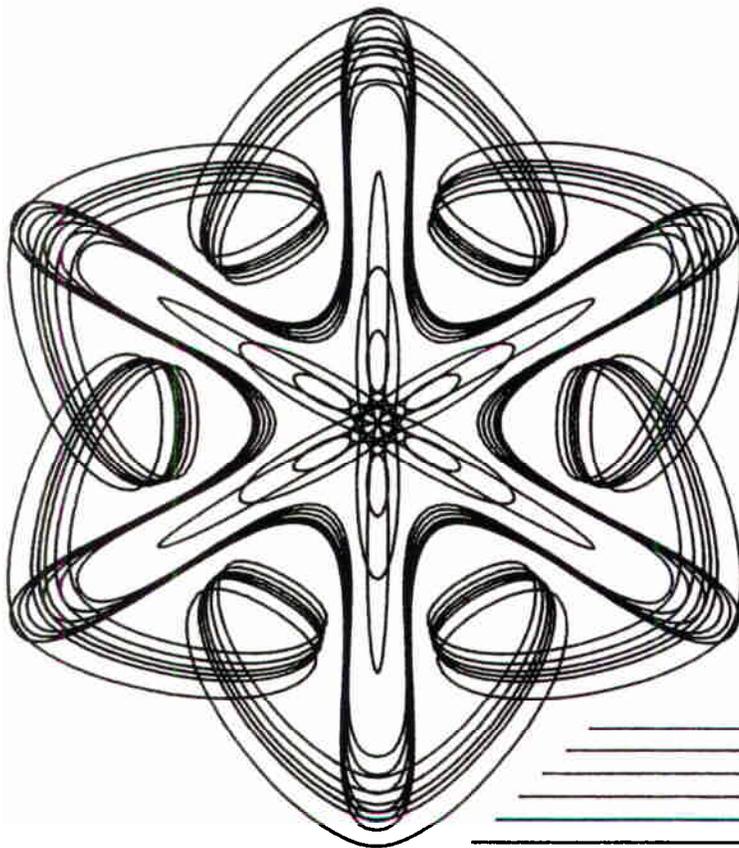


Session III

Specific Targetry Problems

Moderators: M. Berridge, D. Maylotte



At one time, baseball umpires sat
behind home plate in rocking chairs.

Session III : Specific Targetry Problems

Marc Berridge and Don Maylotte, Co Chairs

Although this session was originally titled Specific Targetry Problems, in the usual spirit of the workshop it drifted to cover whatever was of most interest to the participants. In this case, that seemed to be the production of ^{13}N ammonia by a variety of routes, followed by a brief discussion of specific activity problems. There were five abstracts submitted before the workshop concerning ammonia production. Two of these, from NIH and U. of PA, treated the water target with added ethanol, one from CWRU treated the water target with added hydrogen pressure, and two from the SRL/Wash. U. St. Louis collaboration treated the ^{12}C solid target with low energy deuteron bombardment. In addition, Jerry Bida and Jean-Luc Morelle were pressed into presenting their respective work in irradiation of carbon in the form of Bucky balls, thin foils, and fabric. Since the last workshop we have learned that clinical quantities of ammonia can be made using a low energy accelerator with a modification of Buckingham and Clark's method and chemical reduction, and that the work of Tilbury and Dahl and Mulholland et al. has been extended into robust systems for rapid direct ammonia production with the more conventional cyclotrons. On the topic of the water target, it is clear that the production problems have been solved. However, the only bit of data which is clear concerning the functioning of that target is that higher gas pressures are advantageous. Previously proposed mechanisms for direct ammonia production are not entirely consistent with the new data, including the pressure dependence. Much remains to be learned about the chemistry going on even in these old and widely used targets. For the carbon targets, taking ^{12}C and ^{13}C together, the main problem seemed to be one of controlling the recoil environment, and thereby controlling the chemistry and target yield. Several original strategies were presented, all of which add new information to the discussion and progress toward more efficient targets. The carbon targets still have room for practical improvement through target design.

Overview on Ammonia Production

Marc Berridge

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I thought it would be interesting to dredge out some of the old papers on ammonia production because that is the topic of most contributions to this session. A non-exhaustive literature review resulted in 37 references on ammonia production. In the first six months of 1993 there were 14 publications which dealt with N-13 ammonia in some way. In spite of the fact that ammonia is now something of a commodity there is still a fair amount of work being done. On the other hand, not much of it could be called really new. Previous information and methods are being refined or extended, and this is justified by the high demand for radiopharmaceutical ammonia. Although earlier papers dealt with recoiling hot atoms and their products and discussed N-13 ammonia, the first paper which I found that could be called production-oriented was

Welch MJ "Production of active molecular nitrogen by the reaction of recoil nitrogen-13" *J.C.S. Chem Commun.* Vol: 21, pg: 1354 (1968)

a study of recoil reactions of $^{12}\text{C}(\text{d},\text{n})^{13}\text{N}$ using CO_2 in nitrogen gas as target material. That paper defined the product distribution which is still with us: N_2 , NO , and N_2O . Yields were low, but high enough to be considered a production technique. In 1971, three papers:

Hunter WW, Monahan WG "[N-13]Ammonia: A new physiologic radiotracer for molecular medicine" *J. Nucl. Med.* Vol: 12, pg: 368 (abs) (1971)

Tilbury RS, Dahl JR, Monahan WG, Laughlin JS "The production of N-13 labeled ammonia for medical use" *Radiochem. Radioanalyt. Lett.* Vol: 8, pg: 317-323 (1971)

Welch MJ, Lifton JF "The fate of nitrogen-13 formed by the C-12(d,n) reaction in inorganic carbides" *J. Am. Chem Soc.* Vol: 93, pg: 3385 (1971)

represented a move to carbide targets with the same nuclear reaction. The solid targets retained the radioactivity and were dissolved in acid or base to release ammonia. Methane was also investigated as target material, constituting the first direct in-target production of ammonia, which was dissolved straight into saline solution. At this early date the process time was considerably shortened, radiation dose to the chemist reduced, and ^{13}N ammonia had been proposed for nuclear medicine imaging, with impressive heart images being displayed. Saturation yields for the processes were 1, 2 and 8 mCi/ μA , respectively producing up to 20 mCi. Purity was still relatively low at 80-90%. Then came a classic paper:

Buckingham PD, Clark JC "Nitrogen-13 solutions for research studies in pulmonary physiology" *Int. J. Appl. Radiat. Isotopes* Vol: 23, pg: 5-8 (1972)

which introduced production from irradiation of a graphite block target. The activity could not initially be removed from the target. In an original approach, CO_2 was used to burn the target material and release the ^{13}N . Some CO_2 was converted to CO in the process which was then catalytically re-oxidized to CO_2 on-line for removal in a base trap. The ^{13}N

production yield was 8 mCi/ μ A at saturation.

At the end of 1973 the ^{16}O reaction was introduced with oxygen gas and water targets.

Krizek H., Lembares N., Dinwoodie R., Gloria I., Lathrop K.A., Harper P.V. "Production of radiochemically pure N-13 NH_3 for biomedical studies using the O-16(p, α) reaction" *J. Nucl. Med.* Vol: 14, pg: 629 (abs) (1973)

Lathrop K.A., Harper P.V., Rich B.H., Dinwoodie R., Krizek H., Lembares N., Gloria I. "Rapid incorporation of short-lived cyclotron produced radionuclides into radiopharmaceuticals" *Proc. Conf. Radiopharm. Lab. Cmpds.*, IAEA-SM-171-46 Vol: 1, pg: 471-481 (1973)

The product was distilled for purification. A large percentage of the product was nitrate, which was converted to ammonia by reduction with titanium trichloride. The ammonia was being used for the determination of myocardial blood flow. Additional work from St. Louis using the carbon target also added a distillation step to the workup and raised the purity from this system to 97%.

Straatmann MG, Welch MJ "Enzymatic synthesis of nitrogen-13 labeled amino acids" *Radiat. Res.* Vol: 56, pg: 48-56 (1973)

Welch MJ, Straatmann MG "The reactions of recoil N-13 atoms with some organic compounds in the solid and liquid phases" *Radiochim. Acta.* Vol: 20, pg: 124-129 (1973)

They also carried the carbon target concept to a fascinating extreme by irradiating diamonds, though the cost of a target load of industrial diamonds was actually quite reasonable. The yield obtained from a suspension of diamond dust in water was 70%. Ethanol was also tried as a target material for the carbon reaction, rather than as an additive as we will see discussed later in this session.

Two years later, the $^{16}\text{O}(p,\alpha)$ reaction reappeared on oxygen gas,

Parks NJ, Peek NF, Goldstein E. "The synthesis of N-13 labeled atmospheric gases via proton irradiation of a high pressure oxygen target" *Int. J. Appl. Radiat. Isotopes* Vol: 26, pg: 683 (1975)

to give a familiar product spectrum of nitrogen, NO and NO_2 . Devarda's alloy was introduced for the reduction of oxides of nitrogen to ammonia,

Vaalburg W, Kamphuis JAA, Beerling van der Molen HD, Reifers S, Rijskamp A., Woldring MG "An improved method for the cyclotron production of N-13 labeled ammonia" *Int. J. Appl. Radiat. Isotopes* Vol: 26, pg: 316-318 (1975)

and gave advantages in yield, speed, and purity (for synthetic use) over the TiCl_3 technique, though it had the disadvantage of being mechanically more difficult to handle and clean remotely a series of syntheses.

Suzuki and Iwata in 1977 made a unique observation, leading one to wonder what the original

intent or expectation of the investigators was, when they added ammonia in small amounts to the water target.

Suzuki K., Iwata R. "A novel method for the production of N-13 N₂: proton irradiation of an aqueous solution of ammonia." *Radiochem. Radioanalyt. Lett.* Vol: 28, pg: 263-268 (1977)

They discovered that a tremendous amount of nitrogen gas was produced, and also observed hydrazine in the labeled product mix. In 1978-79 techniques improved somewhat, recirculating water targets were explored, and interest expanded beyond ammonia and nitrogen gas with the intentional production and use of labeled nitrite. The saturation yields had improved up to 32 (from a 27 MeV beam) from previous numbers in the neighborhood of 15.

Parks, N.J.; Krohn, K.A. "The synthesis of N-13 labeled ammonia, dinitrogen, nitrite, and nitrate using a single cyclotron target system" *Int. J. Appl. Radiat. Isotopes* Vol: 29, pg: 754-756 (1978)

Lindner L., Helmer J., Brinkman G.A. "Water "loop" target for the in-cyclotron production of N-13 by the reaction O-16(p,α)N-13" *Int. J. Appl. Radiat. Isotopes* Vol: 30, pg:506-507 (1979)

McNaughton G.S., More R.D. "The use of a 3 MeV Van de Graaff accelerator for the production of N-13 labeled ammonium and nitrate ions for biological experiments." *Int. J. Appl. Radiat. Isotopes* Vol: 30, pg: 489-492 (1979)

McNaughton and Moore in 1979 presented the first of the low energy particle irradiation techniques for the production of ¹³N, using a 3 MeV beam on the C12 target. They were limited in beam current, but produced a saturation yield of 0.01 which gave them on the order of 100 μCi, sufficient for their purposes. This concept has been extrapolated into the use of very high current instruments which we are seeing today.

Tilbury RS, Dahl JR "N-13 Species formed by proton irradiation of water" *Radiat. Res.* Vol: 79, pg: 22-33 (1979)

Also in 1979 came another landmark paper with one of the more complete studies of the target chemistry and product distributions under various conditions. Tilbury and Dahl reconfirmed that nitrate is the major product when production beam doses are used, and the results of Suzuki and Iwata that ammonia leads to production of labeled nitrogen gas. But then they investigated the addition of organic materials to the target. This was undoubtedly the first application of organic molecules used not as target material (for the ¹²C reaction) but as additives intended to alter the target chemistry. Ethanol, ascorbate, and formate caused a dramatic shift in the product distribution from nitrate to ammonia as the major product. In fact, though the paper is primarily mechanistic with production aspects buried in the data, one can calculate from the data presented (saturation yield of 25 mCi/ μA, 99% production of ammonia to beam doses of 6-8 μA·hrs) that 375-500 mCi of radiopharmaceutical grade ammonia was being produced directly in the target. The authors were unhappy with this yield because they had in mind much larger quantities for synthetic use. Among the additives investigated it was reported that ethanol was the most effective for causing a high ammonia yield in the target. The implication of this result went largely unnoticed for a few years.

In 1983 carbon made a reappearance as a target material, in the $^{13}\text{C}(p,n)$ reaction. A much greater amount of activity was produced with this reaction from a given amount of beam on carbon. Nitrogen gas was produced and converted to ammonia with hydrogen in a microwave discharge.

Ferrieri R.A., Schlyer D.J., Wieland B.W., Wolf A.P. "On-line production of N-13 nitrogen gas from a solid enriched C-13 target and its application to ^{13}N ammonia synthesis using microwave radiation" *Int. J. Appl. Radiat. Isotopes* Vol: 34, pg: 897-900 (1983)

Bida G., Wieland BW, Ruth TJ, Schmidt DG, Hendry GO, Keen RE "An economical target for nitrogen-13 production by proton bombardment of a slurry of C-13 powder in O-16 water" *J. Label. Compds. Radiopharm.* Vol: 23, pg: 1217-1218 (abs) (1983)

Koh K., Finn R., Wooten T., Dwyer J., Sheh Y., Sinnreich J. "External tandem target system for efficient production of short-lived positron emitting radionuclides" *IEEE Trans. Nucl. Sci.* Vol: 30, pg: 3064-3066 (1983)

Also, a liquid slurry target with ^{13}C was investigated on a 10 MeV machine. Impressive yields of ammonia were eluted from the target with water. The tandem target arrangement was introduced, but with the same target designs and chemistry as seen previously, allowing the simultaneous production of ^{15}O and ^{13}N .

In 1986 work on the reactions excitation function stimulated a closer look at the different energy ranges that could be used for production and what the requirements are for target designs for different energy and beam current parameters.

Sajjad M, Lambrecht RM, Wolf AP "Cyclotron isotopes and radiopharmaceuticals XXXVII. Excitation functions for the O-16(p,alpha)N-13 and N-14(p,pn)N-13 reactions" *Radiochim. Acta.* Vol: 39, pg: 165 (1986)

Heselius S.-J, Schlyer DJ, Wolf AP "A diagnostic study of proton beam irradiated water targets" *Appl. Radiat. Isot. (Int. J. Radiat. Appl. Instrum. Part A)* Vol: 40, pg: 663-669 (1989)

In 1989 Brookhaven National Laboratory presented data concerning the internal behavior of the water target. The topic is still current for this meeting at which we have already seen additional data on bubble formation and suppression and treatment of the causative factors. Though much has been learned, the question is still a valid one.

