NUCLEOPHILIC SUBSTITUTION VERSUS ELECTRON TRANSFER; 2. SN₂ AT FLUORINE AND ELECTRON TRANSFER ARE COMPETING AND DIFFERENT PATHWAYS IN ELECTROPHILIC FLUORINATIONS

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Summary: A comparison between the observed rate constants of electrophilic fluorinations and the calculated rates for electron transfer gives for the first time kinetic proof that nucleophilic attack at fluorine has to occur in order to explain the high reaction rates. The low yields of fluorinated products under conditions where ET becomes important are an indication that SN_2 and ET are competing and different pathways.

Electron transfer (ET) theory is gaining increasing importance as a tool to rationalize or predict chemical reactivity.^{1,2} The mechanism of nucleophilic substitution reactions, in particular, in connection to ET and the question whether SN_2 and ET are competing processes or the two extremes of a common mechanism is currently under extensive investigation.³ Electrophilic fluorination reactions have so far escaped a quantitative and unambiguous analysis and little has been known about the mechanism of the fluorine transfer.⁴ We have shown recently that the enolate of a cutronellic ester - a potential precursor to a 5-hexenyl-type radical clock - reacts with electrophilic fluorinating agents to give exclusively open-chain α -fluorinated products.⁴ This led us to exclude free radicals as intermediates on the way to the fluorinated products. The characterization of an isomerized, but not fluorinated ester indicated that ET could be the source of secondary products, but we were unable to exclude a two-step ET route as a pathway to Nu-F with a fast in cage recombination of the radicals prior to diffusion. In this paper we wish to report evidence that *direct nucleophilic attack at fluorine is the only pathway which can account for the observed rate constants and that under certain conditions ET is a competitive and different pathway in the reaction of a variety of nucleophiles with N-fluoro-sultam <u>1</u>.*

Scheme 1:

$$R^{1}R^{2}N-F + Nu^{\Theta} \underbrace{\begin{bmatrix} R^{1}R^{2}N-F-Nu \\ K_{SN2} \end{bmatrix}^{\neq}}_{B} R^{1}R^{2}N-F + Nu^{\Theta}} \underbrace{\begin{bmatrix} R^{1}R^{2}N^{\Theta} \\ R^{1}R^{2}N-F \\ R^{1}R^{2}N-F \\ Nu^{\Theta} \end{bmatrix}}_{P} \underbrace{\begin{bmatrix} R^{1}R^{2}N^{\Theta} \\ R^{1}R^{2}N^{\Theta} \\ Nu^{\Theta} \end{bmatrix}}_{R^{1}R^{2}N^{\Theta}} radical derived products}$$

If one considers the reaction of a nucleophile with an electrophilic fluorinating agent containing a nitrogen-fluorine bond, two different pathways to Nu-F are concervable (scheme 1): a.) nucleophilic attack at fluorine leading to Nu-F via a an SN₂-type transition state (route A), and b.) ET from the nucleophile to R^1R^2NF to give Nu^{\odot} and a reduced derivative of the fluorinating agent. If a radical/radical-anion pair is formed, it will have to react via a very fast fluorine radical transfer inside the solvent cage to give Nu-F (route B-C) since the highly unstable radical-anion is likely to dissociate - possibly during ET (dissociative ET)⁵ - with loss of the fluoride anion to give radical derived products which do not contain fluorine (route B-D). A way to distinguish between nucleophilic attack at fluorine (route A) and an electron transfer pathway (route B-C) as possible

pathways to the fluorinated products is to compare the measured rate constant of a fluorination reaction k_{obs} to the rate constant for electron transfer k_{ET} , which can be calculated according to equation (1):⁶

$$k_{\text{ET}}(\text{M}^{-1}\text{s}^{-1}) = Z \times e^{-\Delta G^{\#}}$$
 equation (1)

