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First Electronic Investigation of the Structure of Alkenes Compatible to Carbon Radicals Bearing a Single Fluorine Atom

Yoshio Takeuchi,* Shun-ichi Kawahara, Takanori Suzuki, Toru Koizumi, and Hiroyuki Shinoda*

Faculty of Pharmaceutical Sciences, Toyama Medical & Pharmaceutical University,
Sugitani 2630, Toyama 930-01, Japan

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In order to look into the electronic course of the Michael addition of α-fluorocarbon radical to alkenes, theoretical MO calculations and experiments were attempted. The SOMO values and atomic charges for the α-carbon radical of ethyl *β*-phenylpropionate (**4a**) and that of the α-fluoro analog (**4b**) and HOMO and LUMO values and atomic charges for three representative alkenes, acrylonitrile (**6**), styrene (**7**), and propene (**8**), were calculated using 6-31G and 6-31G* methods. The results are as follows: (i) In the case of simple radicals such as **4a**, interaction between the SOMO of radicals and the LUMO of alkenes seems dominant, and therefore, **4a** should react with **6** more readily than **7** or **8**. (ii) Those radicals having an electron-withdrawing group (EWG) such as fluorine become more electrophilic, considering the energy level differences between the SOMO of radicals and the HOMO and LUMO of alkenes. (iii) The energy level difference between the SOMO of **4b** and the HOMO of **7** is smaller than that between the SOMO of **4b** and the HOMO of **6** or **8**, and further, the terminal carbon atom in **7** is more negatively charged than that in **6** or **8**. Therefore, electrophilic radicals such as **4b** should be more reactive toward **7** than **6** or **8**. On the basis of these predictions, the denitrative alkylations of α-fluoro-α-nitroalkanoic esters (**1a** and **1b**) with **7**, having no EWG but being conjugated with an aromatic ring, were found to give the α-alkylated α-fluoro esters (**3c** and **3d**, respectively) in much improved yield when compared with those reactions with **6** having a conjugated EWG. This result provides an important synthetic strategy toward useful monofluoro molecules.

Introduction

The enhancement and alteration of biological activity in many natural product classes by the selective introduction of a single fluorine atom are a proven cornerstone strategy of medicinal and bioorganic chemistry.[1] Site-selective preparation of monofluoro molecules, however, is often very difficult because of the high reactivity of fluorinating agents in direct fluorination of organic compounds. In addition, the reluctance of a fluorine-bearing carbon to undergo both electrophilic and nucleophilic alkylations often complicates synthetic strategies. With these factors in mind, we have recently developed general and regioselective pathways to nonlabile tertiary alkyl fluorides that involve radical alkylations with various alkenes at the fluorine-bearing carbon atoms.[2] This novel methodology features successive introduction of three different alkyl groups onto fluorine-bearing prototertiary carbon fragments.

Scheme 1

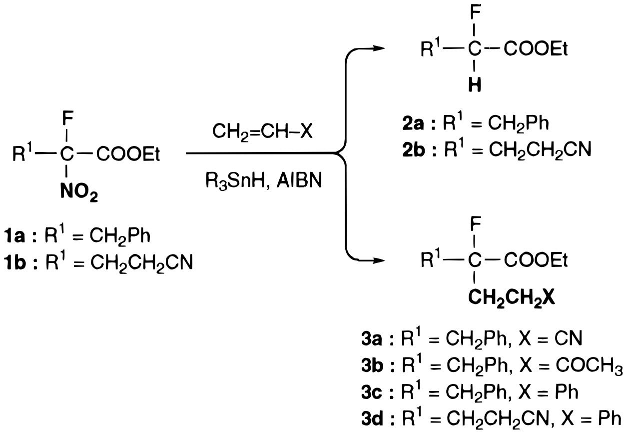

Table 1. Derivative Alkylation of 1 with Alkenes Using R$_3$SnH

entry	R^1	X	yield (%) 2	yield (%) 3	R$_3$SnH
1	CH$_2$Ph	CN	51	9	Bu$_3$SnH
2	CH$_2$Ph	COCH$_3$	44	14	Bu$_3$SnH
3	CH$_2$Ph	Ph	30	47	Bu$_3$SnH
4	CH$_2$CH$_2$CN	Ph	32	38	Bu$_3$SnH
5	CH$_2$Ph	Ph	18	68	Ph$_3$SnH
6	CH$_2$CH$_2$CN	Ph	20	66	Ph$_3$SnH
7	CH$_2$Ph	CN	−[a]	−[a]	Ph$_3$SnH

[a] Starting material recovered.

