Electrochemical generation of electrophilic n.c.a. ^{18}F-fluorinating reagents impossible?

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Introduction

Fluorine-18 is the most widely used radionuclide in positron emission tomography (PET) due to its extraordinary decay properties [1]. Currently the radioorganic syntheses of no-carrier-added (n.c.a.) ^{18}F-labelled products are practically limited to nucleophilic procedures. This complicates or excludes n.c.a. syntheses of many putative radiotracers for PET and demands for n.c.a. electrophilic ^{18}F-labelling.

The unanswered question whether an electrochemical oxidation of n.c.a. [^{18}F]fluoride can lead to an electrophilic [^{18}F]fluorine analogue is therefore of major interest. Since in organic fluorochemistry N-F compounds are known as highly effective and selective electrophilic fluorinating agents [2], they were chosen to be synthesized with n.c.a. [^{18}F]fluoride.

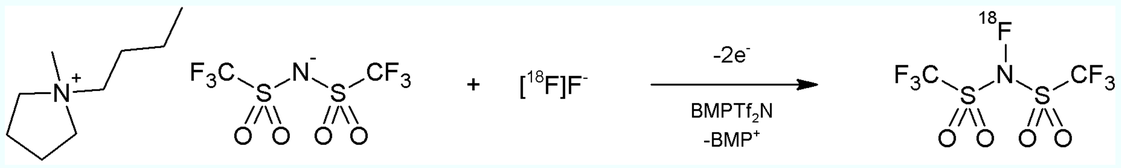


Fig. 1: *Electrosynthesis of N-[^{18}F]fluoro-bis(trifluoromethylsulfonyl)imide.*

Bis(trifluoromethylsulfonyl)imide (Tf_2N^-) appeared as a putative suitable precursor for electrosynthetic experiments with 1-butyl-1-methylpyrrolidinium (BMP^+) as counter ion. Due to its excellent physical and electrochemical properties this ionic liquid serves as conducting salt, solvent and starting material at once and offers a simplified performance by avoiding major side reactions.

Cyclic voltammetry

As the basis for assessing the electrochemical properties of $BMPTf_2N$ was analyzed by cyclic voltammetry (CV). This allows to investigate the oxidation behavior of Tf_2N^- and enables to evaluate an electrosynthetic procedure.

Cyclic voltammograms of $BMPTf_2N$ showed two succeeding oxidation steps. The first step may lead to a resonance-stabilized radical before further oxidation causes the generation of an unstable cation and finally the decomposition of the compound.