 ΔG^{\neq} is the activation energy for the ET step between a donor (D) and an acceptor (A) and can be calculated using the quadratic activation energy-driving force relationships⁷ developed by Marcus⁸ for outer-sphere ET or Saveant⁵ for dissociative ET. ΔG^{\neq} is a function of the redox potentials (E^o) of the two reaction partners and the so-called reorganization energy λ of the ET step, which is half the sum of the reorganization energies of the two reaction partners.^{1,7} One problem associated with this formalism is the determination of the redox potentials which have to be used in the calculation of ΔG^{\neq} : since, electrochemically, the N-fluoro-sultam 1 is reduced irreversibly (E1/2= -1.21 V versus SCE (CH3CN, nBu4NClO4, glassy carbon electrode),9 it must be assumed that the measured half-wave potential reflects a considerable overpotential which is associated with the reductive cleavage of the N-F bond in analogy to the reduction of alkyl halides.⁵ The E^o value used in this work is based on the kinetics of the reaction of 1 with tetramethyl p-phenylene diamine (TMPDA),¹ which does not lead to a fluorination but gives instead the dark-blue radical cation at a rate constant k_{obs} =1.3×10⁻³ M ¹s⁻¹ (CH₃CN, 22°C) Since rigorous experimental parameters for N-F compounds are still lacking, we made the assumption that λ_{NF} would be high and comparable to the only nitrogen-halogen derivative studied in detail so far, i.e. N-bromo-succinimide^{1a} (λ =72 kcal/mol). With a λ_{NF} of 70 kcal/mol, equalling k_{ET} to k_{obs} for this reaction, equation (1) with Z=3x10¹¹ M⁻¹s⁻¹ allows one to calculate an E°_{NF} of -0.67 V vs. SCE. These two parameters have been used to calculate the rate constants kET in the table. The choice of a significantly lower resp. higher value for $\lambda_{\rm NF}$ (e.g. 50 resp. 90 kcal/mol) does only lead to minor changes in E^o_{NF} (-0.77 resp. -0.52 V) and the two extreme sets of parameters give only very small differences on the calculated rate constants k_{ET}. The required parameters for the nucleophiles are taken from literature or are estimations based on comparable compounds.

The experimental rate constants (k_{obs}) of representative reactions are determined by following the reaction of the corresponding nucleophiles with the fluorinating agent (both at equal concentration, between 0.05 and 0.3 M solutions) and by quenching the reaction mixture after various time periods with 0.1 N HCl or saturated aqueous ammonum chloride.¹⁰ Plotting 1/[Nu] or 1/[1] versus time gives straight lines with a slope equal to the rate constant.¹¹ The yields of isolated fluorinated products after warming up the reaction mixture to room temperature and quenching as above are reported in the table. In some cases products derived from radical intermediates are obtained; their yields are indicated in parentheses (see table).

The following conclusions can be drawn from the table:

1. The ratio k_{obs}/k_{ET} reveals that the observed rate constants for the fluorinations of enolates <u>3</u> and <u>4</u> are $\geq 3.3 \times 10^{11}$ resp. $\geq 3.8 \times 10^{7}$ times faster than ET is predicted to occur under these conditions. We take these high ratios as the first evidence that SN₂ at fluorine has to occur. Electron transfer alone would be too slow by several orders of magnitude to explain the observed reaction rates.

2. The ratio k_{obs}/k_{ET} becomes smaller for organometallic nucleophiles $\underline{5}$ and $\underline{6}$. This does not mean that the fluorination is shifting towards an ET mechanism: the fact that the yield of fluorinated product decreases as the possibility of ET increases is in our view an indication that ET is becoming a competing reaction which does not lead to fluorinated products. This confirms our observations with a radical clock⁴ and can be rationalized by a dissociative ET from the nucleophile to the fluorinating agent, a process in which fluorune is lost as fluoride annon. Preliminary experiments confirm such a dissociative pathway in the electrochemical reduction of $\underline{1}$.¹²

This means that $\lambda_{\rm NF}$ is essentially determined by the bond dissociation energy as shown by Savéant.^{5,13} 3. The oxidation potential of the nucleophile allows one to estimate roughly whether a reaction is likely to occur: nucleophiles with high E° do not react with $\underline{1}$, even at higher temperature. This is not only the case for silvl enol ether $\underline{2}$ (E^o= +1.6 V), but also for aromatic nucleophiles such as anisole (E^o= 1.3 V) or benzene (E^o= 2.79 V).¹

