the perpendicular conformation as the predicted lowest-energy conformation by a small margin. Previous studies with smaller basis sets found the planar structure to be the lowest-energy conformation. The results indicate that the placement of an electron-donating group (O^-) in the para ring position acts to increase the fluoride character of the fluoromethyl group and that this effect is not substantially modulated by the placement of fluorines on the ring.

Introduction

Despite the fact that naturally occurring organofluorine compounds are very rare, there is great interest in the fluorinated derivatives of biologically active compounds.[1,2] Fluorine substitution can lead to dramatic electronic effects that impact solubility, lipophilicity, acidity, binding, and numerous other properties with minimal steric consequences. The ability to track a fluorinated compound in a biological medium by ^{19}F NMR makes this a useful approach for determining the metabolic fate of compounds and in deciphering the reaction mechanisms of enzymes. Also, the ^{18}F isotope plays an important role in nuclear medicine applications such as PET (positron emission tomography) imaging.[3] For these reasons, fluoro and trifluoromethyl substituents are used extensively in drug design as well as in mechanistic or metabolic investigations. Thus, a fundamental understanding of how fluoro substituent effects are mediated is beneficial not only to the physical organic community but also to the biological and bioorganic chemistry communities.

A case in point is the pyridoxal 5′-phosphate-dependent enzyme tyrosine phenol-lyase (TPL), which catalyzes the hydrolytic cleavage of tyrosine to phenol and ammonium pyruvate (Scheme 1).

TPL has also been used to catalyze the reverse reaction allowing for the synthesis of fluorinated tyrosines starting from the appropriate fluorinated phenols and ammonium pyruvate or β-substituted amino acids (e.g., β-Cl alanine or serine) with a very high degree of stereoselectivity.[4−6] This is a very useful reaction since the incorporation of fluorotyrosines into proteins or oligopeptides offers unique opportunities for enzyme mechanistic studies.[7] For example, ring fluorination of tyrosine provides a means for modulating the phenolic K_a over a range of 5 orders of magnitude.[8−10] Phillips and coworkers used the fluorinated tyrosines as substrates in mechanistic studies of TPL itself, and several interesting features of the reaction mechanism were discovered.[5] To prepare β-fluorinated derivatives of tyrosine, β,β,β-trifluoroalanine was reacted with fluorophenols in the presence of TPL (Scheme 1). However, this did not produce the desired β,β-difluorotyrosine. Instead, there



(1)

is a rapid elimination of fluoride ion producing the β-keto

(1) Welch, J. T.; Eswarakrishnan, S. *Fluorine in Bioorganic Chemistry*; Wiley and Sons: New York, 1991.
(2) Resnati, G. *Tetrahedron* **1993**, *49*, 9385.
(3) Alazraki, N. P.; Mishkin, F. S. *Fundamentals of Nuclear Medicine*; Society of Nuclear Medicine: New York, 1984.
(4) von Tersch, R. L. Biochemical and Chemical Properties of the Carbon−Carbon Lyase, Tyrosine Phenol-Lyase. Ph.D. Dissertation, University of Georgia, 1991.
(5) von Tersch, R. L.; Secundo, F.; Phillips, R. S.; Newton, M. G. Preparation of Fluorinated Amino Acids with Tyrosine Phenol Lyase. In *Biomedical Frontiers of Fluorine Chemistry*; American Chemical Society: Washington, DC, 1996; p 96.
(6) Phillips, R. S.; Fletcher, J. G.; von Tersch, R. L.; Kirk, K. L. *Arch. Biochem. Biophys.* **1990**, *276*, 65.
(7) Brooks, B.; Benisek, W. F. *Biochemistry* **1994**, *33*, 2682.
(8) Voronkov, M. G.; Lopgrev, V. A.; Popova, L. I.; Tatarov, G. P.; Voronova, L. K.; Ignat'ev, N. V.; Byalkovskii, K. L. *Dokl. Akad. Nauk SSSR* **1975**, *225*, 326.
(9) Holmes-Farley, S. R. *Langmuir* **1988**, *4*, 766.
(10) Rubinson, K. A. *J. Phys. Chem.* **1984**, *88*, 148.

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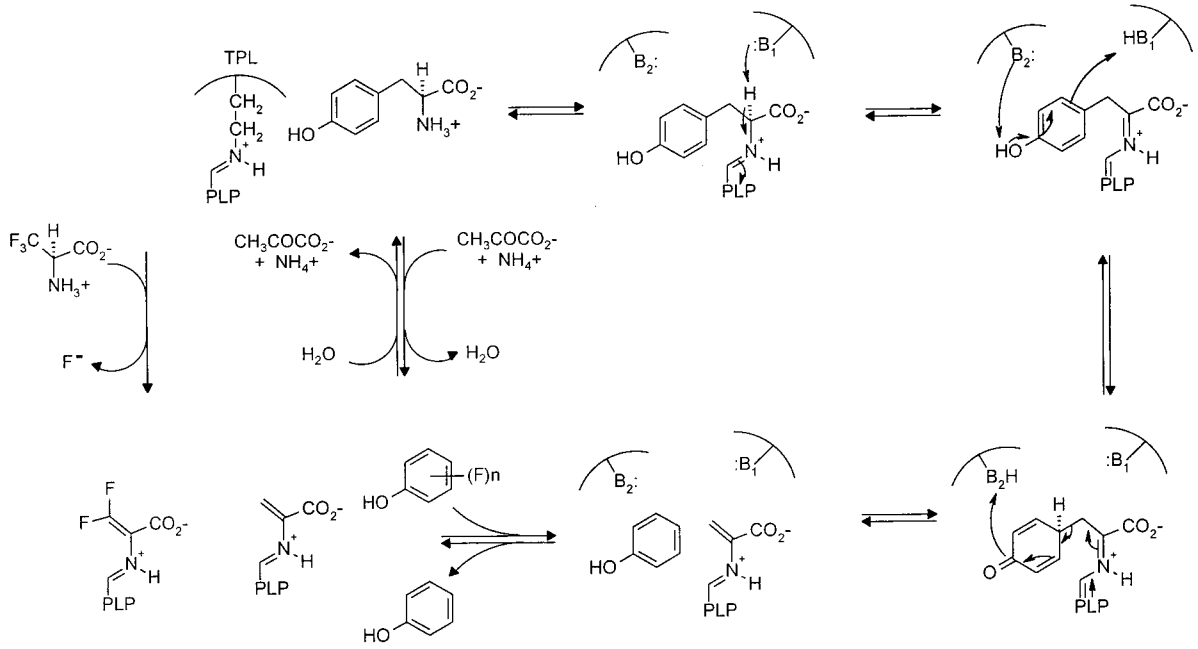
Scheme 1



