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Abstract

Positron emission tomography (PET) is a powerful *in vivo* imaging technique capable of providing dynamic information on biochemical processes in the living human subject. Applications of PET in oncology, neurology, psychiatry, cardiology and other medical specialties continue to grow. The use of PET relies on the characteristics and availability of appropriately labeled radiopharmaceuticals. Carbon-11 is one of the most useful radionuclides for PET chemistry, since its introduction into a biologically active molecule do not modify the biochemical properties of the compound. $^{11}\text{C}$Carbon dioxide ($^{11}\text{CO}_2$), produced by cyclotron, is the most common and versatile primary labeling precursor in the production of $^{11}\text{C}$-labeled radiopharmaceuticals.

**Keywords:** positron emission tomography, Carbon-11, radiopharmaceutical, molecular imaging, cyclotron

1. Introduction

Carbon-11 ($^{11}\text{C}$) is an artificial radioisotope of carbon. Crane and Lauristen made the production of this short-lived radionuclide and investigated its physical properties in 1934 [1]. They demonstrated that carbon-11 decays by positron emission to the stable nuclide $^{11}\text{B}$ [Eq. (1)]. Due to its favorable decay characteristics ($t_{1/2} = 20.33$ min, $98.1\%$ by $\beta^+$ emission, $0.19\%$ by electron capture), carbon-11 was considered as a useful labeling tool for medical purposes. The first biological application of carbon-11 was published by Ruben in 1939 who investigated photosynthesis in plants using $^{11}\text{C}$carbon dioxide [2]. The potential of $^{11}\text{C}$-labeled compounds for non-invasive probing of physiological and biochemical processes in humans was subsequently realized [3]. The first carbon-11 experiment on humans was performed by Tobias in 1945 who studied the fixation of $^{11}\text{C}$carbon monoxide by red blood cells [4]. However, the use of carbon-11 was
limited in next 20 years [5]. This delay was a consequence of easy access to reactor-produced carbon-14 from the 1950s, which superseded the use of cyclotron-produced carbon-11. Until late 1950s, the concepts of emission and transmission tomography were introduced by David Kuhl and Roy Edwards. The interest in carbon-11 was renewed and the application of carbon-11 was extended in 1960s.

\[
{^{11}C \rightarrow ^{11}B + \beta^+ + \nu_e + 0.96 \text{ MeV}} \quad 98.1\%
\]

\[
{^{11}C + e^- \rightarrow ^{11}B + \nu_e + 1.98 \text{ MeV}} \quad 0.19% \quad (1)
\]

Decay of carbon-11 by positron emission or electron capture.

Positron emission tomography (PET) is a type of functional molecular imaging technique using probes, known as radiotracers, consisting of bioactive molecules tagged with positron-emitting radionuclides [6]. As carbon-11 undergoes positron emission decay, it emits a positron. The positron travels a short distance in the surrounding tissue until it collides with an electron. The annihilation produces a pair of gamma rays, which are emitted simultaneously in nearly opposite directions with energy of 511 keV each. The photons can be detected by pairs of collinearly aligned detectors in coincidence. The detectors of a PET system are installed in a ring-like pattern, which allows measurement of radioactivity through the organ of interest at large angles and radial distances. The three-dimensional images can be generated by reconstruction (Figure 1). The ability to image and monitor molecular events in vivo and in real time is of great value for unveiling a detailed picture of fundamental biochemical and physiological processes in living organisms [7]. Information about metabolism, receptor/enzyme function, and biochemical mechanisms in living subjects can be obtained directly from PET imaging studies. The recent development of hybrid instrument combines functional PET with an anatomical modality such as computerized tomography (CT) or magnetic

![Figure 1](Image)

**Figure 1.** The principle behind PET imaging: (a) the injection of radiopharmaceuticals; (b) positron travels a short distance and collides with an electron, then two 511 keV gamma rays emit simultaneously at approximately 180° to each other after annihilation; (c) system detects gamma rays and then generates three-dimensional images.
resonance imaging (MRI). The fusion offers more precise images with accurate functional assessment from PET and anatomical information from CT or MRI. Applications of PET in oncology [8–12], neurology [13–16], psychiatry [17–19], cardiology [20, 21] and other medical specialties [22–24] became one of the fastest growing area in radiology [25].

