Journal of Labelled Compounds and Radiopharmaceuticals
J. Labelled Cpd. Radiopharm. **44**, 1-5 (2001)

A convenient production of [^{13}N]Nitrogen for ventilation studies using a nitrogen gas target for ^{11}C production

D. Le Bars

CERMEP, 59 Bd Pinel, 69003 Lyon France

Short Title: $^{13}N_2$ production with a $^{11}CO_2$ target

Keywords: $^{13}N_2$, $^{11}CO_2$, ventilation studies, PET

e-mail lebars@univ-lyon1.fr, www.cermep.fr

SUMMARY

Taking advantage of the $^{14}N(p,pn)^{13}N$ reaction occuring during the $^{14}N(p,\alpha)^{11}C$ carbon dioxide production, pure [$^{13}N]N_2$ suitable for PET ventilation studies was produced in a standard nitrogen gas target for ^{11}C-production ("carbon-11 target"), after elimination of $^{11}CO_2$ and short-lived oxygens.

INTRODUCTION

It is well known (1) that from a physiological point of view, because its low solubility in plasma, ^{13}N-nitrogen (10.0 min half life) as an inert radioactive gas, is the best tracer for PET ventilation studies in animals and man. [$^{13}N]N_2$ production has been described in litterature via a $^{12}C(d,n)^{13}N$ reaction by the irradiation of CO_2 or a graphite matrix target (2), or via the $^{16}O(p,\alpha)^{13}N$ reaction on water, reduction to NH_3 and action of NaOBr (3), or via $^{16}O(p,\alpha)^{13}N$ reaction on CO_2 (4) and finally via the $^{13}C(p,n)^{13}N$ reaction on amorphous ^{13}C carbon target (5). As none of these targets are available on our IBA Cyclone 18/9 cyclotron, the $^{14}N(p,pn)^{13}N$ reaction obtained as a by-product at the $^{11}CO_2$ production using the $^{14}N(p,\alpha)^{11}C$ reaction was interesting alternative since the same target and target gases could be used both for the ^{11}C and the ^{13}N production. It is known from the excitation functions that for proton energies above 12 MeV (6,7,8) significant amounts of [$^{13}N]N_2$ are produced via the $^{14}N(p,pn)^{13}N$ reaction; normally, the subsequent chemistry extracts only the $^{11}CO_2$ and [$^{13}N]N_2$ escapes in the

Received 17 March 2000
Revised 30 July 2000
Accepted 14 August 2000

synthesis process. The aim of this work was to achieve efficient trapping or elimination of $^{11}CO_2$, ^{11}CO, $^{14}O_2$ and $^{15}O_2$ (that may be present in a small percentage depending on target and irradiation conditions (6, 7)), to yield pure [^{13}N]N_2 for ventilation studies in a routine PET clinical environment.

MATERIALS AND METHODS

Gases were of the highest commercial purity, ie Linde nitrogen N60 with 0.1 % O_2 for the ^{11}C-target gas, nitrous oxide N2.5 as reference. Chemicals were obtained from Aldrich, Prolabo or Carlo Erba. Nitric oxide reference was produced by the reaction of acidified iron sulfate with sodium nitrite (9). The target was a standard ^{11}C-target from IBA, internal volume 60 ml operated at 20 bar (total volume 1.2 l), with He window and water target cooling. The incident 18 MeV proton beam was degraded to 16 MeV by the 25 μm vacuum and 500 μm target aluminium windows. The pressure of the gases is reduced to 1.5 bar after the target. Three traps (30 cm long silica glass column, 0.9 cm id) are filled with 1) 20 g of soda lime (2 to 5 mm, 8 mesh), 2) 30 g of copper oxide (2 to 5 mm) in a 700 °C furnace and 3) 20 g of soda lime (2 to 5 mm). A 40 m length of 6 mm OD stainless steel tubing carrys the radioactive gas from the cyclotron vault to the PET camera room. Radioctivity was measured with a Capintec CRC 12 chamber, either directly or via a calibrated 10 ml volume loop. A mass flowmeter (0-500 ml.min^{-1}) delivered the radioactive gas in the PET camera room. Radiogaschromatography was performed on a Delsi 200 GPC, equipped with a Alltech CTR 1 concentric column, inner column porous polymer mixture (Porapak Q), outer column activated molecular sieve, operated at 50°C with 1 bar N55 He as carrier gas and catharometer (TCD) detection. Radioactivity was measured with a Beckman 170 γ monitor.

