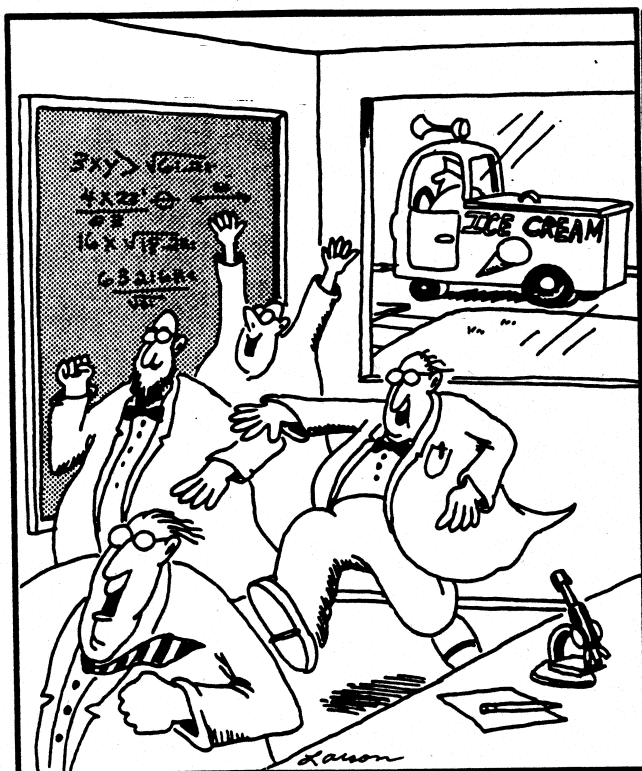




## Third Session

### Target Chemistry and Radiochemistry Plasma Effects Specific Radioactivity

Co-Chairs: Richard Ferrieri, Stefan Zeisler  
Richard Ehrenkaufer, David Schlyer



# **Surface-Sensitive Analysis of Materials Used in [F-18]Electrophilic Fluorine Production.**

## **II. Effects of Post-Passivation Exposure**

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### **Introduction**

It has long been recognized that, of all the radiolabeled compounds commonly used in PET, [ $^{18}\text{F}$ ]F<sub>2</sub> production and recovery is perhaps the most reliant on heterogeneous factors [1,2,3,4]. We maintain that a complete understanding of the plethora of processes that can occur in this target system, in the presence and absence of particle beam, must include a thorough surface analytical investigation. To this end, we have reported results of an investigation of metals suitable for use in [ $^{18}\text{F}$ ]F<sub>2</sub> target systems [5]. Further, using X-Ray Photoelectron Spectroscopy (or ESCA), we have begun probing the surface chemistry that results from the interaction of dilute fluorine gas mixtures with these metals under typical [ $^{18}\text{F}$ ]F<sub>2</sub> production conditions. The work described herein and that from a previous report [6] detail what we have found to date via ESCA for metal/surface interactions under non-irradiation conditions.

### **Experimental**

Metal samples were selected based on prior use as fluorine gas target bodies, and included gold, OFHC copper, nickel-200 and 6061-T6 aluminum foils. An electroformed nickel target body was used as the source of electroformed nickel. All samples were cleaned using ultrasonic baths of chloroform, acetone, and methanol, in that order. The samples spent approximately 15 minutes in each bath. The materials in the first set of exposures (described below) were air dried for 8 hours. The materials in the second set of exposures were dried in an air oven at 160 °C for 18 hours.

Exposures to dilute fluorine mixtures were carried out in an aluminum exposure chamber. The inside of the chamber is 2" diameter by 2.75" long. Foil samples are held in teflon tubing, slit lengthwise and mounted vertically in the chamber. The chamber has a threaded lid with an O-ring seal. Gases are introduced and removed through this lid. As close to the lid as possible there is a brass body/stainless steel bellows sealed valve (Nupro #B-2H2).

The chamber is connected to the gas manifold by 1/8" o.d. aluminum tubing. The system schematic is presented in Figure 1. All tubing in the manifold is 1/16" o.d., .030" bore stainless steel. All valves in the system are stainless steel body/stainless steel bellows sealed valves (Nupro #SS-2H2). The manifold has three gauges to monitor gas pressure. One Bourden tube gauge with 0-1000 psig pressure range is nearest the chamber. Another compound Bourden tube gauge (-30 mm Hg to 30 psig range) monitors moderate pressures in the manifold. A thermocouple gauge measures manifold vacuum more accurately. There are gas introduction ports for the argon (UHP/Zero grade 99.999%, Air Products) or oxygen

(Research grade 99.999 %, Air Products) and the fluorine mixture (15 % in argon, Spectra gases), a vent to atmosphere through a copper soda lime trap, and the evacuation port. The manifold is pumped through a liquid nitrogen cooled trap and stainless steel soda lime trap. Evacuation is provided by a mechanical pump which is equipped with another thermocouple gauge.

Figure 1. Sample exposure manifold

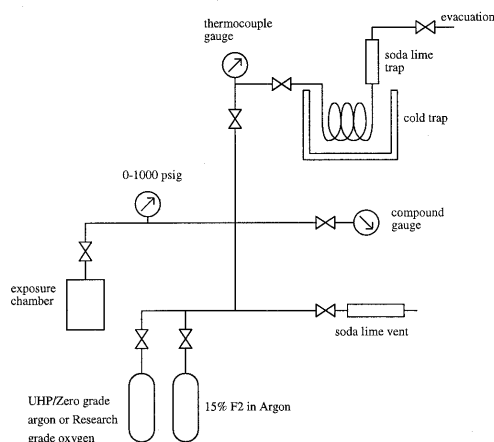
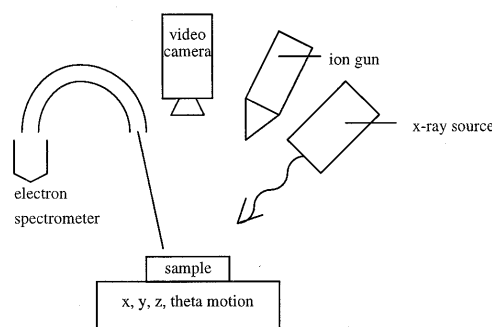


Figure 2. ESCA apparatus schematic



The first set of samples were exposed according to the following protocol. The foils were loaded into the exposure chamber, the exposure chamber was connected to the system and evacuated. The chamber was then backfilled with 20 psig of 15 % fluorine in argon, followed by 160 psig of oxygen and re-evacuated twice. Finally, the chamber was filled to 20 psig with the 15 % fluorine in argon, then filled to 160 psig with oxygen, giving a final concentration of 2.98 % fluorine, 16.9 % argon, with an oxygen balance. The samples were left in this state for 13 hours. At the end of exposure, the chamber was evacuated and backfilled with 20 psig of argon twice. The valve on the chamber was closed and the chamber disconnected from the system. It was transported to the Manufacturing Analysis Center at the Y-12 site of Oak Ridge National Lab in this condition.

At Y-12, the chamber was introduced into an argon filled glove box where samples were prepared for introduction into the ESCA equipment. The samples were already attached to a sample holder with high vacuum adhesive (Torr-Seal). The sample holder was loaded into a transport chamber that kept the samples in argon and mated with the introduction chamber of the ESCA equipment. The samples were introduced to the vacuum of the ESCA spectrometer where they remained under vacuum for 9 days before analysis was begun.

The second set of samples were exposed according to the following protocol. The foils were loaded into the exposure chamber, the exposure chamber was connected to the system and evacuated. The chamber was then backfilled with 20 psig of 15 % fluorine in argon and re-evacuated twice. Finally, the chamber was filled to 20 psig with the 15 % fluorine in argon. The samples were left in this state for 18 hours. At the end of exposure, the chamber was evacuated and backfilled with 20 psig of argon twice. The valve on the chamber was closed. The samples remained in this state for 6 days. At this point the chamber was opened to air conditioned room air. The samples were left exposed to ambient air during the drive to Oak Ridge. On that day the temperature was 65 °F and the relative humidity was 72 %. By the time the samples were introduced to the system vacuum they had spent 1 hour 20 minutes exposed to ambient conditions. Analysis of the samples began promptly upon introduction into the spectrometer.

ESCA or x-ray photoelectron spectroscopy (XPS) is a surface analysis method that can give limited chemical state information, and has an information depth (in the case of this work) of

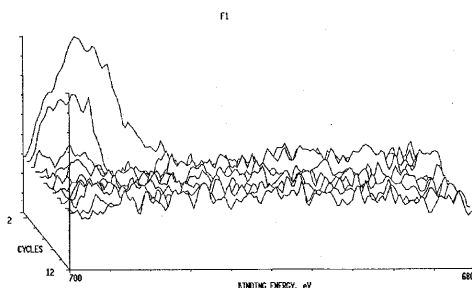
40 Å. A sample is bombarded with x-rays and the rate versus energy of the resulting photoelectrons is recorded. Coupled with a sputtering ion gun to remove thin layers of material, this method allows depth profiling of the surface in question. A schematic of this system is shown in Figure 2. The reader is referred to prior work [6] for a description of ESCA/XPS terminology.

## Results and Discussion

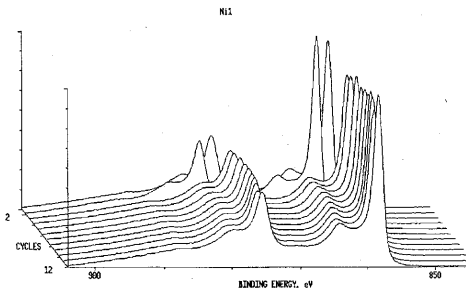
### I. Dilute Fluorine/Oxygen Exposure

The gold and OFHC copper samples exposed to the fluorine/argon/oxygen mix had very similar results to the previous fluorine/argon work [6]. The differences between the two series are that the current set of samples was exposed to oxygen as well as fluorine and argon, that the samples were air dried before exposure this time versus a brief oven dry on the last, and saw 13 hours exposure time this time versus 65 hours previously. Fluorine, oxygen and carbon were detected on the gold before sputtering, and were all removed with the first 30 second sputter cycle (Figure 3). Undesired charging of the samples resulted in some shifts to the peaks, but no broadening of the gold peak was detected, indicating that the materials were physically adsorbed rather than chemically bound to the base metal. Undesired charging of the copper sample rendered those data of limited value other than the observation that the copper spectrum appears to be that of the base metal.

**Figure 3.** Fluorine montage on gold exposed to fluorine and oxygen.



**Figure 4.** Nickel montage on electroformed nickel exposed to fluorine and oxygen.

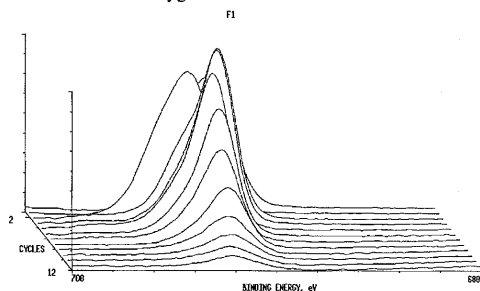


No fluorine was detected on either the nickel-200 or electroformed nickel samples either before or after sputtering. The nickel-200 had no detectable oxygen or carbon, but the nickel peak was significantly broadened. Since no contaminants were detected to account for any nickel chemical state other than the pure metal, it is assumed that the peak broadening is a measurement artifact. The electroformed nickel did have detectable oxygen and carbon on the surface which was for the most part readily removed in the first 30 seconds of sputtering. The nickel peak for this material was not broadened and shifted only slightly after the first sputter (Figure 4). This shift is also ascribed to charging effects, and no chemical state change of the nickel is justified.

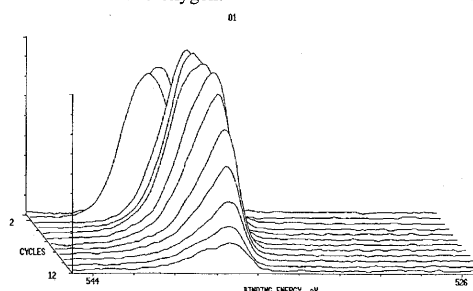
The relationship of fluorine exposure to aluminum remains the most complex of the materials studied. Fluorine and oxygen are present throughout the 1000 Å region analyzed (Figures 5-7). The aluminum peak was significantly broadened, and showed a marked change in shape versus sputter time, indicating chemical state changes (Figure 8). A fit of the data to 3 separate peaks was attempted to quantify relative concentrations of  $\text{AlF}_3$ ,  $\text{Al}_2\text{O}_3$  and the elemental form, but the fit was inconclusive. The poorness of fit can be ascribed to charging issues. However a qualitative shift from substantially oxide/fluoride at the surface to substantially base metal at the end of sputtering is observed.



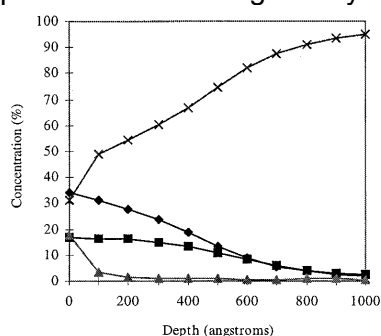
**Figure 5.** Fluorine montage on 6061-T6 Aluminum exposed to fluorine and oxygen.



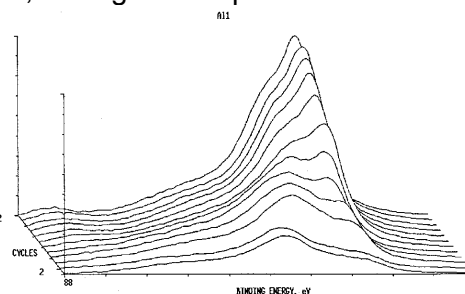
**Figure 6.** Oxygen montage on 6061-T6 Aluminum exposed to fluorine and oxygen.



The method of mounting the samples in this case (Torr-Seal) appears to have made comparisons with the prior study of fluorine and argon difficult. Where comparisons are appropriate few differences are noted. In both cases gold and copper exhibit simple physical adsorption of the gases to which they are exposed. Neither nickel material showed as much oxygen or fluorine as in the previous work, but in both cases whatever material is on the surface is again physically adsorbed rather than chemically bound. The absence of fluorine on the nickel materials may be due to the shorter exposure time. Additionally, the long time spent under vacuum combined with the heating of the substrate due to sputtering on adjacent materials may have caused the adsorbed materials to migrate elsewhere. Aluminum is the only material that appears to be chemically reactive with both fluorine and oxygen. Similar shifts in the peaks occur to similar depths. The concentration of oxygen is higher and fluorine correspondingly lower in these samples exposed to oxygen as compared to the previous fluorine/argon only exposures, as might be expected.



**Figure 7:** Atomic concentration of fluorine, oxygen, carbon and aluminum vs. sputter time on 6061-T6 Aluminum exposed to fluorine and oxygen.



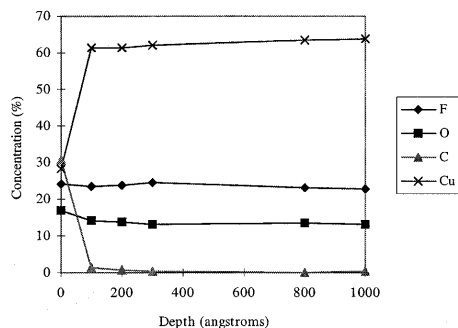
**Figure 8:** Aluminum montage on 6061-T6 Aluminum exposed to fluorine and oxygen.

## II. Ambient Air Post Dilute Fluorine/Argon Exposure

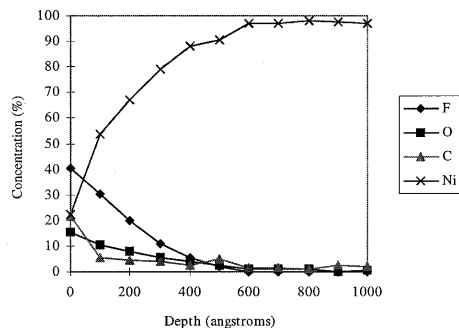
The gold exposed to the fluorine/argon mix and subsequently to ambient air is very similar to the prior two cases. Fluorine again is present, but sputters off in the first 60 seconds. The gold peak is characteristic of the pure base material. The copper material is markedly different from the prior studies. Fluorine and oxygen are present in substantial concentrations throughout the 1000 Å depth studied (Figure 9). Three peaks are visible in the spectrum corresponding to copper, at 932.6 eV, 936.3 eV and 943.5 eV. The first peak is clearly the unshifted  $\text{Cu}(2p_{3/2})$  corresponding to elemental copper. The second peak is at the right energy shift to be identified as  $\text{CuF}_2$  [7]. The third peak can be correlated to a so called "shake-up satellite" peak of  $\text{CuO}$ . Although the  $\text{CuO}$  main peak is not identified, it may likely lie near enough to the elemental peak to evade detection. Considering the presence of fluorine and oxygen well into the material, both species are assumed present based on the relative concentrations of these two elements; the fluorine to oxygen ratio is 2:1 implying equal parts  $\text{CuF}_2$  and  $\text{CuO}$ . The relative areas of the three peaks confirm this ratio. The thick fluoride layer, not observed on previous samples, is assumed due in some way to the long



drying oven cycle. This created a thick oxide layer on the surface before exposure to fluorine. Whether a larger number of surface sites were activated in this process, or the alternate morphology of a thick oxide hampered sputtering, thereby making the fluoride layer appear thicker, is unclear, albeit possible (H. Meyer, private communication).

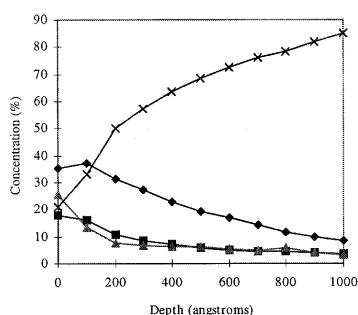


**Figure 9:** Atomic concentration of fluorine, oxygen, carbon and copper vs. sputter time on OFHC copper exposed to fluorine then ambient air.

