

## Gaseous SF<sub>3</sub><sup>+</sup>: An Efficient Electrophilic Monofluorinating Agent for Five-Membered Heteroaromatic Compounds

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Reactions of gaseous SF<sub>3</sub><sup>+</sup> ions with furan, thiophene, pyrrole, and several of their alkyl derivatives were performed via MS<sup>2</sup> experiments and found to occur readily both by electron abstraction and F<sup>+</sup> transfer. Then, by performing MS<sup>3</sup> experiments, the F<sup>+</sup> transfer products—the protonated monofluorinated molecules—were mass-selected and deprotonated by a second reaction with a stronger base. F<sup>+</sup> transfer from gaseous SF<sub>3</sub><sup>+</sup> followed by deprotonation promotes therefore C–H by C–F replacement in five-membered heteroaromatic compounds and the efficient gas-phase synthesis of their neutral monofluorinated derivatives.

### Introduction

Organofluorides, relatively inert compounds with high thermal and mechanical resistance, have found numerous applications: as lubricants, coatings, propellants, refrigerants, solvents, fire extinguisher agents, anesthetics, drugs, blood substitutes, dyes, liquid crystals, surfactants, textile chemicals, and agrochemicals.<sup>1</sup> Fluorination of organic compounds drastically changes their chemical and physical properties; fluorination increases thermal and oxidative stability, alters electronic effects, and increases lipophilicity, and fluorine closely mimics hydrogen in steric requirements. To drug development, for instance, organofluorides are vital since they display much-enhanced therapeutic efficacy and pharmacological activity.<sup>2</sup>

Perfluorination (complete C–H to C–F substitution) of organic compounds is usually straightforward, but controlled and selective monofluorination particularly for regio- or stereoselective incorporations of fluorine is often a challenging task. Many fluorinating agents are too vigorous, and HF loss from reaction intermediates is frequently facile, and very exothermic.<sup>3</sup>

Fluorinating agents function either as nucleophilic (F<sup>-</sup>) or electrophilic (F<sup>+</sup>) sources of fluorine. Nucleophilic fluorinating agents such as alkali metal fluorides, tetraalkylammonium fluorides, polypyridinium hydrogen fluoride, sulfur tetrafluoride, and diethylaminosulfur trifluoride (DAST) have long been known and employed.<sup>4</sup> Electrophilic fluorinating agents have been developed more recently;<sup>5</sup> by promoting electrophilic attack at centers of high electron density they offer alternatives

when nucleophilic or free radical sources of fluorine fail. Fluorine, the most electronegative element, tends not to behave as an electrophile, yet several electrophilic fluorinating agents have been developed by withdrawing electronic charge from fluorine through inductive effects or by placing excellent leaving groups adjacent to fluorine, or by combining both strategies.<sup>5</sup> Acetyl hypofluorides (CF<sub>3</sub>COOF), CF<sub>3</sub>OF, and CaSO<sub>4</sub>F and N–F compounds such as *N*-fluoropyridinium, *N*-fluoroperfluoropiperidine, and dihydro-*N*-fluoro-2-pyridone are typical electrophilic fluorinating agents.<sup>5</sup> Gaseous F<sub>2</sub>, despite its high reactivity, toxicity, and tendency to react as a radical, has also been used as a good electrophilic fluorinating agent.<sup>6</sup>

Although not often an easy task, selective monofluorination can be performed for most classes of organic compounds, i.e., alkanes, alcohols, ketones, benzene rings, halides, and amines.<sup>7</sup> Selective fluorination of five-membered heteroaromatic compounds has been, however, a most difficult task. Synthesis of only a few fluorinated five-membered heteroaromatic compounds under controlled conditions has been performed, mainly via two routes: (i) cyclization of fluorinated dienes and dienophiles, and (ii) direct ring fluorination. Some substituted 3-fluoropyrroles, 3-fluorohydroxypyroles, 3-fluorofurans, and 2-fluorothiophenes<sup>8</sup> have been synthesized via cyclization of fluorinated dienes. Direct ring fluorination, a more straightforward and synthetically convenient route, is however much less selective and often results either in hydro/dihydro compounds or polyfluorinated rings, or both. Controlled monofluorination is even more difficult and only a few successful syntheses of mono-

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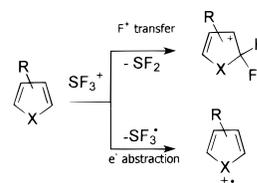
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fluoro heteroaromatic compounds have been reported. Using CsF, Lemaire et al.<sup>9</sup> synthesized 3-fluorothiophene from 2-bromo-3-chlorothiophene. Using F<sub>2</sub> diluted in an inert gas, Fornarini et al.<sup>10</sup> performed monofluorination in low yields (0.7–6.2%) of *N*-methylpyrrole, of several substituted thiophenes, and of thiophene. Several furans and pyrrole, however, when submitted to the same fluorination reaction, form no monofluorinated products. We found no reports on successful monofluorinations of pyrrole and simple furans.

