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Electrophilic fluorination of aromatic compounds with NF type reagents: kinetic isotope effects and mechanism

Gennady I. Borodkin,[a,b,*] Pavel A. Zaikin[a,b] and Vyacheslav G. Shubin[a]

[a] *Vorozhtsov Novosibirsk Institute of Organic Chemistry, Acad. Lavrentiev ave. 9, 630090, Russia*
[b] *Novosibirsk State University, Pirogov st. 2, 630090, Russia*

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Abstract—H/D Isotope effects in fluorination of aromatic compounds with NF type reagents have been studied to reveal the reaction mechanism. The results obtained are consistent with a polar S_EAr mechanism. Small deuterium isotope effects ($k_H/k_D = 0.86$–0.99) show that decomposition of a Wheland-type intermediate is not rate determining. The first example of a 1,2-hydrogen shift accompanying electrophilic fluorination of arenes has been observed in the fluorination of 1,3,5-trideuterobenzene.

Fluorinated aromatic compounds are of increasing significance for agrochemical, pharmaceutical and chemical uses.[1] However, the selective direct introduction of fluorine into aromatic molecules is still only a partly solved problem.[2,3] In the last two decades, various types of *N*-fluoro compounds have been found to be appropriate fluorine sources for milder and selective fluorination of organic compounds.[3–6] Interest in NF type reagents was aroused with reports on *N*-fluorobenzenesulfonimide, 1-fluoropyridinium, 1,1′-difluoro-2,2′-bipyridinium and 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane salts, which are commercially available.[3–6] Although details of the synthesis and characterization of NF reagents have been published, little information appears to have been reported concerning the mechanism of their interaction with arenes.[3–6] From the observed isomer distributions, which show predominant *ortho–para* substitutions to electron-donating ring substituents, the reactions are considered to be the typical electrophilic aromatic substitutions.[4,7,8] Note that neither free nor solvated F^+ cations are implicated in the reactions; the enthalpy of F^+ formation is very high compared with the values for the other halonium ions (Cl^+, Br^+ and I^+).[4]

At present two general possible pathways for electrophilic fluorine transfer have been considered: nucleophilic displacement at fluorine (polar mechanism, S_EAr) and single electron transfer involving a radical cation species as a discrete intermediate (SET mechanism) (Scheme 1).[3,6] The question of which of these mechanisms is correct is, as yet, unresolved and it is possible that different arenes are fluorinated by different mechanisms (cf. Refs. 6,7,9,10).

This letter reports a kinetic isotope study of the reaction of NF reagents 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (F-TEDA-BF_4) **1**, 1,1′-difluoro-2,2′-bipyridinium bis(tetrafluoroborate) **2** and *N*-fluorobenzenesulfonimide **3** with benzene, mesitylene and naphthalene. A reaction pathway involving nucleophilic displacement at the fluorine atom has been proposed as the main process. Such a mechanism was determined from the fluorination of mesitylene and durene with F-TEDA-BF_4 in MeCN and 1-ethyl-3-methylimidazolium triflate.[7] As the ionization potentials of benzene (9.24384 eV) and naphthalene (8.1442 eV) are higher than that of durene (8.025 eV), a SET mechanism for their fluorination could hardly be operative.[†]

Keywords: Fluorination; NF Reagent; Mechanism; Kinetics; Deuterium isotope effects; 1,2-Shift.
* Corresponding author. Tel.: +7 383 330 7651; fax: +7 383 330 9752; e-mail: gibor@nioch.nsc.ru

[†] Ionization potentials were obtained from the NIST Chemistry WebBook (http://webbook.nist.gov/).

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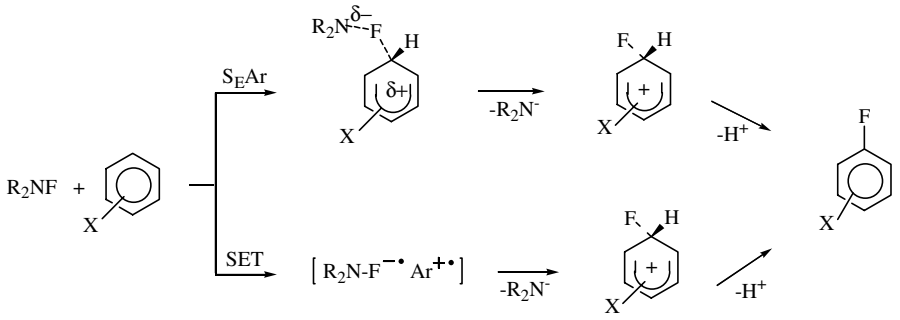
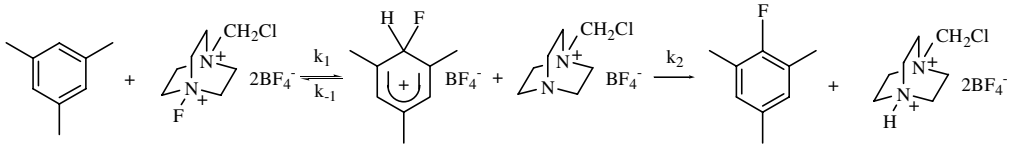


Scheme 1.