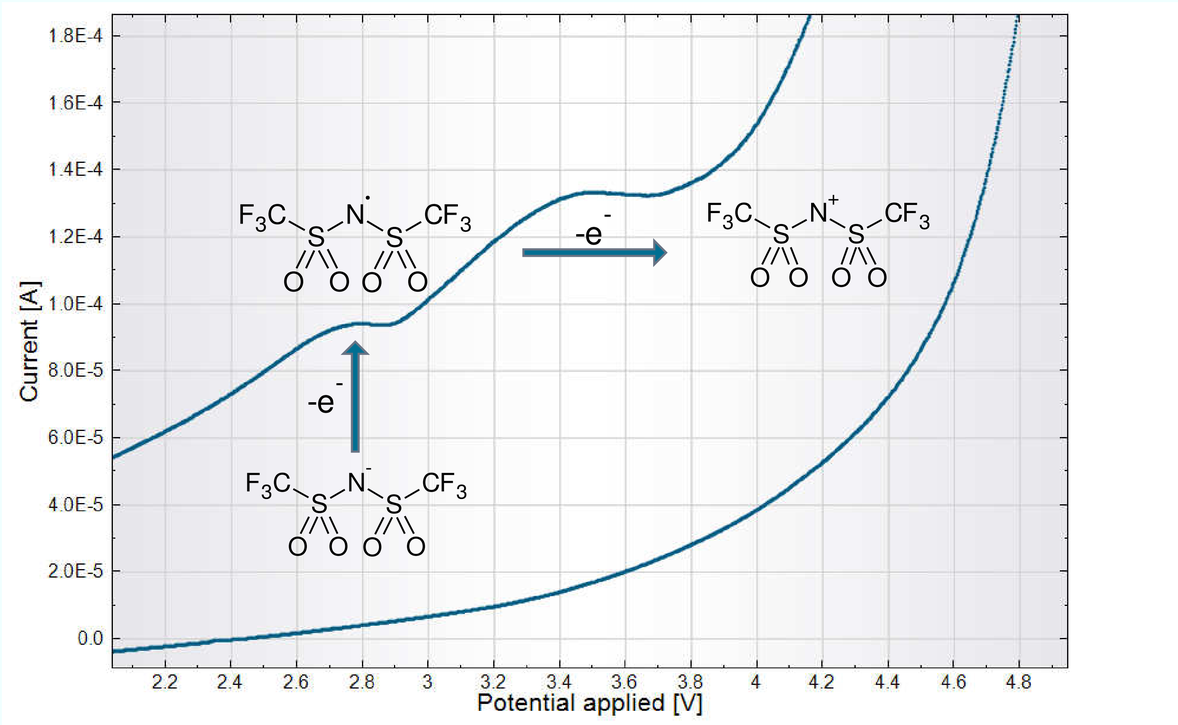


Fig. 2: *Cyclic voltammogram of pure $BMPTf_2N$ between -5 V and 5 V at 25 mV/s on platinum vs. Ag/AgCl.*

Electrosynthesis

Electrosynthetic experiments were carried out in an established electrochemical cell [3]. After intercalating [^{18}F]fluoride from the aqueous solution into glassy carbon at a tension of 20V the cell was dried with acetone and helium for further electro-synthesis with the ionic liquid.

The ionic liquid was added into the dried cell. Since formation of fluorine radicals from fluoride at potentials >4V was reported [4] intercalated fluoride and Tf_2N^- were expected to co-oxidize and recombine on the surface of the electrode at a tension of 6-8 V to form N-[^{18}F]fluoro-bis(trifluoromethylsulfonyl)imide.

Anisole as model was treated with the solution of the electrosynthesis at 80°C for 15 minutes to prove the presence of an electrophilic fluorinating reagent via formation of [^{18}F]fluoroanisole. Products were separated from their ionic contents, extracted with chloroform and analyzed by radio-HPLC.

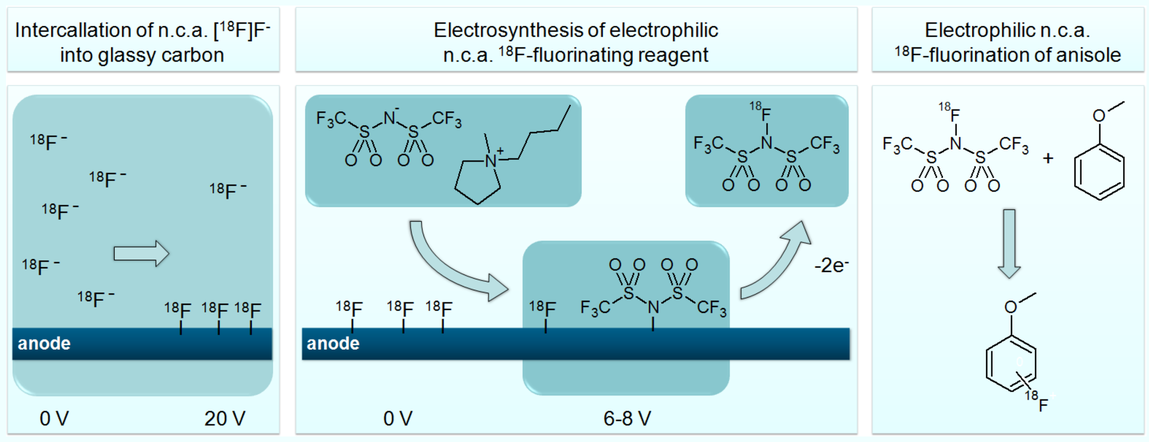


Fig. 3: *Electrosynthesis of N-[^{18}F]fluoro-bis(trifluoromethylsulfonyl)imide and monitoring concept.*

