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Selective fluorination of *m*-tyrosine by OF_2

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Abstract

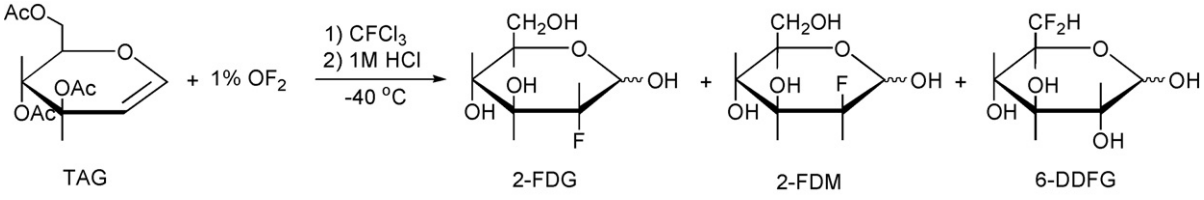
Fluorine-18 labeled aromatic amino acids are routinely used as tracers in positron emission tomography (PET) to study *in vivo* metabolic processes. The most versatile method for the production of such radiotracers is electrophilic fluorination of the aromatic amino acid with $[^{18}F]F_2$, which is most commonly produced by the gas-phase nuclear reaction $^{18}O(p, n)^{18}F$. Although $[^{18}F]F_2$ is the major product, considerable amounts of $[^{18}F]OF_2$ (up to 20%) are also produced. Electrophilic fluorination reactions of L-phenylalanine, 3-nitro-L-tyrosine, 4-nitro-DL-phenylalanine, 3,4-dihydroxyphenyl-L-alanine (L-DOPA), 3-*O*-methyl-L-DOPA, 3,4-dimethoxy-L-phenylalanine, *p*-tyrosine and *o*-tyrosine in H_2O and of *m*-tyrosine in anhydrous HF (aHF), CF_3SO_3H, CF_3COOH, CH_3COOH, HCOOH and H_2O using OF_2 were investigated. Although F_2 is an efficient fluorinating agent in aHF, electrophilic fluorination reactions using OF_2 were shown to be most efficient in less acidic media such as H_2O. In addition, and contrary to reports that OF_2 and F_2 have similar reactivities, *m*-tyrosine was the only aromatic system studied that was fluorinated by OF_2 and this was optimum in H_2O for the fluorinated *m*-tyrosine isomers (total yield, $4.35 \pm 0.04\%$). The presence of $[^{18}F]OF_2$ byproduct has no significant impact on the fluorination of aromatic amino acids investigated in this study and the subsequent production of their corresponding ^{18}F-labeled radiotracers for patient use.

Keywords: Oxygen difluoride; Electrophilic fluorination; Fluorine-18; PET; Fluoro-*m*-tyrosine

1. Introduction

Four fluorides of oxygen have been synthesized and structurally characterized, namely O_4F_2, O_3F_2, O_2F_2, and OF_2, all of which are powerful oxidants and fluorinating agents [1]. It has been shown that the stabilities of the aforementioned compounds decrease with increasing number of oxygen atoms, making OF_2 the most stable oxygen fluoride known.

Since its initial preparation by Lebeau and Damiens in 1927 [2], OF_2 has been utilized as an oxidizing or fluorinating agent in organic and inorganic syntheses. For example, OF_2 has been employed in the oxidation of primary aliphatic amines [3], fluorination of aromatic systems through fluorodestannylation reactions [4], and addition reactions, where OF_2 adds across carbon–carbon or sulfur–oxygen double bonds [5–13]. Moreover, the direct fluorination of 3,4,6-tri-*O*-acetyl-D-glucal (TAG) by OF_2 (Eq. (1)) has been shown to result in the production of 2-deoxy-2-fluoro-D-glucose (2-FDG). Fluorine-18 labeled 2-FDG is currently the most widely used radiotracer in diagnostic imaging [14]:



(1)

Several synthetic routes have been used to prepare OF_2, including the reaction of fluorine with aqueous alkali solutions [15], 60% $HClO_4$ [16], H_5IO_6 [17], hydrated alkali fluorides [18], or HOF [19]. More recently, Satyamurthy et al. [20] reported the