Scheme 2.

First, we investigated the kinetics of the interaction of mesitylene (MesH) with F-TEDA-BF_4 **1** in MeCN using an iodometric titration method[9] (Scheme 2).

The steady-state approximation, applied to the σ-complex, gives Eq. 1.

$$\ln([\mathrm{MesH}]/[\mathbf{1}]) = k([\mathrm{MesH}]_0 - [\mathbf{1}]_0)t + \ln([\mathrm{MesH}]_0/[\mathbf{1}]_0) \quad (1)$$

where $k = k_1k_2/(k_{-1} + k_2)$.

A good linear dependence of ln[MesH]/[**1**] on the time (t) was observed (Fig. 1). The determination of the second-order rate constants at different temperatures [$k_{273.2\,\mathrm{K}}$, $(1.41 \pm 0.02) \times 10^{-5}$, $k_{303.8\,\mathrm{K}}$, $(5.67 \pm 0.04) \times 10^{-4}$, $k_{312.0\,\mathrm{K}}$, $(1.85 \pm 0.01) \times 10^{-3}$ and $k_{323.0\,\mathrm{K}}$, $(5.54 \pm 0.08) \times 10^{-3}$ $\mathrm{M^{-1}\,c^{-1}}$] gave the following values for the activation parameters: $E_a = 88 \pm 3$ kJ/mol, $\lg A = 12.0 \pm 0.5$, $\Delta H^{\neq} = 86 \pm 3$ kJ/mol, $\Delta S^{\neq} = -24 \pm 9$ J/mol K. The high $\Delta H^{\neq}$ value and low absolute $\Delta S^{\neq}$ value correspond to enthalpy control of the reaction with the strong C–F bond formation in the rate-determining step.

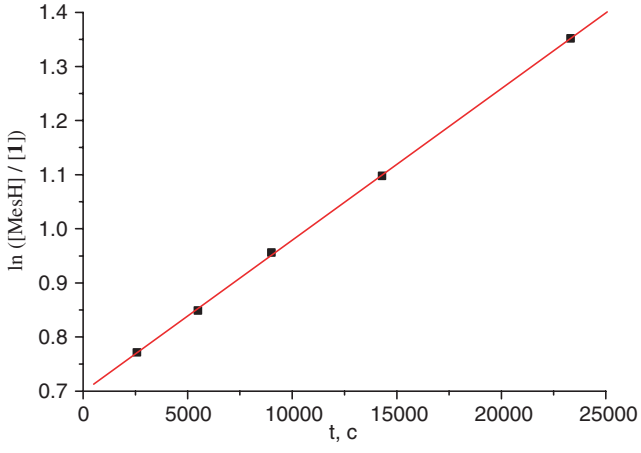
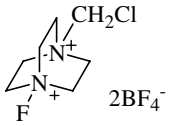
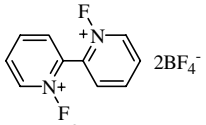
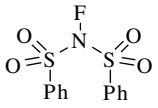


Figure 1. Plot of ln([MesH]/[**1**]) versus time (t) at 303.8 K (r 0.9999).

Kinetic isotope effects are widely used to elucidate the mechanisms of electrophilic aromatic substitution.[11] We measured k_H/k_D isotope effects in the reactions of NF reagents with aromatic compounds using GC–MS (Table 1). Competitive fluorinations of the corresponding light and heavy hydrocarbons were carried out in most cases. Small deuterium isotope effects showed that decomposition of Wheland complexes is not a rate-determining step. We observed smaller than unity isotope effects (cf. Refs. 12–14). The effect was insensitive to solvent variation. The source of the secondary deuterium isotope effect in the fluorination reactions under study can be elucidated by the following analysis. A hyperconjugative stabilization of the σ-complex by the C_α–H (C_α–D) bond should give $k_H/k_D > 1$ while an $sp^2 \rightarrow sp^3$ rehybridization at the C_α-atom should result in $k_H/k_D < 1$.[14] An electron-donor effect of deuterium should be important in the case when deuterium is at positions 1, 3 or 5 of the σ-complex [cf. $\sigma_p^+(\mathrm{D}) = -0.001$].[15] In all cases, $k_H/k_D < 1$ can be attributed to the prevalence of the $sp^2 \rightarrow sp^3$ rehybridization effect and also to the electron-donor effect of deuterium. The k_H/k_D values in the fluorination of mesitylene and naphthalene with F-TEDA-BF_4 are smaller than those in the fluorination of these compounds with *N*-fluorobenzenesulfonimide (Table 1). According to the Hammond postulate,[16] in the case of the more active reagent F-TEDA-BF_4, the transition state should be more 'early'. It should result in a decrease of the hyperconjugative effect of C–H(D) bond.

