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# Use of SF<sub>6</sub> for the production of electrophilic <sup>18</sup>F-fluorination reagents

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## ABSTRACT

Electrophilic <sup>18</sup>F-fluorination is an important method for production of tracers for positron emission tomography. The most commonly employed <sup>18</sup>F-fluorination reagents [<sup>18</sup>F]F<sub>2</sub>, [<sup>18</sup>F]Selectfluor bis(triflate) and [<sup>18</sup>F] NFSi allow for the synthetically simple and fast introduction of fluorine-18 into organic molecules, in particular those containing electron rich aromatic rings. For the time being the best method for the production of [<sup>18</sup>F]F<sub>2</sub> gas, the most common electrophilic reagent, is a post-target production which applies a high voltage electrical discharge to promote the <sup>19</sup>F/<sup>18</sup>F isotopic exchange between [<sup>18</sup>F]MeF and carrier F<sub>2</sub> gas.

The aim of this study was to develop a new method for the production of electrophilic <sup>18</sup>F-fluorination reagents which would avoid use of toxic and very reactive carrier  $F_2$  gas. In this study the use of SF<sub>6</sub> as an alternative to carrier  $F_2$  gas was tested. Experiments were carried out in two different matrix gases: Ne and Xe. The electrophilic <sup>18</sup>F-fluorination reagent produced was used for the labelling of two model compounds (6-[<sup>18</sup>F] fluoro-*L*-DOPA and [<sup>18</sup>F]Selectfluor bis(triflate)) in order to prove its feasibility.

This proof-of-concept study showed that  $SF_6$  in Xe can be used in place of  $F_2$  for the production of electrophilic [<sup>18</sup>F]F<sub>2</sub> gas. When  $SF_6$  in Ne was used only trace amounts of [<sup>18</sup>F]F<sub>2</sub> was observed.

#### 1. Introduction

Positron emission tomography (PET) is a diagnostic technique which allows the imaging of biological processes in living organisms. This imaging modality visualises the distribution of radioactivity from biologically active molecules that have been labelled with a positron emitting radionuclide. Due to its numerous favourable characteristics such as the clean  $\beta^+$  decay (97%), low positron energy ( $E_{\beta max} = 635$  keV) and convenient half-life ( $t_{1/2} = 109.8$  min), fluorine-18 is the most commonly used of all the radionuclides that are suitable for the production of PET tracers.

Nucleophilic <sup>18</sup>F-fluorination is the most frequently employed approach for the introduction of fluorine-18 into organic molecules. The complementary electrophilic <sup>18</sup>F-fluorination route is an important method for the production of PET tracers since it allows access to molecules that are difficult to reach by the nucleophilic approach.

 $[^{18}\text{F}]\text{F}_2$ , the simplest electrophilic fluorination reagent, can be produced in-target by a cyclotron through the  $^{20}\text{Ne}(d,\alpha)^{18}\text{F}$  [1,2] or  $^{18}\text{O}$  (p,n)<sup>18</sup>F [3,4] nuclear reactions carried out on gas targets, or by post-target production methods from aqueous  $[^{18}\text{F}]\text{fluoride}$  [5,6]. Since its publication by Bergman and Solin in 1997 [6], the application of a high

voltage electrical discharge to promote the  ${}^{19}F/{}^{18}F$  isotopic exchange has been a highly useful method for the production of  $[{}^{18}F]F_2$  gas as the molar activity (A<sub>m</sub>) is significantly higher when compared to A<sub>m</sub>'s achieved by the in-target methods. This post-target approach starts from the conversion of cyclotron-produced  $[{}^{18}F]$ fluoride to  $[{}^{18}F]$ MeF through reaction with MeI. Next, the  $[{}^{18}F]$ MeF, purified by gas chromatography, is mixed with a low amount of non-radioactive carrier F<sub>2</sub> gas in neon in a quartz discharge chamber and atomized by a high voltage electrical discharge. The  $[{}^{18}F]F_2$  formed is bubbled through a solution of labelling precursor without any further purification. This technique has been used for the production of different PET tracers in Turku PET Centre for more than twenty years [7].