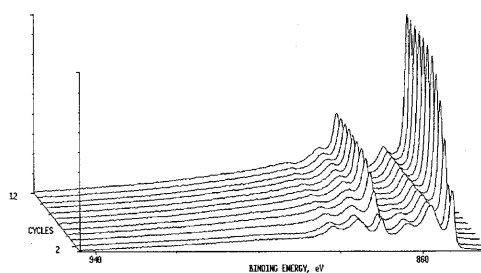


**Figure 10:** Atomic concentration of fluorine, oxygen, carbon and nickel vs. sputter time on nickel-200 exposed to fluorine then ambient air.

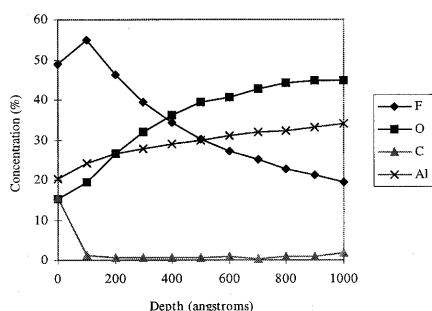
Both nickel materials showed surface conversions that were similar to each other and (after revisiting prior data) to the nickel-200 material that had been exposed to a fluorine argon mix and not to ambient air. Fluorine and oxygen were found in significant quantities 500 Å into the nickel-200 and throughout the 1000 Å studied on the electroformed nickel (Figures 10, 11). The spectrum corresponding to nickel shows three peaks throughout the depth studied on both materials (Figure 12). The unshifted peak at 852.6 eV, corresponding to elemental nickel, grows in area as the samples are sputtered, and is sharp and well defined. The second obvious peak, shifted higher by 5.2 eV, corresponds well with reported data for  $\text{Ni}_2\text{O}_3$  or nickel halides. However to obtain a reasonable fit at all depths studied, a third peak needed to be inserted at a shift of 1.0 eV which corresponds quite well with  $\text{NiO}$ , and which grows by a factor of 6 over the depth studied. As with the copper, the relative concentration of the fluoride and both oxides can only be assumed from the relative concentration of fluorine and oxygen.



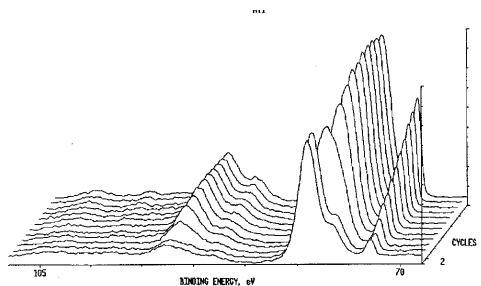
**Figure 11:** Atomic concentration of fluorine, oxygen, carbon and nickel vs. sputter time on electroformed nickel exposed to fluorine then ambient air.



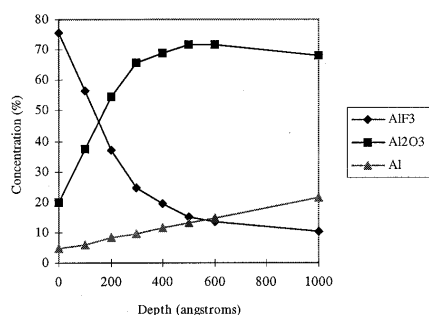
**Figure 12:** Nickel montage on nickel-200 exposed to fluorine then ambient air.



**Figure 13:** Atomic concentration of fluorine, oxygen, carbon and aluminum vs. sputter time on 6061-T6 aluminum exposed to fluorine then ambient air.



**Figure 14:** Aluminum montage on 6061-T6 Aluminum exposed to fluorine then ambient air.



**Figure 15:** Percent of area for peaks corresponding to AlF<sub>3</sub>, Al<sub>2</sub>O<sub>3</sub> and aluminum metal vs. sputter time on 6061-T6 aluminum.

The aluminum sample showed films with a similar fluoride layer and a much thicker oxide layer as compared to the previous exposure to fluorine and argon without subsequent exposure to ambient air. As before, fluorine is detected well into the material ( $> 1000 \text{ Å}$ ) but analysis of the spectrum corresponding to aluminum shows that within 200 - 300 Å most of the AlF<sub>3</sub> has been removed [8] (Figure 13). The aluminum spectrum has an extremely well resolved elemental aluminum peak, and a visible shift from the fluoride to the oxide form (Figure 14). At the surface, the material is 76.7 % AlF<sub>3</sub>, 18.5 % Al<sub>2</sub>O<sub>3</sub>, and 4.8 % elemental aluminum. At 300 Å the AlF<sub>3</sub> has dropped to 24.8 %, the oxide is 65.7 %, and the base metal is 9.4 %. By 1000 Å depth the percentages are 10.2 %, 68.2 % and 21.5 % respectively (Figure 15). As observed in the past, fluorine is detected in significant quantities below the point where the AlF<sub>3</sub> has for the most part been sputtered off. Whether this is evidence of molecular fluorine diffusing into the material, or knock-on fluorine penetration as a by product of sputtering, or impaired sputtering due to surface morphology is unclear, although the latter two appear more likely.

## Conclusion

Regardless of the preparation method, aluminum both passivates and sorbs fluorine when exposed at ambient temperatures. This is true to a lesser degree with both types of nickel and with copper if they are highly oxidized. Once aluminum, copper and nickel are passivated, where such passivation may include formation of metal oxide as well as metal fluoride layers, reexposure to ambient conditions appears to have little or no effect on the fluoride film. Only gold is resistant to passivation in all cases studied.

However, as a matter of practice these targets continue to be prey to subtle and sophisticated processes that dramatically affect recovery of the desired radioisotope and the specific activity as well. If retreatment of the surface is required after exposure to ambient conditions then the stable passivated oxide and fluoride films created on nickel, copper and aluminum do not appear to be the sole key to healthy target production. It now appears that simple adsorption plays an equal role with chemical conversion or passivation of the surface

in these cases. Except in the case of gold, adsorbed or wetted molecular fluorine layers are only possible after the surface is passivated, and then may be interfered with by contaminants. These layers are very loosely bound, and inherently evanescent. In our work they are observed to disappear over a matter of days in vacuum at ambient conditions. Like any adsorbed layer, they are temperature unstable.

The role of unwanted contaminants in the formation of a passivation layer or adsorption of fluorine has not been studied, and merits further investigation. The temperature and time stability of adsorbed fluorine can be studied easily, and does not require the complication of sputtering the sample between analyses. Additionally, it remains our hope to study the surface properties of these same materials after exposure to the multiple species environment of a [ $^{18}\text{F}$ ]electrophilic fluorine production target. We believe that work will yield a complete picture of the relative importance of adsorption, contamination and passivation in these targets.

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### Discussion:

Q: K. Dowsett: What area are you scanning over ?

A: I used the smallest analysis area that was available. It's just something like 1/10,000 in<sup>2</sup>.

Q: K. Dowsett: And did you see any variation from one point to another ?

A: We did two points on all the foils, they were essentially identical in all the cases. What I should say about it, the sputter gun profile is actually much larger, it's about 4 mm x 2 mm oval, and we could barely squeeze two of those on. But we didn't see any effects where we had cross-sputtered, in other words, we didn't sputter off all the carbon on one spot and then moved to the other spot and the carbon's gone. We still found carbon there, so that's a good sign.

C: T. Ruth: It would be interesting to go to the conditions where you know that you passivate the surface and then expose it to air briefly. That's the case we are facing, you have the passivated surface and then you have to go into the target and then put it back together. It would be good to know what you have to do to get it passivated again.

A: That's right. I assume that the second set of data represented that, but it would be nice if you could actually do the analysis. One thing is, when you do the analysis, you sputter, you remove your material, you expose it to air. It's hard to do that. You cannot take the stuff in, not sputter it and at least check that you've got a fairly good chunk of fluorine on there. On the aluminum, on the last one we had, we found a fairly good passivated dry fluoride layer when we profiled through after it has been exposed to air, and it was still there.

Q: T. Tewson: Do you have any idea whether you have any HF mixed in with your fluorine ? Fluorine typically has a little HF in it.

A: We haven't done analysis on the bottle. It's a fairly old bottle with 15 % fluorine in argon. There may be some.

### **Andy Roberts, University of Wisconsin: Fluorine Production with the Two Shoot Method**

I was actually listed to talk about *fluoride* targets, but I am not going to do that. I shall talk a little about *fluorine* targets. This is more on a practical level of how these things are operating.

This is targetry we are doing on the MC40 at Hammersmith, usual target system. The existing targetry was there for  $F_2$  production via  $Ne(p,\alpha)$ , a nickel 200 body, that was just not working out very well, low yields. It had a pretty big window, so you had to keep the beam currents low, large volume, a lot of gas. So we just started over, scrapped the whole system and take the best what is out there now, and throw it together, namely going with the two-shoot method on oxygen-18 instead of using the deuterons on neon, then going with the aluminum target business.

In the two-shoot method, you are making F-18 by shooting on the  $^{18}O-O_2$  gas with protons, you cryo-trap back the  $^{18}O-O_2$ , then you refill it up with some gas and a little bit of  $F_2$  and you get out your magical  $^{18}F-F_2$ . It's that step that is the most interesting one and what I would like to see more from Bill is if they can explain what's going on.

The target itself is just your basic gas target, it's similar to the one I stuck on the RDS at Wisconsin. There's a couple of differences, we are coming in at 19 MeV (protons). I've got a thick aluminum window on it, 0.7 mm, so we are burning a fair bit of power in there, taking it from 19 down to 14.5 MeV in the gas. It's a simple system, there aren't any target valves until you get out to the manifold which is about 15 meters away. You fill it to about 400 psi oxygen for the main shoot, generally we run at about 40  $\mu A$ . We had no problems with the windows. The O-rings on this one were Viton, they do break down after a while, after about 50 runs or so.

Just a couple of numbers. We run at 40  $\mu A$  for 30 minutes, then do a post shoot after that, fill it up with about 80  $\mu mol$  of  $F_2$ . Under those conditions, you typically get in hand about 450 mCi of  $F_2$  and make some 65 mCi of FDOPA. Once we ran for a couple of hours at 45  $\mu A$  and we made as much as 1.7 Ci of  $^{18}F-F_2$  and a couple of hundred mCi of FDOPA. The best specific activity we were able to get out of this target was something like 20 mCi/ $\mu mol$ .



We saw the same kind of carrier effects that you see with a C-11 target, when you drop the amount of  $F_2$  that you put in there, and your yield drops. The reason for that is a mystery. You would expect that kind of thing if you would fill the target to lower levels you are sticking a bigger percentage to the goop that is in the target, but that doesn't seem to be the case. If you look at the amount of  $F_2$  you put in vs. the amount of  $F_2$  you get out after irradiating it, it's rock solid, even down here at the low levels. You're still recovering the stuff, so that's not the reason that the yield is low. If you have to make a longer post shoot, that may also make sense at the lower levels of  $F_2$ . But there is something else going on, we can never recover the stuff with the low levels. I think there is some potential for some interesting work down there if you want to try to get higher specific activity. We are not talking about specific activities that are really high, we are talking about things where you can use a little of an expensive precursor instead of a lot of expensive precursor.

One quick comment since we have been talking a lot about exposing these things to air. This is a case where it absolutely makes no difference. We leave it open on a shelf for weeks, slap in on, flush a little  $F_2$  gas through it, don't even irradiate it. The yield's just as high if you shoot as it is several runs down the line.

C: T. Ruth: We use the same type of system for  $F_2$  production. The nice thing with it is that you can do the oxygen irradiation, recover the oxygen, and do a fluorine irradiation and do FDOPA, do another fluorine irradiation, do another FDOPA or other  $F_2$  kind of reaction without ever recharging the target because there is sufficient F-18 left in the target that you can do several post irradiations.

A: Typically we didn't do that. We just get it all out and split it into different cells and do various things with it.

Q: J. Clark: Andy, just a quick one. Do you have any evidence of a time course of recovery of this high specific activity fluorine ? If you leave it in the target a long time, did it get more and more difficult to get it out ? From Bill's data, the cold fluorine is really deep down. And if your time course is allowing the F-18 to do some sort of kinetic exchange through the depth then it gets worse and worse as time goes on. So if you left it till next morning...

A: Yes. I haven't left it that long, but I've left it all day and not seen a change in the yield. So it's not something dramatic, it's not that you have to pull it off within half an hour or you lose it all. On the order of several hours afterwards for the second shot, and it's not drifting through.

### **Richard Ferrieri, Brookhaven: Carbon Dioxide Adsorption on Aluminum**

Something Bill presented caught my eye, and I just wanted to show one overhead slide. Six years ago, at PSI, I had shown data from electron induced desorption studies on 6061 aluminum and what we call reactor grade aluminum which is a very soft aluminum. We looked with a mass spectrometer at the carbon ion being thrown off the surface. One sees a spectrum much like this on a clean surface, on the 6061 Al there's two states of carbon, you see some of a third state on the softer aluminum. I had coordinated this with a temperature profile and surface binding energies of these states. This time scale is in seconds, and the longer the seconds, the higher the surface binding energy, so this peak here represents something that is more tightly bound.

We did an exposure study to 100 ppm  $CO_2$  and you see a growth of this peak here that coincides to that little satellite peak here. From this early work here you can see how aluminum tend to form sponge like aluminum oxide layers which can gather  $CO_2$  carrier and

throw it back out during irradiation and taint your specific activity of the  $^{11}\text{C}$ - $\text{CO}_2$ . I am wondering whether anybody has thought about potential passivants for the  $^{11}\text{C}$  target. The fact that you can passivate, create a surface of aluminum fluoride with the aluminum oxide being buried now 300 angstroms deep, whether this might be a surface less prone to gathering carbon and throwing it back out during irradiation.

C: J. Clark: What about all these people who put oxygen in their nitrogen ? You really put in a very active passivant. Some people can only get there carbon targets to work with oxygen in it. That may be a clue to your passivation proposal.

C: R. Ferrieri: I think the effects we see with oxygen are only temporary. I would like to try a fluorine passivation on an old aluminum target to see what effect that might have.

Q: T. Ruth: Wouldn't you be concerned about forming  $\text{CF}_4$  then ?

A: A. Roberts: It doesn't happen. I've tried it. We didn't find anything except for  $\text{CO}_2$  and a little bit of  $\text{CO}$ .

C: T. Tewson: Mike Berridge has a technique whereby he washes his target out with phosphoric acid. This provides him with a passivated surface which brings the  $\text{CO}_2$  out without having to add oxygen to it. It also brings out the  $\text{CO}_2$  in a form that allows him to make acetone. If he adds oxygen to his target mixture he can't make acetone from the  $\text{CO}_2$ .

C: R. Ferrieri: This is actually a technique we used for new aluminum targets before we pressed them into service. When we see that a target becomes dirty or we changed a window we do a plasma etching. We have a mixture of neon and 5 % oxygen. We fill the target and do a bombardment at 25  $\mu\text{A}$  for 10 minutes. After repeated etchings we see the fall-off in activity which tells us that the specific activity is in fact increasing. That's an in situ way of doing it. The target gas can be bought as a research grade from Matheson, so you're not introducing any other carbon during that process.

C: ...(inaudible)... Adding oxygen is a good thing to do. We found the longer we use our targets without disrupting them, the better they perform in fact. About phosphoric acid treatment. This is something we used 10 years ago. That had the effect of improving recovery from those targets.

C: J. Link: I have the same experience. As our specific activity goes up, we do add 500 ppm of oxygen. We have no change in the amount of carbon dioxide recovered from our target. That's one of our most stable parameters. We do get pretty much theoretical yields out of the target. I did have one experience, after everybody said 'o, my yields out of the target go down'. When I was trying to improve my specific activity I ended up putting a trap in place, that was a basic trap to trap  $\text{CO}_2$  out of my target gas. When I did that, all of a sudden a month or two later my yields started to go down. What had happened was a very small amount of basic dust from the solid adsorbent had gone into the target. I am not saying anybody else in this room has done something that dumb. What I found was that after 150 feet of tubing, after several months there was just a very basic coating on the inside of my target that we just wiped off, got rid of the adsorbent trap and everything went back to normal.

I am not saying that anybody else is doing that, but I do know that the simple explanation of oxygen isn't going to hold for all of us. I am getting sometimes 50  $\text{Ci}/\mu\text{mol}$ , it doesn't make any difference in target recovery. And those are statistically significant numbers.

## David Schlyer, Brookhaven: N-13 Ammonia Production in a Cryogenic Target

We tried to make ammonia directly in a cryogenic target using carbon dioxide as the target material. We reported some time ago on fluoride production from O-18 labeled CO<sub>2</sub>. We tried to extend this to ammonia. This is done cryogenically, it's a little difficult to see the nice reflections inside get confusing, it's essentially a can where you put liquid nitrogen in and freeze the carbon dioxide at liquid nitrogen temperatures.

So these are the results that we got from that. It's interesting, down here the carbon dioxide irradiated in a frozen state, we get very high percentages of nitrate and nitrite, just about 10 % ammonia. You'll hear more about what happens in the liquid state, but when we add water to it, it changes a little bit, but not significantly. We still get a very high percentage of nitrate and nitrite. The difference is that we are seeing a different kind of chemistry going on depending on the temperature of the carbon material. We are seeing different radiolytic processes going on. When we did this irradiation on a water target we essentially produced 95%+ ammonia when you irradiate this water in a frozen state, but as you know, if you irradiate it in the liquid state, you get essentially 95 % nitrates and nitrites. So we have changed the chemistry by changing the physical state of the material.

