

4. Production of Carbon-14 and Preparation of Some Key Precursors for Labeling Organic Molecules

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ABSTRACT

Production of carbon-14 on 50 GBq scale has been performed by neutron irradiation of aluminium nitride target in the JMTR. This nuclide is separated in carbon dioxide form by combustion of the irradiated target at 1100°C with oxygen. The [^{14}C] carbon dioxide liberated thus is trapped in caustic solution and finally recovered as [^{14}C] barium carbonate.

Some precursors useful for incorporating carbon-14 into a given organic molecule have been prepared. Precursors such as [^{14}C] sodium acetate, [^{14}C] methanol and [^{14}C] potassium cyanide are prepared by rather conventional methods involving carbonation of methyl magnesium iodide, reduction of carbon dioxide with lithium aluminium hydride and reduction of carbonate with metallic potassium in the presence of ammonium salt, respectively. A catalytic polymerization of acetylene is used to prepare benzene.

INTRODUCTION

Carbon-14 ($t_{1/2}$; 5730y) is an important radionuclide for the preparation of a variety of labeled organic molecules. They are widely used as a tracer in biological and pharmacological studies due to the favourable properties of emitting only low energy beta particles, which are adequate for radioactivity measurement and autoradiography.

Carbon-14 is produced by the nuclear reaction of $^{14}\text{N} (n, p) ^{14}\text{C}$ in a reactor. We started production on 50 GBq scale in 1970 when a long term irradiation became available in the JMTR. Target materials which were being used at that time were beryllium nitride and aluminium nitride. From the irradiated beryllium nitride, carbon-14 is separated as carbon dioxide by dissolving the irradiated target in sulfuric acid, followed by treatment of an oxidizing agent (1). Carbon-14 produced in the irradiated aluminium nitride, on the other hand, is extracted as carbon dioxide by dry oxydation procedure (2). The latter method was chosen because it can be performed with simple apparatus (3). As target material, sintered tablet of aluminium nitride was found to be preferable to powdery one from the viewpoint of easy remote handling due to its increased hardness. In addition, it is advantageous feature that the content of natural carbon decreases after sintered at high temperature. Consequently, reduction of specific activity of the carbon-14 product can be minimized.

Preparation of ^{14}C -labeled compounds is in most cases different from that of ordinary organic compounds. Preparation has to be carried out with

[^{14}C] carbon dioxide, the only starting material for labeling, at early stage of reactions. It is well-known that carbon dioxide undergoes some useful reactions to provide various key compounds such as [^{14}C] sodium acetate, [^{14}C] methanol, [^{14}C] potassium cyanide and [^{14}C] benzene by way of [^{14}C] acetylene. Many carboxylic acids including acetic acid are prepared by carboxylation of Grignard reagents or organo-metallic compounds with carbon dioxide (4). Some procedures for preparing methanol and potassium cyanide by reduction of carbon dioxide or carbonate have been reported (4). Reduction of carbonate to carbide is often used to prepare, from which labeled benzene can be prepared by catalytic polymerization (5)-(8). We have been prepared these key compounds according to the published methods with some modification.

The present paper describes the production procedures of carbon-14 and four kinds of ^{14}C -labeled key compounds in detail. Short discussion on technical problems is also presented.

PRODUCTION OF CARBON-14

Powdery AlN purchased from Nippon Denko Co. Ltd. was used as a target material after sintering as described below. It is desirable that the target material has high nitrogen content and low carbon content to obtain high specific activity ^{14}C product. The contents of nitrogen and carbon in the AlN were in the range of 30 to 34 % and 0.027 to 0.053 %, respectively. The powdery AlN is molded into tablets under a pressure of $0.9 \text{ ton}\cdot\text{cm}^{-2}$ and sintered at 1000°C for 1 hour under He atmosphere. Table 1 shows the difference in contents of nitrogen and carbon in sintered and not-sintered AlN.

Table 1 Content of nitrogen and carbon in AlN before and after sintering at 1000°C

AlN	Content (%)	
	Nitrogen	Carbon-12
before sintering	33.4 (100)	0.037 (100)
after sintering	32.0 (96)	0.023 (62)

As is seen in the table, the content of carbon decreases considerably after sintering, whereas that of nitrogen does slightly.