The use of PET relies on the availability of appropriately labeled radiopharmaceuticals. Carbon-11 is one of the most useful radionuclides for PET chemistry, since the carbon is present in any organic molecule so that the introduction of carbon-11 in a molecule does not modify the properties of this molecule. In addition, the short half-life of carbon-11 allows for consecutive in vivo studies with injections of various radiotracers in the same subject on the same day. The pioneering work in the area of radiochemistry at the Washington University in 1960s demonstrated the great potential of $^{11}\text{C}$-labeled compounds in biological sciences [5]. The simple cyclotron production of $^{11}\text{C}$-carbon dioxide ($^{11}\text{CO}_2$) made it possible to be extensively used as a starting point for the synthesis of different kinds of $^{11}\text{C}$-labeled compounds [26–28]. With the increasing demand of radiotracers and continuous developments of organic chemistry, a number of methodologies have been developed in recent years to enhance production of $^{11}\text{C}$-radiotracers both from a technical and chemical point of view. However, $^{11}\text{C}$ carbon dioxide is still the most common and versatile primary labeling precursor in the production of $^{11}\text{C}$-labeled radiopharmaceuticals. This chapter focus on the use of $^{11}\text{C}$ carbon dioxide as the starting point for radiolabeling PET radiopharmaceuticals (Scheme 1).

2. Carbon-11 chemistry

2.1. Cyclotron: generation of carbon-11

Several nuclear reactions can be used to produce carbon-11 [29, 30]. Among these processes the $^{14}\text{N}(p,\alpha)^{11}\text{C}$ nuclear reaction is by far the most convenient and most commonly used method.
of producing carbon-11. The reaction is performed by high-energy proton bombardment of a cyclotron target containing nitrogen gas. Depending on the addition of gas (up to 2% of O\textsubscript{2} or 5–10% of H\textsubscript{2}) to the nitrogen gas in the target, carbon-11 can be obtained as [\textsuperscript{11}C]CO\textsubscript{2} or [\textsuperscript{11}C]CH\textsubscript{4} (Scheme 2). [\textsuperscript{11}C]Carbon dioxide is the most important and versatile primary labeling precursor for \textsuperscript{11}C-labeling. Cyclotron-produced [\textsuperscript{11}C]CO\textsubscript{2} can be used directly for the \textsuperscript{11}C-labeling of organic molecules (Scheme 1).

2.2. Radiochemistry: general considerations

Carbon-11 is a radionuclide that emits high-energy radiation. Therefore, the traditional hands-on manipulations used in synthetic chemistry are not feasible. In order to avoid unnecessary radiation exposure to the operators, the radiosynthesis of PET tracer needs to be undertaken by automated or remote-controlled synthesis equipment housed inside lead-shielded fume hoods (hot-cells) [6, 7]. This is also important from the perspective of good manufacturing practice (GMP) where a reproducible and operator-independent production is required to control the quality of the radiopharmaceuticals. Figure 2 shows the radiochemistry laboratory at University of Michigan and a typical carbon-11 radiosynthesis module.

The half-life of carbon-11 is sufficiently long for synthesis and purification. However, the radiochemical yield is a function of chemical yield and radioactive decay. Thus the radiosynthesis time should be kept as short as possible. Ideally, a \textsuperscript{11}C-radiopharmaceutical is synthesized,
purified, formulated and analyzed within a timeframe of roughly 2–3 physical half-lives of the radionuclide, or 40–60 min for carbon-11. In addition, the strategies for the radiolabeling should aim to introduce carbon-11 in the synthetic sequence as late as possible [31–33].

The specific radioactivity (SA), a measure of the radioactivity per unit mass of the final radio-labeled compound, is another important aspect of $^{11}$C-chemistry. Since only a trace amount of $^{11}$C-carbon dioxide is generated in the cyclotron, the theoretical maximum specific radioactivity for $^{11}$C-radiolabeled compound is $3.4 \times 10^5$ GBq/μmol. However, it is practically impossible to achieve this number, because of unavoidable isotopic dilution by naturally occurring