Anyway, this is the chemistry that is going on in the ammonia target when you convert ammonia which is the primary product (from work that was done by Bob Dahl and other folks a long time ago) by oxidation. First you get ammonia, then you gradually oxidize it through a series of radical processes to the nitrates and nitrites. What we are doing by freezing the target is inhibiting these processes.

Q: R. Dahl: Dave, when you bombard solid CO<sub>2</sub> you get ammonia. Obviously you are not adding hydrogen to that to begin with, so there must be hydrogen as a contaminant which isn't much which I find surprising. Could you comment on that ?

A: Well, the hydrogen comes from the water, I think, because we rinse through this system to remove the nitrates and nitrites from the surface. When you do this bombardment in the carbon dioxide target, the nitrates and nitrites stick to the surface, so we can remove the carbon dioxide by cryogenic pumping, then rinse out with a little water and then you get the nitrates and nitrites out in the water solution. So it's a very simple system in that sense. There may be traces of water left in the target during the next irradiation. That may be the source of hydrogen for the ammonia.

## Gerald Bida, Shreveport: <sup>13</sup>N Production from <sup>13</sup>C-CO<sub>2</sub>

We took a standard aluminum body target that we had been using for some prototypical experiments looking at perhaps different ways of making N-13 ammonia at 11 MeV protons. The slurry target, while it works reasonably well, has obviously a long history of problems being fraught with clogging frits and so forth, so I just reasoned: what better material to try and get N-13 recoils out of a gas ? I reasoned that loading up my target in combination with some sort of an aqueous environment ...

What we did was we actually flayed the top portion of the aluminum target body so that could just get a little more of <sup>13</sup>C-CO<sub>2</sub> in the target itself, but the flayed portion was in fact out of the beam strike. I didn't look too much on variations in the level to which I filled the target with water. I stuck with roughly one third of the target volume was water and the remainder was the <sup>13</sup>C-CO<sub>2</sub>, obviously for no other reason than just to increase the amount of C-13 target material in the beam strike. My recollection here is that the data in black lettering was just using natural abundance <sup>12</sup>C-CO<sub>2</sub> as the overpressure gas, reasoning that if I had the O-16



content of natural abundant  $\text{CO}_2$  - if this was going to work at all – we'll get some level of recoils going into the water and take a look at what the product distribution is. Then, if there's anything going on at all with the C-13 in the  $\text{CO}_2$ , with all the baseline saturation activity that I accumulated using natural abundant  $\text{CO}_2$  I could then make some kind of a reasonable statement like 'the C-13 is actually doing something, at least improving the saturation activity'. As you can see in the very last column, we indeed affected a reasonable increase in the overall saturation activity. Unlike some of the results we just saw from Dave Schlyer, the limited amount of data that I do have for the  $^{13}\text{C}$ - $\text{CO}_2$  under the conditions that we took a look at, I do see in fact reasonable quantities of ammonia. Keep in mind, however, I actually had to add a slight overpressure of hydrogen gas. In the absence of hydrogen gas, it's still 64 %, that's still usable, but the addition of the hydrogen apparently got it's attention in terms of making quite a bit more ammonia.

# Multi-particle Bombardment and In-target Chemistry of Porous Carbon Materials

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## Introduction

Motivation for research into tailoring the porosity and dimensions of some form(s) of carbon for the charged particle production of nitrogen-13 was provided nearly a decade ago in response to the limited performance of the slurry target [1] and to design parameters proposed for a next generation cyclotron. This tailored carbon would be one component of a two-phase target system, a combination that has met with a respectable level of success [2-6]. In addition to the desired feature of *in situ* [ $^{13}\text{N}$ ] ammonia production via p or d irradiation, a discussion of the rationale and materials processing results for a candidate porous carbon (PC) preparation are given elsewhere [6].

The 7.4 MeV proton irradiation of candidate materials has now been extended to include deuteron, helium-3 ( $\alpha$ -3) and helium-4 ( $\alpha$ -4) bombardments. The natural abundance material has promise as a target to produce  $^{13}\text{N}$  from deuteron bombardment or proton bombardment of an enriched version, as well as the production of all four commonly used PET isotopes from helium-3 bombardment of a two-phase system. Regarding helium-3, while the specific activity of carbon-11 from a PC/water target is not expected to be high, it is anticipated that it could support preparation of clinically important [ $^{11}\text{C}$ ]labeled natural products (e.g., sugars, fatty acids and amino acids). As before [6], experimental results will be compared to the escape fraction estimated via a compound-nucleus based model.

## Experimental

### *Target irradiations*

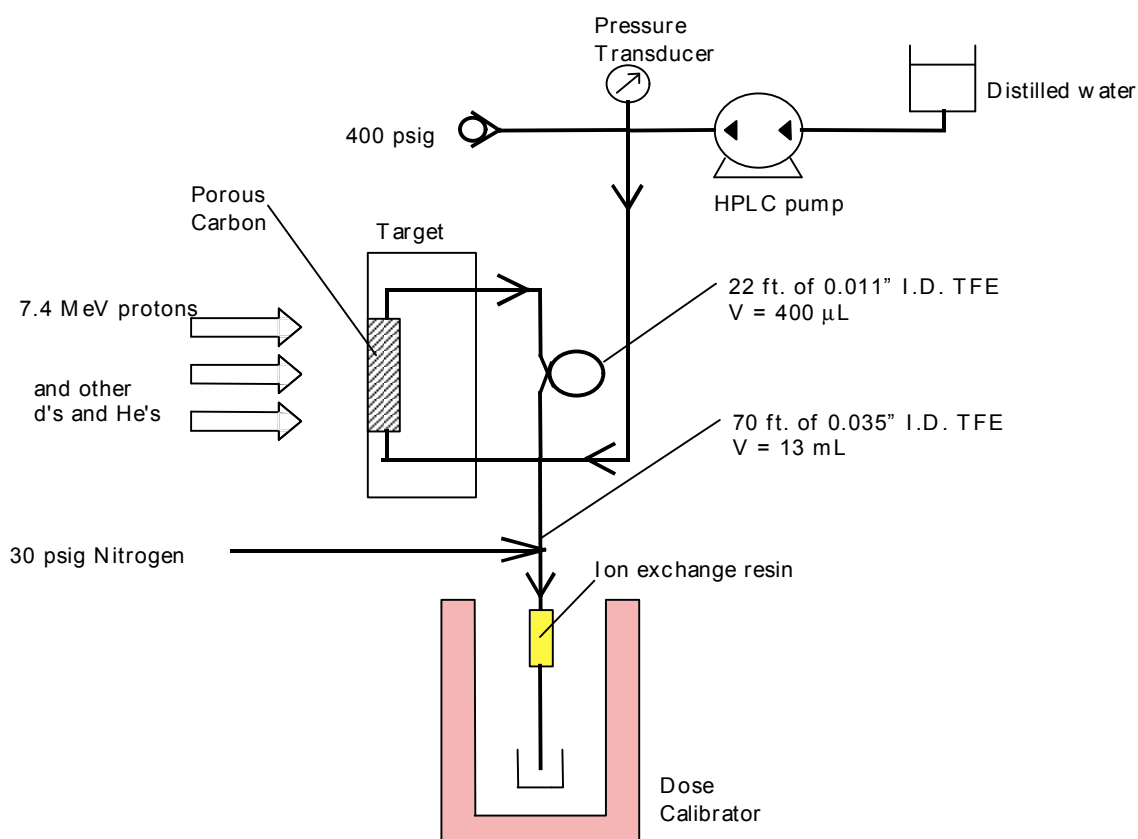
Irradiations were performed on the Duke University PET Facility's TCC CS-30 four-particle fixed energy cyclotron. Charged particle beams were collimated to 10 mm diameter and general beam shape and position monitored via four electrically isolated graphite leaves within the collimator assembly. Target assemblies utilized were standard CTI RDS 112 units; however, two different target body materials were used, i.e., aluminum and silver. Further, these bodies differed in water flow migration pattern through the porous carbon. Beam strike dimensions for both targets were 2 mm deep by 10 mm diameter. Target designs allowed for both water cooling of the target body and helium cooling of the target foils.

On-target particle energies were manipulated via a judicious selection of vacuum (Havar: Hamilton Precision Metals, Lancaster, PA), target (Havar) and degradation (Grafoil: Fiber Material, Inc., Biddeford, ME) or tantalum foils. These foils were positioned between the vacuum isolation and target body foils. Because of the necessity to minimize target foil deflection away from the porous carbon caused by the pressure drop through the carbon and ancillary delivery lines, it was necessary to operate the single-pass helium window coolant at elevated pressures. This helium thickness was taken into account in the beam-on-target

calculations. The estimated (TRIM [7]) energies were 5 MeV ( $D^+$ ), 14.8 MeV ( $^3He^{2+}$ ) and 22.5 MeV ( $^4He^{2+}$ ). The  $D^+$  and  $^4He^{2+}$  energies were chosen in order to minimize interference from other nuclear reactions [8,9]; whereas the  $^3He^{2+}$  energy was selected to closely coincide with that of the He-3 RFQ linac [10].

### Experimental procedure

The experimental arrangement and procedures were a modification of those previously reported [6]. A schematic of the apparatus used for target evaluation is shown in Figure 1. System pressures were varied by adjusting the length of 0.011 in. ID tubing placed at the exit end of the target assembly. This process facilitated variation of the rate of water flow through the porous carbon. For low flow rates (ca. 1 cc/min), after EOB, radioactivity was washed from the beam strike and narrow-bore tubing to a point just past the 30 psig nitrogen isolation valve. The aqueous radioactive bolus was then transferred to the collection site via the 30 psig nitrogen (see Fig. 1). At the higher target water flow rates, the transit time was sufficiently short to preclude use of the transfer  $N_2$  gas. Here, water flow continued until a decrease in dose calibrator activity was observed.



**Fig. 1:** Apparatus for porous carbon irradiations.

### Product identification

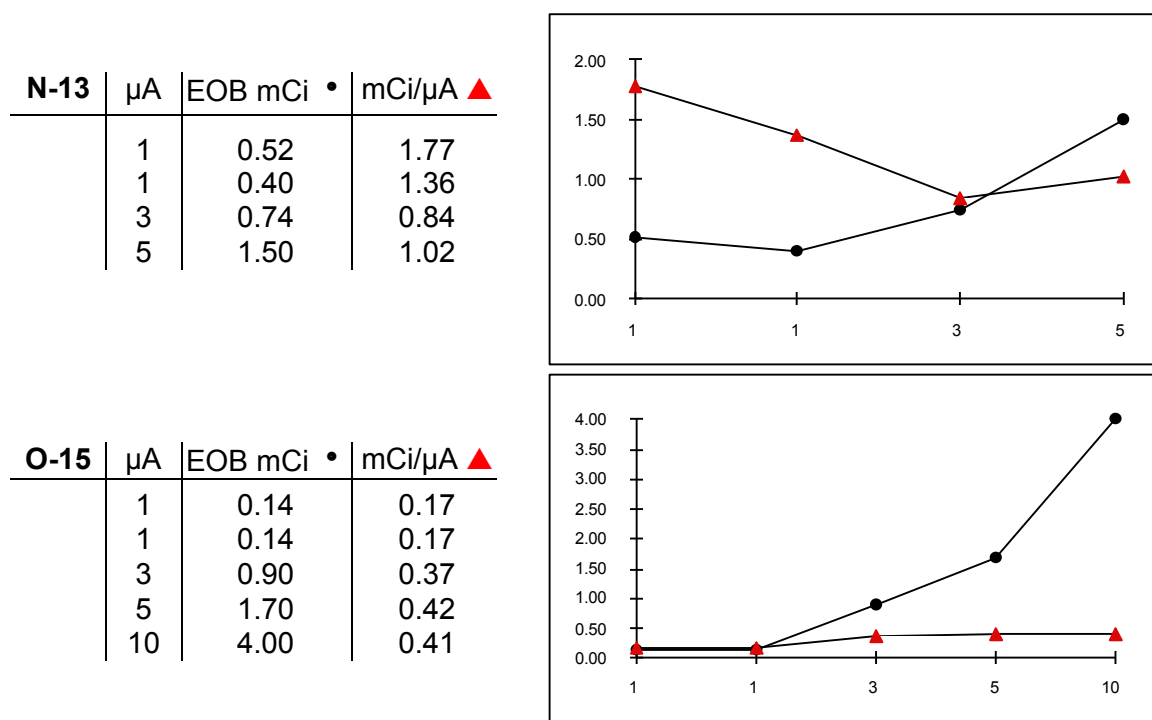
Radiolabeled product analyses were mainly confined to  $\alpha$ -3 irradiations. For this purpose, a combination of radioanalytical methods and chemical reactant/adsorbent traps were used. Scouting identification included the use of Waters Alumina N Sep-Pak and Alltech IC-OH cartridges, Bio-Rad AG11A8 ion retardation resin, Ascarite, soda lime and strong aqueous hydroxide. In the aqueous effluent from  $\alpha$ -3 irradiations,  $[^{18}F]F^-$  was identified via r-TLC (silica gel; 95:5 acetonitrile/water) and r-HPLC (25 cm Whatman Partisil10 SAX; 0.05 M phosphate buffer; pH 3.3; 1.0 cc/min), oxidized and reduced  $[^{13}N]$  species via r-HPLC. Gaseous C-11

species were identified via r-GC(Alltech CTR I; 1/4" x 6 ft; ambient; 50 cc/min helium). No attempt was made to identify the form(s) of O-15 product(s); however, as no gaseous O-15 was observed, the product is assumed to be H<sub>2</sub><sup>15</sup>O.

## Results and Discussion

### Deuteron and Helium-4 Irradiations

The two different proprietary porous carbon lot samples used in the previous investigation [6] were also used in this study, recognizing that these formulations were tailored for interaction with protons. Unfavorable results with lot # 277-40 limited its use. Thus, results reported herein are for lot # 275-22 only. An aluminum target body that had single entrance and exit ports for water flow through the porous carbon was used for irradiations with d and  $\alpha$ -4. All d and  $\alpha$ -4 experiments were conducted at a 1 cc/min target water flow rate and bombardment times were 5 min duration, except the 10  $\mu$ A  $\alpha$ -4 run (10 min). Beam-off target pressures ranged between 300-350 psig. Radionuclides observed from deuteron irradiations included <sup>17</sup>F from <sup>16</sup>O(d,n) and <sup>13</sup>N from <sup>12</sup>C(d,n), whereas only O-15 from <sup>12</sup>C( $\alpha$ ,n) was observed in the  $\alpha$ -4 studies. No attempt was made to quantitate the F-17 data.



**Fig. 2:** Summary of D<sup>+</sup> and <sup>4</sup>He<sup>2+</sup> irradiation of Sandia porous carbon lot # 275-22

Results for d and  $\alpha$ -4 irradiation of 275-22 plus water are given in Figure 2. For N-13 production from d, a five-fold increase in beam current resulted in a three-fold increase in EOB activity; however, for O-15 production, a five-fold beam current increase yielded a twelve-fold increase in EOB activity, whereas the increase was twenty-eight-fold for the irradiation at 10  $\mu$ A. It is recognized that, in this two-phase target system, a majority of the heat generated is removed via mass flow of water through the porous medium plus vaporization of this same water, as opposed to convective heat transfer to the target body cooling water. For a 1 cc/min water flow rate, roughly 42 W can be removed via vaporization. After accounting for mass flow and higher operating pressure ( $\geq$  300 psig), at  $\geq$  5  $\mu$ A of 22.5 MeV  $\alpha$ -4, steam is undoubtedly the fluid present in the two-phase target, a situation that effectively renders the target more carbon dense. Thus, the dramatic O-15 increase with  $\alpha$ -4

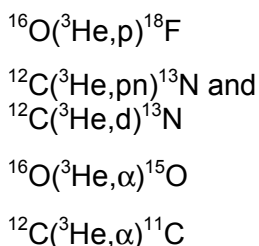
beam current can be rationalized to a certain extent. Referring to Figure 1, steam production was observed for the 10  $\mu\text{A}/10\text{ min}$   $\alpha$ -4 experiment. Thirty seconds after the irradiation commenced, radioactivity began accumulating in the dose calibrator plus alternating segments of water and gas were observed in the delivery line. Given the delivery line volume, radioactivity would not be expected in the dose calibrator for a ten minute irradiation; however, water undergoes a 1500-fold volume increase upon transition to steam. These particular observations present an interesting alternative to target operation and activity transfer.

The thick target yield (TTY) for N-13 production from  $^{12}\text{C}(\text{d},\text{n})$  is roughly 19 mCi/ $\mu\text{A}$  for 5 MeV deuteron bombardment [11]. A carbonaceous material with a density that is 19 % of solid carbon and 78 % void volume would have an expected TTY of 6.7 mCi/ $\mu\text{A}$ . The average TTY observed here for N-13 production using porous carbon is indicative of a 19 % recovery fraction from the solid matrix. Similarly for O-15 production, the average TTY observed translates to a recovery fraction of 5.8 % when compared to the weight adjusted yield for solid carbon (G.T. Bida, unpublished data from BNL).

The reduction of water density in the transition to steam will contribute to a change in recovered activity in two ways. The activity produced will increase due to a larger weight percentage of the desired (solid) target material, but recovered fraction will decrease due to the higher likelihood of remaining in or recoiling into the same solid. The extent to which these effects offset each other and affect the total recovered fraction stated above is unknown.