Gas-phase reactions performed in the mass spectrometer environment provide a unique opportunity to investigate intrinsic chemical reactivities of ions and neutral molecules without the interference of solvents or counterions, and to perform fast and powerful screening for potential reactants and model reactions.<sup>11</sup> In the gas phase, several potential electrophilic fluorinating agents are readily available; they have been tested<sup>12</sup> and F<sup>+</sup> transfer observed in some cases. Dillard and Troster<sup>12a</sup> performed the first electrophilic fluorination (F<sup>+</sup> transfer) in the gas phase; they used SF<sub>5</sub><sup>+</sup> to transfer F<sup>+</sup> to NH<sub>3</sub> and several amines, and R<sub>n</sub>NSF<sub>m</sub><sup>+</sup> ions were formed after single and double HF elimination. Bohme et al.<sup>12b</sup> also observed F<sup>+</sup> transfer from SF<sub>5</sub><sup>+</sup> to S<sub>2</sub>F<sub>10</sub>. More recently, Cipollini et al.<sup>12c</sup> found that ionized fluorine (F<sub>2</sub><sup>+</sup>) transfers F<sup>+</sup> to argon, CO, and N<sub>2</sub>, and Grandinetti et al.<sup>12d,e</sup> used gaseous NF<sub>2</sub><sup>+</sup> ions to activate CO via ionic fluorination, subsequently using the highly electrophilic F–CO<sup>+</sup> product ion to promote unprecedented carbonylations of inert C–H bonds in benzene and toluene, and the N–H bond in NH<sub>3</sub>. Sparrapan et al.<sup>12f</sup> reacted gaseous SF<sub>n</sub><sup>+</sup> (*n* = 1–5) ions with O<sub>2</sub>, CO, CO<sub>2</sub>, H<sub>2</sub>O, and N<sub>2</sub>O, and with benzene, acetonitrile, and pyridine,<sup>12g</sup> but observed no F<sup>+</sup> transfer. Instead, the SF<sup>+</sup> ion was found to react readily with O<sub>2</sub> and N<sub>2</sub>O by O-abstraction to form F–SO<sup>+</sup> and with benzene by H-by-SF<sup>+</sup> replacement that led to the functionalization of the inert benzene C–H bond forming ionized benzenesulfonyl fluoride (C<sub>6</sub>H<sub>5</sub>–SF<sup>+</sup>).<sup>12g</sup>

Scheme 1



Wong et al.<sup>12h</sup> reacted SF<sub>3</sub><sup>+</sup> with several pyridines and also observed no F<sup>+</sup> transfer; instead, SF<sub>3</sub><sup>+</sup> pyridine adducts and dimers were formed to great extents.

SF<sub>3</sub><sup>+</sup> displays a relatively low F<sup>+</sup>-detachment energy (176 kcal/mol),<sup>13</sup> and should be, according to a recent absolute oxidizer strength scale,<sup>14</sup> a potential oxidative fluorinating agent. Herein we report on the reactions of gaseous SF<sub>3</sub><sup>+</sup> ions with several five-membered heteroaromatic compounds. With furan, thiophene, pyrrole, and some of their alkyl-substituted derivatives, gaseous SF<sub>3</sub><sup>+</sup> is found to react both by (i) electron abstraction that yields M<sup>+</sup> and (ii) F<sup>+</sup> transfer that yields (MF)<sup>+</sup>; that is, the protonated monofluorinated derivative (Scheme 1).

By applying MS<sup>3</sup> scans, the (MF)<sup>+</sup> products were then mass-selected and effectively deprotonated by a second ion/molecule reaction with a stronger base so as to accomplish C–H by C–F replacement and the gas-phase synthesis of the neutral monofluorinated heteroaromatic compounds. Gaseous SF<sub>3</sub><sup>+</sup> promotes therefore formal C–H by C–F replacement and acts as an efficient electrophilic fluorinating agent in gas-phase monofluorination of five-membered heteroaromatic compounds.