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| a $[^{11}]$C-Carfentanil. | b 3-Amino-4-(2-$[^{11}]$C)dimethylaminomethylphenylsulfonyl)-benzonitrile. | c $[^{11}]$C-Dihydrotetrabenazine. | d $[^{11}]$C-Flumazenil. | e $[^{11}]$C-Meta-hydroxyephedrine. | f N-acetyl-N-[2-$[^{11}]$C]methoxybenzyl]-2-phenoxo-5-pyridinamine. | g 1-(2,4-dichlorophenyl)-4-cyano-5-(4-$[^{11}]$C)methoxyphenyl)-N-[piperidin-1-yl]-1H–pyrazole-3-carboxamide. | h Pittsburgh Compound B. | i 1-$[^{11}]$C-Methyl-piperidin-4-yl propionate. | j N-[2-[4-(2-$[^{11}]$C)methoxyphenyl]-1-piperazinyl]ethyl]-N-(2-pyridinyl)cylohexanecarboxamide. |

Table 1. $^{11}$C-radiotracers in University of Michigan PET center for clinical application.
carbon-12 species during the processes. Typical specific activities of $^{11}$C-radiolabeled compounds are in the order of 50–1000 GBq/μmol [34]. For imaging a patient, less than 1 GBq of radioactivity is normally enough. That means very low amounts of compound need to be administered for PET imaging, typically in picomolar to nanomolar scale. This prevents undesired pharmacological or toxic effects during the in vivo studies. Thus, a labeling pathway should be designed to minimize contamination of carbon-12 species. Furthermore, due to tracer levels of carbon-11, the amount of the non-radioactive reagents is in large excess (about $10^3$–$10^4$ fold), which drives the reaction at pseudo first order kinetics. By consequence, small impurities in reagents or solvents may have a significant influence on the reaction outcomes. Therefore, the quality of regents used in radiosynthesis needs special attention.

Radiopharmaceuticals can range from the small and simple to the large and complex. A tracer should be designed in such a way that it can be probing a specific function within the organ of interest [3]. It is important that the physical half-life of the radionuclide matches the biological half-life of the studied process. For example, carbon-11 is not suitable for radiolabeled peptides or antibodies, which need a few hours of blood circulation to accumulate the activity in a tumor.

2.3. Application of carbon-11: examples of radiopharmaceuticals

Since its infancy in the early 1960s, PET has attracted increasing attention as a powerful tool for investigating the biochemical transformations of drugs and molecules in the living system. With the development of PET imaging technology and novel synthetic methodology, $^{11}$C-labeled radiopharmaceuticals have been extensively used for the highly sensitive non-invasive measurement of biochemical physiological processes in living human subjects. As examples, Table 1 summarizes $^{11}$C-radiotracers available in University of Michigan PET center for routine clinical application.

3. $^{11}$CCarbon dioxide: starting point for labeling PET radiopharmaceuticals

The simple cyclotron production of $[^{11}\text{C}]$carbon dioxide gave a starting point for the synthesis of important classes of compounds such as carboxylic acids [26], aldehydes [27], and alcohols [28]. However, due to low chemical reactivity of $[^{11}\text{C}]$\(\text{CO}_2\), a broad spectrum of different $^{11}$C-labeled synthetic intermediates have been prepared as useful secondary labeling precursors (Scheme 1). With the increasing importance of PET in medical research and continuous developments of novel organic chemical techniques, $^{11}$C-labeling methodology is rapidly growing. This chapter addresses selected commonly used methods and examples. For more detailed information see comprehensive reviews [7, 54, 55]

3.1. $[^{11}\text{C}]$\(\text{CO}_2\) direct incorporation

$[^{11}\text{C}]$Carbon dioxide is the most important and versatile primary labeling precursor for $^{11}$C-radiolabeling, since it is produced directly from cyclotron. The electrophilic carbon in $[^{11}\text{C}]$
CO$_2$ can be used as a carbonyl source and trapped by an appropriate nucleophilic component. For example, [$^{11}$C]acetate as a PET radiopharmaceutical for both myocardial imaging and cancer detection was synthesized via methyl magnesium chloride with [$^{11}$C]CO$_2$ (Scheme 3) [56].

The [$^{11}$C]carboxymagnesium halides also can be converted into more reactive [$^{11}$C]carboxylic acid chloride to form amide with amines. The important 5HT$_{1A}$ receptor ligand WAY100635 was produced by this manner (Scheme 4) [52, 53].