#### *Helium-3 Irradiations*

At 14.8 MeV  $\alpha$ -3, it is possible to generate all four of the biogenic PET isotopes via:

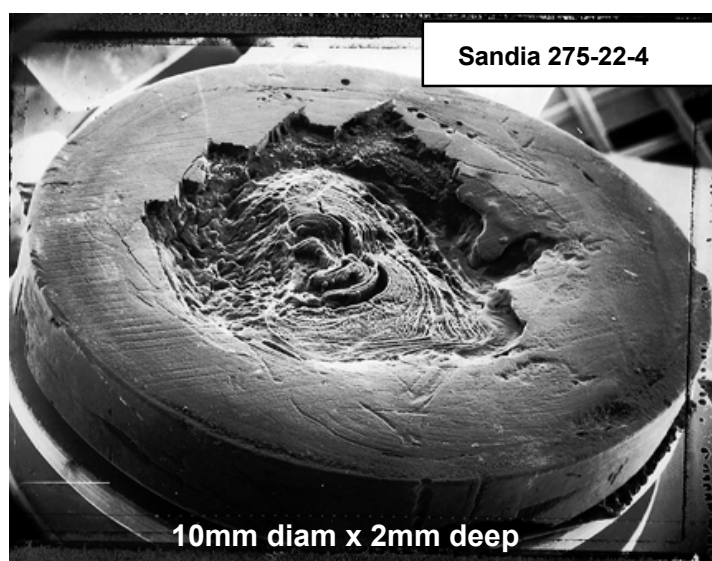


This subsection reports preliminary results for the product identification and yields observed for helium-3 irradiation of a two-phase target consisting of porous carbon plus flowing natural abundance water. Data for changes observed in the porous carbon as a function of beam current are also presented.

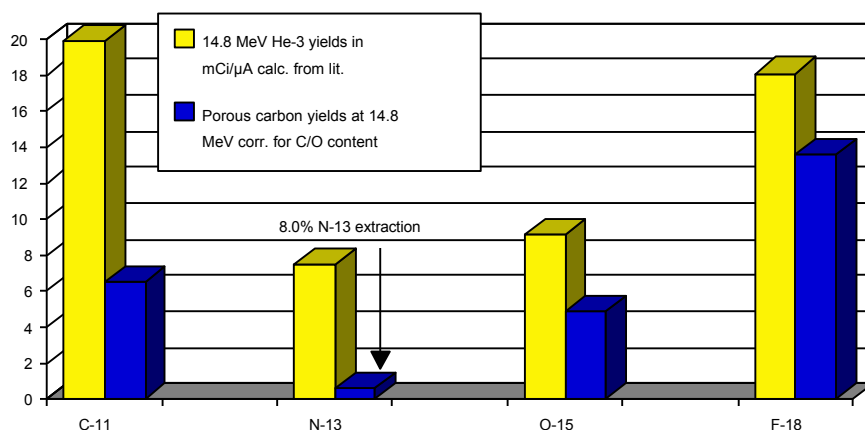
In addition to the aluminum target body described above, a silver target body was also used for the helium-3 experiments. It comprised a single inlet plus four exit ports that afforded flow from the center of the porous carbon uniformly outward to the perimeter of the material. Experiments were performed at 3 cc/min target water flow rate and two beam-off pressure regimes: the first averaged 208 psig, the second averaged 34 psig. Irradiation times ranged from 5-30 minutes; all irradiations were of 20 min duration for the carbon morphology experiments. Currents used in the morphology study were 0.5, 1, 2 (two runs), 3 (three runs) and 5  $\mu\text{A}$ . Between each run, the target was disassembled and the condition of the PC was noted.

Results for the  $\alpha$ -3 irradiation of 275-22 plus water are summarized in Figures 3 and 4. In addition, the following radiolabeled species were identified: F-18 as fluoride ion(r-TLC and r-HPLC), N-13 as ammonia (15-20 %), nitrite (55 %) and nitrate (r-HPLC) and C-11 as 50:50 CO/CO<sub>2</sub> (r-GC). The observed [ $^{11}\text{C}$ ]labeled products are consistent with the behavior of recoil

C-11 in a water vapor environment [12]. Prior to intentionally monitoring the state of porous carbon as a function of beam current, observed target pressure drop and chronologically decreasing yields signaled a potential carbon degradation mechanism. Initial deterioration of the PC was observed at 3  $\mu\text{A}$ , with the final condition (shown is irradiated side) presented in Figure 3. At 3 cc/min, about 15 W of heat can be removed via mass flow, another 125 W is removed via water vaporization. These observations are indicative of a carbon degradation mechanism that may involve the presence of steam [13]. It is interesting to note that PC did not undergo deterioration after 12  $\mu\text{Ahr}$  of 7.4 MeV proton irradiation; however, our  $\alpha$ -3 observations are not totally surprising as alpha tracks are notorious for producing significant short-range damage in materials [14].



**Fig. 3:** 10X SEM of porous carbon after 9.5  $\mu\text{Ahrs}$  of 14.8 MeV  $\alpha$ -3 irradiation.



**Fig. 4:** Observed and calculated thick target yields for helium-3 irradiation of 275-22.

Thick target yields for C, N, O and F from helium-3 were calculated from literature cross sections and adjusted for the beam strike weight fraction of C and O. In Figure 4, these yields are compared with the experimental yields measured for helium-3 irradiation of porous carbon/water. The N-13 extraction efficiency from  $^{12}\text{C}$  ( $^3\text{He}$ , d/pn) is estimated to be about 8 %, while C-11 extraction is about 33 %.

**Tab. 1:** Comparison of calculated and experimental TTY for 5 MeV  $\text{D}^+$  and 14.8 MeV  $^3\text{He}^{2+}$  irradiation of PC/water.

Product nuclide	Calc. TTY [mCi/ $\mu\text{A}$ ]	Exp. TTY [mCi/ $\mu\text{A}$ ]	Max. TTY [mCi/ $\mu\text{A}$ ] <sup>1</sup>	Extraction efficiency (%)	
				model	expt.
$^{11}\text{C}$ from He-3	13.5	6.5	20	68	33
$^{13}\text{N}$ from He-3	4.13	0.6	7.5	55	8.0
$^{15}\text{O}$ from He-3	8.71	4.9	9.1	96	54
$^{18}\text{F}$ from He-3	12.4	14	18	69	78
$^{13}\text{N}$ from 5 $\text{D}^+$	4.65	1.25	6.75	6	19
$^{13}\text{N}$ from $\text{H}^+$ (0.091 $\mu\text{m}$ fibers)	0.116	0.177	0.212	55	83
$^{13}\text{N}$ from H (0.3 $\mu\text{m}$ fibers)	0.147	0.160	0.263	56	61

<sup>1</sup> calc. from lit. cross sections and corrected for carbon (or oxygen) content of target material.

#### Comparison with Model

Yields were calculated for the d and  $\alpha$ -3 reactions using a modification to the model previously developed for proton irradiation of PC/water [6]. The model assumes alternating layers of carbon and water and a compound-nucleus interaction only.

For each layer of either solid or liquid, four histories are calculated. At the point where the bombarding particle enters the layer of choice, the maximum and minimum energy reactions are calculated. For purposes of this description, these are called case 1 and case 2. In the center of mass frame, these correspond to the forward directed and backward directed recoils, respectively. The kinematics may be such that the minimum energy recoil is either backward or forward in the lab frame. The maximum energy recoil is always forward directed. The energy loss of the recoil in each case is calculated in alternating layers of solid and liquid. The starting layer is determined by the layer of origin and the recoil direction. The calculation proceeds until the recoil has insufficient energy to traverse a layer. If the layer is not solid, the recoil is scored as recovered. Similar calculations are done for the reaction at the point where the bombarding particle exits the layer of choice. For purposes of this description, these are called cases 3 and 4.

These four cases are given equal weight in the calculation. For example, presume that the forward directed recoil originating from the point where the bombarding particle enters the layer of choice stops in a solid, but the other three recoil cases stop in a liquid. Then the recoil escape fraction for *this layer only* is 75 %.

The differential thick target yield for the reaction and layer of choice is calculated by integrating the cross sections over the energy window that is determined by the entrance and exit energy of the bombarding particle for this layer. That thick target yield is multiplied by the layer specific recoil fraction above. The thick target yields for all layers are summed to give

an entire target calculated yield. Results of these calculations are compared to the experimental findings in Table 1.

With the exception of N-13 production, the calculated and experimental TTY's differ by roughly a factor of two or less. The reasonable agreement with C, O and F production via  $\alpha$ -3 irradiation suggests that these helium-3 reactions are adequately described by the compound-nucleus model. Previously, helium-3 reaction cross sections calculated based on the compound-nucleus model have shown qualitative agreement with experimental values [15]. When consideration is given to the simplifying assumptions and boundary conditions used in the model versus the uncertainties encountered in the experimental data, the factor of two difference in experiment vs calculation is quite remarkable. For example, the modeled results fall prey to variations among literature cross sections used. Moreover, the simplifications required to make the calculation possible at the level of a spreadsheet program are quite significant. Only two positions (front and back) of each layer are used, as well as two center of mass recoil angles ( $0^\circ$  and  $180^\circ$ ). A larger number of equally weighted cases in the center of mass distribution or throughout each layer could be incorporated. This would involve recoil tracks in the off axis direction. The assumption of a microscopic geometry of layers versus the real geometry (clumps of spheres) may also be open to challenge. Meanwhile, the experimental data are plagued by an uncertain continuum of water/steam phases, as mentioned earlier, due to the difficulties in removing heat from these types of two-phase targets. Other experimental problems include porous carbon degradation, variation in products generated and uncertainties in exact on-target energies.

These inherent uncertainties notwithstanding, the deuteron and helium-3 production of N-13 warrant further consideration. For a compound-nucleus reaction, maximum, minimum and most probable recoil energies can be easily calculated [16]. For the 5 MeV  $D^+$  case, the most probable recoil energy affords nascent N-13 with a range of about 0.8  $\mu\text{m}$  in carbon of 2.25  $\text{g}/\text{cm}^3$ . For 14.8 MeV  $\alpha$ -3, the  $^{11}\text{C}$  and  $^{13}\text{N}$  most probable recoil ranges are comparable (about 2  $\mu\text{m}$  in 2.25  $\text{g}/\text{cm}^3$  dense carbon [7]). Thus, the low recovery fraction for the  $D^+$  case can be reconciled to some extent; however, insufficient recoil energy does not seem to be the most likely explanation for the poor  $^{13}\text{N}$  recovery. Given the results shown in Table 1 for modeling the 7.4 MeV proton case [6], experimental uncertainties are more likely to be the reason for the observed discrepancies.

Porous carbon/water targets may still be of some utility for the deuteron production of  $^{13}\text{N}$  from natural abundance carbon. However, the structural integrity of the material as it exists now is unsuitable and more work in this area is suggested. Should it be possible to improve the survivability of the porous material under more intense irradiation, not only might the apparent recoil recovery fraction increase (due to more carbon remaining in the beam strike region), but the use of this material as a target for routine production of  $^{13}\text{N}$  could be justified.

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## Decomposition of Carbon-Rich Target Materials

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### Introduction

The consumption of carbon under charged particle irradiation has been observed for both proton irradiation of a two-phase target composed of amorphous carbon/water [1] and helium-3 irradiation of a two-phase target composed of microcellular porous carbon/water [2]. If these materials in this target configuration are to function effectively as alternatives for [ $^{13}\text{N}$ ] ammonia production, it is important that the degradation phenomenon be understood and mitigated. The non-ionizing environments of microwave and heat plus the uniquely hostile conditions of heterogeneous sonication [3] were chosen to initiate the process of decoupling possible radiation-induced decomposition mechanisms from processes resulting from elevated temperature and pressure due to beam heating and target operation.

In order to determine the possible effects of charged particle irradiation on solid carbon target materials used for N-13 production, various carbon materials [carbosieve, buckminsterfullerene, pyrolyzed poly(styrene sulfonic acid), and porous carbon from poly(acrylonitrile)] were subjected to conditions of microwave, ultrasound, and steam at elevated temperature and pressure. The mass and composition observed before and after exposure to these conditions were investigated in terms of their relevance to material loss [1] due to radiation-induced decomposition and/or a carbon-steam reaction [4].

### Experimental

#### *Ultrasound.*

The carbon samples were placed into small glass vials and weighed. Deionized water was added to each vial to cover the sample. The vials were septum capped, vented and then individually suspended in a sonicator with the water level of the sonicator just above the water level in the vial. The samples were exposed to sonication for 10 min., and then filtered and washed with acetone to remove excess water to facilitate the drying process. Upon evaporation of the acetone, the samples were reweighed.

#### *Microwave.*

The carbon samples were placed into small glass vials and weighed. Deionized water was added to each vial to cover the sample. The vials were septum capped, vented and then individually placed in a microwave oven and heated on high power for 1 min., allowed to cool, and then filtered and washed with acetone. Upon evaporation of the acetone, the samples were reweighed.

#### *Elevated Pressure and Temperature.*

The  $\text{C}_{60}$  carbon sample was placed into the sample holder of an oxygen bomb device from a bomb calorimeter. Deionized water (50 mL) was added to the bomb with the sample holder placed just above the level of the water. The bomb was placed in an oven at 150-200 °C overnight in order to establish equilibrium between the liquid water and its vapor. The bomb was depressurized and the sample was allowed to cool. The  $\text{C}_{60}$  sample was then filtered and washed with acetone.

## Conclusions

All samples were examined under a reflected light microscope (ca. 4-20X magnification) before and after the experiments (Figure 1). Under the conditions investigated, both microwave and ultrasound had essentially no effect on sample mass or composition. Results were inconclusive for the condition of elevated temperature and pressure. Sample composition appeared to be unchanged; however, no data were available in regard to the sample's mass due to contamination that occurred during the heating process. Unfortunately, the inconclusive nature of the elevated T/P experiments does not allow elimination of a possible carbon-steam reaction as the sole carbon consumption explanation or as part of a detrimental synergistic process involving the charged particle environment.

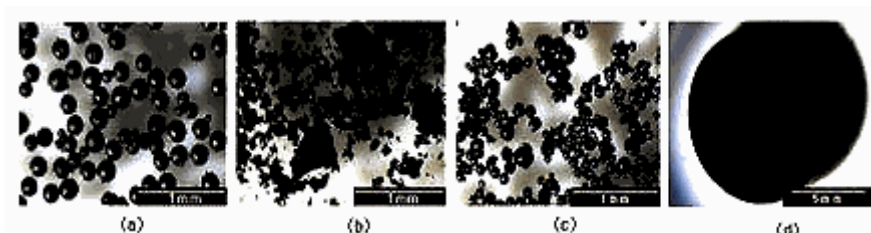


Fig. 1: a) Carbonsieve, b) C<sub>60</sub>, c) Sulfonated poly(styrene), d) Poly(acrylonitrile)

## Acknowledgments

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## **Quartz Micro-Fiber Target for Production of O-15 Ozone for Pulmonary Applications - Computer Modeling and Experiments**

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Ozone is an oxidative gas with high chemical reactivity, produced in the troposphere through a complex interaction between sunlight, nitrogen dioxide, and oxygen. The U.S. Environmental Agency (EPA) has set a standard for ozone not to exceed 0.12 ppm for more than one hour more than one day per year. 150 million people in 96 major regions of the U.S. are exposed to up to three times this concentration. The enormous costs of compliance to the EPA air quality standard makes a cost-benefit analysis based on quantitative data highly desirable. Acute toxicity is better understood than chronic toxicity. Ozone induces toxic damage to the lung at a small but specific site, the alveolar region most proximal to the terminal bronchiole (sparing the distal regions), but no method has been available to experimentally measure the dose gradient through the nasopharynx, trachea, individual lung lobes, and extra-pulmonary tissues. After successfully completing interspecies investigations with mechanically ventilated animals (supported by existing funding), we hope to be able to justify human studies using  $^{15}\text{O}$ -ozone and positron emission tomography (PET) if accompanying unlabeled ozone can be reduced to acceptable levels.

The current target (five designs previously tested) produces  $^{15}\text{O}$ -ozone with the extracted 27 MeV proton beam of the Duke CS-30 cyclotron as shown in Figure 1 (dimensions, materials of construction, and typical operating parameters as indicated). Quartz fibers were very recently obtained, courtesy of Michael Fay at Schuller International (Mountain Technical Center, Glass Technology Laboratory, Littleton, CO 80127). They are 99.90 %  $\text{SiO}_2$  and were received in a 90 % dense state with a mean diameter of 1.3  $\mu\text{m}$  (standard deviation 1.56, range from 0.11 to 9.98). In accordance with Schuller advice, we heated them in vacuum to 1000  $^{\circ}\text{C}$  to densify, reduce surface area, and drive off 8 % chemically absorbed water. The fibers were then fluffed apart by hand using a dissecting microscope to obtain 99.5 % porosity before cutting into disks and stacking with a slight interference fit into the polished stainless steel target tube. SEM characterization of the resulting final fiber diameter distribution is planned.

Some possible recoil escape events leading to the formation and recovery of  $^{15}\text{O}$ -ozone and related radiochemical species are depicted schematically in Figure 2. The recovery of labeled gases is accomplished by flow in a reverse direction to the beam, because the excitation function for  $^{16}\text{O}(\text{p,pn})^{15}\text{O}$  [1] drops from 64 mb at the 26.7 MeV entrance energy on the gas to 30 mb at the 22 MeV exit, and the transit time is reduced for the richer activity fraction recovered out the front target port.

A Monte Carlo computer program named LAYERTAR [2], which incorporates TRIM [3], uses a clipped Gaussian 8 mm beam geometry and uniform thickness flat plate equivalents to model the fiber layers for the above described target geometry. A new version called FIBTAR is under development to address the issues of fiber geometry, including the effect of varying array and diameter distributions. FIBTAR was implemented to predict batch target yields for a fixed entrance and energy condition and varying combination of fiber mass and argon gas

pressure. The results shown in Figure 3 indicate the recovered yield is flat over a wide range of fiber mass loadings, a result of increasing total yield being countered by rising loss of activity due to burial in a subsequent layer as the argon pressure decreases.

