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Journal of Fluorine Chemistry 121 (2003) 9–14
JOURNAL OF FLUORINE CHEMISTRY
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# Syntheses of [$^{18}$F]5-fluoro-3-nitro-L-tyrosine

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Received 10 October 2002; accepted 11 November 2002

**Abstract**

The detection of 3-nitro-L-tyrosine has been used as a biomarker of ''reactive nitrogen species'' in biological matrices and has been an ongoing challenge in analytical chemistry. In this work, fluorine-18 labelled 5-fluoro-3-nitro-L-tyrosine (FNT) was synthesized as a potential radiotracer to probe the biological fate of 3-nitro-L-tyrosine. The synthesis of [$^{18}$F]FNT was carried out by reaction of [$^{18}$F]3-fluoro-L-tyrosine with $NaNO_3$ in TFA solvent for 5 min at 4 °C. The radiochemical yield (RCY) of [$^{18}$F]FNT was 96 ± 2% and [$^{18}$F]3-fluoro-L-tyrosine, was 29 ± 1%, relative to [$^{18}$F]3-fluoro-L-tyrosine and [$^{18}$F]$F_2$, respectively. The syntheses of [$^{18}$F]FNT were also accomplished by direct fluorination of 3-nitro-L-tyrosine with [$^{18}$F]$F_2$ and by nitration of L-tyrosine with $NaNO_3$, followed by fluorination, in TFA (4 °C) or anhydrous HF (−65 °C) solvent. The latter two synthetic routes produced [$^{18}$F]FNT in 13.5 ± 1.5% RCY, within 1 h. Products were characterized by use of $^{1}$H, $^{13}$C and $^{19}$F NMR spectroscopy and mass spectrometry.
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*Keywords:* Nitrotyrosine; Fluoronitrotyrosine; L-Tyrosine; Fluorine-18; Positron emission tomography; Reactive nitrogen species

## 1. Introduction

Aromatic nitration is one of the most extensively studied reactions in synthetic and theoretical chemistry [1,2]. Aromatic nitration also occurs *in vivo* by the action of ''reactive nitrogen species'', which are being increasingly proposed as contributors to tissue injury in several human diseases. The detailed mechanisms by which these species cause modifications in biomolecules is not completely understood [3]. The *in vivo* detection of 3-nitro-L-tyrosine is considered to be a biomarker for ''reactive nitrogen species'' in a biological matrix, however, the *in vivo* formation and fate of 3-nitro-L-tyrosine is a controversial subject [3–5].

A number of analytical procedures for the separation, detection and quantification of 3-nitro-L-tyrosine have been developed including UV, HPLC, GC, MS and biochemical techniques [6]. Labelled compounds have also been considered for the detection and quantification of 3-nitro-L-tyrosine. For example, $^{15}$N-labelled tetranitromethane has been used to synthesize [$^{15}$N]3-nitro-L-tyrosine [7] and [$^{15}$N]-labelled tyrosines in proteins [8] as new NMR probes for nitrotyrosines. Thus, a radiolabelled derivative of 3-nitro-L-tyrosine could also be useful for the detection and quantification of 3-nitro-L-tyrosine.

The goals of the present work were to develop rapid methods for the synthesis of fluorine-18 ($^{18}$F, 97% $\beta^+$, $E_{max} = 0.635$ MeV, $t_{1/2} = 109.7$ min) labelled 3-nitro-L-tyrosine, which could be used as a probe in studies of the biological function of 3-nitro-L-tyrosine by means of positron emission tomography (PET). The present study reports three synthetic routes to [$^{18}$F]5-fluoro-3-nitro-L-tyrosine ([$^{18}$F]FNT).

