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NUCLEOPHILIC SUBSTITUTION VERSUS ELECTRON TRANSFER: 1. ON THE MECHANISM OF ELECTROPHILIC FLUORINATIONS

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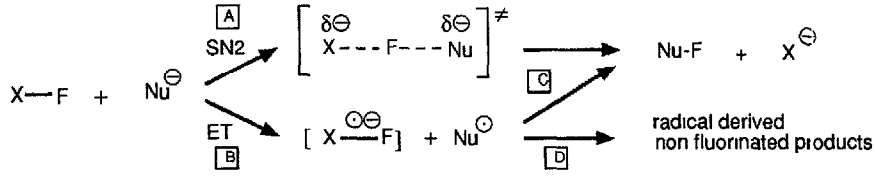
Summary: The reaction of a citronellic ester enolate with electrophilic fluorinating agents gives open chain fluorinated products only. The absence of rearranged fluorinated products in this system - a potential precursor to a 5-hexenyl-type radical clock - indicates that free radicals are not intermediates on the path to fluorinated products.

Electrophilic fluorinating agents have received increasing attention during the last few years, especially since stable and selective reagents have been made available.[1-4] There has been a considerable dispute about the possible mechanism of such an electrophilic fluorine transfer,[5,6] stimulated in part by the high enthalpy of formation of $F^{\oplus}$ in the gas phase (420 kcal/mol) and by the identification of radical products or intermediates, which have in general been taken as arguments for a two-step pathway where an electron transfer (ET) precedes a fluorine radical transfer. Based on the identification of the radical cation $NF_3^{\odot\oplus}$ in the reaction of NF_3 with F_2 in the presence of a strong Lewis acid, Christe[6] argues that nucleophilic attack at fluorine with heterolytic fission is unlikely in general. An SN_2 pathway in the reaction of CF_3OF with nucleophiles is questioned by DesMarteau[7] and Levy et al.[8] based on regioselectivities or reaction rates of the fluorination of alkenes. Umemoto suggests an electron transfer as the first step in fluorinations with N-fluoro-pyridinium salts.[9] Radicals have also been detected in the reactions of XeF_2,[10] CH_3COOF,[11] N-fluoro-perfluoro-piperidine[12] and others.[4]

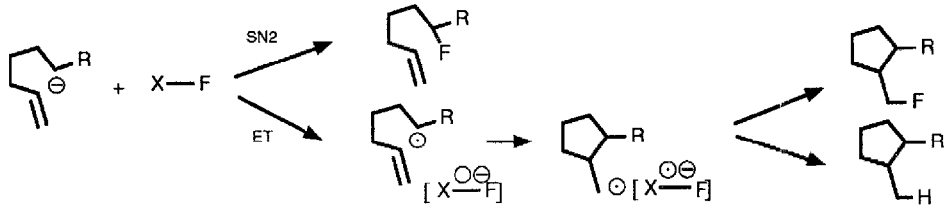
Scheme 1: Possible pathways in the reaction $Nu^{\ominus}$ + X-F:



All of these analyses suffer, however, from one major disadvantage: none allows one to ascertain whether the observed radical intermediates lie on the reaction path which leads to the fluorinated products or whether they are formed in a reaction competing with the fluorine transfer. Therefore a distinction between a direct nucleophilic attack at fluorine in a classical SN_2-type transition state (route A) and a two-step pathway where ET first gives a free radical $Nu^{\odot}$ which then, in a second step, leads to Nu-F (route B-C) has so far not been possible. The possibility that ET might lead exclusively to non-fluorinated, radical derived products (route B-D) has in general not been considered.[13] A better knowledge of the mechanism of such electrophilic fluorinations would however greatly facilitate the design of new reagents and the choice of optimal reaction conditions. One way to investigate this question would be to use a radical clock,[14] in this case for instance a carbanion containing a 5-hexenyl carbon chain which gives, after electron transfer to the fluorinating agent, a radical that cyclizes to a cyclopentylmethyl

radical (scheme 2). If a free radical $Nu^{\odot}$ is formed as an intermediate on the way to Nu-F, then rearranged fluorinated products should be obtained. If, however, a radical $Nu^{\odot}$ is formed, but does not lead to the fluorinated Nu-F, then isomerized but non-fluorinated products should be found. In this paper we wish to report our results on the fluorination of a nucleophile which is a potential precursor to a radical-clock-type 5-hexenyl structure with four readily available fluorinating agents.