However, the reaction of α-fluoro-α-nitro ester **1a** with Bu$_3$SnH in the presence of a large excess of Michael acceptors CH$_2$=CHX (X = CN or COCH$_3$) produced mainly the unwanted compound **2a** while the addition product **3a** or **3b** was formed only in low yield (Scheme 1, Table 1, entries 1 and 2).[2,3] In an attempt to overcome this problem, we look into, for the first time, the electronic compatibility of alkene structures with α-fluorocarbon radicals, based on the examination of MO calculations. Reactivities of fluorine-bearing carbon radicals have been

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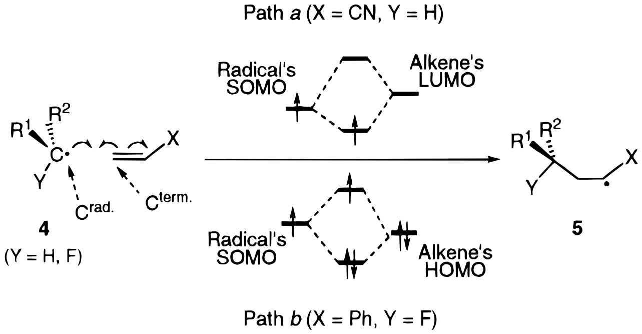


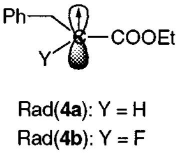
Figure 1. Path *a*: Orbital interaction between the SOMO of nucleophilic radicals and the LUMO of alkenes. Path *b*: Orbital interaction between the SOMO of electrophilic radicals and the LUMO of alkenes.

to date little documented in spite of their potential wide usefulness, especially in organofluorine chemistry.

Results and Discussion

α-Carbon radicals of simple alkanoic esters behave, in general, as soft nucleophiles when they interact with activated alkenes, e.g., $CH_2{=}CHCN$. The LUMO of such active alkenes, which strongly interacts with the singly occupied molecular orbital (SOMO) of radicals **4**, is dispersed over the double bond. Therefore, the interaction between the LUMO of alkenes and the SOMO of radicals is important during the course of the formation of Michael adduct radicals **5** (Figure 1, path *a*). In contrast, the SOMO of the carbon radicals bearing electron-withdrawing groups (EWG) such as fluorine at the α position is generally considered to be at lower energy levels, and consequently, the radicals inevitably become more electrophilic. In this case, the interaction between the HOMO of alkenes and the SOMO of carbon radicals should be dominant in the radical addition reaction (path *b*).[4] In fact, the strong electronegativity of fluorine sometimes interferes with or alters the course of reactions when compared to the analogous reaction involving nonfluorinated compounds.[5]

The ab initio MO calculations with both 6-31G and 6-31G* basis sets were performed on a DEC α-3000 computer. Wave functions were calculated using the GAUSSIAN 92 program.[6] When calculations for open shell electron configurations were performed employing the widely-used unrestricted Hartree–Fock (UHF) procedure, the SOMO could not be recognized and even the HOMO of the α electrons did not comprise the orbitals of the radical carbon atom. On the other hand, the SOMO in an electron configuration of the doublet state was clearly identified with the restricted open shell HF (ROHF) procedure, and it consisted mainly of the orbitals of the radical carbon atom. Therefore, the ROHF method with the 6-31G basis set was applied for the radicals of both ethyl β-phenylpropionate (**4a**) and the fluorinated analog **4b**. It was found that the SOMO level of **4b** was lower than that of **4a**, as expected. However, the Mulliken net atomic charge (δC^{rad}) of **4b** was slightly more negative than that of **4a**. Seemingly, orbital control is prior to charge control in this case, considering the fact that reaction of **1a** with **6** produced the addition product **3a** in poor yield[2,3] (Figure 2).