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formation of $[^{18}F]OF_2$ as a reaction byproduct (up to 5% for double shoot and up to 20% for the single shoot irradiation methods) under the high-pressure and high-energy irradiation conditions of a proton cyclotron gas target using the nuclear reaction, $^{18}O(p, n)^{18}F$ and according to Eqs. (2)–(4). Prior studies from our laboratory have also indicated the presence of $[^{18}F]OF_2$ (up to 5%) in the double shoot irradiation method [21]:

$$O_2\ (\text{stable}) \overset{10\,\text{MeV}\ \ H^+}{\rightleftharpoons} 2O^{\bullet} \quad (2)$$

$$O^{\bullet} + F^{\bullet} \rightarrow OF^{\bullet} \quad (3)$$

$$OF^{\bullet} + F^{\bullet} \rightarrow OF_2 \quad (4)$$

The increasing popularity of the ''double shoot'' method [21,22] for the production of electrophilic agents used for the syntheses of PET imaging agents requires a fuller understanding of the electrophilic fluorination properties of OF_2. Positron emission tomography is commonly used for the *in vivo* visualization of brain functions such as blood flow, metabolism, enzyme activity, neuroreceptors and neurotransporters [23]. An important category of PET tracers for brain imaging are ^{18}F-labeled aromatic amino acids such as $[^{18}F]$6-fluoro-3,4,-dihydroxy-L-phenylalanine (6-FDOPA) [24] and $[^{18}F]$6-fluoro-L-*meta*-tyrosine [25]. It is therefore important to investigate the fluorinating ability of OF_2 towards aromatic amino acids and to establish whether or not OF_2 gives rise to other fluorinated aromatic amino acids occurring in the product mixture that may prove difficult to separate, thus contributing to PET image background noise.

2. Results and discussion

2.1. Fluorine-18 labeled OF_2

The formation of $[^{18}F]OF_2$ in the gas target of an 11 MeV proton cyclotron in the nuclear reaction, $^{18}O(p, n)^{18}F$, occurs simultaneously with that of $[^{18}F]F_2$, making the separation of the two species very difficult to impossible. Moreover, the isolation of $[^{18}F]OF_2$ has not been reported. In order to quantify the relative amounts of ^{18}F-labeled products that result from the fluorination of aromatic amino acids using OF_2, attempts were made to synthesize and isolate $[^{18}F]OF_2$. The method used in this study involved the direct fluorination of anhydrous KF/$KF{\cdot}2H_2O$ in micromolar quantities and is a modification of the gram-scale synthesis reported by Pullen et al. [18]. Parameters reported by these workers could not be replicated in our laboratory owing to the scale and reaction conditions required for the production of radiotracers having applications in diagnostic imaging. Formation of OF_2 can be confirmed by its reaction with TAG in $CFCl_3$ which, unlike the reaction of TAG with F_2, results in the formation of 6-deoxy-6,6-difluoro-D-glucose (6-DDFG) [14]. The attempted syntheses did not, however, result in OF_2 formation which was confirmed by the absence of 6-DDFG in the ^{19}F NMR spectra when the effluent gas was passed through $CFCl_3$ solutions of TAG. Consequently, fluorinations of the aromatic systems investigated in this study were carried out using unlabeled OF_2.

2.2. Solvent and isomer effects

Solvent acidity has been shown to play an important role in the direct fluorination reactions of aromatic amino acids [26]. In attempts to find a suitable solvent medium for the fluorination of aromatic amino acids by OF_2, the effect of solvent acidity was also studied using *m*-tyrosine (MT) as the substrate. Direct fluorination of MT using F_2 results in the formation of 2-, 4-, 5- or 6-fluoro-*m*-tyrosine (6-FMT), the degree of which varies with solvent acidity [27].