## Experimental Section

Gaseous SF<sub>3</sub><sup>+</sup> was produced by 70 eV electron ionization of SF<sub>6</sub> and then reacted, and the products were analyzed via double- (MS<sup>2</sup>) and triple-stage (MS<sup>3</sup>) mass spectrometric experiments<sup>15</sup> performed with an Extrel (Pittsburgh, PA) pentaquadrupole mass spectrometer.<sup>16</sup> The instrument, denoted as Q<sub>1</sub>Q<sub>2</sub>Q<sub>3</sub>Q<sub>4</sub>Q<sub>5</sub>, is composed of a sequential arrangement of three mass analyzing (Q<sub>1</sub>, Q<sub>3</sub>, Q<sub>5</sub>) and two "rf-only" ion-focusing reaction quadrupoles (q<sub>2</sub>, q<sub>4</sub>). When performing ion/molecule reactions via MS<sup>2</sup> experiments, Q<sub>1</sub> was used to mass select SF<sub>3</sub><sup>+</sup> for further reactions in q<sub>2</sub> with a selected neutral reagent. Ion translational energies were set to near 1 eV as calibrated by the *m/z* 39:41 ratio in neutral ethylene/ionized ethylene reactions.<sup>17</sup> Product ion mass spectra were acquired by scanning Q<sub>5</sub>, while operating Q<sub>3</sub> in the broad band rf-only mode. The target gas pressures in q<sub>2</sub> caused typical beam attenuations of 50–70%, viz., multiple collision conditions were used, which increase reaction yields and promote collisional quenching of both the reactant and product ions.<sup>15b</sup>

For the MS<sup>3</sup> experiments, Q<sub>3</sub> was used to mass select a q<sub>2</sub> product ion of interest for further 15 eV collision-induced dissociation with argon in q<sub>4</sub>, while scanning Q<sub>5</sub> to acquire the mass spectrum. The 15 eV collision energies were taken as the voltage difference between the ion source and the collision quadrupoles. The indicated pressures in each differentially pumped region were typically 2 × 10<sup>-6</sup> (ion-source), 8 × 10<sup>-6</sup> (q<sub>2</sub>), and 8 × 10<sup>-5</sup> (q<sub>4</sub>) Torr.

Ab initio molecular orbital calculations were carried out by using Gaussian98.<sup>18</sup> The geometries of the isomeric (MF)<sup>+</sup>

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(13) The 176 kcal/mol energy for F<sup>+</sup>-detachment from SF<sub>3</sub><sup>+</sup> (SF<sub>3</sub><sup>+</sup> → SF<sub>2</sub> + F<sup>+</sup>) was calculated at the Becke3LYP/6-311++G(d,p) level.

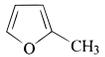
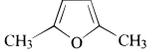
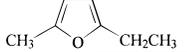
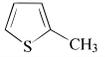
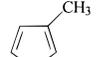
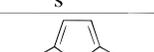
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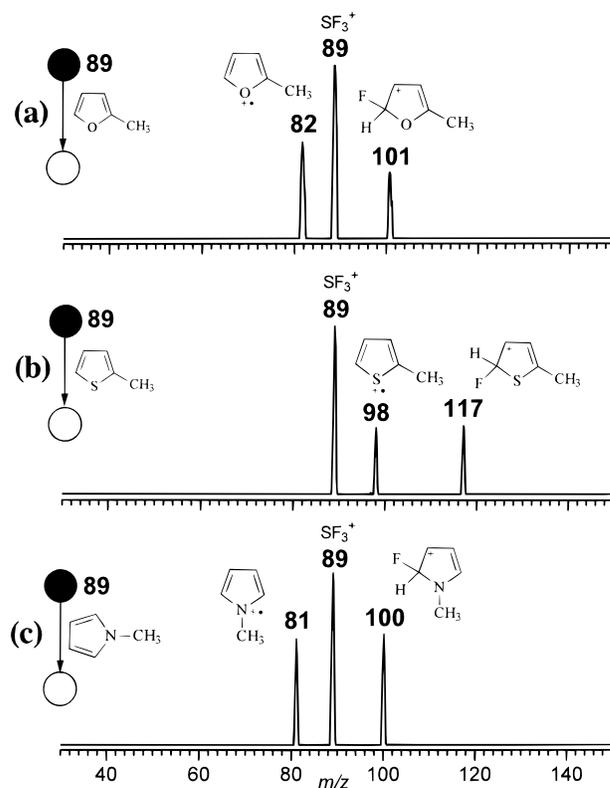
**Table 1.** F<sup>+</sup> Transfer [(MF)<sup>+</sup>] and Electron Abstraction (M<sup>+</sup>) Products (*m/z*), the (MF)<sup>+</sup>/M<sup>+</sup> Ratios, and the Ionization Potential (IP) of the Neutral Reactants for Reactions of SF<sub>3</sub><sup>+</sup> with the Five-Membered Heteroaromatic Compounds

Compound	(MF) <sup>+</sup> ( <i>m/z</i> )	M <sup>+</sup> ( <i>m/z</i> )	(MF) <sup>+</sup> /M <sup>+</sup> Ratio	IP (eV)
	87	68	0.81	8.90
	101	82	0.69	8.38
	115	96	0.58	7.80
	129	110	0.21	--
	103	84	0.68	8.85
	117	98	1.04	8.61
	117	98	0.91	8.84
	131	112	0.97	8.10
	86	67	0.10	8.02
	100	81	1.05	7.94

products (Table 1) were fully optimized at the HF/6-311G(d,p) level of theory whereas improved energies were obtained by using single point calculations at the MP2/6-311G(d,p) level and by incorporating valence electron correlation calculated by second-order Møller–Plesset (MP2) perturbation theory,<sup>19</sup> a procedure denoted as MP2/6-311G(d,p)//HF/6-311G(d,p). To calculate reaction energy changes, DFT calculations<sup>20</sup> at the Becke3LYP/6-311++G(d,p) level<sup>21</sup> were employed. Structures were visualized using Molden.<sup>22</sup>

