

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.

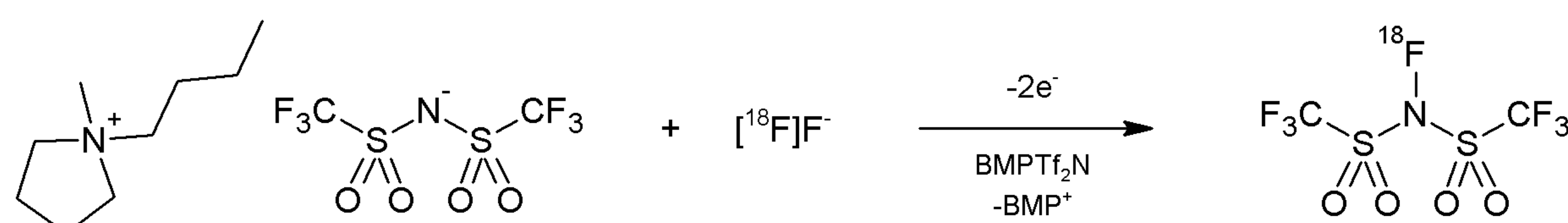


Fig. 1: Electrosynthesis of N-[^{18}F]fluoro-bis(trifluoromethylsulfonyl)imide.

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.

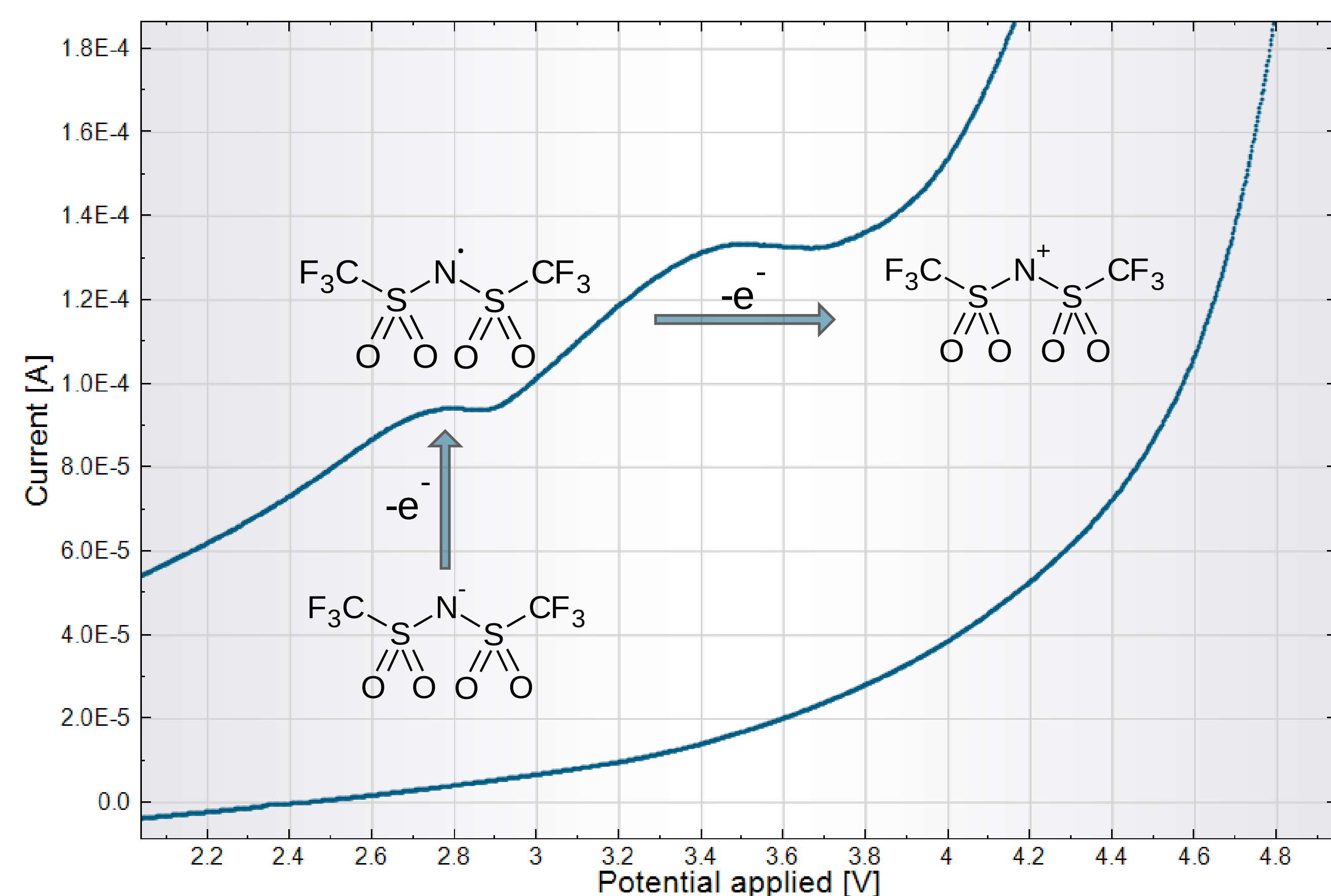


Fig. 2: Cyclic voltammogram of pure BMPTf_2N between -5 V and 5 V at 25 mV/s on platinum vs. Ag/AgCl.

