II. 1. Preparation of $^{11}$C-radiopharmaceuticals from $[^{11}]C$[methyl triflate by Loop Method

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Since $[^{11}]C$methyl triflate ($[^{11}]C$MeOTf) was introduced as a more reactive
$[^{11}]C$methylation agent than $[^{12}]C$methyl iodide ($[^{11}]C$MeI)$^1$, several radiosyntheses of $^{11}$C-
labelled compounds have been improved by substituting $[^{11}]C$MeOTf for $[^{11}]C$MeI$^{2-4}$. Especially it is reported that radiochemical yields and reproducibility in the synthesis of
frequently used $[^{11}]C$raclopride can be greatly increased using $[^{11}]C$MeOTf$^6$.

Noting that $[^{11}]C$MeOTf is a more reactive and less volatile agent, we expected that it
could be easily trapped by a small volume of precursor solution and rapidly reacted without
heating. This led us to develop a simple loop method suitable for automated preparation of
$^{11}$Cradiopharmaceuticals from $[^{11}]C$MeOTf. It is a very simple, convenient method using a
loop of narrow plastic tubing as a reaction vessel to retain a precursor solution$^6$.

$[^{11}]C$Carbon dioxide was produced with a Cypris HM12 cyclotron (Sumitomo
Heavy Industries, Inc.) and converted to $[^{11}]C$MeI by the catalytic gas-phase iodination
reaction via $[^{11}]C$CH$_4$ (GE Mel MicroLab). $[^{11}]C$Methyl iodide, swept with a He flow at 35
mL/min, was passed through the AgOTf-Graphpac GC column$^1$ heated at 200°C, affording
$[^{11}]C$MeOTf.

Demethylraclopride triflate or nodoxepin triflate (approx. 1 mg) was dissolved in
methylethylketone (MEK; 0.1 mL) and NaOH (1.2 M, 2 mL) was added. The whole
precursor solution was injected into a looped PTFE tube (i.d. 0.75 mm x 50 mm long), which
was then flushed with He for a short while. The loop was then connected to an automated
system (Fig. 1). The automated procedure consists of the following 5 steps (Fig. 2).

1. The $[^{11}]C$MeOTf was passed through the loop.
2. The loop was rinsed with 1 mL of HPLC solvent and this volume was collected into
   a glass reservoir.
3. The reaction mixture was transferred into an HPLC injection loop using a suction
   syringe.
4. The mixture was injected onto an HPLC column.
5. The desired product eluting from the column was collected. 

$[^{11}C]$Raclopride was purified on a YMC ODS A-324 column with a solvent system of 10 mM H$_3$PO$_4$-MeCN (65/35) at a flow rate of 5 mL/min and $[^{11}C]$doxepin on a Tosoh TSG-Gel ODS-80 with a solvent system of 33 mM HCO$_2$NH$_4$-MeCN (62.5/37.5) at a flow rate of 8.5 mL/min.

As expected trapping efficiencies of flowing $[^{11}C]$MeOTf by the loop were high enough with less than 0.1 mL of precursor solution. They were 65±10% for $[^{11}C]$raclopride and 92±7% for $[^{11}C]$doxepin.

After trapping of $[^{11}C]$MeOTf, the reaction was quenched by passing the HPLC solvent through the loop and more than 80% of the $^{11}$C-radioactivity collected from the loop was usually found as $[^{11}C]$raclopride. Thus the reaction of $[^{11}C]$MeOTf with demethylraclopride seems to be very prompt even at room temperature. The overall radiochemical yield of $[^{11}C]$raclopride from $[^{11}C]$MeOTf was usually more than 50% (EOB).

On the other hand, radiochemical yields of $[^{11}C]$doxepin were observed to vary from 20% to over 80%, depending on the mass ratio nordoxygen to methyl triflate. The rest of $^{11}$C-radioactivity was assigned to $[^{11}C]$methyleneoxepin. Considering that the formation of this $[^{11}C]$dimethylated product was almost negligible with $[^{11}C]$MeI, this can be explained by the difference in reactivity between $[^{11}C]$MeOTf and $[^{11}C]$MeI. As it is known that the order of the S$_{N}$2 reaction rate of methylation with amines is normally tertiary amine > secondary amine > primary amine, more reactive MeOTf produces the dimethylated product, methyldoxepin from the methylated product, doxepin (Fig. 3). Thus, higher radiochemical yield of $[^{11}C]$doxepin can be achieved only by using high specific activity $[^{11}C]$MeOTf or, as a less desirable alternative, by increasing the amount of precursor. $[^{11}C]$Doxepin was prepared in over 50% radiochemical yields (EOB) from high specific activity $[^{11}C]$MeOTf.

References

Fig. 1  A flowchart of the automated loop system.

Fig. 2  A typical profile of radioactive and UV traces during [14C]raclopride preparation.

Fig. 3  The reaction of [14C]MeOTf with nordoxepin.