Binding Properties of Aromatic Carbon-Bound Fluorine

Andrew V. Razgulin[†] and Sandro Mecozzi*[,†,‡]

Department of Chemistry and School of Pharmacy, University of Wisconsin, 777 Highland Avenue, Madison, Wisconsin 53705

Received January 20, 2006

A systematic computational analysis of the ability of aromatic carbon-bound fluorine to participate in hydrogen bonding and electrostatic interactions has been completed. The interaction energies between the most common fluoroaromatics used in medicinal chemistry and both water, the prototypical hydrogen bond donor, and several cations have been calculated at different levels of theory (HF, MP2, DFT). Our results show that aromatic fluorine can participate in significant hydrogen bonds and can also interact with charged molecules.

Introduction

Fluorine, the most electronegative element, has a number of physical properties that are unmatched by any other functionality found in organic molecules of medicinal interest. Its high electronegativity and orbitals of size similar to those of carbon make the carbon−fluorine bond the most energetic bond in which a carbon atom can participate (E_{diss} = 112.9 (CH_3−F), 125.4 (C_6H_5−F) kcal/mol).[1] Also, for the same reasons, fluorine can induce significant stereoelectronic effects in the organic molecules in which it is introduced.[2] The difference in electronegativity between carbon and fluorine generates a large dipole moment in this bond that, when combined with the electrostatic distribution of a specific molecule, may contribute to the molecule's ability to engage in intermolecular interactions. This is particularly true in aromatic systems where the introduction of fluorine changes the electrostatic distribution of the molecular surface and may also induce new binding sites localized in proximity of the fluorine atoms. Covalent fluorine is very important in medicinal chemistry even if it is not common in natural products.[3] The application of organic fluorine in rational drug design has been often limited to partially predictable effects on metabolism. Rates of metabolism can be reduced or metabolic pathways can be redirected to avoid production of toxic species.[4]

Increasing evidence has been appearing in the literature implicating the participation of aromatic fluorine in the binding of fluorinated drugs to proteins and drug receptors.[5] Mono- or difluorination of phenyl groups in drugs can lead to improved protein binding. A systematic analysis of the contribution of aromatic fluorine in fluorinated thrombin inhibitors[6] showed that the 4-fluorophenyl derivative **1** (Figure 1) showed a decrease in K_i of about 5.4-fold ($\Delta\Delta G \approx 1$ kcal/mol) over the nonfluorinated variety. Other modifications, including those with 4,*n*-difluoro substitution patterns, failed to match the magnitude of the effect. A crystal structure of thrombin with the 4-fluorophenyl substituted inhibitor was solved at 1.67 Å resolution to reveal a 3.15 Å interaction of the aromatic fluorine with the side chain amide group of Asn98[6] (distance given is that between heavy atoms).

In another example, the structures of the complexes between 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase and several fluorinated inhibitors consistently showed a short (∼3 Å, F−N) contact between one aromatic fluorine and Arg590 of the host enzyme.[7] The conserved nature of the interaction suggests that the fluorine is partially responsible for the stabilization of the complex. Also, a systematic scan of a variety of substituents for a series of 7-(substituted aryl)-3,5-dihydroxy-6-heptenoic (and heptanoic) acids and their lactone derivatives,[8] always for the inhibition of HMG-CoA reductase, revealed that the inhibitor with the highest activity contained a 4-fluorophenyl moiety (**2**, Figure 1). A dramatic effect is also found in the family of antibiotics of which fluoroquinolone **3** (Figure 1) represents an example. Removal of the fluorines in **3** reduces the drug activity and its antibacterial spectrum.[9] These examples indicate that aromatic fluorine can contribute significantly to the action of compounds of medicinal interest. The ability of carbon-bound fluorine to participate in intermolecular interactions has recently been receiving more attention. The crystal structure of the first enzyme found to be involved in biological fluorination, a bacterial 5′-fluoro-5′-deoxyadenosine synthase,[10] was solved in the presence of its substrate. The complex was observed in a geometry corresponding to the time frame immediately following the substrate fluorination step. The fluorine was found to engage in a hydrogen bond with the amide NH of Ser158 (N−F distance = 3.1 Å). Another important example of the participation of aromatic fluorine to the binding of small molecules to the active site of an enzyme is represented