Four sintered tablets, each of which weighs 8 g, are packed in an aluminium capsule and the capsule is welded hermetically. Five capsules together with spacers are packed in a capsule holder and welded hermetically. The airtightness of the capsules and the holder is confirmed by He leak test. Totally 160 g of the AlN in a capsule holder are irradiated in a beryllium reflector region in the JMTR for 12 to 14 cycles. The JMTR is normally operated at 50 MW for about 110 days in 5 cycles per year. The operation period of each cycle is 12 days. Thermal and fast neutron fluxes are approximately $2 \times 10^{14} \text{ cm}^{-2}\cdot\text{s}^{-1}$ and $0.5 \times 10^{14} \text{ cm}^{-2}\cdot\text{s}^{-1}$, respectively.

The irradiated target is transferred to a vessel in an apparatus for separation of carbon-14 as shown in Fig. 1. The irradiated AlN tablets are placed in a porcelain crucible (A) and heated in an electric furnace (B) at 1100°C in a stream of O_2 . A quartz tube filled with wiry CuO (C) is connected to the end of the furnace to oxidize any ^{14}C compounds into $^{14}\text{CO}_2$. The $^{14}\text{CO}_2$ is absorbed in a carbon-free NaOH solution (D) under O_2 flow and $\text{Na}_2^{14}\text{CO}_3$ formed is then converted to $\text{Ba}^{14}\text{CO}_3$ by addition of BaCl_2 solution.

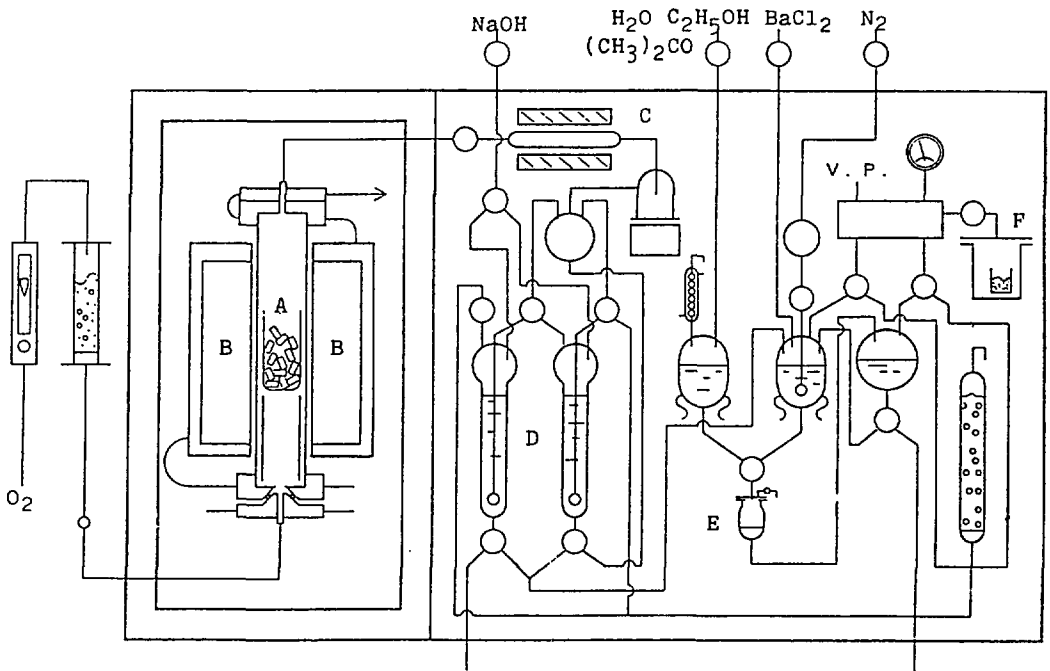


Fig. 1 Apparatus for separation of ^{14}C from the irradiated target

The precipitate of $\text{Ba}^{14}\text{CO}_3$ is collected by filtration on a filter (E), washed with distilled water, ethanol and acetone. It is dried in a vessel (F) under vacuum. Typical results of productions are shown in Table 2.