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 electrosynthesis with the ionic liquid.

The ionic liquid was added into the dried cell. Since formation of fluorine radicals from fluoride at potentials $>4\text{V}$ 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.

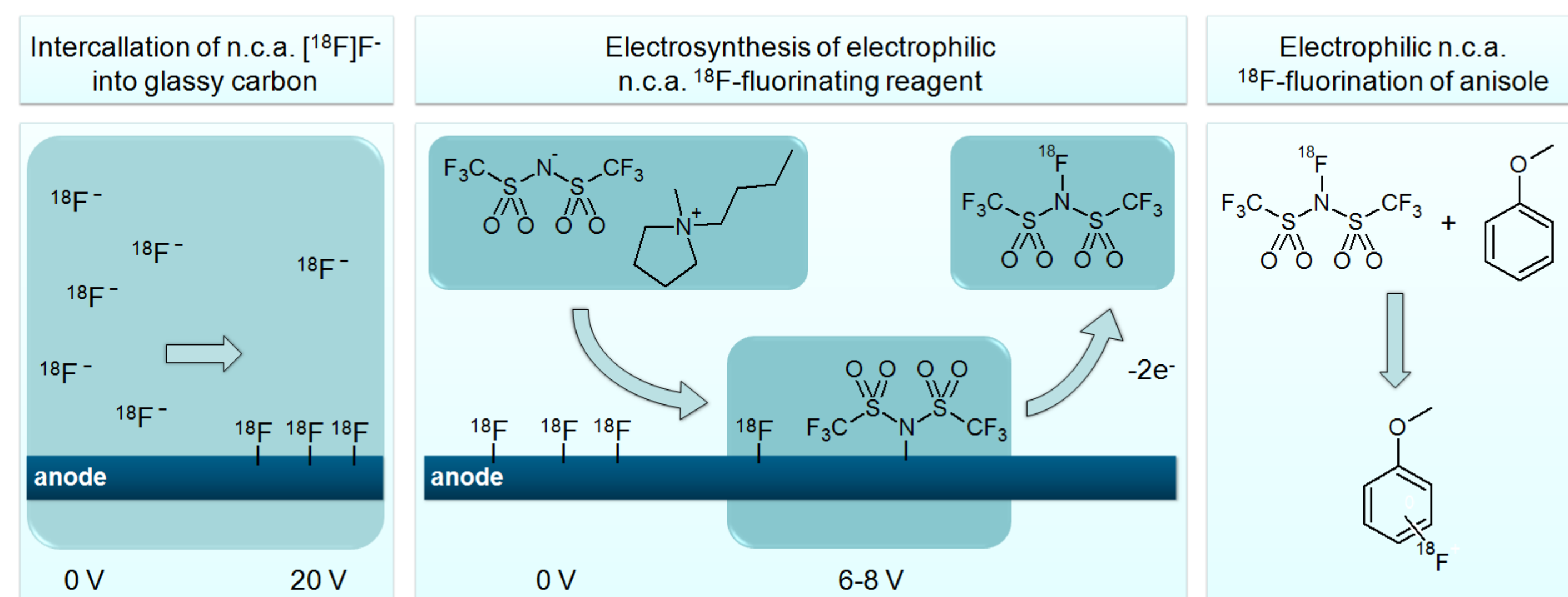


Fig. 3: Electrosynthesis of N-[^{18}F]fluoro-bis(trifluoromethylsulfonyl)imide and monitoring concept.

Radio-HPLC

Radio-HPLC was performed with a Luna PFP column in acetonitril - water (v/v 40:60). The reference compound $\text{Tf}_2\text{N-F}$ 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 $\text{Tf}_2\text{N-F}$ 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