## Discussion

**SF<sub>3</sub><sup>+</sup> Reactions.** As Figure 1 exemplifies for 2-methylfuran (Figure 1a), 2-methylthiophene (Figure 1b), and *N*-methylpyrrole (Figure 1c), the product ion mass spectra for reaction of mass-selected SF<sub>3</sub><sup>+</sup> ions with the five-membered heteroaromatic compounds (M) displays only



**Figure 1.** Double-stage (MS<sup>2</sup>) product ion mass spectra for reactions of SF<sub>3</sub><sup>+</sup> with (a) 2-methylfuran; (b) 2-methylthiophene; and (c) *N*-methylpyrrole. In the terminology used to describe MS<sup>n</sup> experiments and scan modes, a filled circle represents a fixed (or selected) mass; an open circle, a variable (or scanned) mass. The neutral reagent or collision gas that causes the mass transitions are shown between the circles. For more details on this terminology see refs 15.

two major products of two competing reactions (Scheme 1): (i) electron abstraction that yields M<sup>+</sup> and (ii) F<sup>+</sup> transfer that yields (MF)<sup>+</sup>.

Table 1 summarizes, by listing the *m/z* ratios of the (MF)<sup>+</sup> and M<sup>+</sup> products, the product ion mass spectra for the SF<sub>3</sub><sup>+</sup>/M reactions. Table 1 also compares, by listing the (MF)<sup>+</sup>/M<sup>+</sup> abundance ratios, the relative reactivities of the five-membered heteroaromatic compounds (M) toward F<sup>+</sup> transfer from, and electron abstraction by SF<sub>3</sub><sup>+</sup>.

Alkyl substitution on furan, thiophene, and pyrrole results in higher electron density of the ring  $\pi$  electron cloud; hence, nucleophilicity increases, and the ionization potential (IP) decreases (Table 1), favoring both F<sup>+</sup> transfer and electron abstraction. As compared with furan, the (MF)<sup>+</sup>/M<sup>+</sup> ratio decreases from 0.81 to 0.21 for 2-ethyl-5-methylfuran; hence, alkyl substitution favors preferentially electron abstraction (M<sup>+</sup>) for the furans. For the thiophenes, however, alkyl substitution favors preferentially F<sup>+</sup> transfer, and the (MF)<sup>+</sup>/M<sup>+</sup> ratio increases from 0.68 for furan to near 1.0 for the 2-, 3- and 2,5-(di)methyl derivatives. Of all the heteroaromatic compounds investigated, pyrrole displays the lowest IP, and consequently, the highest relative yield of the electron abstraction product and a (MF)<sup>+</sup>/M<sup>+</sup> ratio as low as 0.10. For *N*-methylpyrrole, however, despite its slightly lower IP than pyrrole, F<sup>+</sup> transfer is substantially favored, and the (MF)<sup>+</sup>/M<sup>+</sup> ratio increases substantially to 1.05. In solution, the same trend was observed: using

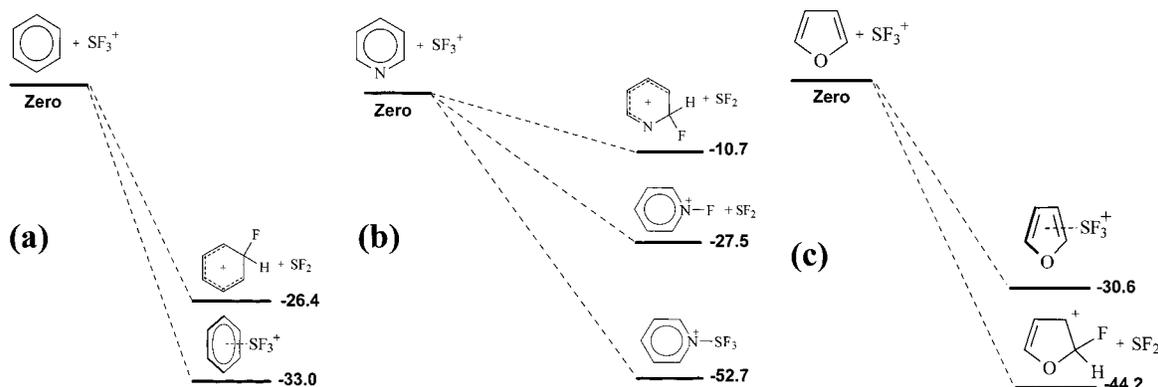
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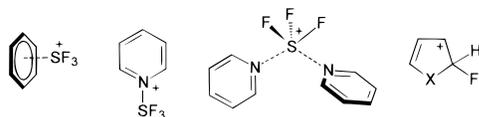
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**Figure 2.** Becke3LYP/6-311++G(d,p) energy changes for reactions of SF<sub>3</sub><sup>+</sup> with (a) benzene; (b) pyridine; and (c) furan. The total energies are, in hartree: benzene: -232.31124, (benzene + F)<sup>+</sup>: -331.85033, (benzene + SF<sub>3</sub>)<sup>+</sup>: -929.76015, pyridine: -248.35121, N-F<sup>+</sup> pyridine: -347.89211, C2-F<sup>+</sup> pyridine: -347.86538, (pyridine + SF<sub>3</sub>)<sup>+</sup>: -945.83179, furan: -230.08784, (furan + F)<sup>+</sup>: -329.65531, (furan + SF<sub>3</sub>)<sup>+</sup>: -927.53325, SF<sub>2</sub>: -597.89946, SF<sub>3</sub><sup>+</sup>: -697.39655.