Table 2 Production of carbon-14 by neutron irradiation in the JMTR

Target		Irradiation			Yield		
Sample No.	AlN (g)	Irradiation Position	Irradiation Time (h) (cycle)	Particle fluence ($\times 10^{21}$)	$\text{Ba}^{14}\text{CO}_3$ (g)	Specific activity ($\text{GBq}\cdot\text{m mol}^{-1}$)	Total activity (GBq)
1	160.7	E-8	6179 (14)	5.96	4.92	2.11	52.6
2	164.3	J-5	6103 (14)	5.42	4.63	2.04	47.8
3	163.6	E-7	5768 (12)	5.81	5.81	1.81	53.4
4	163.3	E-8	5792 (12)	6.01	6.01	1.92	58.6
5	167.7	E-6	6234 (14)	6.03	6.03	1.92	58.8

Carbon-12 content in the sintered target material

1.2 : 0.014 % 3.5 : 0.013 % 4 : 0.026 %

Specific activity of the products ranging from 1.81 to 2.11 $\text{GBq}\cdot\text{m mol}^{-1}$ is equivalent to approximately 77 to 90 % abundance of ^{14}C . Dilution with natural carbon is mainly due to the original content in the target materials used. Yields are close to the expected values estimated from extrapolation in smaller scale experiments.

Decomposition of the target materials during irradiation was observed by radio-gaschromatographic analysis of the gases produced in the capsule. Presence of N_2 , O_2 and He was confirmed. Both N_2 and O_2 are likely to be

decomposition gases, while He is a fraction of replacing gas used in the process of welding the capsule. However, any possible ^{14}C compounds reported in the literature such as $^{14}\text{CH}_4$, $(\text{NH}_2)_2^{14}\text{C}=\text{NH}$, $^{14}\text{CO}_2$ etc. (4) were not detected. Maximum quantity of decomposition gas was 112.5 cm^3 when a target was irradiated to $7.3 \times 10^{21} \text{ cm}^{-2}$. Inner pressure of the capsule was estimated to be $15.6 \text{ kg}\cdot\text{cm}^{-2}$ which was lower than burst pressure of the aluminium capsules.

PREPARATION OF KEY PRECURSORS

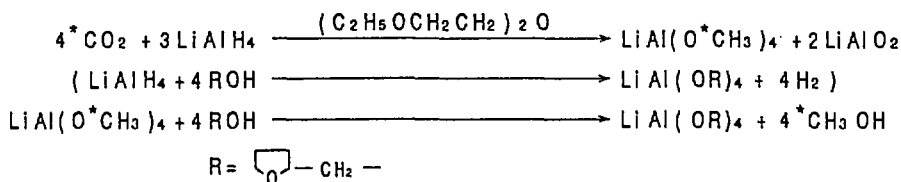
[1- ^{14}C] SODIUM ACETATE

[1- ^{14}C] sodium acetate has been prepared by the Grignard reaction. The Grignard reagent, CH_3MgI , is prepared by dropwise addition of CH_3I in dry ether to magnesium ribbon in dry ether with stirring under dry N_2 atmosphere. An excess CH_3MgI in ether is frozen with liquid N_2 in a flask on a Grignard carbonation apparatus. After evacuation of the flask, $^{14}\text{CO}_2$ produced from $\text{Ba}^{14}\text{CO}_3$ with concentrated H_2SO_4 is introduced into the flask. The reaction flask is isolated from the vacuum line and the mixture is stirred at -20°C with Dry Ice-aceton for 20 minutes. The stirred mixture is treated with water while cold to destroy the excess of CH_3MgI and then with NaOH solution. The mixture is transferred into a distillation flask containing AgNO_3 to remove free iodine and acidified with 50 % H_2SO_4 . The product, [1- ^{14}C] acetic acid, is steam-distilled in a receiver. The distillate is titrated with standard NaOH solution. The chemical yields of 1 to 3 m mol scale preparations are higher than 95 %. The solution is evaporated to dryness under reduced pressure. The residue is dissolved in warm 90 % methanol and [1- ^{14}C] sodium acetate is recrystallized by cooling the solution. The radiochemical purity determined by radio-paper chromatography is higher than 99 %.

The use of higher concentration and too much excess of the Grignard reagent causes the formation of by-products. The Grignard reagent of 0.2 to 0.4 m mol $\cdot\text{ml}^{-1}$ and 4 times the number of millimoles of $^{14}\text{CO}_2$ have been used for the carbonation reaction.

