

Research Article

Preparation of [^{11}C]formaldehyde using a silver-containing ceramic catalyst

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Summary

A ceramic material, prepared from kaolin doped with silver ions in various concentrations, was evaluated as a catalyst for the conversion of [^{11}C]methanol into [^{11}C]formaldehyde in a gas flow system. Employment of [^{11}C]methanol with a minimized water content, 300 mg of catalyst (20% of silver) at 500°C and a carrier gas flow rate of 40 mL/min resulted in a radiochemical decay-corrected [^{11}C]formaldehyde yield of 67% relative to [^{11}C]methanol. Wet [^{11}C]methanol under the same conditions gave 54% of [^{11}C]formaldehyde. Copyright © 2003 John Wiley & Sons, Ltd.

Key Words: [^{11}C]formaldehyde; carbon-11; synthesis; silver catalyst

Introduction

[^{11}C]Formaldehyde is a useful labelling agent for compounds required in positron emission tomography studies. It has been applied mainly in reductive methylations^{1–5} and more recently also in ring-closure reactions.^{6–10} The customary method of synthesis consists of passing [^{11}C]methanol, obtained by reduction of [^{11}C]carbon dioxide with lithium aluminium hydride, over hot silver or iron–molybdenum in the presence of oxygen.^{1,2,11,12} The disadvantage of this method is the

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dependence of the yield on the temperature and the state of the catalyst. Also enzymes have been employed in the conversion of [^{11}C]methanol into [^{11}C]formaldehyde. Very high yields were reported^{13–15} but this technique is complicated and produces [^{11}C]formaldehyde in the aqueous phase only. Recently a low-temperature reduction of [^{11}C]carbon dioxide was proposed⁷ but in our hands this method gave predominantly [^{11}C]formic acid.¹⁶

We propose a novel robust method of making [^{11}C]formaldehyde based on the dehydrogenation of [^{11}C]methanol. Li *et al.*¹⁷ and Dong *et al.*¹⁸ have reported that methanol can be efficiently and selectively converted into formaldehyde using a kaolin-based ceramic catalyst doped with silver ions. In contrast to the metallic silver that is used in the habitual dehydrogenation of [^{11}C]methanol to [^{11}C]formaldehyde, this catalyst contains highly stabilised Ag^+ ions. This is believed to be at the origin of the success of this catalyst in converting methanol into formaldehyde. Passage of a mixture of vaporized aqueous methanol (60%) and air over the catalyst at 620°C gave a very high formaldehyde yield (89%) together with some carbon monoxide and carbon dioxide (about 7%).¹⁷ When using dry methanol in an inert vector gas with exclusion of oxygen a somewhat lower yield was obtained (70%) but with a 100% selectivity for formaldehyde, thus without any side products such as carbon monoxide or carbon dioxide.¹⁸ In the present study we evaluate this catalyst for its use in the production of no-carrier-added [^{11}C]formaldehyde as a precursor in radiopharmaceutical chemistry. [^{11}C]methanol was prepared by reduction of [^{11}C]carbon dioxide with lithium aluminium hydride in THF followed by solvent evaporation and hydrolysis.¹⁹ Using a flow system, the distilled [^{11}C]methanol, that was either essentially free from water (hydrolysis with di(ethyleneglycol) butyl ether/1% of water) or mixed with water vapour (hydrolysis with water), was carried by an inert vector gas through the heated catalyst and the outflow gases were analysed for [^{11}C]CH₂O, [^{11}C]CO₂, [^{11}C]CO, [^{11}C]HCOOH and [^{11}C]CH₃OH as a function of the temperature, the quantity and the silver content of the catalyst, and the flow rate.

Results and discussion

It became rapidly clear that the conditions described by Li *et al.*¹⁷ for wet methanol were difficult to transpose as such to the no-carrier-added