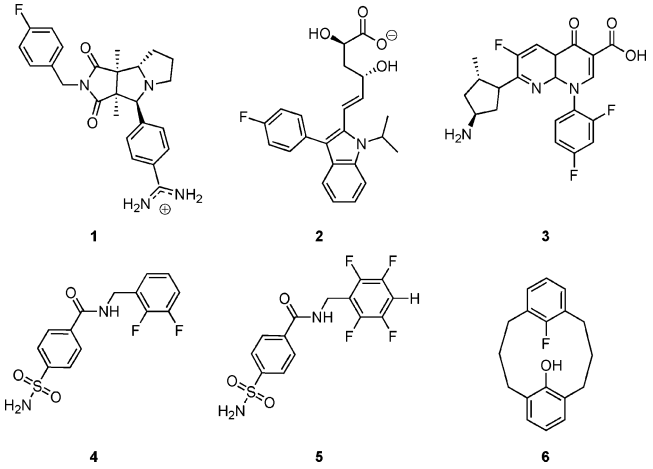

Figure 1. Examples of aromatic-fluorine-containing molecules in which a participation of the fluorine atoms to intermolecular interactions has been proposed.

* To whom correspondence should be addressed. Phone: 608-262-7810. Fax: 608-262-5345. E-mail: smecozzi@wisc.edu.
[†] Department of Chemistry.
[‡] School of Pharmacy.

10.1021/jm0600702 CCC: $33.50 © 2006 American Chemical Society
Published on Web 12/21/2006

by the binding of the small fluoroaromatic inhibitors **4** and **5** (Figure 1) to carbonic anhydrase II.[11] On the basis of the inhibition data, two binding models were proposed. One model relied on dipolar contacts between the fluorobenzene and Phe131, and the other model utilized stacking of the fluorobenzene with Phe131.

In light of their importance, significant effort has been invested to study fluorine-mediated interactions and further evidence has been accumulating for *aromatic* carbon-bound fluorine-mediated hydrogen bonds in small molecules. The hydrogen bond between the hydroxyl group in 2-fluorophenol and the neighboring fluorine was calculated to be 2.92 kcal/mol at the MP2 level,[12] 3.0 kcal/mol by DFT methods,[13] 2.3 kcal/mol by gas chromatography,[14] and 1.44 kcal/mol [15] by far-IR measurements, while two independent IR investigations put the strength of this hydrogen bond at 0.9 [16] and 1.19[17] kcal/mol. The fluorine-containing 9-fluoro-18-hydroxy[3.3]-metacyclophane (**6**, Figure 1) has also been used to study this class of interactions. The cyclophane crystal structure shows a 20:80 hydrogen-bonded to non-hydrogen-bonded ratio. In solution, a distinct low-field shift of the phenolic OH proton was observed in the ^{1}H NMR spectrum compared to that of the F-free analogue. Additionally, OH···F through-space coupling was observed. Hydrogen bond strength was estimated to be 0.20−0.88 kcal/mol for this system.[18] Crystal structure database surveys[6,19,20] found a number of complexes and compounds that have aromatic fluorine mediated hydrogen bonds. The most pronounced case is that of a complex between water and calcium bis[2-fluorobenzoate].[21] The O−H···F angle was determined to be 170°, while the OH···F bond length was 2.02 Å.

Several theoretical studies have also addressed the ability of aromatic fluorine to participate in intermolecular interactions. The hydrogen bond between fluoroethene and water was found to be 1.48 kcal/mol at the MP2/TZV++(3d,1f,1p) theory level when only the distance between the two molecules was optimized.[20] Also, an ab initio investigation was carried out on the fluorobenzene···water and *p*-difluorobenzene···water systems.[22] The interaction strength at the MP2/6-311++G(2d, p) level with and without basis set superposition error correction was calculated to be 4.15 and 4.28 kcal/mol, respectively. The study employed full optimization of the complexes. The fluorine−hydrogen distance was 2.11 and 2.15 Å, respectively. Complex formation was due in both cases to two separate interactions: a hydrogen bond between the fluorine in fluorobenzene and the hydrogen on water; another hydrogen bond between the water oxygen and one of the aromatic hydrogens in fluorobenzene. Additionally, π-type complexes have been identified between fluorobenzene and hydrogen chloride[23] and ab initio studies have been performed on the fluorobenzene−methanol π-complex.[24] Kim and co-workers identified π-type complexes between water and fluorobenzene, as well as *p*-difluorobenzene.[22] π-Type complexes depend on the increased electrophilicity of the π-clouds rather than through direct fluorine-mediated contacts and therefore do not represent a direct contribution from the aromatic fluorines.