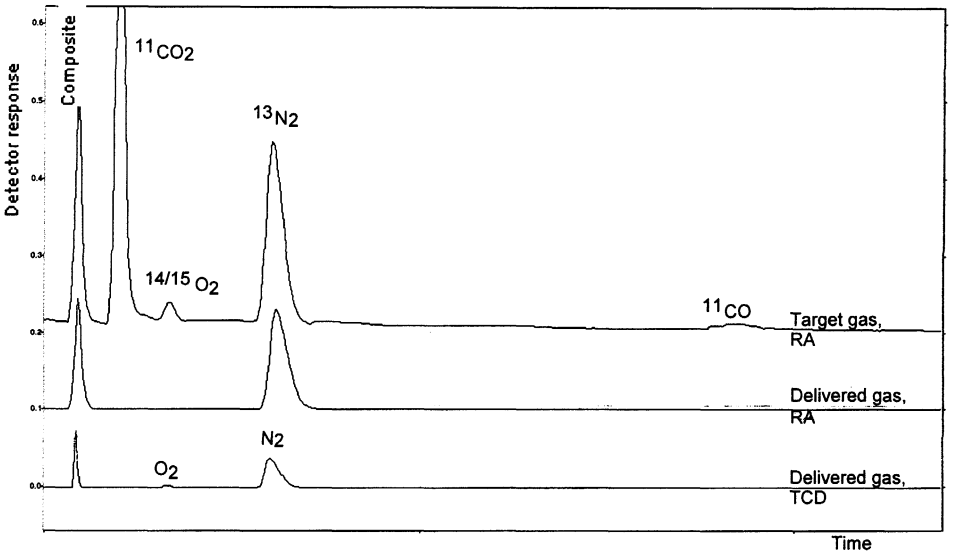
RESULTS

1. GPC Analysis

In our conditions, the Alltech CTR I column separates the gases of interest in less than 10 minutes: after the composite peak (N_2, O_2, NO, CO not separated in inner column at 50 °C), CO_2, N_2O were separated, and outer column elutes O_2, N_2, NO and CO (10). NO_2 and O_3 are retained (2).

2. Analysis of target gas after irradiation

Figure 1 (upper trace) shows the radioactive GPC analysis of the target gas obtained after a 20 min 20 μA bombardment (TCD analysis (stable gas) reports only O_2 and N_2 peaks):



In Table 1, the decay correction calculation to injection time (EOB + 4') on the peak areas gave the following results (n=2):

Table 1

Gas	Retention time, min	% of total
$^{11}CO_2$	1.02	76.5
$^{15}O_2$	1.68	3
$^{13}N_2$	3.03	19.5
^{11}CO	9.13	0.5

3. Implementation of Traps - Delivery to PET camera room

After introduction of a sodalime trap for $^{11}CO_2$ and CuO trap at 700 °C for oxydation of ^{11}CO, GPC on the gas delivered to the PET camera room (Fig 1, lower trace, radioactivity) shows the disappearance of unwanted peaks . Again, TCD analysis reports only O_2 and N_2 peaks (composite peak is an artefact due to the CTR1 column).

4. Production results

a/ Bolus mode

[^{13}N]N_2 Bolus production was measured on a 20 ml aliquot of the collected gas (1.1 l), controlled by GPC, decay-corrected to GPC injection time (EOB + 4 minutes, n=2) :

Table 2	Irradiation	Total activity	$^{13}N_2$	$^{11}CO_2$
	20 μA / 5 min	385 mCi	85 mCi	280 mCi
	20 μA / 10 min	760 mCi	180 mCi	560 mCi
	20 μA / 20 min	1070 mCi	210 mCi	815 mCi
	20 μA / 30 min	1360 mCi	280 mCi	1035 mCi

b/ Continuous production mode

After 15 minutes equilibration period, Table 3 reports production of $^{13}N_2$ in the PET camera room with a 20 μA beam (n=3):