In 1989-90 Mulholland reported a new variation, that the irradiation of water under hydrogen pressure caused ammonia production in the target. They also proposed mechanisms to help in explaining their observations, postulating that carrier N_2 was the intermediate in the target being labeled by ^{13}N by nitrogen exchange.

Mulholland GK, Sutorik A., Jewett DM, Mangner TJ, Kilbourn MR "Direct in-target synthesis of $[\text{N-13}]\text{NH}_3$ by irradiation of water under hydrogen pressure" *J. Nucl. Med.* Vol: 30, pg: 926 (abst) (1989)

Mulholland, GK; Kilbourn, MR; Moskwa, JJ. "Direct simultaneous production of $[\text{O-15}]\text{water}$ and $[\text{N-13}]\text{ammonia}$ or $[\text{F-18}]\text{fluoride ion}$ by 26 MeV proton irradiation of a double chamber water target."

Appl. Radiat. Isot. (Int. J. Radiat. Appl. Instrum. Part A) Vol: 41, pg: 1193-1199 (1990)

Patt J.T., Nebeling B., Stocklin G. "Water target chemistry of nitrogen-13 recoils revisited" *J. Label. Compds. Radiopharm.* Vol: 30, pg: 122 (1991)

Production yields were reported to be useful. Additional mechanistic studies were reported by the Julich group, showing the distributions of nitrate, nitrite and ammonia again as a function of beam dose and dose rate along with the discovery of hydroxylamine under certain conditions. Use of radical scavengers allowed them to show that radical chemistry was important in the production of other materials from ammonia, and that ammonia is produced very simply by proton abstraction reactions.

A production oriented paper in 1991 reintroduced the concept of ethanol addition originally presented by Tilbury and Dahl. The results concerning direct production of large amounts of ammonia and product distributions were reproduced. Higher pressures were used on the target, which gave better results at higher beam currents. Nitrogen gas was again observed as the primary product other than ammonia.

Wieland B., Bida G., Padgett H., Hendry G., Zippi, E., Kabalka G., Morelle J-L., Verbruggen R., and Ghyoot M. "In-target production of N-13 ammonia via proton irradiation of dilute aqueous ethanol and acetic acid mixtures" *Appl. Radiat. Isot. (Int. J. Radiat. Appl. Instrum. Part A)* Vol: 42, pg: 1095-1098 (1991)

Ferrieri RA, MacDonald K, Schlyer DJ, and Wolf AP "Proton irradiation of dilute aqueous ethanol for in-target production of [N-13]ammonia: studies on the fate of ethanol." *J. Label. Compds. Radiopharm.* Vol: 32, pg: 461-463 (abst) (1993)

Satyamurthy N, Bida GT, Cook JS, Barrio JR "Post-irradiation C-13 and H-2 NMR analysis of aqueous ethanol and acetic acid solutions for in situ [N-13]ammonia production" *J. Nucl. Med.* Vol: 34, pg: 239P (abst) (1993)

A trend is now noticeable over several publications. When any reducing environment is used in the target nitrate is no longer produced as the product at high beam dose, but is replaced by nitrogen gas. As a corollary to this, one needs to ask what happens to the ethanol in the target and how it functions to cause ammonia production. There is very little ethanol present, so it is not a major safety issue for clinical use, but this remains a central question which must be answered before an understanding of the target chemistry can be achieved. There is a discrepancy between the results of the Brookhaven group and those of Bida et al. in the amount of oxidized products observed. Formaldehyde, acetaldehyde and carbon dioxide have been observed. The amount of these products seen is probably strongly dependent on the irradiation conditions, though insufficient data exists at the moment to allow any statement of what the dependency might be. It seems that the amount of pressure applied to the target during irradiation is an important parameter for suppressing both nitrogen gas and oxidized organics production.

The progression since 1970 has therefore moved through deuterons on carbon to protons on oxygen, through gas targets, water targets and solid targets. Products observed have been

nitrate, nitrite, ammonia, nitrogen, hydroxylamine and a few other minor products. The current area of interest is direct in-target methods for production of ammonia to take some of the time and apparatus burden off of busy chemistry laboratories which need to produce the material clinically and routinely. The question now is: where are we going to go from here? The answer should be to try to understand the target chemistry better, and to follow that knowledge into target enhancements. Another 'new' area which will be presented in this session, and a concept which has been in the background for many years, is the use of low energy deuteron irradiation of carbon-12 and low energy proton irradiation of carbon-13. These approaches have recently become feasible for clinical use due to the development of accelerators which can produce very high beam currents at low energy, making up in number of particles for the loss of energy and reaction cross section.

A large portion of this session of the workshop is devoted to the further refinements which can now be added to this considerable body of work. I believe it is important to try to keep in mind the need for understanding of mechanisms of product formation in these targets. The main processes are proton abstraction to give ammonia and abstraction of atoms in gas and condensed phases from O₂, CO, CO₂, C=C, NN, or C-metal bonds to give N₂, NO, N₂O, CN and NM products. Interestingly, no reaction of hot-atom nitrogen was observed with O₂, only reaction of excited N₂. Further reactions of hydroxyl, oxygen, and HO₂ radicals with ammonia and/or nitrogen were proposed to reoxidize it eventually to nitrate and nitrite. A contradictory observation appeared that hot atom nitrogen did not react with nitrogen gas.

Questions:

Mike Welch: You missed some earlier references. Martin Cayman tried to make nitrogen gas to do nitrogen fixation studies in 1940 and made ammonia, biologists at Michigan Volk made ammonia from ¹³C, and Joe Varna who is now a colleague of mine at Washington University made it from graphite and then oxidized it in aqueous solution in 1954. So there are, sort of, plant biology references. An interestingly enough, the mechanism you called hot atom chemistry probably isn't. If you look at the Straatman paper all of the products change enormously with radiation, so the products you observe are almost certainly radiation chemistry and not hot atom chemistry.

Berridge: I hope I did not imply that most of what I discussed was hot atom chemistry. I think about the only thing that was hot atom was some of the proton abstractions. In addition to the ones you mention, there is one other reference I know I missed which was somewhat intriguing, a 1.7 MeV deuteron reaction on carbon-12 in about 1973, but I forget the authors on that one.

A Novel Solid Graphite Target for the Production of ^{13}N -Ammonia^(a)

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INTRODUCTION

This paper describes a technique for rapid and efficient in-situ extraction of ^{13}N activity from solid graphite after deuteron beam bombardment. This technique is particularly applicable to the production of ^{13}N at low bombarding energy (less than 5 MeV), and was developed for use with the 3.7 MeV Tandem Cascade Accelerator (TCA) developed at Science Research Laboratory (SRL). Use of this target at deuteron beam energies as low as 1.2 MeV has been investigated and has led to the design of an ultra-low energy ^{13}N -ammonia generator described in an accompanying paper.⁽¹⁾

The various techniques used for the in-target production of ^{13}N with cyclotron beams cannot be used for isotope production at low bombarding energy because of the high thresholds of the commonly used $^{16}\text{O}(p,\alpha)^{13}\text{N}$ and $^{13}\text{C}(p,n)^{13}\text{N}$ reactions. The $^{12}\text{C}(d,n)^{13}\text{N}$ nuclear reaction has a low threshold energy (0.33 MeV) and a high yield at low bombarding energy. A charcoal slurry target using this reaction has been investigated for use with a 3.5 MeV deuteron beam.⁽²⁾ However, the requirement for a foil target window with any liquid or gas phase target is incompatible with isotope production at 1.2 MeV beam energy because a large fraction of the beam energy will be deposited in the window itself. Carbon-12 in the form of solid graphite is an excellent accelerator target material. A solid graphite target can be placed directly in the accelerator vacuum beam line, thereby eliminating the need for a target window.

Nitrogen-13 has been extracted from irradiated graphite for biological studies since 1940.⁽³⁾ Several workers have shown that ^{13}N can be extracted from graphite at high temperatures with an appropriate sweep gas.^(5,6) However, the activity produced was primarily in the form $^{13}\text{N}\text{N}$, and this is not an ideal precursor for synthesis of ammonia. Described below is a technique whereby the graphite is combusted in-situ and activity extracted in the form of ^{13}N -nitrites and nitrates, which can be readily converted to ^{13}N -ammonia. Since ^{13}N activity is produced in a thin layer close to the target surface during irradiation with low energy deuterons, only this thin layer of graphite must be combusted to extract the activity. Consequently, a single target pellet may be used for multiple ^{13}N production runs. A rapid and efficient technique for trapping the released activity and converting it to ^{13}N -ammonia was developed at Washington University¹ and is described elsewhere in these proceedings.⁽⁸⁾ This chemical synthetic technique, used in

^(a) This work has been accepted for publication in Nuclear Medicine and Biology, January 1994 (ref 10).

conjunction with the graphite target and extraction system described below, allows the production of clinically useful quantities of ^{13}N -ammonia with very low energy deuteron beams.

METHODS

The experiments described below were performed using a 3.7 MeV TCA at SRL. Experiments in which the deuteron range in the target was an important parameter, such as the determination of the required thickness of graphite combusted for efficient extraction of ^{13}N , were performed at the design energy for the ultra-low energy ^{13}N -ammonia generator of 1.2 MeV.⁽¹⁾ Experiments in which the bombarding energy was less important, such as determination of the most efficient trapping system, were performed at the somewhat higher beam energy of 2.4 MeV since the TCA beam transport optics are designed for more efficient operation at higher beam energy. For the same reason, experiments requiring a high beam power on target were performed at high beam energy (3.2 MeV).

Target Design

A schematic cross-sectional drawing of the windowless, solid graphite target used in the experiments is shown in Fig. 1, and a photograph of the target assembly is shown in Fig. 2. A graphite pellet was mounted inside an evacuated ceramic tube surrounded by a water cooled radio-frequency heating coil. After target irradiation, the target chamber was isolated from the accelerator vacuum system with a gate valve, O_2 gas was admitted into the chamber, and the RF coil was energized. The time varying magnetic field created by the coil produced eddy currents in the graphite and resistive heating by these currents rapidly elevated the graphite temperature. Since the graphite itself is directly heated while other components of the target remain at near ambient temperature, this heating method is both more efficient and more rapid than conventional methods using resistive heaters. For the target design shown in Fig. 2, 750W of RF power elevated the graphite temperature to the value at which combustion begins ($\sim 750^\circ\text{C}$) in less than 1.5 minutes. During combustion, the O_2 gas was recirculated through the chamber with a peristaltic pump. The total mass of graphite combusted was controlled by limiting the quantity of oxygen introduced into the target chamber.

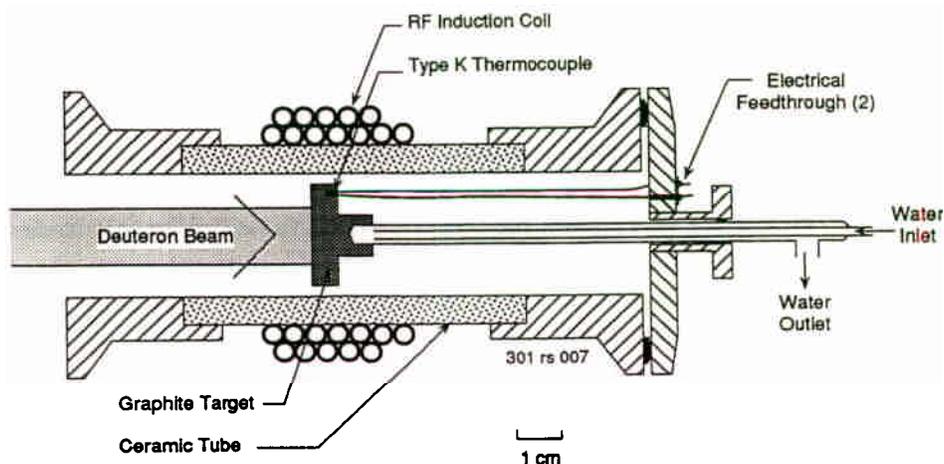


Figure 1: Schematic cross-section of the windowless ^{13}N production target.

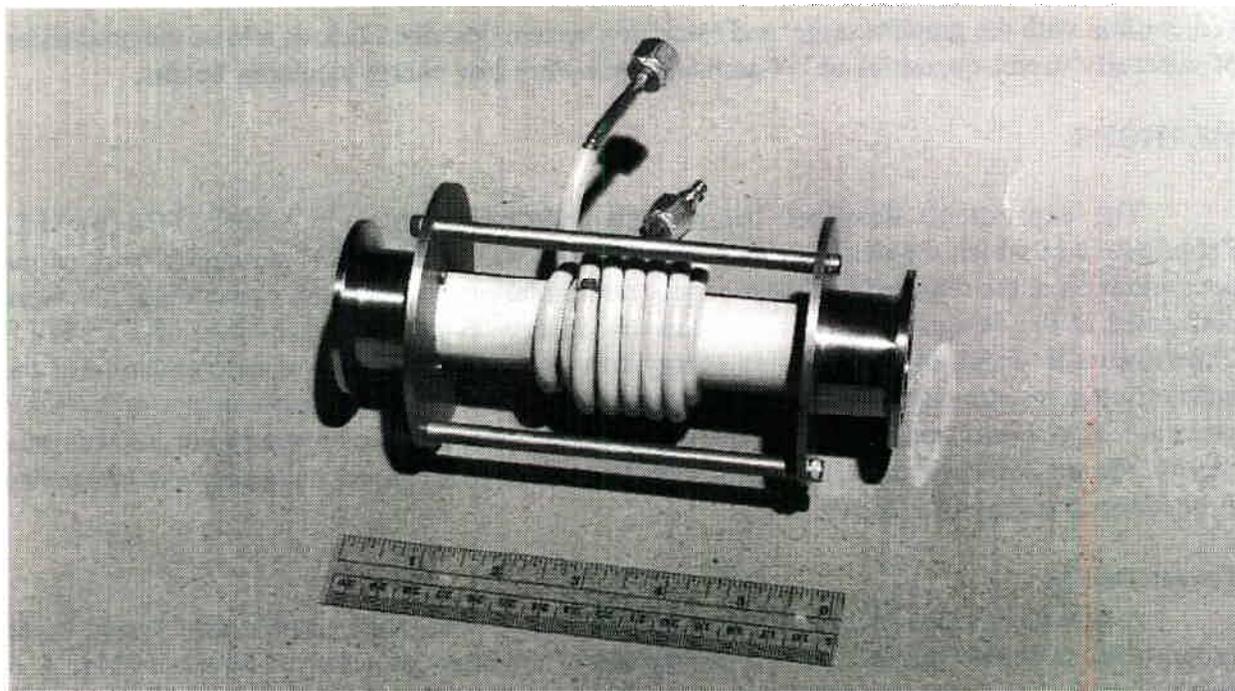


Figure 2: ^{13}N target assembly

The graphite pellet was disc shaped with a diameter of 1.9 cm and a thickness of 0.64 cm. The pellet stem was threaded onto a thin-walled, water-cooled stainless steel tube assembly to provide some conductive cooling during deuteron beam bombardment. Thermal contact between the graphite and the stainless steel tube was enhanced with a commercial heat transfer agent (Watlube, Watlow Electric Co.). A type K (Chromel-Alumel) thermocouple was inserted into a hole in the back of the pellet, as shown, to monitor the target temperature during irradiation and combustion. Type K thermocouple wire was chosen because of its relatively high oxidation resistance.