This article describes a comprehensive and systematic theoretical analysis of the ability of aromatic-carbon-bound fluorine to engage in hydrogen bonds and electrostatics-based intermolecular interactions. High-level ab initio/DFT calculations were carried out on complexes between a series of fluorinated aromatics commonly encountered in compounds of medicinal interest and water, as an optimal model for a hydrogen bond donor, and cations. The energetics and the geometries of the resulting complexes were analyzed to understand the binding patterns of aromatic fluorinated molecules.

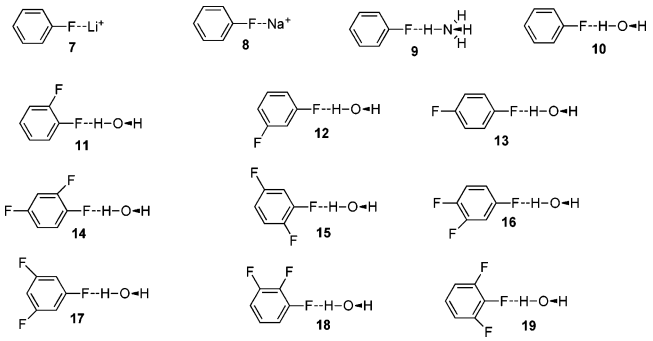

Figure 2. Structure of the complexes between the most common fluoroaromatics found in compounds of medicinal interest and the lithium ion (**7**), the sodium ion (**8**), the ammonium ion (**9**), and water, the prototypic hydrogen bond donor (**10**−**19**). The angles CFH and FHO were constrained to 180°, while the noninteracting water hydrogen was confined to a plane perpendicular to the aromatic ring.

Methods

All ab initio calculations were carried out using the Gaussian 98[25] package on a 50-processor Linux-based computer cluster. The geometries of the complexes were examined using GaussView 3.0. The initial geometries of each model compound were built manually in the **z**-matrix format. The starting geometries for the first set of optimizations were chosen so that the F···H−X angle was set to 180° and the starting F···H distance was set between 2 and 3 Å depending on the complex. The angles CFH and FHO were constrained to 180°. Also, the water hydrogen not directly interacting with the fluorine was constrained in a plane perpendicular to the aromatic ring. The interaction energy was calculated by using the supramolecular approach. In this method, the interaction energy of a dimer AB (the supermolecule) is obtained by directly subtracting the energy of the isolated monomers, A and B, from the total energy of the dimer: $DE_{int} = E(\text{dimer}) - E(\text{mon}_A) - E(\text{mon}_B)$. All MP2 level calculations were corrected for the basis set superposition error (BSSE) using the counterpoise method.[26] The deformation energy of the monomers in the complex was taken into account in the BSSE estimate. NBO analysis was done using the NBO 5.0[27,28] module in Gaussian 98. Electrostatic potential surfaces were generated by mapping HF/6-31G** electrostatic potentials onto surfaces of molecular electron density (0.002 e/Å) and color coding, using the software SPARTAN 5.0.[29] In all surfaces shown here, the potential energy values range from −25 to +25 kcal/mol with red signifying a value greater than or equal to the maximum in negative potential and with blue signifying a value greater than or equal to the maximum in positive potential.

Results and Discussion

A series of ab initio calculations using Hartree−Fock (RHF), second-order Møller−Plesset (MP2), and density functional theory (DFT) with the 6-311++G(d,p) basis set were carried out to evaluate the participation of aromatic-carbon-bound fluorine in intermolecular interactions. We have confined our analysis to the most common fluoroaromatic systems found in compounds of medicinal interest (Figure 2). We considered the interaction of aromatic fluorine with water, the prototypic hydrogen bond donor, and with a variety of cations (Table 1). In order to minimize additional interactions between the water oxygen and the aromatic hydrogens,[22] the angles CFH and FHO were constrained to 180°. Also, the water hydrogen not directly interacting with the fluorine was constrained in a plane perpendicular to the aromatic ring.

