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Fluorine-18 chemistry in micro-reactors

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Abstract

Recent applications of micro-reactor (microfluidics) technology to radiofluorination chemistry within our laboratory are presented, based on use of either a simple T-shaped glass micro-reactor or a more advanced microfluidics instrument. The topics include reaction optimization and radioligand production, in particular the study of the radiofluorination of diaryliodonium salts, [^{18}F]fluoride ion exchange with xenon difluoride, esterification with [^{18}F]2-fluoroethyl tosylate, and the syntheses of [^{18}F]fallypride, [^{18}F]FBR and [^{18}F]SL702 from [^{18}F]fluoride ion.

Keywords

micro-reactor; microfluidics; fluorine-18; fluorination; PET

Introduction

It is increasingly recognized that micro-reactor (or microfluidics) technology can provide considerable advantages in radiochemistry with short-lived positron-emitting fluorine-18 ($t_{1/2}$ = 109.7 min).[1–5] Possible benefits to be derived from this technology include: (1) the use of smaller amounts of materials, especially non-radioactive precursor, which may be precious or difficult to obtain; (2) easier and more efficient radioactive product purification; (3) reduced radiation exposure to radiochemists by allowing more efficient radiosynthesis with less radioactivity; and (4) potential for scale-up and a high degree of automation.

We have used micro-reactor technology to optimize radiofluorination procedures and to produce radioligands reliably and reproducibly for molecular imaging in rodents with positron emission tomography (PET).[6–15] Other groups are also exploring microfluidics in PET chemistry.[16–20] This presentation tracks the growth of our research in this area covering the early development of a simple glass T-shaped micro-reactor to recent progress in several areas of fluorine-18 chemistry in a more advanced microfluidics instrument. Our examples showcase some of the various benefits of using microfluidics in fluorine-18 chemistry.

Results and Discussion

[^{18}F]3-(3-Pyridinyl)propionic-2′-fluoroethyl ester by esterification

As a proof-of-principle study, our first examples of radiosyntheses with a simple hydrodynamically-driven glass micro-reactor were those of ^{18}F-labeled esters (Figure 1).[6] 2-[^{18}F]Fluoroethyl esters are sometimes proposed as PET radiotracers.[21] Such esters may be prepared by reactions of carboxylic acid salts with [^{18}F]2-fluoroethyl tosylate (**4**). The synthesis of the model 2-fluoroethyl ester **3** in moderate yield from the reaction of **1** with 2-fluoroethyl tosylate (**2**) required warming the micro-reactor to 80 °C. Yields were dependent on reactant concentration and flow rate. At lower flow rate, a higher concentration of reactant **1** gave more ester **3**. The reaction could be performed with as low as 0.75 μg (5 nmol) of **1** in 10 μL of solution. Reactions of **1** with the labeling agent **4** at 80 °C, at infusion rates of 1 μL/

min, gave the corresponding ^{18}F-labeled ester **5** in 10% decay-corrected radiochemical yield (RCY). This device had however limited scope for control of temperature and reaction stoichiometry. Radiosyntheses were necessarily carried out at < 2 mCi level because the procedure was not highly automated.

[^{18}F]Fallypride by aliphatic nucleophilic substitution

A commercial coiled-tube micro-reactor (NanoTek; Advion) subsequently became a convenient platform for the study of ^{18}F-labeling with microfluidics in our laboratory. Radiosynthesis of the brain dopamine D_2 receptor radioligand, [^{18}F]fallypride (**7**)[22] from the tosylate-precursor **6** was rapidly optimized in this apparatus, with respect to the effects of precursor amount, reaction temperature, flow rate and [^{18}F]fluoride ion to precursor concentration ratio (Figure 2).[7] Each radiosynthesis used low amounts (20–40 μg; 39–77 nmol) of **6** and [^{18}F]fluoride ion/K 2.2.2 (0.5–2.5 mCi). RCYs of **7** (up to 88%) were reproducible. The low amounts of material used in each radiosynthesis allowed crude **7** to be purified rapidly on an analytical-size reversed phase HPLC column, preceding formulation for intravenous injection. Scale-up of the reaction was achieved by continuously infusing precursor and [^{18}F] fluoride ion solutions into the reactor to obtain **7** in much greater radioactivity (> 10 mCi). In this instrument, **7** was conveniently synthesized in small doses (0.3–1.5 mCi) for micro-PET studies in rodents.

[^{18}F]FBR by aliphatic nucleophilic substitution

[^{18}F]FBR (**9**) is an effective TSPO radioligand[8] which is now being used to study inflammatory conditions in human subjects.[23,24] We have shown that **9** can be produced in high RCY in the Advion microfluidic apparaus (Figure 3). Below 90 °C the RCY of **9** was lower in slightly wet acetonitrile than in anhydrous acetonitrile. However, this difference in RCYs disappeared when the reactor temperature was raised above 110 °C. RCYs reached 85% at 110 °C. Further temperature increase gave no improvement in RCY. The synthesis of the main metabolite (**11**) of **9** was also investigated in the microfluidic apparatus under similar conditions. The RCY was substantially lower than for **9** over the temperature range 30–150 °C. **9** and **11** were each prepared with this microfluidic apparatus in sufficient amounts for intravenous injection into rodents.

