C-11 Production with MC-50 Cyclotron and Synthesis of L-[\textit{\textsuperscript{11}}C-Methyl] Methionine

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Abstract

L-[\textit{\textsuperscript{11}}C-methyl] methionine was prepared via no-carrier-added(nca) fast S-alkylation of L-homocysteine with [\textit{\textsuperscript{11}}C]CH\textsubscript{3}I using solid support (Al\textsubscript{2}O\textsubscript{3}/KF) at room temperature in ethanol. The radiochemical yield of methylation was 90.2%. After reaction, no radiochemical impurity was detected but traces of L-homocysteine precursor were monitored by UV detector. The purification was archived by passing successively through a C\textsubscript{18} and alumina Sep-Pak. The radiochemical purity of L-[\textit{\textsuperscript{11}}C-methyl] methionine was over 98% after purification and total elapsed time to prepare was 10min from [\textit{\textsuperscript{11}}C]CH\textsubscript{3}I delivery.

1. Introduction

\textit{\textsuperscript{11}}C-11 (T\textsubscript{1/2}=20.4min.) is one of the important positron emitting radionuclides for positron emission tomography(PET). It can replace natural carbon in a biologically active compound without altering its physiological properties. Physical properties of C-11 are given table 1.
Table 1. Physical properties of C-11

<table>
<thead>
<tr>
<th>Physical properties</th>
<th>20.4 min.</th>
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<tbody>
<tr>
<td>Half-life</td>
<td>20.4 min.</td>
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<tr>
<td>Decay mode</td>
<td>β⁺(99.76), EC(0.24)</td>
</tr>
<tr>
<td>E_max of β⁺</td>
<td>960 keV</td>
</tr>
<tr>
<td>Range of β⁺ in water</td>
<td>~4 mm</td>
</tr>
<tr>
<td>Principal γ-rays</td>
<td>511(199.6%) keV</td>
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</tbody>
</table>

C-11 is usually produced by the irradiation of high purity nitrogen gas using \(^{14}\)N(p, \(α\))\(^{11}\)C nuclear reaction. The C-11 reacts with traces of oxygen to give \(^{11}\)CO₂, which is an important precursor for C-11 labelled radiopharmaceuticals[1].

In this study, the target system was designed and fabricated. The \([^{11}\text{C}])\text{CH}_3\text{I} was prepared using GE MeI microlab. The \([^{11}\text{C}])\text{methylmethionine} was synthesized.

![Fig. 1. Decay scheme of C-11](image)

2. Experiment

2.1. Design of target

The target for the production of \([^{11}\text{C}])\text{CO}_2 was fabricated with pure Al. The entire target system was shown in Fig. 1. The target chamber was fabricated in conical shape. The diameter of the inlet window is 16 mm, that of the exit window is 28.5 mm and the length of the target chamber is 15 cm. The volume of the target chamber is 57.5 ml. The cooling water jacket was welded on the target chamber by
electron beam. The front window was fabricated with Al, and it acts as a beam degrader, which moderates 35MeV proton beam down to 13MeV. The front window was designed to be cooled effectively by water.

SS tubing (O.D.=1/8", I.D.=1/16") was used to transfer the target gas before and after irradiation.

2.2. Production of $[^{11}\text{C}]\text{CO}_2$

All experiments for the production of $[^{11}\text{C}]\text{CO}_2$ were carried out on MC-50 cyclotron at KCCH. The proton beam of MC-50 cyclotron for radionuclides production is generally available at the energy of 35MeV, and the beam enters the actual target material at 13.1MeV after degradation by the Al entrance windows, calculated by the Williamson's stopping power data. Various C-11 Production routes are given table 2.

$[^{11}\text{C}]\text{CO}_2$ was produced on MC-50 cyclotron by the $^{14}\text{N}(p,\alpha)^{11}\text{C}$ nuclear reaction on nitrogen(99.999% purity) containing 0.5% oxygen at 176.4psi. Bombardment was carried out for 15-30min with 30$\mu$A beam of 35MeV protons. At the end of bombardment (EOB), the target was vented through a flow regulator set to 500ml/min into a loop of stainless steel tube immersed in liquid nitrogen. The radioactivity trapped in the loop was 994-1,142mCi, decay corrected to EOB. The target used at Korea Cancer Center Hospital is shown in Figure 2.

