

Investigation of Radical Cation in
Electrophilic Fluorination by ESI-MS

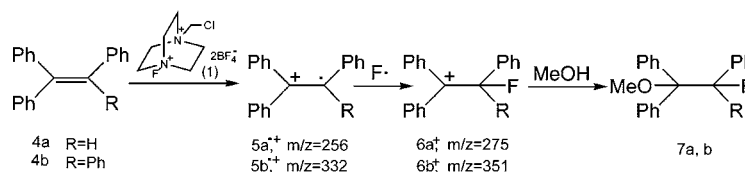
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ABSTRACT



Reaction solutions of selectfluor (1) with triphenylethylene (4a) and tetraphenylethylene (4b) were monitored by ESI-MS and ESI-MS/MS. Detection and characterization of the key radical cationic intermediates $5a^+$ and $5b^+$ fully supports the SET mechanism in electrophilic fluorination as depicted above.

In recent years, a number of N–F fluorinating agents have emerged as generally safe, easy to handle, selective sources of electrophilic fluorine. These are either neutral, R_2NF compounds or quaternary ammonium $R_3N^+FA^-$ salts where A^- is a nonnucleophilic anion.¹ Of all the N–F agents, 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octanebis-(tetrafluorobor-ate) (selectfluor, F-TEDA- BF_4) (1) (Figure 1) has been the subject of considerable interest as a powerful and user-friendly (nongaseous, nonexplosive, less-toxic), site-selective, electrophilic fluorinating agent since its discovery in 1980.² However, there is currently no single widely accepted mechanism for electrophilic fluorination. There is the view of an initial charge-transfer complex that undergoes electron and fluorine radical transfer steps as postulated by Umemoto and DesMarteau and substantiated by Kochi's

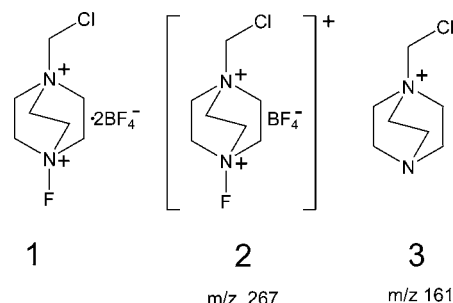


Figure 1. Selectfluor (1) and ions derived from 1.

studies in the broader context of electrophilic aromatic substitution.³ On the other hand, the radical clocks experiment presented by Differding and Saveant et al. seems to rule out an ET pathway for fluorination of their substrates, and an S_N2 displacement on fluorine is invoked as the most likely mechanism.⁴ Both SET and S_N2 pathways lead to the

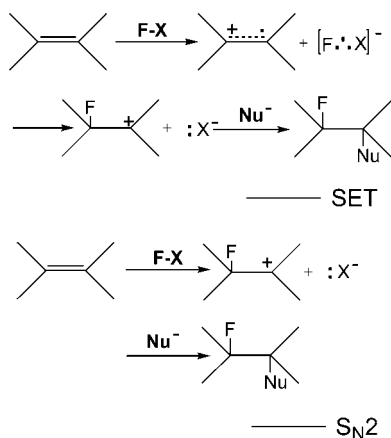
* Fax: (+86)21-64166128.

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same product, in this case a fluorinated carbocation, as shown in Scheme 1. The difference between the two mechanisms

Scheme 1. Single- and Two-Electron Processes in the Presence of **1** Can Result in Identical Products



is probably smaller than it appears, and the limits of current methods to study extremely fast reactions inhibit the definitive elucidation of the operative mechanism.

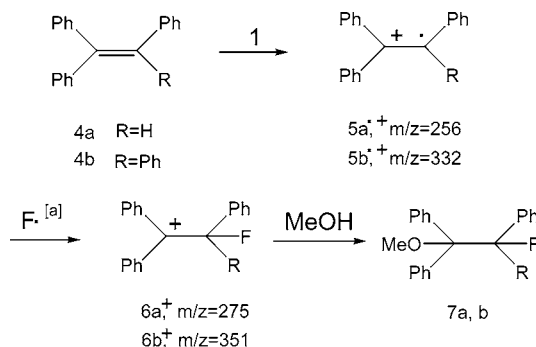
Selectfluor and the other compounds of this general class are the only electrophilic fluorination reagents for which no clear evidence has been found for the intermediacy of radical intermediates. However, the fact that 2,2,6,6-tetramethylpiperidine *N*-oxide (TEMPO), which is oxidized by a suitable oxidant (Cl_2 , Br_2 , XeF_2 , etc.) by liberation of a single electron,⁵ reacts rapidly with selectfluor⁶ strongly suggests that selectfluor can participate in SET reactions. In addition, theoretical calculations and X-ray crystallographic analysis suggest that the fluorine center has more radical than “fluoronium” character.⁷ On the basis of this evidence and on additional data supporting SET with other N–F reagents, it is probable that SET also occurs with selectfluor.

