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PREPARATION OF ^{18}F-LABELLED N-FLUOROPYRIDINIUM TRIFLATE

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SUMMARY

N-Fluoropyridinium triflate was labelled with ^{18}F proceeding through N-trimethylsilylpyridinium triflate and [^{18}F]F_2 diluted to 1% in Ne. A typical experiment afforded this new fluorine-18 transfer reagent with up to 46% radiochemical yield. The specific activity of ^{18}F-labelled N-fluoropyridinium triflate was determined by iodometric titration to be in the range of $4 \cdot 10^{-8}$ mg/Bq (1.5 mg/mCi; $1.67 \cdot 10^{-4}$ Ci/μM).

Key Words: ^{18}F-Labelling, N-[^{18}F]Fluoropyridinium triflate, preparation, analysis, mass spectra.

INTRODUCTION

N-Fluoropyridinium compounds prepared by the reaction of pyridine/F_2 adducts with the salts of strong acids, with trimethylsilyl triflate or nonaflate, were first reported by Umemoto and Tomita in 1986 [1]. Meinert isolated a stable (below 0°C) N-fluoropyridinium fluoride [2], which has been shown to react with uracil and its nucleosides uridine and 2′-deoxyuridine yielding the 5-fluoro substituted antimetabolites [3].

N-Fluoropyridinium salts provoked our interest as potential ^{18}F-labelling reagents, especially as precursors for the selective transfer of fluorine-18 to carbon atoms of high electron density.

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N-[^{18}F]Fluoropyridinium triflate is suggested as the first member of a series of analogous N-fluoro-compounds which merit attention as easily prepared new fluorine-18 labelled precursors in radiopharmaceutical preparations. The addition of fluorine carrier was necessary but may not be crucial in some applications such as the preparation of fluorine-18 labelled chemotherapeutics.

EXPERIMENTAL

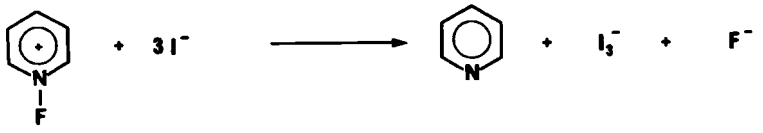
We obtained N-[^{18}F]fluoropyridinium triflate directly by cleavage of the N-Si bond in N-trimethylsilylpyridinium triflate with molecular [^{18}F]F_2. A typical reaction was carried out in CH_3CN at -42°C (CH_3CN/CO_2 bath).

N-Trimethylsilylpyridinium triflate. N-Trimethylsilylpyridinium triflate was prepared by reaction of equimolar amounts of trimethylsilyl triflate with pyridine. An inert, dry atmosphere was maintained during the reaction. Trimethylsilyl triflate (100 mM, 18.2 ml) was dissolved in 200 ml of dry diethyl ether. The solution was cooled to -10°C (ice/ethanol). Dried and freshly distilled pyridine (7.8 g dissolved in 100 ml of ether) was then added dropwise with vigorous stirring while keeping the temperature between -10 and -5°C. Pure N-trimethylsilylpyridinium triflate precipitated during the reaction. The product was separated by suction filtration and washed several times with 100 ml fractions of ether. The yield was quantitative (mp 215.5°C; recrystallized from CH_3CN/ether).

N-[^{18}F]Fluoropyridinium triflate. [^{18}F]F_2 was produced by the $^{20}Ne(d,\alpha)^{18}F$ reaction in neon, which contained 1% F_2 [6]. The ^{18}F yield produced from two successive irradiations of 30 min, each with a 10 μA beam, was approximately $2.96 \cdot 10^9$ Bq (80 mCi), and was obtained with $4 \cdot 10^{-4}$ M F_2. The radioactive gas mixture was bubbled through a cold (-42°C bath temperature) solution of $3 \cdot 10^{-4}$ M of trimethylsilylpyridinium triflate in dry CH_3CN at a rate of about 50 ml/min. The solvent was evaporated to complete dryness under reduced pressure and the residue was treated for a short time with a small portion (1 ml) of cold diethyl ether. The ether was immediately removed by inversed filtration using a Schlenk tube equipped with a frit. The remaining material was then recovered by backwashing the frit with 2 ml of CH_3CN leaving $1.37 \cdot 10^9$ Bq (37 mCi) of the labelled product. After decay of ^{18}F, the co-produced N-fluoropyridinium triflate was precipitated with diethylether from the CH_3CN solution. Fine white crystalls were obtained (55 mg; mp 184°C; lit. [1] 187°C) corresponding to a 75% yield with respect to N-trimethylsilylpyridinium triflate. This was in accord

with the radiochemical yield of 46% at the end of synthesis, assuming that the final precipitation of N-fluoropyridinium triflate was not completely quantitative.

