Journal of Fluorine Chemistry, *59* (1992) 157–162

Preliminary Note

On the relative power of electrophilic fluorinating reagents of the N–F class*

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(Received March 9, 1992; accepted May 10, 1992)

Abstract

Electrochemical measurements have been employed as a measure of the relative chemical reactivity of a series of N–F class electrophilic fluorinating reagents. A correlation has been found between the potential for the first one-electron reduction of the reagents and their observed reactivity in synthetic fluorination reactions. Comparative electrochemical data in acetonitrile and dimethylformamide are reported.

Electrophilic fluorinating reagents are of great importance in the synthesis of biologically active molecules and have been the subject of intense study [1, 2]. There is great interest in developing improved (easily handled, storable, transportable, commercially viable) reagents that retain strong fluorinating reactivity. With the modest number of reagents that are now known, it was felt that an ordering of reactivity on a thermodynamic scale would be of value. We report here the results of electrochemical measurements on the reduction reaction of a series of electrophilic fluorinating agents.

The fluorination reagents studied are listed in Table 1. Reagents **1** [3] and **5** [4] were prepared as described previously. Compounds **4** [5] (Allied Signal), **6** and **7** [6] (Aldrich), **9** and **10** [7] (Kali Chemie), were obtained from the indicated commercial sources. A sample of **8** [8] was received from F. A. Davis (Drexel University). The new N–F reagents **2** and **3** were prepared by direct fluorination at −35 °C of a CH_3CN solution of the corresponding *N*-mono-substituted salt precursors [9, 10].

Cyclic voltammetry (CV) studies were carried out with 0.001 to 0.005 M solutions of reagents **1** through **10** in dry acetonitrile or DMF (Aldrich) using 0.10 M tetrabutylammonium tetrafluoroborate or triflate (Southwest

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*Presented in part at the 13th Int. Symp. Fluorine Chem., Bochum, Germany, Sept. 1991.
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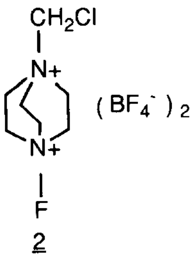
0022-1139/92/$5.00

TABLE 1

Peak reduction potentials of selected electrophilic fluorinating reagents

Reagent		$E_{\mathrm{p,\ reduction}}$ in acetonitrile (V vs. SCE)	$E_{\mathrm{p,\ reduction}}$ in DMF (V vs. SCE)
N-fluoro-bis[trifluoromethylsulfonyl]imide[a]	**(1)**	+0.18	
1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane ditetrafluoroborate	**(2)**	−0.04	−0.06
1-Fluoro-4-methyl-1,4-diazoniabicyclo[2.2.2]octane ditriflate	**(3)**	−0.09	−0.06
N-Fluoropyridinium pyridine heptafluorodiborate	**(4)**	−0.34	
N-Fluoroquinuclidinium triflate	**(5)**	−0.37	−0.56
N-Fluoropyridinium triflate	**(6)**	−0.47	−0.63
N-Fluorocollidine triflate	**(7)**	−0.73	
N-Fluoro-benzenesulfonimide	**(8)**	−0.78	
N-Methyl-*N*-fluoro-*p*-toluenesulfonamide	**(9)**	−2.10	
N-Propyl-*N*-fluoro-p-toluenesulfonamide	**(10)**	−2.20	

[a] Data taken without added electrolyte.



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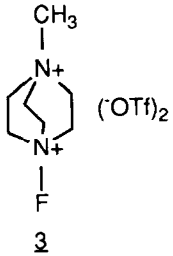

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Analytical and Fluka, respectively, recrystallized from ethyl acetate and dried *in vacuo* at 60 °C) as a supporting electrolyte. There was apparently enough residual water in these salts to react with **1**; hence this reagent was analyzed in the absence of supporting electrolyte. Potentiostatic correction for solution resistance was used in all experiments but was especially critical in this case. Experiments were undertaken with a BioAnalytical Systems 100B potentiostat. A freshly polished 3-mm diameter platinum disk electrode was used for all reagents; **2** and **6** were also studied with gold and glassy carbon electrodes. All data were referenced to the aqueous saturated calomel electrode (SCE).

In the CV experiments, a single chemically irreversible reduction wave was observed for each reagent. An example for **2** is shown in Fig. 1. Peak reduction potentials (E_p) were determined under identical conditions for all reagents except for reagent **1**, which was obtained in the absence of supporting electrolyte. The E_p value for **1** is therefore a rough value, since electrolytic diffusion may have shifted the wave. Results are listed in Table 1. Values were reproducible to within ±0.05 V for each reagent. Values of E_p shifted with different electrode materials; at gold electrodes E_p values were more positive, and at the glassy carbon electrode values were shifted negative. Data are reported at platinum due to better reproducibility at this surface. Chronocoulometry experiments were carried out to determine the number