More recently, [$^{11}$C]CO$_2$ fixation further expanded the synthetic possibility for [$^{11}$C]-labeling by direct incorporation of [$^{11}$C]CO$_2$. The first report on [$^{11}$C]CO$_2$ fixation was the synthesis of [$^{11}$C]-labeled carbamates [57, 58]. The scope of this method was broadened to [$^{11}$C]ureas and [$^{11}$C] oxazolidinones via the formation of an [$^{11}$C]-labeled isocyanate or carbamoyl anhydride intermediate [54, 58–60]. For example, the reversible monoamine oxidase B (MAO-B) radioligand, [$^{11}$C]SL25.1188, previously prepared using the technical demanding [$^{11}$C]phosgene approach, was radiolabeled in high yield via [$^{11}$C]CO$_2$ fixation [61, 62]. This radioligand was recently translated for human PET imaging (Scheme 5) [54, 63].

### 3.2. [$^{11}$C]Methylation

The introduction of [$^{11}$C]methyl iodide as a second labeling precursor 30 years ago was one of the great milestones in PET radiochemistry [64, 65]. So far, the most common method in [$^{11}$C]-labeling is heteroatom (N, O, S) methylation. Converting [$^{11}$C]MeI to more reactive [$^{11}$C]methyl triflate ([$^{11}$C]MeOTf) [64, 66] by passing [$^{11}$C]MeI through a small column containing silver triflate around 200°C [67] significantly increases efficiencies of [$^{11}$C]-methylation. This innovation makes it possible to [$^{11}$C]-methylate heteroatoms in 3–5 min at room temperature.

[$^{11}$C]Methyl iodide can be prepared via two methods (Scheme 1). The so-called “wet” method developed in 1976 [64, 65] is based on reducing [$^{11}$C]CO$_2$ using LiAlH$_4$ followed by reaction with hydroiodic acid. An alternative method, referred to as the “gas phase” method, was developed in the 1990s. This method exploits the reduction of [$^{11}$C]CO$_2$ by H$_2$/Ni at 350°C and then conversion of [$^{11}$C]methane into [$^{11}$C]MeI by iodination with iodine vapor at high temperatures (700–750°C) in the gas phase [66, 68].

The incorporation of the [$^{11}$C]methyl group into a target molecule is generally simply alkylation on N-, O-, and S-nucleophiles (e.g., HED, DTBZ, methionine). The tracer amount of [$^{11}$C]MeI or [$^{11}$C]MeOTf in the reaction leads to extraordinary stoichiometry. The stoichiometric relation can reach a factor of 10$^4$:1 resulting in pseudo-first order kinetics of heteroatom methylation reactions. Therefore, the conversion rate is highly increased and the reasonable radiochemical yields can be reached within short reaction times of 3–5 min. The problems with polyalkylation in normal stoichiometric methylation of amines do not occur in the [$^{11}$C]-methylation processes.

The reaction can be performed using a traditional vial-based approach (e.g., CFN, FMZ) or using solid support either on-cartridge (e.g., choline) or flow-based loop methods (e.g., PIB, DASB, raclopride) (Figure 3) [39, 41, 43]. All these methods are very convenient from automation perspective. The use of commercially available fully automated synthesis modules for production of clinical radiopharmaceutical doses enhances the speed, efficiency, reliability, and safety of radiosyntheses, as well as compliance with GMP regulations. For detail procedures see [38–43].

Figure 3. Representative $^{11}$C-radiotracers labeled by methylation.
To further expand the number of $^{11}$C-labeled compounds, the development of novel $^{11}$C-C bond forming reactions continues to gain attention. For example, several palladium-mediated cross-coupling reactions have been shown to be effective $^{11}$C-labeling. The first application was reported in 1995 [69]. The feasibility of incorporating $^{11}$Cmethyl groups into arenes, alkenes as well as alkanes was demonstrated by the reaction with the corresponding organostannanes and boranes in Stille and Suzuki cross-coupling reactions (Scheme 6) [70]. Due to the toxicity of the precursor and reagents used, the purification and quality control are more complicated comparing with those of simply methylation. Considering the short half-life of carbon-11, the application of this method for clinical dose production is currently underexploited. With the development of techniques and simplification of processes, this labeling strategy could be more widely adopted.

3.3. $^{11}$C]Cyanation

$^{11}$C]HCN is another important secondary labeling precursor (Scheme 1), because nitriles are not only frequently present in biologically active molecules but also represent a versatile functional group that can be readily converted into $^{11}$C-labeled amides, carboxylic acids or amines (Scheme 7) [54, 71]. $^{11}$C]HCN is usually prepared by the reduction of $^{11}$C]CO$_2$ to $^{11}$C]CH$_2$, using H$_2$ over nickel (400°C), and then converted into $^{11}$C]HCN by reaction with NH$_3$ over platinum at elevated temperature (950°C) [72].