Rad(**4a**): Y = H
Rad(**4b**): Y = F

Radical	Y	SOMO (eV)	$\delta C^{rad.}$ (e)
Rad (**4a**)	H	− 2.560	− 0.115
Rad (**4b**)	F	− 2.930	− 0.161

Figure 2. SOMO energy level and net atomic charge (δC^{rad}) of radicals **4a** and **4b** calculated by ROHF/6-31G.

Table 2. Partial Charges of the Radical-Accepting Carbon (δC^{term}) and HOMO and LUMO Values of the Alkenes 6–8

	δC^{term} (e)		HOMO (eV)		LUMO (eV)	
alkene	6-31G	6-31G*	6-31G	6-31G*	6-31G	6-31G*
6	−0.299	−0.337	−10.771	−10.822	+2.608	+2.802
7	−0.369	−0.412	−8.243	−8.206	+2.961	+3.043
8	−0.362	−0.396	−9.688	−9.715	+5.105	+5.248

On the other hand, HF calculations using both 6-31G and 6-31G* basis sets were carried out for three representative alkene models ($CH_2{=}HX$), i.e., acrylonitrile (X = CN, **6**) having a conjugated EWG, styrene (X = Ph, **7**) having no EWG but being conjugated with an aromatic ring, and propene (X = Me, **8**) having neither an EWG nor a conjugated system. Net atomic charges (Mulliken) of the terminal carbon atoms (δC^{term}) of the double bond in alkenes **6**–**8** and both the HOMO and LUMO values of these alkenes are shown in Table 2.

The results can be summarized as follows: (i) In the case of simple radicals such as **4a**, interaction between the SOMO of radicals and the LUMO of alkenes seems dominant, and consequently, the radicals would be nucleophilic and should react with **6** more readily than **7** or **8**. (ii) However, those radicals having an EWG such as fluorine become more electrophilic, considering the energy level differences between the SOMO of radicals and the HOMO and LUMO of alkenes.[7] (iii) The energy level difference between the SOMO of **4b** and the HOMO of **7** is smaller[7] than that between the SOMO of **4b** and the HOMO of **6** or **8**, and further, the terminal carbon atom in **7** is more negatively charged than that in **6** or **8**. Therefore, electrophilic radicals such as **4b** should be more reactive toward compound **7** than **6** or **8**.

On the basis of the results derived from these calculations, we attempted the denitrative alkylations of **1a** and **1b** with **7**, under conditions similar to the alkylation with **6**. This produced the alkylated products **3c** and **3d**, respectively, in much improved yield (Table 1, entries 3 and 4). Moreover, when Ph_3SnH, which is more electrophilic than Bu_3SnH,[8] was employed for these reactions,

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(7) The energy level differences (by 6-31G) between the SOMO of the fluorinated radical **4b** and the HOMO (or LUMO) of **6**, **7**, and **8** are 7.841 (5.538), 5.313 (5.891), and 6.758 (8.035) (eV), respectively. In the case of the simple radical **4a**, however, the corresponding energy differences are 8.211 (5.168), 5.683 (5.521), and 7.128 (7.665) (eV), respectively.

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alkylation proceeded more smoothly (entries 5 and 6). This result can be ascribed to the difference of the relative reactivity between α-fluoro radicals **4** and adduct radicals **5** toward R_3SnH (R = Bu or Ph). The reaction of **1a** with **6** did not occur at all when Ph_3SnH was used for denitration. These results are in good agreement with expectations based on the theoretical considerations.

Conclusion

The first successful combination of theoretical MO calculations and experiments is offered in order to look into the alkene structure most compatible to the carbon radicals bearing a single fluorine atom. Unexpectedly, styrene was found to be a much better Michael acceptor than active olefins such as acrylonitrile in C−C bond formation with α-fluorocarbon radicals. There have been so far no reports concerning radical C−C bond construction at a carbon bearing a single fluorine atom.[9] We believe our results provide important information on the design and synthesis of aliphatic monofluorides, for use in both basic[10] and applied[1] fluorine chemistry.