Radio-HPLC

Radio-HPLC was performed with a Luna PFP column in acetonitril - water (v/v 40:60). The reference compound Tf_2N-F is only accessible by direct fluorination with hazardous elemental fluorine [5] and was prepared in collaboration with adequately equipped external partners. As expected it showed decomposition in aqueous medium [6]. Decomposition products, however, could not be identified clearly and ^{18}F-labelled Tf_2N-F could not doubtlessly be attributed. Reaction with anisole after electrosynthesis led to formation of an n.c.a. ^{18}F-labelled product co-eluted with co-injected 4-fluoroanisole on RP-HPLC (Fig. 4 and 5).

Fig. 4: *Chromatogram of the radioactive product*

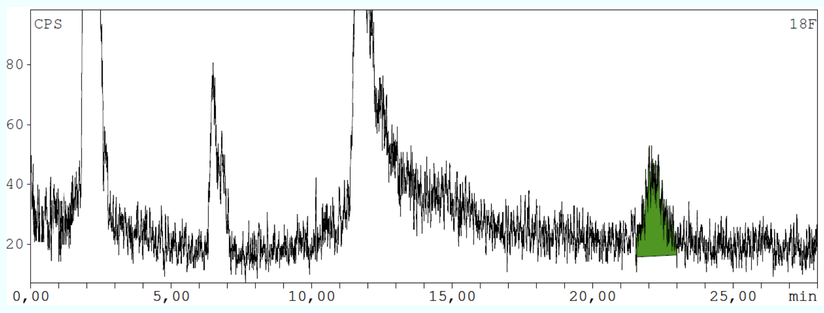
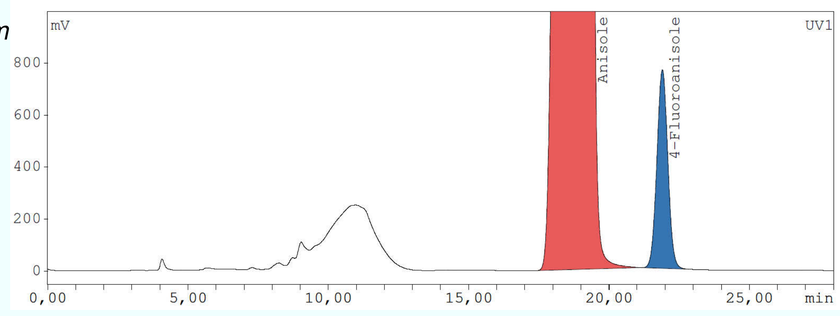


Fig. 5: *UV-Chromatogram with coinjected standard*



Unfortunately, this process exhibits low reproducibility and varying yields of labelled organic products. The mixture of product was always rather complex due to electrochemical side reactions. A reduced and subsequently ^{18}F-labelled derivative of the cation BMP^+ is assumed to be the major product.

Conclusion

Although unambiguous and direct identification of [^{18}F]Tf_2N-F by co-injection of [^{19}F]Tf_2N-F could not be achieved, the following conversion of the electrosynthetic intermediate with an activated arene led to an ^{18}F-labelled compound. Thus, production of an n.c.a. electrophilic ^{18}F-fluorinating reagent from [^{18}F]fluoride appears principally probable and further exploration of the electrochemical method warranted.

References

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Acknowledgements

The authors wish to thank Prof. Dr. H. Willner (Bergische Universität Wuppertal) and Prof. Dr. K. Seppelt (Freie Universität Berlin) for preparing the reference compound Tf_2N-F. This work was supported by BMBF MediWing, MoBi-Chip, FKZ 13N10272.