(eq 1) compound that appears to depend on the presence and placement of fluoro substituents on the ring. Ring fluorination is observed to substantially *increase* the lifetime of β-fluorinated tyrosines (by several orders of magnitude when four fluorines are placed on the ring). Clearly, the ring fluorines will increase the acidity of the phenolic hydrogen. But that does not explain why the elimination of fluoride, which should be better facilitated by a more acidic phenol group, is impeded by ring fluorination. A possible interpretation of this finding is that fluoro groups on the ring retard charge delocalization due to their electron-withdrawing capability, which in turn results in less negative charge being delocalized to the fluoromethyl group (diminished fluoride character).

In the current work, we have carried out an investigation of the degree of charge delocalization in 4-fluoromethylphenoxide anions (Figure 1). The following specific questions are of interest: (1) to what extent is charge from the phenoxy anion delocalized onto the fluoromethyl group, and (2) how is that charge delocalization affected by fluoro substitution on the ring? We will address the first question by making comparisons to the compound lacking the phenoxide anion (benzyl fluoride). The possibilities for the second question are that ring fluorines increase the fluoride character of the fluoromethyl group through π-donation, decrease the negative charge on the fluoromethyl fluorine via an inductive effect, or have no effect on the flow of charge from the phenoxy anion to the fluoromethyl group. Examining this question allows one to rule in or rule out the possibility that the mechanistic affects in the TPL-catalyzed reaction described above are attributable to inherent electronic differences that are introduced by the presence of fluorine in the β-position of tyrosine (i.e., they are a ground-state effect as opposed to a transition-state effect). We will also examine how both of these issues are impacted by the presence of an aqueous medium.

One way to express charge delocalization in these systems is to make use of a "double-bond/no-bond" resonance structure as shown in eq 2. A similar effect has been investigated in the fluoromethyldimethylamine

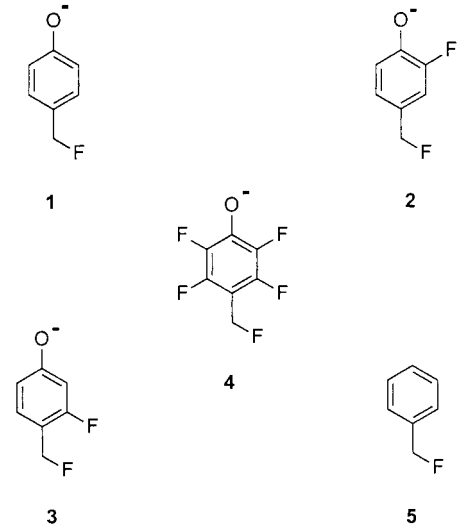
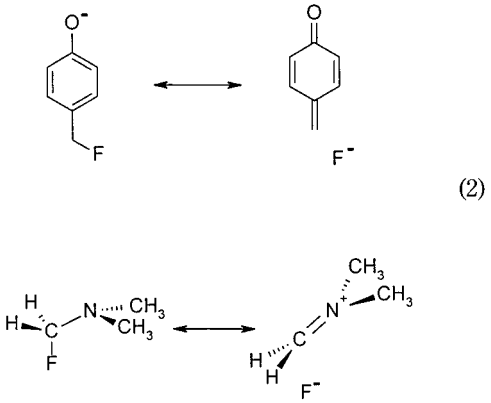


Figure 1. Compounds under study: 4-fluoromethylphenoxide (**1**), 2-fluoro-4-fluoromethylphenoxide (**2**), 3-fluoro-4-fluoromethylphenoxide (**3**), 2,3,5,6-tetrafluoro-4-fluoromethylphenoxide (**4**), and benzylfluoride (**5**).

system (bottom of eq 2), and the expected geometrical and conformational consequences of the double-bond/no-



(2)

bond resonance structure were found.[11] We have chosen the phenoxide anions, as opposed to the neutral phenols, as our model system for two reasons: (a) the phenolic hydrogen is removed early in the reaction mechanism of TPL, and (b) the O^- substituent has a much larger σ_P constant (−0.81 versus −0.38 for OH[12]), which should better facilitate detection of the delocalization of charge and its modulation by ring fluorination.

As stated above, determining the extent of charge delocalization from the phenoxide anion to the fluoromethyl group will be accomplished by removing the oxy anion, leaving benzyl fluoride. The examination of the solvent and ring substituent effects on these systems has the additional benefit of allowing for a comparison with an important series of papers by Schaefer and co-workers on the benzyl fluoride system.[13−15] On the basis of calculations at the HF/6-31G(d)//HF/6-31G(d) and MP2/6-31G(d)//MP2/6-31G(d) levels and NMR studies, they have concluded that the preferred conformation in isolation for benzyl fluoride has the C−F bond oriented in the plane of the aromatic ring and the energetic maximum along the C(Ar)−CH_2F rotational profile exists when the C−F bond is perpendicular to the ring. As will be shown below, the opposite energetic ordering is predicted when the basis set is augmented with diffuse functions. However, in either case, the energy difference between the planar and perpendicular conformations is very small. The C(Ar)−C(sp^2) rotational profiles for benzyl fluorides were also found to be dependent on the solvent medium and substituents on the ring. Schaefer et al. have postulated that a hyperconjugative effect involving π-donation from fluorine is at work in systems such as 4-fluorobenzyl fluoride, which favors the conformation with the C−F bond perpendicular to the aromatic ring. In contrast, Wiberg and Rablen have argued against the importance of π-electron donation by fluorine unless the delocalization leads to stabilization of a full positive charge.[16] By comparing the C(Ar)−C(sp^3) rotational profiles for the fluoromethyl phenoxide anions and those of benzyl fluoride, we will be in a position to determine whether a substituent that is known to be a strong π-donor ($\sigma_P = -0.81$ for O and 0.15 for F[12]) produces a conformational effect that is consistent with the hyperconjugative argument of Schaefer et al.[15]