### Scheme 2



diluted F<sub>2</sub>, Fornarini et al.<sup>10</sup> were able to fluorinate N-methylpyrrole but not pyrrole.

**Ab Initio Calculations. SF<sub>3</sub><sup>+</sup> Reactivity with Benzene, Pyridine, and the Five-Membered Heteroaromatic Compounds.** SF<sub>3</sub><sup>+</sup> shows drastically different reactivity toward benzene, pyridine, and five-membered heteroaromatic compounds. SF<sub>3</sub><sup>+</sup> fails to transfer F<sup>+</sup> to both benzene and pyridine; it reacts with benzene by electron abstraction or  $\pi$ -complexation forming a stable, loosely bonded adduct (Scheme 2).<sup>12g</sup> With pyridine, SF<sub>3</sub><sup>+</sup> forms a stable N-covalently bonded adduct, and this adduct reacts further with pyridine to form an abundant, loosely bonded dimer (Scheme 2).<sup>12h</sup> SF<sub>3</sub><sup>+</sup> forms, however, no adduct with the five-membered heteroaromatic compounds; it reacts instead by electron abstraction and, most interestingly, by electrophilic fluorination (F<sup>+</sup> transfer) to form the monofluorinated molecule in its protonated form (Scheme 2).

To help rationalize this drastic change in SF<sub>3</sub><sup>+</sup> reactivity, DFT<sup>20</sup> calculations at the Becke3LYP/6-311++G(d,p)<sup>21</sup> level were performed for reactions with benzene, pyridine and the model five-membered heteroaromatic compound furan. Three of the most common reactions of SF<sub>3</sub><sup>+</sup> were considered: covalent adduct formation,  $\pi$ -complexation, and F<sup>+</sup> transfer, and Figure 2 summarizes the results in simplified potential energy diagrams.

For benzene (Figure 2a), both SF<sub>3</sub><sup>+</sup>  $\pi$ -coordination and electrophilic fluorination (F<sup>+</sup> transfer) are quite exothermic, but  $\pi$ -coordination is more exothermic and thermodynamically favored. Similarly for pyridine (Figure 2b), N-coordination of SF<sub>3</sub><sup>+</sup> and F<sup>+</sup> transfer to both nitrogen and the ring are all exothermic, but SF<sub>3</sub><sup>+</sup> N-coordination is the most favorable and far the most exothermic. No stable SF<sub>3</sub><sup>+</sup>  $\pi$ -coordinated adduct was found for pyridine. For furan (Figure 2c), SF<sub>3</sub><sup>+</sup>  $\pi$ -coordination (the O-coordinated adduct is unstable at this level) and F<sup>+</sup> transfer to the ring are also considerably exothermic, but F<sup>+</sup> transfer is now far more thermodynamically favored.