In order to avoid the use of highly reactive and toxic  $F_2$  gas in the production of  $[^{18}F]F_2$ , we decided to replace it with a milder gaseous source of  $F_2$ . It is known that  $SF_6$  can be dissociated by an electrical discharge or plasma to create  $F_2$  as well as different S-F species [8,9]. This suggests that  $SF_6$  can be used as an alternative to  $F_2$  in the discharge-promoted production of  $[^{18}F]F_2$ . Due to its inert and nontoxic nature,  $SF_6$  is safe to use in the laboratory, moreover, the high density (6.17 g/L) of  $SF_6$  makes it easy to dose the necessary small portions of gas.

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Fig. 1. Syntheses of 6-[18F]fluoro-L-DOPA, [18F]Selectfluor bis(triflate) and [18F]F-DPA.

This research focuses on the use of  $SF_6$  gas for the synthesis of electrophilic  ${}^{18}$ F-fluorination reagents. Presented herein are the result for the reaction carried out in two different matrices; Ne and Xe.

The use of Xe as the matrix gas can potentially promote the production of  $[^{18}F]XeF_2$  [10,11] which is also an electrophilic  $^{18}F$ -fluorination reagent [12–16]. It is relatively stable in solvents such as acetonitrile (MeCN), dichloromethane (DCM) or trichlorofluoromethane (Freon-11) [17] and can be used for the production of PET tracers.

For this study  $6 \cdot [{}^{18}F]$  fluoro-*L*-DOPA has been used as a model molecule to demonstrate the presence of  ${}^{18}F$ -labelled electrophilic species and to facilitate radioHPLC analysis. It is a well-known radio-pharmaceutical, commonly used for the PET imaging of dopaminergic systems [18]. The electrophilic  ${}^{18}F$ -fluorination reagent produced by this method was also used for synthesis of  $[{}^{18}F]$ Selectfluor bis(triflate) [19] and subsequently  $[{}^{18}F]$ F-DPA, a tracer for the imaging of the translocator protein 18 kDa (TSPO) [20] (Fig. 1).

#### 2. Results and discussion

2.1. Formation of electrophilic <sup>18</sup>F-fluorination reagents and synthesis of 6-[<sup>18</sup>F]fluoro-L-DOPA

Electrophilic <sup>18</sup>F-fluorination reagents and subsequently 6-[<sup>18</sup>F]

fluoro-*L*-DOPA were successfully synthesised when 1% SF<sub>6</sub> in Xe was used as the source of carrier fluorine for the reaction (Fig. 2A). The high voltage electrical discharge (32–36 kV) was applied to the SF<sub>6</sub>/Xe/[<sup>18</sup>F] MeF gas mixture in a quartz chamber for 10, 50, 100 or 150 s. The resulting gas mixture containing electrophilic <sup>18</sup>F-fluorination species was immediately used for the synthesis of  $6 \cdot [^{18}F]$  fluoro-*L*-DOPA. For discharges of 50–150 s, the tracer was produced with good radio-chemical yield (RCY, determined by radioHPLC analysis of the crude product) and A<sub>m</sub> (Table 1). The increase of the discharge time from 50 to 100 or 150 s did not result in any significant changes in RCY or A<sub>m</sub>. However, when the discharge was carried out for 10 s only trace amount of the desired product was observed.

For the reactions carried out with a 4 times higher starting activity the 6-[ $^{18}$ F]fluoro-*L*-DOPA was isolated by semi preparative radioHPLC and resulted in 22  $\pm$  7 MBq of the final product with a radiochemical purity (RCP) of 93  $\pm$  7%.

For the reactions carried out in Ne only trace amounts of  $6-[^{18}F]$  fluoro-*L*-DOPA were detected regardless of the duration of the discharge (Fig. 2B).

#### 2.2. Spectrometric analysis

Spectrometric analyses of the light emitted during the discharge were carried out for both  $SF_6/Xe$  and  $SF_6/Ne$  gas mixtures.