Methods

Ab initio molecular orbital calculations have been carried out on the anions shown in Figure 1 for the conformations shown in Figure 2. Geometry optimizations were carried out with the 6-31+G(d)[17−19] basis set at the Hartree−Fock and MP2 levels and with the hybrid B3LYP density functional employing Becke's[20] three-parameter method using the LYP[21,22] correlation functional with the 6-311+G(2d,p)[17,18,23,24] basis set. All calculations were carried out with the Gaussian94 program package.[25] For those conformations that could adopt a planar structure, calculations were carried out under the constraint of C_s symmetry. All stationary points were characterized as minima or rotational transition states with frequency calculations performed at the HF/6-31+G(d)//HF/6-31+G(d) and B3LYP/6-311+G(2d,p) levels. Semiempirical calculations were also carried out with the AM1[26] Hamiltonian and the SM2[27] solvation model of Cramer and Truhlar using the program AMSOL.[28] This solvation model has been found to give quite reasonable results in the past for fluorophenols and fluorophenoxides.[29] This solvation model, while a continuum model, also contains a term that is meant to capture first hydration-shell effects and has also been used to study charge delocalization effects in aromatic systems.[30]

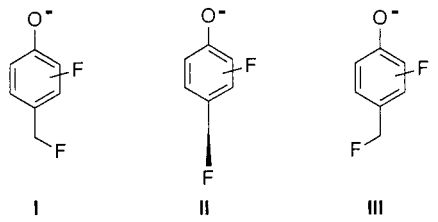


Figure 2. Planar (I and III) and perpendicular (II) conformations for the 4-fluoromethylphenoxide anions, and benzylfluoride by analogy, that have been considered in this work.

Results and Discussion

Tables 1−5 contain the calculated conformational energy differences and solvation free energies for compounds **1**−**5** (Figure 1). Compounds **1**−**4** allow for a study of the positional dependence of the ring fluorine substituent as well as the effect of maximum substitution by fluorine. Compound **5** is included as a reference point to allow for an understanding of the impact of the oxyanion substituent. The conformations considered are I−III as shown in Figure 2. In conformations I and III, the CH_2−F bond eclipses the aromatic ring. In the case of asymmetrically substituted rings (compounds **2** and **3**), the CH_2−F bond can be directed to the same side as the ring fluorine (conformation I) or to the opposite side (conformation III). In conformation II, the CH_2−F bond is perpendicular to the ring.

Aqueous Solvation Free Energies. Because the TPL enzymatic reaction takes place in an aqueous medium, we are interested in understanding the effects of aqueous

(11) Christen, D.; Mack, H. G.; Rüdiger, S.; Oberhammer, H. *J. Am. Chem. Soc.* **1996**, *118*, 3720.
(12) March, J. *Advanced Organic Chemistry*, 3rd ed.; John Wiley and Sons: New York, 1985.
(13) Schaefer, T.; Bernard, G. M.; Bekkali, Y.; McKinnon, D. M. *Can. J. Chem.* **1996**, *74*, 1626.
(14) Schaefer, T.; Beaulieu, C.; Sebastian, R.; Penner, G. *Can. J. Chem.* **1990**, *68*, 581.
(15) Schaefer, T.; Schurko, R. W.; Sebastian, R.; Hruska, F. E. *Can. J. Chem.* **1995**, *73*, 816.
(16) Wiberg, K. B.; Rablen, P. R. *J. Org. Chem.* **1998**, *63*, 3722.
(17) Clark, T.; Chandrasekhar, J.; Spitznagel, G. W.; Schleyer, P. v. R. *J. Comput. Chem.* **1983**, *4*, 294.
(18) Frisch, M. J.; Pople, J. A.; Binkley, J. S. *J. Chem. Phys.* **1984**, *80*, 3265.
(19) Hariharan, P. C.; Pople, J. A. *Theor. Chim. Acta* **1973**, *28*, 213.
(20) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.
(21) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev.* **1988**, *B37*, 785.
(22) Miehlich, B.; Savin, A.; Stoll, H.; Preuss, H. *Chem. Phys. Lett.* **1989**, *157*, 200.
(23) McClean, A. D.; Chandler, G. S. *J. Chem. Phys.* **1980**, *72*, 5639.
(24) Krishnan, R.; Binkley, J. S.; Seeger, R.; Pople, J. A. *J. Chem. Phys.* **1980**, *72*, 650.
(25) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A. *Gaussian94*, Revision E.2; Gaussian, Inc.: Pittsburgh, PA.
(26) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Sewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902.
(27) Cramer, C. J.; Truhlar, D. G. *J. Comput.-Aid. Mol. Des.* **1992**, *6*, 629.
(28) Cramer, C. J.; Truhlar, D. G. *QCPE Bull.* **1991**, *11*, 57.
(29) Urban, J. J.; von Tersch, R. L.; Famini, G. R. *J. Org. Chem.* **1994**, *59*, 5239.
(30) Cramer, C., J.; Truhlar, D. G. *J. Am. Chem. Soc.* **1991**, *113*, 8552.

Table 1. Calculated Conformational Energy Differences[a] and Solvation Free Energies[a] for 4-Fluoromethylphenoxide (1)

	conformation		
method	I	II	III[f]
gas phase			
AM1//AM1	0.1	0.0	
HF/6-31+G(d)//HF/6-31+G(d)	5.1 (4.8)[b]	0.0	
MP2/6-31+G(d)//HF/6-31+G(d)	6.0 (5.7)	0.0	
MP2/6-31+G(d)//MP2/6-31+G(d)	6.3 (6.0)	0.0	
B3LYP/6-311+G(2d,p)// B3LYP/6-311+G(2d,p)	6.4 (6.1)	0.0	
aqueous phase			
SM2 (ΔG_{solv})[c]	−61.6	−61.6	
MP2+$\Delta\Delta G_{solv}$[d]	6.3	0.0	
B3LYP+$\Delta\Delta G_{solv}$[e]	6.4	0.0	

[a] In kcal/mol. [b] Values in parentheses are corrected for differences in HF/6-31+G(d)//HF/6-31+G(d)-calculated zero-point vibrational energies. [c] Solvation free energies calculated at the AM1−SM2 level. [d] Conformational energy differences calculated at the MP2/6-31+G(d)//MP2/6-31+G(d) level corrected for differences in solvation free energies calculated at the AM1−SM2 level. [e] Conformational energy differences calculated at the B3LYP/6-311+G(2d,p)//B3LYP/6-311+G(2d,p) level corrected for differences in solvation free energies calculated at the AM1−SM2 level. [f] Identical to conformation I.