## 2. Results and discussion

Mixtures of nitric acid and sulfuric acid continue to be the most widely used nitrating agents, however, the strongly oxidizing natures of these systems and environmental considerations have led to the development of more selective reagents and methods [1]. Acid-catalyzed electrophilic aromatic nitration [9] often has the advantage that the solvents are recyclable and nitrations can be achieved under anhydrous conditions. Nitroaromatics that contain fluorine are an interesting class of compounds and have applications in the

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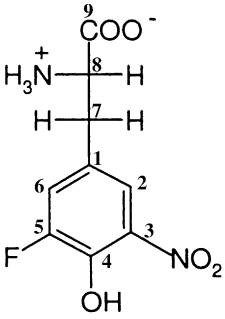
0022-1139/02/$ – see front matter © 2002 Published by Elsevier Science B.V.
doi:10.1016/S0022-1139(02)00334-2

Table 1
Proton, $^{13}C$ and $^{19}F$ NMR parameters for FNT[a]

| | $^{1}H$ chemical shift (ppm) | Coupling constant (Hz) | $^{13}C$ chemical shift[c] (ppm) | Coupling constant (Hz) |
|---|---|---|---|---|
| 5-Fluoro-3-nitro-tyrosine[b]  | $H7_A$ 3.03<br>$H7_B$ 3.16<br>$H8_X$ 4.18<br>H6 7.31<br>H2 7.67 | $^{2}J(H7_A\text{-}H7_B)$, −14.6<br>$^{3}J(H7_A\text{-}H8_X)$, 5.72<br>$^{3}J(H7_B\text{-}H8_X)$, 7.31<br>$^{3}J$(H6-F), 10.7<br>$^{5}J$(H2-F), 2.0<br>$^{4}J$(H2-H6), 2.0 | C-1 132.3 (132.0)<br>C-2 128.1 (125.5)<br>C-3 142.5 (139.5)<br>C-4 148.9 (143.8)<br>C-5 159.0 (159.1)<br>C-6 130.2 (129.3)<br>C-7 41.1<br>C-8 60.2<br>C-9 177.5 | $^{3}J$(C1-F), 6.9<br>$^{4}J$(C2-F), 2.3<br>$^{3}J$(C3-F), 3.1<br>$^{2}J$(C4-F), 16.1<br>$^{1}J$(C5-F), 246.9<br>$^{2}J$(C6-F), 19.2 |

[a] Spectra recorded in $D_2O$ solvent.
[b] The $^{19}F$ chemical shift is −130.7 ppm with respect to external $CFCl_3$ at 30 °C.
[c] Calculated values using fluorine substituent parameters [24] are shown in parentheses.

agrochemical and pharmaceutical industries [10]. Chambers and Skinner [10] have patented a synthetic route to mono- and polyfluoronitrated aromatic compounds by reacting aromatic compounds with a nitrating agent (e.g. aqueous $HNO_3$) in the presence of elemental fluorine. In the present work, three synthetic approaches to [$^{18}$F]FNT were explored: (1) nitration of [$^{18}$F]3-fluoro-L-tyrosine (2) direct fluorination of 3-nitro-L-tyrosine, and (3) a one-pot nitration of L-tyrosine followed by fluorination. Anhydrous HF and TFA were chosen as the solvents for these reactions because they have proven to be useful for acid-catalyzed electrophilic nitration [9] and for the direct fluorination of aromatic amino acids [11–17].

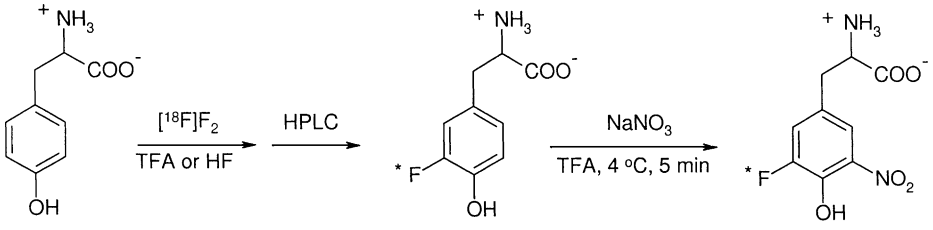
### 2.1. Nitration of 3-fluoro-DL-tyrosine and [$^{18}$F]3-fluoro-L-tyrosine

In previous work [18], 5-fluoro-3-nitro-DL-tyrosine was synthesized by reaction of an ice-cold suspension of 3-fluoro-DL-tyrosine in water with concentrated $HNO_3$ and by allowing the reaction to proceed below 25 °C overnight. In the present work, nitration of 3-fluoro-DL-tyrosine was carried out using an equimolar quantity of $NaNO_3$ in TFA (4 °C) or HF (−65 °C) solvent. Analysis of the reaction mixture using HPLC (UV, $\lambda = 275$ nm) showed that the conversion of 3-fluoro-DL-tyrosine to 5-fluoro-3-nitro-DL-tyrosine was >98% after 5 min. Characterization of 5-fluoro-3-nitro-tyrosine was accomplished by use of $^{1}H$, $^{13}C$ and $^{19}F$ NMR spectroscopy (Table 1).

