III. 1. An Automated $[^{11}\text{C}]\text{H}_3\text{I}$ Synthesis System with Feedback Control for Preparation of High Specific Activity $^{11}\text{C}$-Radiopharmaceuticals

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Introduction

$[^{11}\text{C}]\text{H}_3\text{I}$ is one of the most widely used precursors for $^{11}\text{C}$-labeling. It can be easily and rapidly prepared from $[^{11}\text{C}]\text{O}_2$ according to the following reactions:

$$[^{11}\text{C}]\text{O}_2 + \text{LiAlH}_4/\text{THF} \xrightarrow{1}\text{THF} \xrightarrow{2}[^{11}\text{C}]\text{H}_3\text{OH} \xrightarrow{\text{HI}}[^{11}\text{C}]\text{H}_3\text{I}.$$  

Although the preparation of L-$[^{11}\text{C}]$methionine is representative of the importance of $[^{11}\text{C}]\text{H}_3\text{I}$, versatile utility of the precursor can be found in preparation of many $^{11}\text{C}$-labeled receptor ligands such as N-$[^{11}\text{C}]$methylspiperon,$^{1}$ $[^{11}\text{C}]$RO 151788$^{2}$ and $[^{11}\text{C}]$YM09151-2$^{3}$ by N-$[^{11}\text{C}]$methylspiperon. Consequently high specific activity is always required for this labeling precursor. The carrier is inevitably produced to some extent mainly by the decomposition of the LiAlH4-THF complex in the synthesis of $[^{11}\text{C}]\text{H}_3\text{I}$,$^{4}$ whereas $[^{11}\text{C}]\text{H}_3\text{I}$ with high specific activity can be still obtained by using both the minimum amount of a carefully realed THF solution of LiAlH4 and a rapid synthetic procedure from a large quantity of starting $[^{11}\text{C}]\text{O}_2$.

While a synthesis system is thus not directly responsible for specific activity of $[^{11}\text{C}]\text{H}_3\text{I}$, it is usually required that the system should perform rapidly the whole synthetic procedure in high production efficiency even with the smallest amount of LiAlH4 in THF for reduction of $[^{11}\text{C}]\text{O}_2$. Also a main purpose of automation is to achieve high reliability of a synthesis system in its routine use. We have developed a fully automated $[^{11}\text{C}]\text{H}_3\text{I}$ synthesis system, based on the experience of using the remote-controlled system at CYRIC.$^{4}$ Feedback control has been adopted in the synthesis system using a personal computer coupled with radiation and temperature sensors.
Description of the System and Principle of the Automation

Figure 1 illustrates a schematic flow chart of the present system for the preparation of \([^{11}\text{C}]\text{H}_3\text{I}\) from \([^{11}\text{C}]\text{O}_2\) and Fig.2 shows a whole view of the system. A personal computer (NEC 9801 RX2) is used as a controller. The synthetic procedure incorporated in the system consists of the following main steps:

1. \([^{11}\text{C}]\text{O}_2\) recovery and concentration. The \([^{11}\text{C}]\text{O}_2\) produced is recovered at a target gas flow rate of approximately 1 l/min from the target chamber immediately after the irradiation, and trapped in a copper spiral tube cooled with liq. Ar for concentration before introducing it in the LiAlH\(_4\)/THF.

2. \([^{11}\text{C}]\text{O}_2\) bubbling. The \([^{11}\text{C}]\text{O}_2\) is liberated from the trap by heating with a hot blower and bubbled into the LiAlH\(_4\)/THF solution cooled below 0°C with a cold He flow.

3. THF evaporation. The THF is removed with a He flow by heating.

4. HI injection. One ml of hydroiodic acid is added to the residue after the vessel has been cooled again below 0°C.

5. \([^{11}\text{C}]\text{H}_3\text{I}\) distillation. The \([^{11}\text{C}]\text{H}_3\text{I}\) formed is distilled and transferred under a He current to a reaction vessel for subsequent synthetic reactions.

A radioactivity level at the \([^{11}\text{C}]\text{O}_2\) inlet line to the trap is monitored with one of the radiation sensors to detect both a start and end of the target gas transfer as the level reflects the \([^{11}\text{C}]\text{O}_2\) concentration in the transferred target gas. The other sensor is used to monitor a change in the radioactivity at the reaction vessel, and thus the step 2 is continued until no increase in the activity is observed, and the step 5 is completed by detection of no decrease in the activity. Typical radioactivity curves observed during the synthesis are shown in Fig. 3 along with detection marks of start or end in corresponding step. Two temperature sensors (thermocouple) are employed to control cooling or heating the trap and the reaction vessel, respectively. As shown in Fig. 4, the temperature at the flowing He gas begins to decrease after the THF has been evaporated. Accordingly completion of the THF evaporation can be easily detected with a temperature sensor inserted into one of the outlet ports of the reaction vessel. An automatic thermal mass flow controller is used to control a He flow rate in the system. It is regulated at 20 ml/min for bubbling \([^{11}\text{C}]\text{O}_2\) into the LiAlH\(_4\)/THF, and at 100 ml/min for THF evaporation and \([^{11}\text{C}]\text{H}_3\text{I}\) distillation. This device is also used to check leaking in the system and clogging in the absorbing columns before starting the synthesis.
Performance Results and Discussions