[^{18}F]SL702 synthesis by flow or stopped-flow mode

[^{18}F]SL702 (**14**), a new potential agonist radioligand for brain 5-HT_{1A} receptors, was successfully prepared in the Advion micro-reactor from a nitro-precursor (**12**) in a moderate RCY, similar to that obtained in a conventional microwave procedure (Route A, Figure 4).

Direct ^{18}F for ^{19}F exchange could be a useful route for labeling with fluorine-18 where the target radiotracer is not required to have high specific radioactivity. Although, high specific activity would be required for applications of [^{18}F]SL702, we wished to test the feasibility of performing ^{18}F for ^{19}F exchange for this type of structure. We first investigated the exchange reaction using a low concentration of **13** (Route B, Figure 4). When the flow rate was 5 μL/min, the RCY was about 4%. A ‘stopped flow’ method was introduced to allow longer reaction time in the micro-reactor. For 10 min reaction time the RCY increased to 11%. Further optimization for this and other targets is under investigation.

Syntheses of [^{18}F]fluoroarenes from diaryliodonium salts

Reactions of diaryliodonium salts with [^{18}F]fluoride ion are increasingly useful for the preparation of [^{18}F]fluoroarenes as radiotracers from NCA [^{18}F]fluoride ion.[25,26] The Advion micro-reactor apparatus has enabled us to study the RCYs, product selectivity, kinetics and energetics of these reactions in detail (Figure 5).[10–14] This platform was very convenient for

running multiple reactions rapidly under well-controlled conditions of reactant concentrations, reaction times and reaction temperatures. High RCYs of a vast array of NCA [^{18}F]fluoroarenes were obtained in short reaction times (< 7 min).

[^{18}F]XeF_2 by direct exchange

^{18}F-Labeled xenon difluoride ([^{18}F]XeF_2) is a potentially useful 'electrophilic' radiofluorination agent. We have previously prepared [^{18}F]xenon difluoride by exchange of xenon difluoride with [^{18}F]fluoride ion (as $^{18}F^{-}$-Cs^{+}/K 2.2.2) in dichloromethane at room temperature (Figure 6).[27] This process is attractive because of the availability of [^{18}F]fluoride ion in high activity and high specific activity from the ^{18}O(p,n)^{18}F reaction on [^{18}O]water. We exploited a microfluidic device to study further the influence of different conditions on this reaction.[15] [^{18}F]Xenon difluoride was obtained in high RCY (50%) by exchange of [^{18}F] fluoride ion with xenon difluoride in either dichloromethane or acetonitrile. In acetonitrile, the reaction may be performed in the presence of Cs^{+}, with or without K 2.2.2, or with K^{+}-K 2.2.2 at elevated temperature. The use of a micro-reactor allowed close monitoring of the progress of the exchange reaction with time and temperature. The procedure has potential to produce [^{18}F]xenon difluoride consistently and rapidly, and at a usefully high specific radioactivity.

Conclusions

Research in our laboratory and elsewhere has clearly demonstrated that micro-reactor or microfluidics technology is well suited to PET radiotracer development and production. Our results exemplify some of the potential advantages of this methodology for radiotracer development and synthesis. This technology should be increasingly amenable to greater sophistication to encompass entire radiosyntheses in a versatile high throughput manner and should play a more significant role in advancing PET radiochemistry.

Acknowledgments

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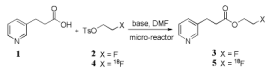

Figure 1.
Labeling of **5** with [^{18}F]2-fluoroethyl tosylate in a simple micro-reactor.

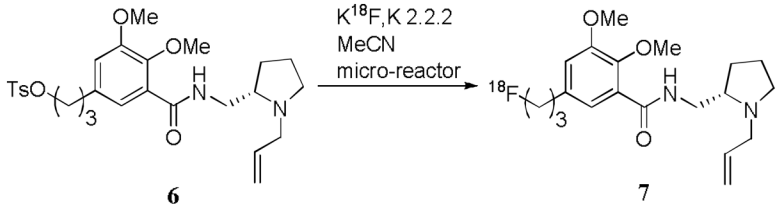

Figure 2.
Synthesis of **7** in a micro-reactor.