LAYERTAR data was used as input to another modeling code using Mathcad software, which takes into account transit time losses due to flow through the target and 30 meters of 0.25 mm bore Teflon delivery line into a 3.6 cc coil loop of tubing in a dose calibrator, and then into a 850 cc capacity Lucite syringe (designed to fit into a dose calibrator). For the case of a 4  $\mu$ A bombardment of 1  $\mu$ m fibers, equilibrium reverse-flow through the target, and a two minute collection in the syringe, the Mathcad model gives results for 100 mg of fiber and 12.6 atm (170 psig) of argon in the target as follows: predictions of 78 cc/min flow, 0.780 mCi in the loop, and 22 mCi in the syringe. The experimental results for these conditions were 71 cc/min flow, 0.234 mCi in the loop, and 5.6 mCi in the syringe. The experimental loop and syringe activity are 30 % and 25 % of the model values, which may be caused by the following: actual target fibers are not flat plates and have a range of sizes, misalignment of the beam may cause losses to the walls not reflected in the model, there may be chemical losses of labeled ozone and possibly oxygen in the target and delivery system, the gas temperature indicated by the thermocouples is about 35 °C which affects argon density, the flow rate was less in the experiment, gas may be more mixed than forward slug flow, and measurement errors should be considered (beam current, gas pressure, flow rate, dose calibrator readings). The model has gas temperature density factors, gas mixing provisions, and a labeled product absorption loss rate constant dependent on calculated fiber surface area and gas flow. We plan to apply these parameters in future modeling.

The experimentally measured decay under the conditions described above is shown in Figure 4. Curve stripping resulted in 44, 10, and 2 min components indicating 5.6 mCi of  $^{15}\text{O}$  at end of collection, with corresponding values of 3.6 %  $^{13}\text{N}$  and 0.36 % of the 44 min half-life. The latter does not fit any likely proton reactions on target materials, and a procedure to collect data for a longer time might permit the observation of combinations like  $^{11}\text{C}$  and a longer lived component (perhaps  $^{18}\text{F}$ ).

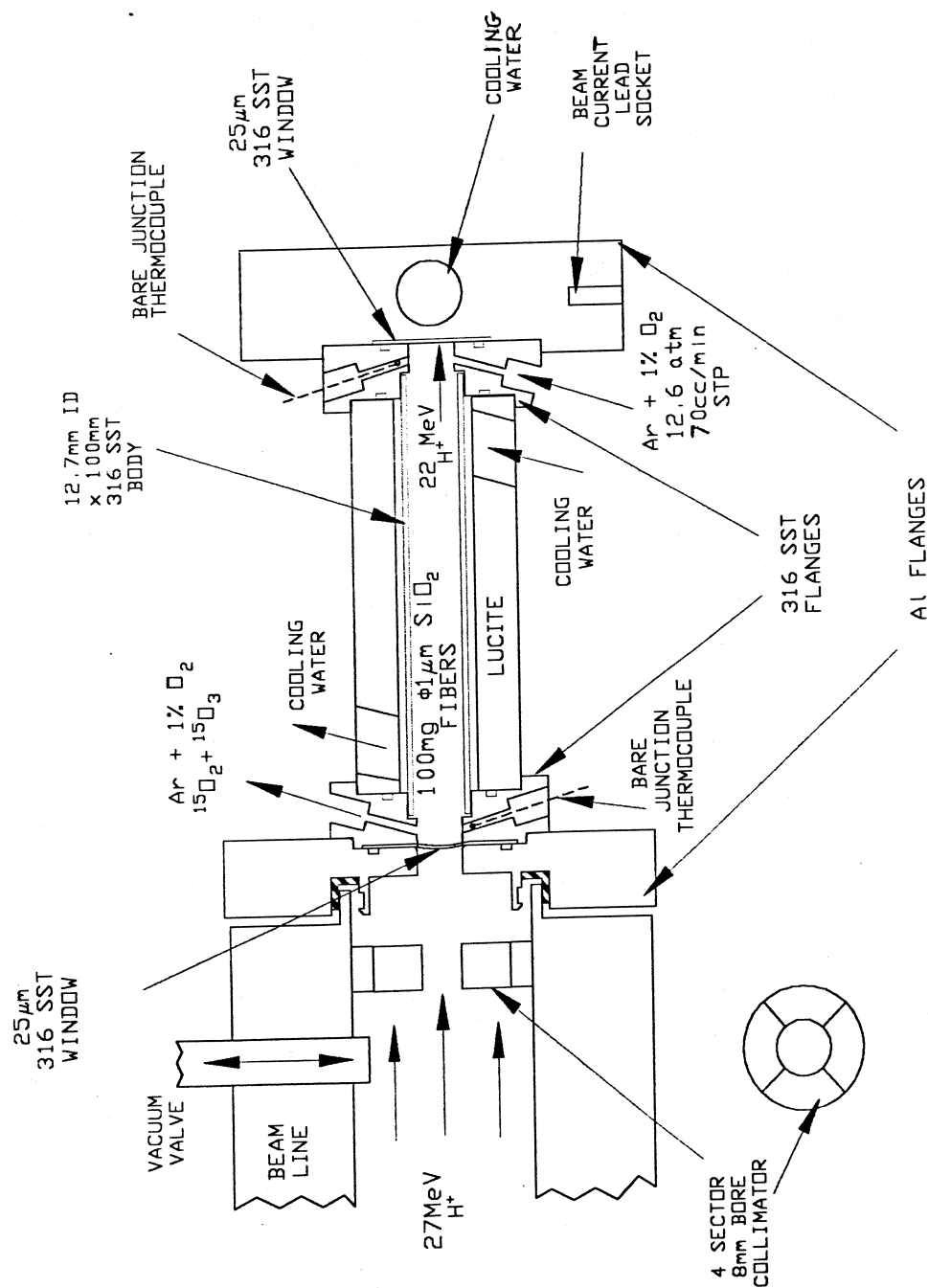
Methods of isolating and identifying labeled ozone are the focus of ongoing work. Using Draeger tubes, we have measured about 90 ppm of unlabeled ozone under the above conditions, indicating the likely presence of labeled ozone. We have done experiments with rats mechanically ventilated through a trachea tube and observed lung distributions typical of ozone. Using cryogenic trapping and release from both silica gel and liquid oxygen has shown promise, and we plan to implement radio-GC to analyze for ozone and oxygen delivered from the target both before and after the long delivery line. We anticipate labeled ozone/oxygen fractions out of the target in the range of 1 to 10 %.

The production and recovery of radiolabeled ozone for pulmonary applications using this target system is feasible, and needs further development and optimization. We have found computer modeling a valuable design tool, and an indispensable guide in analyzing the many interacting parameters prior to planning cyclotron experiments.

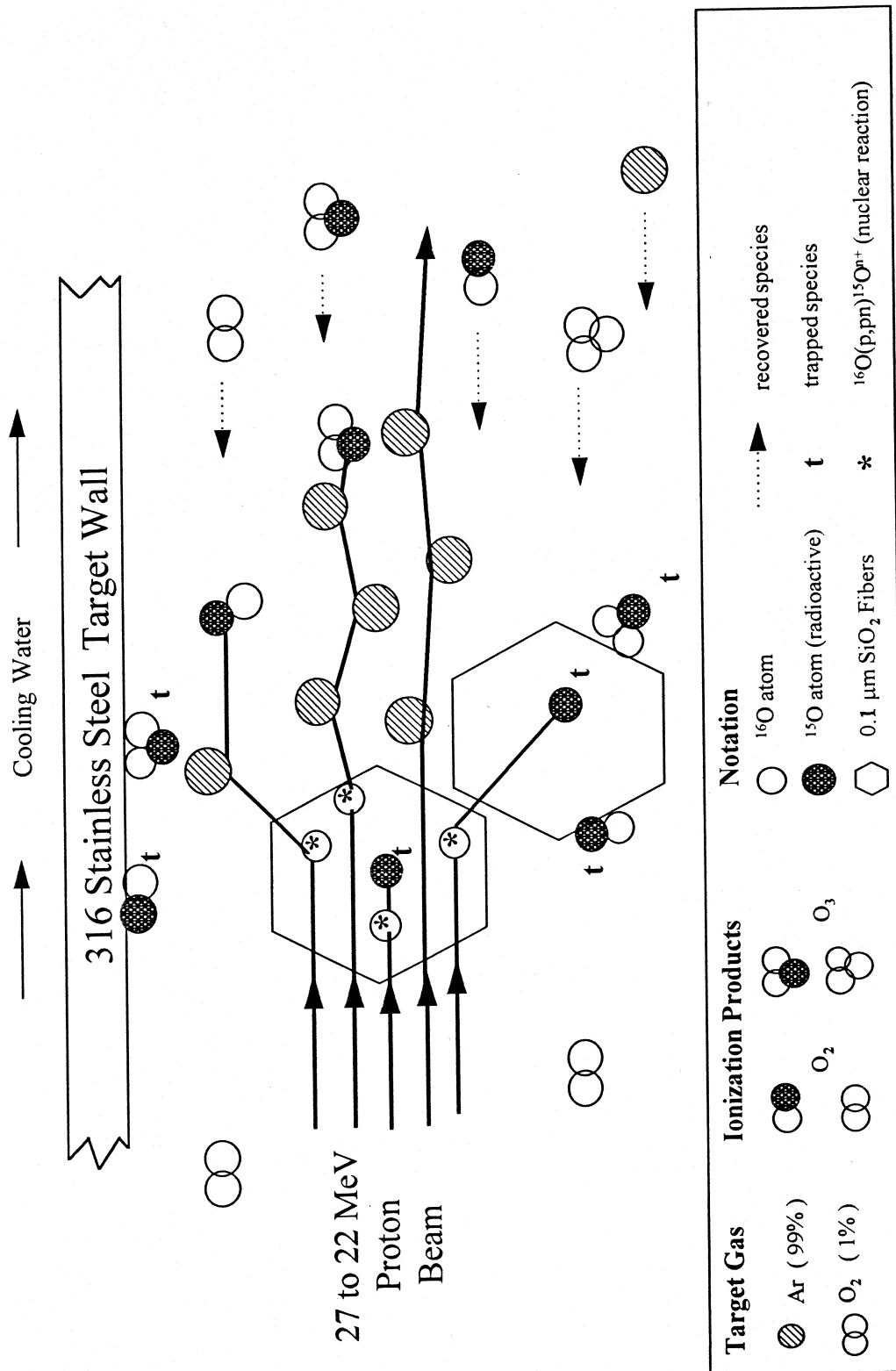
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**Fig. 1: Target Design**



**Fig. 2:** Saturation Yields as a Function of Combinations of Fiber Mass and Argon Gas Pressure in a 10 cm long Target with Proton Entrance Energy of 26.7 MeV. For Reference, a Natural Oxygen Target Yield is 88 mCi/ $\mu A$  and a Solid  $SiO_2$  Target Yield is 47 mCi/ $\mu A$ .

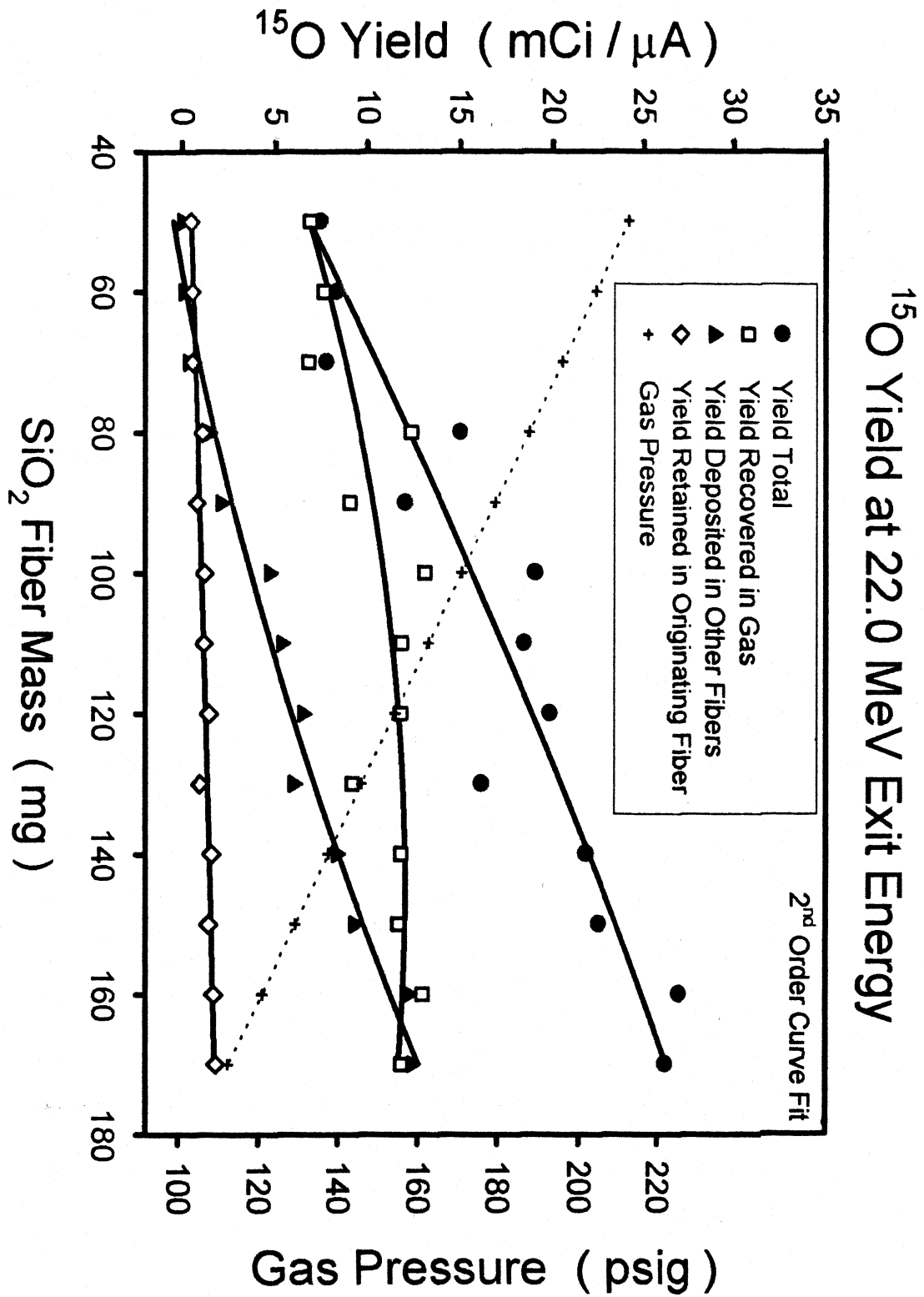


Fig. 3: Recovered Activity for 2 min Collection at 4  $\mu\text{A}$  proton Current

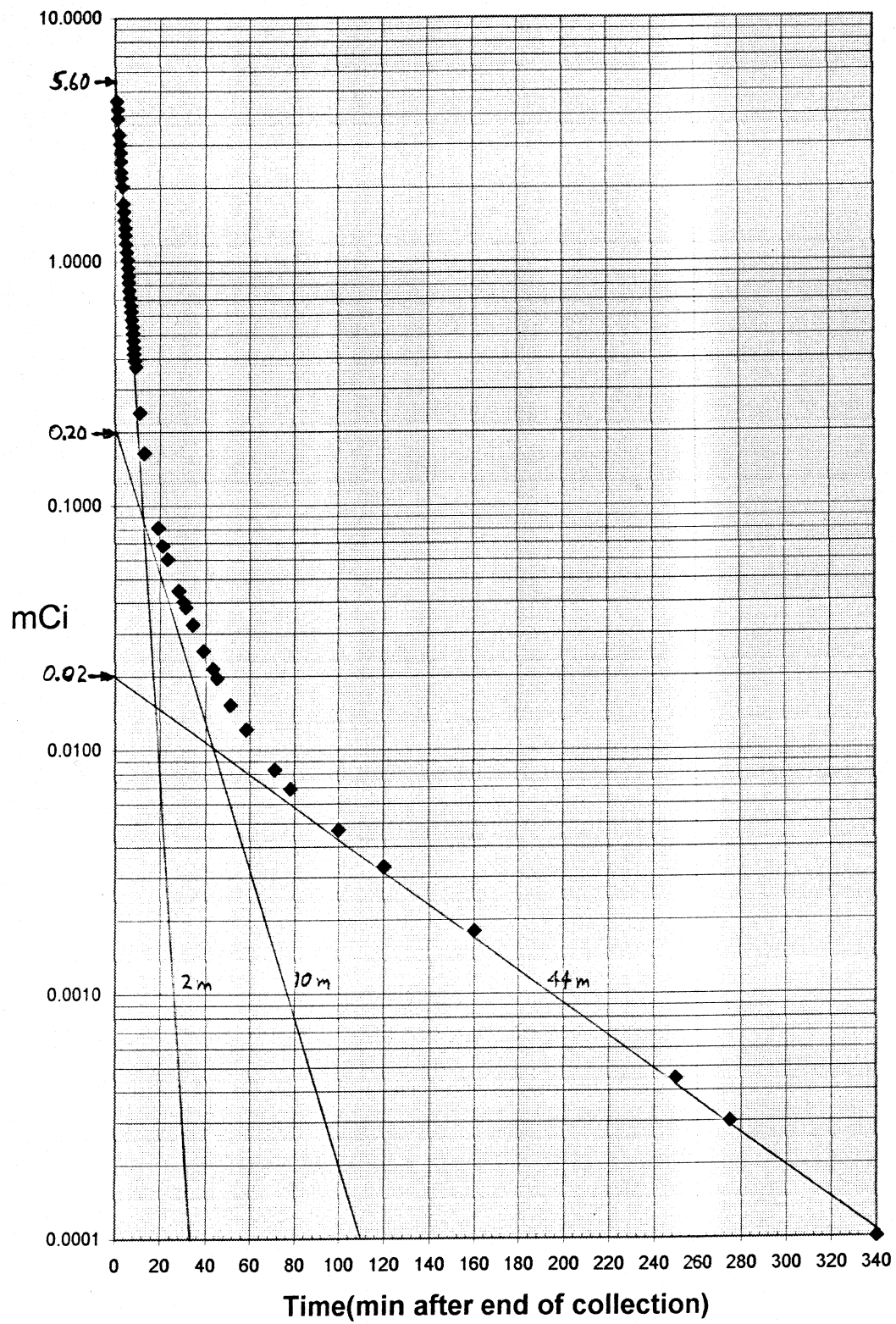


Fig.4: Nuclear and Chemical Recoil Ion Events



## New Strategies in Designing Ultra-Microscale Syntheses

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### Introduction

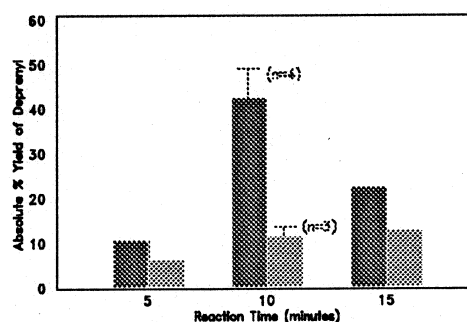
Conventional practices within PET rely heavily on using macroscopic amounts of starting materials in order to sustain chemistry at a reasonable level with some labeled precursor. This process typically requires a rigorous purification scheme during final formulation in order to separate tracer concentrations of the labeled product from these macroscopic amounts of unlabeled starting material. The goal of this work is to ultimately identify and develop new techniques that would allow us to sustain chemistry between tracer concentrations of  $^{11}\text{C}$ -methyl iodide, and near-equivalent amounts of labeling substrate to the degree that both reagents are consumed to a reasonable extent by the process. Of course, at true tracer concentrations one is faced with the challenge of how to spatially confine a pair of reactants.