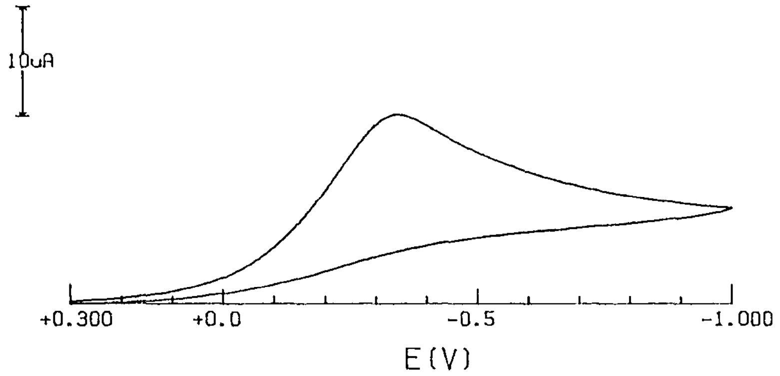
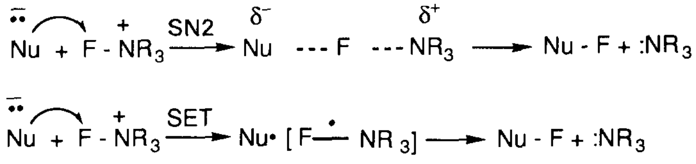


Fig. 1. Cyclic voltammogram of compound **2** at platinum in acetonitrile, with 0.10 M tetrabutylammonium tetrafluoroborate. Scan rate, 0.10 V s^{-1}.

of electrons passed in the reduction waves. A 0.6 V potential step was used, with data analysis undertaken by established methods [11]. The diffusion coefficient of benzophenone was used in the calculations. All waves were found to be one-electron reductions (calculated number of electrons was 1.0 ± 0.3 for the series of reagents).

A comparison of the redox properties and hence the reactivity of the fluorinating reagents is best made on the basis of thermodynamic standard potential ($E°$) values. However, since these were not experimentally accessible, a qualitative comparison based on differences in E_p values was made. The fluorinating reagents listed in Table 1 behave electrochemically as one-electron oxidants, of decreasing oxidizing power (more negative E_p) in Table 1 from reagent **1** to **10**. There appears to be a parallel ordering in decreasing chemical reactivity which is best illustrated by the reported reactions of the reagent **2** with aromatics. *N*-fluorobis[trifluoromethylsulfonyl]imide, $(CF_3SO_2)_2NF$ (**1**) is the most reactive compound. It mono-fluorinates benzene at 22 °C (50% conversion in 18 h) and totally fluorinates anisole even more readily under the same conditions [3]. With reagents **2** and **3**, we have not observed the fluorination of benzene, but anisole is readily converted to a mixture of the 2-fluoro and 4-fluoro derivatives. For **2** there is a 72% conversion to the fluoroanisoles in 6 h at 40 °C. Reagent **3** is less reactive (reaction time of 13 h) [9]. There are no reports of **4** or **5** reacting with aromatics. The *N*-fluoropyridinium triflate reagent **6** fluorinates anisole under less mild conditions (72% conversion after 18 h at 120 °C) than **2** or **3** [6]. Reagent **8** apparently only reacts with the more activated aromatic, 1,3-dimethoxybenzene. The Barnette reagents, **9** and **10** which have more negative E_p values, can yield fluoroaromatics but apparently only by reaction with appropriate aromatic carbanion substrates [7].

The mechanism by which electrophilic reagents function to deliver 'F^+' to organic substrates has been the subject of much controversy [2]. Nucleophilic displacement (SN2) and single-electron transfer (SET) pathways have been proposed [6, 12–15] and are illustrated below for the 4° salt reagents:



In our electrochemical experiments, the reagent undergoes an SET reduction, presumably to a bound fluorine radical species, which then reacts chemically with adventitious substrates or is further reduced to fluoride. For both the nucleophilic displacement and SET pathways there is, in effect, a reduction of the electrophilic reagents. It is therefore reasonable to expect that the reactivity of reagents with a specific nucleophile might correlate qualitatively with their redox potentials, with the most oxidizing reagent (most positive E_p value in Table 1) having the greatest fluorinating power.

In contrast to the SET electrochemical results, most electrophilic reagents chemically undergo a two-electron reduction with I^- in aqueous systems. Reagent **2** in a 1:1 water:acetone solution oxidized I^- and Br^-, but not Cl^- to the elements according to the following stoichiometry, as determined by standard titration versus thiosulfate.

$$F\text{-}\overset{+}{N}R_3 + 2X^- \longrightarrow X_2 + F^- \quad (X = I, Br)$$

Since the thermodynamic potential, $E°$, for aqueous bromide oxidation is +0.846 V vs. SCE, it is clear that reagent **2** is a much stronger oxidizing agent than is indicated by its non-aqueous electrochemical E_p value of −0.04 V vs. SCE. The thermodynamic $E°$ values of **2** and of the other fluorinating reagents must thus be considerably more positive than the E_p values listed in Table 1.

In summary, electrochemical reduction data for electrophilic fluorination reagents are a useful guide to their relative chemical reactivity.

Acknowledgements

We are grateful to Dr R. E. Banks for helpful discussions and to Air Products and Chemicals Inc. for permission to publish this work.

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Note added in proof

Consistent with the above reactivity ordering, reagent **2** has now been shown to fluorinate toluene (80% conversion to 2- and 4-fluorotoluene, in 16 h, in CH_3CN at *c.* 80 °C) [16].