We have previously reported the synthesis of [$^{18}$F]3-fluoro-L-tyrosine by direct fluorination of L-tyrosine with a 29 ± 1% radiochemical yield (RCY) [17]. The nitration of 3-fluoro-DL-tyrosine, described above, was applied to the nitration of [$^{18}$F]3-fluoro-L-tyrosine (Scheme 1) and produced [$^{18}$F]FNT with a RCY of 96 ± 2% with respect to [$^{18}$F]3-fluoro-L-tyrosine. Analytical HPLC analysis of the reaction mixture after nitration of [$^{18}$F]3-fluoro-L-tyrosine with $NaNO_3$ in TFA (Scheme 1) is shown in Fig. 1. The peaks eluting at 5.5 and 7.5 min correspond to unconverted 3-fluoro-L-tyrosine and [$^{18}$F]FNT, respectively, as confirmed by $^{19}F$ NMR spectroscopy. Furthermore, the peak assigned to 3-fluoro-L-tyrosine in the reaction mixture showed an increase in peak area when spiked with 3-fluoro-DL-tyrosine.

### 2.2. Fluorination of 3-nitro-L-tyrosine

The direct fluorination of 3-nitro-L-tyrosine using [$^{18}$F]$F_2$ (Scheme 2) resulted in RCYs of 13 and 15% in TFA and HF, respectively, for [$^{18}$F]FNT. Structural characterization of FNT was accomplished by use of $^{1}H$, $^{13}C$ and $^{19}F$ NMR spectroscopies and positive ion electrospray mass spectrometry, which showed a protonated molecular ion at




Scheme 1.

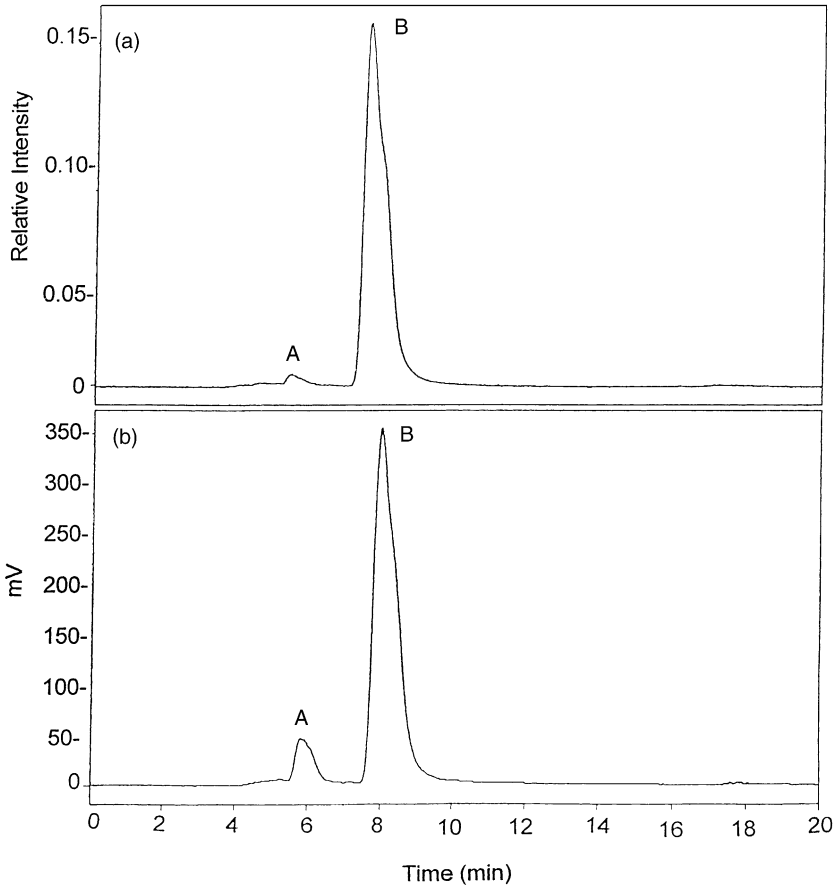
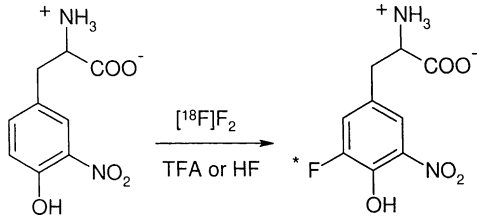