RESULTS

Extraction of ^{13}N Activity

A series of irradiation and combustion experiments were performed to determine the relationship between the quantity of oxygen gas introduced into the target chamber, the mass and thickness of graphite combusted, and the percentage of ^{13}N activity extracted. In order to minimize diffusion of ^{13}N activity away from the target surface, the experiments were performed using an ultra-low porosity graphite. (ZL-3, UCAR Carbon Company) First, the target was irradiated with the TCA deuteron beam (1.2 MeV, 5 μA for 2 minutes) to produce 490 μCi of ^{13}N activity. After each irradiation, a measured amount of oxygen gas was admitted into the target chamber. The chamber was then pressurized to 1 atmosphere with He gas, the recirculation pump was started, and the RF coil was energized in order to combust the graphite. Following combustion, the graphite target was removed from the target chamber and placed in the well of a radioisotope calibrator (Capintec CRC-12) to determine the residual activity remaining in the

lattice. The target was also weighed and measured, to determine the mass combusted and the approximate amount of graphite burned from the front face.

The mass of graphite combusted was found to be proportional to the amount of oxygen admitted to the target chamber. Mass was lost almost entirely from the front face and circumference of the targets, and not from the back surface or threaded stem. Approximately 40 mg of graphite must be combusted to extract 99% of the activity produced in the target. Measurements of the target dimensions after this series of experiments gave a value for the corresponding thickness of graphite which must be removed from the front face of the target to extract 99% of the activity of $13.2 \pm 2.4 \mu\text{m}$. This value is approximately equal to one deuteron range at 1.2 MeV.

Graphite pellet lifetime is an important parameter if this target is to be used to supply isotope for patient procedures. For the target design shown in Fig. 2, it should be possible to reduce the thickness of the 6.4 mm thick graphite pellet by at least a factor-of-two without compromising its mechanical integrity. Using the value discussed above of a $13 \mu\text{m}$ decrease in thickness per combustion yields a useful life of about 250 combustion cycles. For a clinical production schedule of 6 patients per day with two ^{13}N -ammonia injections per patient, target replacement would be required approximately every 4 weeks. In order to ensure that the usable target lifetime is not limited by erosion of the non-irradiated target surfaces, the target sides can be coated with a non-combustible material, such as boron nitrite. Preliminary results indicate that spraying the target sides with a boron nitrite aerosol spray (Carborundum Co., Niagara Falls, NY) can reduce unwanted combustion of these surfaces.

The lifetime estimate discussed above assumes that the extraction efficiency is independent of the number of irradiation and combustion cycles and total mass removed. The extraction of activity from the low porosity graphite irradiated with 2.4 MeV deuterons was found to be very reproducible. A single graphite pellet was used for 6 consecutive irradiation and combustion cycles in which approximately $125 \mu\text{m}$ was removed from the front face of the pellet per combustion. The extraction efficiency after the last irradiation was still greater than 98%. Since at 1.2 MeV beam energy the amount of graphite required to be combusted will decrease from approximately $125 \mu\text{m}$ to less than $13 \mu\text{m}$, this result indicates that the pellet should be re-usable for at least 58 irradiation and combustion cycles without significant degradation in extraction efficiency. Further experiments are planned to determine the usable graphite pellet lifetime over which high extraction efficiency can be maintained.

Experiments were performed to investigate target performance under high power deuteron beam irradiation conditions. In one experiment, the target was irradiated with a 225 Watt deuteron beam (3.2 MeV, 70 μA) for 10 minutes. During bombardment, the graphite pellet temperature increased to 1030 °C and stabilized at this value. The target vacuum pressure remained well within the limits for accelerator operation (less than 10^{-5} torr) during bombardment, indicating that target outgassing at temperatures of up to at least this value is not a problem. In addition, the measured ^{13}N yield of 604 mCi was in good agreement with the calculated yield of 570 ± 20 mCi for these bombardment conditions,⁽¹⁰⁾ confirming that the loss of ^{13}N activity due to outgassing during bombardment did not occur. This result is consistent with published data that show that nitrogen is first released from heated graphite in vacuum at 1700°C⁽⁹⁾.

Trapping of Extracted ^{13}N Activity

A gas recirculation system was used to trap the extracted ^{13}N activity in two identical traps mounted in series. A solid phase trap containing 5% NaOH in 2 g of silica gel held in a 6 ml syringe was used. The choice of the trapping medium and trap preparation are discussed in detail in Refs. 8 and 11. Following deuteron beam bombardment, the gate valve between the target chamber and the accelerator beam line was closed and the valves between the target and the gas recirculation loop were opened. Approximately 275 std-ml of oxygen gas were admitted into the loop, raising the pressure to 440 torr. Helium gas was then added to bring the total pressure to 2-3 psi above one atmosphere. A peristaltic pump provided a flow rate in the loop of 280-360 std-mL/min. During combustion, the activity in the traps was continuously monitored by placing them in the well of a radioisotope calibrator. The trapped activity reached a maximum value approximately 3.5 minutes after the RF heating coil was energized, after which the traps were separated and the activity in each trap was measured. In several experiments, the graphite target was removed following combustion in order to measure the residual activity by placing it in the well of a radioisotope calibrator.

A series of eight trapping experiments were performed using the TCA deuteron beam. The target was bombarded with a 2.4 MeV, 5 μA beam for 1 minute to produce 2.22 mCi. The average trapping efficiency^(b) obtained was $78 \pm 3.5\%$. The trapping efficiency was found to depend strongly on the gas flow rate: when the gas flow rate in the recirculation loop was reduced to 140 std ml/min, the trapping efficiency was reduced by approximately a factor of two. In all cases, 95% or more of the total trapped activity was found in the first trap, indicating that a single trap is sufficient. In one experiment, 9.5 mCi of ^{13}N were produced in the target and a trapping efficiency of 82% was obtained, showing that efficient trapping can be achieved at higher ^{13}N activities. One graphite target pellet was irradiated and combusted a total of six consecutive times. The trapping efficiency remained high over this number of combustion cycles, indicating that the extraction of multiple batches of ^{13}N from a single graphite pellet is feasible.

An additional experiment was performed to demonstrate that the extraction and trapping performance reported above can be extrapolated to high ^{13}N activities. The graphite target was irradiated with the TCA beam to produce approximately 200 mCi of ^{13}N -activity. Oxygen was admitted to the target flow loop which included a single trap and the RF coil was energized when the activity in the target had decayed to 150 mCi. The extraction efficiency measured in this experiment was 99% and the decay-corrected trapping efficiency was 66%, which is within two standard deviations of the efficiencies reported above for the smaller amounts of ^{13}N activity. The measured peak in real trapped activity (not decay-corrected) was 83 mCi. Since the experiment was performed at a higher deuteron beam energy of 3.2 MeV, a higher partial pressure of O_2 gas was required to provide efficient extraction, and no helium gas was added. The effective gas flow rate through the trapping and recirculation loop for this gas mixture was lower than in the 2.4 MeV experiments because of the dependence of flow meter calibration on gas composition. It is possible that the somewhat lower effective flow rate was responsible for the lower measured trapping efficiency, since we had previously observed a strong dependence of trapping efficiency on gas flow rate.

Production of ^{13}N -Ammonia

^{13}N -activity trapped in the 5% NaOH/silica gel traps was converted to ^{13}N - ammonia using a chemical synthetic technique developed at Washington University⁽⁸⁾ in which the traps are eluted and the eluate is catalyzed with Raney-Nickel at elevated temperature to produce $^{13}\text{NH}_3$ in a total time of approximately 5 minutes. In three of the trapping experiments described above, the traps were eluted with 1-2 ml of distilled water and an average elution efficiency of 85% was measured. In one experiment, the eluted activity was converted to $^{13}\text{NH}_3$ using the apparatus described in reference 8. The decay corrected conversion efficiency from eluate to ammonia was measured to be 68%. Thus, the net decay-corrected conversion efficiency of trapped activity to ^{13}N -ammonia was 58%.

SUMMARY

This paper describes a highly efficient technique for the rapid, in-situ extraction and trapping of ^{13}N from irradiated graphite in a chemical form suitable for conversion to $^{13}\text{NH}_3$. The experiments described above have demonstrated that greater than 99% of the ^{13}N activity produced by target irradiation with 1.2 MeV deuterons can be extracted by combustion of a 13 μm thick graphite layer, and that multiple ^{13}N production runs can be performed using a single graphite pellet. Compatibility of the target with high power deuteron beam bombardment was established and production of up to 600 mCi of ^{13}N activity in this target was demonstrated.

A technique for efficient trapping of the ^{13}N activity released by combustion of the graphite pellet was developed. Use of a solid phase 5% NaOH/silica gel trapping medium allowed trapping of nearly 80% (decay-corrected) of the extracted ^{13}N activity in a time period of 3.5 minutes. The conversion of trapped activity to $^{13}\text{NH}_3$ with a decay-corrected efficiency of 58% was accomplished using a new technique developed at Washington University.^(8,10) The experiments reported above have demonstrated that this trapping medium can be used to trap the quantities of ^{13}N activity required for the production of clinically useful batches of ^{13}N -ammonia. Using the conversion time of 5 minutes reported in reference 8, the highest activity trapped in our experiments, 83 mCi (not-decay corrected), will produce over 30 mCi of ^{13}N -ammonia.

The ^{13}N -ammonia production system described above is suitable for use with any accelerator used to generate PET radioisotopes. (Proton-only machines could use this technique with an enriched ^{13}C target to produce ^{13}N via the $^{13}\text{C}(p,n)^{13}\text{N}$ reaction). However, the technique is especially suitable for ^{13}N -ammonia production at beam energies of less than 5 MeV since a target window is not required. The use of this target in an ultra-low energy 1.2 MeV accelerator-based ^{13}N -ammonia generator is under investigation and is described elsewhere in these proceedings.⁽¹⁾

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Questions:

Tom Ruth: Was there any outgassing of the target material observed during the run?

Hughey: No, and none was observed in the high current runs. There is some outgassing of a new target under its first beam, or it can be outgassed with the induction oven. And in sequential runs there was no evidence of outgassing due to oxygen entrained from previous runs, the results were repeatable throughout a series of runs.

Tatsuo Ido: 25% of the nitrogen-13 came out of the target as N_2 and so was in that form in the graphite lattice, is that so?

Hughey: Yes.

Ido: So did you think of trying hydrogen gas with microwave heating to make ammonia directly?

Hughey: No, that has been done previously, but it seemed easier to reduce the majority of the activity, nitrogen oxides, to ammonia.

Rich Ferrieri: Since this is a windowless target, when you remove the target, do you experience adsorption of oxide impurities from exposure to air?

Hughey: We don't remove the target, and ultimately on a multitarget machine there will be multiple ports. But if you do remove it, or use a new target, it is sufficient to outgas the carbon with the induction oven for five to ten minutes.

Mike Channing: How do you do inductive heating on solid carbon?

Hughey: Carbon is a electrical conductor. For induction, you need a conductor, and it helps if it's not really a very good conductor. So it works very well because you can set up the inductive currents and the resistance of the material causes the heating. It was about 750W of RF power that was needed to raise the temperature to 750°C in 1.5 minutes. The advantage is that only the graphite is directly heated, none of the ceramics except by radiative heating from the hot graphite.

Joanna Fowler: Did you try just heating the block under vacuum? Were there any volatile radioactive products present?

Hughey: No we did not look at that.

Jerry Nickles: Did you take a look at glassy carbon or any diamond-like surfaces?

Hughey: No, just graphite, and especially low porosity graphite. It burns well at these temperatures.

Production of N-13 Ammonia Using a Solid Graphite Target and the $^{12}\text{C}(\text{d},\text{n})^{13}\text{N}$ Nuclear Reaction

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INTRODUCTION

With the appearance of new low energy accelerators dedicated to the production of short-lived isotopes (1-3), comes new approaches to the production of radiopharmaceuticals. The nuclear reaction $^{12}\text{C}(\text{d},\text{n})^{13}\text{N}$ was chosen for this study because of its low energy threshold (0.33 MeV) and therefore compatibility with these low energy accelerators. Low porosity graphite was chosen as the target material; irradiated graphite has been used since 1940 to extract N-13 for biological studies (4-8) but in most cases the activity was obtained as N-13 nitrogen. Kjeldahl digestion (9,10) and microwave irradiation (11) have also been applied to obtain N-13 ammonia. We studied the extraction of N-13 nitrogen from a solid graphite target after deuteron beam irradiation and heated in an atmosphere of pure oxygen, we identified the species formed and converted them to N-13 ammonia.

EXPERIMENTAL

The study was conducted using the Washington University Cyclotron Corporation CS-15 cyclotron. A pellet of low porosity graphite was placed in an aluminum holder and bombarded with 8 MeV deuterons at a beam current of 8 μA for 2 minutes, to produce about 15 mCi of radioactivity. The N-13 species were extracted after removing the graphite pellet from the target chamber and heating it in a furnace (800°-850° C) while passing pure oxygen as a sweep gas over the hot target. The gases were recirculated through a close loop (2-3 psi above atmospheric pressure) by means of a peristaltic pump. Analysis of N-13 nitrogen present in the recirculating gases was done by gas chromatography (GC).

Different trapping materials such as aluminum shavings, soda lime, aluminum oxide or silica gel with different modifiers, were studied for their ability to trap the recirculating N-13 activity. The best trapping material was found to be 5% NaOH absorbed in silica gel. The elution of the activity from this trap was performed with water and its radiochemical composition determined by HPLC and ion chromatography (IC).