[^{11}C]methanol situation. The above authors used vaporised 60% aqueous methanol while our wet [^{11}C]methanol was generated by hydrolysis with water (100 μl) of the no-carrier-added [^{11}C]methoxy complex obtained after LiAlH_4 reduction of [^{11}C]CO $_2$ resulting in a much higher $\text{H}_2\text{O}/\text{CH}_3\text{OH}$ ratio. Li *et al.*¹⁷ also used air at a precise $\text{O}_2/\text{CH}_3\text{OH}$ molar ratio of 0.42. They reported 89% yield for formaldehyde and 7% for CO and CO $_2$ taken together, for a catalyst temperature of 620°C. Our system contains less than 1 μmol [^{11}C]methanol which is inherent to the no-carrier-added production method of carbon-11. Any addition of oxygen to the nitrogen carrier gas (e.g. 2% of O_2) caused complete over oxidation to [^{11}C]CO and [^{11}C]CO $_2$. Even the use of pure nitrogen (< 1 ppm O_2) gave rise to over 40% of [^{11}C]CO and [^{11}C]CO $_2$ although the yield of [^{11}C]formaldehyde was an appreciable 54% relative to liberated [^{11}C]methanol at an optimized flow rate of 40 ml/min. Both lattice oxygen and adsorbed oxygen on the catalyst have been proposed as the oxygen source in this type of reaction.²⁰ In view of the sub-micromolar level of [^{11}C]methanol it is not surprising that our optimum temperature of 450°–500°C was lower than the literature value of 620°C.

Instead of aqueous methanol Dong *et al.*¹⁸ used, on the same catalyst, just methanol vapor in an inert vector gas and under rigorous exclusion of oxygen. They reported a yield of 70% and a selectivity of 100% for formaldehyde for a catalyst temperature of 600°C. To mimic these conditions we produced [^{11}C]methanol vapor using di(ethyleneglycol) butyl ether containing 1% of water for hydrolysis of the complex obtained after LiAlH_4 reduction of [^{11}C]CO $_2$, and subsequent distillation employing an inert sweeping gas.²¹ Figure 1 shows the yields of the various products relative to liberated [^{11}C]methanol as a function of temperature. The amount of catalyst was 300 mg (5-mm pathway) and the non-optimized flow rate was 20 ml/min. The [^{11}C]formaldehyde yield shows a broad plateau from 400°C up to the highest temperature studied (600°C) with an optimum of 53% at 500°C. It is accompanied by a constant amount of [^{11}C]CO of around 30%. The [^{11}C]formaldehyde yield could still be improved to 67% by increasing the flow rate to 40 ml/min (top curve, Figure 1). This improvement was balanced by an equal decrease in the yield of [^{11}C]CO while that of [^{11}C]CO $_2$ was not affected. The yield of [^{11}C]CO $_2$ was relatively low, especially at those temperatures that gave the best [^{11}C]formaldehyde yields. [^{11}C]Formic acid was virtually absent except for a few percent where [^{11}C]CO $_2$ was at its lowest. This is in accordance with theoretical calculations by Yumara

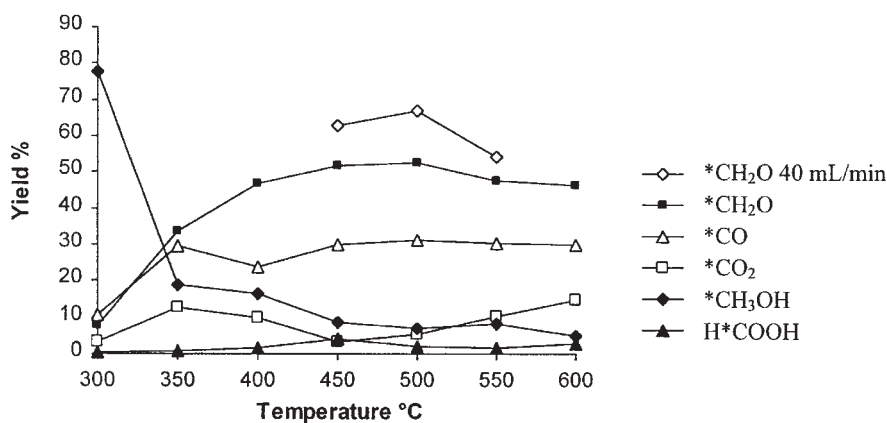
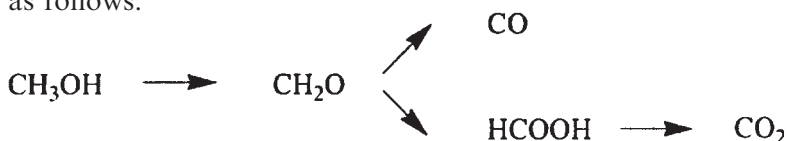