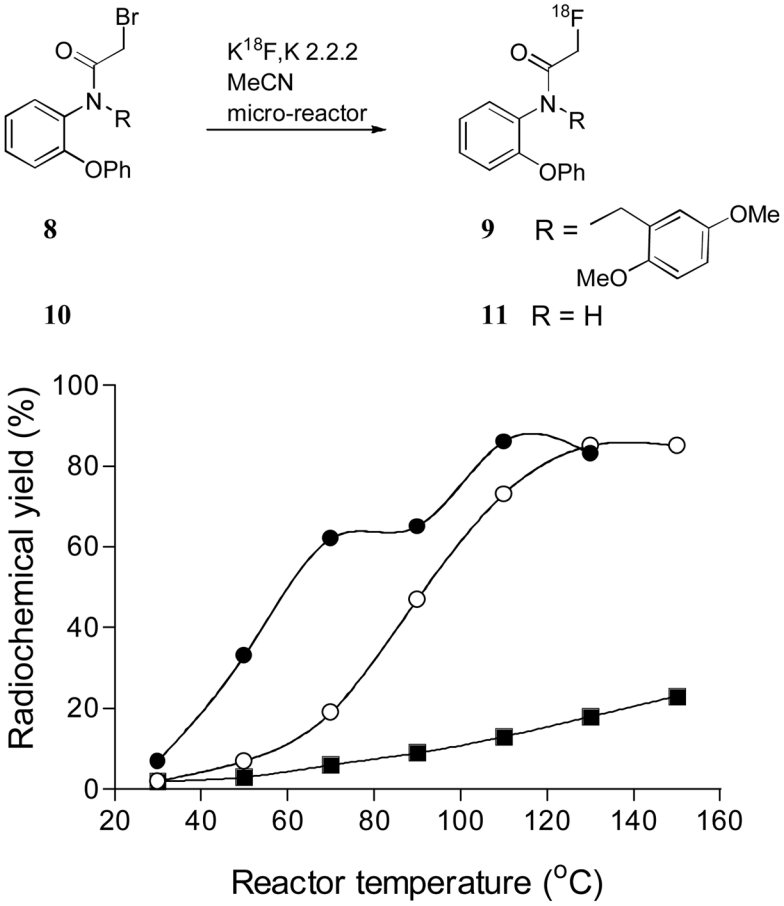

Figure 3.

Synthesis of **9** and **11** in a micro-reactor and temperature dependence of RCYs of **9** in anhydrous acetonitrile (●) or acetonitrile with 0.3% v/v water (○), and of **11** in anhydrous acetonitrile (■).

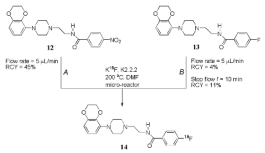

Figure 4.
Synthesis of **14** in a micro-reactor by aromatic nucleophilic substitution in a nitro-precursor (Route A) or from ^{18}F for ^{19}F exchange (Route B).

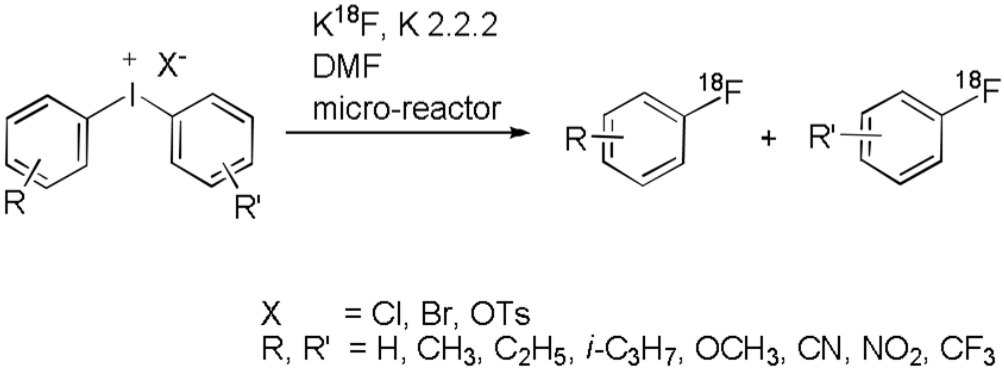

Figure 5.
Reactions of diaryliodonium salts with [^{18}F]fluoride ion to produce [^{18}F]fluoroarenes in a micro-reactor

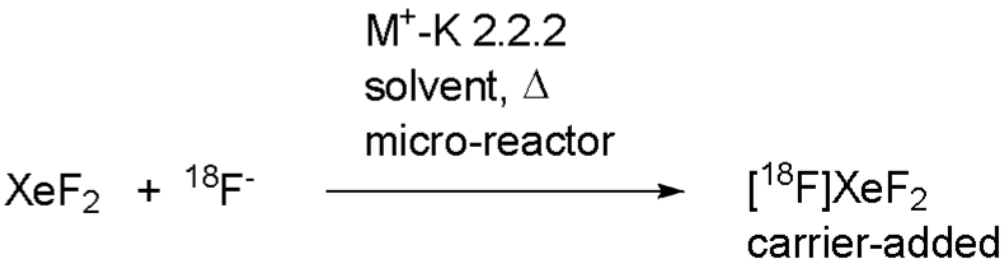

Figure 6.
Preparation of [^{18}F]xenon difluoride by exchange with [^{18}F]fluoride ion in a micro-reactor