Fig. 2. A Chromatogram of the  $6 \cdot [^{18}F]$ fluoro-*L*-DOPA synthesis carried out with SF<sub>6</sub>/Ne B Chromatogram of the  $6 \cdot [^{18}F]$ fluoro-*L*-DOPA synthesis carried out with SF<sub>6</sub>/Xe.

#### Table 1

Results of the syntheses of 6-[<sup>18</sup>F]fluoro-*L*-DOPA with different duration of the discharge. For Entry 7 a four times higher starting activity was used (for entries 1–6 starting activity was 17  $\pm$  2 GBq). Radiochemical yields (RCY) and molar activities (A<sub>m</sub>) were determined based on radioHPLC of the crude product.Entry.

	Matrix gas	Discharge time (s)	Activity of crude product solution (MBq)	A <sub>m</sub> (GBq/ μmol)	RCY (%)	N
1	Ne	10	47	-	0.4	1
2	Ne	100	77 ± 34	-	$0.5 \pm 0.4$	3
3	Xe	10	190	-	1	1
4	Xe	50	$144 \pm 7$	$0.8 \pm 0.1$	$11 \pm 1$	3
5	Xe	100	$178 \pm 22$	$0.9 \pm 0.1$	$13 \pm 1$	3
6	Xe	150	$132 \pm 20$	$0.8 \pm 0.1$	$8 \pm 2$	3
7	Xe	100	$297~\pm~94$	$2.2~\pm~0.5$	$23 \pm 9$	5

Characteristic emission lines for fluorine and sulfur were observed in the spectrum which was taken during discharge in the SF<sub>6</sub>/Ne gas mixture (Fig.  $3B_{Ne}$  and  $3C_{Ne}$ ). For the SF<sub>6</sub>/Xe mixture no emissions lines for fluorine were observed (Fig.  $3B_{Xe}$ ). However, the characteristic emission lines from sulfur were detected (Fig.  $3C_{Xe}$ ).

Ionic and atomic Xe emission lines were detected when the discharge was carried out in SF<sub>6</sub>/Xe (Fig.  $3D_{Xe}$ ). The weak emission lines at 260, 350, 460 nm are characteristic for both ionic Xe and the XeF\* excimer (Fig. 4) [21–23]. Ne emissions lines were also detected in the SF<sub>6</sub>/Xe mixture since it was used as a transfer gas and therefore was also present in the discharge chamber (Fig.  $3D_{Xe}$ ).

In both gas mixtures weak emission lines from oxygen (777 nm),

hydrogen (656 nm) and silicon (several emission lines in range of 243–253 nm) were detected.

## 2.3. Labelling of [<sup>18</sup>F]Selectfluor bis(triflate) and [<sup>18</sup>F]F-DPA

The electrophilic <sup>18</sup>F-fluorination species made by discharge in SF<sub>6</sub>/ Xe were successfully used for the synthesis of [<sup>18</sup>F]Selectfluor bis(triflate) (Fig. 5), which was confirmed by the radioLC–MS analysis of the crude reaction mixture (Fig. 5A).

The crude solution of  $[^{18}F]$ Selectfluor bis(triflate) was used for the synthesis of  $[^{18}F]$ F-DPA resulting in 2% RCY and  $A_m$  of 1.3 GBq/µmol (Fig. 5B).

# 2.4. [<sup>18</sup>F]XeF<sub>2</sub> analysis

RadioHPLC analysis of the solution of the gas mixture created during discharge dissolved in MeCN did not indicate the presence of  $[^{18}F]XeF_2$ . When the solution was co-injected with nonradioactive reference of XeF<sub>2</sub> and immediately analyzed by radioHPLC no  $[^{18}F]XeF_2$ was detected (Fig. 6A). Analysis of the same solution after 20 min showed traces of  $[^{18}F]XeF_2$  produced by isotopic exchange. 4 h after synthesis 12% of activity detected by radioHPLC corresponded to  $[^{18}F]$ XeF<sub>2</sub> (Fig. 6B).