Table 3	Flow	Activity.ml^{-1}	Activity.min^{-1}
	60 ml.min^{-1}	80 μCi.ml^{-1}	4,8 mCi.min^{-1}
	100 ml.min^{-1}	120 μCi.ml^{-1}	12 mCi.min^{-1}
	150 ml.min^{-1}	180 μCi.ml^{-1}	27 mCi.min^{-1}

DISCUSSION

We found that the amount of [^{13}N]N_2 produced in a ^{11}C-target by the competing $^{14}N(p,pn)^{13}N$ reaction was sufficient for clinical use. Analysis of target gases at the end of 5 to 30 min 20 μA irradiation shows the presence of *ca.* 20 % of $^{13}N_2$, significant amounts of $^{15}O_2$ (with probable traces of $^{14}O_2$) and ^{11}CO, and *ca.* 75 % of $^{11}CO_2$. Trapping of $^{11}CO_2$ was easily performed with soda lime, this basic media presenting the added advantage of being able to trap oxides of nitrogen (even if the probability of their presence is very low at this percentage of oxygen in target (2,11)). Elimination of ^{11}CO was more difficult: after unsuccessful experiments with Pd catalysts, we choose to oxydise the traces of CO in CO_2 with a CuO trap operating at 700 °C (2), followed by another soda lime trap. $^{14}O_2$ and $^{15}O_2$ compounds were simply eliminated due to exchange on CuO and physical time of transfer between the target and the PET camera room, the transit time being estimated at 8-10 minutes (Traps, 40 m 6mm OD SS tubing, 60-100 ml.min^{-1}).

In our configuration, the system produces more than 10 mCi.min^{-1} for a 100 ml.min^{-1} flow 40 metres away from the target under 20μA bombardment, or in bolus mode (1.1 l) more than 200 mCi after 20

minutes irradiation. These values exceed largely the requirements for ventilation studies, for example 5 to 7 mCi.min^{-1} in continuous mode in a large animal. The purity of [^{13}N]N_2 was further evaluated by a 1 hour decay curve analysis on blood samples after [^{13}N]N_2 ventilation, showing a mono-exponential decay in excellent fit with a 10.0 min period (R=0.998).

Moreover, from a radioprotection point of view, our results confirm that $^{13}N_2$ can be produced in large amounts in nitrogen targets for ^{11}C-production and could escape in the atmosphere unless caution steps are taken: either by degrading the incident proton energy on the ^{11}C-target to under 12-14 MeV (lowering the quantity of nitrogen-13 produced, possibly at the detriment of $^{11}CO_2$ production), or more conveniently a simple gas bag collecting residual $^{13}N_2$ in the hot cell will allow decay before release.

ACKNOWLEDGEMENTS

The help of the chemistry team and fruitful comments from Dr D. Comar and Dr L. Cinotti are gratefuly acknowledged.

REFERENCES

1. Nosil J. *et al. Phys. Med. Biol.* **21**: 749-759 (1966)

2. Clark J.C. and Buckingham P.D. *Short-lived radioactive gases for clinical use* Butterworth & Co (Publisher) Ltd (1975)

3. Van der Mark Th.W. *et al. J. Nucl. Med.* **25**:1175-1182 (1984)

4. Murata K. *et al. Radiology* **158**:303-307 (1986)

5. Austin S. *et al. Nucl. Inst. Meth.* **126**:373-377 (1975)

6. Langström B. *Acta Universitatis Upsaliensis 555* Uppsala (1980)

7. Qaim *et al. Pet radionuclide production* in *Stocklin G. and Pike V.W. Radiopharmaceuticals for Positron Emission Tomography, developments in Nuclear Medicine 24*, Kluwer Academic Publishers (1993)

8. Casella V.R. *et al. Radiochim. Acta* **25**:17-20 (1978)

9. Blanchard A.A. *Inorg. Syn.* **2**: 126-128 (1946)

10. Alltech Data sheet U8700

11. Tewson T.J. *et al. Appl. Radiat. Isot.* **40**:765-768 (1989)

