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Production of Oxygen-15, Nitrogen-13 and Carbon-11 and of their Low Molecular Weight Derivatives for Biomedical Applications

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The production and the medical use of the short-lived radioisotopes of the 3 major elements of the biosphere, ^{13}N, ^{11}C and ^{15}O, require the vicinity of a cyclotron, of radiochemistry laboratories and of a suitably equipped medical unit. The authors describe and discuss the methodological and practical aspects of the routine, high efficiency, production of these gases, with the specifications that result from their medical use.

Introduction

For the past 15 years, short-lived radioactive gases have won a growing interest in nuclear medicine. Oxygen-15, nitrogen-13 and carbon-11 have a wide field of biological applications resulting both from their biological and chemical properties and from the particular conditions of their detection *in vivo*.

These radioisotopes are β^+ emitters, with half-lives of 2.07 min for ^{15}O, 9.97 min for ^{13}N and 20.4 min for ^{11}C. The coincidence detection of the 511 KeV γ photons which appear back to back from the annihilation of the positrons is achieved in conditions of high spatial resolution and high sensitivity, and permits a correction of the measurements for self-attenuation. These peculiar conditions of detection are the basis of emission tomography, which provides, slide by slide, the quantitative picture of the equilibrium distribution of the positron-emitting element in the organism to which it was administered.[1]

These ^{15}O, ^{13}N and ^{11}C are the only short-lived radioisotopes of the 3 most common elements in the biosphere. Molecular $^{15}O_2$ allows the study of O_2 extraction from blood in several organs, e.g. the brain.[2] With $C^{15}O_2$ and $^{11}CO_2$, the blood circulation and exchange of carbon dioxide in the lungs can be measured.[3] $H_2{}^{15}O$ permits measurement of exchangeable water, particularly in the pulmonar oedema.[4] ^{13}N inhaled in molecular form is also a means for the study of lung volume.[5] $^{13}NH_3$, after intravenous infusion, diffuses in the organism according to the local blood flows, allowing one to follow them, for instance in the brain[6,7] and in the myocardium.[7,8] This radioelement is used to label several molecules of metabolical interest, especially the amino acids.[9] ^{11}C offers the possibility of labelling various cells, metabolites, transmettors and drugs, e.g. ^{11}CO-red blood cells,[10] ^{11}C-hexoses,[11] ^{11}C-fatty acids,[12] ^{11}C-amino acids,[13] ^{11}C-catecholamines,[14] ^{11}C-chlorpromazine[15].

These radioisotopes are not currently used at their full potential for applications in medicine and biology, principally because their production and utilization require the proximity of a cyclotron, a nuclear laboratory and a clinic fitted out with adequate means of investigation. These conditions are met at the Cyclotron Research Center in the University of Liège.

Type of Targets and Nuclear Parameters

The use of gaseous rather than solid targets for the production of these radionuclides offers several advantages: (1) no necessity of mechanical handling of the irradiated target; (2) no destruction of the target; (3) no long and dangerous chemical separation as the undesirable products are withdrawn through traps; (4) precise determination of the range of the incident charged particles and of the yield of production; (5) the facility to control the energy of the particles in the whole target—by closely adapting the range of energy of the particles in the target with the cross-section curve of the irradiated element, it is possible to decrease or to avoid the contaminating reactions.

The nuclear reactions likely to be involved in the production of these radioisotopes are listed in Table 1.

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TABLE 1. Principal possible methods of production of ^{15}O, ^{13}N and ^{11}C

Reactions	Q (MeV)	Reaction threshold (MeV)	Isotopic abundance (%)
$^{14}N(d, n)^{15}O$	+5.06	2.36	99.6
$^{14}N(d, \alpha n)^{11}C$	−5.14	5.88	99.6
$^{14}N(d, dn)^{13}N$	−10.55	12.06	99.6
$^{14}N(d, t)^{13}N$	−4.30	4.91	99.6
$^{14}N(d, 2n)^{14}O$	−8.115	9.27	99.6
$^{16}O(d, \alpha n)^{13}N$	−7.44	8.37	99.756
$^{16}O(d, t)^{15}O$	−9.411		99.756
$^{17}O(d, tn)^{15}O$	−13.553		0.039
$^{12}C(d, n)^{13}N$	−0.281	0.328	98.9
$^{13}C(d, 2n)^{13}N$	−4.2	4.9	1.1
$^{16}O(d, dn)^{13}N$	−7.44	8.37	99.756
$^{12}C(d, t)^{11}C$	−12.463		98.9
$^{13}C(d, tn)^{11}C$	−17.411		1.1
$^{14}N(p, \alpha)^{11}C$	−2.92	3.13	99.6
$^{14}N(p, d)^{13}N$		8.9	99.6
$^{14}N(p, pn)^{13}N$	−10.55	11.3	99.6
$^{15}N(p, n)^{15}O$	−3.54	3.8	0.366
$^{16}O(p, \alpha)^{13}N$	−5.21	5.5	99.756