Scheme 2:



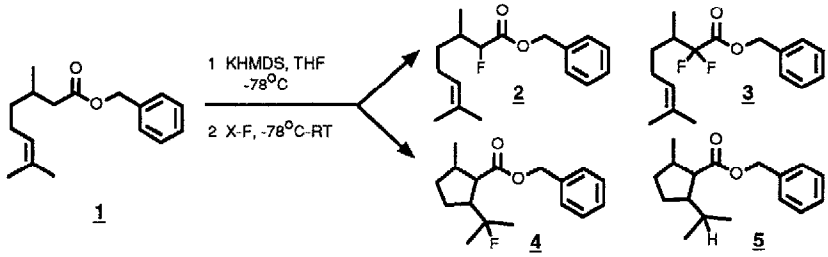
Since we have shown that reagents **6** and **7** react with enolates to give the corresponding α-fluoro-carbonyl compound in good yields,[1,2] the benzyl ester[15] **1** of citronellic acid is chosen both for its availability and its low volatility. In a standard procedure ester **1** is deprotonated by potassium hexamethyl disilazide (1.2 equiv, 1 h) at -78°C in THF and treated with the corresponding fluorinating agent (1.3 equiv). After stirring at low temperature for 1 h, the reaction mixture is warmed up to room temperature, quenched with 0.1 N HCl and analyzed by ^{19}F- and ^{1}H-NMR. The ^{19}F-NMR reveals that the α-fluorinated **2** and **3** are the only fluorinated products detectable in the reaction mixture.[16] By comparison with our recently described difluorinations,[3] we assume that **3** is formed after deprotonation in situ of **2** by excess base or unreacted enolate, thus leading to varying amounts of the starting ester **1**, which is found in the reaction mixture. No fluorine signal can be detected between -130 and -150 ppm (upfield from $CFCl_3$), the region where the signal for **4** would be expected.[17] With reagents **6**-**8**, no other product can be detected. With xenon difluoride, however, in addition to **2** and **3**, 10% of **5** are found, but again no **4** can be detected. The results are summarized in the table.

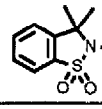
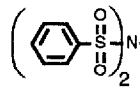
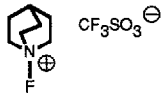
The following conclusions can be drawn: 1.) the absence of cyclic fluorinated **4** with all four reagents is a proof that free radicals with a half-life greater than the probes half-life are not intermediates on the pathway to the fluorinated products. If a radical were formed by oxidation of the enolate, it should cyclize, as shown independently by reduction of the α-bromo-citronellate with tributyl tin hydride.[18] 2.) The fact that 0.7-1.1 equivalents of fluorine are incorporated with reagents **6**-**8** without detectable amounts of isomeric products is an indication that no free radicals are formed at all in these reactions. 3.) Xenon difluoride is able to oxidize the enolate to the corresponding radical. The formation of **2** and **3**, together with the formation of isomerized, but not fluorinated **5** and the complete absence of **4** can be taken as an indication that the fluorinated and the non-fluorinated products are formed via different pathways: the latter with the occurrence of free radicals, the former not.