**Regioselectivity of Fluorination.** Ab initio calculations at the MP2/6-311G(d,p)//HF/6-311G(d,p) level were

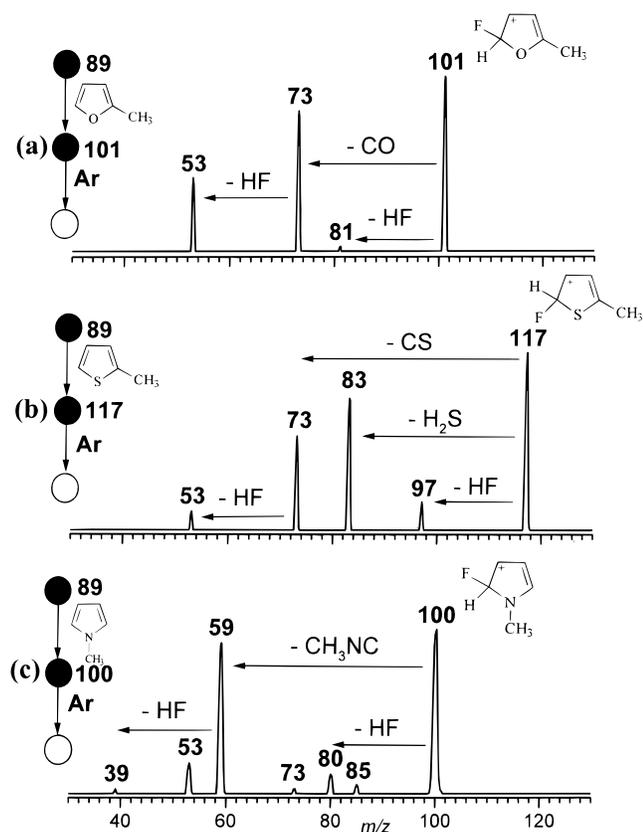
**Table 2.** MP2/6-311G(d,p)//HF/6-311G(d,p) Electronic and Relative Energies of Possible F<sup>+</sup> Transfer Products of the Five-Membered Heteroaromatic Compounds

Structure	X	R <sup>1</sup> , R <sup>2</sup>	Fluorine Position	Total Energy (hartrees)	Relative Energy (kcal/mol)	
	O		1-	-328.52085	127.2	
			2-	-328.72355	0	
			3-	-328.69047	20.8	
	S		1-	-651.27564	32.7	
			2-	-651.32780	0	
			3-	-651.31358	8.9	
	NH		1-	-308.78804	69.0	
			2-	-308.89806	0	
			3-	-308.88109	10.7	
	O	2-CH <sub>3</sub>	2-	-367.91184	5.3	
			3-	-367.89057	18.6	
			4-	-367.87884	26.0	
			5-	-367.92028	0	
			S	2-	-690.51130	3.8
	3-		-690.49948	11.3		
	4-		-690.49604	13.4		
	5-		-690.51742	0		
	3-CH <sub>3</sub>		2-	-690.51509	0	
			3-	-690.49643	11.7	
			4-	-690.49783	10.8	
			5-	-690.50938	3.6	
			NCH <sub>3</sub>	2-	-348.07354	0
	3-		-348.05794	9.8		
			O	2-CH <sub>3</sub> , 5-CH <sub>3</sub>	2-	-407.10764
3-		-407.07792			18.7	
S		2-			-446.27877	0
2-C <sub>2</sub> H <sub>5</sub> , 5-CH <sub>3</sub>		3-	-446.24816		19.2	
		4-	-446.24963		18.3	
		5-	-446.27833		0.3	
		S	2-		-729.70116	0
			3-		-729.68723	8.7

also used to investigate the regioselectivity of F<sup>+</sup> transfer, and Table 2 lists the total and relative energies of all possible F<sup>+</sup> transfer products. As has also been observed in extensive studies on electrophilic reactions of five-membered heteroaromatic compounds in solution,<sup>23</sup> the ortho C2 and C5 ring carbons are found to be by far the most thermodynamically favored sites for F<sup>+</sup> addition in the gas phase.

**Collision-Induced Dissociation.** Table 3 summarizes the triple-stage (MS<sup>3</sup>) collision-induced dissociation (CID) product ion mass spectra of the protonated monofluorinated heteroaromatic compounds formed in reactions with SF<sub>3</sub><sup>+</sup> whereas Figure 3 exemplifies those for the (MF)<sup>+</sup> products of methylfuran, methylthiophene, and

(23) (a) Bosshard, P.; Eugster, C. H. in *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Boulton, A. J., Eds.; Academic Press: New York, 1966; Vol. 7, p 377. (b) Gronowitz, S. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic Press: New York, 1963; Vol. 2, p 1. (c) Alan Jones, R. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Boulton, A. J., Eds.; Academic Press: New York, 1970; Vol. 11, p 384.



**Figure 3.** Triple-stage ( $MS^3$ ) CID product ion mass spectra for the protonated monofluorinated heteroaromatic compounds formed in reactions of  $SF_3^+$  with (a) 2-methylfuran; (b) 2-methylthiophene; and (c) *N*-methylpyrrole.

