

PRODUCTION OF CARBON-11 LABELLED METHYL IODIDE BY
DIRECT RECOIL SYNTHESIS

R. Wagner[‡], G. Stöcklin^{**}, and W. Schaack
Institut für Chemie 1 (Nuklearchemie),
Kernforschungsanlage Jülich GmbH,
D-5170 Jülich, FRG

SUMMARY

A novel method for a one-step on-line production of no carrier added $^{11}\text{CH}_3\text{I}$ is described. The method makes use of recoil reactions of ^{11}C -atoms, produced via the $^{14}\text{N}(p,\alpha)^{11}\text{C}$ -process in a gaseous $\text{N}_2\text{-HI}$ flow target system. The radiochemical yield of $^{11}\text{CH}_3\text{I}$ under optimized conditions is 25 %. Separation from $^{11}\text{CH}_4$ which is formed with a radiochemical yield of 45 % and from high boiling by-products is readily achieved by washing and trapping procedures. Up to 90 mCi of pure $^{11}\text{CH}_3\text{I}$ have been produced with specific activities of about 300 Ci/mmol after a 40 minute collection time.

Key Words: ^{11}C , ^{11}C -Methyl iodide, Recoil synthesis

INTRODUCTION

The short-lived positron emitter carbon-11 ($T_{1/2} = 20.5$ min) and its labelled compounds have gained increasing interest for in-vivo studies of regional functions in conjunction with positron emission tomography. Only a limited number of precursors for rapid labelling can be obtained by direct recoil methods in sufficiently high specific activity. These are ^{11}CO , $^{11}\text{CO}_2$, H^{11}CN and $^{11}\text{CH}\equiv\text{CH}$ (for a review see ref. 1). Other useful compounds for syntheses such as

* Present address: Max-Planck Institut für Hirnforschung,
Forschungsstelle für Hirnkreislaufforschung,
Ostmerheimer Str. 200, D-5000 Köln 91, FRG

** Requests for reprints should be directed to this author.

$^{11}\text{CH}_3\text{I}$, H_2^{11}CO (2-3) and $^{11}\text{COCl}_2$ (4-6), however, demand chemical procedures, which are more time-consuming. Furthermore, the activity is generally not carrier-free because of dilution with inactive carbon impurities. In the case of the methylation reagent $^{11}\text{CH}_3\text{I}$ the highest specific activity obtained in a labelled compound (methionine) was 1000 Ci/mmol (7), achieved with a highly complicated remote control synthesis and preceding purification of the nitrogen gas from traces of CO_2 .

On the basis of the hot atom chemistry of recoiling carbon-11 atoms (cf. e.g. 8) it seemed possible to prepare ^{11}C -labelled methyl iodide via reactions of ^{11}C atoms in HI (9).

EXPERIMENTAL

For the production of $^{11}\text{CH}_3\text{I}$, N_2 (99.9995 %, Messer Griesheim) and HI (98 %, Merck-Schuchardt or Baker) were used without further purification.

The flow target system for production of $^{11}\text{CH}_3\text{I}$ is shown in Figures 1 and 2. The gas target (AlMg 3)^{*} is 600 mm long and has a volume of 424 ml. The water-cooled front window consists of an aluminum plate (AlCuMgPbF38)^{**} centrally machined to 0.5 mm thickness. Since the gas target is operated only slightly above atmospheric pressure, it is not a thick target, and a water-cooled beam-stop is required. The target gas mixture is blended by adjusting needle valves to the appropriate flow rates. Generally the total flow rate was 1000 ml/min at a N_2/HI -ratio of 85/15.