Fig. 1. HPLC trace of the reaction mixture after the nitration of [$^{18}$F]3-fluoro-L-tyrosine (A) using $NaNO_3$ in TFA solvent at 4 °C for 5 min to produce [$^{18}$F]FNT (B) (Scheme 1): (a) UV, $\lambda = 275$ nm and (b) [$^{18}$F]-radioactivity trace.



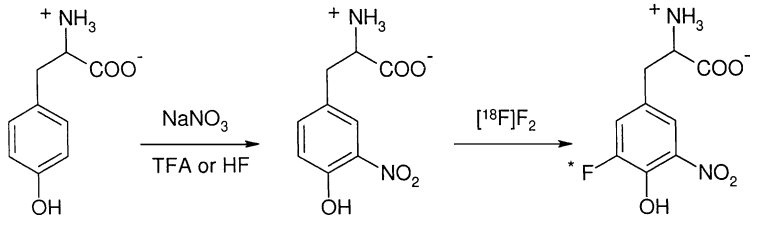

Scheme 2.

$m/z = 245$ $[M + H]^+$. The syntheses and preparative HPLC purifications of [$^{18}$F]FNT were completed within 1 h. It should be noted that 3-nitro-L-tyrosine was not separated from [$^{18}$F]FNT under the HPLC conditions used in this study.

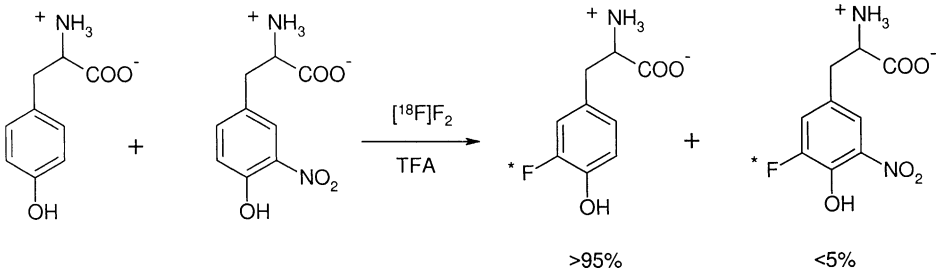
In view of the significantly lower RCY in Scheme 2, compared with that resulting from direct nitration of [$^{18}$F]3-fluoro-L-tyrosine in Scheme 1, the development of HPLC methods to optimize this separation were not pursued further.

### 2.3. One-pot nitration and fluorination of L-tyrosine

One-pot nitrations of L-tyrosine in TFA and HF solvents, followed by fluorination using [$^{18}$F]$F_2$, were also carried out in the present study (Scheme 3). The conversion of L-tyrosine to 3-nitro-L-tyrosine was >98% (determined by HPLC; UV, $\lambda = 275$ nm). The products of these reactions were characterized by $^1$H, $^{13}$C and $^{19}$F NMR spectroscopies and by positive ion electrospray mass spectrometry,




Scheme 3.




Scheme 4.

which showed protonated molecular ions at $m/z = 227$ and 245 $[M + H]^+$ corresponding to 3-nitro-L-tyrosine and [$^{18}$F]FNT, respectively.

Substitutions at positions 3- and 5- on the aromatic ring of L-tyrosine were expected in view of the higher electron densities at these positions that arise from the electron donating properties of the hydroxyl group. We have recently shown that the same sites are susceptible to electrophilic aromatic substitution in L-tyrosine and L-α-methyltyrosine [17]. The RCY of [$^{18}$F]FNT, after a one-pot nitration of L-tyrosine using $NaNO_3$ followed by fluorination with [$^{18}$F]$F_2$ (Scheme 3), was 14 and 12% in TFA and HF, respectively.

