C−F Bond Activation by Aryl Carbocations: Conclusive Intramolecular Fluoride Shifts between Carbon Atoms in Solution and the First Examples of Intermolecular Fluoride Ion Abstractions

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The chemistry of selective C−F bond activation is undergoing a surge of interest due to the scientific and commercial importance of fluorocarbons.[1] However, to date investigations of C−F bond activation in solution usually have involved transition metal complexes or alkali metals. As part of a new approach to C−F bond activation, we were interested in the possibility of using *carbocations* to abstract fluoride from organic molecules through a three-center transition state or intermediate. Although cationic fluoride transfers involving hypervalent [C−F−C]+ interactions are documented in the gas phase in work by Morton,[2] reports of such intermolecular abstractions in solution are virtually nonexistent, and the published cases of intramolecular shifts are fraught with controversy.[3] In fact, the question of whether such shifts of fluoride could ever occur in solution has been a source of continuing debate. In this communication, we describe intramolecular fluoride shifts between carbon atoms in solution (Scheme 1) and the first documented examples of analogous *intermolecular* fluoride abstractions between an aryl cation and its counterion.

In the gas phase the reactivity of carbocations is enhanced by the absence of solvent;[2] in solution, cations of comparably high reactivity must be generated to provide the driving force for fluoride transfers. It would also be best to generate the carbocations in nonnucleophilic media, employing substrates that contain nonsolvolytically active C−F bonds. Our approach was to use aryl diazonium salts, from which highly reactive aryl cations are known to be generated in solution through mild thermolysis.[4] We chose to investigate biphenyl diazonium salts **1** in the belief that upon the formation of aryl cation **2**, F⁻ transfer through a six-membered ring (structure **3**) would be favorable (Scheme 1). To minimize trapping of counterion X⁻

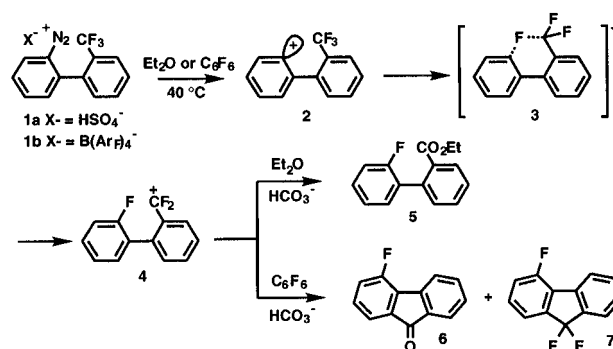**Scheme 1.** An Intramolecular Fluoride Ion Shift

Table 1. Fluoride-Shifted Products from the Decomposition of Salts **1**

entry	salt	solvent	yield (%)			
			5	**6**	**7**	**8**
a	**1a**	Et₂O[a,c]	20	0	0	0
b	**1a**	Et₂O[b,c]	77	0	0	0
c	**1a**	C₆F₆[b,c]		55	0	0
d	**1a**	C₆F₆[b,d]		35	20	0
e	**1b**	C₆F₆[b,c]		49	0	8

[a] Reaction run under N₂ gas. [b] Reaction run under O₂ gas. [c] Reaction quenched by stirring with 10% aqueous NaHCO₃. [d] Reaction mixture purified directly on neutral alumina.