* Mg 2.6-3.4 %, Mn 0-0.5 %, Cr 0-0.3%

** Cu 3.5-5.0 %, Pb + Sn + Bi + Cd + Sb 1.0-3.0 %, Mg 0.4-1.8 %, Mn 0.5-1.0 %

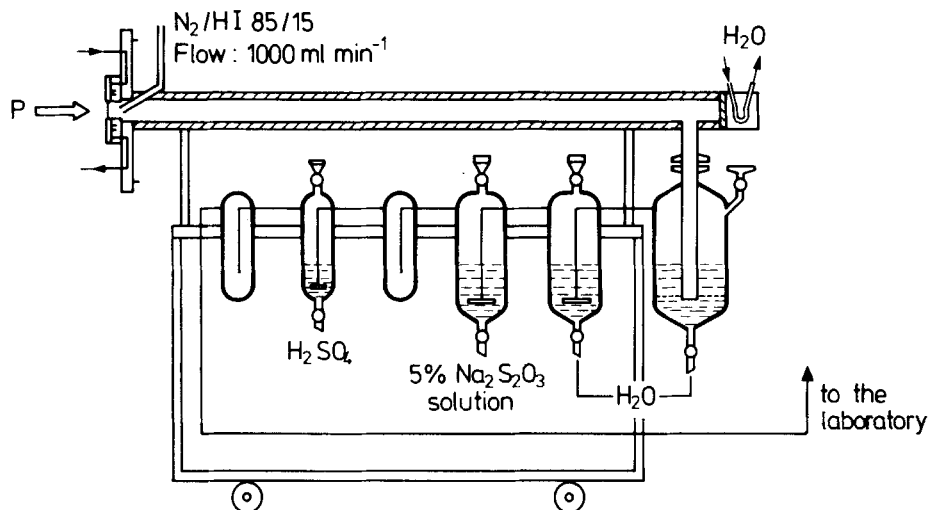


Fig. 1. Target and gas purification system.

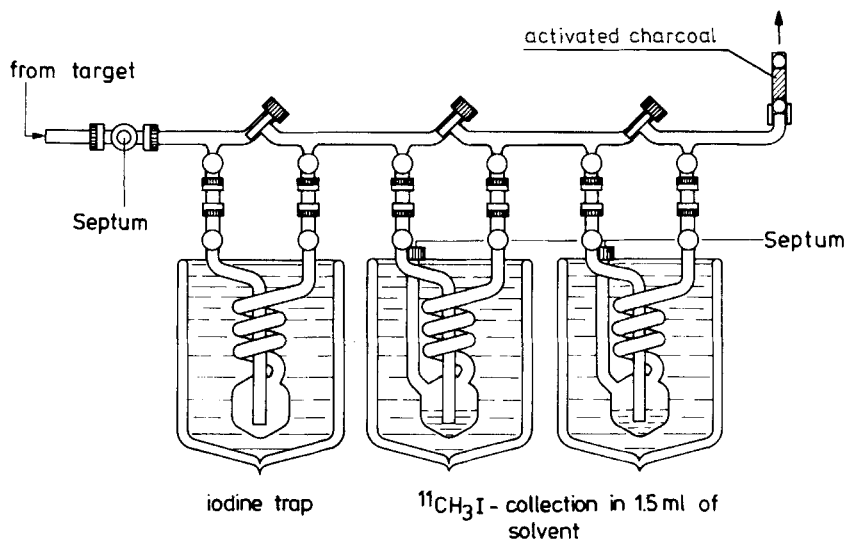


Fig. 2. Collection of $^{11}\text{CH}_3\text{I}$.

Stopcocks: Glass-Teflon, joints: Cajon Ultra-Torr Union.

Irradiations were carried out at the Jülich compact cyclotron CV 28 with proton energies of 16, 18 and 20 MeV and beam currents up to 25 μ A. Further variation of the on-gas-proton energy was achieved by using target windows of different thickness (0.5 and 0.8 mm). Thus, the on-gas-energies ranged from 10.1 to 17.2 MeV. The degradation of the beam energy in the gas was only between 2.8 and 4.3 MeV.

Behind the target the gas is washed with water and a 5 % solution of $\text{Na}_2\text{S}_2\text{O}_3$ and dried with concentrated sulfuric acid. In this way, HI, radiolytically produced I_2 and some high boiling radioactive by-products are quantitatively removed. As demonstrated in inactive test runs with mmol quantities of CH_3I , practically no CH_3I is retained in the washing bottles under these conditions. The gas is then led into the laboratory through a 1/4" teflon tubing. The collecting system (Fig. 2) consists of three pyrex traps cooled to dry ice temperature. The first one serves as an additional purification trap for removal of traces of iodine and water. In the second and third trap the methyl iodide is collected by bubbling the gas through an appropriate solvent (see below). A small tube filled with activated charcoal is placed at the outlet for safety reasons. Under the described conditions, only $^{11}\text{CH}_3\text{I}$ is retained in solvents such as toluene, ethanol etc. (see below).