**Table 3: The  $m/z$  Ratios and Relative Abundances (in parentheses) of the Ionic Fragments Observed in the Triple-Stage ( $MS^3$ ) CID Product Ion Mass Spectra of the  $F^+$ -Transfer Products Formed in Reactions of  $SF_3^+$  with the Five-Membered Heteroaromatic Compounds**

(MF) <sup>+</sup> product ion <sup>a</sup> ( $m/z$ )	neutral loss				
	HF	CX	CX + HF	H <sub>2</sub> X	others
87	none	59(100)	none	none	none
101	81(4)	73(100)	53(53)	none	none
115	95(92)	87(31)	81(100)	none	none
129	109(34)	101(17)	81(100)	111(17)	73(100), 86(24)
103	none	59(100)	53(15)	none	none
117	97(21)	73(83)	53(15)	83(100)	none
117 <sup>b</sup>	97(29)	73(49)	none	83(100)	none
131	111(22)	87(14)	67 (7)	97 (100)	none
86	none	59(100)	none	none	none
100	80(14)	59(100)	none	none	85(7), 55(21)

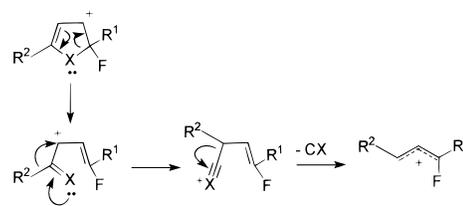
<sup>a</sup> For M see Table 1. <sup>b</sup> The 3-isomer.

methylpyrrole. Note that these spectra represent, to the best of our knowledge, the first spectrometric data collected for 2-fluoropyrrole and the four 2-fluorofurans.

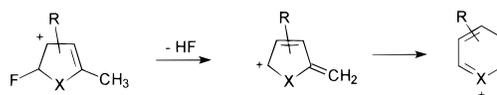
As expected for even-electron cations, the protonated monofluorinated heteroaromatic compounds dissociate mainly by losing neutral molecules. Loss of CX (X = O, S, NH, NCH<sub>3</sub>) is favored and observed for all the (MF)<sup>+</sup> products (Figure 3, Table 3). Assuming fluorination at C2 (and/or C5), as expected and strongly suggested by the calculations, loss of CX can be conveniently rationalized by the pathways depicted in Scheme 3, yielding resonance-stabilized and relatively stable allylic cations.

Only for the alkyl-substituted molecules is loss of CX from (M + F)<sup>+</sup> followed by loss of HF whereas this loss

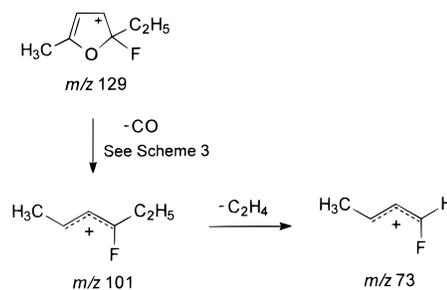
**Scheme 3**



**Scheme 4**



**Scheme 5**



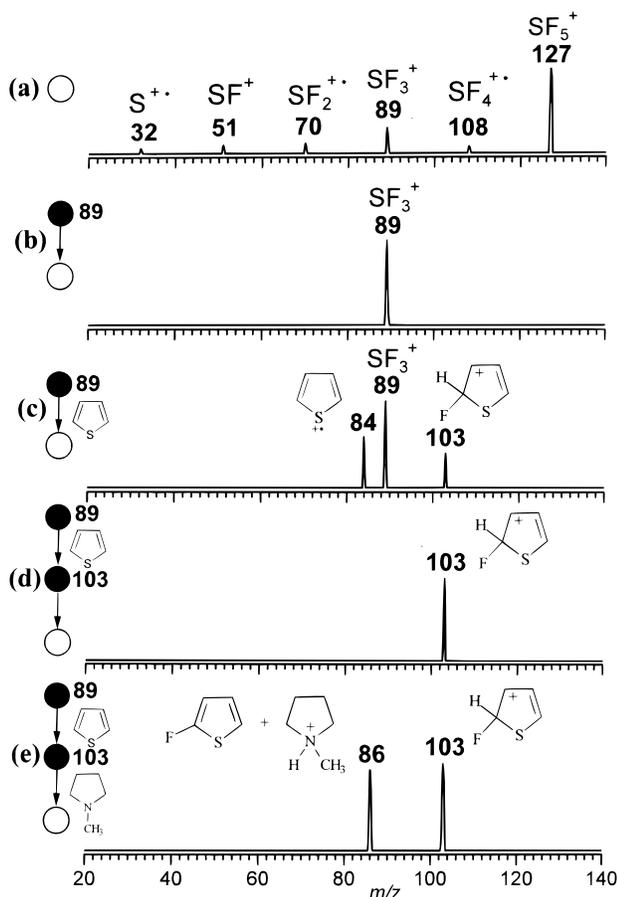
also occurs to considerable extent directly, that is, as a primary dissociation. Loss of HF most likely involves, therefore, an H provided by the alkyl substituent, and a mechanism for such a loss is rationalized in Scheme 4. Fast ring expansion of the resulting carbocation, a widely accepted mechanism,<sup>24</sup> is likely to occur after HF loss, yielding stable heteroaromatic cations: pyrilium or thiopyrilium ions, or protonated pyridine.