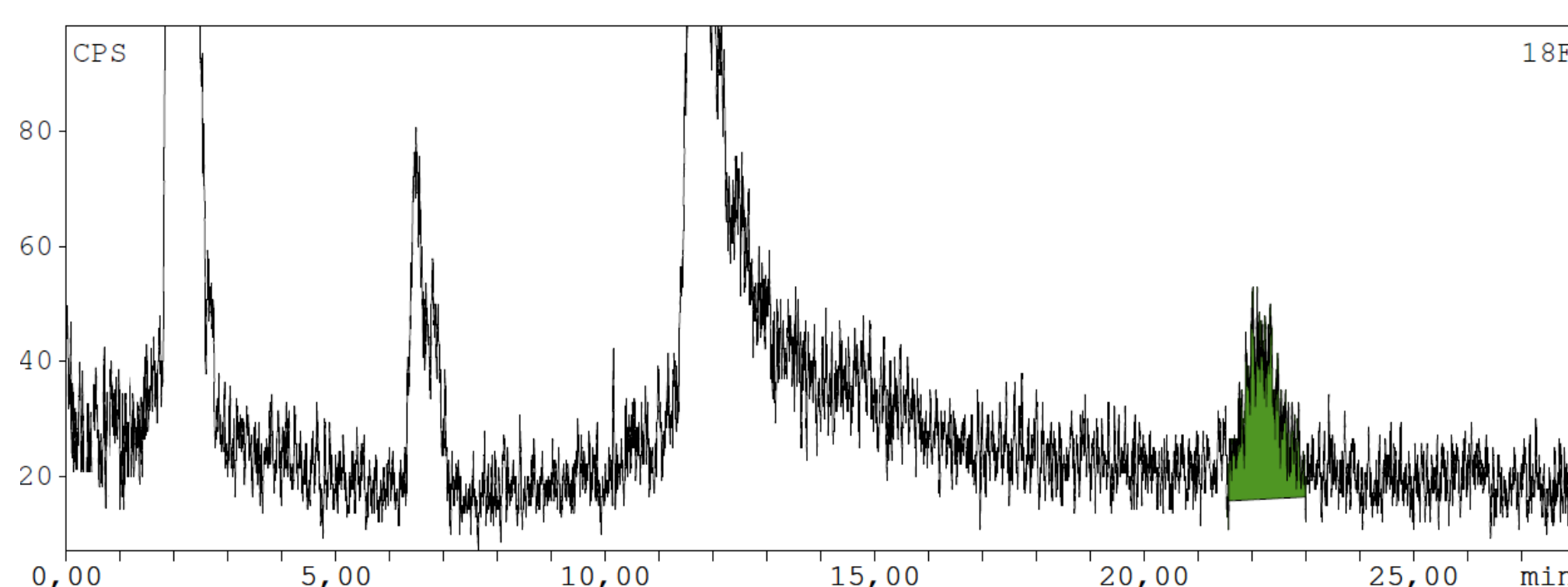
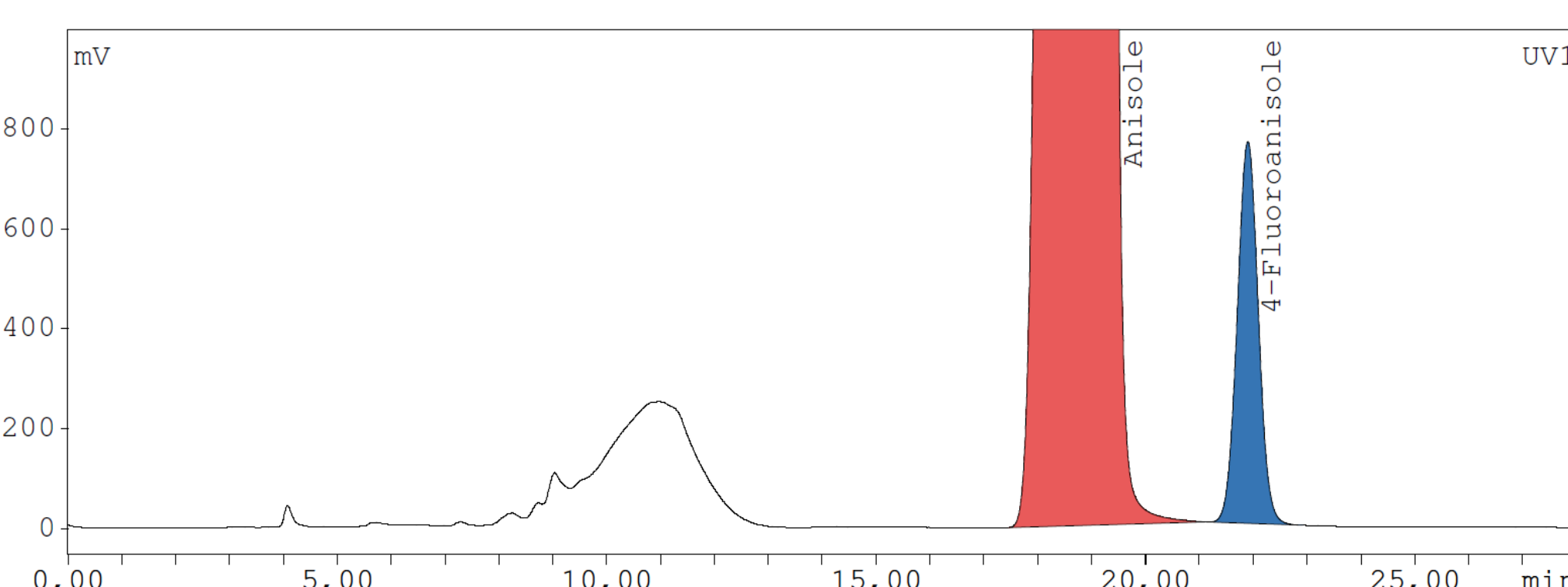


Fig. 5: UV-Chromatogram with co-injected standard



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 $^{18}\text{F}\text{Tf}_2\text{N-F}$ by co-injection of $^{19}\text{F}\text{Tf}_2\text{N-F}$ 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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