Production of [^{15}O]Water at Low-Energy Proton Cyclotrons

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Abstract

We report a simple system for producing [^{15}O]H$_2$O from nitrogen-15 in a nitrogen/hydrogen gas target with recycling of the target nitrogen, allowing production on low-energy proton-only accelerators with minimal consumption of isotopically enriched nitrogen-15. The radiolabeled water is separated from the target gas and radiolytically produced ammonia by temporary freezing in a small trap at −40 °C.

Keywords: PET, Oxygen-15, Oxygen-14, Medical Cyclotron

Introduction

The short-lived isotope oxygen-15 is a clinically important radiotracer for positron emission tomography (PET). [^{15}O]Oxygen is used for metabolic oxygen consumption measurements, [^{15}O]carbon monoxide is used for lung perfusion and blood distribution measurements, and [^{15}O]water is used for measuring regional cerebral blood flow (e.g. Beason-Held et al., 1999). Oxygen-15 is commonly produced by deuteron bombardment of a nitrogen gas target via the ^{14}N(d,n)^{15}O reaction. Deuterons are not available on medical accelerators that are designed only for low-energy protons, thus ^{15}O must be produced via the ^{15}N(p,n) ^{15}O reaction on a target of isotopically enriched nitrogen-15 (Clark et al., 1987). The common need to produce multiple ^{15}O batches for a single study can thus lead to prohibitive costs because the enriched isotope is expensive. The impracticality of repetitive flow studies is circumvented by adopting the system described herein.

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Oxygen-15 is commonly extracted from the production target by the addition of a small (0.2 to 1%) addition of natural oxygen (or sometimes CO_2) to the target gas. The $[^{15}O]$oxygen can be used directly or chemically processed to form other molecules such as CO, CO_2, or H_2O (Clark et al., 1987). $[^{15}O]H_2O$ can also be produced directly in the target by adding about 5% hydrogen to the nitrogen target gas (Ferrieri and Wolf, 1983; Ferrieri et al., 1994). This route has the advantage of high specific activity due to the lack of added oxygen carrier material, but a disadvantage is that large amounts of ammonia are radiolytically produced (Buckley et al., 2000).

The high freezing point of water suggests the possibility of using a cold trap to separate $[^{15}O]H_2O$ from the target gas, allowing reuse of the expensive enriched $^{15}N_2$. This technique can also separate water vapor from the produced ammonia, as well as many other potential chemical or radiological contaminants, such as CO or N_2O, that might otherwise require scavenging traps (Mackey et al., 1999). Simple cooling systems can reach useful temperatures for temporarily freezing water vapor, without retaining these unwanted products. Thus clean, high specific activity $[^{15}O]H_2O$ can be produced by the cryoseparation system we describe.

The radiowater system was developed as part of a nuclear physics research project known as BEARS (Powell et al., 2000; Powell et al., 2003). In BEARS, short-lived radioisotopes produced by the LBNL Life Science Division medical cyclotron are ionized and accelerated by the Nuclear Science Division 88-Inch research cyclotron, in order to perform nuclear physics experiments (Guo et al., 2005). The radiowater separation technique was first developed to allow oxygen-14 production from a natural nitrogen target without addition of any carrier oxygen, which if used would overload the ion source vacuum of the 88-Inch cyclotron. Later the ^{14}O production system was extended to oxygen-15 by adding systems for reusing expensive nitrogen-15 target gas.

Herein we detail the application of this radiowater separation technique for PET studies, in particular for $[^{15}O]$water production at proton-only accelerator facilities. As much of the development described in this paper was initially performed with oxygen-14, and as $[^{14}O]H_2O$ has been proposed as a potentially superior radiotracer to $[^{15}O]H_2O$

(Sajjad et al., 2002) due to its shorter half-life (71 s versus 122 s), we report results for both ^{14}O and ^{15}O.

Methods and Materials

Activity was produced with a CTI RDS-111 (CTI Incorporated, Knoxville, TN) cyclotron, providing beams of up to 40 µA of protons, with an energy of approximately 10.6 MeV after losses in the vacuum and target entrance windows. The target design was a modified CTI conical gas target, (8.3 mm entrance, opening to 21 mm over a 70 mm internal length) , providing a volume of about 7 mL (Alvord and Zigler, 1995). The inner surfaces of the aluminum target body were electroplated with gold. The entrance window was unplated 25 µm Havar. The target body was mounted in the standard CTI water-cooled, 8-target turret system.

Recovery and reuse of the nitrogen target gas was accomplished with a high-pressure stainless-steel syringe from Harvard Apparatus (Holliston, MA, USA). This syringe was 200 mL in volume, sufficient to unload the target to less than an atmosphere. It was driven by a 550 mL pneumatic cylinder (Powell et al., 2005), sufficient to pressurize the target to about 1650 kPa (240 PSI) with available compressed air of 580 kPa (84 PSI) (see Fig. 1).