Analysis of N-[^{18}F]fluoropyridinium triflate. The amount of reactive fluorine in N-[^{18}F]fluoropyridinium triflate, which is transferable to a nucleophilic carbon, was determined by iodometric titration with 10^{-2} N $Na_2S_2O_3$ solution based on the following sequence:



Accordingly 1 ml of 10^{-2} N $Na_2S_2O_3$ corresponded to 1.2358 mg of N-fluoropyridinium triflate. Various preparations were investigated not only when the radioactivity had decayed but also with a freshly prepared product. Unreacted fluorine and volatile material were removed by repeated pumping and flushing with argon. Each determination was made at 5 different concentrations with labelled and non-labelled N-fluoropyridinium triflate. It was found from these experiments that the mean amount of reactive fluorine was in the range of 88-94%. Using this data, the specific activity of N-[^{18}F]fluoropyridinium triflate was calculated to be $4 \cdot 10^{-8}$ mg/Bq = $1.67 \cdot 10^{-4}$ Ci/μM ($\varepsilon = \ln A_i/A^* = 16.1$, where A_i = specific activity of the perfect carrier free state, A^* = specific activity, which was measured for the sample [4]).

The identification of N-[^{18}F]fluoropyridinium triflate by conventional HPLC and TLC methods failed. ^{19}F-NMR and mass spectroscopy were therefore used to verify the chemical identity of the N-[^{18}F]fluoropyridinium triflate preparations. All the labelled samples from the above mentioned experiments contained sufficient fluorine carrier for performing the respective measurements and were compared with separately prepared N-flouropyridinium triflate. All data corresponded well to this reference material. ^{19}F-NMR spectroscopy was performed at 470.6 MHz on a Bruker AM-500 spectrometer. Samples were dissolved in CH_3CN in a standard 5 mm NMR tube. External shift referencing was made by immersing a 2 mm capillary containing C_6F_6 diluted in C_6D_6. The C_6F_6 signal appeared at -87.279 ppm relative to trifluoroacetic acid in D_2O (= 0 ppm) as calibrated previously. A relatively sharp unresolved signal was observed for the N-fluoropyridinium triflate at a large downfield shift of δ_F =

123.291 ppm. This signal appeared to arise from one fluorine nucleus compared to the three fluorine nuclei of the $CF_3SO_3^-$ group at δ_F = -2.925 ppm, as expected. No other fluorinated products were detected. The protons in N-fluoropyridinium triflate are much more deshielded than in pyridine itself. The spectrum (AA'BB'CX type), measured in CD_3CN at 500 MHz exhibited 3 multiplets with large second order effects, where $\delta_{H-2,H-6}$ = 9.18 ppm , $\delta_{H-3,H-5}$ = 8.225 ppm and δ_{H4} = 8.646 ppm respectively. Proton fluorine couplings could be estimated by decoupling experiments $^3J_{HF}$ = 15.023 Hz, $^4J_{HF}$ = 5.323 Hz, $^5J_{HF}$ = 1.83 Hz.

The usual mass spectrum showed the M^+-HF peak at m/e = 227 (high resolution 226.986346), which corresponded exactly to $[C_6H_4NO_3SF_3]^+$. This was in accord with the expected scheme of fragmentation for N-fluoropyridinium triflate. Secondary ion mass spectroscopy (SIMS, ionization with Cs^+; sample dissolved in dimethylformamide), quite unusual for such low molecular weight compounds, was indeed very well suited for the final characterization of N-fluoropyridinium triflate preparations [5]. The N-fluoropyridinium cation appeared as the base peak (100%) at m/e = 98 and not the pyridinium cation dominating the normal spectrum. Fluorine was lost from the fragment ion of mass 98 yielding the pyridinium cation at m/e + 1 = 80.12 mass units (75.61%) indicating clearly that the N-F bond is present (Fig. 1).