Several protic solvent media, namely, aHF (Hammett acidity, $H_o = -15.1$) [28], CF_3SO_3H ($H_o = -13.8$) [28], CF_3COOH, CH_3COOH, HCOOH and H_2O, were utilized for the fluorination of MT (Table 1). It was shown that, unlike F_2, fluorination by OF_2 was less efficient in superacidic media. Fewer byproducts and higher ratios of fluorinated MT isomers were formed in solvent media of lower acidity as determined by analytical HPLC (Fig. 1). After analysis of the reaction mixtures by ^{19}F NMR spectroscopy, each sample was spiked with known quantities (1.03 and 2.07 ± 0.04 μmol) of the internal standard, *m*-fluoro-DL-tyrosine. Fluorine-19 NMR peak integrations of the spiked reaction mixtures were then used to calculate reaction yields (Table 1). It was shown that the highest yield (4.35 ± 0.04%) and lowest amounts of fluorinated byproducts were obtained when H_2O was used as the solvent for fluorination of MT with OF_2. The ^{19}F NMR spectrum of 6-FMT (−129.3 ppm, complex multiplet), 4-FMT (−138.4 ppm, doublet of doublet of doublets, $^3J(F - H_5) = 11.3$ Hz, $^4J(F - H_6) = 4.2$ Hz, $^4J(F - H_2) = 7.4$ Hz), and 2-FMT (−142.2 ppm, doublet of doublets, $^4J(F - H_4) \approx {}^4J(F - H_6) = 7.1$ Hz) agree with those reported in the literature [29].

Table 1
Effect of solvent acidity on the fluorination of *m*-tyrosine by OF_2

Solvent	Temperature (°C)	Product	Relative amounts (2:4:6)	Yield ± 0.04%[a]	Fluorinated by-products[b] (%)
H_2O	23	2-, 4-, and 6-FMT	33:20:47	4.35	0
HCOOH	23	2-, 4-, and 6-FMT	26:8:66	2.17	60
CH_3COOH	23	2- and 6-FMT	30:0:70	2.19	67
CF_3COOH	23	2- and 6-FMT	30:0:70	2.60	74
CF_3SO_3H	23	2- and 6-FMT	9:0:91	1.41	85
aHF	−60	FMT not formed	–	–	–

[a] Yields are reported with respect to OF_2.
[b] Percentages of fluorinated byproducts were calculated from the total integrated peak intensities in ^{19}F NMR spectra.