Electrospray ionization (ESI) is an interesting “ion-fishing” technique, which is known for its ability to transfer ions to the gas phase without inducing undesirable side reactions,⁸ and the composition of ESI-generated ions often closely reflects that in solution.^{9,10} ESI-MS is rapidly becoming the technique of choice for solution mechanistic studies in chemistry and biochemistry.¹¹ In the present work, we describe the use of ESI-MS and ESI-MS/MS to monitor reaction solutions of selectfluor with triphenylethylene and

tetraphenylethylene. Detection and characterization of the key radical cationic intermediates fully supports the SET mechanism in electrophilic fluorination.

Control experiments were performed first. The ESI mass spectra (see Supporting Information) of two aryl-substituted olefins **4a** and **4b** showed no signals for the radical cations **5a^{•+}** and **5b^{•+}** (Scheme 2). Then, the reactions of **1** with **4a**

Scheme 2. Fluorination of Aryl-Substituted Olefins by Selectfluor **1**^a



^a F^\bullet is derived from **1**.

and **4b** were monitored by the ESI/TOF-MS¹² under the same conditions.¹³ The aim is to intercept the radical cationic intermediates **5a^{•+}** and **5b^{•+}** resulting from the SET pathway, though the radical intermediates are too unstable to detect even using the radical traps such as TEMPO.² However, the ESI (+)-MS spectra collected for such reactions were exciting. Shortly after 1–3 min of the reaction of olefin **4a**, some species were detected as major ions (Figure 2a): **3⁺** of m/z 161, **2⁺** of m/z 267 (Figure 1), [**3** + F – H]⁺ of m/z 179, [**3** + 2F – 2H]⁺ of m/z 197,¹⁴ **5a^{•+}** of m/z 256, and **6a^{•+}** of m/z 275. The ESI (+)-MS spectrum for the reaction of olefin **4b** (Figure 2b) showed four of the same major ions **3⁺** of m/z 161, **2⁺** of m/z 267, [**3** + F – H]⁺ of m/z 179, [**3**

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(12) See Supporting Information.

(13) Triphenylethylene, tetraphenylethylene, and selectfluor were purchased from Aldrich (Milwaukee, WI), they were used without further purification. Methanol was obtained from Fisher (Fair Lawn, NJ). In the control experiments, solutions of olefins **4a** 20 $\mu\text{mol L}^{-1}$ or **4b** 0.5 $\mu\text{mol L}^{-1}$ in acetonitrile were examined by MS. The reacting solutions were prepared by adding selectfluor (3.0 mg, 8.5 μmol) and methanol (10 μL) into the solution of **4a** and **4b** (1.0 mL), respectively, used in the control experiments.

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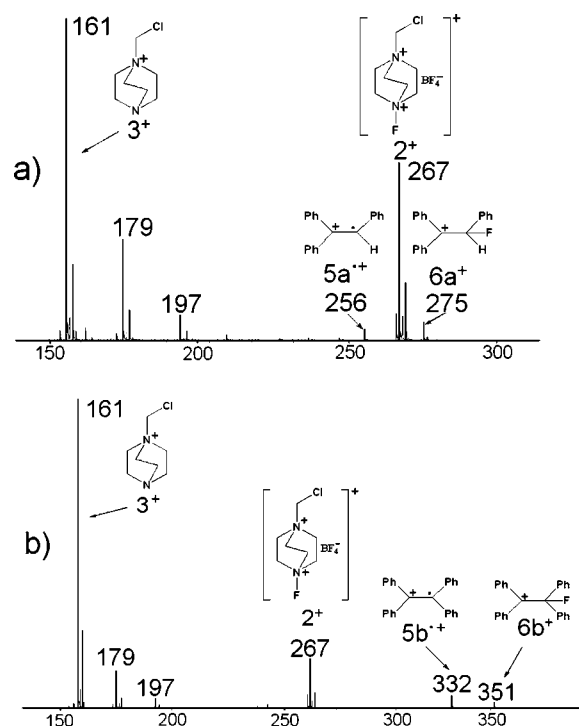


Figure 2. Positive ESI mass spectrum of the reacting solutions of (a) **4a** + **1** + methanol and (b) **4b** + **1** + methanol.

+ 2F – 2H]⁺ of *m/z* 197,¹⁴ but, as expected, **5a**^{•+} of *m/z* 256 from olefin **4a** was replaced by **5b**^{•+} of *m/z* 332 from **4b**. **6a**⁺ of *m/z* 275 was replaced by **6b**⁺ of *m/z* 351. Detection of the cationic intermediates **6a**⁺ and **6b**⁺ could not help us distinguish between SET and S_N2 mechanisms, for both pathways lead to the same fluorinated carbocation. However, detection of the radical cationic intermediates **5a**^{•+} and **5b**^{•+} makes the SET mechanism more likely.

