Fluorine-18 Labeling of Methionine Derivatives in the Presence of Xenon Difluoride[1)]

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Radiofluorination of protected methionine derivatives were examined in the presence of xenon difluoride (XeF_2). The simple reaction procedure with ^{18}F-tetrabutylammonium fluoride and XeF_2 led *N*-Boc-methionine esters to corresponding ^{18}F-fluoromethyl thioethers. The deprotection of the obtained labeled compounds was unsuccessful. This method expands the range of target molecules that can be labeled by fluorine-18 for noninvasive clinical measurements using positron emission tomography.

Key words fluorine-18; positron emission tomography; xenon difluoride

Noninvasive imaging of a specific biochemical or physiological function by positron emission tomography (PET) is a powerful tool in clinical diagnosis, neuroscience, and many other fields of medical and biological science. Among the short-lived positron emitting radionuclides, fluorine-18 ($t_{1/2}=110$ min) is the most attractive from the viewpoint of radiosynthesis, radiopharmaceutical design, and radiology as well as clinical diagnosis.[2)] Although some efforts have been made to examine the synthesis and the biological activity of ^{19}F-fluorinated amino acids,[3)] the number of reports on fluorine-18 labeled amino acids is limited.[4)] Carbon-11 is another representative positron emitter with a half-life of 20.4 min, and methionine labeled with this nuclide is widely used in cancer diagnosis. Therefore ^{18}F labeled methionine analogs should be promising.[5)] The report of fluorination of methionine derivatives by xenon difluoride (XeF_2)[6)] encouraged the author to examine its application to ^{18}F chemistry.

Although the feasibility of stable XeF_2 is well established[7)] there have been only limited examples of fluorine-18 labeled xenon difluoride (^{18}F-XeF_2). Schrobilgen *et al.* reported the synthesis of ^{18}F-XeF_2 by distillation of carrier added (CA) $H^{18}F$ (a radioisotope which was intentionally diluted by stable isotope) into XeF_2.[8)] Chirakal and colleagues reported the reaction of CA $^{18}F_2$ and Xe to afford ^{18}F-XeF_2.[9)] These two methods ensured the synthesis of ^{18}F-XeF_2 but required special synthetic apparatus. Patrick *et al.* reported on the fluorodecarboxylation reaction in the presence of XeF_2.[10)] The simple work-up they employed was to mix the anhydrous fluorine-18 labeled tetrabutylammonium fluoride ($(n\text{-Bu})_4N^{18}F$), XeF_2, and a substrate in CH_2Cl_2. The present author applied this procedure to the fluorination of a methyl thioether moiety. *N*-Boc-protected methionine esters were prepared and allowed to react as shown in Fig. 1.

The incorporation of ^{18}F proceeded with CA (n-$Bu)_4N^{18}F$ in CH_2Cl_2 (Table 1).[11)] The radiochemical yield of a methyl ester was superior to that of a *t*-butyl ester. Patrick *et al.* suggested that isotopic exchange between ^{18}F-fluoride and XeF_2 would not occur under the present reaction conditions and the XeF_2 catalyzed generation of a cationic species which captures radioactivity.[10)] This XeF_2-catalyzed radiofluorination mechanism could also be applied to the present result and CH_3CN might have an adverse effect on the generation of the active intermediate. The three previous studies employed CA fluorine-18, which reduces the specific radioactivity and therefore the sensitivity of measurement with the radiopharmaceutical thus obtained.[8–10)] However, no carrier added ($(n\text{-Bu})_4N^{18}F$ was also found ineffective in this synthesis by direct comparison.

Janzen *et al.*[6)] and others[12)] reported on the instability of the CFH_2S– group with acid treatment. The deprotection of the labeled derivatives with CF_3COOH was also unsuccessful in the present experiment. Only a polar compound which was considered to be ^{18}F-fluoride was observed with this treatment.

In summary, incorporation of ^{18}F into the methylthioether moiety of the protected methionine derivatives was observed in the presence of XeF_2. Deprotection with CF_3COOH to obtain radiofluorinated methionine was unsuccessful. But the method employed here is very simple and easily accessible as it requires no special treatment (*i.e.*, introduction of a leaving group) to the substrates. ^{18}F labeling of methionine containing small peptides such as substance P[13)] appears promising. This new reaction should enlarge the range of target molecules that can be labeled for the imaging of biological processes with

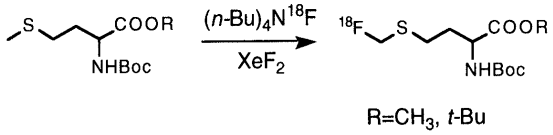

Fig. 1. Reaction Scheme

Table 1. Radiochemical Yield of ^{18}F-Fluorinations

$(n\text{-Bu})_4N^{18}F$	Solvent	Substrate	Radiochemical yield
NCA	CH_3CN	*N*-Boc-methionine methyl ester	No reaction
CA	CH_3CN	*N*-Boc-methionine methyl ester	No reaction
NCA	CH_2Cl_2	*N*-Boc-methionine methyl ester	No reaction
CA	CH_2Cl_2	*N*-Boc-methionine methyl ester	12.3%
CA	CH_2Cl_2	*N*-Boc-methionine *t*-butyl ester	1.9%

The Reaction mixture was stirred at room temperature for 60 min. NCA, no carrier added; CA, carrier added.

PET.

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References and Notes

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11) Aqueous solution of ^{18}F-fluoride was obtained by proton irradiation of 20% ^{18}O-enriched water (Enritech, Israel) using an MCY-1750 cyclotron (Shimadzu, Japan) and circulating water target system (NKK, Japan). To the ^{18}F-fluoride solution tetrabutylammonium hydroxide (5 μmol, Wako Pure Chemical, Japan) or tetrabutylammonium fluoride (5 μmol, Sigma-Aldrich, USA) was added to obtain NCA or CA $(n\text{-Bu})_4\text{N}^{18}\text{F}$, respectively. The mixture was dried at 80 °C under a nitrogen gas stream and *in vacuo*. The residue was cooled to −20 °C and XeF_2 (12 μmol, Sigma-Aldrich, U.S.A.) and a substrate (20 μmol) were added. The reaction vessel was sealed and warmed to ambient temperature. The reaction mixture was analyzed by radio TLC. The TLC plate (Kieselgel 60 F_{254}, Merck, Germany) was cut into pieces and radioactivity was counted with a gamma counter (ARC-2000, Aloka, Japan) after development in diethylether : *n*-hexane (3 : 7).
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