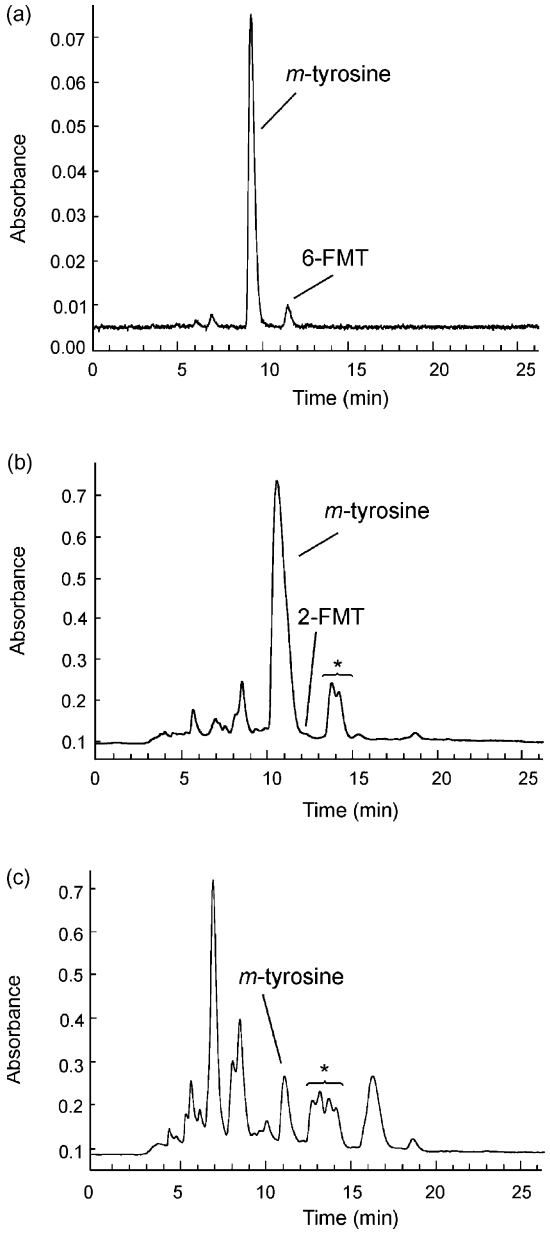

Fig. 1. UV chromatograms for reaction mixtures resulting from the fluorination of MT at 23 °C in (a) H_2O, (b) CH_3COOH and (c) CF_3COOH. The asterisk (*) denotes peaks corresponding to 4- and 6-FMT isomers which cannot be specifically assigned because of overlap and more intense byproduct peaks.

The effect of the electron donating OH substituent at the *ortho*-, *meta*- and *para*-positions on the fluorination of aromatic amino acids by OF_2 was studied using *o*-, *m*- and *p*-tyrosine as the substrates. Contrary to expectations, MT was the only isomer shown by ^{19}F NMR spectroscopy and HPLC to be fluorinated by OF_2, showing that OF_2 is, in this instance, a highly selective fluorinating agent.

2.3. Fluorination by OF_2

In order to investigate the suitability of OF_2 as a fluorinating agent for aromatic amino acids, several systems were studied in which the electron density in the π-system was directed towards different ring sites using electron withdrawing and electron donating ring substituents. The solvent medium used for this study was H_2O because it produced the highest isomeric ratios of 6- and 4-fluoro-*m*-tyrosine and smallest amounts of fluorinated byproducts in the fluorination of MT.

Initially, L-phenylalanine, which contains the *ortho*- and *para*-directing electron donating alanine group, was examined. Although direct fluorination of L-phenylalanine results in the formation of 2-, 3-, and 4-fluoro-L-phenylalanine isomers [29], analytical HPLC and ^{19}F NMR spectroscopy indicated that fluorination with OF_2 did not result in the formation of fluorinated phenylalanine.

The fluorination of DL-tyrosine, which contains two electron donating (alanine and hydroxyl) groups, was also studied with the aim to further localize the electron density in the π-system in order to promote the electrophilic fluorination by enhancing the nucleophilicity of the phenyl ring at the activated sites. The direct fluorination of DL-tyrosine has been shown to result in the formation of 3-fluoro-DL-tyrosine [30], however, fluorination using OF_2 did not yield any fluorinated tyrosine isomers.

Compounds with greater electron localization in the π-system were also investigated by the use of additional hydroxyl substituents (L-DOPA) and utilization of the stronger electron donating CH_3O-group (3-*O*-methyl-L-DOPA and dimethoxy-L-DOPA). As previously reported, direct fluorination of L-DOPA in non-superacidic solvent media results in the formation of 2- and 5-FDOPA [26], whereas direct fluorination of 3-*O*-methyl-L-DOPA and dimethoxy-L-DOPA results in the formation of 3-*O*-methyl-6-fluoro-L-DOPA and 2-, 5- and 6-fluoro-dimethoxy-L-DOPA isomers [31]. The fluorination of L-DOPA, 3-*O*-methyl-L-DOPA and dimethoxy-L-DOPA by OF_2, however, did not result in any fluorinated aromatic products as indicated by analytical HPLC and ^{19}F NMR spectroscopy. Similar results were obtained when electron withdrawing NO_2 substituted derivatives were used as substrates, namely, 3-nitro-L-tyrosine and 4-nitro-DL-phenylalanine.

3. Conclusion

The effect of solvent acidity on the fluorination of MT using OF_2 was studied and it was shown that, in contrast with the reactivity of F_2 in superacids, OF_2 is a more efficient fluorinating agent in less acidic solvent media. The use of H_2O as the solvent medium for fluorination of MT resulted in the formation of FMT isomers in $4.35 \pm 0.04\%$ yield.