Finally, the eluted activity in solution was easily converted to N-13 ammonia using Raney-nickel and NaOH (12). A solid phase system using a Raney-nickel/silica gel mixture to trap the activity followed by *in situ* heating in 5% Hydrogen in nitrogen (saturated with water vapors) also produced N-13 ammonia.

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RESULTS

The percent of N-13 nitrogen present in the recirculating gases was determined by GC to be 18.5% the rest of the activity (80%) was trapped in the 5% NaOH/Silica gel trap, was eluted with water (94%) and analyzed by IC. All the eluted activity was found to be in the chemical form of N-13 nitrites (98.7%) and nitrates (1.3%).

The overall radiochemical yield for the liquid phase reduction of these N-13 oxides into N-13 ammonia was about 44%. The overall radiochemical yield for the *in situ* reduction with a homogenate of Raney-nickel in 5% NaOH/silica gel was about 37% \pm 8%, comparable to the liquid phase reduction. In both cases the product was collected in a dilute HCl (0.1N) and had a radiochemical purity close to 100% (HPLC). Two samples were analyzed for non-radioactive NH_4^+ by IC using conductivity detection and they show a value of 5.25 ppm; nickel ion was present at 100 ppb level.

CONCLUSIONS

1. The N-13 activity induced in a solid graphite target was efficiently trapped in 5% NaOH/silica gel and identified as N-13 nitrites.
2. Raney-nickel was used to reduce N-13 nitrites to N-13 ammonia.
3. This technique has been successfully applied to a Tandem Cascade Accelerator (TCA, SRL See accompanying B. Hughey's paper)

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Questions:

Mike Channing: You used a continuous flow of oxygen over the target to produce nitrogen oxides. Did you ever try to pass that gas directly over a catalyst to make ammonia, as opposed to trapping the products first?

Dence: No. The difficulty was that it was likely that we would use a recirculating system for the combustion, and this would make it difficult to use an on-line system without recirculating the combustion products or reduction products back to the target chamber.

Channing: I understood that you needed to recirculate to improve the efficiency of trapping rather than of combustion, is that true?

Dence: Yes, that was the first goal, through the circulation of course, and then by mounting the Raney nickel *in situ* in the recirculation, trapping and conversion were accomplished. To specifically answer your question, we did not try particular metals for the ammonia conversion. What we did do, was to take a pellet of the induced activity and heat it in a furnace in the presence of hydrogen up to 200°C, and we did not see any ammonia. We tried hydrogen in the induction furnace to convert the activity, but that did not work.

EXPERIENCES WITH A NEW HIGH PRESSURE WATER TARGET FOR THE PRODUCTION OF [¹³N] AMMONIA.

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ABSTRACT

We present preliminary results on the operation of a newly designed high-pressure water-ethanol target for *in-situ* production of [¹³N]Ammonia. Our results show some similar trends as those reported by Wieland et al.¹ and Korsakov et al.² when parameters like ethanol concentration, target pressure, beam current and irradiation dose are considered. More than 100 mCi of [¹³N]Ammonia -- >99% purity-- ready for injection are routinely produced in 10 min. runs.

INTRODUCTION

To satisfy the demand for PET studies based on [¹³N] labeled Ammonia from our nuclear cardiology group, a new H₂¹⁶O target was designed for the JSW3015 Cyclotron. The recently developed¹ high-pressure water-ethanol technique offers considerable advantages over other methods like Devarda's reduction of [¹³N] labeled nitrate or nitrite or the ¹³C slurry target. Our major goal was to minimize development time for this new target while providing a reliable and simple to operate system. This constraint forced us to focus our efforts into issues specifically related to satisfy the requirements of a clinical protocol. Most of our test runs were dedicated to develop quality control procedures and reproducibility of results.

TARGET

The target body is machined from a single piece with the following characteristics:

Material :	Al	Diameter :	14 mm	Length :	10 mm
Volume :	1.6 cm ³	Front foil :	525 μm Al	Front Seal :	Neoprene O-Ring
Fill/Empty Port:	1/4-28 NF flat bottom fitting		Cooling : 3 lt./min. water (10° C)		
Pressure Test:	46 bars (680 psi)				

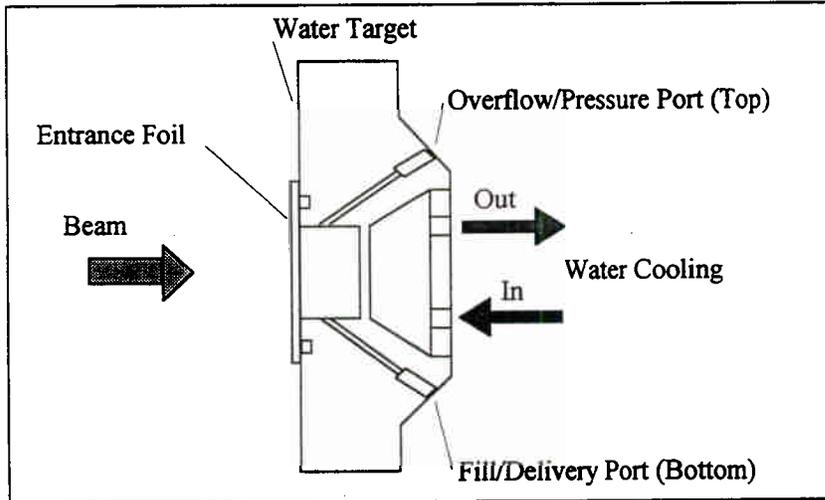


FIGURE 1

Figure 1 shows details of the target body. Top and Bottom Ports have threaded fittings reducing dead volume. The back wall of the target cavity is only 1 mm thick to improve cooling efficiency. The water cooling port with inlet/outlet fittings was welded to the target body.

TARGET LOADING

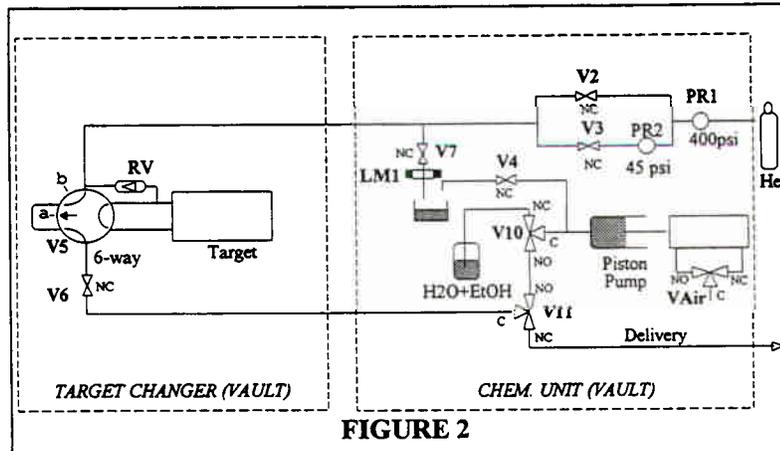


FIGURE 2

Fig. 2 shows a schematic of the target loading and delivery system.

All lines in contact with the target material are 1/8" Teflon tubing (thick wall) except those connecting target to V5, RV and V6 which are 1/16" PEEK tubing.

Extensive modification to our existing software were needed to accommodate this new process.

Components:

V2,V3,V4,V6,V7	Skinner Valve : #3121BSN1EC00NOM3J1C2	Two-way. NC. Stainless. Neoprene Seal.
V10,V11	Skinner Valve : #3133BSN1GCADNOM3J1C2	Three-way. MP. Stainless. Neoprene Seal.
RV	Upchurch: Relief valve. Back-pressure regulator # P-752 - adjustable.	
V5	Rheodyne Valve : # 7010P - SS - 6-way	

EXPERIMENTAL PROCEDURE

Target loading is done through computer operation. First, all lines are swept with He gas (UHP) at 45 psi for 20 seconds. Water fills the target from the bottom port by means of a piston pump. Our current target arrangement presents no dead volume. An extra cycle of the piston pump is added after water is detected by the overflow switch LM1. V6 and V7 are closed and the target pressurized through V2. While pressure is being applied, V5 is switched, isolating the pressurized target. The pressure relief valve was adjusted to open at 400 psi (He), and showed very reproducible results over a series of measurements.

As part of our standard protocol, the sterile water bag with the diluted ethanol is replaced once a week. The target is loaded and emptied twice and a third target load --all of them cold-- is dumped into the hot cell to check integrity of the system. During production days the target is flushed only once before the first irradiation. Overall target loading process takes approximately five minutes. Transferring the target into the delivery vial is accomplished in two minutes.

The irradiated product is delivery from the target by He gas (45psi) through an Alltech Maxi-Clean IC-OH cartridge for removal of impurities and a 0.2 μm vented Millipore filter into a 10 ml sterile vial. Total volume recovered into the delivery vial is close to 1 cm^3 . Finally, the product is rendered isotonic by adding 4 ml of a solution containing NaCl.

Target irradiations were done with 22 MeV protons from the JSW3015 Cyclotron. Average beam energy on target is estimated³ to be around 19 MeV after degradation through the foils. The beam is collimated to 1 cm diameter and beam spatial distribution and positioning is periodically checked with help from a quartz window and video camera. Selection of beam energy --22 MeV instead of 13 MeV as we also have available-- was dictated by our recently adopted single-frequency operational mode.

Over a period of two months more than 40 runs were completed. As explained before, developing a protocol for rapid production of the radiopharmaceutical was our primary concern. For this reason several different experimental configurations mainly related to analysis of the final product were used. Therefore only 25 % of our runs present some valuable information related to production yields. The remaining runs were used for quality control and protocol optimization. A typical configuration used to identify percentage composition of different chemical species labeled with ^{13}N consisted in delivering the product into a vial for radioassay while the carrier gas was vented through a zeolite trap at liquid nitrogen temperature also placed in a dose calibrator. After decay counting the product inside the vial to identify other radionuclei contents (typically [^{15}O]Water) the solution was transferred to another vial for further radioassay through a strong anion exchange resin (Maxi-Clean IC-OH). The main component after the transfer was found to be ^{13}N -Ammonia as confirmed by HPLC analysis.

Quality Control

Radio-HPLC was used to analyze product contents with the following parameters:

- **Column** Alltech anion/R , 4.1 x 250 mm
- **Solvent** 4 mM 4-Hydroxybenzoic acid, pH adjusted to 8.5 with solid LiOH.
- **Pump** Knauer HPLC Pump 64
- **Flow Rate** 1.5 mL/min.
- **Detector** NaI
- **Software** Vision IV for PC

Gamma spectroscopy

- **HPGe** 6.6% efficiency

Sterility and pyrogenicity

- **Hospital of the University of Pennsylvania** -- Dept. of Pathology and Laboratory Medicine

RESULTS AND DISCUSSION

Table I shows results for some of the runs performed. Except for a few runs, ratios between ^{15}O and ^{13}N yields remained near unity. There are two alternatives to follow for this problem. Increasing front foil thickness, thus reducing the beam energy even further into a region (16.6 MeV threshold energy for the reaction) where the cross section for production of ^{15}O becomes negligible. The other alternative is to ignore it since ^{15}O -Water is the main radioimpurity found and represents only 0.4% of total activity 20 min. after EOB.

RUN #	Beam Current (μA)	Integrated Current ($\mu\text{A}\cdot\text{min}$)	EtOH Conc. (mM)	He Pressure (psi)	Total ^{15}O -EOB (mCi)	Total ^{13}N -EOB (mCi)	Sat. yield ^{13}N (mCi/ μA)
1	10	100	5	400	75	93	18.5
2	10	100	0	400	80	86.5	17.2
3	10	100	0	400	82	81	16.1
4	10	100	0	300	95	98	19.5
5	15	150	5	350	125	114.5	15.2
6	15	300	5	350	200	215	19.0
7	10	100	2	350	75	75	14.9
8	15	150	2	350	96	124	16.4
9	15	150	2	350	112	126	16.7
10	15	150	2	350	97	100	13.2
11	15	300	2	400	115	210	18.6
12	20	200	2	350	163	150.5	14.9
13	20	200	2	350	135	137	13.6

Results from more than 40 runs can be summarized as follows:

Normal conditions (300-400 psi , 2-5 mM EtOH)

- Target delivers in excess of 90% [¹³N]-Ammonia.
- Volatiles represent less than 2% (almost equally split between ¹³N and ¹⁵O) of total activity.
- No [¹³N]-NO_x detected with HPLC
- Target memory. Runs 2 to 4 where conducted after almost 10³ target volume containing pure water were flushed through the target. Only after run 4 ([¹³N]Ammonia yield > 86%) [¹³N]-NO_x was detected with HPLC.
- Very small amounts of ¹⁸F were found from decayed target samples. Samples taken after passage through IC-OH cartridge showed no signs of ¹⁸F. Near 60 pCi --EOB corrected-- of ²⁴Na were found in the final product from gamma ray spectroscopy of decayed samples. No other long lived radioisotopes were detected.
- Final product pH was found to be 6.4
- Minimum radioisotope purity was estimated to be 99.6% (20 min. after EOB).

CONCLUSIONS

Our saturation yields are near half of those reported by Wieland et al.¹ and similar to those reported by Korsakov et al.² for non-pressurized targets at equivalent beam energies. We can not explain this discrepancy since we accounted for all of the produced activity . If our beam energy were much lower than estimated no ¹⁵O would be produced. EtOH concentrations of 5 mM appear to result in higher yields of ammonia than lower concentrations.

Two minor modifications of our current target setup will proceed very soon. As already mentioned on target beam energy will be reduced to eliminate ¹⁵O production. Target plumbing will be modified to add a dead volume. Better response of the pressure relief valve is expected after this modification. Further experiments will be conducted with this target to elucidate some of the issues.

Design, fabrication and testing of a new target capable of supplying useful doses (~ 100 mCi) of [¹³N]Ammonia was accomplished in a six months period. Routine production of this radioisotope in 10 min. runs requires minimal personnel intervention.

Acknowledgments

We thank Dr. Chyng-Yann Shiue for his recommendations and valuable discussions regarding quality control procedures.

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² M.V. Korsakov et al., Private Communication.

³ TRIM-92 - J.P.Biersack and J.F. Ziegler - PC program to calculate stopping power and ranges of ions in matter.

Questions:

Tom Ruth: What is the foil material, and how thick is it?