Although these results exclude free radical intermediates, it is important to point out that they can not exclude ET followed by fast in cage recombination: they merely fix a lower limit to the rate constant with which a radical/radical-anion pair - if ever it is formed - would have to react inside the solvent cage by a fluorine radical transfer in order to escape diffusion (i.e.≈$10^{10}s^{-1}$) and subsequent isomerization.[14,22] But the exact timing of such a process (bond breaking vs. bond formation) is a more general problem which is currently under debate for SN_2 reactions in general.[23-25] In this context, ET theory has been shown particularly efficient in establishing

unambiguous quantitative relationships between SN_2 and ET rate constants.[25] A detailed analysis of electrophilic fluorinations using ET theory, which confirms our interpretation, is described in the accompanying paper.[26]

Table: Reaction of a citronellic ester enolate with electrophilic fluorinating agents:



Fluorinating Agent X-F	Yields[a]				
	2	3	4	5	1
 6[2]	59 (43)	28 (18)	0	0	<10 (4)
 7[1]	21 (21)	31 (31)	0	0	20 (20)
 8[21]	64 (45)	23 (18)	0	0	13 (6)
XeF_2 9[10]	11 (10)	3 (3)	0	10 (6)	10 (10)

a. NMR yields as determined on the crude reaction mixture using benzotrifluoride as the internal standard. Non fluorinated compounds are calculated by comparing ^{19}F and ^{1}H-NMR spectra (Isolated yields in parentheses)

In summary, the reaction of a citronellic ester enolate with electrophilic fluorinating agents leads exclusively to the corresponding α-fluorinated ester derivatives. The complete absence of cyclic fluorinated products is a proof that the fluorination does not occur via free radical intermediates. The isolation of cyclic, but not fluorinated **5** in the reaction with xenon difluoride is an indication that ET is a competitive process which does not lead to fluorinated products. This should not be limited to the reagents shown in the table, but might as well be the case for other electrophilic fluorinating agents. As a consequence, a number of interpretations in the literature will have to be revised.

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References and notes

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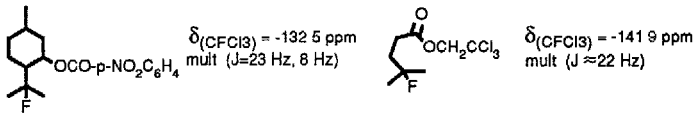
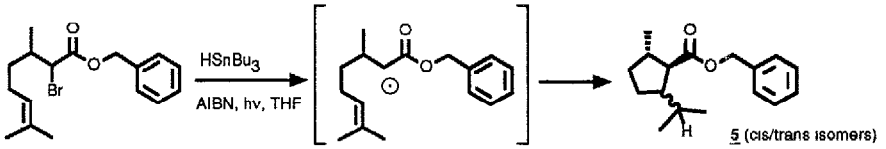
15. Prepared from racemic citronellic acid with oxalyl chloride, benzyl alcohol and pyridine.
16. **3**: two diastereomers: -198.385 ppm (dd, J=48.2 and 24.6 Hz) and -204.004 ppm (dd, J=49.3 and 30.3 Hz); **4**: -112.416 ppm (dd, J=253.2 and 15.1 Hz) and -113.845 ppm (dd, J=253.2 and 15.5 Hz).
17. Compare to:[20]



18. Reacting the α-bromo-citronellic ester, obtained by bromination with N-bromo-succinimide, with tributyl tin hydride/AIBN under irradiation (medium pressure Hg lamp) in THF at -78°C and 0°C gives **5** as a mixture of two isomers in 97% (cis/trans=73:27) and 87% yield (cis/trans=63:37), respectively.[19]



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22. We have avoided so far a discussion about the nature of the species - written formally as $X\text{-}F^{\odot\ominus}$ - which is formed via ET. In analogy to what Savéant has shown for alkyl halides, ET to X-F might well be a dissociative process[23] in which fluorine is lost as fluoride anion (e.g. $X\text{-}F + e^{\ominus} \rightarrow X^{\odot} + F^{\ominus}$) and will thus not end up in fluorinated products. This would obviously be the origin of a competitive pathway.
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