Any other angles and atomic distances were subject to full optimization. Table 1 shows the results for the complexes shown

Table 1. Interaction Energies and Basis Set Superposition Errors of the Complexes Indicated in Figure 1[a]

	RHF			MP2			DFT		
	R(H−F) (Å)	E_{corr} (kcal/mol)	BSSE (kcal/mol)	R(H−F) (Å)	E_{corr} (kcal/mol)	BSSE (kcal/mol)	R(H−F) (Å)	E_{corr} (kcal/mol)	BSSE (kcal/mol)
7	1.75	−28.5	0.5	1.77	−30.8	0.5	1.74	−32.0	0.5
8	2.14	−19.5	0.4	2.16	−20.8	0.4	2.12	−21.3	0.5
9	1.78	−13.1	0.3	1.71	−15.6	0.4	1.68	−15.6	0.3
10	2.23	−1.7	0.2	2.12	−2.3	0.3	2.12	−1.6	0.2
11	2.32	−1.4	0.2	2.16	−2.1	0.2	2.18	−1.3	0.2
12	2.26	−1.4	0.2	2.14	−2.0	0.3	2.16	−1.3	0.2
13	2.24	−1.5	0.2	2.13	−2.0	0.3	2.14	−1.4	0.2
14	2.30	−1.3	0.2	2.18	−1.7	0.2	2.19	−1.1	0.2
15	2.33	−1.1	0.3	2.19	−1.7	0.3	2.22	−1.0	0.2
16	2.27	−1.3	0.2	2.15	−1.8	0.3	2.16	−1.2	0.2
17	2.30	−1.1	0.2	2.16	−1.6	0.3	2.18	−1.0	0.2
18	2.32	−1.1	0.2	2.19	−1.7	0.2	2.21	−1.0	0.2
19	2.34	−1.1	0.3	2.21	−1.7	0.2	2.24	−0.9	0.2

[a] Indicated energies are BSSE corrected.

in Figure 2. Energies calculated at the HF level clearly underestimate fluorine-mediated interactions calculated at the MP2 level. MP2 and DFT calculations show similar numbers, although the DFT results slightly underestimate energies calculated at the MP2 level. The basis set superposition error, estimated with the full counterpoise method, appears to be within 10% of the calculated energies.

The results in Table 1 (MP2) clearly indicate that aromatic fluorine can participate in significantly energetic hydrogen bonds with water (entries 10−19). The most energetic hydrogen bond is found between water and the fluorine in monofluorobenzene (**10**). The corresponding energy of this complex is 2.6 kcal/mol. This energy is lower than that of most hydrogen bonds where the acceptor is an oxygen. However, this energy is large enough to contribute significantly to the binding of fluoroaromatics to active sites and/or receptors. The addition of one more fluorine atom (**11**−**13**) decreases the strength of the hydrogen bond to 2.2−2.4 kcal/mol. Interestingly, the ortho (**11**, −2.4 kcal/mol), meta (**12**, −2.2 kcal/mol), and para (**13**, −2.3 kcal/mol) substitution patterns yield similar binding energies within the BSSE error. The additional fluorine in the trifluorobenzene series (**14**−**19**) yields complexes with water characterized by even smaller energies (1.9−2.0 kcal/mol). The binding of the aromatic fluorine in monofluorobenzene to cations such as lithium, sodium, and ammonium reserves some surprises. The interaction energies are very high, ranging from −31 kcal/mol with the lithium ion to −16 kcal/mol with the ammonium ion. These numbers imply that any time aromatic fluorine has the possibility of interacting with a cation or a molecular surface characterized by an excess of positive charge, the resulting interactions will be strongly stabilizing.

