Positioning a Carbon–Fluorine Bond over the π Cloud of an Aromatic Ring: A Different Type of Arene Activation

Maxwell Gargiulo Holl, Mark D. Struble, Prakhar Singal, Maxime A. Siegler, and Thomas Lectka*

Abstract: *It is known that the fluoro group has only a small effect on the rates of electrophilic aromatic substitutions. Imagine instead a carbon–fluorine (C−F) bond positioned tightly over the π cloud of an aryl ring—such an orthogonal, noncovalent arrangement could instead stabilize a positively charged arene intermediate or transition state, giving rise to novel electrophilic aromatic substitution chemistry. Herein, we report the synthesis and study of molecule 1, containing a rigid C−F···Ar interaction that plays a prominent role in both its reaction chemistry and spectroscopy. For example, we established that the C−F···Ar interaction can bring about a >1500 fold increase in the relative rate of an aromatic nitration reaction, affording functionalization on the activated ring exclusively. Overall, these results establish fluoro as a through-space directing/activating group that complements the traditional role of fluorine as a slightly deactivating aryl substituent in nitrations.*

The fluoro group generally exhibits only a small effect on the rates of electrophilic aromatic substitutions.[1] Reactions involving putative σ-complexes are usually slightly activated by fluorine, whereas aromatic nitrations[2] that involve analogous π-complexes[3] show deactivation. While such classical substituent effects have been well documented in aryl fluorides, we wish to approach the interaction from a different perspective; imagine instead a C−F bond positioned tightly and rigidly over the π cloud of an aromatic ring. Is it possible that such an arrangement could stabilize a positively charged nitroarenium ion intermediate[4] or transition state, thereby giving rise to new reaction chemistry in which the fluoro group is now highly activating? Given the ever increasing importance of fluorine to arene chemistry in particular and organic chemistry in general, a fundamentally different method of activating electrophilic substitutions is of great interest.[5] For our part, we have recently reported studies on the generation of symmetrical fluoronium ions in solution,[6] suggesting to us that under the right conditions fluorine could also play the role of an anchimeric assistor in reaction chemistry.

[*] M. G. Holl, M. D. Struble, P. Singal, Dr. M. A. Siegler, Prof. T. Lectka
Department of Chemistry, Johns Hopkins University
3400 North Charles Street, Baltimore
MD 21218 (USA)
E-mail: lectka@jhu.edu
Homepage: http://lectka.chemistry.jhu.edu/

In this spirit, we report the synthesis of a molecule in which a C−F bond is projected over the π-system of an aromatic ring, imbuing it with unique reactivity. Spectroscopy, crystallography, and reactivity tell the story of a species in which the C−F···Ar interaction plays a prominent role in establishing fluorine as a through-space directing/activating group in aromatic substitutions that complements its traditional role as an aryl substituent (Figure 1). As perhaps the
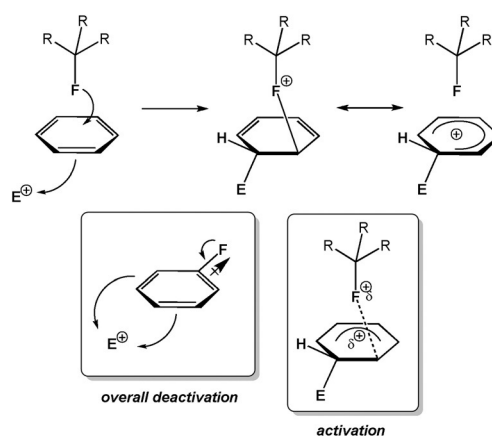

***Figure 1.*** Inductive deactivation of fluoroarene versus fluorine's through-space stabilization of arenium ion.

signature aromatic substitution reaction, we chose nitration as a candidate for initial studies.[7] The generally accepted mechanism for classical nitrations involves the reaction of a nitronium ion with an aromatic ring.[8,9] After π-complex-ation, this step forms a positively charged arenium ion, or "Wheland intermediate," that we believed could be stabilized with the assistance of fluorine from above the π cloud of the ring.[10]

In order to test our hypothesis, we sought to construct a system in which the fluorine atom is projected well within the hexagonal prism of space defined by the aromatic ring. Thus we imagined that the Diels–Alder reaction of dienophile **2**[11] with anthracene[12] would provide a product in which a C−F bond is pointed directly towards one of the two aryl groups (Scheme 1). Heating a mixture of **2** and anthracene produced the desired product **1** (1,2-dichlorobenzene, 180°C, sealed tube, 72% yield).