In addition, the time dependence of the radical cationic intermediates **5a**^{•+} and **5b**^{•+} abundance is shown in Figure 3. Even without further kinetic analysis, it is easily seen that the abundance of **5a**^{•+} (or **5b**^{•+}) first rises rapidly and then decreases slowly.

To confirm the radical cationic intermediates **5a**^{•+} and **5b**^{•+}, we tried to repeat the experiment in the ESI–FTMS.¹⁵ The radical cationic intermediate **5b**^{•+} of *m/z* 332.1558 was detected (calcd for C₂₆H₂₀^{•+}, *m/z* 332.1560) (see Supporting Information). On the other hand, the radical cationic intermediate **5a**^{•+} could not be captured. However, accurate mass of the radical intermediate **5a**^{•+} in Figure 2a could be determined with two reference masses by TOF MS.¹⁶ We obtained the accurate mass 256.1254 (calcd for C₂₀H₁₆^{•+}, *m/z* 256.1246). The accurate mass measurement results indicate that the proposed ion structures correspond to the only chemically reasonable elemental compositions.

To further structurally characterize the radical intermediate **5b**^{•+} via CID, a MS/MS experiment was performed using ESI–FTMS (Figure 4). It was somewhat difficult to obtain the MS/MS of the radical intermediate **5b**^{•+}. CID of **5b**^{•+}

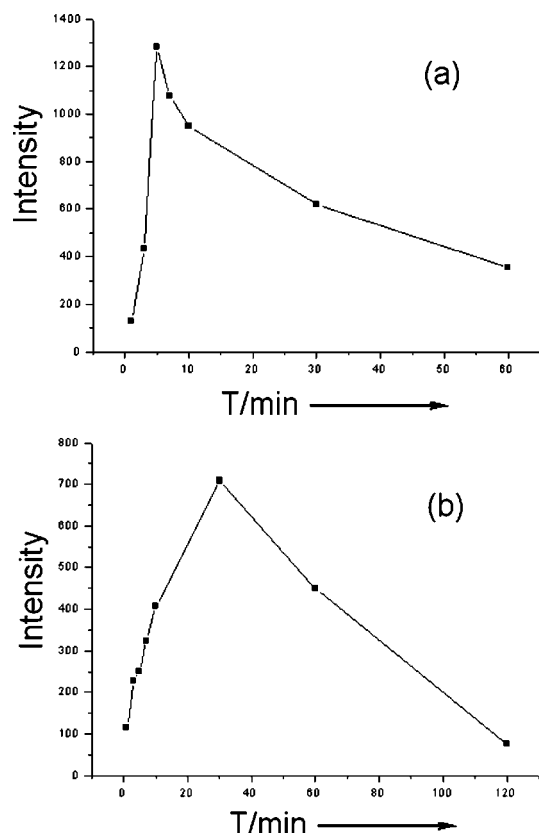


Figure 3. Time dependence of the radical cationic intermediates abundance of (a) **5a**^{•+} and (b) **5b**^{•+}.

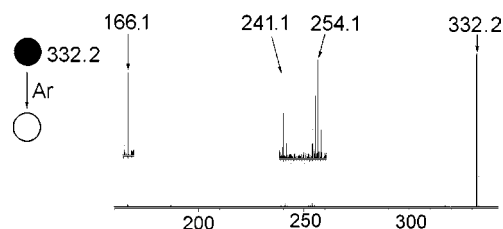


Figure 4. ESI(+)-MS/MS spectrum of **5b**^{•+} at *m/z* 332.2.

resulted in ions *m/z* 254.1085 by loss of benzene (–78.0473 Da; calcd for C₆H₆, 78.0469 Da). Furthermore, the cleavage of C₇H₇[•] (–91.0542 Da; calcd for C₇H₇[•], 91.0548 Da) and diphenylcarbene (–166.0781 Da; calcd for C₁₃H₁₀, 166.0783 Da) to give the respective daughter ions *m/z* 241.1016 and 166.0777 was observed as evidenced by characteristic fragmentations.

In conclusion, the ESI-MS and ESI-MS/MS experiments described herein have proved the SET mechanism of fluorination of multi-phenyl-substituted olefins by mass detection and characterization of their key radical cationic

(15) See Supporting Information.

(16) See Supporting Information.

intermediates **5a**^{•+} and **5b**^{•+}. Further studies in this endeavor are ongoing.

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Supporting Information Available: Additional MS and MS-MS spectra, as well as the type of mass spectrometer. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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