III. 1 Automated Synthesis of $^{11}$CH$_3$I

Iwata R. and Ido T.
Cyclotron and Radioisotope Center, Tohoku University

Various kinds of $^{11}$C-radiopharmaceuticals have been synthesized from the simple compounds of $^{11}$CO$_2$ and $^{11}$CH$_4$ directly produced by the proton irradiation of the nitrogen gas target systems. These compounds are chemically converted to another useful labeling precursors such as $^{11}$CH$_3$I, $^{11}$CH$_2$O and H$^{11}$CN. Because of a short half-life of $^{11}$C(20.38 min), it is generally required that a large quantity of starting radioactivity should be used for the synthesis of them with rapid and remote-controlled techniques.\(^1,2\) Besides, advances in small medical cyclotron and positron emission tomography have made it necessary to develop the automated synthesis of short-lived radiopharmaceuticals for routine use in nuclear medicine.\(^3,4\)

$^{11}$CH$_3$I is widely used for $^{11}$C-labeling on organic compounds with biological or pharmacological activity in their methyl group. It is synthesized from $^{11}$CO$_2$ according to the following reaction scheme,

$$
^{11}\text{CO}_2 \xrightarrow{\text{LiAlH}_4/\text{THF} \quad -20^\circ\text{C}} \xrightarrow{\text{THF} \quad 70^\circ\text{C}} \xrightarrow{\text{H}_2\text{O} \quad -20^\circ\text{C}} \xrightarrow{\text{HI} \quad 100^\circ\text{C}} ^{11}\text{CH}_3\text{I} \quad \text{5)}
$$

where THF is tetrahydrofuran.

The prototype of the automated $^{11}$CH$_3$I synthesis system have been designed to be used for the investigation of the optimal reaction conditions and procedure suitable for the automation. The system constructed consists of the programmable controller and the operation units. Figure 1 shows the flow chart of the operation units. The miniature teflon electronic solenoid valves were used for controlling the gas flow and all the glass reaction vessels were designed to resist the solvent back flow into the gas transfer tube. The controller outputs the 23 independent control signals supplied by an external power source and inputs the 7 stepping signals from the limiter and the temperature controller. It has also the step preset timer (up to 99.9 min/step). The synthesis program was written on the ROMs of the controller by using the switch board and then it was executed by reading it from the ROMs step by step.

The $^{11}$CO$_2$ was continuously swept from the irradiation chamber to the concentration unit, where it was adsorbed on the Molecular Sieve 4A and then desorbed by inserting it into the furnace maintained at 270°C. The released $^{11}$CO$_2$ was then transferred under a He current to the reduction unit, where the vessel containing the LiAlH$_4$ in THF was cooled at -20°C by the blowing of lig. CO$_2$. After the $^{11}$CO$_2$ was bubbled into the LiAlH$_4$/THF, the THF was evaporated out by heating at 70-100°C under the reduced pressure. In the next step, the vessel was cooled again at -20°C and H$_2$O was injected in it to form $^{11}$CH$_3$OH. The $^{11}$CH$_3$OH
was distilled and carried under a He current by raising the temperature up to 100°C through the refluxing HI solution, where it was converted to $^{11}$CH$_3$I, and finally the $^{11}$CH$_3$I was collected in a cold solvent suitable for successive reactions, for example, acetone for the synthesis of L-methionine-[$^{11}$C].

The optimal conditions and procedure have been determined by the several performance tests of the system and the new controller has been constructed with the fixed program shown in fig. 2 and 3. $^{11}$CO$_2$ reacted almost quantitatively with LiAlH$_4$ even when it was bubbled into LiAlH$_4$/THF at a flow rate of 200 ml/min without the concentration process. The concentration of $^{11}$CO$_2$ may be effective only when a flow rate of more than 500 ml/min is used for sweeping it from the irradiation chamber. The total time required for the synthesis of $^{11}$CH$_3$I from $^{11}$CO$_2$ was within 25 min, and the radiochemical yield was constantly over 90% (see Table 1). The radiochemical yield, however, may depend on the preparation of anhydrous THF. It is recommended that THF should be freshly prepared from the careful distillation from LiAlH$_4$ before use.

This automated synthesis system has also demonstrated that $^{11}$CH$_3$I is repeatedly synthesized only by the exchange of the reduction vessel and the transfer tube of H$_2$O with fresh ones with a high radiochemical yield. It can be concluded that this system is suitable for the routine preparation of $^{11}$CH$_3$I.

References

2) Berger, G., Maziere, M., et al., ibid, 30 (1979) 393.
<table>
<thead>
<tr>
<th>Step No.</th>
<th>(Switch)</th>
<th>Operation</th>
<th>Stepping method</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(LEAK TEST)</td>
<td>test a He leak</td>
<td>manual</td>
</tr>
<tr>
<td>2</td>
<td>(SETUP)</td>
<td>heat the reduction vessel at 100°C under a He current</td>
<td>timer(3.0 m)</td>
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<tr>
<td>3</td>
<td></td>
<td>cool the vessel at -20°C under a He current</td>
<td>temperature controller</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>inject the LiAlH₄/THF into the reduction vessel</td>
<td>manual</td>
</tr>
<tr>
<td>5</td>
<td>(START)</td>
<td>bubble $^{11}$CO₂ into the LiAlH₄/THF</td>
<td>timer(up to 16.6 m)</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>evaporate the THF at 70°C under the reduced pressure</td>
<td>timer(3.0 m)</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>evaporate the THF at 100°C under the reduced pressure</td>
<td>timer(1.0 m)</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>evaporate the THF at 100°C under a He current</td>
<td>timer(1.0 m)</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>cool the reduction vessel at -20°C</td>
<td>temperature controller</td>
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<tr>
<td>10</td>
<td></td>
<td>wait for the vessel to be cooled at -20°C</td>
<td>timer(10 s)</td>
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<tr>
<td>11</td>
<td></td>
<td>inject H₂O into the reduction vessel</td>
<td>limitter</td>
</tr>
<tr>
<td>12</td>
<td></td>
<td>distil the $^{11}$CH₃OH and collect the $^{11}$CH₃I</td>
<td>timer(up to 16.6 m)</td>
</tr>
<tr>
<td>13</td>
<td></td>
<td>end</td>
<td></td>
</tr>
</tbody>
</table>
Table 2. Typical performance of the automated $^{11}$CH$_3$I synthesis

*Reagents

LiAlH$_4$/THF : 0.5 ml of THF saturated with LiAlH$_4$

H$_2$O : about 2 ml of distilled water

HI : 5.0 ml of 57 % HI solution

acetone : 1.5 ml

*Flow rate of $^{11}$CO$_2$ sweep gas : 200 ml/min

*Flow rate of a He current : 200 ml/min

*Total synthesis time : 22.0 min

*Radiochemical yield : 95 %

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Fig. 1. Flow chart of the operation units.
Fig. 2. Front panel of the controller with the fixed program.

"LEAK TEST" switch; all the valves are opened for a leak test with a He gas.

"SETUP" switch; the reduction vessel is dried by heating at 100°C under a He current.

"START" switch; ¹¹CO₂ is introduced into the reduction vessel after the injection of LiAlH₄/THF by manual operation.

"INTERRUPT" switch; the sequence is interrupted when an unexpected trouble happens and the manual control is enabled by using the external switch board.