For optimization experiments discontinuous irradiation runs were also carried out using closed cylindrical targets of 100 ml volume which were filled with the gas mixture up to 718 mbar by standard vacuum techniques. After irradiation the target was connected to a vacuum line, carriers were added and aliquots prepared, which were then submitted to radio gas chromatography under conditions described below.

The radiochemical purity and the specific activity of the collected $^{11}\text{CH}_3\text{I}$ were determined by radio gas chromatography using a

Porapak Q column (4 m, 5 mm i.d., 440 K, 100 ml He/min, TCD at 440 K). The eluted $^{11}\text{CH}_3\text{I}$ was adsorbed on activated charcoal and the absolute activity measured in a calibrated Tricarb γ -counter. $^{11}\text{CH}_3\text{I}$ was not carrier-free, probably due to C-impurities from the target surface. The determination of mass was also carried out by gas chromatography using a calibration curve which was taken under the same conditions as the radio gas chromatography of the irradiated sample. Carrier amounts between 0.05 μmol and 1 μmol could be detected, increasing with the time of irradiation.

RESULTS

In order to optimize the product yield of $^{11}\text{CH}_3\text{I}$ it was necessary to determine its dependence on the N_2 -HI ratio and the dose. These experiments were carried out in discontinuous individual experiments. The concentration dependence in Fig. 3 indicates that at a HI-concentration of 10 mol% a radiochemical saturation yield of 25 % $^{11}\text{CH}_3\text{I}$ is obtained. The main product is $^{11}\text{CH}_4$, which is formed in radiochemical yields of up to 45 %. Other products (^{11}CO , $^{11}\text{CO}_2$, ^{11}HCN) decrease to below 2 % at HI-concentrations above about 8 %. The dependence of the product yields at 20 mol% HI on the irradiation dose (Fig. 4) shows that the yields are virtually independent of dose from 10^{-2} to $5 \cdot 10^{-1}$ eV/molecule. Above this dose, a sharp decrease in the yield of all gaseous products is observed down to a total yield of 5 % at 2 eV/molecule. At this dose the activity mainly appears in the form of unidentified higher boiling products which remain at the wall of the irradiation tank.

The simple product spectrum in the gas phase and the relatively high radiochemical yield of $^{11}\text{CH}_3\text{I}$ at moderate doses encouraged us to develop a continuous on-line production method. It is evident from the dose dependence shown in Fig. 3 that the absorbed dose in the

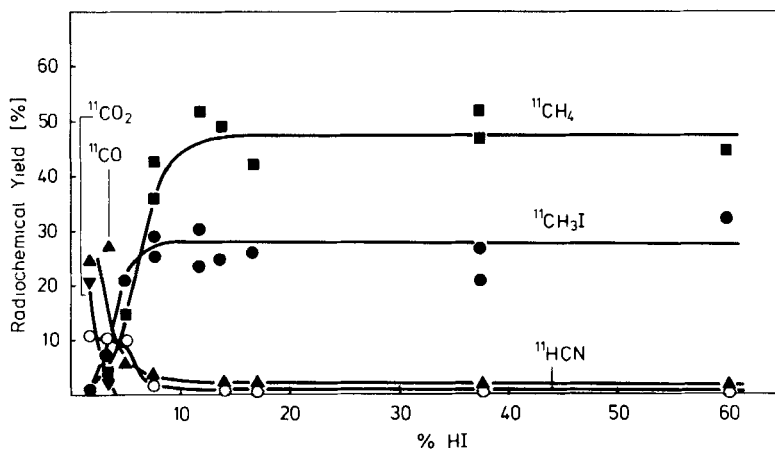


Fig. 3. Dependence of product yields on the HI concentration in a static N_2 -HI gas target. $p = 718$ mbar. Dose: 0.3 eV/molecule. On-gas proton energy: 12.5 MeV. Beam current: $1 \mu A$. Irradiation time: 5 min.