#### 3. Discussion

Practically useful yields of electrophilic <sup>18</sup>F-fluorination reagents were obtained in the experiment where Xe was used as a matrix gas for



Fig. 3. A Photographs and emission spectra of discharges carried out in SF<sub>6</sub>/Xe (left) or SF<sub>6</sub>/Ne (right). On graphs B, C and D x-axes present  $\lambda$  (nm) and y-axes Intensity (arb. units). B Wavelength range in which strong emission lines from atomic fluorine are expected. Note that these emissions are present when Ne is used as a matrix but not in the Xe matrix. C Wavelength range in which strong emission lines from atomic sulfur are expected. Note that atomic sulfur emission are observed from both matrixes. D Wavelength ranges where characteristic emission from matrix gases are expected. Note that in Xe both atomic (neutral) and ionic emission are seen, as well as weaker Ne emission, which presence stems from purification of [<sup>18</sup>F]MeF (see Section 5.3 [<sup>18</sup>F]MeF production). In Ne only atomic emission are seen from the matrix gas. No ionic emissions were observed.



Fig. 4. Optical emission lines recorded from discharge carried out in SF<sub>6</sub>/Xe gas mixture, see also Fig. 3. The lines marked are putatively assigned to XeF\*excimer [21–23].

the SF<sub>6</sub>/[<sup>18</sup>F]MeF discharge reaction. This was demonstrated by the successful synthesis of 6-[<sup>18</sup>F]fluoro-*L*-DOPA and [<sup>18</sup>F]Selectfluor bis (triflate). In contrast, when Ne was employed as the matrix gas low yields were obtained. This suggest that Xe plays a crucial role in the generation of electrophilic <sup>18</sup>F-fluorination reagents.

Spectrometric data showed that no atomic fluorine is observed during the discharge in Xe. At the same time there are clear signals from atomic sulfur, atomic Xe and ionic Xe. This suggest that SF<sub>6</sub> is atomized during discharge but the fluorine immediately interacts with other species. In addition, weak emissions lines at 260, 350 and 460 nm (Fig. 4) were detected. While these have been reported to be emission lines of atomic and ionic Xe they have also all been reported to be characteristic emission lines for the Xe-F<sup>\*</sup> excimer [21–23]. The presence of Xe-F<sup>\*</sup> emission lines would explain the apparent absence of atomic fluorine. Based on this finding we propose that excited Xe-F\* intermediate species are generated during the discharge.

When the discharge was carried out in Ne, a similar interaction did not occur between Ne and F. Even though atomic fluorine was produced and observed during the discharge, the Ne-F\* species is not known to exist. Suggesting that fluorine probably reorganizes into different S-F species and hence only traces of the subsequent electrophilic <sup>18</sup>Ffluorination product can be detected.

RadioHPLC analysis of the solution of the gases generated during discharge in Xe dissolved in MeCN confirmed that only negligible amounts of  $[^{18}F]XeF_2$  were produced in this process. This indicates that the electrophilic reagent which was produced during the discharge is indeed  $[^{18}F]F_2$ . Analysis of the solution containing the dissolved gas and XeF<sub>2</sub> reference showed that  $[^{18}F]XeF_2$  is formed via  $^{19}F/^{18}F$ 



Fig. 5. A radioLC–MS analysis of crude solution of [ $^{18}$ F]Selectfluor bis(triflate) B radioHPLC chromatogram of crude solution of [ $^{18}$ F]F-DPA.



Fig. 6. RadioHPLC chromatograms of solutions made by dissolving the crude gas products from the high-voltage promoted reaction of [ $^{18}$ F]CH<sub>3</sub>F/SF<sub>6</sub>/Xe, the solutions also contained a nonradioactive reference of XeF<sub>2</sub>. Chromatogram A was obtained immediately after the synthesis, the analysis for chromatogram B was performed 4 h after synthesis. The [ $^{18}$ F]XeF<sub>2</sub> seen in chromatogram of panel B is formed through  $^{19}$ F/ $^{18}$ F isotopic exchange.

isotopic exchange reaction.