Table 2. Calculated Conformational Energy Differences[a] and Solvation Free Energies[a] for 2-Fluoro-4-fluoromethylphenoxide (2)

	conformation		
method	I	II	III
gas phase			
AM1//AM1	0.2	0.0	0.00
HF/6-31+G(d)//HF/6-31+G(d)	4.8 (4.5)[b]	0.0	4.5
MP2/6-31+G(d)//HF/6-31+G(d)	5.6 (5.3)	0.0	5.6
MP2/6-31+G(d)//MP2/6-31+G(d)	5.9 (5.6)	0.0	5.7
B3LYP/6-311+G(2d,p)// B3LYP/6-311+G(2d,p)	6.1 (5.8)	0.0	6.0
aqueous phase			
SM2 (ΔG_{solv})[c]	−61.4	−61.2	−60.9
MP2+$\Delta\Delta G_{solv}$[d]	5.7	0.0	6.0
B3LYP+$\Delta\Delta G_{solv}$[e]	5.9	0.0	6.3

[a] In kcal/mol. [b] Values in parentheses are corrected for differences in HF/6-31+G(d)//HF/6-31+G(d)-calculated zero-point vibrational energies. [c] Solvation free energies calculated at the AM1−SM2 level. [d] Conformational energy differences calculated at the MP2/6-31+G(d)//MP2/6-31+G(d) level corrected for differences in solvation free energies calculated at the AM1−SM2 level. [e] Conformational energy differences calculated at the B3LYP/6-311+G(2d,p)//B3LYP/6-311+G(2d,p) level corrected for differences in solvation free energies calculated at the AM1−SM2 level.

solvent on the rotational profiles and charge distributions of the phenoxide anions. The free energies of solvation (ΔG_{solv}), as calculated with the SM2 solvation model, are presented in Tables 1−4. The ΔG_{solv} values are arrived at by subtracting the AM1 gas-phase heats of formation from the free energy in aqueous solution as calculated with AM1−SM2. (This is the procedure recommended by the developers of the AM1−SM2 hydration model.)[31] The resulting ΔG_{solv} corresponds to the free energy change associated with transfer from the gas phase to aqueous solution. The solvation free energies are large, ranging from −52.3 to −61.6 kcal/mol, which is to be expected for anions.

It is quite common for rotational profiles to be significantly affected by aqueous solvation, especially for charged organic compounds. For example, for phenethylammonium ions, conformations that are significantly high in energy in the gas phase become important contributors to the solution conformer distribution because they are

(31) Cramer, C. J.; Truhlar, D. G. *J. Am. Chem. Soc.* **1991**, *113*, 8305.

Table 3. Calculated Conformational Energy Differences[a] and Solvation Free Energies[a] for 3-Fluoro-4-fluoromethylphenoxide (3)

	conformation		
method	I	II	III
gas phase			
AM1//AM1	2.0	0.0	0.1
HF/6-31+G(d)//HF/6-31+G(d)	9.0 (8.6)[b]	0.0	3.9
MP2/6-31+G(d)//HF/6-31+G(d)	9.9 (9.5)	0.0	4.8
MP2/6-31+G(d)//MP2/6-31+G(d)	10.1 (9.7)	0.0	4.9
B3LYP/6-311+G(2d,p)// B3LYP/6-311+G(2d,p)	9.9 (9.5)	0.0	5.5
aqueous phase			
SM2 (ΔG_{solv})[c]	−59.2	−57.9	−57.3
MP2+$\Delta\Delta G_{solv}$[d]	8.9	0.0	5.5
B3LYP+$\Delta\Delta G_{solv}$[e]	8.7	0.0	5.9

[a] In kcal/mol. [b] Values in parentheses are corrected for differences in HF/6-31+G(d)//HF/6-31+G(d)-calculated zero-point vibrational energies. [c] Solvation free energies calculated at the AM1−SM2 level. [d] Conformational energy differences calculated at the MP2/6-31+G(d)//MP2/6-31+G(d) level corrected for differences in solvation free energies calculated at the AM1−SM2 level. [e] Conformational energy differences calculated at the B3LYP/6-311+G(2d,p)//B3LYP/6-311+G(2d,p) level corrected for differences in solvation free energies calculated at the AM1−SM2 level.

Table 4. Calculated Conformational Energy Differences[a] and Solvation Free Energies[a] for 2,3,5,6-Tetrafluoro-4-fluoromethylphenoxide (4)

	conformation		
method	I	II	III[f]
gas phase			
AM1//AM1	1.4	0.0	
HF/6-31+G(d)//HF/6-31+G(d)	7.4 (7.1)[b]	0.0	
MP2/6-31+G(d)//HF/6-31+G(d)	8.1 (7.8)	0.0	
MP2/6-31+G(d)//MP2/6-31+G(d)	8.7 (8.4)	0.0	
B3LYP/6-311+G(2d,p)// B3LYP/6-311+G(2d,p)	8.6 (8.3)	0.0	
aqueous phase			
SM2 (ΔG_{solv})[c]	−52.3	−51.8	
MP2+$\Delta\Delta G_{solv}$[d]	8.6	0.0	
B3LYP+$\Delta\Delta G_{solv}$[e]	8.1	0.0	

[a] In kcal/mol. [b] Values in parentheses are corrected for differences in HF/6-31+G(d)//HF/6-31+G(d)-calculated zero-point vibrational energies. [c] Solvation free energies calculated at the AM1−SM2 level. [d] Conformational energy differences calculated at the MP2/6-31+G(d)//MP2/6-31+G(d) level corrected for differences in solvation free energies calculated at the AM1−SM2 level. [e] Conformational energy differences calculated at the B3LYP/6-311+G(2d,p)//B3LYP/6-311+G(2d,p) level corrected for differences in solvation free energies calculated at the AM1−SM2 level. [f] Identical to conformation I.