Gonzales-Lepera: It is aluminum, 0.5 mm thick. I attempted to measure and to calculate the beam energy on the water. The calculation told me the energy would be lower, but I observed a lot of O-15, so I estimate at least half the beam is still coming through with about 19 MeV, from the cross sections and the quantity of O-15 produced. The threshold for O-15 production is 16.6 MeV. I was expecting to bring the beam to or below 17.5 MeV. I'm still getting similar amounts of O-15 and N-13 at EOB. Since there is so much N-13 made, we can afford to use short bombardments and allow the O-15 to decay. We observe 0.4% water at 20 min post-bombardment.

We also observed a target memory effect after using 5 mM ethanol solutions. After 10 flushes of the target (300 mL) with clean water we still obtained high yields of ammonia. After several liters of wash water, the effect persisted but then suddenly the product distribution reverted to nitrate and nitrite. We used only aluminum and peek components, except for neoprene target O-rings. We can speculate about the absorption and retention of ethanol in the O-rings or in the apparatus.

Mike Channing: Is the anion exchange cartridge that you used silica based?

Gonzales-Lepera: It is the Maxiclean ICOH.

Channing: We use the BioRad ion exchange membrane, and it cuts down on the fluoride by about one half, but a silica based column would probably be much better due to adsorption of fluoride.

Gonzales-Lepera: As I said, we did not observe any fluoride after allowing the sample to decay for about six hours. We sampled the product before and after passing through the anion exchange cartridge, and the sample from before the cartridge showed a small F-18 peak on HPLC at that time, but the treated sample did not.

Channing: I found it strange that you said that you had good yields of ammonia without use of ethanol, was that right?

Gonzales-Lepera: Yes, I was still getting about 90% ammonia due to the memory effect, but after a while that yield was gone.

Roy Tilbury: Your target memory effect reminds me of what we called the first run of the day effect when Bob Dahl and I were doing these experiments a long time ago. What we found was that a fresh target with just pure water would produce a large percentage of N-13 ammonia at low beam currents, and then this yield dropped off and could be reproduced in later runs. We attributed this to induced radioactivity in the foil window, or the target chamber, which was causing radiolysis in the target water and subsequent radiochemical effects.

Rich Ferrieri: If I recall, Roy, from some of the earlier work you indicated that if you took steps to purge the water with argon you also saw a large rise in the ammonia yield. I notice that in this work the water is prepared for a weeks use in a bag. There may be effects here from absorption of oxygen by the water while it sits in the bag.

Gonzales-Lepera: No, I used these HPLC containers, which are actually open to the atmosphere, but I tried two things. One was HPLC water, then when things were working I switched to one-liter sterile water bags, and we inject the ethanol into the water bag.

Ferrieri: You took no steps to purge with argon, or anything like that?

Gonzales-Lepera: No.

Ferrieri: That could play some role in the removal of oxygen, which could be a source for radiolytic oxidation of ammonia to nitrate and nitrite.

Gonzales-Lepera: I followed the Korsakov paper, and do apologize for the error in the reference and will try to get it straight, where they do mention de-aerated samples showed no difference compared to untreated water. We chose to take the more straightforward method.

Marc Berridge: I think this memory effect is probably real. If we do something similar, irradiating a target only after a couple of washes, we find that we go straight back to nitrate. It makes no difference in the product distribution whether we take great pains to sparge the water, or even vacuum distill it under argon. So it sounds as if your system does have some sort of memory effect caused by ethanol hanging up in a dead volume somewhere in the system.

Gonzales-Lepera: We did try to eliminate that with extensive washing and by flushing the water out with helium between washes.

Experience with the NIH Ethanol Water Target

Michael Channing
National Institutes of Health

Summary: A water target was presented, constructed entirely of Titanium with a 30 μ m Titanium foil using 5mM ethanol addition and pressurization with helium. Irradiation was done with a JSW 1710 cyclotron with incident 17.5 MeV protons reduced in the entrance foil to about 16.8 MeV. Energy deposition was 1 eV/molecule. Formaldehyde was detected at 48 ppm and ethanol at 196 ppm in the product. 70% of the ethanol was degraded during irradiation, possibly due to a lower energy deposition in terms of eV/molecule. A polymer SAX membrane resin was used to remove radionuclidic and radiochemical impurities. Sparging the target water with He or O₂ gas did not alter the amount of ammonia produce in a given run by more than a few percent. Suggested improvements were to use silica based ion exchange material, and to use entrance foils thick enough to drop the beam energy below the ¹⁵O threshold.

Questions:

Marc Berridge: Rich Ferrieri, don't you have any comments on the fate of the ethanol and the amount of formaldehyde observed here? What is going on?

Rich Ferrieri: Mike's point is well taken. There are differences between his experiments and ours. Mainly, ours were not high pressure.

Channing: Our target was a closed target, we did not add any pressure, but there was some generated by radiolysis.

Ferrieri: What dose rate did you use?

Channing: 10 μ Amps for 5 minutes, so 50 microamp minutes.

Ferrieri: So the target pressure might be in the range of 150 psi. In the experiments we ran, we overpressured with only one atmosphere of helium gas, so this is really a different experiment altogether. We saw complete decomposition of the ethanol, and a distribution of formic acid, formaldehyde, carbon dioxide, carbon monoxide. That seemed to agree with the earlier work of Wieland, where they saw complete decomposition of ethanol also. Also another point: sparging of helium will do very little to remove oxygen from water. You need to sparge with a gas that is equivalent in molecular weight, which is why argon is preferred. I'm intrigued that you saw very little change when you sparged with oxygen gas. That is in direct disagreement with Tilbury and Dahl who saw significant changes in the ammonia yield. Roy, you want to make a comment, or Bob?

Channing: I measured the concentrations of oxygen in the water after helium sparging, and it was 1.4 ppm vs. over 200 ppm oxygen after sparging with oxygen.

Bob Dahl: We're both here, so maybe can remember some of this. I don't see a problem with this. In this work the radiation dose is so high that conversion to nitrate and nitrite exceeds the effects of sparging and everything else. We saw sparging effects somewhere around a tenth of an eV per molecule. Roy?

Roy Tilbury: The comment about sparging with helium not having any effect on product distribution struck me as contrary to what we had observed. That's the only comment I would make at this time.

Dahl: It seems to me that we observed the conversion to nitrate and nitrite was over, and there were no further effects after a low radiation dose. We are dealing with radiation chemistry here so it is important to take into account the target volume and the average energy deposition per molecule. Our target volume was 23 mL, this is 10, others are 0.6, and it is also a matter of how long you bombard and how hard. We might get more consistency if everyone's numbers were put on this same basis.

Jerry Bida: I think Marc is trying to egg us on into the formaldehyde fray, so let's go for it. I can't speak very quantitatively, but from the C-13 NMR work we did at UCLA it is clear that the product distribution in the ethanol-spiked high pressure target is dependent on the target configuration and radiation conditions. Consistent with what Rich sees, we observe over 90% ethanol decomposition into the variety of products he mentioned. At 10 MeV, 400 psi pressure, you see mainly carboxylic acids which are easily removed by ion exchange. As for formaldehyde in the injectable dose, the concentration in normal blood is between 2 and 3 micrograms per gram of blood. With a 10 MeV beam, formaldehyde is really not an issue.

In-Target Preparation of [¹³N]Ammonia: Target Design and Chemistry

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Over the past several years, efforts to implement the reported methods for direct in-target production of [¹³N]ammonia have brought interesting results. Before the most recent series of reports on dilute ethanol solutions for ammonia production, the available information concerning organic additives was not detailed; and we were intrigued, primarily by the regulatory advantages, by the possibilities of direct ammonia production under hydrogen pressure without the use of organic additives. Therefore we have explored the products given by use of hydrogen gas over a small-volume water target as a function of gas pressure and of beam dose and dose rate. We also investigated the effects of pressure alone by using helium or nitrogen gas to pressurize the target. The target was aluminum or copper-nickel, with a volume of 3 mL, pressurized with 1-8 atm. hydrogen and irradiated with a Scanditronix MC17 with 17 MeV protons. Beam currents to 30 μ Amp for 30 min were used. The targets were designed with a gas head space over the target water to prevent water losses by bubble formation at high beam dose and to allow good contact between the water and the hydrogen gas. The head space allowed substantially higher beam current and irradiation times to be used. Entrance foils (Havar) were chosen thick enough to drop the incident energy below the ¹⁵O production threshold, so ¹⁵O contamination was not observed.

The chemistry in this target does not seem to be simple, and is not well understood. However, there were several observations which may be of use to form hypotheses and propose new experiments. Both ethanol and hydrogen pressure caused direct formation of ammonia in the target. Ethanol alone caused high ammonia yield at low beam doses which gradually dropped as beam dose increased. The by-products in the presence of ethanol were mainly NO_x. The effectiveness of ethanol was dependent on pressure, with the percentage of ammonia in the target rising with increasing helium or nitrogen pressure. In contrast, hydrogen pressure caused only 80% of the product to be ammonia in the best cases, but maintained its effectiveness at much higher beam doses than ethanol. The major side product when hydrogen was used was elemental nitrogen, with only small amounts of NO_x and hydroxylamine being produced. Further, the ammonia yield rose with hydrogen pressure up to approximately 80% yield, then was unaffected by further pressure, implying that there are at least two mechanisms of nitrogen gas formation, one of which is not affected by hydrogen pressure. Addition of ammonia to the target water caused massive nitrogen gas production, but carrier ammonia was not generated in sufficient amount in the normal target to produce the observed product distribution. Addition of hydrazine and hydroxylamine did not increase nitrogen gas production, nor did nitrogen gas itself, eliminating these materials as reaction intermediates. Therefore, the formation of nitrogen gas was not consistent with previous mechanisms proposed for that process. The necessary nitrogenous intermediates leading to nitrogen gas could not be identified. Production up to 200 mCi of ammonia at lower beam dose was possible with only hydrogen pressure. Up to 800 mCi was produced with higher beam dose by combining medium pressure hydrogen with 3 mM ethanol in the target water. Clinical production levels were easily achieved within three minutes from the beginning of bombardment using low hydrogen pressures and no ethanol.

Questions:

Rich Ferrieri: Just a comment about your hot vs. thermal mechanisms. By virtue of the way the nitrogen is produced you have to consider electronic spin states and the differences in their reactivities. For example, in gas phase work we did when Ren Iwata was at Brookhaven we found that about 80% of the recoil atoms were produced in electronically excited 2D , 2P state. These will react with molecular nitrogen. The 4S ground state however will not react with nitrogen unless the thermal energy is above $2500^{\circ}C$ before you see any exchange at all. The effects of spin state on reactivity will also extend to liquid phase reactions.

Berridge: The problem that I have even with that is to explain the fact that pressurizing the target with nitrogen gas does not change the N_2 yield. I did not get down as far as mechanisms for exchange into nitrogen because it did not seem to matter how much nitrogen I had in my target.

Ferrieri: That's an interesting observation. I don't have an answer for that.

Tim Tewson: A potentially mundane explanation is that both your hydrogen and your helium had nitrogen in them. Enough that you could reach saturation in the water, because nitrogen is not very soluble in water. In fact with the normal method for analyzing hydrogen and helium it would be remarkably difficult to find relatively small amounts of nitrogen.

Berridge: That's definitely true. If it's in the tank there is not much you can do.

Mike Channing: My comment was similar, I was wondering if you know the specific activity of the nitrogen.

Berridge: We did GC work, but we did not get a specific activity measurement, because with our GC setup it is very difficult to exclude atmospheric contamination. All I can say is that we could not tell the difference between a clean helium or hydrogen sample and a sample of the target gas.

Ren Iwata: We have a circulating target in a pressurized hydrogen atmosphere, at two atmospheres, which gives 99% ammonia production. I think the circulation of the water helps to dissolve the hydrogen in the water, and allows a high yield at low pressure. It is easier to circulate the water, it is natural abundance and not expensive so that there is no reason not to use a larger volume for circulation.

Berridge: Yes, that is a different mechanical situation but an interesting observation. Of course, at low but useful beam current a good yield is obtained with that pressure in a non-circulating target also.

Carlos Gonzales-Lepera: What was your target material?

Berridge: Actually we had two targets. One was aluminum, and the other began life as a fluorine-18 target, nickel plated copper, and we milled it out to give a head space so it had nickel

and copper exposed to the water. The two behaved identically and we did not see impurities in the final product.

John Gatley: I have two questions. The first is did you look for N_2O as well as N_2 ?

Berridge: No, we did not look specifically for N_2O .

Gatley: And the other one is thrown out completely at random, but what about cyanide as source of environmental nitrogen? Have you tried putting cyanide in the target?

Berridge: Well, I thought I'd tried everything but the kitchen sink, but I missed that.

[¹³N]AMMONIA PRODUCTION VIA DEUTERON IRRADIATION OF BUCKMINSTERFULLERENE

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INTRODUCTION

The most common nuclear reactions used for the accelerator production of nitrogen-13 are graphically summarized in Figure 1. At present, [¹³N]ammonia is generated in ample quantities for PET imaging purposes by the interaction of relatively energetic (6-17 MeV) protons with an oxygen-16 rich target (natural abundance water) or carbon-13 rich target.¹⁻⁴ Natural abundance carbon must be used for the low energy deuteron production⁵ of ¹³N and is the target of choice in preliminary results for ¹³N production using 8 MeV ³He²⁺.⁶ In some cases, the ¹³N produced is already in the form of ammonia,³ while in others, the radiolabeled species must be chemically converted to ammonia.¹ In order to meet the anticipated growth in clinical use of this important MBF tracer and to keep pace with the development of smaller, lower energy accelerators that can operate at ≤ 8 MeV incident particle energy,⁷ sufficient ¹³N can only be readily produced with a carbon-rich target (see Figure 1).

The use of a carbon/water slurry target for the low energy charged particle production of ¹³N has certain attractive features, including reuse of the target material. Further, the desired radiochemical form of the ¹³N, i.e., [¹³N]NH₃, is produced *in situ*. However, this target configuration is not without limitations. It is theoretically possible to produce hundreds of millicuries of ¹³N at modest beam currents of 20-30 μA for particle energies as low as 6-7 MeV. However, due to the random packing nature of amorphous carbon powder, the density of carbon (by volume) in the beam strike of the slurry target is only 15%. The situation is further exacerbated due to the carbon particle size. Because the recoil range of the nascent ¹³N atoms from a 10 MeV proton reaction is of the order of 1 to 2 microns in carbon, which is an order of magnitude less than the average amorphous carbon particle size, the fraction of ¹³N that "escapes" from the carbon matrix is approximately 30-50%. Thus, it is estimated that the ¹³N contribution from the ¹³C(p,n) nuclear reaction in the current slurry target is only about 10% of the theoretical maximum. Another serious limitation of the slurry target is the inability to operate the target at elevated (≥ 10 μA) beam currents for extended periods of time. Nitrogen-13 production yields are observed to be irreproducible under these conditions and the carbon powder is prematurely consumed, possibly due to beam induced processes. It has been shown that carbon reacts at elevated temperatures with oxygen dissolved in water.⁸ Finally, via SEM, it has been observed that continuous irradiation of the amorphous carbon powder results in production of microscopic hair-like structures. This can lead to marked water flow restriction due to blockage of the frits used to confine the powder.