A previously reported method for the discharge-promoted production of XeF<sub>2</sub> was carried out using a 1:2 mixture of Xe and F<sub>2</sub> [10,11]. The quartz reaction vessel was kept at room temperature and the mild discharge was induced by induction coil for up to 10 h. In the presented system, the energy provided by the discharge is high enough to break S–F and C–F bonds in SF<sub>6</sub> and MeF molecules, respectively. The strength of these S–F and C–F bonds is higher than that of the Xe–F bond [11], suggesting that XeF<sub>2</sub> would not be stable under the discharge applied.

The results obtained for the syntheses of  $6 \cdot [^{18}F]$  fluoro-*L*-DOPA using  $[^{18}F]F_2$  produced from SF<sub>6</sub>/Xe mixture and varying lengths of the high voltage discharge shows that SF<sub>6</sub>/Xe mixture needs a longer discharge time (50–150 s) to promote the reaction than the reaction with F<sub>2</sub>/Ne (10 s) [6]. The longer discharge needed for the production of  $[^{18}F]F_2$  from SF<sub>6</sub>/Xe mixture is most probably caused by the formation of different S–F species which are decomposed further to elemental fluorine during discharge.

Production of  $6 \cdot [1^{18}F]$  fluoro-*L*-DOPA, [<sup>18</sup>F]Selectfluor bis(triflate) and subsequently [<sup>18</sup>F]F-DPA proved that the electrophilic labelling reagent produced can not only be used for direct labelling, but also for production of different electrophilic reagents such as [<sup>18</sup>F]Selectfluor bis(triflate), which can be used for further synthesis.

This is a successful proof-of-concept study where we demonstrated that it is possible to produce an electrophilic <sup>18</sup>F-fluorination reagent without the need for toxic fluorine gas. While there is need for optimization with regard to RCY and  $A_{\rm m}$ , the molar activity is already

relatively high, 2.2 GBq/µmol, compared to molar activates of 0.1–1.3 GBq/µmol achieved by in-target production methods [2,4]. While the presented method is technically challenging, it is not more demanding than previously reported methods [1–4,6] since it circumvents the use of non-radioactive  $F_2$  gas.

#### 4. Conclusion

This proof-of-concept study shows that it is possible to produce a relatively high molar activity electrophilic <sup>18</sup>F-fluorination reagent from SF<sub>6</sub> and [<sup>18</sup>F]MeF. Particularly, we showed that when Xe was employed as the matrix gas in the high voltage discharge reaction a usable RCY was obtained.

The presence of Xe during the discharge is a critical factor for this reaction since only low amounts of electrophilic <sup>18</sup>F-labelling species were generated when the reaction was performed in Ne.

Negligible amounts of  $[^{18}F]XeF_2$  were observed as a product of the discharge promoted reaction, thus we propose that the electrophilic  $^{18}F$ -fluorination reagent formed is  $[^{18}F]F_2$  gas.

The  $[^{18}F]F_2$  generated by this method was successfully used for the synthesis of 6- $[^{18}F]$ fluoro-*L*-DOPA and could also be converted into a milder <sup>18</sup>F-fluorination reagent such as  $[^{18}F]$ Selectfluor bis(triflate) which could subsequently be used for labelling reactions.

Further development of this method should be focused on increasing the yield at this level of carrier which would also result in an increase in molar activity.