[^{14}C] METHANOL

[^{14}C] Methanol has been prepared by the reduction of $^{14}\text{CO}_2$ with LiAlH_4 , followed by alcoholysis. The reaction sequence is as follows.



Lithium aluminium hydride is dissolved in bis-(2-ethoxyethyl) ether which is previously purified by fractional distillation under reduced pressure. A supernatant solution containing LiAlH_4 is placed in a flask equipped with a magnetic stirrer, a reflux condenser, a pressure equalizing dropping funnel containing tetrahydrofurfuryl alcohol and two receivers connected in series to an attachment to vacuum manifold. The flask is evacuated and closed off from the manifold. Dry $^{14}\text{CO}_2$ is vacuum-distilled into the flask and the mixture is stirred at 0°C for 1 hour. After the reduction is

complete, tetrahydrofurfuryl alcohol is added dropwise to the mixture with stirring. Nitrogen is admitted to the system, and the mixture is refluxed for 1 hour with stirring. The product together with some solvents is distilled under reduced pressure into the receiver cooled with liquid N_2 . Radio-gaschromatographic analysis of the product showed the presence of impurities consisting of $H^{14}CHO$, C_2H_5OH and water. The gaschromatographic set-up consists of a thermal conductivity detector (TCD) and a stainless steel column packed with 15 % PEG-1000 on Uniport B as a stationary phase. The radioactivity of organic samples leaving the TCD cell is oxidized to $^{14}CO_2$ and detected with a GM detector.

For purification of the crude product, a simple preparative gas chromatographic set-up as shown in Fig. 2 is used.

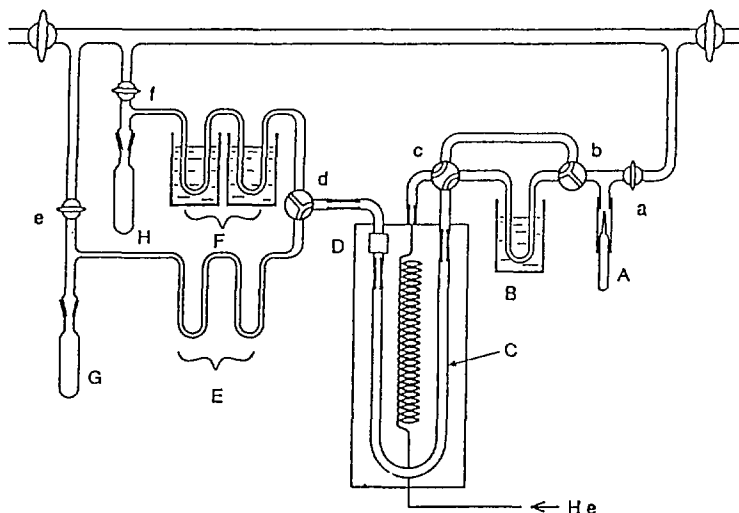


Fig. 2 Preparative gaschromatograph for the purification of crude $[^{14}C]$ methanol

A; Ampoule containing sample, B; Injection part,
C; Column, 20mmx2m, packed with PEG-20m, D; TCD,
E,F; Cold traps, G,H; Collector, a-f; Glass cocks.

The set-up consists of a specially designed injection device (B), a stainless steel column of 10 mm x 2 m packed with PEG-20m (C), a TCD cell (D) an oven and cold traps (E,F). The crude product collected in an ampoule (A) is vacuum-distilled into the injection device and is vaporized by heating. The product is then introduced into the column under He flow. The purification is achieved at 30 °C under He flow of 70 ml·min⁻¹. Figure 3 shows an example of separation of a crude product. As is seen on the gaschromatogram methanol can be separated well from the impurities.