The integration of photochemical processes with chemistry carried out in supercritical fluids has provided a new strategy for engineering "designer" microscopic reactors suitable for ultra-microscale syntheses using methyl iodide. This strategy capitalizes on the ability of organic co-solvents to "cluster" within binary mixtures of supercritical fluids thus creating structured molecular cages around potential reactants, and thereby limiting their ability to diffuse throughout the medium [1,2].

### Results

We've designed an optical cell capable of sustaining fluid pressures up to 5000 psi and temperatures to 125 °C that also permits the introduction of UV light through a fiber optic. In actual application of this approach, we have probed microscale photosyntheses of L-deprenyl using methyl iodide, and have carried out systematic studies measuring reaction yields as a function of UV stimulation, temperature, fluid pressure and composition, reaction time, as well as reagent concentration. We've established that the combination of UV light, heat and pressurized fluid can promote efficient chemistry yielding 45 % of deprenyl from as little as 0.9  $\mu\text{mol}$  of the nor substrate (25 times less than in conventional practices), and tracer concentrations of methyl iodide. We found that UV light can increase methylation rates by as much as 4-fold over similar reactions conducted with just heat, and suspect that this is due to geminate radical recombination within the cage.

**Fig. 1.** Effect of light and reaction time on L-Deprenyl yields: 4000 psi SCF ( $\text{CO}_2$  + 5 % acetonitrile), cell at 95 °C, 0.9  $\mu\text{mol}$  substrate. (absolute % yield of deprenyl vs. reaction time)



We've been employing well established photochemical systems to probe the structure of these solvent cages. For example, geminate radical recoupling reactions induced by the photochemistry of certain benzyl ketones are ideal for investigating distance-dependent interactions between radical fragments [3].

The implication of these "designer" microscopic reactors to PET tracer synthesis is that one not only can conceive of carrying out ultra-microscale syntheses, but perhaps stereoselective

syntheses as well. If one introduces a chiral co-solvent into the supercritical fluid, the molecular cage created by such a co-solvent cluster may possess a certain spatial orientation that is conducive toward selective stereochemistry within the cage.

### Acknowledgments

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### Discussion:

Q: T. Ruth: What is the mechanism you think in terms of why the one case ...(inaudible)... to butanol worked and then you are changing the pressure...

A: I think it has to do with the methyl versus the ethyl projection. But I'm quite surprised that a slight difference in size like that really has that enormous an effect. What I want to do is a series of systematic studies varying the size of those projections in methyl, all the way up to maybe a benzyl group.

Q: T. Ruth: Has anyone done electro-molecular calculations?

A: No, that's something I actually to broached with a few people of our department, but they don't seem to want to jump on this. I don't know whether it's too labour intensive or there is no interest there or whatever. Actually there is somebody at UCLA, Davis, that really gets into this sort of thing, so I was going to try to work up a collaboration with her.

Q: First time you did that, did you question your data, Rich? When you got that result?

A: I ran it several times. Well I questioned my student's data.

### Jeanne Link, Seattle: Gas Phase Methyl Iodide Production

I was asked to just briefly represent what we presented in part last year on making methyl iodide. That was something that I was privileged to work on with John Clark after Peter Larsen came up with the idea. And what I have from methyl iodide just to review, and this has been shown before, is that at University of Washington we make methane external to the target, we make CO<sub>2</sub> in our target because we only have one carbon target. We make methane, and then we have very small 1/8" o. d. stainless steel trap that's less than 25 cm long in which we trap the methane. Then the methane, while it is trapped, is flushed because there is hydrogen and nitrogen gas coming through here. Then helium is passed through the Porapak trap, through a quartz tube, in which there is iodine vapor, and then free radical processes change the methane to methyl iodide. We trap the methyl iodide in a cold trap with liquid argon, this is just a 1 mL Corning test tube. What you can't see is there's another vent

out of this tube that goes to a bag. We trap all our products, so we have quantitative yields. We warm this trap and go through a few grains of ascarite to trap any  $I_2$  that has come through, most of the  $I_2$  is trapped here, and we go into whatever reaction vial we are using for the methylation. The total process takes about 10 minutes. It's about 4 to 5 minutes after production of methane, our main time is required for making the methane and emptying our target which is quite large.

We have seen this specific activity, this is the question that Rich and David were asking. Our yields with the methyl iodide system, except when I am varying conditions, are 30 – 55 % radiochemical conversion. The specific activities can vary quite a bit. They start at about 3,000 Ci/mmol and go up to 50,000, so that's the highest I have. This was a time in 1995 when I was developing the chemistry and my  $I_2$  concentration was still low. Then we were getting fairly high yields. At that point I had been making methane with a nickel oxide catalyst that was over 10 years in the tube and has been used for a long time. I let a student use it and they blew the tube out and I lost my catalyst. My specific activity was very bad and I had to condition it for two months to get the specific activity back up.

This is what I have been getting when I went to a remote system instead of a fairly manual system. I didn't know I'd have so much variability. What I found was surprising to me. These are not bad specific activities, some of them are very good specific activities. My specific activity is not from the target, it is actually in the system. I developed my system because I have very little space into a system that I pull out of the hot cell and just put in when I need it. That may be a mistake, because what I see is that when I do multiple runs at a given day my specific activity starts out at about 5,000 and goes up during run 2 and run 3. It also seems that I have small leaks in my system where I get methane, probably from the atmosphere on the Porapak and not fully cleaning it off before I start my runs.

I have shown that the yield is totally dependent on the  $I_2$  concentration by looking at vapor pressure. I am still using single pass because I am trying to understand the kinetics of it. Tom's going to talk about recycling and recirculating.

I've now taken the same idea and changed from iodine to chlorine because I spent less time on methyl iodide and have been trying to make phosgene for a  $\beta$ -adrenergic tracer (CTP12177). I have taken that same methyl iodide system including the Porapak trap and added a valve that goes to a new system for phosgene. The traditional method for making phosgene is to pass chlorine and methane over a copper chloride catalyst. It has certainly been in the literature for years. I have taken chlorine gas, added it to methane and just passed it over quartz at high temperature, that also was in the literature. I converted it to carbon tetrachloride which is what you usually get with the copper chloride catalyst.

The conversion is depended on temperature. You can go to low temperatures and you get predominantly monochloromethane, then dichloromethane, then chloroform and then carbon tetrachloride. The radioactivity trace for two runs of a GC (these are gradient) ... dichloromethane and monochloromethane come out in here, at low temperatures – again, this is a quartz tube, I have no catalyst -, this is the trichloromethane, this is carbon tet' which goes to phosgene. At the higher temperature in quartz you get virtually quantitative conversion. (Q: What's the residence time in the tube?) - It's flowing at 25 mL per minute, the tube volume is approximately 5 or 6 mL. It's very short, it's very fast. In fact, what I found out recently is my yields go up. My conversion to phosgene as I go through the iron is about 50 %, my specific activity goes up if I'm faster. That's the state of what I am doing with this free radical type work.

Now the phosgene has problems, because you next go through an iron catalyst and our specific activity is up to 9,000 Ci/mole, not as high as I do for the methyl iodide at this point.



Q: J. Clark: Jeanne, just for the record, what method did you use for measuring specific activity for methyl iodide?

A: For measuring specific activity I wasn't able to measure the carbon tetrachloride, so for the methyl iodide I'm labeling metaraminol to make meta-hydroxyephedrin and then I'm doing HPLC and doing a full linear regression on each with five points at least per curve on each product. So it's the final product and it goes through some more steps before I measure it. But it's only at one step.

Q: Jeanne, you mentioned in your article on this, that the conversion to methyl iodide was dependent upon the concentration of iodine. You got your best yields at a certain concentration of iodine vapors in the system. How can you control that iodine concentration if that is indeed in that case?

A: It is dependent on the iodine concentration, I never reach saturation. The problem is twofold. It's in the paper, the exact number. The yield goes up and then it goes down as I go up in concentration. I control right now the concentration with just heating and looking at it for the right color. I'm installing a system with a photodiode to look at the color and then control the heating, as a feedback mechanism to the actual vapor concentration, which is a color of metric, it's linear with UV absorbance at 450 nm and even down at 350 nm, because you saturate it at 450 nm. So I don't control it very well right now. I can just look at it and get close. And that's probably why I have more variability and what I'm building in is a feedback mechanism with essentially a photodiode type.

Q: But do you think it's going to be possible to do adequate control of that if that is indeed a critical parameter or is it just luck of the draw? What it happens to be is what you get? And you want to try and predict...

A: Well, I never get less than 30%. You have a lot of control over when you heat up the power pack, when you lift it or don't lift it. It's not that hard to get within the right amounts. My normal yields are between 40 and 50 %. I don't see any problem with recirculating. I think probably that's the easiest way for most people to control it. I'm still trying to really understand this reaction. So probably the easiest for most people would be to recirculate although then you add a pump, you add a huge trap of ascarite. You get big volumes and it turns out.... Well, why don't we get into that discussion after Tom presents his data? Because he has the opposite case. What happens for me is then I start dissolving the methyl iodide and make more of it but it dissolves in the condensed iodine.

### **Tom Ruth, TRIUMF: Recirculating Methyl Iodide System**

We start with a methane target because we only have one target, because everything we are interested in is making methyl iodide. I talked about the methane production system yesterday and essentially we come out of the target through a valve through the Porapak trap in liquid nitrogen and up into the waste. For the quality control people, we trap all our waste, we don't put it up the stack (in case anyone is listening). We have a heater here for  $I_2$  to get the iodine there, we are very close to Seattle and we've talked to Ken and Jeanne about this whole process, and we recognize the importance of having the color. We've looked vaguely at different ways of having a photodiode as well to try to monitor that. (Q: Is this visual spectrometry, Tom ?) Yes. Optical spectrometry with all our eyes to see if this is the same color that Jeanne had. Then essentially we trap this and then we start the recirculating system. We have a pump here, we pump through the iodine in this chamber, this is tricky to get the right temperature, you have a flowing gas, and where do you measure the temperature ?



I think we haven't fully optimized the temperature, nor the temperature for getting the iodine. Nevertheless, we trap the methyl iodide here. We have also a coil to trap the iodine. That's something if you are building these systems you have to be careful that if you don't have the temperature right or the flow, you can in one quick pass transfer iodine from this location to this location. If you get a big layer of iodine on this end, the iodine will trap the methyl iodide. So this is something you have to watch for.

There's several recirculations before we optimize the trapping of the methyl iodide, at which point then we simply flush the system out to get rid of any methane and then we transfer the product. We have a radiation detector here and here as well as in the product. We monitor the pressure in the system and the flow. (The remainder of the talk was not recorded.)

#### Discussion:

Q: ...(inaudible)...Can you mention the methylphenidate specific activity? Does it have a very strong UV absorbance?

A: No, it's a real problem where it really responds. We're using UV, but it's still... we've made a curve ...

C: And it's probably the sample, inject a big sample.

C: T. Ruth: We've struggled with specific activity with LAH systems. But with this system it's so... People were resistant to the idea of having to go through this because once you get a system working you don't want to change, but once we got this system up and running everyone who ever mentioned LAH in our lab, people strangle him.

Q: R. Ferrieri: Would you or Jeanne like to comment on a comparison on methyl iodide made from this method versus methyl iodide from conventional methods in terms of doing labeling? When you look at the radio-HPLC traces is this a cleaner method? I think you mentioned that on the phone to me.

A: Yes, I forgot to bring that slide. The UV, if you just take just the gross UV from the preparative HPLC, with the conventional method you see lots of various UV active things and if you do it with the gas phase, the only thing you see is essentially the precursor plus the radioactive peak. It really cleans it up very nicely. At least for the raclopride.

Q: R. Ferrieri: With your methylphenidate, out of curiosity, I don't know about your synthetic methods. Comment on the ...(inaudible)... distributions? I mean, the gas we're getting about 40 % of ...(inaudible)... from whatever, it's probably the acid hydrolysis when you're stripping of the blocking agent on the amine group. I'm just wondering whether any of that might be the result of our method of making methyl iodide, stuff carrying over which could be causing this diastereimization of starting material. And I wondered whether you saw any differences?

A: We recently saw problems with getting the retro instead of getting the O-3. But that was due I think we were down to very small amount and Joe divided it up and we probably had too much space to that. But other than that, that's the first time we've encountered that problem. And we think that was related to the base concentration, but I don't think it has anything to do with the labelling itself.

Q: T. McCarthy: Have you just taken this straight out of the NDO system and using the activity right away did you have it to put across any scrubbing tube?



A: We have that famous trap here but that's an ascarite trap. As Jeanne said, she uses a very small one, because she does a single path, but because we are recirculating we have a fairly large trap. But that doesn't seem to cause any problems.

Q: T. McCarthy: And you are using that as dry ascarite or you moisten it?

A: No, it's dry.

C: J. Link: It's interesting, because I thought that would give a problem, because his ascarite trap is about the size of a 600 mL beaker and mine is a Luer slip fitting, which is half full and there is virtually no difference.

C: We got the GE-box and we are packing ours with quite a bit of ascarite and we moisten it a little bit but we're not using anyway near that amount.

A: T. Ruth: Since we've seen Jeanne's 'micro-micro', compared to ours, we've cut down the volume of it, but we still physically have a fairly large amount. Is it 50 mL worth of ascarite, Joe ? It's less, so we've cut it back quite a bit.

C: But Steve will also show that we also have to clean ours a little bit to get rid of other contaminants. And then the reactivity is just phenomenal.

A: T. Ruth: The thing is that you can do is tens of these runs without doing a cleanout. If you haven't done this, you really must, this is the only thing I can say.

Q: The limiting factor as far as the number of runs is just keeping the iodine in?

A: Keeping the iodine in and I guess if your traps get too messy, you want to clean. So if you start taking something apart it's probably easier to clean the whole thing up and start afresh. But it really is a transfer of iodine from one side to the other.

Q: P. Larsen: I have a question about the single pass reaction. Have you considered to try to do the reaction with bromine instead, in order to produce monobromomethane, that could also be very convenient starting material for methylations?

A: J. Link: I think we should be looking at a lot of the halogen reactions. I have no interest in that compound right now, but someone else was talking to me about it. And I expect we'll be hearing a lot of people trying this.

C: Yes, the ... group did a lot of work to make the methylbromide some while back..

Q: Tim Tewson: The raclopride synthesis has a reputation of not being very robust. Do you find it more robust with this method than with the other method?

A: T. Ruth: Without a question. In the liquid phase making methyl iodide that way we struggle with yield and specific activity both of those issues are totally gone. We never have had a problem with producing or delivering really high specific activity in decent yields of raclopride.

C: So it's cleaner, it's more robust and the specific activity is better. Sounds like a good system.

A: T. Ruth: Yes.

Q: (hardly audible; about changing tubes)



A: T. Ruth: No, we only have two tubes and we just rotate them. - Except for the ones we drop.

C: J. Link: I guess this is my favourite thing about this system besides the fact I don't have to have a THF still any more. I work with two organic chemists, one who is in the audience. And the thing I like about methyl iodide so much is that if they're are doing something that's unstable instead of... it used to be with lithiumaluminumhydride they go, ok how much time?.. and I go well, ten minutes, twenty minutes, five minutes, I'm not sure. You know, it'll be about that, but I would never be quite sure on the minute. Now all I do is, I put it in the cold trap and I say, now go get your precursor ready and you tell me when you are ready. And then when they are ready I just lift it up and bubble it through. So that's the really nice part of this.