The potential use of OF_2 as a fluorinating agent for aromatic amino acids was also investigated in the cases of L-phenylalanine, 3-nitro-L-tyrosine, 4-nitro-DL-phenylalanine, 3,4-dihydroxyphenyl-L-alanine (L-DOPA), 3-*O*-methyl-L-DOPA, 3,4-dimethoxy-L-phenylalanine, *m*-, *p*- and *o*-tyrosine. In these studies, the only aromatic system fluorinated by OF_2 was MT. These results indicate that the presence of $[^{18}F]OF_2$ (up to 20%) as a major byproduct resulting from the nuclear reaction, $^{18}O(p, n)^{18}F$, does not have a negative impact on the syntheses of radiofluorinated aromatic amino acids having applications in PET imaging.

4. Materials and methods

4.1. Reagents

Oxygen difluoride (1% in neon, Ozark-Mahoning), helium (Matheson, 99.9999%), D_2O (Cambridge Isotope Laboratories Inc., 99.9%), CF_3SO_3H (Fluka, 99.8%), aHF (Air Products, 99.9%), CF_3COOH (Caledon, 99.9%), glacial CH_3COOH (BDH, 99.7%), HCOOH (Riedel-de Haën, 98%) and HPLC grade CH_3CN (Caledon), L-phenylalanine (Aldrich, 98%), *m*-tyrosine (Aldrich, 98%), DL-tyrosine (Aldrich, 99%), *o*-tyrosine (Aldrich, 96%), L-DOPA (Aldrich, 99%), 3-*O*-methyl-L-DOPA (Aldrich), 3-nitro-L-tyrsoine (Aldrich, 98%), 4-nitro-DL-phenylalanine (Aldrich, 98%), *m*-fluoro-DL-tyrosine (Aldrich), 3,4,6-tri-*O*-acetyl-D-glucal (Aldrich, 98%), anhydrous KF (Aldrich, 99.99+%) and $KF{\cdot}2H_2O$ (Aldrich, 98%) were used without further purification and/or drying. Sterile, deionized water was used in all aqueous procedures.

4.2. Production of $[^{18}F]F_2$

Fluorine-18 labeled F_2 was produced by the nuclear reaction, $^{18}O(p, n)^{18}F$, using a Siemens RDS 112 proton cyclotron, operating at 11 MeV, and the ''double shoot'' method [21,22] in the Nuclear Medicine Department at Hamilton Health Sciences. An aluminum target (11 mL) was pressurized to 14–16 atm with 99% enriched $[^{18}O]O_2$ and irradiated for 20 min using a 30 μA proton beam (production shoot). After irradiation, the $[^{18}O]O_2$ was recovered from the target by condensation at −196 °C into a cryo-trap consisting of molecular sieves (Varian VacSorb) contained in a 316 stainless steel Whitey® cylinder (75 mL). The target was pumped to remove trace amounts of $[^{18}O]O_2$ and subsequently filled with 1% F_2 (40–50 μmol) in neon, pressurized to 20 atm with neon, and irradiated for 10 min in a 15 μA proton beam (recovery shoot). Portions of the $[^{18}F]F_2$/Ne mixture were periodically released from the target into a continuous stream of helium until the target pressure dropped to 2 atm. Helium was used as the sweep gas to transfer $[^{18}F]F_2$ from the target into the hot cell.

4.3. Attempted preparation of $[^{18}F]OF_2$

In a typical reaction, 100 mg of $KF{\cdot}2H_2O$ and 300 mg of anhydrous KF were loaded into a 1/2 in. o.d. FEP U-tube which was attached to two PFA Whitey valves by means of stainless steel Swagelok 1/2 to 1/4 in. reducing unions and lengths of 1/4 in. FEP tubing (Fig. 2).