DISCUSSION

N-Fluoropyridinium triflate has been successfully labelled with ^{18}F with a relatively high yield. N-[^{18}F]fluoropyridinium triflate shows excellent properties as a new electrophilic labelling reagent which transfers fluorine-18 to an sp^2-carbon within a reasonable time and under very mild conditions. Current investigations - upon which we will report later - demonstrated, that Grignard compounds and related carbanions, and enolates react easily with N-[^{18}F]fluoropyridinium triflate to yield the corresponding ^{18}F-labelled products. The examples in Table 1 indicate the scope of this new labelling reagent.

N-[^{18}F]fluoropyridinium triflate is best prepared by cleavage of the N-Si$(CH_3)_3$ bond in trimethylsilylpyridinium triflate using $[^{18}F]F_2$.

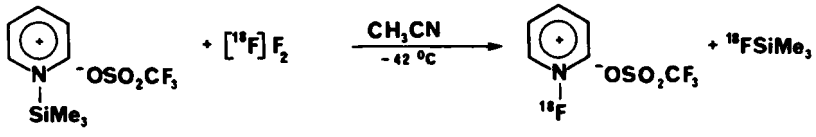
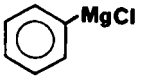
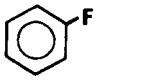
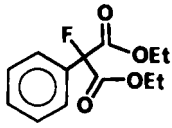
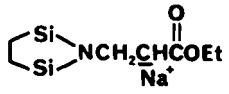
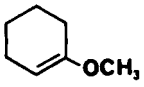
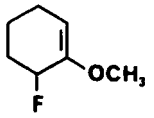


Table 1. Reactions of N-[^{18}F]fluoropyridinium triflate with various substrates[a] [7].

compound[b]	solvent	Reaction [°C]	[min]	Product	(yield) (%)[c]
	THF	5	10		(62)
$CH_3(CH_2)_6MgCl$	diethylether	5	15	$CH_3(CH_2)_6F$	(78)
CH_3Li	diethylether	-78		no reaction	
	THF	0	10		(58)*
	THF	25	60	$NH_2CH_2CHCOEt$ F	(23)*
	CH_2Cl_2	reflux	40		(67)

(a) Equimolar amounts of reactants; 0.07 mM N-fluoropyridinium triflate spiked with $1.85 \cdot 10^8$ Bq (5 mCi; 0.03 mM) of the labelled compound.
(b) Substrate was added to the N-fluoropyridinium triflate in the respective solvent.
(c) Determined either by HPLC or, when indicated by an asterix, by ^{19}F-NMR spectroscopy.

Other preparation methods as reported in [1] either failed under labelling conditions, gave a poor yield, or ended in an immediate decomposition with pyridyl-2-triflate as the final product. In order to avoid decomposition, the starting material should be kept absolutely free from pyridine. This was only possible using recrystallized trimethylsilylpyridinium triflate as the substrate. Labelling was done using up to $4 \cdot 10^{-4}$ M F_2 as carrier. This amount may be reduced to $5 \cdot 10^{-5}$ M F_2 but, at most, an equimolar amount of trimethylsilylpyridinium triflate should be applied. Even a slight excess of substrate was found to be impractical. Thus, the better preparations were obtained by keeping the trimetylsilylpyridinium triflate at a 0.75-0.9 equimolar ratio.