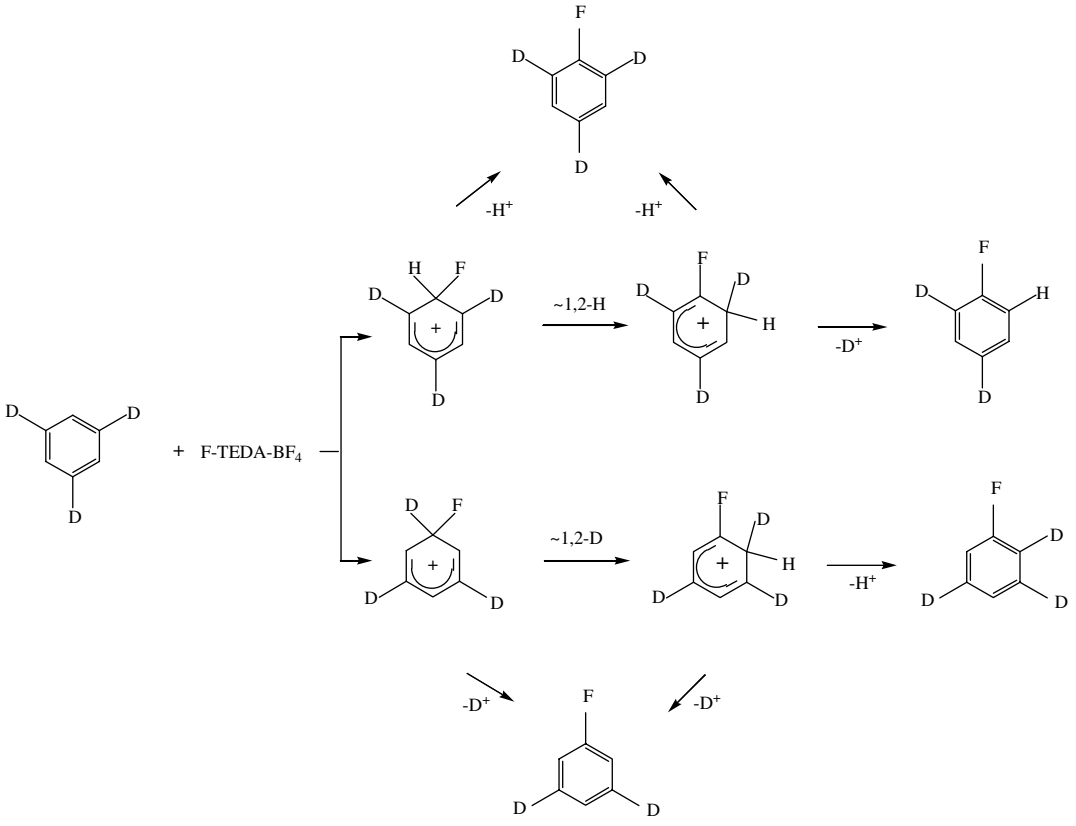
In order to obtain further information about the mechanism of electrophilic fluorination we studied the reaction of F-TEDA-BF_4 with benzene-1,3,5-d_3. The fluorobenzene-d_3/fluorobenzene-d_2 ratio (1.28) determined by GS–MS proved to be rather high, apparently

Table 1. Kinetic isotope effects in the fluorination of aromatic compounds by NF reagents

NF Reagent	ArH	Solvent	Temperature (°C)	k_H/k_D
 **1**	Benzene/benzene-d_6	MeCN	110	0.92 ± 0.06[a]
	Benzene/benzene-d_6	[bmim][BF_4][b]	110	0.89 ± 0.02[a]
	Mesitylene/mesitylene-1,3,5-d_3	MeCN	60	0.89 ± 0.02[a]
	Naphthalene/naphthalene-d_8	MeCN	60	0.86 ± 0.01[a]
 **2**	Benzene/benzene-d_6	MeCN	110	0.86 ± 0.03[a]
	Naphthalene/naphthalene-d_8	MeCN	60	0.91 ± 0.05[a]
 **3**	Mesitylene/mesitylene-1,3,5-d_3	MeCN	110	0.99 ± 0.03[a]
	Naphthalene/naphthalene-d_8	MeCN	110	0.895 ± 0.007[a]
	Naphthalene/naphthalene-d_8	$ClCH_2CH_2Cl$	110	0.889 ± 0.007[a]

[a] This value is given standard deviation of two measurements in mass spectra.
[b] [bmim]—1-Butyl-3-methylimidazolium.

due to 1,2-hydrogen and deuterium migrations in the σ-complexes (Scheme 3). This suggestion was confirmed by ^1H and ^{19}F NMR spectra of the deuterated fluorobenzenes, particularly by the presence of a multiplet at −116.3 ppm in the ^{19}F NMR spectrum relevant to isomeric 2,4-dideuterofluoro- and 2,3,5-trideuterofluorobenzenes formed as a result of these migrations followed by elimination of a proton and deuteron from the respective σ-complexes (Fig. 2). The present case, as far as we are aware, constitutes the first example of 1,2-shifts in Wheland intermediates formed in electrophilic fluorination of aromatic compounds.