Table 5. Calculated Conformational Energy Differences[a] for Benzyl Fluoride (5)

	conformation		
method	I	II	III[c]
gas phase			
AM1//AM1	1.4	0.0	
HF/6-31G(d)//HF/6-31G(d)	0.0	0.8	
MP2/6-31G(d)//MP2/6-31G(d)	0.0	0.6	
HF/6-31+G(d)//HF/6-31+G(d)	0.1 (0.0)[b]	0.0	
MP2/6-31+G(d)//HF/6-31+G(d)	0.9 (0.8)	0.0	
MP2/6-31+G(d)//MP2/6-31+G(d)	1.0 (0.9)	0.0	
B3LYP/6-311+G(2d,p)//B3LYP/ 6-311+G(2d,p)	0.4 (0.3)	0.0	

[a] In kcal/mol. [b] Values in parentheses are corrected for differences in HF/6-31+G(d)//HF/6-31+G(d)-calculated zero-point vibrational energies. [c] Identical to conformation I.

preferentially solvated.[32] In the case of compounds **1**−**4**, one might expect that the conformation that best facilitates charge delocalization away from the phenoxy anion, the perpendicular conformation II, would be least well solvated due to diminished favorable interactions between the oxygen anion and the surrounding water medium. However, this trend does not emerge. In fact, for the fluorophenoxides, there is very little conformational dependence in the solvation free energies (i.e., the different conformers of a given phenoxide anion are roughly equally well solvated). As a result, the gas-phase rotational profile, as predicted by AM1−SM2, is a very close approximation to what is expected to exist in an aqueous environment. It is possible that a continuum solvation model might not capture local hydrogen-bonding effects. However, the SM2 solvation model does contain a first hydration-shell term and includes solvent-induced charge redistribution effects. The model has also proven effective in previous studies of hydrogen-bonded solutes including 1,2-ethanediol[33] as well as for fluorinated phenols and phenoxides.[29]

An estimate of the relative stability in aqueous solution of each of the conformations, provided in Tables 1−4 (labeled as MP2 + $\Delta\Delta G_{solv}$ and B3LYP + $\Delta\Delta G_{solv}$), was arrived at by adding the relative solvation free energies ($\Delta\Delta G_{solv}$) to the conformational energy differences as calculated with the two highest levels of theory in this work. These values are closely approximated by the gas-phase conformational energy differences in most cases. The most significant deviation occurs with the 3-fluoro compound where conformation I is solvated better than conformation II by 1.3 kcal/mol. The tetrafluoro compound (**4**) shows a significant drop-off in the magnitude of solvation free energies. This is consistent with the increased lipophilicity that typically results from fluoro substitution.[34]

Gas-Phase Results. For the fluoromethylphenoxides **1**−**4**, conformation II is found to be the lowest in energy with the ab initio methods. Frequency calculations reveal that conformations I and III are rotational transition states (i.e., there is one imaginary frequency associated with rotation about the C(Ar)−C(sp^3) bond). For compounds **1**−**4**, accounting for electron correlation in the form of MP2 single-point energies at the Hartree−Fock geometries (MP2/6-31+G(d)//HF/6-31+G(d)) results in an increase in rotational barriers on the order of 1 kcal/mol. There is an additional increase upon correlated gradient calculations (MP2/6-31+G(d)//MP2/6-31+G(d)), but the amount is very small. Density functional theory calculations with the B3LYP functional were employed as a means for accessing larger basis sets with implicit treatment of correlation with computational efficiency. In general, the B3LYP/6-311+G(2d,p)//B3LYP/6-311+G(2d,p) energies are nearly identical to the MP2/6-31+G(d)//MP2/6-31+G(d) results. AM1 produces rotational barriers that severely underestimate the ab initio values for the 4-fluoromethylphenoxides.

Table 5 contains the conformational energetic results for benzyl fluoride (**5**). As stated in the Introduction, previous work by Schaefer and co-workers has predicted the planar conformation (I) to be the lowest energy structure.[14,15] Our calculations at the HF/6-31+G(d)//HF/6-31+G(d), MP2/6-31+G(d)//HF/6-31+G(d), MP2/6-31+G(d)//MP2/6-31+G(d), and B3LYP/6-311+G(2d,p)//B3LYP/6-311+G(2d,p) levels all indicate that the perpendicular conformation, II, is the lowest in energy; however, the energy differences are very small. Suspecting that the discrepancy between our results and those of Schaefer et al. was due to the lack of inclusion of diffuse functions in the basis set,[14,15] we performed calculations at the HF/6-31G(d)//HF/6-31G(d) and MP2/6-31G(d)//MP2/6-31G(d) levels. The results were nearly identical to those obtained by Schaefer et al. (except for very small differences in relative conformational energies (ca. 0.03 kcal/mol), which can be attributed to the constraint of planarity that was applied to the aromatic ring (for both conformations) in the work of Schaefer et al.).[14,15] Thus, while the slight differences in energy among the various levels of theory lead to different conclusions as to which conformation is the global minimum, it is evident that all of the theoretical methods predict the fluoromethyl group rotational profile to be extremely flat. This is in agreement with what is found experimentally by electron diffraction.[35]

On the basis of comparison between benzyl fluoride and 4-fluorobenzyl fluoride,[15] Schaefer hypothesized that electron-donating groups in the para position of the ring should favor the perpendicular conformation II because this conformation allows for the greatest overlap between the electron-accepting C−F σ^* orbital of the fluoromethyl group and the aromatic ring. The results obtained here allow for a comparison between benzyl fluoride and a substituted analogue with a much greater electron-donating capability than fluorine, the phenoxide anions. The conformational energies for benzyl fluoride in Table 5 indicate that the preference for the perpendicular conformation is predicted to be between 0.4 and 1.0 kcal/mol at the highest levels of theory employed here. However, placement of an O^- substituent in the para ring position results in dramatic increase in this preference (to 6.3−6.4 kcal/mol for **1**). This difference of over 5 kcal/mol is well within the accuracy to be expected of the levels of theory employed here. Analysis (vide infra) of the geometrical and charge distribution changes that accompany transition from conformation I (planar) to conformation II (perpendicular) are consistent with greater charge delocalization from the oxy anion to the fluoromethyl group as the main cause for the preference for the perpendicular conformation. Thus, it appears that placement of an electron-donating group in the para position of the ring greatly stabilizes the perpendicular conformation of the fluoromethyl group.