#### 5. Experimental

#### 5.1. General

All organic solvents were HPLC grade and purchased from Sigma-Aldrich (Steinheim, Germany). Potassium carbonate ( $K_2CO_3$ ), hydrobromic acid (HBr, 47%), iodomethane (MeI), potassium dihydrogenphosphate ( $KH_2PO_4$ ), silver trifluoromethanesulfonate (AgOTf) and lithium trifluoromethanesulfonate (LiOTf) were also purchased from Sigma-Aldrich. Kryptofix 222 ( $K_{222}$ ) [4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane] and acetic acid (AcOH, 100%) were purchased from Merck KGaA (Darmstadt, Germany). Sodium hydroxide (NaOH, 10.8 M, 32%) was supplied by Riedel-de Haën (Seelze, Germany). N-Formyl-3,4-di-*tert*-butoxycarbonyloxy-6-(trimethylstannyl)-L-phenylalanine ethyl ester (FDOPA precursor) was purchased from ABX (Radeberg, Germany). <sup>18</sup>O enriched water for the production of <sup>18</sup>F was purchased from Rotem Industries Ltd. (Arava, Israel). Gases were supplied by AGA, Linde group (Espoo, Finland). N,*N*-Diethyl-2-(2-(4-(tributylstannyl)phenyl)-5,7-dimethyl-pyrazolo[1,5- $\alpha$ ]pyrimidin-3-yl)acet-

amide (F-DPA precursor) and 1-chloro-methyl-4-aza-1-azoniabicyclo [2.2.2]octane triflate (Selectfluor precursor) were synthesised by previously described methods.

All RCYs were determined by radioHPLC of the crude product.

## 5.2. [<sup>18</sup>F]Fluoride production

 $[^{18}F]$ Fluoride was produced via  $^{18}O(p,n)^{18}F$  nuclear reaction. 2.3 mL of oxygen-18-enriched water was irradiated with a 18 MeV proton beam from a CC-18/9 cyclotron (Efremov Scientific Institute of Electrophysical Apparatus, St. Petersburg, Russia). The water solution containing  $[^{18}F]$  fluoride was passed through an anion exchange cartridge (QMA Sep Pak, Waters Corporation, Milford, MA, USA) and the trapped  $[^{18}F]$ fluoride was eluted to the reaction vessel with a K<sub>2</sub>CO<sub>3</sub>/K<sub>222</sub> solution.

## 5.3. [<sup>18</sup>F]MeF production

 $[^{18}F]$ Fluoride was added to a reaction vessel containing  $K_{222}$  (22–28 mg) and  $K_2CO_3$  (6–8 mg) and followed by 1 mL of MeCN. Azeotropic distillation was carried out at 100 °C for 4 min under a helium flow. Two further additions of MeCN were made (2 × 1 mL) each one flowed by 4 min evaporation. MeI in MeCN (1.5 mmol in 1 mL) was added to the dry  $[^{18}F]$ KF/ $K_{222}$  complex and the reaction mixture was heated at 100 °C for 60–90 s. The resulting  $[^{18}F]$ MeF was purified by gas chromatography, using Ne as the transfer gas, and was trapped in a stainless steel loop submerged in liquid N<sub>2</sub> [6].

## 5.4. $[^{18}F]F_2$ production

After trapping, the stainless steel loop containing  $[^{18}F]$ MeF was allowed to warm to room temperature and 1.2 µmol SF<sub>6</sub> in Xe or Ne (4 bar of 1% SF<sub>6</sub> in Xe or Ne) were used to transfer the trapped  $[^{18}F]$ MeF in Ne to the quartz discharge chamber. The gas mixture was excited by a high voltage electrical discharge (32–36 kV, 400 µA) for 10, 50, 100 or 150 s. The resulting gas was subsequently used for the synthesis of 6- $[^{18}F]$ fluoro-*L*-DOPA or  $[^{18}F]$ Selectfluor bis(triflate).

# 5.5. Synthesis of 6-[<sup>18</sup>F]fluoro-L-DOPA

The gas mixture produced during the high voltage discharge was bubbled through a solution of FDOPA precursor (3–3.3 mg) in Freon-11 (600  $\mu$ L) and AcOH (25  $\mu$ L). The solvent was evaporated under Ne flow. Deprotection was carried out in HBr (300  $\mu$ L) at 130 °C for 5 min. The reaction mixture was diluted with 150  $\mu$ L of NaOH and 1 mL of HPLC eluent (7 mM KH<sub>2</sub>PO<sub>4</sub> solution).