Figure 1. Product spectrum after passage of [¹¹C]methanol over the catalyst (20% Ag⁺) at 20 ml/min (only top curve at 40 ml/min) as a function of temperature

*et al.*²² on the oxidation of methanol by a FeO⁺ species that may be comparable to our stabilised Ag⁺. These calculations predict a further rapid oxidation of formic acid to CO₂ and propose a reaction sequence as follows:



A path length of 5 mm (300 mg of catalyst) was found to be the optimal length. When longer, the [¹¹C]formaldehyde yield goes down accompanied by a comparable increase in [¹¹C]CO yield while [¹¹C]CO₂ is less affected. Apparently the contact time with the catalyst determines the [¹¹C]formaldehyde/ [¹¹C]CO ratio. Using less catalyst gave an increase in non-reacted [¹¹C]methanol. Diminishing the silver content from 20 to 10% did not greatly alter the yield of all the products. However, with a Ag content of 2% the yield of [¹¹C]formaldehyde dropped considerably while a corresponding increase in non-reacted [¹¹C]methanol yield was found; the yield of [¹¹C]CO remained unchanged. This confirms that the presence of Ag⁺ ions in the catalyst is essential for its activity and selectivity.

All experiments for optimization were done with a relatively low radioactivity level of ~20 mCi (740 MBq) of [¹¹C]CO₂. Large-scale experiments at maximal [¹¹C]CO₂ production yielded, as expected, up to 650 mCi (24 GBq) of [¹¹C]formaldehyde calculated for end of

bombardment. However, we found that the use of di(ethyleneglycol) butyl ether/1% water instead of water in the hydrolysis step gave rise to a lowering of the specific radioactivity from 1600 mCi/ μ mol (hydrolysis with water) to 500mCi/ μ mol. In fact, we were able to show that di(ethyleneglycol) butyl ether can be a source of up to 1 μ mol of formaldehyde, probably by slight decomposition, both at the heating stage for distillation of [¹¹C]methanol and on the catalyst (by traces of di(ethyleneglycol) butyl ether carried along with the vector gas). Thus in order to have the highest possible yield and a maximum specific radioactivity it is advisable to look for another way of generating water-free [¹¹C]methanol. Alternatively, the use of water instead of di(ethyleneglycol) butyl ether gives a quite acceptable yield too (54%) and avoids the carrier problem. We found though that in any case traces of THF are also a source of formaldehyde (decomposition on the catalyst) and care should be taken that this solvent is completely removed before hydrolysis of the [¹¹C]methoxy lithium aluminium hydride complex. However, minor traces of THF will always be present and it may be advantageous to replace THF with diethyl ether, which is easier to evaporate, in order to attain even higher specific radioactivities.

Experimental

Materials and methods

Reagents: Lithium aluminium hydride (1M in tetrahydrofuran, “low ¹²C”) was obtained from ABX Company (Radeberg, Germany), formaldehyde (37% in water), 5,5-dimethyl-1,3-cyclohexanedione (dimedone), kaolin and di(ethyleneglycol) butyl ether from Aldrich and dry THF from Fluka.

HPLC: Column: Aminex HPX-87 H (BioRad), 300 mm \times 7.8 mm; temperature: 44°C; eluent: 1 mM sulphuric acid in water; flow rate: 0.6 ml/min; detection: Geiger–Müller radiation detector and differential refractive-index detector; retention times (peak summits): formaldehyde and formic acid (coinciding): 13.5 min, methanol: 18.4 min.

Catalyst preparation: The catalyst was prepared according to Li *et al.*¹⁷ using various silver concentrations. A mixture of kaolin (Al₂Si₂O₅(OH)₄, 40 g) and dilute nitric acid (5%, 200 ml) was refluxed for 4 h and then filtered. The solid was dried in vacuum over phosphorus pentoxide and finely ground (36.5 g). It was mixed with a solution of silver nitrate

(14.14, 7.08 or 1.42 g for 20, 10 or 2% of Ag, respectively) in water (150 ml). The slurry was evaporated to dryness in a rotary evaporator. The residue was aged over 14 h at 80°C and then dried at 120°C over 15 h, ground and heated at 1200°C for 9 h. (warning: NO₂ development at 420°C). Finally the white solid was ground to a powder which was used as the catalyst.