### 2.4. Relative reactivity of [$^{18}$F]$F_2$ towards L-tyrosine and 3-nitro-L-tyrosine

The RCYs of [$^{18}$F]FNT resulting from the direct fluorination of 3-nitro-L-tyrosine (Schemes 2 and 3; 13.5 ± 1.5%) are lower than those resulting from the direct fluorination of L-tyrosine in TFA (28%) and HF (30%). The lower RCYs in the present work are not surprising because the electron withdrawing nitro group renders the aromatic ring less susceptible to electrophilic aromatic substitution. Cacace and Wolf [19] have reported that the relative reactivity of aromatic substrates with $F_2$ increases with increasing

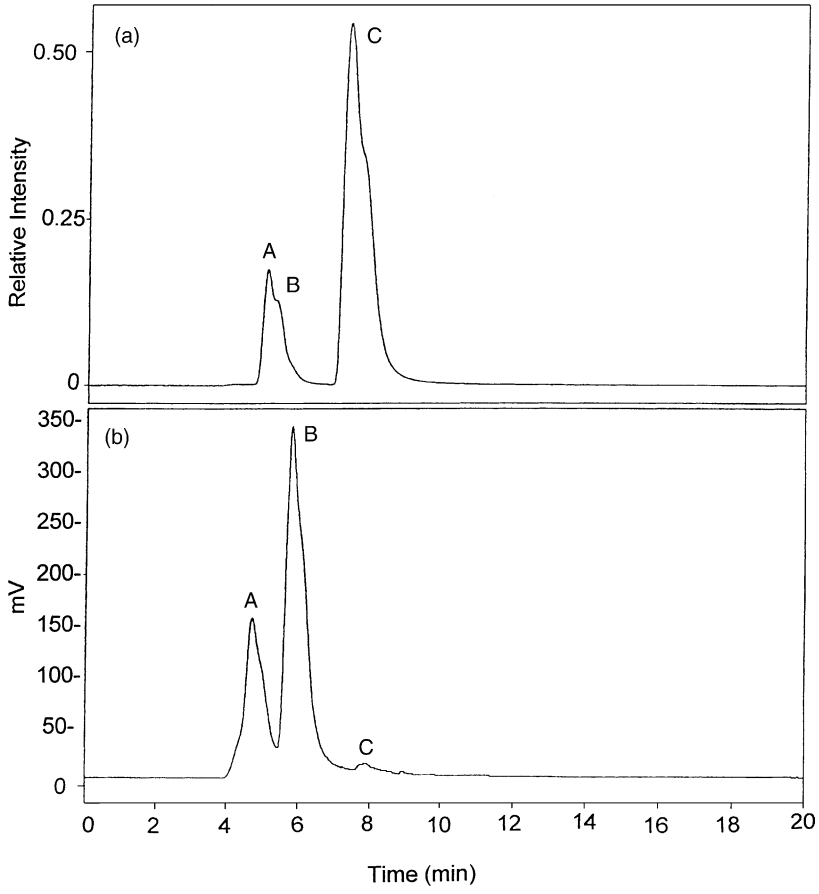



Fig. 2. HPLC trace showing the relative reactivity of [$^{18}$F]$F_2$ towards three-fold molar excesses of both L-tyrosine and 3-nitro-L-tyrosine in TFA solvent at 4 °C (Scheme 4). The labels A, B, and C correspond to unidentified fluorine-containing species, [$^{18}$F]3-fluoro-L-tyrosine and [$^{18}$F]FNT, respectively: (a) UV, $\lambda = 275$ nm and (b) [$^{18}$F]-radioactivity trace.