$^{11}$C]HCN can be used directly to form $^{11}$Cmethyl-2-cyanoisonicotinate and $^{11}$C]1-succinonitrile by a Reissert-Kaufmann type reaction (Scheme 7a) and Michael addition (Scheme 7b), respectively [73]. It may convert to $^{11}$CCuCN and react with aryl halides through the Rosenmund-von Braun reaction for the synthesis of $^{11}$C]LY2232645 (Scheme 7d) [74–76]. $^{11}$C-labeled amino acids, for example, $^{11}$C]Sarcosine, can be prepared using $^{11}$C]HCN in the Strecker reaction (Scheme 7c) [51, 77, 78]. In recent years, palladium-catalyzed and copper-mediated cyanations have gained increasing attention [79–82]. Vasdev and co-workers employed arylboronic acids and $^{11}$C]CsCN to prepare aromatic $^{11}$C-nitriles (Scheme 7f), which was applicable to a broad range of substrates [80].

3.4. $^{11}$C]Carbonylation using $^{11}$C]CO

$^{11}$C]Carbon monoxide is an attractive secondary precursor for $^{11}$C-chemistry since the wide variety of carbonyl containing molecules can be synthesized through carbonylation reactions. $^{11}$C]CO is readily available by the reduction of $^{11}$C]CO$_2$ over zinc or molybdenum [83, 84]. However, the application of $^{11}$C]CO was underexploited due to its poor reactivity and low solubility in organic solvents. Until recently, new methods have been developed to overcome

![Scheme 6. Synthesis of $^{11}$C]M-MTEB by Suzuki or Stille reactions.](image)
the shortcomings, from technical and chemical points of the view [85–88]. The first report was by Kihlberg and co-workers in 1999, where $^{11}$C|CO was allowed to react in a small autoclave under high pressure (>350 Bar) [89]. Low-pressure and ambient temperature techniques have been achieved lately [90–92]. The most widely applied $^{11}$C-carbonylation method used $^{11}$C|CO is the palladium-mediated carbonylation reaction [93–96]. Rhodium-catalyzed carbonylation reactions provide an alternative route for the introduction of $^{11}$C|CO into organic molecules [97–99]. Free-radical photoinitiated $^{11}$C–carbonylation reactions have been used to synthesize $^{11}$C-labeled aliphatic acid, esters and amides recently (Scheme 8) [100–104].

![Scheme 7. Some transformations in $^{11}$C|HCN radiochemistry: (a) radiosynthesis of $^{11}$C|methyl-2-cyanoisonicotinate by a Reissert-Kaufmann type reaction; (b) direct formation of $^{11}$C|succinonitrile via Michael addition; (c) the Strecker reaction for the synthesis of $^{11}$C|Sarcosine; (d) and (e): $^{11}$C|CuCN can be reacted with aryl halides through the Rosenmund-von Braun reaction to afford $^{11}$C|LY2232645 and other aromatic $^{11}$C|nitriles; (f) copper-mediated synthesis of aromatic $^{11}$C nitriles from arylboronic acids.](image-url)

![Scheme 8. Free-radical photoinitiated $^{11}$C-carbonylation reaction.](image-url)
4. Future perspectives

This review introduces the field of carbon-11 radiochemistry through a general overview, but is not meant to be comprehensive. As the field is fast growing, more traditional chemists join the radiochemistry arena worldwide. Carbon-11, one of the most important radioisotopes in nuclear medicine, is foreseen to have endless opportunities for further innovation. Due to the short half-life, efficiency and simplicity is always the key to $^{11}$C-labeling techniques. Recently developed transition-metal-mediated reactions have broadened the labeling scope and allowed $^{11}$C-labeling of a range of different bioactive molecules.

$^{11}$C-chemistry is a hybrid science between organic chemistry and engineering. To meet the growing demand and increasing regulation of radiopharmaceuticals, the fully automated or kit-like synthetic devices have been developed and will be required to be used in the manufacture of clinical doses to improve the reliability and safety.

Furthermore, synthetic pathways with better economical output and environmental management is another important aspect. The first example of a green radiochemistry laboratory at University of Michigan successfully prepared 11 radiopharmaceuticals for routine clinical application using ethanol as the only organic solvent [105]. The removal of all other organic solvents from the process simplifies production and quality control testing. The robust and reliable methods are increasingly applied in various PET facilities around the world.

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