One hour irradiation at a beam current of 10 µA for the production of $^{[11]}\text{C}O_2$ was carried out using 18 MeV proton at CYRIC. From an estimated $^{11}\text{C}$ production yield of 23.7 GBq (640 mCi), an average yield of 14.8 GBq (400 mCi) of $^{[11]}\text{C}H_3$I was obtained 8 min after the irradiation, corresponding to a decay-corrected yield of 83 %, and approximately 10 % of the $^{11}\text{C}$-activity was found in the reaction vessel. However, it is reasonable that $^{11}\text{C}$-radioactivity remains in the reaction vessel to some extent because the controller finishes the final step when a $^{[11]}\text{C}H_3$I distillation rate decreases to less than the $^{11}\text{C}$ decay rate. Table 1 lists typical performance results of the synthesis obtained with the present system. The first step in the synthesis depends on a $^{[11]}\text{C}O_2$ production system. It usually takes more than 3 min to recover the entire $^{[11]}\text{C}O_2$ from the target chamber at a maximum target flow rate of 1 l/min since the $^{[11]}\text{C}O_2$ in 2.4 l of a nitrogen target is transferred from a more than 20 m distant target site.

A THF solution of LiAlH$_4$ was prepared from 20 mg of LiAlH$_4$(Fluka) and 10 ml of freshly distilled THF under an inert atmosphere. A 100 µl of the solution was used for the preparation. Specific activity of the $^{[11]}\text{C}H_3$I produced with the present system was measured by synthesized $^{11}\text{C}$-labeled receptor ligands of $^{[11]}\text{C}YM-09151-2$ and $^{[11]}\text{C}pyrilamine$. The average specific activity was 37 GBq/µmol (1 Ci/µmol) at 45 min after the irradiation, and this value is high enough for clinical application of these $^{11}\text{C}$-radioligands to PET receptor studies.

In conclusion, it can be said that the present automated $^{[11]}\text{C}H_3$I synthesis system is very suitable for routine preparations of high specific activity $^{11}\text{C}$-receptor ligands due to its high reliability by feedback control.

References

Table 1. Typical performance results of the $[^{\textit{11}}\text{C}]\text{H}_3\text{I}$ synthesis with the automated system

<table>
<thead>
<tr>
<th>Step No.</th>
<th>Operation</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$[^{\textit{11}}\text{C}]\text{O}_2$ recovery and concentration</td>
<td>207 sec</td>
</tr>
<tr>
<td>2</td>
<td>$[^{\textit{11}}\text{C}]\text{O}_2$ bubbling THF evaporation</td>
<td>85 sec</td>
</tr>
<tr>
<td>3</td>
<td>THF evaporation</td>
<td>86 sec</td>
</tr>
<tr>
<td>4</td>
<td>HI injection</td>
<td>28 sec</td>
</tr>
<tr>
<td>5</td>
<td>$[^{\textit{11}}\text{C}]\text{H}_3\text{I}$ distillation</td>
<td>90 sec</td>
</tr>
<tr>
<td></td>
<td>Overall procedure</td>
<td>496 sec</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(8.3 min)</td>
</tr>
</tbody>
</table>
Fig. 1. A schematic flow chart of the automated $^{11}$C$\text{H}_3$I synthesis system.

SV: Solenoid valve, TV: Pneumatic PTFE valve, 
PV: Pinch valve, NV: Needle valve, 6WV: 6-way valve, 
PR: Pressure regulator, FC: Thermal mass flow controller, 
AC: Pneumatic cylinder, HB: Hot blower, HT: Heater, 
TS: Temperature sensor, RS: Radiation sensor, 
CC: Charcoal, PO: Phosphorus pentoxide, SL: Soda lime, 
HI: Hydroiodic acid.

Fig. 2. A whole view of the automated $^{11}$C$\text{H}_3$I synthesis system.
Fig. 3. Typical radioactivity curves during the $[\text{^{11}C}]\text{H}_3\text{I}$ synthesis.

Fig. 4. A temperature curve at the He gas flowing with THF.