The excitation function, the values of energy balance (Q), of the threshold of the reaction, of the isotopic abundance of the target nuclei and the possibility of eliminating the contaminating elements prescribed the choice, for the production of ^{15}O, ^{13}N and ^{11}C, of the following reactions:

$$^{14}N(d, n)^{15}O;\ ^{12}C(d, n)^{13}N;\ ^{14}N(p, \alpha)^{11}C.$$

Equipment

Figure 1 illustrates the equipment for the production of radioactive gases.

The cyclotron is a variable-energy, compact, CGR-MeV device.

The irradiation cell admits the beam transport system and the basic equipment of the terminal. It also contains the circuit of hot radiochemistry and of purification of the gases, which is provided with electromagnetic valves for remote control.

The gas treatment laboratory contains: (1) a unit of gas inlet which switches the different gases to be irradiated toward the target, (2) a unit of distribution of the irradiated gases which sends them pressured back to atmosphere pressure, measures the activities and controls the flow rates before utilization in the

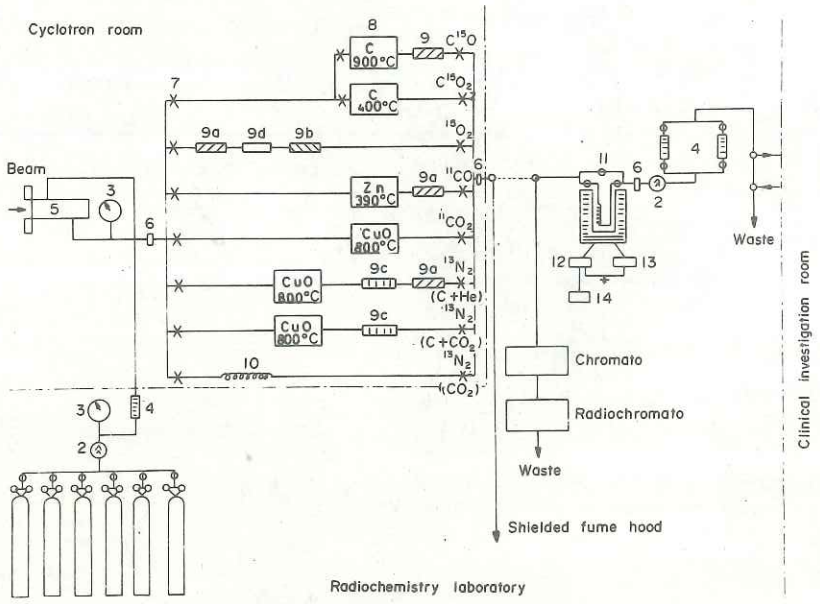

FIG. 1. Description of the whole set-up for the production, the control and the utilization of the short-lived radioactive gases: 1. Sweep/target gases. 2. Needle valve. 3. Pressure gauge. 4. Flowmeter. 5. Target. 6. Filter. 7. Solenoid valves. 8. Furnaces. 9. Traps. (a) soda lime, (b) silica gel, (c) magnesium perchlorate, (d) activated charcoal. 10. Copper spiral. 11. High pressure ionization chamber. 12. d.c. amplifier. 13. E.H.T. supply. 14. Chart recorder.

medical zone, (3) a unit of control, regulation and measurement, including chemical and radiochemical analysis, (4) a unit of labelling which shunts the system.

The medical laboratory is shielded from the radiation background of the gas treatment laboratory with a 50 cm thick, compact beton wall. It is equipped with a multiprobe coincidence detector for clinical applications.