activation of the aromatic ring in the order: nitrobenzene << benzene < toluene << anisole. Because the RCY of an $^{18}$F-labelled fluoroaromatic compound is indicative of the efficiency of fluorine substitution on the aromatic ring, it was of interest to determine the relative reactivity of [$^{18}$F]$F_2$ towards three-fold molar excesses of both L-tyrosine and 3-nitro-L-tyrosine in TFA at 4 °C (Scheme 4). The results of this competition experiment revealed that the reactivity of fluorine towards L-tyrosine was considerably higher than towards 3-nitro-L-tyrosine, which was determined from the distribution of radioactivity and peak integration after preparative HPLC and from integration of the $^{19}$F NMR spectrum of the reaction mixture. The combined RCY of [$^{18}$F]3-fluoro-L-tyrosine and [$^{18}$F]FNT was 26% (relative to [$^{18}$F]$F_2$), with >95% of the activity arising from [$^{18}$F]3-fluoro-L-tyrosine. Fig. 2 shows HPLC traces of the reaction mixture resulting from this competition experiment. The peaks eluting at 4, 5.5 and 7.5 min correspond to (an) unknown fluorine-containing species, [$^{18}$F]3-fluoro-L-tyrosine and [$^{18}$F]FNT, respectively. These results clearly show that the aromatic ring of L-tyrosine is more susceptible to substitution by fluorine, under the present experimental conditions, than the relatively deactivated aromatic ring of 3-nitro-L-tyrosine, accounting for the lower RCY after fluorination of 3-nitro-L-tyrosine when compared with that of L-tyrosine in TFA [17].

### 2.5. Comparison of the synthetic routes to [$^{18}$F]FNT

Of the three new synthetic methods for [$^{18}$F]FNT that are described in the present study (Schemes 1–3), the direct nitration of [$^{18}$F]3-fluoro-L-tyrosine (Scheme 1) is the preferred route because the nitration of [$^{18}$F]3-fluoro-L-tyrosine is fast (5 min) and efficient (96 ± 2% conversion to [$^{18}$F]FNT). This method also produces [$^{18}$F]FNT of high radiochemical purity because all of the L-tyrosine precursor is easily removed immediately following fluorination with [$^{18}$F]$F_2$. The present study also showed that fluorination of L-tyrosine is more efficient than fluorination of the relatively deactivated aromatic ring of 3-nitro-L-tyrosine. However, the one-pot method of nitration followed by fluorination of L-tyrosine (Scheme 3) offers an alternative general route to the syntheses of nitrofluoroaromatic compounds. For $^{18}$F-labelled nitrofluoroaromatic compounds requiring high specific activities for PET applications, nucleophilic methods using no-carrier-added $^{18}F^-$ can be used for the syntheses of $^{18}$F-aromatics [20], and the resulting compounds should prove to be easily nitrated, as established by the present study.

## 3. Conclusions

Efficient synthetic methods leading to the syntheses of [$^{18}$F]FNT have been developed in the present study. The direct nitration of [$^{18}$F]3-fluoro-L-tyrosine using $NaNO_3$ in TFA at 4 °C produced [$^{18}$F]FNT with a RCY of 96 ± 2% with respect to [$^{18}$F]3-fluoro-L-tyrosine within 5 min. This method offers the highest radiochemical purity and yields of [$^{18}$F]FNT at this time and is well suited for the routine production of [$^{18}$F]FNT in a hospital environment. The present work also establishes that [$^{18}$F]FNT can be synthesized by direct fluorination of 3-nitro-L-tyrosine in TFA or HF solvent using [$^{18}$F]$F_2$ in a RCY of 13.5 ± 1.5% relative to [$^{18}$F]$F_2$.

## 4. Experimental

### 4.1. General experimental procedures

Precautionary measures should be established prior to repeating aspects of this work, particularly when $^{18}$F and anhydrous HF are employed. Before commencing work with anhydrous HF, first-aid treatment procedures [21–23] should be available and known to all laboratory personnel.

#### 4.1.1. Materials

Enriched [$^{18}$O]$O_2$ ($^{18}$O, min 99 atom%, Isotec), neon (99.999%, Air Products), anhydrous hydrogen fluoride (Air Products), 1% $F_2$ in neon (Canadian Liquid Air), helium (99.9999%, Matheson), L-tyrosine (Fisher), 3-nitro-L-tyrosine (Aldrich), 3-fluoro-DL-tyrosine (Aldrich), sodium nitrate (Caledon), trifluoroacetic acid (Caledon), glacial acetic acid (British Drug Houses), and HPLC grade acetonitrile (Caledon) were used without further purification.