Separation of the radiolabeled water was accomplished with a cold trap consisting of a 15 cm length of 1.0 mm (0.040") ID, 1.59 mm (1/16") OD, stainless steel tubing. The tubing was partially crimped in alternating perpendicular 1 cm sections to both reduce internal volume and promote mixing. The trap was bent in a single loop and slipped into a length of 1 cm (3/8") ID silicone foam pipe insulation (McMaster-Carr, Los Angeles, CA, USA), the other end of which was directly coupled to the cold-air port of a vortex tube (Model 106 with an 8L bushing, Vortec, ITW Air Management, Cincinnati, OH, USA) (see Fig. 1). Vortex tubes are simple and inexpensive mechanical devices that take dried compressed air and produce separate hot and cold air streams (Hilsch, 1947). A throttle valve on the hot exhaust controls the relative temperature and airflow of the two streams. The vortex tube was capable of cooling the entire trap to -37

to -40 °C (measured by a thermocouple in the exit of the silicone tube) using the available laboratory air pressure of 580 kPa (84 PSI).[1] Cooling time needed was one to two minutes. Twenty amperes of current directed through the stainless steel trap tubing for 2 seconds[2] was sufficient to vaporize and release the water. A six-port, low dead-volume, HPLC injector valve V1 (Valco Instruments, Houston, TX, USA) served to switch the cold trap between the target-syringe unload line and an activity delivery line (Fig. 1).

Figure 1 shows the production system. The target is loaded and unloaded through valves V1 and V2 by the pneumatically driven syringe. The vortex-tube-cooled cold trap temporarily retains the water vapor while the six-port injector valve V1 switches the trap from the target-syringe unload line to the activity delivery valve V3. After a brief flush of the trap to waste to eliminate residual target gases, the water is vaporized by a 2 sec application of the heating current and delivered in a flow of helium. The production, separation and delivery cycle is computer automated. Total time from end of irradiation to delivery is less than 20 seconds.

The target was typically loaded to pressures of about 1650 kPa (240 PSI), sufficient to achieve near thick-target production yields. For ^{14}O, a mixture of 5% hydrogen in natural abundance nitrogen was used (Bay Airgas, San Leandro, CA, USA), which could optionally be diluted with pure nitrogen to investigate the effect of lower hydrogen ratios. For ^{15}O, the target system and syringe was first flushed several times with pure hydrogen (Scott Specialty Gases, San Bernardino, CA, USA). The target was left with one atmosphere of hydrogen, sufficient to contribute about 5% to the final gas mix. The syringe was then drawn back, pulling a partial vacuum, and 98%+ enriched $^{15}N_2$ (Cambridge Isotope Laboratories, Andover, MA, USA) was added from a 1 L bottle until the desired final pressure was reached. This was determined by adding $^{15}N_2$ in small amounts and measuring the target pressure with the syringe driven in.

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[1] Lower temperatures would be available with higher operating pressures.

[2] For protection against accidental over heating, the silicone foam surrounding the trap is fire resistant, and a minimum air flow is always applied through the vortex tube to prevent possible melting of plastic components.

The radiolabeled water was transferred to a hotcell in a 300 mL/min stream of helium through roughly 10 m of 0.076 mm (0.030") ID polyethylene tubing (at room temperature). The water was collected by either bubbling in saline, freezing in a cold trap at dry ice temperatures, or absorption on Ascarite II® (Thomas Scientific, Swedesboro, NJ, USA). In all cases, the activity was measured in a CR-15 radioisotope dose calibrator (Capintec, Inc., Ramsey, NJ, USA), read out by computer. A LabVIEW interface provided real time display and multiple-isotope decay analysis. The factor used to correct observed ^{14}O dose, needed to account for the effect of the additional 2.3 MeV gamma ray, was taken to be 0.50±0.02 (Sajjad et al., 2002).

Results and Discussion

Tests runs were performed for production of both ^{14}O and ^{15}O. Irradiation parameters were 150 seconds at 30 µA of 10.6 MeV protons, and the water vapor was collected by bubbling though a 20 mL vial of saline in the dose calibrator. The long, unheated line from cold trap to hot cell limited the complete rapid transfer of the water vapor, even at 300 mL/min helium flow. The maximum activity in the saline occurred at around 45 seconds after end of irradiation; this activity was 9.8 GBq (265 mCi) of $H_2^{15}O$ or 0.59 Gbq (16 mCi) of $H_2^{14}O$.