$[^{14}C]$ POTASSIUM CYANIDE

The preparation of $[^{14}C]$ potassium cyanide has been carried out by heating the mixture of K, $Ba^{14}CO_3$ and NH_4Cl in a sealed tube. A quartz tube, one end of which is adaptable to a glass cock, is used for the reaction. To a mixture of $Ba^{14}CO_3$ and NH_4Cl (molar ratio of 1 : 2) in the tube, is added excess K, which has previously been cleaned by filtering the melted K on a glass fiber. The tube is evacuated and closed. The K is melted by heating and the contents are mixed well by shaking. The tube is placed in an electric furnace kept at 630 °C and heated for 1 hour. The tube

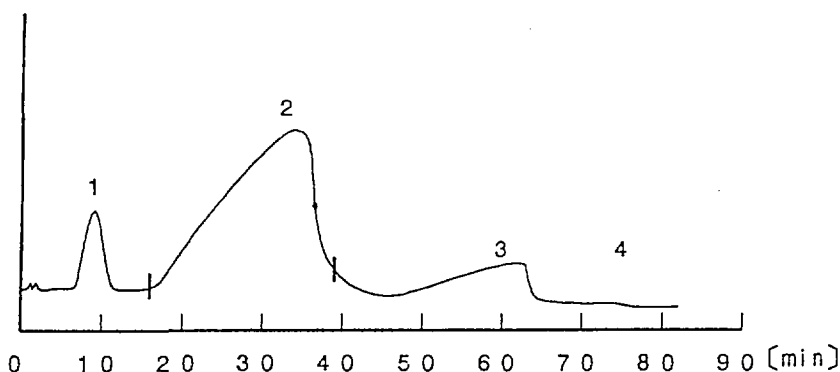


Fig.3 Gaschromatogram of crude (¹⁴C)methanol on PEG20m column (10 mm φ × 2 m)

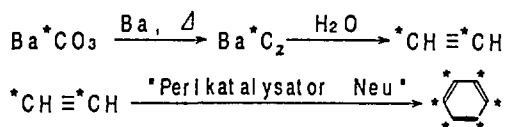
1; Formaldehyde, 2; Methanol 3; Ethanol, 4; Water

is cooled and opened. The excess K is destroyed by careful addition of methanol through the hole of glass cock. The mixture is transferred into a distillation flask and acidified with H₂SO₄. The product, H¹⁴CN, is distilled into a receiver containing excess NaOH solution. The chemical yield determined by titration with AgNO₂ is 90 to 95 %.

The solution is condensed to small quantity by distillation. The solution is acidified with H₂SO₄ and H¹⁴CN is distilled into two receivers which are connected in series, the first receiver containing equimolar KOH to H¹⁴CN and the second one containing additional KOH to recover H¹⁴CN completely. The solution in the receivers is evaporated to dryness under vacuum. The chemical purity of K¹⁴CN obtained from the first vessel is about 90 %. It is very difficult to obtain dehydrated cyanide without containing excess KOH, because evaporation under vacuum cannot be achieved without loss of H¹⁴CN. Purification by extraction of crude K¹⁴CN from liquid NH₃ has been achieved where necessary. Radio-paper chromatographic analysis shows only one peak on the R_f value corresponding to that of KCN.

[U-¹⁴C] BENZENE

[U-¹⁴C] Benzene has been prepared by combination of the reactions as shown below, consisting of reduction of carbonate to carbide, formation of acetylene and polymerization of acetylene with catalyst.



[¹⁴C] Barium carbide is prepared by heating Ba¹⁴CO₃ with Ba metal in a Pyrex glass tube under He atmosphere. [¹⁴C] Barium carbonate and finely divided Ba are heated in a tube with a flame and the mixture ignites soon. The tube is cooled and placed in a flask equipped with a dropping funnel containing water, N₂ gas inlet, two cold traps connected in series for collecting ¹⁴CH≡¹⁴CH. Water is added dropwise to the carbide and ¹⁴CH≡¹⁴CH

formed is trapped in the vessels cooled with liquid N_2 in a stream of N_2 . The reaction mixture is refluxed for 1 hour to recover $^{14}CH\equiv^{14}CH$ completely. The acetylene is then dried over P_2O_5 .

For catalytic polymerization of $^{14}CH\equiv^{14}CH$, the method using catalyst "Perlkatalysator Neu" (Kali-Chemie AG) has been applied. The apparatus is shown in Fig. 4.