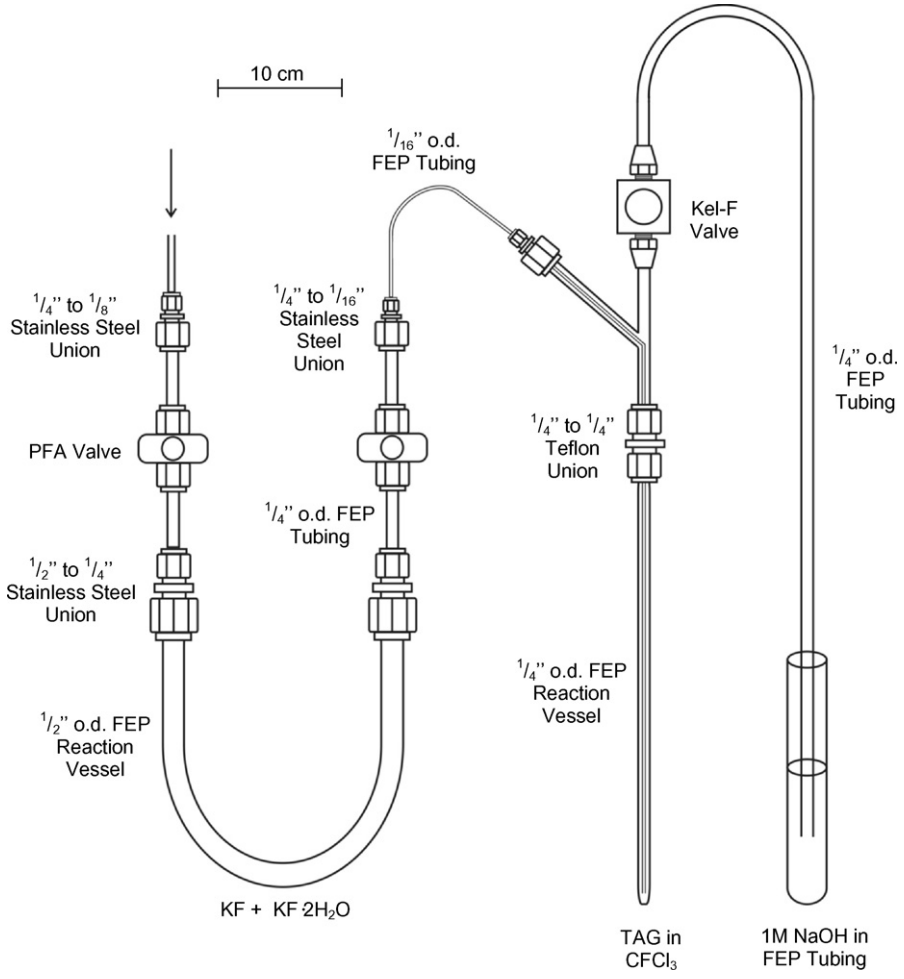

Fig. 2. Schematic diagram of the apparatus used in the attempted synthesis of $[^{18}F]OF_2$.

One end of the U-tube was connected to the $[^{18}F]F_2$ target, while the other end was connected to a 5/16 in. o.d. × 5/32 in. i.d. FEP reaction vessel that was, in turn, attached to an FEP Y-piece by means of a 1/4 in. Teflon Swagelok union. A length of 1/16 in. o.d. × 1/32 in. i.d. FEP tubing, connected to a valve of the U-tube, was fed through the sidearm of the Y-piece into a reaction vessel containing 13 mg of TAG in 0.5 mL of $CFCl_3$. The other arm of the Y-piece was connected, through a 1/4 to 1/16 in. Teflon reducing union, to a length of 1/16 in. o.d. FEP tubing that was immersed in 1 M NaOH. The U-tube, containing an equimolar mixture of anhydrous KF and $KF{\cdot}2H_2O$, was pressurized with $[^{18}F]F_2$ (typically 60 ± 5 μmol of F_2 was used) and was agitated for 110 min at room temperature, after which the gas was passed through the TAG solution. The fluorinated reaction mixture was then analyzed by ^{19}F NMR spectroscopy after hydrolysis using 1.2 M HCl carried out over 17 min at 130 °C.