A more generally applicable measurement is the total amount of activity trapped and released by the cold trap, as determined by a decay-curve analysis after longer delivery times. This can be expressed as a saturation yield per µA by correcting for the finite irradiation time and dividing by the beam current. These results are shown in Table 1. The saturation yield was 0.78 Gbq (21 mCi) per µA for $[^{15}O]H_2O$ or 0.045 Gbq (1.2 mCi) per µA for $[^{14}O]H_2O$.

These saturation yields can be compared to the known radioisotope production yields for ^{15}O (Takács et al., 2003) and ^{14}O (Nozaki and Iwamoto, 1981). As shown in Table 1, we observe about 30% of the theoretical activity. Efficiency tests of the cold trap indicated that water is not held indefinitely at these temperatures, but that the current system is sufficient to catch, flush (5 s), and release to the delivery line approximately

90% of the radiolabeled water. Thus, the low yields likely represent poor production and/or extraction of water vapor from the target.

The target used in this work is quite small relative to many that have been used for radioisotope production. In such targets, short-lived radiolytically produced radical species can interact with target walls that are in close proximity to the beam path (Powell et al., 2003). This can lead to permanent loss of the desired radioisotopes. Alternately, the loss can be temporary, as further interactions with radical species can return the material to gaseous form. These effects can produce variations in chemical saturation yield dependant on target-gas composition, irradiation current density, and/or irradiation time. Buckley et al. (2000 and 2004) have studied the production of [^{11}C]methane in nitrogen/hydrogen targets of a variety of geometries and surface materials. They find significant reductions in yield at higher beam currents and lower fractions of hydrogen (5% versus 10%), as well as dependence on choice of surface material. However, measurements with [^{14}O]H$_2$O (performed during development of BEARS) did not show significant dependence of saturation yield on either hydrogen fraction (from 1% to 5%) or beam current (from 5μA to 40 μA). This suggests that oxygen isotopes are being radiolytically processed to H$_2$O and not chemically bonding to the chamber walls. It follows that the low measured yields (30% of theoretical) are likely due to adsorption of water vapor on target surfaces, leading to poor extraction efficiency. An improvement in production efficiency may be realized by development of a heated target system in place of the current water-cooled design.

Choice of target-chamber surface material seemed to have a very significant effect on saturation yield. As described in the previous section, the aluminum target used in this work was plated with gold. Attempts to use a non-plated aluminum target for [^{14}O]H$_2$O production resulted in very low yields likely from isotopic exchange effects with the aluminum oxide surface (Powell et al., 2003). Two or three layers of Al$_2$O$_3$ are known to isotopically exchange with oxygen in the gas phase at temperatures of around 500 °C (Bielansk and Haber, 1991), and radiolysis should cause similar effects.

The presence of radioisotopic contaminants was determined from the activity decay-curve analysis. The [^{14}O]water samples in saline contained an admixture of 4.1%

of ^{15}O, which represents 5.6% of calculated saturation activity. This agrees well with the amount expected from the 0.36% natural abundance of ^{15}N. Determining the amount of ^{14}O contamination in the [^{15}O]water was complicated by the short half-lives of these two isotopes, the shorter half-life of the ^{14}O, and the relatively small amount of ^{14}O. The measurement provided only an upper limit of 2% of saturation activity. The expected amount, calculated from the 98%+ quoted enrichment of the nitrogen-15, is $\leq 0.13\%$. Also produced with ^{14}O is a large amount of ^{11}C from the (p,α) reaction on ^{14}N, presumably in the form of CH_4, CO, or CO_2. Unaffected by the cold trap, this activity should remain in the target gas and buildup over multiple runs. However, a small amount, about 0.03 mCi per run or 0.1% of ^{14}O, was identified in the saline solution.

Considerable amounts of ammonia are radiolytically produced in the target (Buckley et al., 2000), and this will raise the pH of the radiotracer solution unless separated (Ferrieri et al., 1994). With our system, the ammonia is separated by the cold trap, and no increase in pH was detected even from ten consecutive batches of radiolabeled water trapped in 20 mL of saline.

Although perhaps not applicable to the relatively short number of irradiations for medical use, it was found that target yields tended to drop with the number of irradiations. A loss rate of about 1% per irradiation was observed during continuous operation in support of BEARS nuclear physics experiments. After long-term operation, up to 48 hours with hundreds of short irradiations, the target was removed. On inspection, a white residue was observed on the inner walls of the target chamber; cleaning off the residue restored production yields. Alternatively, replacing the reducing hydrogen/nitrogen target gas with an oxidizing mix of oxygen/helium and irradiating for a short period appears to alleviate the problem. It is not clear whether this residue affects target chemistry or simply increases adsorption of water vapor.