Nu-F

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Nu.		E ⁰ Nu	λ _{NU}	Solvent t ^o C	k _{obs} M⁻¹s⁻¹	k _{ET} M⁻¹s⁻¹	k _{obs} /k _{ET}	Nu-F(%)
OSiMe ₃	<u>2</u> ¹⁴	+1.6	20	сі(сн ₂) ₂ сі 60 ⁰	<< 10 ⁻⁶ (a)	6.3x10 ⁻²⁴	<1.6x10 ¹⁷	No reaction
Me → COOEt K⊕ COOEt	<u>3</u> 15	+0.34	60	Et ₂ O 0 ⁰	≥8 0x10 ⁻²	2.4x10 ⁻¹³	≥3 3x10 ¹¹	94
CH	ĸ⊕ ³ <u>4</u> ¹⁶	-0 4	50	THF -78 ⁰	≥3.2x10 ⁻²	8.3x10 ⁻¹⁰	≥3.8x10 ⁷	80 ^b
	<u>5</u> ¹⁷	-0.34	30	THF -75 ⁰	1 9x10 ⁻²	1.2x10 ⁻⁷	1 6x10 ⁵	72 ^b
MgBr	<u>6</u> 18	-0.24	70	THF/Et ₂ O 0 ⁰	6 8x10 ⁻²	1 4x10 ⁻⁷	4.8x10 ³	17 (ET.74%) ^C
Me ₂ N	^{Me} 2 <u>7</u> 1	0 01	10	CH ₃ CN 22 ⁰	1 3x10 ⁻³	1 3x10 ⁻³	1	0 (ET≈100%) ^d

Table: Rate constants of the reactions of 1 with nucleophiles

a. Reaction too slow to be measured

No other reaction products could be isolated

c 62% naphthalene and 12% 2-(1-naphthyl)-tetrahydrofuran were isolated d. The dark-blue radical-cation TMPDA^{OO}was obtained No fluorinated TMPDA derivatives could be characterized

To summarize, these results show for the first time that SN₂ at fluorine occurs. There are no reasons why such an SN_2 pathway should be limited to N-fluoro-sultam <u>1</u> and we propose that SN_2 at fluorine is a general pathway through which fluorine can be transferred to a nucleophile in electrophilic fluorinations. Therefore the radicals which are observed in a number of fluorination reactions do probably not lie on the reaction path which leads to the fluorinated products, but are formed in a competing ET reaction. To what extend such an ET route will compete with the SN₂ reaction will certainly depend in part on the redox potentials and the reorganization energies of the reaction partners, but a more detailed analysis will have to be undertaken. The extension of these results to other electrophilic fluorinations should allow to adjust nucleophiles and fluorinating agents according to their redox potentials and thus permit, for the first time, the choice of optimal reaction conditions. In a more general context, we think that electrophilic fluorinating agents represent an almost ideal tool for the investigation of the SN₂ reaction in general and its relation to ET in particular, since a clear distinction exists between SN₂, which leads to fluorinated products, and ET, which does not.19

Acknowledgement: We thank Profs. L. Eberson and J.M. Savéant for helpful discussions concerning ET theory.

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- 7. In equation 1:

$$\Delta \mathbf{G}^{\neq} = \frac{\lambda}{4} \left[1 + \frac{\Delta \mathbf{G}^{0}}{\lambda} \right]^{2}$$

$$\Delta \mathbf{G}^{0} = \Delta \mathbf{G}^{0} - (Z_{A} \cdot Z_{D} - 1) e^{2} f / D r_{12}^{\text{ref } 22}$$

$$\Delta \mathbf{G}^{0} = -23 \ 06 \ (\mathbf{E}^{\circ}_{\text{red } \langle A \rangle} - \mathbf{E}^{\circ}_{\text{ox } \langle D \rangle} (\text{Volt})) \text{ in kcal/mol}$$

$$\lambda = \frac{1}{2} \left[\lambda_{D} + \lambda_{A} \right] \text{ in kcal/mol}$$

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- 13. An average value of $D^{o}_{N,F}=60$ kcal/mol, together with a small solvent reorganization energy contribution, can rationalize a posteriori our choice of λ .
- 14. E^{o} taken from E^{o} of 1-ethoxy-cyclohexene;²⁰ λ assumed slightly higher than in tetracyanoethylene.¹
- 15. E^o as reported;^{1c} λ approximated as intermediate between an enolate (57 kcal/mol)^{1c} and the delocalized cyclopentadienyl anion (66 kcal/mol).¹
- 16. E° slightly more negative than in propiophenone enolate (-1.31 V);²¹ λ comparable to the value for pinacolone enolate (57 kcal/mol)^{1c}
- 17. E^o assumed comparable to Ph-Li;¹ λ as for alkyl-Li.¹
- 18. E^{o} assumed comparable to Ph-MgBr;¹ λ as for alkyl-MgBr.¹
- 19. In contrast to this, ET from Nu $^{\ominus}$ to R-X in alkylation reactions with alkyl halides gives, via dissociative ET, Nu $^{\bigcirc}$ and R $^{\bigcirc}$ which can still combine to give R-Nu. A clear distinction between the SN₂ and ET pathways to R-Nu is therefore not possible.
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(Received in Germany 10 March 1991)