### **Richard Ferrieri, BNL: Methyl Iodide – Conventional Method**

I have one slide on the conventional system that we have. For those that are still planning on doing synthesis using the conventional lithium aluminum hydride that's it. Take a good heart look at this, because in two weeks this is going to be history. We're taking possession of a GE-box due to be installed at Brookhaven June 24th, so I'm looking forward to that. This has been in our lab for about two years, this is the conventional method of cold trapping the  $^{11}\text{C}$ - $\text{CO}_2$  on-line in a small volume  $\text{LiAlH}_4$ . And our experience has been, we've tried diluting solid LAH, Fluka, in THF. We haven't gone to the extreme of distilling our THF, although this would probably help matters. We actually had worse specific activities under these circumstances. What we are doing now, is we are back to using the Aldrich right out of the bottle. The 1 molar, we don't bother diluting that. What we do is, we are taking a 200 lambda shot right out of the bottle. We're using these Hamilton syringes that have these little valves on the end. They're really kind of a neat little device, you can purge it with argon, keep it pressurized and draw your sample of LAH up in an pressurized argon environment. And if you look, we sat all this in place ahead of time, the syringe, although it's not in place here but it gets set through the PLC. The whole system is evacuated, then backfilled under pressure with argon it's kept flowing. And at the point where we see the  $^{11}\text{C}/\text{CO}_2$  emptying from the target just before it reaches the lab, we dispensed it into this small volume here and this is then cold trapped at  $-5^\circ\text{C}$ . We go through the conventional practice of evaporating. And we can get specific activities in the order of about 6 Ci/ $\mu\text{mol}$  raclopride, cocaine, that sort of thing.

This was a nice system, it's very robust, it's a dual system that allows you to do sequential syntheses, you can switch from the A system to the B system and then wash this out in place later on if you like. So for a while we were doing a lot of cocaine runs. We were banging out 4-6 cocaine runs in a day in rapid sequence. So it was not amenable to washing and try to do a second run. So this was very useful for that purpose. That's all I have to say about the conventional system. In coffee break yesterday we were discussing, somebody has mentioned a German supplier of LAH. And I was quite interested in that and I'm sure people in the audience will certainly be interested.

C: R. Wagner: We are still using the conventional method as well and we got into much trouble preparing our LAH in a big argon glove box with distilled THF and we got quite good results with that. But it's quite sort of trouble and we are storing our vessels, 1 mL each, in small argon box made of glass and that works quite fine. But these people came up to us and asked us whether there is anything they could do for us and we said ok, perhaps it's a good idea with this LAH solution and they got around to do it, gave us some samples and they can now sell it. We tried this, they deliver samples of 1 mL in small septum vessels. We kept them standing on the bench, even after piercing and pierced that, it was slightly more

than 1 mL in our first samples, so we could pierce it five times, to take samples out for our synthesis. And there was no drop in specific activity even in the last sample. We could make raclopride up to a specific activity of about 3 Ci at the time of end of synthesis. So I think this is good enough for our purposes and they sell this and I've got the address here if you want I can write it down.

C: R. Ferrieri: Since we have discussed the possibilities, the GE-box, the MicroLab for production of that and I think Steve Fallis is going to give us a discussion of that and Martin as well will give the commercial side of this.

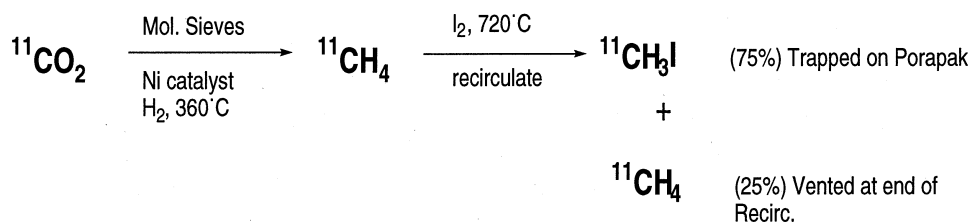
## Production of High Specific Activity [ $^{11}\text{C}$ ]Methyl Iodide Using the GE MicroLab<sup>®</sup>. Evaluation and Testing at Washington University

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For the past several years we have produced [ $^{11}\text{C}$ ]methyl iodide utilizing a remote gantry system. Although this system worked well, it suffered from several disadvantages. This system involves the reduction of [ $^{11}\text{C}$ ]carbon dioxide to methanol followed by conversion to methyl iodide using hydriodic acid [1,2]. The major disadvantage was that the system needed to be cleaned in between each production run, which limited the number of daily runs that can be achieved. Another disadvantage is that for receptor-based ligands requiring long synthesis times, the final specific activity of the tracer is too low for adequate uptake *in vivo*.

Due to these disadvantages, we have evaluated the performance of a PET trace Mel MicroLab<sup>®</sup> from General Electric Medical Systems (GEMS). This device produces high specific activity [ $^{11}\text{C}$ ]methyl iodide by the reaction of [ $^{11}\text{C}$ ]methane with iodine [3,4].



Conversion of [ $^{11}\text{C}$ ]carbon dioxide to the final product is achieved in approximately fifteen minutes and within an additional ten minutes the system is reconditioned, ready to begin another synthesis.

The iodine reaction column needs to be replaced every 7-10 runs. This is easily accomplished using inexpensive materials in less than ten minutes. We have tested this device using [ $^{11}\text{C}$ ]carbon dioxide from both our Japan Steel Works 16/8 (beam current: 40  $\mu\text{A}$ ) and Cyclotron Corporation CS-15 (beam current: 30  $\mu\text{A}$ ) cyclotrons. The target gas used was nitrogen (99.9999 %) containing 0.5 % oxygen (99.997 %). Initial test runs were conducted using short irradiation times of 2-5 minutes. Both cyclotrons were able to routinely produce 50-150 mCi of final product which was trapped in acetonitrile at 0  $^\circ\text{C}$ . Recently typical irradiations of ca. 2.5 minutes using the JSW cyclotron routinely produce 90-100 mCi (end of synthesis) of [ $^{11}\text{C}$ ]CH<sub>3</sub>I which was trapped in 1 mL acetonitrile, THF, acetone or hexanes. Longer irradiation times (25 minutes) furnished up to 1 curie of [ $^{11}\text{C}$ ]methyl iodide. Proper maintenance is essential to the performance of the system. A few simple checks and adjustments prior to each run or when replenishing chemicals ensures excellent and consistent results.

Specific activities of the [ $^{11}\text{C}$ ]methyl iodide were measured by reversed-phase analytical HPLC using an acetonitrile/buffer eluent and monitoring the effluent by UV at 210 nm. The JSW 16/8 cyclotron furnished the highest specific activities, with values greater than 10,000 Ci/mmol. Lower values were obtained from the CS-15 but these are attributed to target design. Reactivity of the [ $^{11}\text{C}$ ]methyl iodide was comparable to that obtained by the standard synthetic route.

In conclusion, we have established that the PETtrace MeI MicroLab is a useful tool for the rapid and efficient production of high specific activity [ $^{11}\text{C}$ ]methyl iodide. In order to finally purify the product methyl iodide, we have constructed a simple tube (0.5 x 10 cm) packed with soda lime and phosphorous pentoxide. The tube removes all traces of water and HI from the final product. This has been documented by success in palladium-catalyzed Suzuki alkylations of hydroborated alkanes; a reaction which is extremely sensitive to the presence of HI.

### Acknowledgments

We would like to acknowledge the assistance of David Ficke, William Margenau and Keith Lechner. This work was supported by NIH grant HL13851 (to MJW).

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### Discussion:

Q: How big is that box ?

A: The box is about 21 inches high by about 16 inches wide and it's about 9 inches deep. And we've got it conveniently just stuck away in the corner of a hood and the front panel and the top is all you really need access to. When you are changing tubes, the tube gets inserted then in a hole in these ovens here just through the top of the box, so you don't have to open up. This is just opened up so that you can take a picture of it. The iodine tube gets inserted and the iodine tubes they are made of quartz and they are easily cleaned and reused and they are inexpensive. The manufacturer makes them for \$12 each..

Q: R. Ehrenkaufer: So there isn't really much turnaround time, when you want to do a second run?

A: Once I get the activity I push a button, 12 min later you have.... of a 2.5 min run on the cyclotron we get between 90 and 100 mCi without fail. And you know it's time to change the tube when it drops below 90. You know it's time for a new tube, because the next run after that will be about 50 or 60. So it's very predictable and useful.

Q: Did you say the box's width is 60 inches?

A: 16, about 16. .... If you install the tubes, it's always a good idea to check the fluids through the box. There are three fluids that you can check really quick, do a quick leak test, maybe about five minutes of installation. And if those fluids are not set at the specs, then the yields can vary. But as long as you keep them there and check it's very reproducible.

C: J.Clark: We've got one of these boxes too and I'd like to share our experience with you. How do you measure specific activity? On your raw material or your end products?

A: We measure the end product, methyl iodide.



Q: J. Clark: And how do you do that?

A: Reverse phase HPLC.

Q: J. Clark: Using what detector?

A: UV.

C: J. Clark: We do the same, but there are people around who criticize that methodology. Is anybody in the audience willing to stand up and justify this criticism?

A: S. Fallis: Now, from the impurities in the solvents reacting you are not seeing everything. We use very high grade acetonitrile to cannon our mobile phase and we're quite happy with it.

C: J. Clark: It's interesting to see that Jeanne and Tom were actually measuring end products. There is quite a differential between this recirculating system and the single path. We've got 30 Ci/ $\mu$ mol out with ours without even trying on the raw material.

C: R. Wagner: Just one last question to that, because I'm not always sure if we all agree on the same time base for our specific activity calculations. I didn't have calculated back the raclopride, I gave the specific activity at end of synthesis. So most of the people I think are using end of bombardment or something like that. I'm not pretty sure what everybody is using. So that should be quoted some time at least.

C: P. Larsen: We've been doing a lot of determinations of both the methyl iodide and the final product and I agree that the best way to do it is to use the final product. We see that it's difficult to analyze the methyl iodide, it has a low absorption, so you have to go to a very low wave length, and that means it's very sensitive to noise from impurities and solvents and so on. And another problem, if you have high amounts of activity, the methyl iodide seems to be unstable. So if you make an analysis, a few seconds after it comes out of the machine you'll have a very pure product. But if you wait fifteen, twenty minutes it may be half of it has decomposed.

C: J. Link: I guess I have to disagree. I think we have to measure the final specific activity of our products. But if you can technologically manage to measure your precursor, then you understand the chemistry better and what's going on. So I admire the people who are measuring methyl iodide. It's a difficult measurement to get at these high specific activities.

### **Martin Orbe, GEMS: Comments on the GE Methyl Iodide Box**

Most of the things which I was planning to say has already been said, so I will be pretty short. This is the system we talk about. It's the box, it's the control system and the controller. And we deliver everything and we also deliver a package of 10 quartz tubes which you can wash out and reuse if you want. Or if you don't want, you can buy another 10 package from us or go to some other supplier. I can assure it's cheaper from somebody else, I know that. (Chairman R.E.: 'We'll make a note of that !') That's just the way it is. I'm sorry.

Steve already gave a presentation of the principal of the method, trapping of carbon dioxide on a molecular sieve, which we think is a very useful method to avoid the liquid nitrogen. It has a reduction to methane and then a conversion of the methane to methyl iodide. We have already talked about the beneficial things. You get a good product, I don't think I should mention that, maybe we skip that slide. We go over to where we have the systems, so you can talk to the people there. St. Louis has already presented their results so far and John



Clark has also mentioned he has it. We have it in four more places. In Zurich, the Universitätsspital there, by Prof. van Schultes. In Tübingen, with the group of Prof. Machulla. And then at the Karolinska Institute, where it's used by Prof. Houdy and several others by the way. They will have a poster on the chemistry meeting on their results. And they have connected the methyl iodide system with a methylation system which has been developed by Peter Larsen. This system in Tübingen, by the way, is working together a methylation system from Nuclear Interface. We are trying explore the possibility to have a package solution. It's also used in Korea in some sort of medical center. We have four more systems which are going to be installed very soon. The one in Brookhaven, one more in Germany in München, one more in Korea and also one going together with our cyclotron in Vienna. I believe that all sites, I know that all sites use the methyl iodide system and I believe most of them, all of them are happy with it. I recommend you to contact people from each individual sites and discuss their experiences with the box.

What do we do in house, to ensure you get something which is working? All are tested hot by standard procedure to meet the criteria, to see if we can meet the yield criteria and some kind of specific activity criteria. These are not optimized systems, we usually do one or two hot productions on the systems to meet the criteria, to allow us to ship the units. We also see a kind of variation which has been reported on the specific activity. We have seen between 2.7 and 11 Ci/ $\mu$ mol. We measure our specific activity by trapping in methanol and injecting in a HPLC with UV detection. We always make a standard curve on the same methanol the same day as we make the methyl iodide to ensure that we have some kind of understanding of what is happening, even though the method is in question. I think we have a good control over the specific activity anyway. We have made very few real full batch productions. We made one when John and Mike and Prof. Ido visited us in Uppsala, where we produced little over 1 Ci of methyl iodide with a specific activity which was actually close to 30 Ci/ $\mu$ mol.

Some short results from Tübingen. I received a fax from them yesterday, they have made 82 productions, they are using fairly small amounts of methyl iodide, between 10 and 150 mCi. This is the result from this year. They had three failures during this time. The system was not able to produce methyl iodide. In one case you could clearly see it was due to running out of iodine, the reasons in two cases I couldn't trace it from the fax I received. They have made up to ten productions in one day, usually it's two or three. They have labelled ten different compounds, mainly amphetamine analogues, raclopride and methionine. And in two cases they have measured the specific activity, on these two compounds and the specific activities were 8 and 13 Ci/ $\mu$ mol and this is end of bombardment corrected. This is actually all I wanted to say.

#### Discussion:

C: T. Ruth: Just another comment about these systems is that with the gas phase, you can really reduce the starting material you use as well, at least by a factor of two if not more. Which really helps with the specific activity of the final product I think.

C: R. Ehrenkaufer: And the choice between CO<sub>2</sub> or methane really has to do with what target you have available. There's really no other reason for preferring the one over the other, is there ?

A: We have chosen to use CO<sub>2</sub> as a starting material as most of you have already CO<sub>2</sub> targets out there. And some of you want to use CO<sub>2</sub> for other purposes as well. So that's the main reason, why we chose to not go to methane as a starting material.



C: T.Ruth: We went to methane for two reasons. One, you eliminate the one extra step of the furnace etc. And the other is potentially higher specific activity in terms of not having to worry about CO<sub>2</sub> in the atmosphere.

Q: What's the current cost of that system?

A: We have a list price of it at \$90,000.

Q: What's the sale price?

A: It's about the same. Talk with your local dealer.

Q: A question. You recommended to contact the people who use the system. I did and I was told the system is not tight. A question of radiation exposure of course to the environment. Do you know the problem, did you something against?

A: Yes, I know there is a problem here in Germany, where you are allowed to emit 200 Bq/m<sup>3</sup> in your hot cell. And we can not meet this.

C: This was not in Germany in this case.

A: Yes, there is some kind of activity leaking out. The sealings for the quartz tube are two membranes which you penetrate and there is some activity coming out there. It's in the range of; actually I'm not sure about the quantity.

C: We've got a sensor in our stack. We haven't seen any serious leaks from the box at all. All our waste gases are vented down into the cyclotron where they're allowed to decay before they're released.

C: J. Link: Just to answer your question. After seeing what happened with the new NiO catalyst in actually seeing the specific activity difference, it seems to me if you can make it in the target, you are better off.



## High Specific Activity 1- $^{11}\text{C}$ Ethyl Iodide – Preliminary Results

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We have prepared 1- $^{11}\text{C}$ ethyl iodide for the synthesis of S-ethylisothiourea, a selective inhibitor of inducible nitric oxide synthase (iNOS) [1]. Literature procedure for the synthesis of 1- $^{11}\text{C}$ ethyl iodide involves the reaction of  $^{11}\text{C}$ CO<sub>2</sub> with a Grignard reagent (i.e., methyl magnesium bromide) dissolved in diethyl ether, followed by reduction with LAH and in-situ iodination with HI. Our observed radiochemical yield and purity for this one-pot reaction are around 70 % and 90 % respectively. The major drawback with this method is the very low specific activity obtained for the final product which, in our hands, never exceeded 200 Ci/mmol (range 0.7-200 Ci/mmol).

We identified the major source of the problem to traces of ether left during the course of the reaction even after careful evaporation under vacuum. Ethyl ether is readily hydrolyzed and iodinated with HI and it is ethyl iodide produced in this way that coelutes during distillation. Grignards are also known to form stable complexes with ether molecules which are difficult to remove [2]. The use of THF as a solvent for both Grignard and LAH has been unsatisfactory, giving the desired product in low yields and poor radiochemical purity.

Several approaches have been taken to improve the synthesis. One was to use a solid phase system for the iodination, similarly to what has been done with  $^{11}\text{C}$ methyl iodide [3]. The first of the phases used, triphenylphosphine diiodide on alumina, also hydrolyzed diethyl ether. Three other phases triphenylphosphine-imidazole-iodine, diphosphorous tetraiodide and methyltriphenyl phosphonium iodide, all bound to alumina were investigated. The results were unsatisfactory with all of them due to lack of reproducibility, instability after heating, and poor conversion efficiency. We also attempted an in-situ conversion with chlorotrimethylsilane/sodium iodide in acetonitrile after distillation of the  $^{11}\text{C}$ ethanol, but were also unsuccessful in the iodination, due mainly to the extreme sensitivity of the iodinating reagent to traces of moisture.

Our most recent approach consists of generating the  $^{11}\text{C}$ ethanol from reaction with Grignard reagent and LAH in solvents of higher boiling points such as butyl ether and diglyme. The  $^{11}\text{C}$ ethanol is then gently distilled and passed through a bed of HI-silica gel (1:1) followed by a plug of plain silica. This phase quantitatively adsorbs the alcohol at room temperature and after heating to above 120 °C, the product iodide can be released in a stream of nitrogen. Traces of HI and water are removed by passage of the gases through a soda lime-potassium hydroxide and phosphorous pentoxide column. This procedure produces 1- $^{11}\text{C}$ ethyl iodide at higher specific activity (600-800 Ci/mmol) but with low yields. Attempts to increase the yield and further improve the specific activity are under way.

### Acknowledgments

This research was supported by NIH grant HL13851. We wish to thank Drs. T. J. McCarthy, D. Reichert and J. A. Katzenellenbogen for useful suggestions and discussions.