The ^{19}F NMR spectrum (300 MHz) of adduct **1** showed a single resonance at −180.5 ppm, split into a complex multiplet. This resonance is within the range seen for other secondary C−F bonds,[13] an observation that, in isolation, made it initially unclear whether any notable interaction was
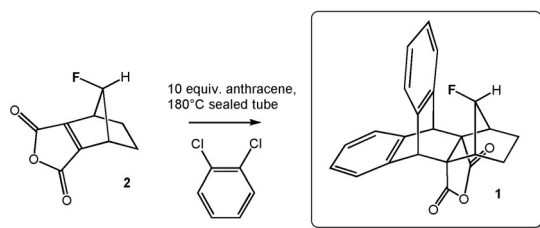
Scheme 1. Synthesis of **1**.

occurring. In fact, relatively little is known about through-space interactions of C−F bonds with the interiors of aromatic rings—from the exterior, ring currents are believed to have only a minimal relative impact on the chemical shifts of the fluorine atoms of aryl fluorides.[14]

We hypothesized that the interior placement of fluorine would result in an upfield shift in the ^{19}F NMR spectrum, in analogy to the well documented upfield shift[15] of hydrogen in C−H bonds projected within the shielding zones of aromatic rings (indeed, analogs of **1** with inward pointing hydrogen atoms do see shielding, vide infra). In one impressive precedent, Pascal et al. have observed a large upfield shift (−155 ppm) of the ^{19}F resonance in a Si−F bond projected towards the center of an aromatic ring in a cyclophane, attributed to a ring current effect.[16] In a recent example, Chang et al. instead observed downfield shifts in C−F bonds, attributable in part to steric compression.[17] However, note that the C−F bonds in the latter case reside outside the prism and perhaps outside the shielding zone of the ring. Thus, the question of what happens when a C−F bond is projected within remains unsettled. In order to characterize **1**, we then turned our attention to control species, the first being alkene **3** (Figure 2), in which a C=C double bond is positioned near the C−F bond rather than an aromatic ring.[11] When the ^{19}F spectra of these two molecules were compared, we observed the signal of **3** 30 ppm downfield of **1**, an observation that is roughly consistent with an enhanced ring current effect in the aromatic system.

On the other hand, when the ^{19}F spectrum of *in*-fluoride **1** was compared to that of *out*-fluoride **4** (the synthesis of **4** is shown in the Supporting Information), whose fluorine atom is considerably farther away from the aromatic ring, a different observation was made. The *in*-fluoride **1** resonates 15.8 ppm downfield from *out*-fluoride **4**, contrary to what we expected. To shed light on what is going on, we turned our attention to density functional (DFT) calculations. Using the F−Ar distances and angles in the optimized structures of **1** and **4** as starting points (ωB97xd/6-311 + G** = "B97"),[18] we approximated the interactions as virtual atoms positioned above a benzene ring.[19] Employing the nucleus independent
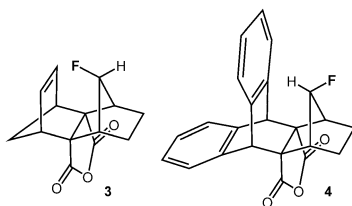
chemical shift (NICS) protocol in Gaussian, we calculated that the virtual atom corresponding to the *in*-fluorine should be more shielded than the "out" virtual atom (although the latter is still within the shielding zone of the π cloud of the arene ring).[20] Something is therefore happening to deshield the ^{19}F atom of **1**. One explanation, consistent with Chang's results, also involves steric compression. For example, **1** is less stable than **4** by 8.3 kcal mol^{-1} (at B97, see the Supporting Information), mainly due to nonbonded interactions between F and the arene ring.[21] Congruently, Martin et al. have shown that C−H bonds that are aligned along the vertical C_2 axis of a C_{2v} symmetric C=C bond (e.g. in ethylene) are deshielded when present within 3.0 Å of the horizontal plane of the molecule (even though NICS indicates this area to be a shielding zone).[22] Orbital compression[23] may be responsible for the deshielding—in our case, the electron cloud about the fluorine atom would be distorted anisotropically. How can steric compression of the C−F bond be otherwise quantified? One way is to examine ^{13}C–^{19}F NMR couplings—as the bond is compressed, the magnitude of the coupling increases.[24,25] This is in fact what we find; the C−F coupling is greater in *in*-fluoride **1** than *out*-fluoride **4** by 21 Hz.