The importance of electrostatics in the interaction of aromatic fluorine with cations and hydrogen bond donors can be visualized using electrostatic potential surfaces. Figure 3 shows the electrostatic potential mapped onto isoelectron density surfaces for all possible fluoroaromatics. The asymmetric distribution of potential on the surface of these molecules rationalizes the trend seen with the binding energies. The fluorine atom in monofluorobenzene is characterized by a larger negative potential than the fluorine in multiply fluorinated aromatics. This difference explains why the energy of the hydrogen bond between monofluorobenzene and water is larger than the corresponding energies in di- and trifluorobenzenes. Also, simple visual analysis of the electrostatic potential surfaces corresponding to tetra- and pentafluorobenzene allows the easy prediction that these highly fluorinated aromatics will interact with hydrogen bond donors and cations with lower energies than the less fluorinated benzenes.

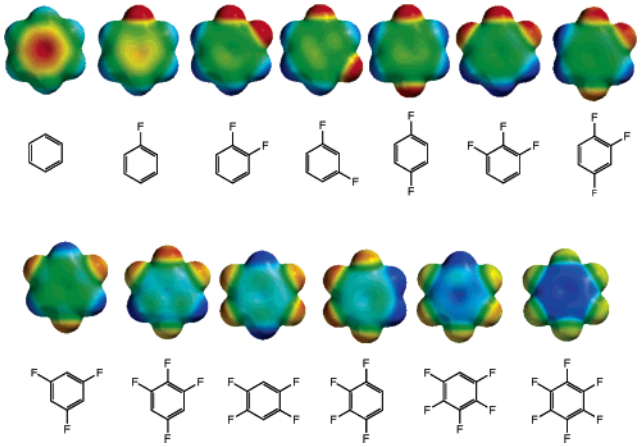

Figure 3. Electrostatic potential surfaces of all possible fluoroaromatics mapped on isoelectron density surfaces (0.002 e/Å). Red means a value greater than or equal to the maximum in negative potential, and blue means a value greater than or equal to the maximum in positive potential.

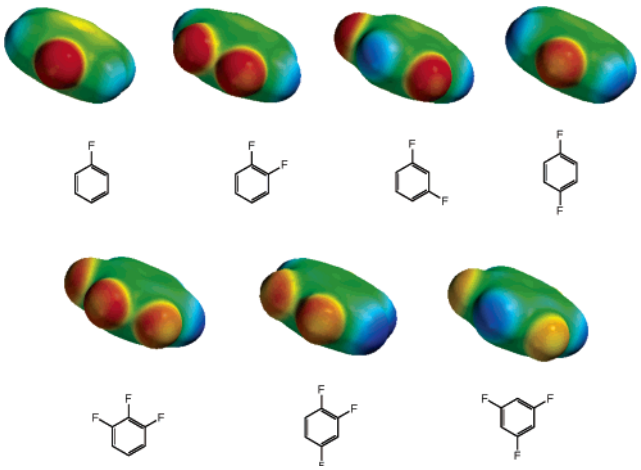

Figure 4. View from the edge of the electrostatic potential surfaces of di- and trifluorobenzenes.

Figure 4 shows the edges of the electrostatic potential surfaces for fluoroaromatics containing up to three fluorine atoms. It is interesting to note that *m*-difluorobenzene shows a peculiar pattern: two fluorine atoms able to participate in hydrogen bonds surround a very acidic aromatic hydrogen. This unusual pattern generates three adjacent binding sites within

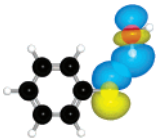

Figure 5. NBO analysis of the interaction between the fluorine in fluorobenzene and water in the fully optimized complex. An overlap between one lone pair on fluorine and a hybrid antibonding orbital of water partially accounts for the hydrogen-bonding ability of aromatic-carbon-bound fluorine.

the same molecule, suggesting a greater ability of this fluoroaromatic to participate in the binding of biologically important molecules.

The nature of the hydrogen bond between aromatic fluorine and water can be probed by using natural bond orbital analysis. The interaction between the fluorine in monofluorobenzene and water is partially due to an orbital interaction between a lone pair on fluorine and a hybrid unfilled antibonding orbital on water (Figure 5). The overlap between the two orbitals indicates the extent of the interaction.

Thus, the hydrogen bond between the fluorine in monofluorobenzene and water can be thought of as due to two independent contributions: electrostatics and partial covalency. This is the situation normally encountered in the majority of hydrogen bonds and shows that aromatic-fluorine-mediated hydrogen bonds should be considered classical hydrogen bonds.