Scheme 3.

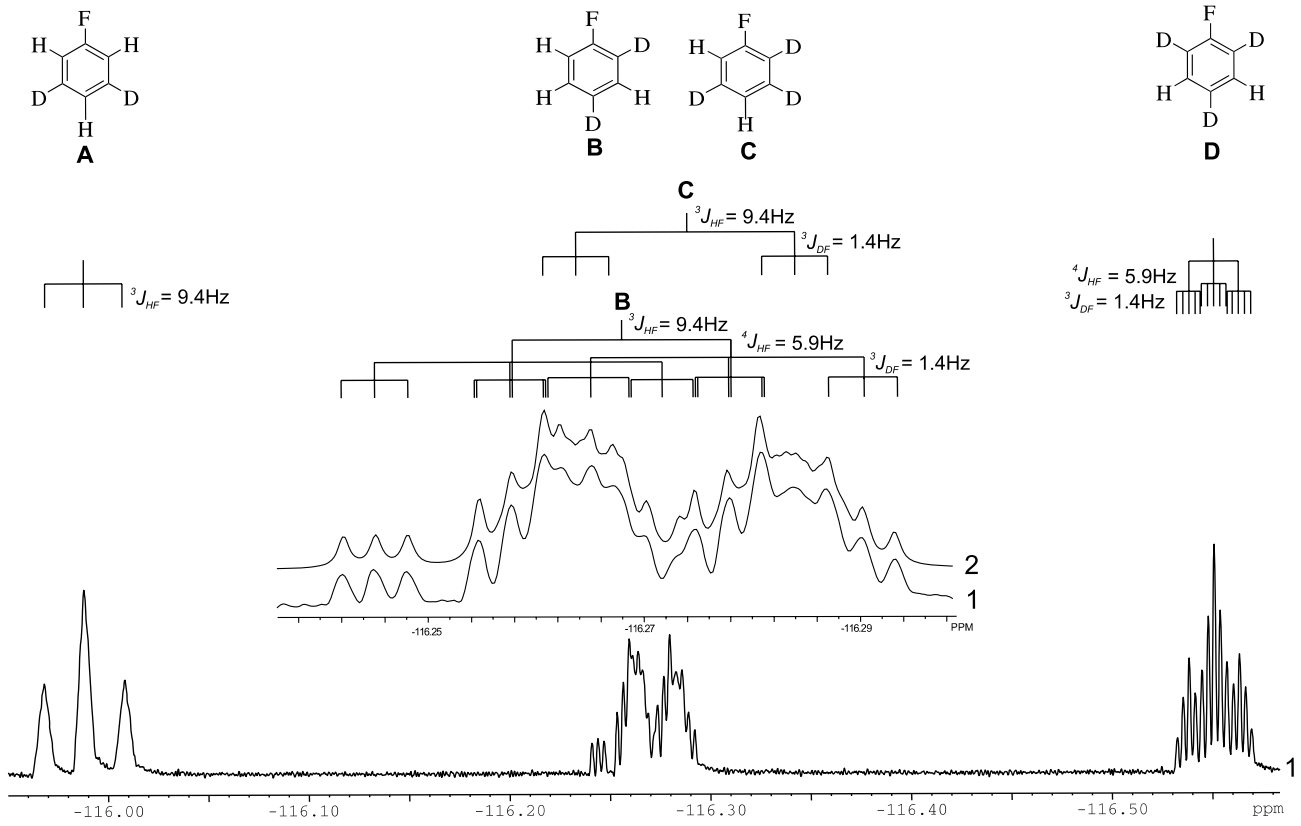


Figure 2. ^{19}F NMR spectrum (1) of deuterofluorobenzenes (470 MHz, CD_3CN) formed in the reaction of benzene-1,3,5-d_3 with F-TEDA-BF_4 in CD_3CN at 110 °C and computer simulation of the spectrum (2). Chemical shifts are referenced to $CFCl_3$ with C_6F_6 as a secondary external standard (−162.9 ppm). The ratio of **A**:**B**:**C**:**D** = 1.0:0.5:0.8:1.1.

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