A crystal of **1** suitable for X-ray determination was grown from a mixture of CH_2Cl_2 and Et_2O. The structure reveals the fluorine positioned slightly asymmetrically, but still well over the aromatic ring (Figure 3). Intermolecular interactions in the crystal lattice likely skew the position of the F atom and break the C_s symmetry of the molecule, as the nearest carbon atoms on the aromatic ring are ca. 2.68 and 2.75 Å (2.72 Å at B97) away. The molecule retains full C_s symmetry in silico; the predicted C−F distance (B97) is 1.37 Å, which is shortened a bit from the distance predicted for the *out*-fluoride **4** (1.39 Å). This is consistent with the increased C−F coupling in the NMR spectrum of **1** relative to **4**.

In this study, X-ray data were collected at subatomic resolution (0.40 Å) to obtain a more accurate description of the atomic electron density in the crystal. The experimentally observed density along the C−F bond shows a slight anisotropy in which the electron cloud around the fluorine atom has been distorted (Figure 4). A region of low density lies across the bond, and is bent away from the C−F line, consistent with bond compression. As a control, we were able to draw a static deformation electron density map of a similar structure that lacks the influence of the ring (see the Supporting Information). The C−F bond in the control does

Figure 2. Alkene **3** and arene **4**.
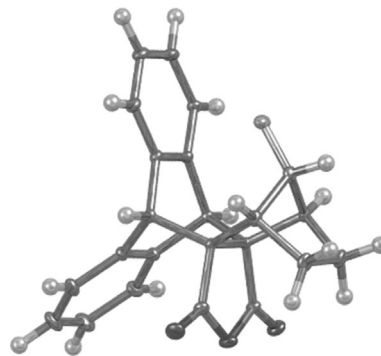
Figure 3. Displacement ellipsoid plot (50% probability level) of **1** at 110(2) K.
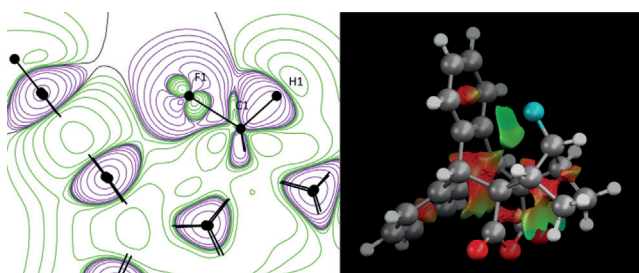
Figure 4. Left: Static deformation electron density map in the plane H1, C1, F1 of **1**, 2D slice along the molecule's plane of symmetry. Violet regions represent electron density (positive) and green regions represent holes (negative). Right: Noncovalent interaction (NCI) plot of **1**. The bluish region between F and the arene indicates an attractrive interaction (red regions are repulsive interactions).

not deviate from the C−F line. A noncovalent interaction (NCI) analysis (Figure 4) was also performed on **1** using the molecular coordinates of the crystal structure.[26] The model predicts a slightly attractive interaction between fluorine and the arene, suggesting that a complex interplay of forces may be at work.

The unique structure of **1** serves a dual purpose in measuring reactivity in electrophilic aromatic substitution. The aromatic ring proximate to fluorine (ring **A**) serves as the probe, whereas unperturbed ring **B** (distal from F) serves as an internal control. A good place to start would be a common substitution reaction such as a nitration. For example, the addition of a nitronium ion to the position of ring **A** as in **5** should generate partial positive charge at the arene carbon attached to the bridgehead. In turn, lone pairs on fluorine can exert a through-space stabilizing influence on the transition state, and the resulting arenium ion **5** as well.