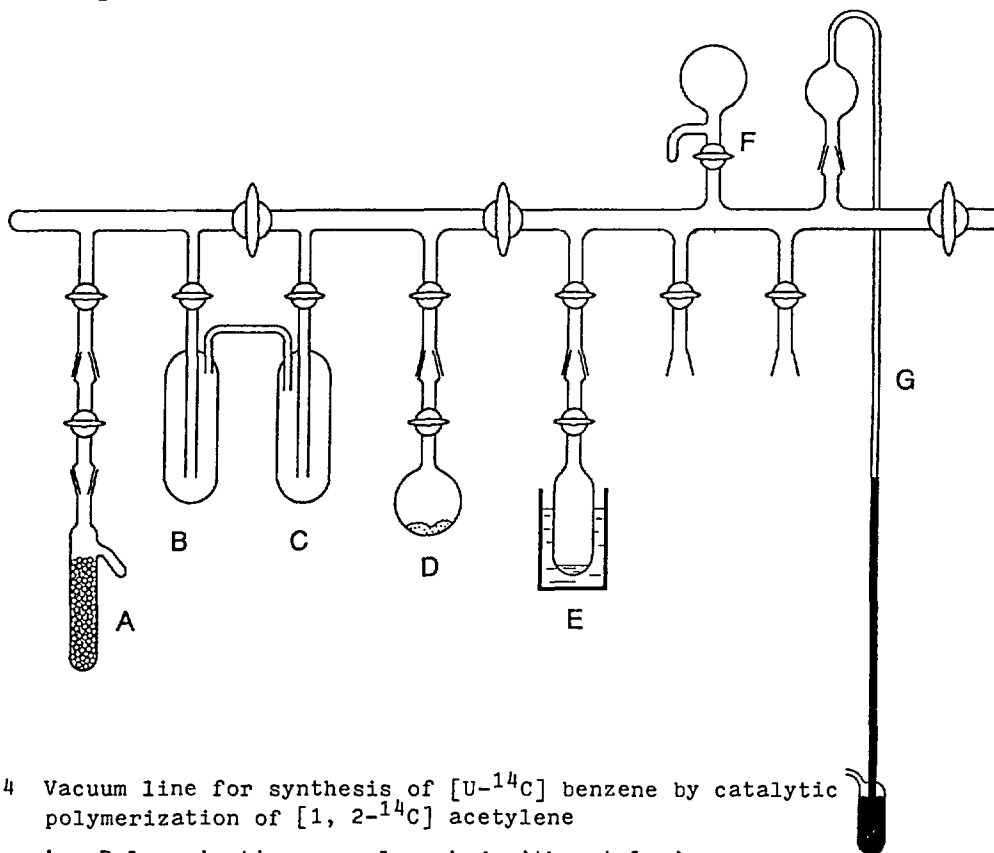


Fig. 4 Vacuum line for synthesis of $[U-^{14}C]$ benzene by catalytic polymerization of $[1, 2-^{14}C]$ acetylene

A; Polymerization vessel packed with catalysis,
 B and C; Liquid nitrogen trap, D; Dehydration flask containing P_2O_5 , E; Flask for collection of $[U-^{14}C]$ benzene,
 F; Gas storage and aliquoting bulb, G; Manometer.

The catalyst is placed in a polymerization vessel (A) and activated by heating overnight at $300^\circ C$ under vacuum. Acetylene is introduced into the vessel by vacuum-transfer and absorbed on the catalyst in a short time. The vessel is heated overnight at $50^\circ C$. $[U-^{14}C]$ Benzene produced on the catalyst is released by heating at $200^\circ C$ and transferred into the traps (B, C) cooled with liquid N_2 under vacuum. $[U-^{14}C]$ Benzene is dried over P_2O_5 (D) and collected in a vessel (E). Radiochemical yields of typical preparations on 37 GBq scale were 72 to 86 % based on $Ba^{14}CO_3$. Radio-gaschromatographic analysis showed that the product was pure enough not to need further purification.

This method enables us to prepare benzene with specific activity six times that of $Ba^{14}CO_3$. We have been successfully prepared benzen with the specific activity of about $2 \text{ GBq m}\cdot\text{mol}^{-1}$ by using 1 g of the catalyst to every 1 m mole of acetylene. Polymerization of $^{14}CH\equiv^{14}CH$ and subsequent procedures can conveniently be carried out in a vacuum-manifold.

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