by the aryl cation, we felt a weakly coordinating anion would be necessary.[5]
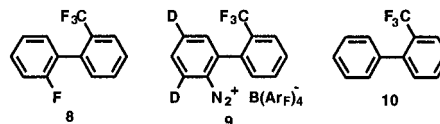
Mild heating (40 °C) of diazonium salt **1a**[6] in ether resulted in N₂ evolution over the course of 15 min.[7] The reaction was stirred with 10% aqueous NaHCO₃ for 15 min, and chromatography over silica afforded ester **5** (20%) as the major product (Table 1, entry a). Decomposition of **1a** under an atmosphere of O₂ increased the yield of **5** to 77% (entry b). O₂ is known to be an effective radical scavenger that shuts down competing chain pathways.[8] Heating (40 °C) of **1a** in C₆F₆ instead gave ketone **6** in 55% (entry c). Workup of this reaction by stirring with H₂¹⁸O led to the incorporation of the label into the carbonyl group of **6**,[9] indicating that hydrolysis is the final step in the fluoride shift process.[10] Fluorene trifluoride **7**, however, could be isolated along with **6** (C₆F₆ solvent) upon chromatography of the crude reaction mixture over neutral alumina *without aqueous workup* in 20% yield (entry d).[11] Whereas the ArCF₃ moiety is fairly stable to hydrolysis (hot concentrated H₂SO₄ hydrolyzes ArCF₃ over the course of several hours),[12] molecules that contain the Ar₂CF₂ or ArCF₂OR moieties are considerably less stable, and can hydrolyze to the corresponding benzophenones and benzoic acids in aqueous acidic solution at ambient temperatures. In our hands, **7** is moisture sensitive and readily hydrolyzes to ketone **6** either in aqueous HCO₃⁻ over the course of 0.5 h or on silica gel. Remarkably, when wet **1a** (2−3 equiv

(1) For a review of C−F bond activation employing metals, see: Kiplinger, J. L.; Richmond, T. G.; Osterberg, C. E. *Chem. Rev.* **1994**, *94*, 373. For recent monographs on organic fluorine chemistry see: *Synthetic Fluorine Chemistry*; Olah, G. A., Chambers, R. D., Prakash, G. K. S., Eds.; Wiley: New York, 1992. *Chemistry of Organic Fluorine Compounds II. A Critical Review*; Hudlicky, M., Pavlath, A. E., Eds.; ACS Monograph 187; American Chemical Society: Washington, DC, 1995.

(2) (a) Shaler, T. A.; Morton, T. H. *J. Am. Chem. Soc.* **1989**, *111*, 6868. (b) Stams, D. A.; Thomas, T. D.; MacLaren, D. C.; Ji, D.; Morton, T. H. *J. Am. Chem. Soc.* **1990**, *112*, 1427. (c) Shaler, T. A.; Morton, T. H. *J. Am. Chem. Soc.* **1994**, *116*, 9222.

(3) In previous fluoride shift claims a dissociative mechanism involving free fluoride in solution could not be ruled out. For an overview see: (a) Olah, G. A. *Halonium Ions*; Wiley: New York, 1975. (b) Olah, G. A.; Prakash, G. K.; Krishnamurthy, V. V. *J. Org. Chem.* **1983**, *48*, 5116. (c) Peterson, P. E.; Bopp, R. J. *J. Am. Chem. Soc.* **1967**, *89*, 1283. (d) Ciommer, B.; Scwarz, H. *Z. Naturforsch.* **1983**, *38B*, 635.

(4) Zollinger, H. *Azo and Diazo Chemistry*; VCH: Weinheim, 1994; pp 161−277.

(5) For a review of weakly coordinating counterions, see: Strauss, S. H. *Chem. Rev.* **1993**, *93*, 927.

(6) CAUTION! All diazonium salts we report herein are potentially explosive compounds and should be handled with care behind protective shielding both in the solid state and in solution.

(7) We measured gas evolution with a Clausen-Kaas microhydrogenationer: Clausen-Kaas, N.; Limborg, F. *Acta Chem. Scand.* **1947**, *1*, 884.

(8) For a discussion, see: Galli, C. *Chem. Rev.* **1988**, *88*, 765.

(9) ¹⁸O/¹⁶O isotope ratios were measured by MS.

(10) Free fluoride ion in the aqueous layer after workup was determined by ¹⁹F NMR, which revealed roughly the expected amounts (e.g. 2 equiv relative to starting diazonium salt **1a**).

(11) GC analysis of the crude reaction mixture indicates the generation of **7** in substantial amounts over the course of the reaction.