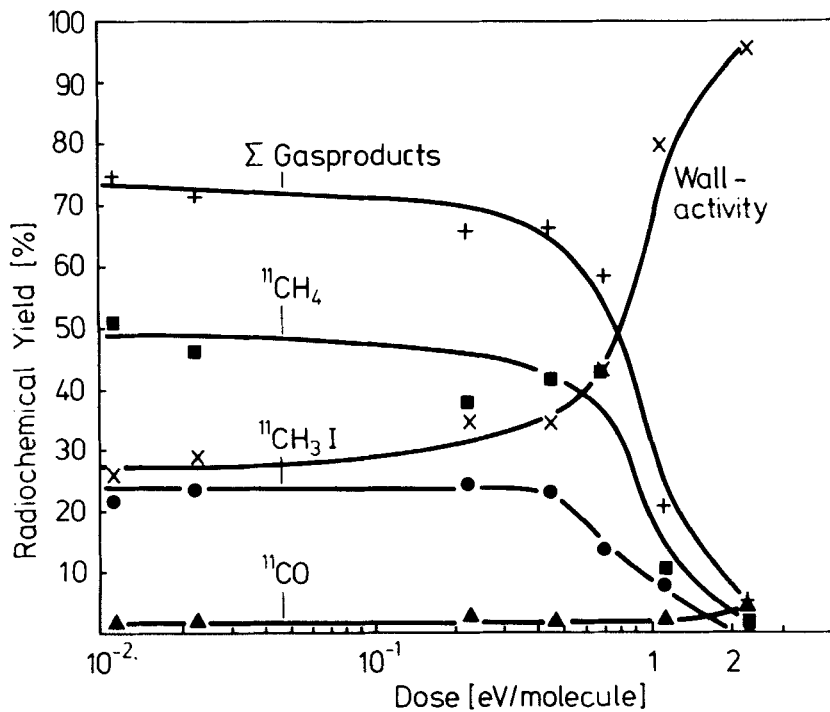


Fig. 4. Dose dependence of the product yields in a static N_2 -HI gas target. $p = 718$ mbar. N_2 :HI = 4:1.

gas must not exceed 0.5 eV/molecule. At this rather low dose significant activities can only be obtained in a flow target with high flow rates. Taking into account the target parameters mentioned above, a N₂-HI mixture with 15 % HI and a beam current of 10 μA, the required flow rate is about 1000 ml/min. The energy absorption in the target and in the window was calculated from the elemental stopping powers (ref. 10, for further details see also ref. 9).

Separation from the other radioactive products is simple. ¹¹CH₄ and ¹¹CO are not trapped in the collection solvent, whereas over 90 % of the ¹¹CH₃I is retained in the first collection trap (see Fig. 2). Collection of the ¹¹CH₃I without solvent was unsuccessful even at liquid N₂-temperature due to the high flow rate. Many different solvents can be used, as long as they remain liquid at 195 K. Toluene, ethanol, tetrahydrofuran, ether and acetone were almost equally effective. If a gas chromatographic separation is required, e.g. for quality control, toluene is the solvent of choice, because it is eluted after the ¹¹CH₃I under the chromatographic conditions given above.

In an empirical approach we also optimized the production rates of ¹¹CH₃I for the flow system. In Fig. 5 the collected ¹¹CH₃I-activity is plotted as a function of beam current for different on-gas energies. It can be seen that for on-gas energies of 17.2 and 10.1 MeV the performance of the system is nearly identical. At the other energies much less ¹¹CH₃I-activity could be collected. The non-linear relation between beam current and collected activity is mainly due to the dose dependence. However, the relationship is more complicated than that shown in Fig. 4, since it reflects the influence of three parameters: the beam current, the energy dependence of the cross section and the dose dependence with changing energy and beam current. The arrows in Fig. 5 indicate the beam currents corresponding to a dose of 0.5 eV/molecule for

each individual energy. It can be seen that at these or slightly higher values saturation occurs, indicating a compensation of radiolytic destruction of $^{11}\text{CH}_3\text{I}$ and increasing ^{11}C -production rate. The $^{11}\text{CH}_3\text{I}$ activity in Fig. 5 was obtained in a 20 min collection time. By increasing the time to 40 min, we obtained up to 90 mCi of pure $^{11}\text{CH}_3\text{I}$ with specific activities of about 300 Ci/mmol at the end of the collection time.