For reasons stated in the Introduction, we are also interested in determining whether the charge delocalization is impeded by the introduction of electron-withdrawing fluoro substituents on the ring. It has been observed by von Tersch et al.[5] that fluoro substitution on the ring significantly increases the lifetime of β,β-difluorotyrosines. Because the degradation process of the β,β-difluorotyrosines involves the elimination of fluoride ion from the β-position (eq 1), von Tersch et al. suggested that ring fluorination extends the lifetime of the β,β-difluorotyrosines by impeding the charge delocalization, thus diminishing the anionic character of the fluorine that is to be eliminated.[5] The degree of charge delocal-

(32) Urban, J. J.; Cronin, C. W.; Roberts, R. R.; Famini, G. R. *J. Am. Chem. Soc.* **1997**, *119*, 12292.
(33) Cramer, C. J.; Truhlar, D. G. *J. Am. Chem. Soc.* **1994**, *116*, 3892.
(34) Mann, J. *Chem. Soc. Rev.* **1987**, *16*, 381.
(35) Abraham, R. J.; Hearmon, R. A.; Traetteberg, M.; Bakken, P. *J. Mol. Struct.* **1979**, *57*, 149.

ization can be revealed in the calculations via a number of factors including the conformational energy differences (charge delocalization is best accommodated by conformation II), geometries, and charge distributions. In the sections below we will examine how each of these factors is impacted by fluorine substitution on the ring.

Conformational Energy Differences. At the MP2/6-31+G(d)//MP2/6-31+G(d) level, introduction of a fluorine in the 2 position results in a decrease in the preference for the perpendicular conformation, but the magnitude is very small. For **1**, the planar conformation I lies 6.3 kcal/mol above the perpendicular, whereas for **2**, the two possible planar conformations, I and III, lie 5.9 and 5.7 kcal/mol above the minimum, respectively. Thus, if the magnitude of the preference for conformation II is correlated to the degree of charge delocalization, there is a slight diminishing of charge delocalization upon introduction of a fluorine on the ring ortho to the phenoxide anion. Introduction of a fluorine on the 3 position of the ring (**3**) places a fluorine meta to the phenoxide anion and ortho to the fluoromethyl group. The energy for conformation I is increased to 10.1 kcal/mol above the minimum, presumably due to local repulsive effects between the ring fluorine and the fluoromethyl fluorine. Conformation III, where the ring fluorine is on the opposite side of the molecule, lies only 4.9 kcal/mol above the ground state. This raises the question as to why the fluorine has apparently exerted a larger substituent effect when placed meta to the phenoxy anion than when it is placed ortho. Presumably, the fact that the energetic penalty associated with the planar conformation III for compound **3** is smaller than that for conformation I of compound **2** can be attributed to a favorable electrostatic interaction between the negatively charged ring fluorine and the positively charged hydrogens of the fluoromethyl group. Such an interaction is not possible when the fluorine is in the 2-position of the ring. It would therefore appear that the effect of ring substitution on conformational energy differences may be impacted greatly by local steric and electrostatic effects and thus not be representative of simple inductive and resonance substituent effects on the aromatic ring. Changes in the calculated charge distribution and geometry that accompany rotation about the C(Ar)−C(sp^3) bond may be a better indicator of the substituent effects caused by ring fluorination. Such an analysis will be presented below.

Geometries. The delocalization of charge from the phenoxide anion to the fluoromethyl group should be accompanied with certain specific geometrical changes that can be predicted by examination of the double-bond/no-bond resonance structure shown in eq 2 (i.e., shortening of the O−C and C(Ar)−C(sp^3) bonds and lengthening of the C−F bond). Because the perpendicular conformation, II, allows for the greatest overlap between the electron-accepting C−F σ^* orbital and the aromatic ring, one would expect conformation II to exhibit these geometrical changes when compared to conformation I (or III when appropriate). Examination of selected geometrical features calculated at the MP2/6-31+G(d) and B3LYP/6-311+G(2d,p) levels compiled in Tables 6 and 7 reveals that this is the case. The same trends are observed for the HF/6-31+G(d) level, but that data is not shown for brevity. Inspection of the MP2/6-31+G(d) geometries (Table 6) indicates that moving from conformation I to conformation II is accompanied by a decrease in O−C bond length of 0.002, 0.006, 0.005, and 0.004 Å for compounds **1**, **2**, **3**, and **4**, respectively. There is a more dramatic effect on the C(Ar)−C(sp^3) and C−F bonds. The C−C bond decreases by 0.031, 0.029, 0.033, and 0.031 Å, respectively for compounds **1**, **2**, **3**, and **4**. The C−F bond increases by 0.038, 0.035, 0.043, and 0.035 Å, respectively for compounds **1**, **2**, **3**, and **4**. Similar trends are seen for the B3LYP/6-311+G(2d,p) geometries in Table 7. Thus, the calculated geometries are consistent with the double-bond/no-bond resonance structure becoming a more important contributor when the C−F bond is oriented perpendicular to the aromatic ring.

Table 6. Selected Bond Lengths[a] Calculated at the MP2/6-31+G(d)//MP2/6-31+G(d) Level

compound		conformation I	conformation II	conformation III[b]
1	$^-$O−C	1.287	1.285	
	C−CH_2F	1.501	1.470	
	CH_2−F	1.425	1.463	
2	$^-$O−C	1.282	1.276	1.281
	C−CH_2F	1.501	1.472	1.501
	CH_2−F	1.423	1.458	1.423
3	$^-$O−C	1.283	1.278	1.283
	C−CH_2F	1.503	1.470	1.498
	CH_2−F	1.415	1.458	1.424
4	$^-$O−C	1.272	1.268	
	C−CH_2F	1.504	1.473	
	CH_2−F	1.411	1.446	
5	C−CH_2F	1.506	1.495	
	CH_2−F	1.410	1.421	

[a] In angstroms. [b] Conformation III identical to conformation I for compounds **1**, **4**, and **5**.