Experimental Section

General Information. The ab initio MO calculations were carried out with the aid of the GAUSSIAN 92 program implemented on a DEC α-3000 computer. Geometries of the alkene compounds **6**−**8** were fully optimized with both 6-31G and 6-31G* basis sets at the HF level of theory. For α carbon radicals, **4a** and **4b**, the ROHF procedure has been employed because the SOMO in an electron configuration of the doublet state is clearly identified. Only the 6-31G basis set has been used in the geometry optimizations of α carbon radicals due to the insufficient memory space of our computer machine. ^{1}H (500 MHz) and ^{13}C (75 MHz) NMR spectra were measured in $CDCl_3$ with Me_4Si as the internal standard. ^{19}F NMR (254 MHz) spectra were measured in $CDCl_3$ with $CFCl_3$ as the internal standard. Upfield shifts are quoted as negative δ values.

General Procedure for the Alkylation of 1 with 6 or 7. A solution of α-fluoro-α-nitro carboxylic ester[2] **1a** or **1b** (0.10 mmol) and alkene **6** or **7** (1.3 mmol) in dry benzene (20 mL) was heated at reflux under N_2 gas, while a mixture of R_3SnH (0.11 mmol) and AIBN (0.06 mmol) in dry benzene (5 mL) was added dropwise by means of a syringe. The whole mixture was heated at reflux for 30 min and concentrated. The residue was dissolved in CH_3CN (5 mL), and the solution was washed with hexane (3 mL × 2) to remove organotin compounds. Concentration of the CH_3CN solution gave an oil which was purified by preparative TLC to afford **3a**,[3] **3b**,[3] **3c**, or **3d**, respectively.

Ethyl 2-Fluoro-2-(phenylmethyl)-4-phenylbutyrate (3c): bp 65−67 °C (bath temperature, 0.05 mmHg); IR (neat) ν = 1758, 1734, 1604, 1496, 1455; ^{1}H NMR δ = 1.18 (t, $J_{H,H}$ = 7.2 Hz, 3H), 2.08−2.36 (m, 2H), 2.55−2.86 (m, 2H), 3.15 (dd, $J_{H,F}$ = 25.6, $J_{H,H}$ = 14.3 Hz, 1H), 3.20 (dd, $J_{H,F}$ = 34.0, $J_{H,H}$ = 14.3 Hz, 1H), 4.12 (m, 2H), 7.16−7.34 (m, 10H); ^{13}C NMR δ = 14.1 (s), 29.6 (s), 39.0 (d, $J_{C,F}$ = 21.7 Hz), 43.6 (d, $J_{C,F}$ = 21.8 Hz), 61.5 (s), 97.2 (d, $J_{C,F}$ = 191.2 Hz), 126.1 (s), 127.2 (s), 128.3 (s), 128.4 (s), 128.5 (s), 130.2 (s), 134.4 (s), 140.8 (s), 170.6 (s); ^{19}F NMR δ = −165.9 (dddd, $J_{F,H}$ = 31.1, 28.0, 20.2, 10.7 Hz); MS *m/z* 300, 280. Anal. Calcd for $C_{19}H_{21}FO_2$: C, 75.98; H, 7.05. Found: C, 75.89; H, 7.00.

Ethyl 4-Cyano-2-fluoro-2-(2-phenylethyl)butyrate (3d): bp 58−61 °C (bath temperature, 0.1 mmHg); IR (neat) ν = 2250, 1755, 1738, 1603, 1497, 1455; ^{1}H NMR δ = 1.34 (t, $J_{H,H}$ = 7.2 Hz, 3H), 2.07−2.86 (m, 8H), 4.26 (q, $J_{H,H}$ = 7.2 Hz, 2H), 7.16−7.31 (m, 5H); ^{13}C NMR δ = 11.8 (s), 14.2 (s), 29.3 (s), 33.2 (d, $J_{C,F}$ = 22.9 Hz), 39.0 (d, $J_{C,F}$ = 21.8 Hz), 62.3 (s), 95.3 (d, $J_{C,F}$ = 190.1 Hz), 118.4 (s), 126.4 (s), 128.3 (s), 128.6 (s), 140.1 (s), 169.6 (s); ^{19}F NMR δ = −168.7 (tt, $J_{F,H}$ = 29.4, 12.4 Hz); MS *m/z* 263, 243. Anal. Calcd for $C_{15}H_{18}FNO_2$: C, 68.42; H, 6.89; N, 5.32. Found: C, 68.62; H, 6.73; N, 5.49.

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Supporting Information Available: ^{1}H, ^{13}C, and ^{19}F NMR spectra for new compounds (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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