#### 4.1.2. Synthetic methods

The general experimental procedures for the fluorination of aromatic amino acids in the present work were conducted as previously described [17]. Separation of L-tyrosine from [$^{18}$F]3-fluoro-L-tyrosine by preparative HPLC was carried out using a reverse-phase column (Phenomenex M9 Partisil 10/50, ODS-3) and an aqueous solution of 5% $CH_3CN$ with 0.1% TFA (v/v) as the mobile phase and a flow rate of 3.0 mL min$^{-1}$. The eluate from the column was monitored with a fixed wavelength UV detector (280 nm) and a Geiger-Müller counter (Bicron SWGM B980C) coupled to a rate meter (Bicron Erik-Tech™). Preparative HPLC analysis of the reaction mixture (Scheme 1) showed one major UV peak having the same retention time as L-tyrosine at 13.5 min and another major peak at 16 min. The radiochromatogram of the same sample showed peaks at 8, 9.5, 11, 13 and 16 min. The peak eluting at 16 min contained the majority of the radioactivity and was collected, evaporated to dryness and redissolved in 0.5 mL of 0.1% HOAc and the evaporation process was repeated. Sodium nitrate (2 mg, 24 μmol) in 1 mL of TFA was added to the dry residue and reacted at 4 °C for 5 min. The products were confirmed to be [$^{18}$F]3-fluoro-L-tyrosine and [$^{18}$F]FNT by use of HPLC and $^{19}$F NMR spectroscopy. The present separation method offers the advantage, over our previous method [17], of avoiding the use of a buffered mobile phase and a second HPLC

purification step. The TFA was evaporated and the sample was redissolved in 0.1% HOAc and used for characterization. Preparative HPLC conditions used for the products of fluorination of 3-nitro-L-tyrosine and for the study of the relative reactivity of [$^{18}$F]$F_2$ towards L-tyrosine and 3-nitro-L-tyrosine were identical to those described above except that the mobile phase was an aqueous solution comprised of 20% $CH_3CN$ and 0.1% TFA. Under these conditions, L-tyrosine eluted at 8.5 min and [$^{18}$F]FNT eluted at 9.5 min.

Aliquots of the reaction mixture and of purified [$^{18}$F]FNT were analyzed on a reverse-phase HPLC column (Phenomenex, ODS-2, 0.9 cm × 25 cm) and an aqueous solution of 20% $CH_3CN$ with 0.1% TFA as the mobile phase using a flow rate of 3.0 mL min$^{-1}$. Under these conditions, 3-fluoro-L-tyrosine and [$^{18}$F]FNT eluted at 5.5 and 7.5 min, respectively. The identity of the peak eluting at 5.5 min was confirmed by spiking the reaction mixture with 3-fluoro-DL-tyrosine. The eluate from the column was passed through a Waters 490E programmable multiwavelength UV detector (275 nm) and a Beckman radioisotope detector (Model 170). Both detectors were connected to a Waters Millennium Chromatography Manager.

### 4.2. Nuclear magnetic resonance spectroscopy

Proton $^{13}$C and $^{19}$F NMR spectra were recorded on a Bruker Avance 200 spectrometer and referenced at 30 °C to external $Me_4Si$, $Me_4Si$ and $CFCl_3$, respectively, and were acquired at 200.200, 50.328 and 188.376 MHz, respectively. All spectra were recorded unlocked and without spinning the samples. Proton spectra were obtained in eight scans, in 16 K memories over 4.1 kHz spectral widths corresponding to an acquisition time of 2.02 s and a resolution of 0.25 Hz/data point. Carbon-13 spectra were obtained in 25,000 scans, in 16 K memories over 12.6 kHz spectral widths corresponding to an acquisition time of 0.652 s and a resolution of 0.77 Hz/data point. Fluorine-19 spectra were obtained in 300 scans, in 32 K memories over 17.4 kHz spectral widths corresponding to an acquisition time of 0.939 s and a resolution of 0.53 Hz/data point.

## Acknowledgements

We thank the Natural Sciences and Engineering Research Council of Canada for the award of a postgraduate scholarship (N.V.) and for support in the form of a research grant (G.J.S.). We also thank Dr. Russell A. Bell and Dr. Frank J. Laronde for helpful discussions.

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