The criteria important to the successful performance of a slurry target include: i) carbon beam strike density, ii) carbon particle size, iii) structural integrity and iv) chemical stability under irradiation conditions. Based on these considerations, materials other than amorphous carbon have been investigated for their use in [¹³N]NH₃ production, including i) deuteron irradiation of porous graphitic carbon (PGC)⁹ and ii) spherical carbonized beads prepared via pyrolysis of functionalized poly(styrene/divinylbenzene)

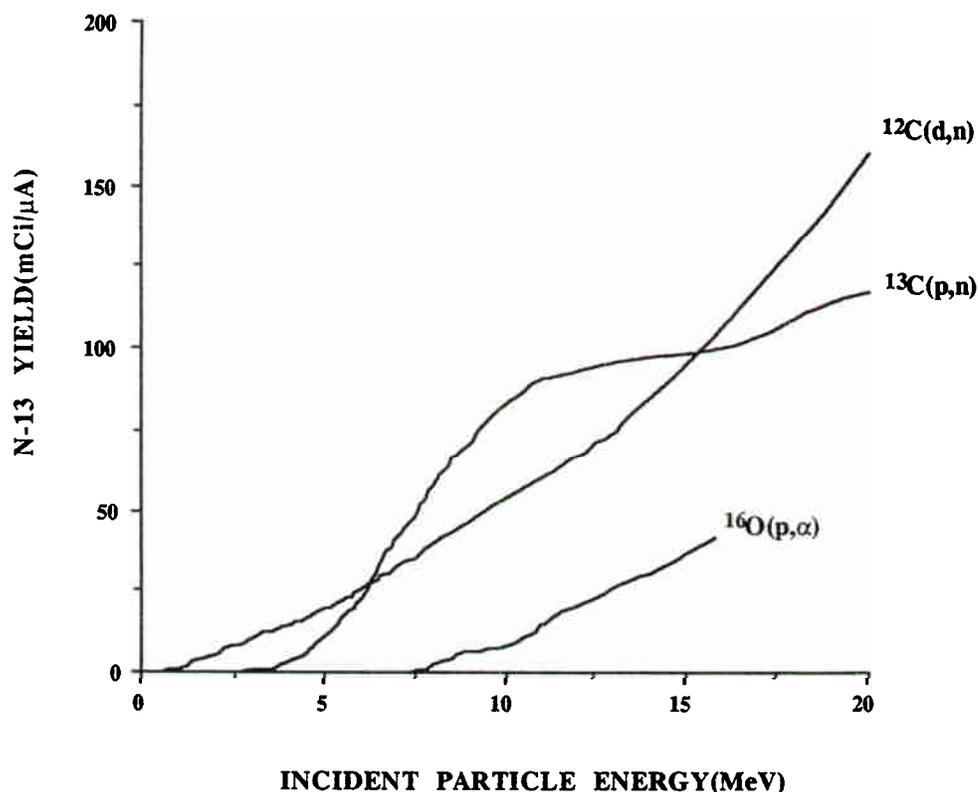


Figure 1. ^{13}N production thick target yields.

resins(PS DVB).¹⁰ In terms of production level capabilities, both approaches met with limited success. Recent work on the isolation and characterization of solid mixed fullerenes(known as fullerite)¹¹ suggests that this form of carbon may be potentially advantageous in [^{13}N]ammonia production. Some of the properties of fullerenes that may prove favorable are enumerated here: i) unlike graphite or amorphous carbon, fullerenes are crystalline, e.g., C_{60} crystallizes in a face-centered cubic lattice.¹² This property should result in an improved carbon beam strike density; ii) while fullerenes are carbon dense, the closed hollow-cage structure of fullerene molecules may facilitate ^{13}N hot atom recoil into the surrounding aqueous environment, a necessary step for production of ammonia.¹³ The radius of the C_{60} skeleton has been measured by X-ray powder diffraction to be 3.53 Å;¹² iii) the octahedral interstices in the C_{60} fcc unit cell are 4.12 Å in diameter, thus providing a natural porosity for aqueous intercalation.¹⁴ The chemical and radiation stability of fullerite under irradiation conditions required for ammonia production is unknown. Although radiation damage and oxidation of C_{60} may occur under typical irradiation conditions,^{15,16} the extent to which these processes take place and/or compromise fullerite performance remains to be determined. Preliminary data for ^{13}N yields and radiochemical identification are presented below for the low energy deuteron irradiation of fullerite under varying conditions of beam current, irradiation time, and water flow rate.

RESULTS AND DISCUSSION

Details of the experimental methods can be found elsewhere.¹⁷ The results of this preliminary investigation into the use of buckminsterfullerene for biomedical imaging applications are summarized in Table 1. In addition to these data, ^{13}N saturation yields were observed to be independent of beam currents from 5-10 μA and water flow rates from 1-3 cc/min. Also, the major radiolabeled products

observed were ^{13}N -labeled ammonia and ^{17}F -labeled fluoride ion, as determined in previous work.¹⁰ As anticipated, the carbon fraction (volume %) in the target beam strike was a factor of two greater than that observed in the amorphous carbon slurry target.¹⁹ The primary objective of this study was to establish whether the naturally occurring carbon density, porosity and hollow-cage structure of fullerite could result in improved ^{13}N yields when compared to other carbon forms. A rigorous comparison demands that different materials be subjected to identical experimental conditions. However, in lieu of these data, a comparison of results from the literature for ^{13}N production from deuteron irradiation of various carbon forms are given in Table 2. All three carbon forms have overlapping grain sizes, whereas the porous graphitic carbon has the highest carbon beam strike fraction. The poor ^{13}N saturation yields obtained for carbonized beads derived from derivatized poly(styrene/divinylbenzene) were rationalized on the basis of the dimensions of the beads vs the recoil range of nascent ^{13}N .¹⁰ Further, no data are available on the porosity of these beads. A commercially available porous graphitic carbon²⁰ used in HPLC applications has been used as a target material for ^{13}N ammonia production.⁹ The authors concluded that the ^{13}N extraction efficiency was a function of the material's porosity and grain size. PGC is characterized by high porosity (60%), with pore diameters on the order of 250 Å. While the carbon beam strike fraction was reportedly high, the extraction efficiency was low, most likely because of the limited ^{13}N recoil energy vs graphitic carbon grain size. The ^{13}N extraction efficiencies measured for fullerenes appear to support the premise that this carbon form's natural porosity and structure facilitate ^{13}N ammonia production under the experimental conditions described herein. The lower ^{13}N extraction efficiency observed for PS DVB, which involved more energetic ^{13}N recoils, lends some support to this conclusion. On the basis of ^{13}N extraction efficiency, fullerite as a target material appears to be comparable to amorphous carbon, but better than PS DVB. Work is in progress to determine the long term structural stability and chemical reactivity under conditions of charged particle bombardment in an aqueous environment.

Table 1. 4.3 MeV Deuteron Irradiation of Buckminsterfullerene.

Approximate Mesh size	Carbon fraction (%)	Beam current (μA)	Saturation Yield corr. to 100% C (mCi/μA)	Practical extraction efficiency (%) ¹
100-120	28	5 ²	5.4	34
100-120	30	5	4.2	27
100-120	30	7.5	3.6	22
100-120	30	10	5.7	36

¹Based on cross section data of Firouzbakht et al.¹⁸

²Avg. of six expts. at 1.5 cc/min flow rate.

Table 2. Summary of Deuteron Irradiation of Various "CARBON" Forms.

Target material (grain size in μm)	D ⁺ (MeV)	Carbon fraction (% by vol.)	% extraction eff. @ beam current (μA)
PS DVB (25-290)	6.3	25-30	10 (5)
PGC (38-100)	2.9	54	12.1 (5.5)
C ₆₀ (125)	4.3	28-30	22-36 (5-10)

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Questions:

Bruce Wieland: How are you containing the Bucky balls in the target?

Bida: With half-micron stainless steel frits. The Bucky balls replace the amorphous carbon in the slurry target.

Wieland: Is this the 2mm deep by 10 mm diameter beam strike target? Which has a volume of 160 μL ?

Bida: Yes, that's the target, but the total beam strike and void volume is on the order of 350 μL .

Tom Ruth: What is the cage size of C_{60} compared to that of the nitrogen atom? How does that help in the target chemistry?

Bida: In the case of amorphous carbon packed randomly, the N-13 recoil atom has a good chance of encountering a neighboring carbon atom. The material thickness is much greater than the range of recoil nitrogen. With the C_{60} cavity, seven angstroms is well in excess of the dimensions of the nitrogen atom, and there is very little neighboring carbon into which it could recoil. It stands a better chance of recoiling into the aqueous medium.

Tim Tewson: The problem with Bucky balls is that they are really sticky, in that everything likes to stick to the outside of them. For example, early preparations of them were 45-50% toluene, something like that. They've improved somewhat, but they still have things stuck on the outside. I would guess that if you don't have a problem of nitrogen recoiling into carbon in the middle, then you would have a problem with it doing so on the outside.

Bida: That may very well be true.

Roy Tilbury: What is the cost and availability of the material?

Bida: When I first purchased it, it was about \$250 a gram and in good supply. Improvements have dropped the price to about \$100 a gram and there is plenty available.

Bida: As an aside while I have the opportunity, I would like to add a footnote to yesterday's discussion of the Brookhaven O-18 enriched CO_2 solid target. At Dr. Welch's behest, I found on page 223 of Spinks and Woods that solid and liquid CO_2 are quite susceptible to radiolytic decomposition while gaseous CO_2 is little affected. The bulk of that work was done in 1955, much of it here at Brookhaven.

An experimental Carbon/steam stack target for in-situ production of $[^{13}\text{N}]$ ammonia with low energy deuterons.

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Summary

Continuing our investigations aiming at the production of clinically useful amounts of ^{13}N ammonia with low energy deuterons¹ via the $^{12}\text{C}(d,n)^{13}\text{N}$ reaction², thin carbon foil/steam stacks were built and tested. Using 3.3 MeV deuterons, practical $^{13}\text{NH}_4^+$ saturation yields of around one $\text{mCi}/\mu\text{A}$ were delivered by such systems. A few runs were also performed with a stack of woven carbon fiber fabric³ and steam layers. Yields of around 2 $\text{mCi}/\mu\text{A}$ were recovered in the aqueous phase.

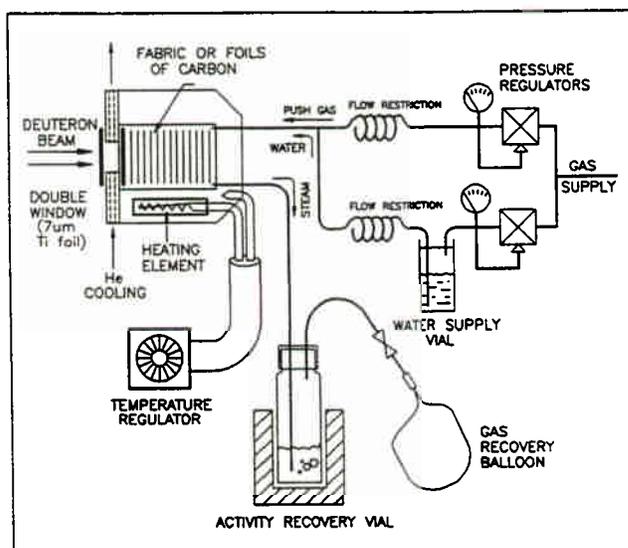


Figure 1: Experimental set-up

Basic principle

^{13}N atoms are produced in the carbon by deuteron bombardment. If the carbon is thin enough, their recoil energy allows a fair fraction of them to escape out of the carbon and slow to a standstill in the water vapor surrounding the carbon. The aqueous and carbon-rich environment, known to be favorable to ammonium generation in ethanol-water targets⁴ and in carbon-water "slurry" targets⁵, is reproduced here with the water in the gas phase.

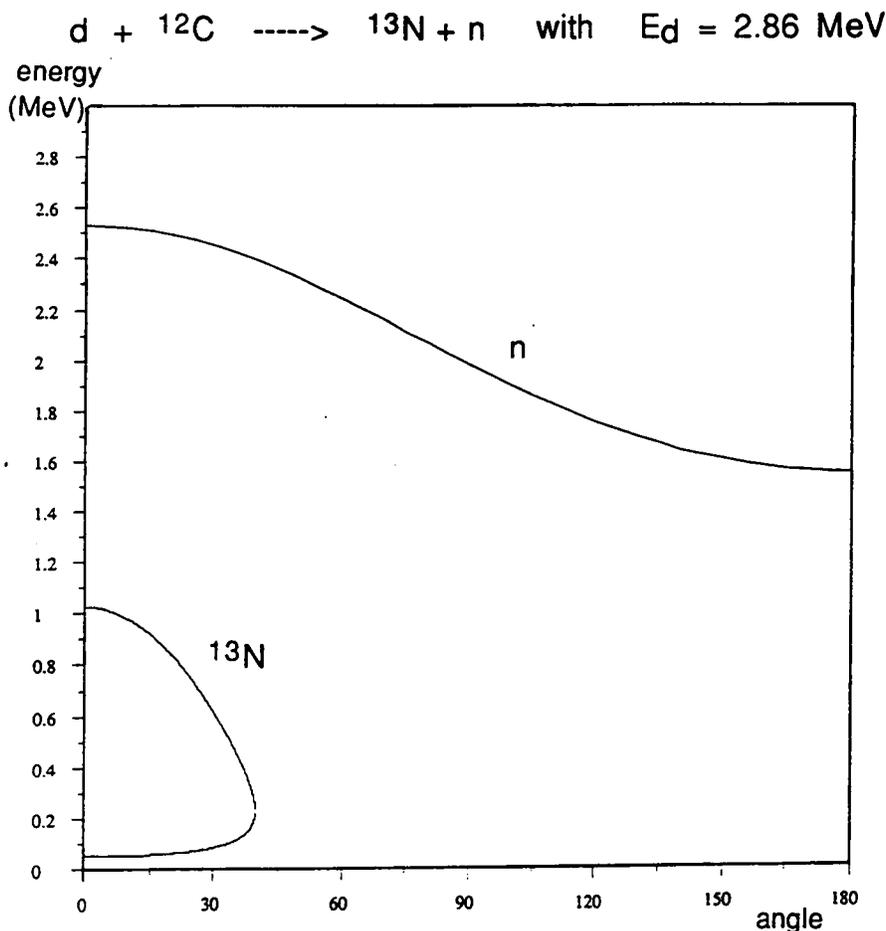


Figure 2: Recoil energy vs angle of emission of the outgoing ${}^{13}\text{N}$ and neutron after the reaction of a 2.86 MeV deuteron with a ${}^{12}\text{C}$ atom.