Calculation of the corresponding Wheland intermediates **5**–**10** (at various levels of theory that address long range interactions and dispersion)[27] demonstrates this trend (Table 1). The *in*-F atom stabilizes, in a through-space manner, the **A**-ring derived intermediate **5** when compared to the analogous **B**-ring intermediate **8**, whereas in opposition, the **B**-ring areniums **9** and **10** are favored over **A**-ring areniums **6** and **7**. The geometry of **5** shows fluorine moving closer to the ring towards carbon 4 (*para* to the nitro group of ring **A**) and enhancing the C−F–––Ar interaction in the process (2.53 Å v. 2.72 Å in **1**, B97). The *in*-pointing hydrogen geminal to the nitro group does not interact with fluorine to any extent, leaving the C−F–––Ar interaction as the primary means of stabilization. In contrast, the seminal works of Cram and Hopf have shown that aromatic rings and certain substituents can act as H-bond acceptors in directing the electrophilic substitution of paracyclophanes.[28] An atoms-in-molecules (AIM) analysis[29] of ion **5** shows a bond critical point between fluorine and carbon 4 ($\rho = 0.020$). The fluorine atom can also be described as acting as a Lewis base mediated by the aromatic ring; it is unusual to see an organic fluorine atom acting in such a manner.

When **1** was treated with 1 equiv of ammonium nitrate in a 2:3 mixture of TFAA and MeCN at 25 °C,[30] diastereomer **11** was observed exclusively and in high yield (89%, Scheme 2). Control **4**, designed to gauge the stereoelectronic

Table 1: Computed relative energies of **10**–**15** [ΔE_{rel} AΔB of arenium ions (Wheland intermediates)]. Functionals with dispersion and long range corrections were chosen.[18b, 27]

5: R₁=F, R₂=H
6: R₁=H, R₂=F
7: R₁=H, R₂=H

8: R₁=F, R₂=H
9: R₁=H, R₂=F
10: R₁=H, R₂=H

Method/Basis Set	ΔE_{rel} [kcal]		
	8–5	**9–6**	**10–7**
ωB97xd/6-311+G**	5.2	−2.5	−2.2
CAM-B3LYP/cc-pvdz	5.5	−1.8	−2.2
APFD/6-311+G**	4.5	−1.9	−1.8
LC-wPBE/6-311+G**	5.9	−2.5	−2.2
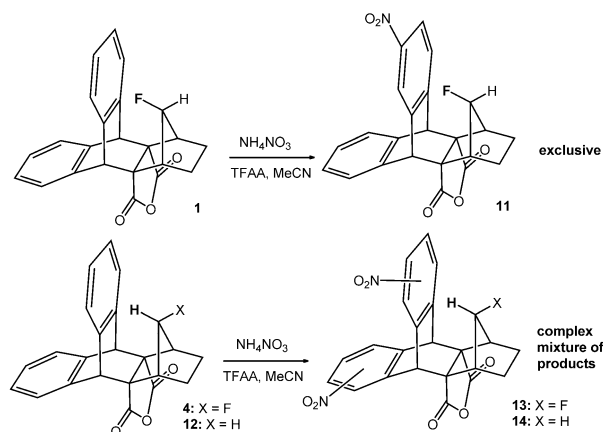
Scheme 2. Starkly different reactivity of **1** compared to **4** and **12**.

effect of the fluoro group, instead afforded a ≈ 1:1 mixture of **A:B** ring isomers (**13**). Being distant from the reactive centers, the *out*-F is shown to exert little directing effect on the nitration reactions. Note that the exact nature of the active nitrating species (and thus the π-complex) under these conditions is not known and is beyond the scope of this work (it is posited to involve either a nitronium ion or trifluoroacetyl nitrate).[31,32] Thus for our computations, we employed the Wheland intermediates as models rather than calculated transition states or π-complexes.