(12) Le Fave, G. M. *J. Am. Chem. Soc.* **1949**, *71*, 4148.

of H$_2$O) was employed in the thermolysis,[13] ketone **6** was still isolated in 60% yield! Salt **1b**, containing the weakly coordinating tetrakis[bis(trifluoromethyl)phenyl]borate (B(Ar$_F$)$_4^-$) counterion, exhibits chemistry parallel to **1a** by affording enhanced yields of fluoride-shifted products under O$_2$.[14]

A proposed mechanism for the intramolecular reaction is shown in Scheme 1. Loss of N$_2$ from **1** results in formation of aryl cation **2**[15] that abstracts F$^-$ from the CF$_3$ group to afford more stable benzylic cation **4**[16] through the [C$-$F$-$C]$^+$ transition state or intermediate **3**. In ether, **4** is trapped to form an oxonium ion that is hydrolyzed to ester **5** upon aqueous workup.[17] Ketone **6** arises from cyclization of cation **4** in C$_6$F$_6$ followed by hydrolysis. Further evidence for an intramolecular fluoride ion shift involving a [C$-$F$-$C]$^+$ interaction from the CF$_3$ group to an aryl cationic center is as follows: (1) we observed a secondary kinetic isotope effect (k_H/k_D) of 1.23 when a 1:1 mixture of **1b** and D-labeled isomer **9** reacted to partial completion, consistent with rate-determining formation of an aryl cation;[18-20] (2) increased yields of **5** and **6** in the presence of O$_2$ are consistent with the aryl cation mechanism; (3) submitting 2-(trifluoromethyl)biphenyl (**10**) as an additive to the decomposition of **1** resulted in quantitative recovery of **10**; and (4) additionally, MO calculations at the 3-21G level indicate that **4** should be more stable than **2** by 45 kcal/mol—a substantial driving force for isomerization.[21]

In one instance (Table 1, entry e) we observed a small amount of tetrafluoride **8**, in which F$^-$ must have been abstracted *intermolecularly*. We speculated that this product may have arisen from B(Ar$_F$)$_4^-$. Consequently we considered that phenyl cation itself could abstract F$^-$ intermolecularly from R$_3$C$-$F if the C$-$F bond were present as part of a complex counterion, in which ion pairing could bring the reactive bond into proximity.

When we heated salt **11** to 60 °C under O$_2$ in C$_6$F$_6$, it gradually discolored (eq 1).[22] A vacuum was applied and the volatile

products and solvent were caught in a dry ice trap. Assays of the condensate by GC and NMR showed it to contain PhF (**12**) (55% yield from **11**).[23] A secondary kinetic isotope effect k_H/k_D of 1.21 for each ortho position was observed[24] when a 1:1 mixture of **11** and labeled isomer **13** was pyrolyzed to partial completion in ether solution, again consistent with rate-determining formation of an aryl cation. Evidence that shifted fluoride originates from a CF$_3$ group of B(Ar$_F$)$_4^-$ was obtained by the isolation of ketone **14**, which presumably forms through
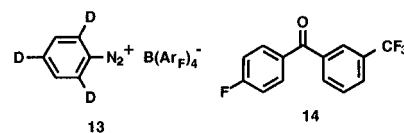
alkylation of PhF in the para position,[25] protonolysis of the borate counterion by the equivalent of liberated protons,[26] and aqueous workup. We believe it is this alkylation that limits the overall yield of PhF. We also found that treatment of NaB(Ar$_F$)$_4$ with SbF$_5$ in CH$_2$Cl$_2$ in the presence of PhF produces ketone **14** as the major product, presumably by the same pathway as the reaction of salt **11**.[27]

In conclusion, we have demonstrated C$-$F bond activation using aryl cations and have provided the first definitive examples of intramolecular and intermolecular fluoride abstractions in solution. Further work is aimed at the intermolecular activation of other fluorocarbons and the synthesis of characterizable fluoronium ions containing hypervalent [C$-$F$-$C]$^+$ bonds in solution.

Supporting Information Available: Spectroscopic details for all new compounds and details on the conduct of decomposition reactions, isotope effect studies, and the synthesis of diazonium salts (10 pages). See any current masthead page for ordering and Internet access instructions.