For the F<sup>+</sup> transfer products of the substituted thiophenes ( $m/z$  117 and 131), loss of H<sub>2</sub>S is the major dissociation pathway, and the absence of such fragmentation for protonated, unsubstituted monofluorinated thiophene ( $m/z$  103, Table 3) suggests that hydrogens of the alkyl group participate in the H<sub>2</sub>S loss.

Particularly for protonated 2-ethyl-5-methyl-fluorofuran ( $m/z$  129), the spectrum displays an additional and major fragment of  $m/z$  73 (Table 3) that corresponds to the loss of a neutral C<sub>3</sub>H<sub>4</sub>O molecule. As depicted in Scheme 5, this dissociation can be easily rationalized assuming that F<sup>+</sup> addition occurs as predicted by the calculations (Table 2), that is, at the C2 position.

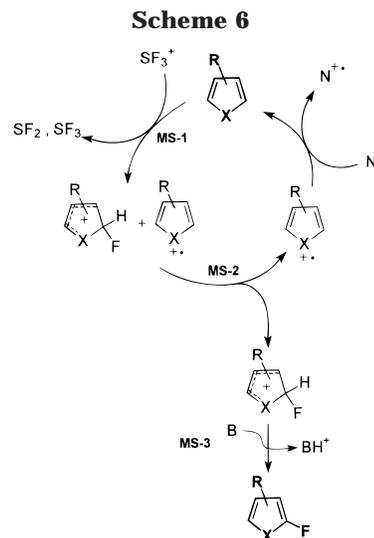
**Gas-Phase Synthesis of Monofluorinated Five-Membered Heteroaromatic Compounds.** The F<sup>+</sup> transfer products are protonated molecules; hence, their deprotonation via a second reaction with a stronger base should lead to the formal gas-phase synthesis of the corresponding neutral monofluorinated heteroaromatic compounds (Scheme 6). Yet, for 2-fluoropyrrole and the four fluorofurans, this approach would represent the first synthesis of their monofluorinated derivatives. As also depicted in Scheme 6, the ionized heteroaromatic molecule, formed competitively by electron abstraction, could also be isolated, in principle, from the F<sup>+</sup> transfer product by mass-selection, reneutralized by electron transfer, and recycled to the first reaction cell as to achieve maximum conversion.

(24) Health, T. G.; Allison, J.; Watson, J. T. *J. Am. Chem. Soc.* **1991**, *2*, 270.



**Figure 4.** Mass spectra resulting from pentaquadrupole scans used to test partially the conversion cycle depicted in Scheme 6, and to accomplish the gas-phase synthesis of 2-fluorothiophene. The cycle starts with (a) formation of SF<sub>n</sub><sup>+</sup> ions ( $n = 0-5$ ) by 70 eV EI of SF<sub>6</sub> and the recording of the full mass spectrum (MS). The cycle then proceeds by (b) MS<sup>2</sup> selection of the desired reactant ion: SF<sub>3</sub><sup>+</sup> of  $m/z$  89; (c) reaction of the mass-selected SF<sub>3</sub><sup>+</sup> ions with thiophene; (d) MS<sup>3</sup> selection of the desired reaction product: protonated 2-fluorothiophene of  $m/z$  103; and (e) its deprotonation with *N*-methylpyrrolidine that yields protonated methylpyrrolidine of  $m/z$  86 and the desired final product: neutral 2-fluorothiophene.

Triple-stage (MS<sup>3</sup>) pentaquadrupole mass scans were therefore used to test partially the conversion cycle depicted in Scheme 5, and to accomplish the desired syntheses. The cycle via the deprotonation route is



exemplified for monofluorothiophene in Figure 4: (i) SF<sub>n</sub><sup>+</sup> ions ( $n = 0-5$ ) are formed by 70 eV EI of SF<sub>6</sub> (Figure 4a); (ii) the desired reactant ion, SF<sub>3</sub><sup>+</sup> of  $m/z$  89, is mass-selected by Q1 (Figure 4b), and (iii) reacted in q2 with thiophene yielding protonated monofluorothiophene of  $m/z$  103 (Figure 4c); and then, (iv) protonated 2-fluorothiophene of  $m/z$  103 is mass-selected by Q3 (Figure 4d), and (v) reacted in q4 with *N*-methylpyrrolidine yielding the protonated methylpyrrolidine of  $m/z$  86 and the desired neutral 2-fluorothiophene (Figure 4e). Similar successful experiments were performed with the other protonated monofluorinated heteroaromatic compounds.

## Conclusion

In gas-phase reactions, SF<sub>3</sub><sup>+</sup> ions readily transfers F<sup>+</sup> to five-membered heteroaromatic compounds. Then, the resulting protonated monofluorinated compound can be efficiently deprotonated by a second reaction with a stronger base. Therefore, C–H by C–F substitution is accomplished and gaseous SF<sub>3</sub><sup>+</sup> functions as a gentle and effective electrophilic monofluorinating agent for five-membered heteroaromatic compounds.

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