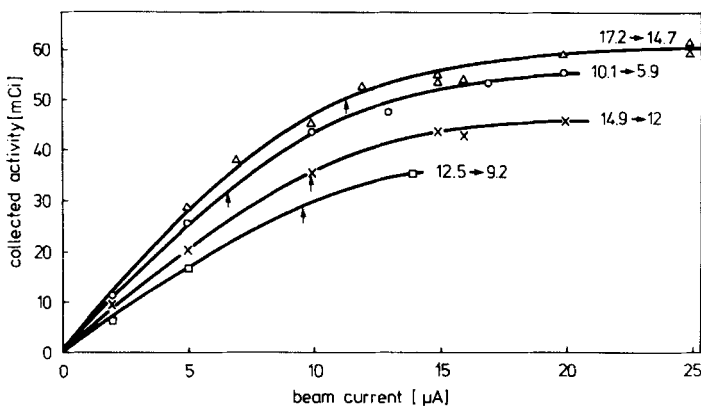


Fig. 5. Dependence of the collected $^{11}\text{CH}_3\text{I}$ -activity (collection time: 20 min) on beam current and beam energy in an N_2 -HI (ratio 4:1); flow target (see text).

During the irradiation, a significant part of the HI is radiolytically decomposed and an iodine deposit is formed on the target wall. This deposit has to be removed from time to time, although no effect on the $^{11}\text{CH}_3\text{I}$ production was observed during several successive runs. In order to minimize HI losses, i.e. to extend the operating period without cleaning, it seemed necessary to minimize the HI-concentration under production conditions of the flow system. Figure 6 shows the dependence of the collected $^{11}\text{CH}_3\text{I}$ -activity on the HI-flow rate. It can be seen that the HI-concentration can be reduced to about 6 to 8 %, which is in agreement with the findings presented in Fig. 3 for a static target. Nevertheless, the target

has to be cleaned after about 10 hours operation time. This is easily accomplished by washing with water and acetone. After drying and flushing the system with nitrogen, the target can be used again. The target window should also be changed after about 30 hours of irradiation time at 25 μA as a precaution against failure.

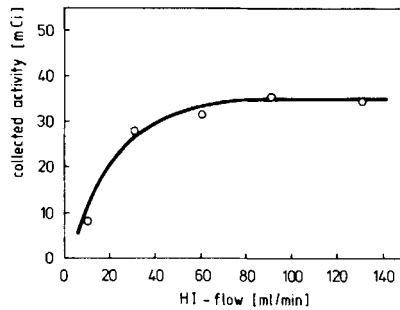


Fig. 6. Dependence of the collected $^{11}\text{CH}_3\text{I}$ -activity on the HI-content of the target gas.

N_2 -flow: 850 ml/min, beam energy: 12.5 MeV,

beam current: 14 μA , collection time: 20 min.

CONCLUSION

The described on-line recoil synthesis of $^{11}\text{CH}_3\text{I}$ in a flow target system is well suited to produce 100 mCi-quantities at specific activities of 300 Ci/mmol. This value is comparable to those achieved by classical methods. It should be emphasized, that the specific activities were obtained without any special precautions against contamination with inactive carbon. The design of the whole apparatus is simple, and the radiation risk for the operator is low, because only very little handling is involved. It should be possible to further increase the total activity by using higher pressures and/or longer targets, since the present target only utilizes about one third of the total excitation function. Thus, the ^{11}C -production rate can be increased by at least a factor of 3. At the same time

the dose rate also increases and higher flow rates are needed to reduce radiation decomposition. Any further optimization will therefore require improved engineering.

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