Conclusions

We carried out a series of ab initio calculations aimed to quantitatively evaluate the participation of aromatic-carbon-bound fluorine in intermolecular interactions. The series of mono- to triflurobenzenes was chosen as representative of the fluoroaromatics most commonly used in compounds of medicinal interest. We focused on the interaction of aromatic fluorine with water as the prototypic hydrogen bond donor and with a variety of cations. Our results demonstrate that aromatic-carbon-bound fluorine can participate in the formation of hydrogen bonds and can also strongly interact with positively charged molecules. These interactions are weaker than those mediated by classical hydrogen bond acceptors such as oxygen and nitrogen but significant enough to affect the binding properties of a fluorinated molecule. The 6-311++G(d,p) basis set used at the MP2 level is needed for a careful estimate of the energy of fluorine-mediated interactions. DFT methods should be used with caution because their application to fluorinated molecules yields results that can underestimate true binding energies.

Acknowledgment. We thank Prof. Frank Weinhold for useful discussions. This work was supported by the National Science Foundation (Grant CHE 0518112) and the University of Wisconsin—Madison.

References

(1) Lide, D. R., et al., Eds. *CRC Handbook of Chemistry and Physics*, 86th ed., CRC Press: Boca Raton, FL, 2005.
(2) Sun, A.; Lankin, D. C.; Hardcastle, K.; Snyder, J. P. 3-Fluoropiperidines and *N*-methyl-3-fluoropiperidinium salts: the persistence of axial fluorine. *Chem.—Eur. J.* **2005**, *11*, 1579−1591.
(3) Harper, D. B.; O'Hagan, D. Fluorine-containing natural products. *J. Fluorine Chem.* **1999**, *100*, 127−133.
(4) Park, B. K.; Kitteringham, N. R.; O'Neill, P. M. Metabolism of fluorine-containing drugs. *Annu. Rev. Pharmacol. Toxicol.* **2001**, *41*, 443−470.
(5) Böhm, H.-J.; Banner, D.; Bendels, S.; Kansy, M.; Kuhn, B.; Müller, K.; Obst-Sander, U.; Stahl, M. Fluorine in medicinal chemistry. *ChemBioChem* **2004**, *5*, *637*−643.
(6) Olsen, J. A.; Banner, D. W.; Seiler, P.; Wagner, B.; Tschopp, T.; Obst-Sander, U.; Kansy, M.; Müller, K.; Diederich, F. Fluorine interactions at the thrombin active site: Protein backbone fragments H−CaC═O comprise a favorable C−F environment and interactions of C−F with electrophiles. *ChemBioChem* **2004**, *5*, 666−675.
(7) Istvan, E. S.; Deisenhofer, J. Structural mechanism for statin inhibition of HMG-CoA reductase. *Science* **2001**, *292*, 1160−1164.
(8) Hoffman, W. F.; Alberts, A. W.; Cragoe, E. J., Jr.; Deana, A. A.; Evans, B. E.; Gilfillan, J. L.; Gould, N. P.; Huff, J. W.; Novello, C. F.; Prugh, J. D.; Rittle, K. E.; Smith, R. L.; Stokker, G. E.; Willard, A. K. 3-Hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors. 2. Structural modification of 7-(substituted aryl)-3,5-dihydroxy-6-heptenoic acids and their lactone derivatives. *J. Med. Chem.* **1986**, *29*, 159−169.
(9) Chu, D. T. W. In *Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications;* Filler, R., Kobayashi, Y., Yagupolskii, L. M., Eds.; Elsevier Science Publishers: Amsterdam, 1993; pp 165−207.
(10) Dong, C.; Huang, F.; Deng, H.; Schaffrath, C.; Spencer, J. B.; O'Hagan, D.; Naismith, J. H. Crystal structure and mechanism of a bacterial fluorinating enzyme. *Nature (London)* **2004**, *427*, 561−565.
(11) Jain, A.; Doyon, J. B. The pattern of fluorine substitution affects binding affinity in a small library of fluoroaromatic inhibitors for carbonic anhydrase II. *Org. Lett.* **1999**, *1*, 183−185.