Table 7. Selected Bond Lengths[a] Calculated at the B3LYP/6-311+G(2d,p)//B3LYP/6-311+G(2d,p) Level

compound		conformation I	conformation II	conformation III[b]
1	$^-$O−C	1.268	1.263	
	C−CH_2F	1.500	1.467	
	CH_2−F	1.415	1.467	
2	$^-$O−C	1.282	1.258	1.264
	C−CH_2F	1.501	1.469	1.500
	CH_2−F	1.423	1.463	1.412
3	$^-$O−C	1.264	1.259	1.264
	C−CH_2F	1.504	1.467	1.498
	CH_2−F	1.404	1.460	1.413
4	$^-$O−C	1.253	1.250	
	C−CH_2F	1.505	1.471	
	CH_2−F	1.400	1.447	
5	C−CH_2F	1.507	1.498	
	CH_2−F	1.396	1.411	

[a] In angstroms. [b] Conformation III identical to conformation I for compounds **1**, **4**, and **5**.

The calculations on compound **5**, benzyl fluoride, allow for a test of Schaefer's hypothesis that the perpendicular conformation, II, should be stabilized by electron-donating groups and result in an increased importance of the no-bond/double-bond resonance structure.[15] The C(Ar)−C(sp^3) bond in benzyl fluoride is 0.011 Å shorter in the perpendicular conformation than in the planar conformation. The C−F bond increases by the same amount upon that conformational change. The magnitude of the bond length changes is significantly increased upon substitution in the para position by the electron-donating O^- group in agreement with Schaefer's hypothesis that electron-donating substituents should act to stabilize the perpendicular conformation.

The question remains as to whether ring fluorination can act to diminish the degree of charge delocalization

from the phenoxy anion to the fluoromethyl group. The MP2/6-31+G(d)-optimized geometries for conformation II indicate that the C−F bond length increases from 1.421 Å in benzyl fluoride to 1.463 Å in compound **1**. An increase in the C−F bond length of 0.042 Å can therefore be attributed to the introduction of the electron-donating O^- in the para position of the ring. The additional introduction of a fluorine at the 2 position of the ring (compound **2**) results in a C−F bond length of 1.458 Å. It can therefore be stated that the presence of the ring fluorine diminishes the effect caused by the para O^- from 0.042 to 0.037 Å. Thus, the effect caused by ring fluorination is much more subtle. When the ring is fluorinated to the fullest extent (**4**), the C−F bond length is 1.446 Å, which is still 0.025 Å longer than the C−F bond length in the perpendicular conformation of benzyl fluoride. It is useful to compare these geometrical changes with other systems where hyperconjugative stereoelectronic effects are at work to provide a point of reference. Christen et al.[11] have studied the anomeric effect in (fluoromethyl)-dimethylamine ($CH_2FN(CH_3)_2$ by gas-phase electron diffraction and ab initio calculations. They have observed that the minimum-energy conformation of (fluoromethyl)-dimethylamine has the C−F bond anti to the nitrogen lone pair. The C−F bond in (fluoromethyl)dimethylamine is found to be 0.019 Å longer than that of CH_3F. Thus, even with four fluorines on the ring, there is a greater degree of charge flow (as measured by C−F bond length changes) in the fluoromethyl phenoxide anions than in (fluoromethyl)dimethylamine.

Rather than using the C−F bond length in benzyl fluoride as a reference point, one can also examine the magnitude in bond length changes associated with the rotation about the C(Ar)−C(sp^3) bond for compounds **1**−**5**. For instance, the C−F bond length increases by 0.038 Å in going from the planar conformation to the perpendicular conformation for **1**. For **2**, the C−F bond lengthens by 0.035 Å in going from conformation I to II or from III to II. For compound **3**, the increase in C−F bond length upon C(Ar)−C(sp^3) bond rotation is increased slightly to 0.043 Å for the change from conformation I to II but is only 0.023 Å for rotation from conformation III to II. Finally, compound **4** shows a 0.035 Å increase in C−F bond length at the MP2/6-31+G(d) level. Similar results are obtained for the B3LYP/6-311+G(2d,p) geometries. Thus, it appears that ring fluorination does not dramatically alter the geometrical changes or presumably the degree of charge delocalization as expressed by the double-bond/no-bond resonance structure that occurs upon rotation about the C(Ar)−C(sp^3) bond. While there appears to be some modulation of the charge flow to the fluoromethyl group by ring fluorination, it is difficult to conclude that this effect alone is responsible for the increased lifetime of the β,β-difluorotyrosines that is observed by von Tersch et al. in the TPL enzyme-catalyzed reaction.[5]

Charges. To examine the electronic distribution in the fluoromethyl phenoxide anions and how it is affected by ring fluorination, the calculated electrostatic charges were also examined. Atomic charges, while a quite useful tool for analysis and as force field parameters, are not a quantum mechanical observable. Any scheme for assigning atomic charges is therefore ultimately arbitrary. For this reason, we have employed two very different charge assignment protocols to assemble the atomic charges presented in Tables 8−11. The charges were calculated based on the MP2/6-31+G(d)//MP2/6-31+G(d) and B3LYP/6-311+G(2d,p)//B3LYP/6-311+G(2d,p)-calculated densities using the Chelpg[36] and Mulliken population analysis[37] methods as implemented in Gaussian94.[25] The

Table 8. Selected Electrostatic Potential-Derived Atomic Charges[a] Calculated at the MP2/6-31+G(d)//MP2/6-31+G(d) Level

compound	atom	conformation I	conformation II	conformation III[b]
1	O	−0.855	−0.854	
	CH_2F	−0.366	−0.399	
2	O	−0.779	−0.761	−0.775
	CH_2F	−0.380	−0.397	−0.368
	ring F	−0.300	−0.298	−0.298
3	O	−0.824	−0.831	−0.824
	CH_2F	−0.378	−0.410	−0.375
	ring F	−0.287	−0.308	−0.320
4	O	−0.678	−0.678	
	CH_2F	−0.404	−0.443	
	ring F:			
	2	−0.211	−0.194	
	3	−0.207	−0.194	
	5	−0.222	−0.217	
	6	−0.186	−0.217	
5	CH_2F	−0.304	−0.298	

[a] In electron units (charge of electron is equal to −1). [b] Conformation III identical to conformation I for compounds **1**, **4**, and **5**.