In addition to the production of high specific activity [$^{14,15}O$]water, no-carrier added CO and CO_2 for medical use is available as an extension of the radiolabeled water trapping technique. In the work with BEARS, the radiolabeled water was converted first to carbon monoxide over graphite granules at 1000 to 1070 °C, then oxidized to CO_2 over

platinum foil at 280 °C (Powell et al., 2003).[3] Conversion yields from [^{14,15}O]water to [^{14,15}O]CO$_2$ were typically 50–60%. No-carrier-added[4] [^{14,15}O]CO is of particular interest: with traditional production methods, concern over carbon monoxide toxicity can require running with suboptimal levels of carrier oxygen, leading to significantly reduced production yields (Clark et al., 1987; Jackson et al., 1993). It should also be possible to produce [^{14,15}O]oxygen by isotopic exchange over metal oxide catalysts, using techniques described by Iwata et al. (1988).

Summary

A simple system has been developed that can separate and deliver radiologically produced water from a nitrogen/hydrogen mix while recycling the target gas, allowing production of [^{15}O]H$_2$O on low-energy proton cyclotrons without significant consumption of enriched ^{15}N$_2$. Alternately, [^{14}O]H$_2$O can be produced from natural abundance nitrogen. The system also separates out many possible contaminants, including the ammonia radiolytically produced in an N$_2$/H$_2$ mix. The [^{15}O]H$_2$O can be easily converted to no-carrier-added [^{15}O]CO or CO$_2$. Meaningful yields of about 30% of oxygen isotope production can be delivered for medical use.

Acknowledgements

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[3] Due to the lack of carrier, care had to be taken not to use high surface area materials like activated carbon or Pt/Pd-coated Alumina pellets. This is similar to effects seen in the low-carrier O$_2$ work described by Berridge et al. (1990). As in that reference, we anecdotally observed a change in the Pt catalyst after an initial period of operation, requiring an increase in operating temperature from 180 to 280 °C.

[4] Though no carrier oxygen is added, some level of water will remain in the target system, thus the radiolabeled product cannot be said to be completely carrier free.

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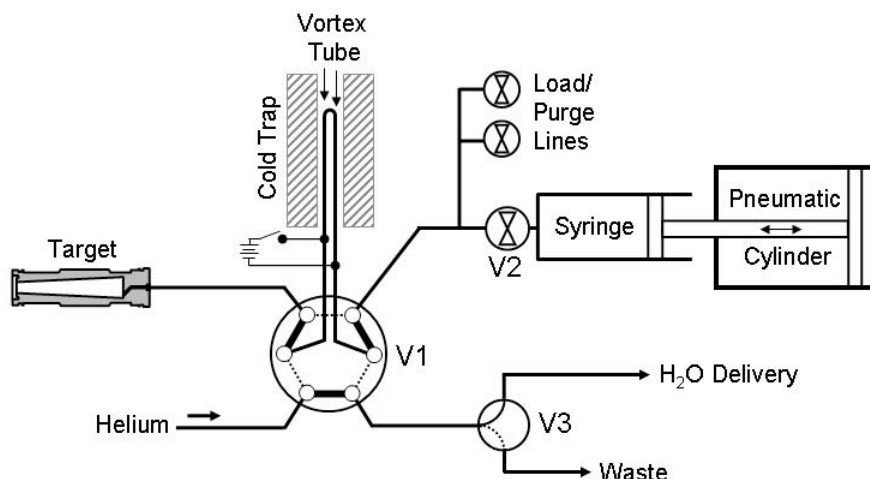
Fig. 1. Schematic of the [^{15}O]water production and separation system. The cyclotron target is unloaded and reloaded by a 200 mL syringe driven by a pneumatic cylinder. A trap cooled by a vortex tube retains the water vapor. The six-port valve V1 switches the trap between the target-syringe and helium-delivery lines. An electric current applied to the trap revaporizes the water for delivery in a flow of helium.

Table 1. Production yields for 30 µA, 150 s irradiations of 10.6 MeV protons on ^{15}N$_2$ or ^{14}N$_2$ plus 5% hydrogen.

Compound	Activity delivered[a] in GBq (mCi)	Saturation Activity in GBq/µA (mCi/µA)	Fraction of Isotope Yield
[^{15}O]H$_2$O	13.5 (364)	0.78 (21)	29%[b]
[^{14}O]H$_2$O	1.0 (28)	0.045 (1.2)	32%[c]

[a] decay corrected to end of irradiation

[b] from Takács et al. (2003), ^{15}N(p,n)^{15}O, 2.66 GBq/µA

[c] from Nozaki and Iwamoto (1981), ^{14}N(p,n)^{14}O, 0.14 GBq/µA (± 15%)