<table>
<thead>
<tr>
<th>Table 2. Nuclear Reaction for the C-11 Production</th>
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<tbody>
<tr>
<td>Nuclear Reaction</td>
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<tr>
<td>$^{14}\text{N}(p,\alpha)^{11}\text{C}$</td>
</tr>
<tr>
<td>$^{11}\text{B}(p,n)^{11}\text{C}$</td>
</tr>
<tr>
<td>$^{10}\text{B}(d,n)^{11}\text{C}$</td>
</tr>
</tbody>
</table>

After completion of $[^{11}\text{C}]\text{CO}_2$ trap, it was heated and transferred to GE MeI microlab to produce $[^{11}\text{C}]\text{CH}_3\text{I}$. 
2.3. Synthesis of $[^{11}\text{C} ]\text{methylmethionine}$

2.3.1 Precursor preparation (Homocystine - Homocysteine)

1g of homocystine in 20ml of liquid ammonia are reduced with 3g of metallic sodium. The excess sodium is destroyed by addition of a few crystals of ammonium iodide, and the ammonia is allowed to evaporate. The last traces of residual ammonia are removed by evacuation of the flask. The flask is flushed with nitrogen, 3.5ml of freshly boiled distilled water are added. 45% hydriodic acid is added until the solution is just acid to litmus. A small amount of decolorizing charcoal is added, and the solution is filtered. 20ml of absolute ethanol are added through the Büchner funnel. The flask is quickly stoppered, the side arm is closed, and the flask is cooled in the refrigerator overnight. The homocysteine is collected under an atmosphere of nitrogen and is washed with ethanol and ether[2]. A total of 700mg is obtained(fig. 3.).

![Chemical reaction diagram](image)

**Fig. 3. Reduction of homocystine to homocysteine**
2.3.2 Solid support preparation

3g of Al₂O₃ are mixed with 2g of KF in 40ml of H₂O, and the water is removed at 50-60°C in a rotary evaporator[3],[4].

2.3.3 S-alkylation reaction

[^\(^{11}\)C\]CH₃I is trapped at 0°C in a suspension of Al₂O₃/KF(10mg) in a solution of L-homocysteine(80\(\mu\)g) in 0.5ml of absolute ethanol. The reaction is allowed to proceed for about 4min at room temperature. 4ml of 0.05M NaH₂PO₄(pH 4.4) buffer is added. The reaction mixture is filtered through a 0.45\(\mu\)m filter, diluted with 13.5ml of 0.05M NaH₂PO₄(pH 4.4) buffer and passed successively through a C18 and an alumina Sep-Pak. The isotonicity of the final solution was obtained by adding 10% NaCl(1.3ml). The solution is filtered through 0.22\(\mu\)m filter to ensure sterility[5].

2.3.4 Quality control

The radiochemical and chemical purities were analyzed by high pressure liquid chromatography(fig. 4.). The analysis were done with µ-Bondapak C18 column(200 x 3.9mm, 10\(\mu\)m, Waters); flow rate 1ml/min; eluent : 3mM NaH₂PO₄[5].

![Fig. 4. HPLC analysis of the purified L-[\(^{11}\)C-methyl] methionine. UV and RI profiles have been recorded simultaneously. Retention time 4.570 min indicates L-[\(^{11}\)C-methyl] methionine in RI profile.](image-url)
3. Results and Discussion

The yield of $^{11}$C$\text{CO}_2$ was about 59mCi/$\mu$A. The yield of $^{11}$C$\text{CH}_3$I was 260-290mCi and the radiochemical purity is over 99%. In the presence of Al$_2$O$_3$/KF, the methylation of L-homocysteine with $^{11}$C$\text{CH}_3$I is very fast and efficient. The yield of methylation was over 90%. After 4min reaction, the radiochemical purity of $^{11}$C$\text{methylmethionine}$ was over 98%. Under the conditions, 150-160mCi of $^{11}$C$\text{methylmethionine}$ can be produced after 30min irradiation at 30$\mu$A. The total elapsed time for the synthesis L-$^{11}$C-methyl] methionine was 10min from $^{11}$C$\text{CH}_3$I delivery. No preparative HPLC seemed to be needed because HPLC analysis showed that the chemical and radiochemical purities of the final solution were high enough to make HPLC purification unnecessary. The mild alkylation reaction make the automation of the L-$^{11}$C-methyl] methionine production much easier.

4. References