Another control involves **12** (see the Supporting Information for the synthesis),[6b, 33] in which the fluorine atom is replaced by hydrogen. It is well established that hydrogen atoms can stabilize positive charge through μ-hydrido bridging[34] and would serve as a benchmark comparison of the role of fluorine. Once again, a mixture of nitrated products involving both rings **A** and **B** was observed (**14**).

Finally, a competitive rate study of the nitration reactions was performed. Fluoride **1** was shown to react much more rapidly than either control **4** or **12**, with a factor of 1500 being a lower bound on this increase over **4** (measurement only limited by the S/N ratio of the NMR experiment, Figure 5),
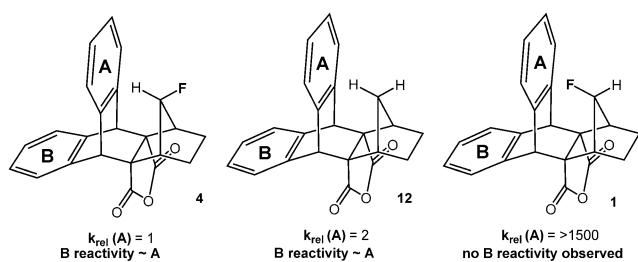
Figure 5. Relative rate study of nitrations of **1** and controls. Conditions: ammonium nitrate in a 2:3 mixture of TFAA and MeCN, room temperature.

presenting the most definitive and compelling evidence of fluorine activation.

In conclusion, we have provided spectroscopic and crystallographic evidence for a molecule in which a C−F bond is projected over the π-system of an aromatic ring. The C−F−−−Ar interaction plays a prominent role in reaction chemistry (e.g. an aromatic nitration), establishing fluorine as a significant through-space activating and directing group that complements and contrasts its traditional role as a weakly perturbing aryl substituent in electrophilic aromatic substitutions.