4.4. Electrophilic fluorination of aromatic amino acids in H_2O, HCOOH, CH_3COOH, CF_3COOH, CF_3SO_3H, and aHF

Substrates (13 mg), were each dissolved in 0.5 mL of solvent and the solution was added to 5/16 in. o.d. × 5/32 in. i.d. FEP reaction vessels connected to FEP Y-pieces. A length of 1/16 in. o.d. × 1/32 in. i.d. FEP tubing, connected to the OF_2 source at one end, was fed through the sidearm of the Y-piece into the reaction vessel. The other arm of the Y-piece was connected to a separate length of 1/16 in. o.d. FEP tubing, which was immersed in 1 M NaOH. In reactions where aHF was utilized as the solvent medium, the reaction vessel and contents were allowed to equilibrate for 30 min at selected temperatures in a liquid nitrogen/CH_3OH bath prior to fluorination. Oxygen difluoride gas (typically 40 μmol) was passed through the substrate solution and the effluent gas was passed through 1 M NaOH before it was vented into the hot cell.

Removal of CF_3SO_3H from the fluorinated MT reaction mixtures were achieved using a 250 mm × 10 mm anion exchange column (Bio-Rad AG 1-X8 in acetate form). The reaction mixture was loaded onto the column and 20 mL of 0.1N HCl was used as the eluent. The eluate was then evaporated on a rotary evaporator and was subsequently analyzed by HPLC.

4.5. Determination of reaction yields for FMT isomers

A 10.3 mg sample of *m*-fluoro-DL-tyrosine was dissolved in 5.00 mL of 0.100 M HCl for use as an internal standard. Two 0.100 mL aliquots of 0.010 M *m*-fluoro-DL-tyrosine were then added stepwise to each reaction mixture, which was analyzed by ^{19}F NMR spectroscopy after each addition. Each aliquot contained 1.03 ± 0.04 μmol of *m*-fluoro-DL-tyrosine, so that ^{19}F NMR peak integrations could be used to calculate the FMT isomer yields.

4.6. Analyses of reaction mixtures by HPLC and NMR spectroscopy

The ring-fluorinated aromatic amino acids were analyzed using a reverse-phase analytical HPLC column (Keystone, Fluophase, 5 μm, 150 mm × 10 mm). A solution of 0.2% CF_3CO_2H in water containing 7% CH_3CN was used as the mobile phase with a flow rate of 2.5 mL min^{-1}. The eluate from the column was monitored by the use of a Waters 490E Programmable Multi-wavelength Detector set at 280, 254 and 230 nm. A typical UV chromatogram of the FMT reaction mixture showed peaks at 9.3 and 11.4 min corresponding to MT and 6-FMT, respectively. The MT peak was identified by injection of a standard solution which eluted at 9.9 min. The peak eluting at 11.4 min was collected and was shown by ^{19}F NMR spectroscopy to be 6-FMT. In addition, the reaction mixture was analyzed by ^{19}F NMR spectroscopy to obtain the relative molar amounts of products. The isomeric ratios of the mono-fluorinated aromatic amino acids were determined by peak integrations of the ^{19}F NMR spectra.

Fluorinated MT isomers were also analyzed by the use of a reverse-phase preparative HPLC column (Keystone, Fluophase, 5 μm, 250 mm × 10 mm). A solution of 17 mg of ascorbic acid in 500 mL of 0.1% aqueous CH_3CO_2H was used as the mobile phase with a flow rate of 3.5 mL min^{-1}. The eluate from the column was monitored by means of a UV detector set at 280 nm. The 6- and 4-FMT isomers, typically appearing at 12.8 and 13.9 min on the UV chromatogram, were collected and analyzed by ^{19}F NMR spectroscopy.

The ^{19}F NMR spectra were recorded on a Bruker Avance 200 (4.6976 T) or DRX-500 (11.7440 T) spectrometer using a pulse width of 1 μs corresponding to a bulk magnetization tip angle of ~90°. Fluorine-19 NMR spectra were obtained at 11.7440 T and were typically accumulated over a spectral width of 14 kHz (acquisition time, 1.16 s), using 300 scans and 32K memories, yielding data point resolutions of 0.35 Hz/point. Fluorine-19 NMR spectra obtained at 4.6976 T were accumulated over a spectral width of 17 kHz (acquisition time, 0.94 s), using 200 scans and 32K memories, yielding a data point resolution of 0.53 Hz/point. Spectra were referenced at 25 °C to external $CFCl_3$. The chemical shift convention used is that positive and negative signs indicate chemical shifts to high and low frequencies relative to that of the reference compound.

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