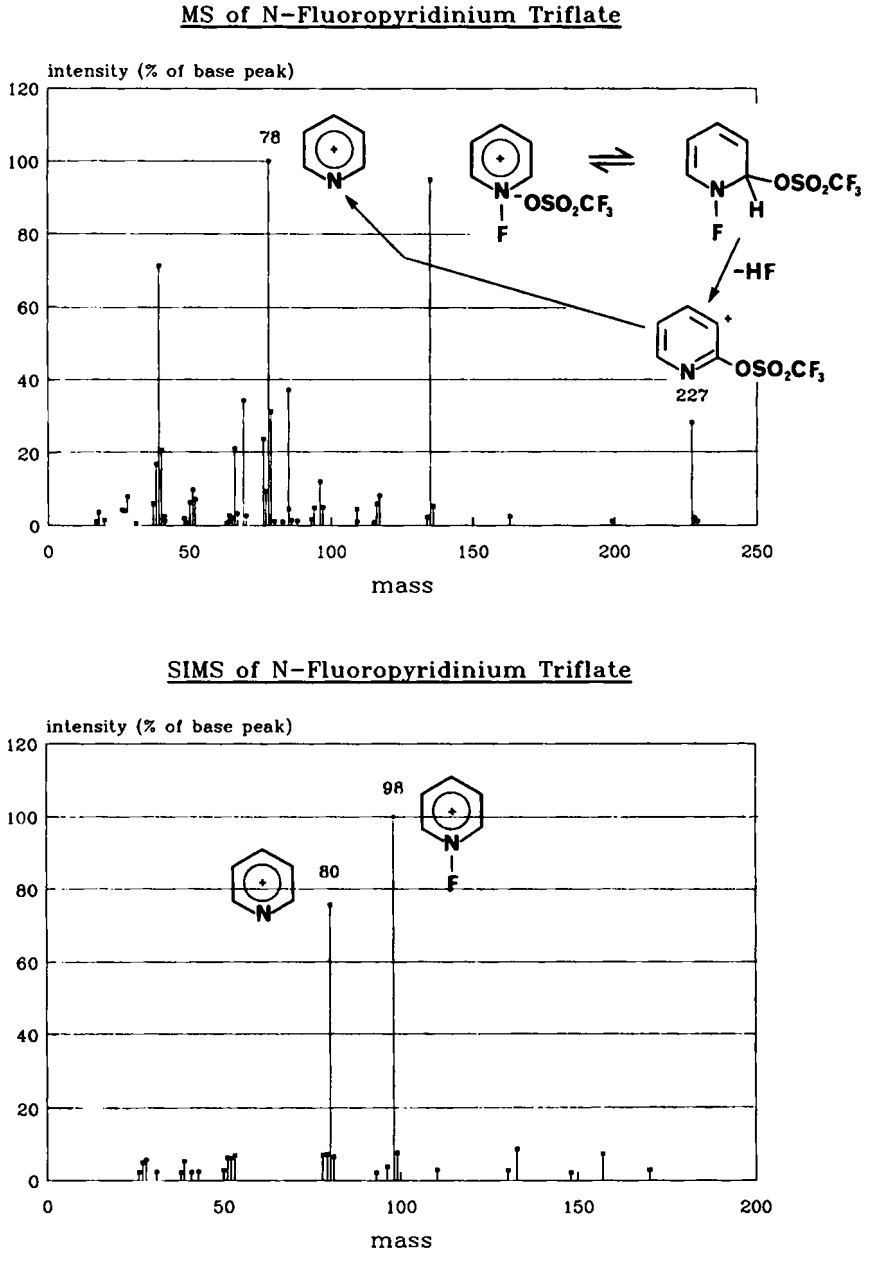


Figure 1. Mass spectra and scheme of fragmentation for N-fluoropyridinium triflate.

CONCLUSION

It has been suggested, that N-fluoro compounds can exhibit considerable reactivity in fluorinations of organic compounds. One of the first reports was published by Banks and Williamson and dealt with the fluorination of 2-nitropropane and malonic ester with undecafluoropiperidine [8]. These authors argued that the fluorine of the >N-F moiety is susceptible to attack by a highly polarisable nucleophile such as a carbanion. This rationale has received little attention, but describes the unique advantage of reagents having fluorine bound to a nitrogen atom of decreased electron density over fluorination using F_2. This objective led us to the preparation of N-[^{18}F]fluoropyridinium triflate as a useful electrophilic ^{18}F-labelling reagent with the potential of effecting selective mono-fluorination of organic substrates which have a highly polarisable sp^2 carbon.

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REFERENCES

[1] Umemoto T. and Tomita K. - Tetrahedron Lett. 27: 3271 (1986).

[2] Meinert H. - Z. Chem. 5: 64 (1965).

[3] Meinert H. and Czech D. - Z. Chem. 12: 293 (1972).

[4] Oberdorfer F. - Int. J. Appl. Radiat. Isot. 36: 329 (1985).

[5] Umemoto T. - Personal communication (1987).

[6] Casella V., Ido T. Wolf A. P., Fowler J. S., McGregor R. R. and Ruth T.J. - J. Nucl. Med. 21: 750 (1980).

[7] We have not examined the advantages of N-[^{18}F]fluoropyridinium triflate compared to other fluorinating reagents nor have we fully demonstrated the scope and limitations of its reactions with organic substrates. Such work is in progress.

[8] Banks R. E. and Williamson G. E. - Chem. Ind. 1864 (1964).