(12) Kovács, A.; Macsári, I. Intramolecular hydrogen bonding in fluorophenol derivatives: 2-fluorophenol, 2,6-difluorophenol, and 2,3,5,6-tetrafluorohydroquinone. *J. Phys. Chem.* **1999**, *103*, 3110−3114.
(13) Korth, G.-H.; de Heer, M. I.; Mulder, P. A DFT study on intramolecular hydrogen bonding in 2-substituted phenols: conformations, enthalpies, and correlation with solute parameters. *J. Phys. Chem.* **2002**, *106*, 8779−8789.
(14) Skvortsov, I. M.; Fedorov, E. E.; Mushtakova, S. P. Energy of intermolecular hydrogen bonding in ortho-substituted phenols and anilines. *Zh. Fiz. Khim.* **1986**, *60*, 2065−2066.
(15) Gerald, L.; Carlson, W. G. F. Torsional frequencies and conformational equilibriums of o-substituted phenols. *J. Phys. Chem.* **1973**, *77*, 1157−1163.
(16) Denisov, G. S.; Sheikh-Zade, M. I.; Eskina, M. V. Determination of the energy of intramolecular hydrogen bonding using competing equilibriums. *Zh. Prikl. Spektrosk.* **1977**, *27*, 1049−1054.
(17) Baker, A. W.; Shulgin, A. T. Enthalpies of intramolecular halogen−hydroxyl interactions. *Can. J. Chem.* **1965**, *43*, 650−659.
(18) Takemura, H.; Kotoku, M.; Yasutake, M.; Shinmyozu, T. 9-Fluoro-18-hydroxy-[3.3]metacyclophane: synthesis and estimation of a C−F- - -H−O Hydrogen Bond. *Eur. J. Org. Chem.* **2004**, 2019−2024.
(19) Dunitz, J. D.; Taylor, R. Oganic fluorine hardly ever accepts hydrogen bonds. *Chem.—Eur. J.* **1997**, *3*, 89−98.
(20) Howard, J. A. K.; Hoy, V. J.; O'Hagan, D.; Smith G. T. How good is fluorine as a hydrogen bond acceptor? *Tetrahedron* **1996**, *52*, 12613−12622.
(21) Karipides, A.; Miller, C. Crystal structure of calcium 2-fluorobenzoate dihydrate: indirect calcium···fluorine binding through a water-bridged outer-sphere intermolecular hydrogen bond. *J. Am. Chem. Soc.* **1984**, *106*, 1494−1495.
(22) Tarakeshwar, P.; Kim, K. S.; Brutschy, B. Fluorobenzene···water and difluorobenzene···water systems: an ab initio investigation. *J. Chem. Phys.* **1999**, *110*, 8501−8512.
(23) Sanz, M. E.; Antolinez, S.; Alonso, J. L.; Lopez, J. C.; Kuczkowski, R. L.; Peebles, S. A.; Peebles, R. A.; Boman, F. C.; Kraka, E.; Cremer, D. The microwave specrum, ab initio analysis, and structure of the fluorobenzene−hydrogen chloride complex. *J. Chem. Phys.* **2003**, *118*, 9278−9290.
(24) Solimannejad, M.; Pejov, L. The case of a very weakly pi-hydrogen bonded fluorobenzene−methanol complex. A gradient-corrected density functional and MP2 study of the ground electronic state potential energy surface. *Chem. Phys. Lett.* **2004**, *385*, 394−402.
(25) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M.

A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, revision A.11.1; Gaussian, Inc.: Pittsburgh, PA, 1998.

(26) Boys, S. F.; Bernardi, F. The calculation of small molecular interactions by the differences of separate total energies. Some procedures with reduced errors. *Mol. Phys.* **1970**, *19*, 553−566.

(27) Glendening, E. D.; Badenhoop, J. K.; Reed, A. E.; Carpenter, J. E.; Bohmann, J. A.; Morales, C. M.; Weinhold, F. *NBO 5.0*; Theoretical Chemistry Institute, University of Wisconsin: Madison, WI, 2001.

(28) Weinhold, F.; Landis, C. R. *Valency and Bonding: A Natural Bond Orbital Donor−Acceptor Perspective*; Cambridge University Press: Cambridge, U.K., 2005.

(29) *Spartan*, version 5.0; Wavefunction, Inc. (18401 Von Karman Avenue, Suite 370, Irvine, CA 92612).

JM0600702