Table 9. Selected Mulliken Atomic Charges[a] Calculated at the MP2/6-31+G(d)//MP2/6-31+G(d) Level

compound	atom	conformation I	conformation II	conformation III[b]
1	O	−0.720	−0.694	
	CH_2F	−0.369	−0.390	
2	O	−0.698	−0.674	−0.698
	CH_2F	−0.364	−0.387	−0.367
	ring F	−0.399	−0.400	−0.402
3	O	−0.707	−0.682	−0.707
	CH_2F	−0.353	−0.384	−0.370
	ring F	−0.389	−0.402	−0.405
4	O	−0.649	−0.618	
	CH_2F	−0.349	−0.370	
	ring F:			
	2	−0.393	−0.384	
	3	−0.396	−0.384	
	5	−0.391	−0.384	
	6	−0.378	−0.384	
5	CH_2F	−0.343	−0.352	

[a] In electron units (charge of electron is equal to −1). [b] Conformation III identical to conformation I for compounds **1**, **4**, and **5**.

Table 10. Selected Electrostatic Potential Atomic Charges[a] Calculated at the B3LYP/6-311+G(2d,p)/B3LYP/6-311+G(2d,p) Level

compound	atom	conformation I	conformation II	conformation III[b]
1	O	−0.823	−0.810	
	CH_2F	−0.361	−0.384	
2	O	−0.764	−0.741	−0.759
	CH_2F	−0.366	−0.393	−0.279
	ring F	−0.274	−0.280	−0.372
3	O	−0.802	−0.793	−0.810
	CH_2F	−0.375	−0.387	−0.368
	ring F	−0.267	−0.269	−0.299
4	O	−0.667	−0.653	
	CH_2F	−0.411	−0.424	
	ring F:	−0.196	−0.191	
	2	−0.171	−0.192	
	3	−0.211	−0.191	
	5	−0.190	−0.192	
	6			
5	CH_2F	−0.283	−0.290	

[a] In electron units (charge of electron is equal to −1). [b] Conformation III identical to conformation I for compounds **1**, **4**, and **5**.

Table 11. Selected Mulliken Atomic Charges[a] Calculated at the B3LYP/6-311+G(2d,p)//B3LYP/6-311+G(2d,p) Level

compound	atom	conformation I	conformation II	conformation III[b]
1	O	−0.694	−0.673	
	CH_2F	−0.331	−0.320	
2	O	−0.710	−0.686	−0.709
	CH_2F	−0.330	−0.317	−0.328
	ring F	−0.370	−0.371	−0.373
3	O	−0.683	−0.661	−0.681
	CH_2F	−0.319	−0.317	−0.322
	ring F	−0.376	−0.392	−0.403
4	O	−0.700	−0.679	
	CH_2F	−0.307	−0.309	
	ring F:			
	2	−0.376	−0.379	
	3	−0.392	−0.405	
	5	−0.413	−0.379	
	6	−0.382	−0.405	
5	CH_2F	−0.301	−0.277	

[a] In electron units (charge of electron is equal to −1). [b] Conformation III identical to conformation I for compounds **1**, **4**, and **5**.

former of these methods produces charges that are derived from fits to the electrostatic potential at the van der Waals surface of the molecule,[36] while the latter assigns charges by partitioning orbital overlap evenly between the two atoms involved.[37] All of the charge derivation methods indicate that the fluorine at the benzyl position bears significantly more negative charge for the phenoxide anions than for benzyl fluoride. However, examination of the Chelpg charges does not indicate that fluoro substitution on the ring acts to diminish the amount of charge transferred to the benzyl fluorine. In fact, the fluorine on the benzyl carbon bears a greater negative charge for compound **4** than for compound **1** based on either the MP2/6-31+G(d)//MP2/6-31+G(d)- or B3LYP/6-311+G(2d,p)//B3LYP/6-311+G(2d,p)-calculated densities. The Mulliken charges do show a systematic variation upon ring fluorine substitution, but the magnitude is small. For example, at the MP2/6-31+G(d)//MP2/6-31+G(d) level, there is only a very small decrease in the negative charge on the fluoromethyl fluorine from −0.390 to −0.370 upon full fluorination of the ring (see charges for conformation II of compounds **1** and **4**). Similar results are seen for the B3LYP/6-311+G(2d,p)//B3LYP/6-311+G(2d,p) Mulliken charges.

(36) Breneman, C. M.; Wiberg, K. B. *J. Comput. Chem.* **1990**, *11*, 361.
(37) Mulliken, R. S. *J. Chem. Phys.* **1955**, *23*, 1833.

Conclusions

We have carried out an investigation of the degree of charge delocalization in 4-fluoromethylphenoxide anions and several ring-fluorinated derivatives. The AM1−SM2 calculations indicated that the planar and perpendicular conformations are solvated nearly equally well, resulting in an aqueous phase rotational profile that is similar to that in the gas phase. Ring fluorination acts to diminish the magnitude of the solvation free energies for both conformations. High level ab initio calculations indicate that the perpendicular conformation is the lowest-energy conformation for the 4-fluoromethylphenoxide anions as well as the parent benzyl fluoride compound. This is in contrast to previous ab initio calculations, lacking diffuse functions in the basis set, which predict the planar conformation to be lower in energy for benzyl fluoride. The conformational energies, geometrical changes, and partial atomic charges all indicate that substitution on the ring by the strongly electron-donating O^- group in the para position results in an increased preference of the perpendicular conformation that results from a delocalization of charge and can be described by the no-bond/double-bond resonance structure. The calculations indicate that this flow of charge is only weakly affected by ring fluorination. The implications for the tyrosine phenol-lyase enzyme are that simple inductive effects alone may not be adequate to fully explain the observed increased stability of the β,β-difluorotyrosines upon ring fluorination. A thorough investigation of the relative energetics of all of the species located along the TPL enzymatic reaction pathway may be required to fully understand the effect of fluorine substitution on this reaction.

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Supporting Information Available: Absolute calculated energies for compounds **1**−**5** in conformations I−III. This material is available free of charge via the Internet at http://pubs.acs.org.

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