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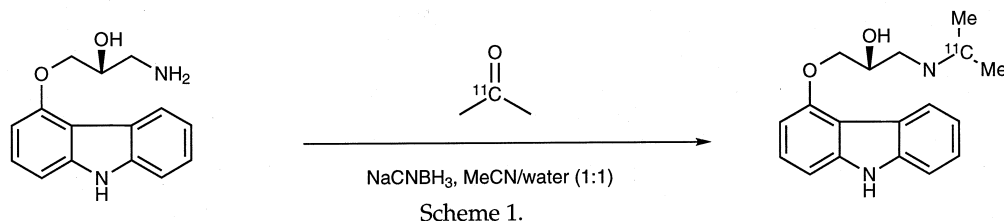
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## Synthesis of [ $^{11}\text{C}$ ]Acetone: Considerations Regarding Stoichiometry

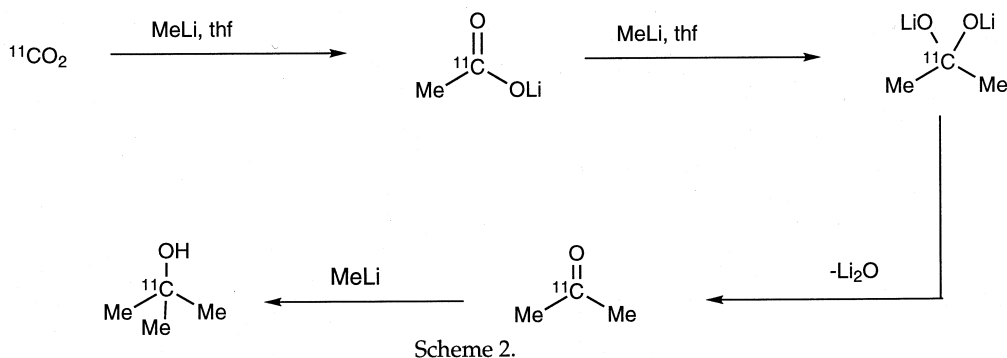
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We are interested in using [ $^{11}\text{C}$ ]carazolol [1] to assess  $\beta$ -adrenergic receptor levels in vivo. The synthesis of this tracer is shown in Scheme 1.

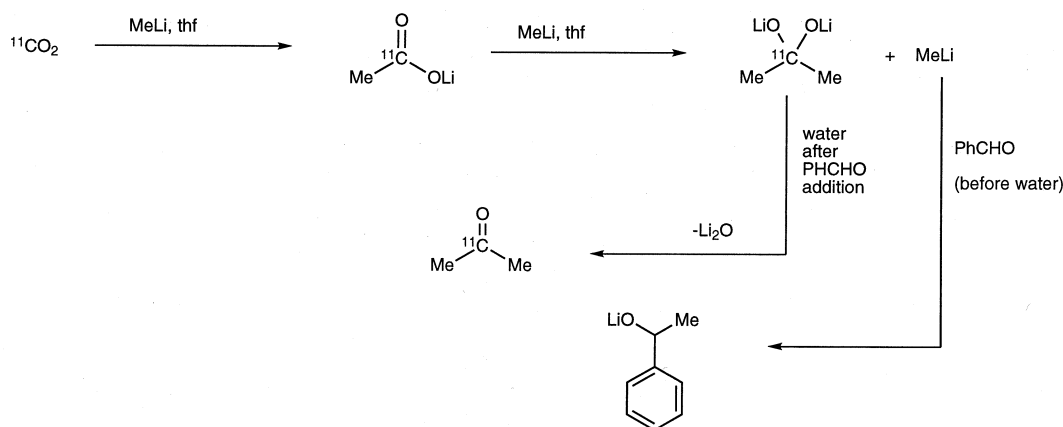


The reliable production of high specific activity [ $^{11}\text{C}$ ]acetone is essential for this nature. With the [ $^{11}\text{C}$ ]CO<sub>2</sub> precursor available to us we found that the methods currently available for the production of 2-[ $^{11}\text{C}$ ]acetone were not adequate [2,3]. These methods involve the addition of two molecular equivalents of either methyl magnesium chloride, or methyl lithium to [ $^{11}\text{C}$ ]carbon dioxide (Scheme 2).



Previous results from our laboratory [4] with different targetry from that now employed gave isopropanol as the major product after reduction with LAH. In our current studies t-[ $^{11}\text{C}$ ]butanol was the major product. The differing results obtained are probably due to different stoichiometries arising from the differing targetry conditions. Therefore, we concluded that using this methodology it is vital to control the amount of methyl lithium since an insufficient quantity will lead to high yields of [ $^{11}\text{C}$ ]acetate, while too much gives high yields of t-[ $^{11}\text{C}$ ]butanol. This was confirmed by a literature review which revealed that the quantity of reagent used to optimize the synthesis of [ $^{11}\text{C}$ ]acetone varied considerably. This implied that no thorough mechanistic based procedure had been developed. We have examined the mechanism of acetone formation as outlined below and based a radiosynthetic strategy in light of this.

We have speculated that the formation of undesired t-butanol arises from the reaction of acetone with excess methyl lithium. To avoid this problem it would be necessary to destroy the excess methyl lithium prior to hydrolyzing the intermediate ketal. Our strategy is to react the excess methyl lithium with benzaldehyde and then quench the entire mixture with water (Scheme 3). Using this approach we have been able to use larger amounts of methyl lithium which in turn increases our trapping efficiency of [ $^{11}\text{C}$ ]CO<sub>2</sub>, and reduces the amount of [ $^{11}\text{C}$ ]acetate formed.



Scheme 3.

In summary we have been able to improve the synthesis of [ $^{11}\text{C}$ ]acetone and can reliably obtain [ $^{11}\text{C}$ ]acetone in good yield with only small amounts of t- $^{11}\text{C}$ ]butanol and [ $^{11}\text{C}$ ]acetate. It is evident from these results that the production of [ $^{11}\text{C}$ ]acetone is extremely sensitive and needs to be optimized to the particular characteristics of the [ $^{11}\text{C}$ ]CO $_2$  precursor available.

### Acknowledgments

We would like to acknowledge the assistance of David Ficke, William Margenau and Keith Lechner and thank Dr. John A. Katzenellenbogen for helpful discussion. This work was supported by NIH grant HL13851(to MJW).

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### Discussion:

Q: T. Tewson: The molar equivalents of methyllithium that you use are absolutely huge. Can you explain that? It seems very strange that you would require a ten thousand fold excess instead of a thousand fold excess. Is anything else happening to the methyl lithium?

A: The only things that we've detected are acetate and the products discussed. No idea what else is going on, haven't been able to detect anything else. The cases where we didn't get any conversion, I mean the acetate is the only peak observed by HPLC. We couldn't detect anything else. But actually we didn't look that hard for some of the other things. We were pushing on to get to products. But we don't know why...I mean obviously you have to connect this to the CO $_2$  that's available to you, but why such a huge excess it's not debatable.

Q: P. Larsen: Have you tried to use the Grignard reagents instead of the methyllithium?

A: No we haven't. With our Grignard balloon we take this to acetate.

## A New Production Method for [<sup>11</sup>C]CO: Reduction of Target-produced [<sup>11</sup>C]CO<sub>2</sub> with Molybdenum

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[<sup>11</sup>C]carbon monoxide was one of the first tracers for blood flow measurements in humans. Since it is less reactive than other [<sup>11</sup>C]labeling agents, it has only found comparatively little application in radiopharmaceutical syntheses. [<sup>11</sup>C]CO has often been used to produce the more aggressive labeling precursor [<sup>11</sup>C]COCl<sub>2</sub> [1], but recently a very promising palladium-promoted cross-coupling reaction for the direct preparation of aromatic ketones from [<sup>11</sup>C]CO has been reported [2].

One well-established procedure for the preparation of [<sup>11</sup>C]CO is the reduction of target-produced [<sup>11</sup>C]CO<sub>2</sub> with zinc metal. The optimum reaction temperature of 390 - 400 °C is very close to the melting point of zinc (420 °C), therefore exact temperature control is required to avoid technical problems. About half of the <sup>11</sup>C radioactivity remains in the zinc powder furnace [3].

We have investigated a new method for the efficient conversion of carrier-free [<sup>11</sup>C]CO<sub>2</sub> to [<sup>11</sup>C]CO on elementary molybdenum. The components Mo-MoO<sub>2</sub> and CO<sub>2</sub>-CO constitute a complex chemical system, and no simple model is available to predict the achievable yield of [<sup>11</sup>C]CO for a given temperature. The main reaction proceeds according to



Equilibrium data show that increasing temperature results in higher CO partial pressure [4]. On the other hand, the carburization of molybdenum by CO



i.e. the decomposition of the desired product, is also promoted at elevated temperatures. Gas flow rates and absorption phenomena of CO on the molybdenum surface strongly affect the reaction time and play an important role in the formation of Mo<sub>2</sub>C layers.

In addition, the reactions of MoO<sub>2</sub>, which is present due to oxidation of Mo by small amounts of air, moisture or CO<sub>2</sub>, with the gaseous components have to be taken into account. MoO<sub>2</sub> is oxidized by CO<sub>2</sub> [5], but also reacts at high temperatures with CO to Mo<sub>2</sub>C [6].

Figure 1 shows a schematic drawing of our [<sup>11</sup>C]CO production system. The CO<sub>2</sub>/CO converter was prepared from a 25 mm i.d. x 150 mm cylindrical quartz vessel with 6 mm quartz tubes on either end (for connection to Swagelok fittings). It was packed with approximately 70 g of molybdenum wire. The quartz vessel was inserted into a vertically mounted furnace consisting of a band heater coil and a ceramic sleeve for insulation. [<sup>11</sup>C]CO<sub>2</sub> produced by proton bombardment of nitrogen gas is pre-concentrated in a cryo trap and then passed through the quartz tube filled with the molybdenum mesh heated to 850 °C. [<sup>11</sup>C]CO is purified from unreacted [<sup>11</sup>C]CO<sub>2</sub> by a soda lime cartridge and collected in a small silica trap (2 g SiO<sub>2</sub> in a 6 mm o.d. x 27 mm stainless steel tube, cooled with liquid argon) from which it can be eluted into the synthesis vessel with a helium stream.

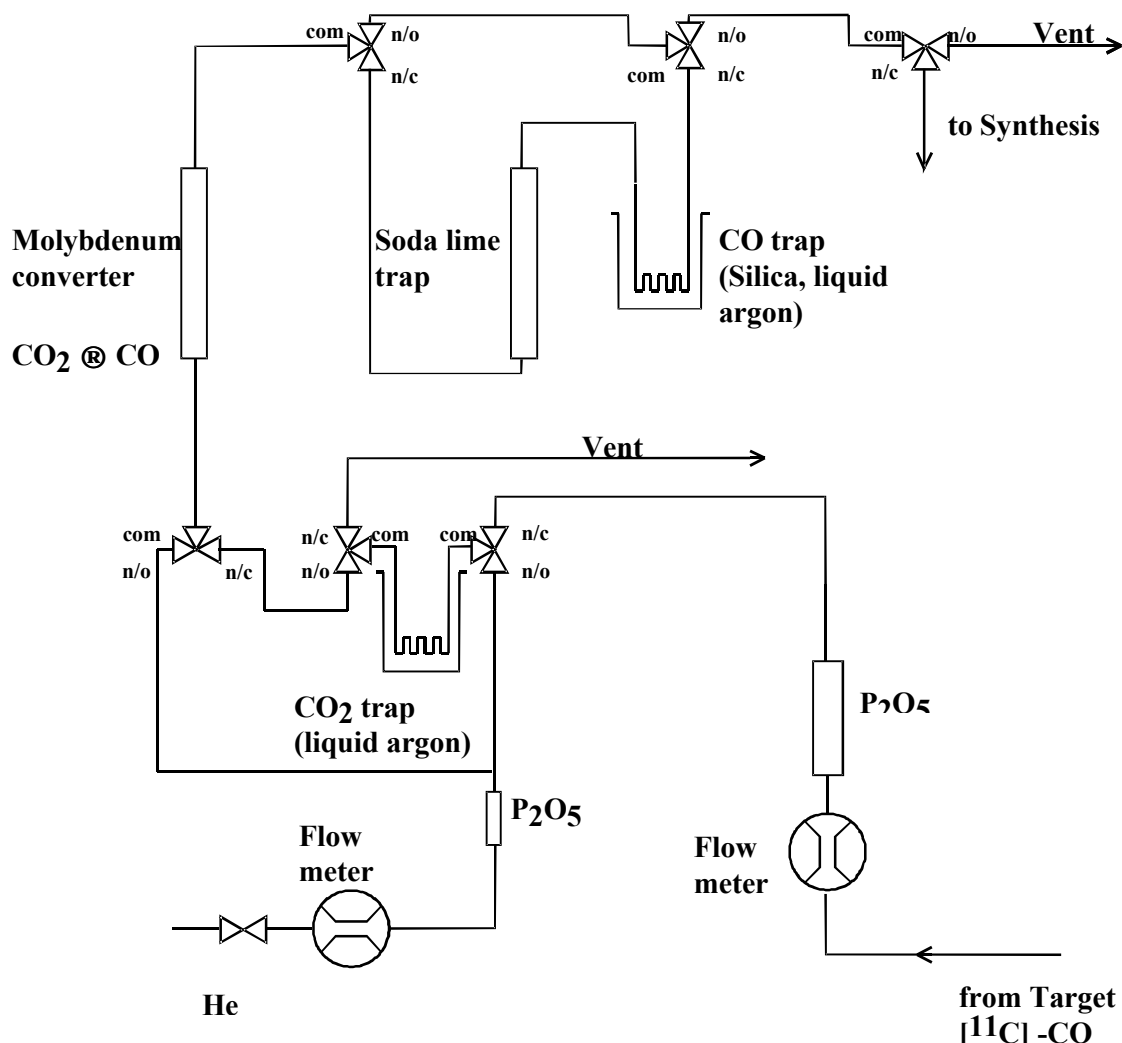
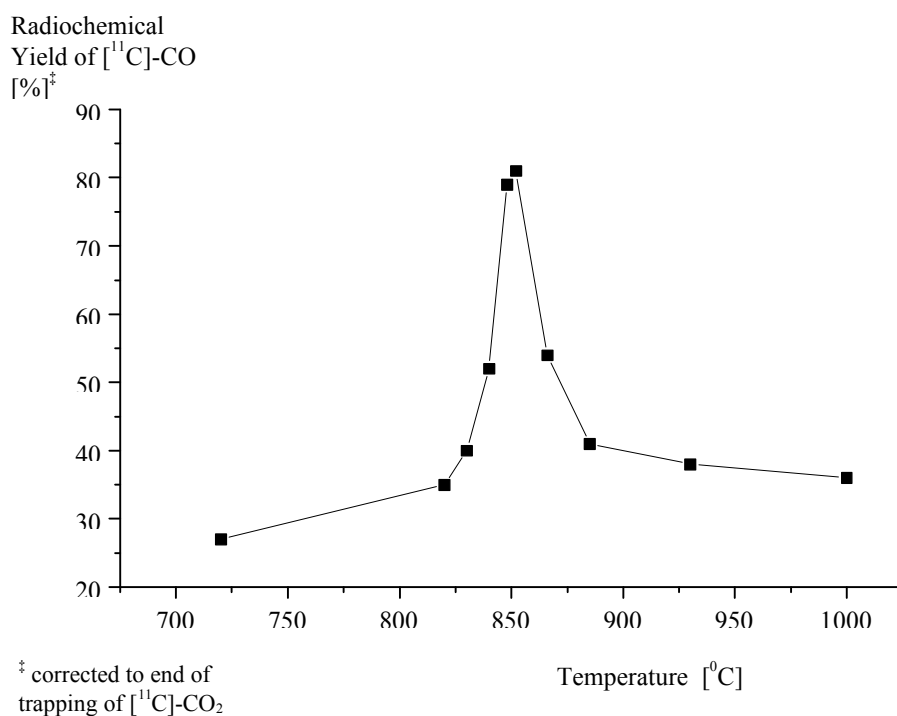


Fig. 1: Flow diagram of the  $[^{11}\text{C}]\text{CO}$  production system

Figure 2 shows the radiochemical yield of CO obtained with our production system as a function of the conversion temperature. Yields are decay corrected to the end of the trapping of  $[^{11}\text{C}]\text{CO}_2$  (about 3 minutes after EOB). The  $[^{11}\text{C}]\text{CO}_2/\text{CO}$  conversion starts below 700 °C and reaches a narrow optimum at 850 °C. The maximum radiochemical yield of 81 % corresponds to a practical yield of 54 % at the end of the trapping of  $[^{11}\text{C}]\text{CO}$  on the silica column (15 minutes after EOB). We have carried out about 100 production cycles without observing any change in the behavior of the converter system. Yields are consistent, typically 25.9 GBq (700 mCi) of  $[^{11}\text{C}]\text{CO}$  from 48 GBq (1.3 Ci) of  $[^{11}\text{C}]\text{CO}_2$  with a specific radioactivity in the order of 555 GBq/ $\mu\text{mol}$  (15 Ci/ $\mu\text{mol}$ , corrected to EOB) as measured by radio-GC. No radioactive contaminants were detected. Radiochemical purity and specific activity of the  $[^{11}\text{C}]\text{CO}$  produced with this system are sufficient for nuclear medical studies with PET.

The developed production system is robust, reliable, easy to operate and suitable for automation. Batches of several hundred millicuries of radiochemically pure  $[^{11}\text{C}]\text{CO}$  have been produced and used successfully for the palladium-mediated synthesis of carbonyl-labeled  $[^{11}\text{C}]\text{benzophenone}$ .



**Fig. 2:** Radiochemical yield of [ $^{11}\text{C}$ ]CO vs. converter temperature

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