Carbon-11: No-carrier-added [¹¹C]carbon dioxide was produced using the nuclear reaction ¹⁴N(p,α)¹¹C by irradiation of a pressurised nitrogen gas target (6 bar) with a cyclotron-generated 20 MeV proton beam. A beam current of 5 μA for 1 min gave rise to ~20 mCi (740 MBq) of radioactive carbon dioxide and these conditions were used for all optimization experiments. For large-scale production the target was irradiated for 30 min at 30 μA yielding ~1.3 Ci (48 GBq) of [¹¹C]carbon dioxide. After irradiation, the radioactive gas was released from the target holder through a drying-column (70 mm × 4 mm) filled with phosphorus pentoxide. The [¹¹C]carbon dioxide was frozen out in a liquid-argon cooled stainless steel coil in a hot cell (outlet through flowmeter F1, Figure 2).

[¹¹C]Formaldehyde Synthesis and Optimization Experiments: The catalyst (various quantities) was held between wads of glass wool in a glass tube (5 mm internal diameter) horizontally placed in a furnace and integrated in a flow system (Figure 2). It was conditioned, immediately before the experiment, under a dry nitrogen stream (20 ml/min) by heating at 550°C for 90 min and subsequently at the working temperature for at least 30 min. The [¹¹C]carbon dioxide was released by removing the trap from the liquid-argon bath. The nitrogen stream (20 ml/min) swept it into a tapered vial (A) containing a mixture of dry THF (70 μl) and lithium aluminium hydride in THF (1M, 10 μl) at room temperature (outlet through flow meter F2). Vial A was placed in the heating block (170°C) in order to evaporate the THF with the nitrogen stream (1 min; outlet through flow meter F2). Vial A was now disconnected from the system in such a way that the catalyst and the vial's contents remained under nitrogen. The radioactivity trapped in A was measured and A was reintegrated into the flow system. In order to expel any air that might have entered the lines, the system was flushed with nitrogen, first for 5 min with F2 as outlet and then for 5 min with F3 as outlet (20 ml/min). Di(ethyleneglycol) butyl ether (300 μl) containing 1% (v/v) of water that had been deoxygenated by bubbling argon gas for 30 min, was added into A by syringe without introduction of any air. The vial was placed in the heating block. The liberated