Experimental Section

General experimental procedures and characterization data can be found in the Supporting Information. CCDC 1453396, 1453397, 1455412, and 1455413 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[1] a) J. F. Bunnett, R. E. Zahlerz, *Chem. Rev.* **1951**, *49*, 273–412; b) J. Rosenthal, D. I. Schuster, *J. Chem. Educ.* **2003**, *80*, 679–690.
[2] J. G. Hoggett, R. B. Moodie, J. R. Penton, K. Schofield, *Nitration and Aromatic Reactivity*, Cambridge University Press, Great Britain, **1971**, p. 47.
[3] G. A. Olah, R. Malhotra, S. C. Narang, *Nitration Methods and Mechanism*, VCH, New York, **1989**.
[4] G. W. Wheland, *J. Am. Chem. Soc.* **1942**, *64*, 900–908.
[5] a) T. Ahrens, J. Kohlmann, M. Ahrens, T. Braun, *Chem. Rev.* **2015**, *115*, 931–972; b) O. Allemann, S. Duttwyler, P. Romanato, K. K. Baldridge, J. S. Siegel, *Science* **2011**, *332*, 574–577.
[6] a) M. D. Struble, M. T. Scerba, M. A. Siegler, T. Lectka, *Science* **2013**, *340*, 57–60; b) M. D. Struble, M. G. Holl, M. T. Scerba, M. A. Siegler, T. Lectka, *J. Am. Chem. Soc.* **2015**, *137*, 11476–11490.
[7] A. M. Tafesh, J. Weiguny, *Chem. Rev.* **1996**, *96*, 2035–2052.
[8] E. D. Hughes, C. K. Ingold, R. I. Reed, *J. Chem. Soc.* **1950**, 2400–2440.
[9] P. M. Esteves, J. W. de M. Carneiro, S. P. Cardoso, A. G. H. Barbosa, K. K. Laali, G. Rasul, G. K. S. Prakash, G. A. Olah, *J. Am. Chem. Soc.* **2003**, *125*, 4836–4849.
[10] We assume that the electronic effects of fluorine on the Wheland intermediate will parallel its effect on analogous π-complexes: J. F. de Queiroz, J. W. de M. Carneiro, A. A. Sabino, R. Sparrapan, M. N. Eberlin, P. M. Esteves, *J. Org. Chem.* **2006**, *71*, 6192–6203.
[11] M. T. Scerba, S. Bloom, N. Haselton, M. Siegler, J. Jaffe, T. Lectka, *J. Org. Chem.* **2012**, *77*, 1605–1609.
[12] D. Biermann, W. Schmidt, *J. Am. Chem. Soc.* **1980**, *102*, 3163–3173.
[13] E. Pretsch, P. Bühlmann, M. Badertscher, *Structure Determination of Organic Compounds*, Springer, Zurich, **2008**, p. 250.
[14] W. R. Dolbier, Jr., *Guide to Fluorine NMR for Organic Chemists*, Wiley, Hoboken, **2009**, p. 75.
[15] I. Alkorta, J. Elguero, *New J. Chem.* **1998**, *22*, 381–385.
[16] S. Dell, N. J. Vogelaar, D. M. Ho, R. A. Pascal, Jr., *J. Am. Chem. Soc.* **1998**, *120*, 6421–6422.
[17] Y. Chang, L. Ho, T. Ho, W. Chung, *J. Org. Chem.* **2013**, *78*, 12790–12794.
[18] a) Gaussian 09, Revision A.1, M. J. Frisch, et al. Gaussian, Inc., Wallingford CT, **2009**; b) D. Chai, M. Head-Gordon, *Phys. Chem. Chem. Phys.* **2008**, *10*, 6615–6620.
[19] A. C. de Dios, E. Oldfield, *Chem. Phys. Lett.* **1993**, *205*, 108–116.
[20] C. Foroutan-Nejad, S. Shahbazian, P. Rashidi-Ranjbar, *Phys. Chem. Chem. Phys.* **2010**, *12*, 12630–12637.
[21] a) M. D. Struble, J. Strull, K. Patel, M. A. Siegler, T. Lectka, *J. Org. Chem.* **2014**, *79*, 1–6; b) R. A. Pascal, Jr., *Eur. J. Org. Chem.* **2004**, 3763–3771.
[22] N. H. Martin, N. W. Allen III, E. K. Minga, S. T. Ingrassia, J. D. Brown, *J. Am. Chem. Soc.* **1998**, *120*, 11510–11511.
[23] E. Kleinpeter, S. Klod, *J. Am. Chem. Soc.* **2004**, *126*, 2231–2236.
[24] I. Nowak, *J. Fluorine Chem.* **1999**, *99*, 59–66.
[25] T. Takemura, T. Sato, *Can. J. Chem.* **1976**, *54*, 3412–3418.
[26] E. R. Johnson, S. Keinan, P. Mori-Sanchez, J. Contreras-Garcia, A. J. Cohen, W. Yang, *J. Am. Chem. Soc.* **2010**, *132*, 6498–6506.
[27] a) T. Yanai, D. Tew, N. Handy, *Chem. Phys. Lett.* **2004**, *393*, 51–57; b) A. Austin, G. Petersson, M. J. Frisch, F. J. Dobek, G. Scalmani, K. Throssell, *J. Chem. Theory Comput.* **2012**, *8*, 4989; c) O. A. Vydrov, G. E. Scuseria, *J. Chem. Phys.* **2006**, *125*, 234109.
[28] a) Z. Pechlivanidis, H. Hopf, J. Grunenberg, L. Ernst, *Eur. J. Org. Chem.* **2009**, 238–252; b) H. J. Reich, D. J. Cram, *J. Am. Chem. Soc.* **1969**, *91*, 3534–3543.
[29] AIMAll (Version 13.05.06), T. A. Keith, TK Gristmill Software, Overland Park KS, USA, **2013** (http://aim.tkgristmill.com).
[30] J. V. Crivello, *J. Org. Chem.* **1981**, *46*, 3056–3060.
[31] G. A. Smythe, G. Matanovic, D. Yi, M. W. Duncan, *Nitric Oxide* **1999**, *3*, 67–74.
[32] S. C. Suri, R. D. Chapman, *Synthesis* **1988**, 743–745.
[33] O. Diels, K. Alder, *Liebigs Ann. Chem.* **1931**, *490*, 236–242.
[34] J. E. McMurry, T. Lectka, *Acc. Chem. Res.* **1992**, *25*, 47–53.