Analytical HPLC of the diluted reaction mixture was performed on a VWR Hitachi LaChrom Elite system with EXChrom Elite Client/Server software (version 3.1.6) with a Waters Atlantis dC18,  $3.9\times150$  mm column (Waters Corp., Milford MA, USA), 7 mM aqueous  $KH_2PO_4$  as the eluent and a flow of 1 mL/min. UV-absorption was measured at a wavelength of 280 nm and the radioactivity was detected with a NaI(TI) scintillation detector.

 $A_{\rm m}$  was determined from the analytical radioHPLC runs. The fraction containing 6-[ $^{18}{\rm F}$ ]fluoro-*L*-DOPA was collected and measured for radioactivity. The UV detector was calibrated with known amounts of nonradioactive 6-fluoro-*L*-DOPA. The molar amount of product was calculated from the area of the corresponding UV peak.

For experiments performed with higher starting activity (Table 1, entry 7) crude reaction mixture was diluted with 150  $\mu$ L of NaOH and 1 mL of HPLC eluent (saline with 0.01% of AcOH and ascorbic acid 200 mg/L). Semi-preparative HPLC was performed using a Phenomenex Luna 5  $\mu$  C18, 10  $\times$  250 mm (Torrance, CA, United States) column with flow = 4 mL/min.

## 5.6. Syntheses of [<sup>18</sup>F]Selectfluor bis(triflate) and [<sup>18</sup>F]F-DPA

 $[^{18}F]F_2$  gas was produced by using SF<sub>6</sub>/Xe and the method described above with 100 s discharge.  $[^{18}F]$ Selectfluor bis(triflate) and  $[^{18}F]$ F-DPA were synthesised according to previously described procedures [19,20].

The crude solution of [<sup>18</sup>F]Selectfluor bis(triflate) was analyzed by radioLC–MS (QTRAP, Applied Biosystems SCIEX, Toronto, Canada) with Phenomenex Kinetex F5 2.1 × 100 mm, 2.6 µm (Torrance, CA, United States) [24]. The crude solution of [<sup>18</sup>F]F-DPA was analyzed by radioHPLC with Merck Chromolith Performance RP-18e (10 µm, 4.6 × 100 mm) column (Merck KGaA, Darmstadt, Germany) [20].

## 5.7. Spectrometric analysis

Spectrometric analysis of light emission during discharge was carried out with a Mechelle 7500 simultaneously recording optical spectrograph (Multichannel Instruments AB, Skarpnäck, Sweden) covering the spectral range from 185 to 1160 nm. The nominal spectral resolving power  $\lambda/\Delta\lambda_{FWHM} = 5200$  is approximately constant over the whole wavelength range. The exposure time was 1 s. Light emitted during discharge was collected and conducted into the spectrometer with an Optran UV 1000/1060 BN optical fiber (CeramOptec GmbH, Bonn, Germany).

Spectra were taken during discharge of SF<sub>6</sub> in both Ne or Xe.

## 5.8. [<sup>18</sup>F]XeF<sub>2</sub> analysis

The gas mixture formed after the discharge of the SF<sub>6</sub>/Xe/[<sup>18</sup>F]MeF mixture was bubbled through 700  $\mu$ L of MeCN with nonradioactive reference of XeF<sub>2</sub>.

The samples of the above mixture were analyzed by analytical radioHPLC using a Sunfire C18, 5  $\mu$ m, 250 mm × 4.6 mm column (Waters Corp., Milford MA, USA) and HCOONH<sub>4</sub> (25 mM) and MeCN (55:45, v/v) as an eluent with 1 mL/min flow at  $\lambda = 250$  nm [25–27].

### 5.9. Statistical analysis

The results were reported as means  $\pm$  SD. All the statistical analyses were performed using Microsoft Excel 2010. The differences between the results obtained using different conditions were tested using the unpaired *t* test. The differences were considered statistically significant if p < 0.05.

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