Evaluating the recoil path length

The thicknesses of the carbon foils and steam layers were selected on the basis of the kinematics of the nuclear reaction and of the range of ${}^{13}\text{N}$ recoils in solid carbon and in steam (these calculations were performed only for the sake of a crude dimensioning of the stack). The outgoing ${}^{13}\text{N}$ and neutron were assumed to be emitted isotropically in the center of mass of the process. For example, the lab reference frame angular distributions of the ${}^{13}\text{N}$ and neutron recoils resulting from the ${}^{12}\text{C}(d,n)$ reaction at some given 2.86 MeV energy, are shown in fig.2 (similar figures could be generated for every other deuteron energy). In this particular case, we see that all the ${}^{13}\text{N}$ ions do recoil in the forward direction, in a solid angle of less than 45° , with a kinetic energy ranging from 25 keV to about 1 MeV. The range of a typical 0.5 MeV recoil ${}^{13}\text{N}$ in carbon is $200 \pm 50 \mu\text{g}/\text{cm}^2$ (depending of the stopping power theory used). Therefore, most of the recoiling ${}^{13}\text{N}$ atoms are expected to exit $100 \mu\text{g}/\text{cm}^2$ carbon layers before they lose all their energy. Figure 3 shows the paths of a typical bunch of 500 keV ${}^{13}\text{N}$ recoil atoms entering a $100 \mu\text{g}/\text{cm}^2$ followed by a 1 mm thick steam layer at 120°C density⁶. It shows that most of the ${}^{13}\text{N}$ recoil atoms will stop in the steam before hitting the next carbon foil.

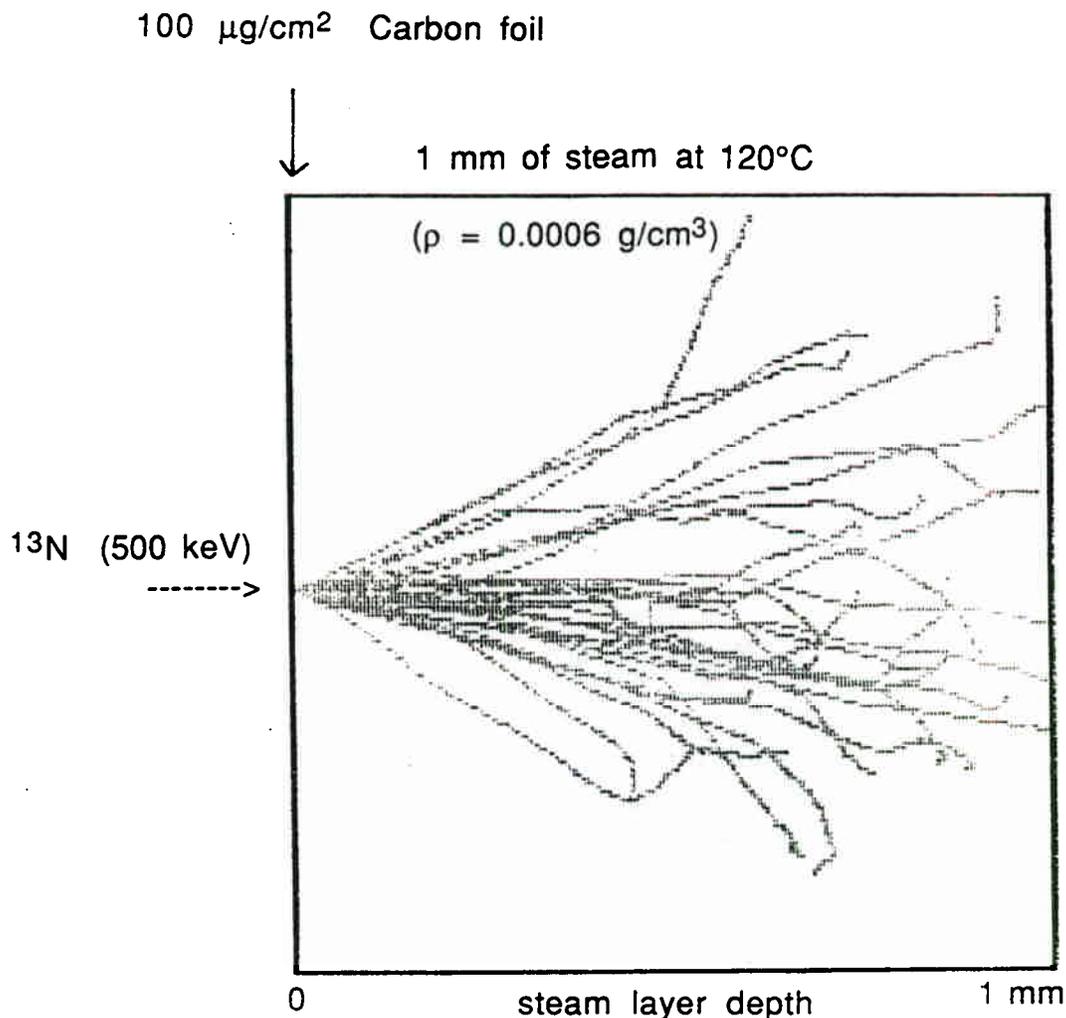


Figure 3: Trajectories of a bunch of ^{13}N particles slowing down from 500 keV to standstill across a $100 \mu\text{g}/\text{cm}^2$ carbon layer followed by 1 mm of water vapor at 120 °C ("TRIM" code, Ziegler, 1987).

Experimental set up

Three stacks were assembled: one made of a pile of 50 foils of $100 \mu\text{g}/\text{cm}^2$ spaced 1 mm apart, a second one made of 60 foils of $100 \mu\text{g}/\text{cm}^2$, spaced 0.8 mm apart and a last one made by piling 6 layers of carbon fiber fabric⁷, $\sim 6.5 \text{ mgr}/\text{cm}^2$, spaced 1.6 mm apart. The length of the stacks were defined to stop 3.5 MeV deuterons.

The target body was stabilized at 120°C. Water vapor (with or without additives) flowed between the foils at atmospheric pressure. The carbon accounted for about 50% of the stopping power in the foil assemblies, and for about 80% in the fabric assembly. The steam condensed at the output of the system and was recovered in a vial. For all three set-ups, gas was often added to speed up the flow of recondensed water at the output of the target system. For some of the runs, the gaseous activity fraction was collected separately in a balloon. Figure 1 shows the tubing layout.

The mechanical details of the construction of the stack can be seen in figure 4. The foils were deposited on the spacing rings by floatation.

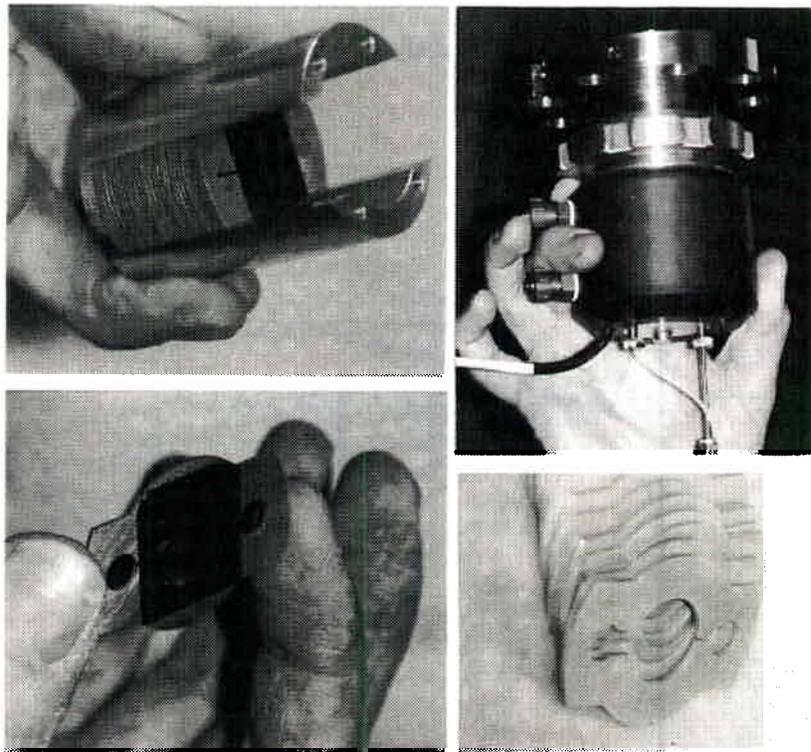


Figure 4: Target, Stack subassembly, foil on a spacer ring.

Results and discussion

The bombardments on the first stack (50 layers of $100 \mu\text{g}/\text{cm}^2$ foil, with 1 mm spacing) were performed at very low beam current with water or water+ethanol vapor flow pushed with He. See results in table 1.

The experiments with the second stack (60 layers of $100 \mu\text{g}/\text{cm}^2$ foil, spaced 0.8 mm apart) were performed with a mixture of water vapor or water+ethanol vapor and hydrogen. See results in table 2.

A last series of short runs was performed with an array of carbon fiber cloth separated by a 1.6 mm water vapor-hydrogen mixture. The results are shown in table 3.

The set of irradiations performed on the first stack (at low beam current, table 1) exhibits a remarkable “ethanol effect” on the product distribution. The amount of ammonium ion is significantly increased at the expense of N_2 . That effect was not observed in the other two series, maybe because the gaseous phase was not systematically collected.

The second set of irradiations (table 2), performed on the 60 Carbon layer stack, shows: that the yields are low when there is no steam between the foils, that the yields obtained with

steam are consistent with the first set discussed above, that the yields remain constant in the 1 to 11.5 μA range, that the highest beam density tested, 20 $\mu\text{A}/\text{cm}^2$, caused no damage to the stack, that steam and gas flow rates do affect the yields and have to be optimised.

Table 1: Foil stack n°1 experiments, sat. yield and product distribution results.

Run n°	Vapor mixture	Beam current	Time of irradi.	Total Saturation yield	[13]NH3 saturation yield	Product distribution		
						Gaseous (N2)	Pos. ions (NH3)	Neg. ions (NOx)
						%	%	%
		(nA)	(min)	(mCi/uA)	(mCi/uA)			
1	pure water	500	10	.964				
2	pure water	500	10	.863				
3	pure water	430	10	.793				
4	pure water	500	10	.800				
5	pure water	530	10	.823	0,36	50	44	6
6	pure water	550	20	.960	0,30	65	31	4
7	pure water	700	15	.815	0,33	53	41	4
8	water with Ethanol	700	15	1.158	0,92	16	79	5
9	water with Ethanol	700	15	1.193	0,93	18	78	4
10	water with Ethanol	650	15	1.194	0,93	17	78	5
target slightly damaged after run n° 10, when changing the water mixture								
11	pure water	720	15	.667	0,29	54	44	2
12	pure water	750	15	.697	0,34	44	50	4
13	water with Ethanol	700	10	.748	0,62	7	83	10
14	water with Ethanol	700	15.25	.900	0,73	9	81	10



Figure 5: carbon fiber fabric, enlarged 1250 x (picture: PET dpt., Duke University, Durham, NC).

Table 2: Foil stack n°2 experiments, sat. yield and product distribution results.

Beam Current (μA)	Irradiat. time (s)	Activity at EOB. Aqueous fraction (μCi)	sat. Yield aqueous fraction ($\mu\text{Ci}/\mu\text{A}$)	Product distribution			Remarks, Experimental conditions Foil stack n°2: 60 foils, 100 $\mu\text{g}/\text{cm}^2$, spaced 0.8 mm
				aqueous phase		gas phase	
				positive ions (%)	negative ions (%)		
0.5	300	8	55				pure H ₂ flow between the foils.
1.0	360	13	37				"
1.0	360	18	52				"
1.0	300	328	1120				steam + H ₂ mixture (30 $\mu\text{l}/\text{min}$ water + 50 cc STP/min H ₂)
1.3	300	302	794				"
1.3	300	301	790				"
1.0	200	157	763				"
1.2	300	252	717				"
1.1	300	230	747	93	<7	-	"
1.1	300	204	664	94	<6	-	"
2.1	300	428	713				"
3.1	300	609	671				"
3.1	300	630	694	96	<4	-	"
2.9	500	920	723				"
3.1	300	611	673				steam + H ₂ mixture (100 $\mu\text{l}/\text{min}$ water + 15 cc STP/min H ₂)
3.1	300	687	756				"
3.2	360	822	755				"
2.6	300	760	998	100	0	-	steam + H ₂ mixture (64 $\mu\text{l}/\text{min}$ water + 17 cc STP/min H ₂)
2.7	600	1373	1016	100	0	-	"
2.8	900	1797	990	100	0	-	water+10mMol ethanol vapor + H ₂ (same flow as above)
2.8	900	1790	1005	100	0	-	"
2.7	900	1838	1052	100	0	-	"
3.7	1240	2786	977				steam + H ₂ mixture (64 $\mu\text{l}/\text{min}$ water + 17 cc STP/min H ₂)
3.0	300	849	967	93% aqueous		7	"
5.0	300	1283	876	-			"
5.0	300	1305	891	-			"
5.6	300	1526	930	-			"
9.0	400	2790	838	95% aqueous		5	"
11.5	300	2762	820	-			"

Table 3: carbon cloth stack n°3 experiments, sat. yield and product distribution results.