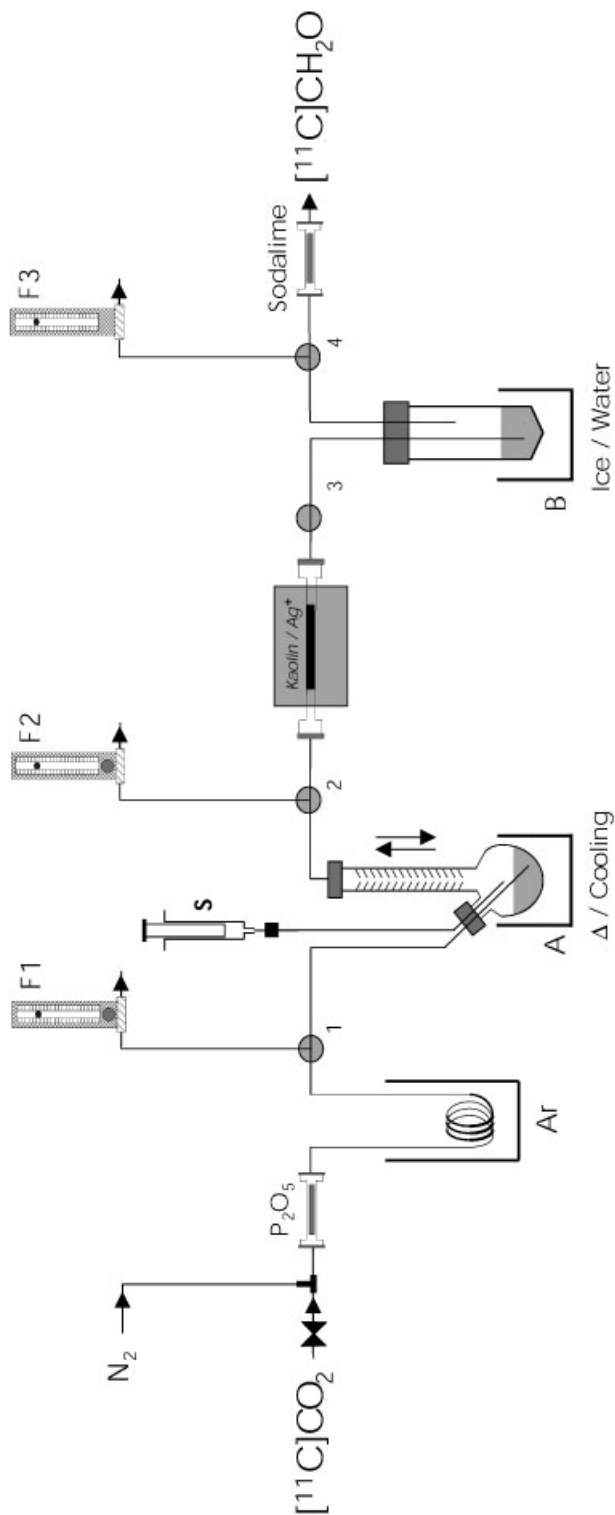


Figure 2. Schematic outline of the flow system for $[^{11}\text{C}]$ formaldehyde synthesis

[^{11}C]methanol was swept by the nitrogen stream (20, 40 or 60 ml/min) for 7 min through the heated catalyst into water (0.5 ml) contained in vial B at 0°C (outlet through sodalime trap). A vigreux unit on vial A should assure that small droplets of di(ethyleneglycol) butyl ether are stopped and that foaming in vial A is contained. Radioactivities were measured in B, the sodalime trap, vial A and the catalyst. Yields of the various products were calculated relative to liberated [^{11}C]methanol (= activity initially trapped in A minus residual activity in A) as follows: [^{11}C]formaldehyde: by dimedone precipitation (see below); [^{11}C]methanol by HPLC; [^{11}C]formic acid = yield by HPLC of co-eluting [^{11}C]formaldehyde and [^{11}C]formic acid together minus [^{11}C]formaldehyde yield from dimedone precipitation; [^{11}C]carbon dioxide: from the radioactivity in the sodalime trap; [^{11}C]carbon monoxide was assumed to be the unaccounted radioactivity.

Experiments with wet [^{11}C]methanol were carried out identically except for the hydrolysis which was done with water (100 μl). In this case [^{11}C]methanol is vaporised together with the water and carried as such through the catalyst.

Determination by dimedone precipitation:^{12,23} Dimedone (1.14 mmol; 0.16 g) was dissolved in methanol (3 ml). This solution was diluted with water (7 ml). An aliquot (~ 10 μl) of the radioactive aqueous solution to be analysed was added to a solution of formaldehyde (400 μmol) in water (400 μmol) and the radioactivity was measured. The above dimedone solution was added to the radioactive solution and the mixture was refluxed for 10 min (100°C). After cooling to room temperature the precipitate was filtered off and the radioactivity in the filtrate and in the precipitate was measured. The radioactivity in the latter gave the [^{11}C]formaldehyde content of the sample.

Large-scale synthesis of [^{11}C]formaldehyde: The following parameters were adopted for the large-scale operation of the system: Catalyst: 20% Ag; 300 mg; 5 mm path length; 500°C. Flow: 40 ml/min. The procedure is the same as described above with the following changes: (1) The vial A is not disconnected for radioactivity measurement. (2) The hydrolysing liquid is added via an external line with syringe S. The line is entirely prefilled with the liquid to avoid introduction of air. (3) The collection time for the [^{11}C]formaldehyde is reduced from 7 to 3 min. After decay to a convenient level the radioactivity was measured. A 50 μl sample of the final [^{11}C]formaldehyde solution was analysed by HPLC. The specific radioactivity was determined by comparison of the HPLC refractive index formaldehyde

peak surface with that of a standard. Absence of [¹¹C]formic acid was checked with the dimedone precipitation method.

Conclusion

A laboratory made silver-ion-doped ceramic material can serve as a catalyst for the preparation of [¹¹C]formaldehyde via the dehydrogenation of [¹¹C]methanol in a flow system. The best radiochemical yields were obtained with [¹¹C]methanol vapour giving up to 67% yield of [¹¹C]formaldehyde relative to [¹¹C]methanol. [¹¹C]Methanol mixed with water vapour gives a lower yield (maximum 54%) but with a much higher specific radioactivity. The temperature range for relatively high yields is rather broad (200°) in both production modes. Thus we have developed a reliable robust method for the production of large amounts of [¹¹C]formaldehyde.

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