(13) For example, when salt **1a** was made in CH$_3$CN/H$_2$^{18}O (3:1), partially dried under vacuum, and decomposed employing the slightly wet solid, the ^{18}O label was incorporated into the carbonyl group of **6** to an 80% extent, which indicates that hydrolysis to ketone **6** occurs primarily under the reaction conditions in this case.

(14) Under N$_2$ in C$_6$F$_6$ solvent, **1b** gives 20% **5** along with 50% 3,3′,5,5′-tetrakis(trifluoromethylbiphenyl), which we interpret to be a radical-derived product from the counterion.

(15) Note that the phenyl cation can conceivably react from either the singlet or the triplet state. If the phenyl cation were to react out of the triplet state, it would in all likelihood still abstract F$^-$, not F·. For example, were the triplet to engage in radical abstraction, it should also react with triplet O$_2$, which the phenyl cation obviously does not, as witnessed by increased yields of fluoride-shifted products in the presence of O$_2$. For a discussion, see: Taylor, R. *Electrophilic Aromatic Substitution*; Wiley: New York, 1990; pp 215−216.

(16) Olah has studied ArCF$_2^+$ species under stable ion conditions in solution: Olah, G. A.; Mo, Y. K. *J. Org. Chem.* **1973**, *38*, 2686.

(17) We monitored the decomposition of **1b** in ether by ^{19}F NMR. As the reaction progresses, the C*F*$_3$ peak of **1b** at δ −58.2 (vs CFCl$_3$) diminishes, to be replaced by two other resonances at δ −116.2 (Ar*F*) and δ +65.8 (consistent with the formation of an electron-deficient benzylic substituent ArC*F*$_2^+$ or ArC*F*$_2$OEt$_2^+$, see: Olah, G. A.; Comisarow, M. B. *J. Am. Chem. Soc.* **1969**, *91*, 2955). The ^{19}F resonance of B(Ar$_F$)$_4^-$ at δ −63.0 is maintained over the course of the reaction.
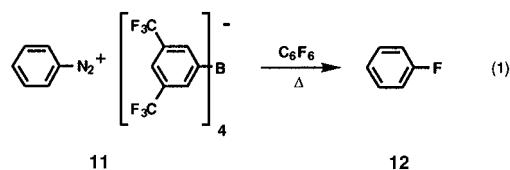
(18) Large secondary kinetic isotope effects are the hallmark of phenyl cation generation in solution: Swain, C. G.; Sheats, J. E.; Gorenstein, D. G.; Harbison, K. G. *J. Am. Chem. Soc.* **1975**, *97*, 791. Swain found that the remote effect due to a deuterium in the 4-position of the diazonium moiety of **1a** is negligible.

(19) Reaction mixtures were analyzed by ^{1}H NMR and ^{2}H NMR to determine the ratio of labeled to unlabeled reactants and products.

(20) Zollinger has found that heterolytic dediazoniations are favored in nonnucleophilic solvents: Szele, I.; Zollinger, H. *Helv. Chim. Acta* **1978**, *61*, 1721.

(21) We performed MO calculations with the Spartan 4.0 program, Wavefunction Inc.

(22) Monitoring of the reaction by ^{11}B NMR showed replacement of the B(Ar$_F$)$_4^-$ counterion at δ −6.60 (vs BF$_3$ in C$_6$F$_6$) by a broad, overlapping resonance at δ −6.40.

(23) Boudjouk has shown that silicenium ions can abstract fluoride from the B(Ar$_F$)$_4^-$ counterion: Bahr, S. R.; Boudjouk, P. *J. Am. Chem. Soc.* **1993**, *115*, 4514.

(24) Once again, we assume a negligible isotope effect for the para position.

(25) Fluorobenzene undergoes Friedel−Crafts alkylation primarily at the para position: (a) *Friedel Crafts and Related Reactions*; Olah, G. A., Ed.; Wiley: New York, 1963. (b) Lichtenberger, J.; Muller, P.; Huguet, M. *Bull. Soc. Chim. Fr.* **1953**, *10*, C45.

(26) The protonolysis of tetraphenylborate has been investigated: Geske, D. H. *J. Phys. Chem.* **1959**, *63*, 1062.

(27) See Supporting Information for mechanistic proposals.