Beam Current (μA)	Irradiat. time (s)	Activity at EOB aqueous fraction (μCi)	sat. Yield aqueous fraction ($\mu\text{Ci}/\mu\text{A}$)	Product distribution		Remarks Experimental conditions Stack n°3 6 layers of carbon fiber fabric, 6.5 mgr/cm ²
				aqueous fraction (%)	gaseous fraction (%)	
				(%)	(%)	
4.5	300	561	425			flow in between the foils: steam + H ₂ mixture (64 $\mu\text{l}/\text{min}$ water + 17 cc STP/min H ₂)
3.8	320	2396	2040	78	22	"
8	400	6762	2284	63	37	"
7	300	4544	2216	64	36	"
4.7	300	2263	1644	65	35	"

The third set of runs, performed on the carbon fiber cloth, exhibits the highest yields recovered in the liquid phase, with in addition, a high fraction of non soluble (N₂) activity. The higher yields cannot be fully explained by the higher carbon to water ratio. This is surprising given the N₁₃ recoil range evaluation: the average fibers are ~6 μm in diameter (as can be seen on fig.5), and the foils less than 0.5 μm thick. The internal structure of the fibers has not yet been investigated.

Conclusions

The carbon fiber cloth method gives a fair yield and is obviously easier to handle than foils. If the product distribution is, as expected, in favor of ammonia and if the 1.5 to 2 mCi/μA(sat) yields are maintained at higher currents, clinically useful [¹³N]ammonia doses for PET studies could be produced every 15 minutes with a 50 to 60 μA, ~3.5 MeV deuteron beam. The reason why the carbon fabric gave better yields remains to be explained. The choice of the push gas (He, H₂, CO₂, ...) is likely to have an influence on the product distribution and requires further testing.

References and notes

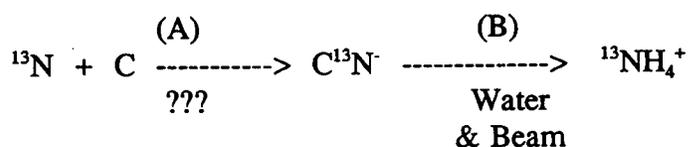
- (1) "Can clinically useful quantities of [¹³N]ammonia be produced with a 3.5 MeV deuteron beam?", J.L. Morelle and E. Liénard, Proceedings of the 4th Int. Workshop on Targetry and target chemistry, PSI Villingen, 1991.
- (2) Cross Sections for the ¹³C(p,n)¹³N and ¹²C(d,n)¹³N reactions, M.Firouzbakht and al. (BNL), Abstracts of the VIII Int. Symp. on Radiopharmaceutical Chemistry p.108, Princeton N.J., June 24-29, 1990.
- (3) The existence and potential usefulness of this material was kindly suggested to us by H. Sipila (Turku University Hospital) and J. C. Clark (Hammersmith Hospital, London).
- (4) "In target Production of [¹³N]Ammonia via Proton Irradiation of dilute Aqueous Ethanol and Acetic Acid Mixtures". B. W. Wieland, et al., Appl. Radiat Isot. Vol.42, N°11, pp.1995-1098, 1991.
- (5) [¹³C]slurry target developed by G. Bida et al.(1986)
- (6) "trim" TRansport of Ions in Matter, Monte-Carlo simulation code, IBM, version 1987 from Ziegler.
- (7) woven carbon fiber fabric, average thickness of 6.5 mg/cm², fiber diameter 5 to 8 μm, fabric type TCM128 purchased in Belgium at "SAB Le Carbone", manufactured by "Le Carbone-Lorraine", France.

Discussion following the [¹³N]ammonia session.

Concerns: in-target [¹³N]ammonia formation mechanism.

J-L. Morelle suggested an alternative or complementary explanation to the scavenging mechanism according to which the carbon containing additives prevent the oxidation of [¹³N]ammonia¹. It can be observed that the various target designs that allow direct production of [¹³N]ammonia have a common feature: they all contain water and carbon under a form or another: i.e. carbon13/water slurry target, ethanol or acetic acid water targets, water target with a small amount of thin carbon powder in suspension and lately his thin carbon foil or fiber/steam deuteron target.

The pathway from native ¹³N to ¹³NH₄⁺, suggested here, assumes the occurrence of CN⁻ as a first step (no idea on how it could happen). The interesting point is that, if CN⁻ were to occur, there are reactions² known to transform CN⁻ into ammonia, especially in the irradiated water chemical environment.

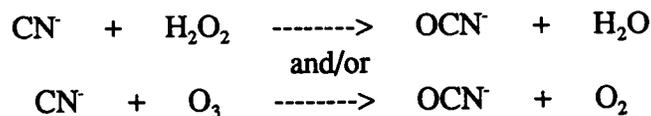


The step A is a pure hypothesis.

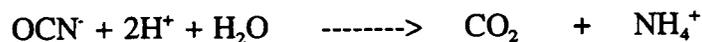
The step B is likely to occur under beam strike conditions. It involves hydrogen peroxide and/or ozone.

The step (B) is itself a two step process:

in the first one, the cyanide is oxidized by hydrogen peroxide and/or ozone to cyanate:



in the second, the cyanate hydrolyzes to ammonium:



NO_x are not mentioned among the end products of any of the various cyanide detoxification processes described in the references. In particular, for the H₂O₂ method, the reactions are said to be highly favourable to ammonia and the remaining cyanide ions are reported as “not detectable”. The hydrolysis is said to be a “slower” process than the oxidizing step. Could the detection of traces of cyanate be a way of investigating this idea?

Acknowledgement: this idea came up from a discussion with David Warichet (University of Louvain-la-Neuve, Chemical Engineering dpt.)

References:

1. Proton irradiation of dilute aqueous ethanol for in-target production of [¹³N]ammonia: Studies on the fate of ethanol. R.A. Ferrieri and al. Abstracts of the IX Int. Symp. on Radiopharmaceutical Chemistry, p.461, Paris 6-10 April 1992.

2. Environmental chemical engineering on cyanide destruction:

-Hydrogen peroxide treatment of gold mills wastes; G.A. Vickell; Proceedings of the Int. Symp. on Tailings and Effluent Management, The Canadian Institute of mining and Metallurgy, Vol 14, p.281 (1989)

-Degussa Catalog "Sodium and Potassium cyanide, properties, reactions, handling", Cyanide detoxification processes, p.40

-Cyanide destruction; N.L. Piret, H.J. Schippers; Extraction Metallurgy '89; Elsevier; p.1041 (1989)

Questions:

John Need: In the experiments at Brookhaven with the carbon-13 powder target the activity that was extracted from the target were consistent with the theoretical calculations based on particle tracks in the material.

Morelle: That's right. I'm giving here the practical yields that are obtained as ammonia for medical use. Actually, compared to what really comes out of the target, this is a fraction. Typically, half of the beam energy is lost on water. One would expect 8 mCi/ μ A at saturation to start, but we lose half of that on the steam, part does not come out of the target, and part comes out as N₂. Now with the carbon fiber fabric target the yield is up to almost 2 μ A at saturation.

John Clark: I'd like to add a bit more on carbon fibers. We are not talking about structural carbon fibers. This is carbon cloth manufactured for chemical protection suits. It has been etched to provide high surface area, and is virtually activated charcoal cloth.

Morelle: The material is also a great advantage over simple fibers, because they are very difficult to work with, while this cloth is really very easy to handle.

Continued Presentation, Jean-Luc Morelle

Summary: Additional observations and theoretical suggestions were presented concerning in-target ammonia production. Addition of carbon powder to a water target was observed to increase ammonia yield, though it gave mechanical difficulties. Tilbury and Dahl previously showed a similar effect of ethanol and acetate. It may be possible that the nitrogen atom combines with carbon to give a cyanide ion, which could be reduced to ammonia. An industrial detoxification method for cyanide uses conditions similar to ours, exposure of cyanide to peroxide and ozone. These materials form cyanate, which can hydrolyze to ammonium ion. There is no evidence yet that this happens in the target, but it is something to consider.

Questions:

Marc Berridge: Have you had a chance yet to look for cyanide in the products?

Morelle: No, we have concentrated on the traditionally known products, and have not done that yet. It may not even be able to come out of the target.

Rich Ferrieri: That's an interesting pathway. The biggest problem I have is that the carbon is designated as just carbon. I don't know of any evidence showing that recoil nitrogen can insert into carbon-carbon bonds. The problem then becomes how the cyano radical is formed. Nitrogen is more prone to abstract hydrogen or react with oxygen species than to insert into carbon moieties.

Morelle: These are valid points. I wanted to put out the idea that if cyanide occurs, it might go to ammonia. The first step is not proven, it is just conjecture.

Berridge: I seem to remember that in at least one case an insertion of nitrogen into an alkene has been observed to give a nitrile.

Bruce Wieland: What is the comparison of the total carbon in the beam strike region in the carbon foil stack versus the carbon cloth?

Morelle: The 100 μg per cm^2 foils are about a third micron thick, and the carbon cloth is 2.5 microns and above. There is much more carbon in the effective beam cross section, so the comparison of the two targets is looking at two different things.

Mike Welch: I have one problem with your mechanism. In a situation where the nitrogen is forced next to the carbon, such as our aluminum carbide target; in a reducing atmosphere you don't see just ammonia, you also see about 15% methylamine. To me, since nobody doing ammonia with ethanol in the target has seen methylamine, that argues against CN as an intermediate.

Carlos Gonzales-Lepera: Has anyone tried pressurizing a water target with carbon dioxide? Also, if there is too much energy lost in the foil target, it might be possible to use a magnetic field to allow you to reduce the foil spacing.

Mike Channing: Did you try any hydrogen mixed with the steam?

Morelle: Yes, the steam was propelled to the target by hydrogen. A low flow of liquid water was moving through the tubing to and from the target, so in order to move the fluid through the lines, a low flow of hydrogen was used and bubbles of hydrogen were interspersed with the water. In the early experiments helium was used. There was no significant change due to the hydrogen.

Berridge: How much hydrogen did you have in the target?

Morelle: There was about a tenth of an atmosphere hydrogen pressure.

General Discussion Session:

A general introduction of the topic of specific activity of tracers was given by Don Maylotte, posing the questions of the required level of specific activity, and the specific activities that are achievable with the intent of bringing out the techniques that are effective for producing useful specific activities.

Tom Ruth: 1 Curie per millimole is a reasonable specific activity to expect from labeling with F_2 .

Mike Welch: Specific activity requirements are very application-dependent. You need high specific activity for receptor work, but a system that has a lot of receptors can tolerate a lower specific activity. But the main problem is often not the specific activity, it is the effective specific activity. How well can you clean up the main compound from other products that also bind to the receptor? This is a separation problem that can drop the effective specific activity.

Joanna Fowler: There's also the problem that the necessary specific activity range is different for every tracer.

Marc Berridge: For fluoride production, lately, I'm personally seeing only about 500-1000 mCi per micromole, which is appalling and there is an interesting anecdote associated with that but the bottom line is that we don't know where the carrier's coming from.

Welch: Is that real specific activity or effective specific activity measured by binding assay?

Berridge: Without taking the rest of the session to explain this, we are very sure that it is real specific activity of the compound itself. What other numbers are people getting?

Welch: The estradiol derivatives give around 4000 Curies/mmol, but most of the carrier is not the fluorine-containing material, it is other receptor binding compounds.

Jeanne Link: We get around 3000 Curies/mmol, but don't do anything special. We see it go down after we change Teflon tubing, and then go up again after we distill or go through deionizing resin. We're pretty sure of the chemical identity and lack of related compounds using two systems, but can't do a receptor assay on fluoromisonidazole. The carrier comes from Teflon.

Mike Channing: At NIH we've had as high as 20,000 Ci/mmol at EOB, but the problem is that only happens rarely. It was measured by HPLC, so you can't rule out that there's a hidden peak, but I believe it. It varies depending on the quality of the target water, and if you have one problem with a target it can take a long time to clean it. The surface chemistry we saw recently implies that it can take a long time to get fluoride out of the surface. We wash the target with base, always use double deionized water and dry it afterwards. Unless there is a good way to measure these levels of fluoride in water all the information will be anecdotal. We are purchasing a high performance capillary electrophoresis apparatus. With stacking, we expect to measure 3-5 ppb fluoride in water.

Dave Schlyer: We're measuring fluoride in water with ion chromatography. We looked at sources of fluoride after sequential irradiations etc. On irradiation you don't see any increase in carrier. However, as it goes through the transport systems with things as innocuous as polyethylene lines, you do see an increase. We attribute this to ubiquitous fluoride in the apparatus. Levels we saw were in the several ppm range after 15 irradiations.

Bruce Mock: Back to the original questions about specific activity, there are two reasons why we need to know the specific activity. The first is to maximize it, but the other is to know what it is so that we can convert activity into micrograms of substrate for modeling purposes. So it is important to know how to measure it for its own sake.

Schlyer: In a series of experiments of displacement reactions on dinitrobenzene, looking at the effects of metal ions, Ag, Ni, Cu, and Fe, we found that they had a large effect in reducing the yield. But we found that the ions were precipitating as carbonate salts, reducing the pH of the solution to reduce the yield. We also found that we can distill the water from base (adding a small piece of sodium metal) to avoid transfer of fluoride into the recovered water.

Maylotte: Let's also ask the question of carbon specific activity, in the past the best has seemed to be about 10,000 Ci/mmole, is that still true and is it routinely obtainable?

Channing: It depends on the synthetic precursor you're making. CO₂ from the target should be determined by the target gas, or about 100,000 Ci/mmole. We see about a tenfold decrease from that because of adsorption to surfaces.

Welch: That's partially due to surfaces, its partially due to CO₂ being preferentially left behind in a vacuum system. How many people use metal O-rings? If you want high specific activity you have to be very careful about the materials in the system. I know that Hopkins does this, and they probably get as high a specific activity as anyone.

Channing: We've just added a GC to the system with a discharge ionization detector. After cryogenic cooling of the target gas, we send it to the GC and find 3 ppm additional CO₂ in the target after irradiation on top of 120 ppm without irradiation. So the irradiation, and therefore the type of O-rings etc, does not make a big difference.

Schlyer: Rich Ferrieri a few years ago looked at the specific activity of CO₂, and found a break point at around 10,000 Ci/mmole at which the radioactivity yield dropped as specific activity went higher. This is a practical consideration for C-11 production.

John Need: Has anyone looked at any of these gasses with a quadrapole mass spectrometer? That is another analytical technique that could be useful for this question to see what there is in the gasses.

Channing: I think that GC can do pretty much the same job with suitable detection methods.

Jacek Kozirowski: GE uses GC with a methanizer, which has been a very good method for specific activity measurement. We've noticed that the contribution of mass from the target is relatively constant, making specific activity dependent on the amount of activity which is produced.

Channing: That's true, which is why we express our measurements in terms of ppm or mass units.

Bida: Rich Hichwa also looked at that issue around the time of the first or second workshop and found that to be true.