Figure 2 gives a more detailed description of the basic equipment of the beam terminal and shows a gaseous target in position. It includes: (1) a standard "CSF" box connected to turbomolecular pump which contains a rotating wire probe allowing rough estimation of the beam profile; information from this and a vacuum gauge are reported in the machine control room. (2) An electropneumatic valve "VAT" protects the vacuum of the cyclotron in case of accidental exposure of the system to the atmosphere. (3) A parallelepiped box, with circular apertures permitting the connection of all useful apparatus for controls or measurements with the help of clamps and flanges. It holds a quartz which enables one to watch the beam by means of a video-camera circuit and is a target for measurement of current; both are retractable. Repairs at this point of the system necessitate breaking the vacuum: a valve with bellows quickly restores a rough vacuum, with the help of an auxiliary pump. (4) A Teflon flange holds a diaphragm of 4 graphite segments, isolated and distributed 90° from one another; the beam is centred by minimizing the equilibrated currents, as measured by 4 galvanometers. 4 cooling fins and a radial copper rod driven in a vacuum fully into the Teflon flange

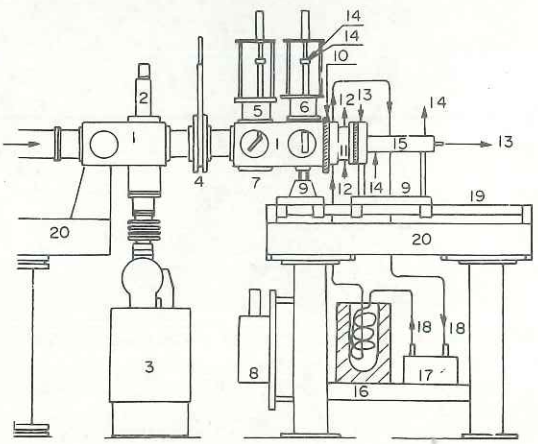

FIG. 2. Detailed description of the equipment of the beam terminal, of the organs of control and of a modular gaseous target: 1–1′. Standard C.S.F. and C.R.S. box. 2. Revolving probe. 3. Turbo-molecular pump. 4. Electropneumatic valve. 5. Removable "quartz". 6. "Faraday cup" with electron suppressor. 7. Side-light. 8. Camera. 9. Supports for standard box and target. 10. Diaphragm. 11. Window holder. 12–14. Input and output of desionized water. 13. Entrance and exit of gas. 15. Gaseous target C.R.C. 16. Liquid air. 17. Circulating pump. 18. He cooling. 19. Carriage way. 20. Under-frame.

can dissipate 4 × 60 W. (5) A window holder, with a cooling ring chamber fastened to a flange, is shut by a metallic window. The window must be thin enough so that the beam can get across with minimum loss of energy and current and strong enough to sustain a pressure of 2–3 kg cm^{-2}. Sheets of "HAVAR" alloy obtained from Hamilton Watch Company, Precision Metals Division, Lancaster, Pennsylvania, have the most interesting characteristics. (6) A gaseous cell, the type of which depends on the gas to be prepared, cooled with de-ionized water.

Each gaseous target is held by a flange identical to that of the window holder. When the two flanges are pressed through an isolating ring, they delimit a chamber into which it is easy to circulate a cooling gas. The cooling gas is helium which flows by means of a pump in a closed circuit including a copper spiral which dips in a Dewar flask.

The cell stands on a carriage which slides on rails allowing a precise and immediate adjustment of the flanges. Care is taken to have it electrically isolated in order to have correct current measurements.

The apparatus for gaseous chromatography is a Tracor MT-150 G with an ultrasonic U-90 detector, perfectly suited for permanent gas detection. This type of control permits the use of several carrier gases. The sampling is made in a shunt of the main line through an ultra-rapid injection valve which avoids any contamination from the surrounding air. The analyses require two 6′ × 1/8″ columns, one filled with Porapak Q (PQ) and the other with a molecular sieve (MS).[17]

The components separated from the gaseous mixture which come out from the exits of the chromatograph are sent onto a NaI probe to estimate the radiochemical impurities.[19] By trapping the radioactive gas by the help of a set of valves it is possible to determine the period of radioactive decay of the contaminants.

Results

Cross-sections

$^{14}N(d, n)^{15}O$

The cross-section values in the literature are in great disagreement. For example, RETZ-SCHMIDT *et al.*[16] present a maximum value of 22 mbarn at 3 MeV, whereas WOHLLEBEN *et al.*[19] give more steep variations going from 100 mbarn at 2 MeV to 300 mbarn at 3 MeV. WIELAND *et al.*[20] give a mean value of 76 mbarn between 2.14 and 5.38 MeV. We have determined by an indirect method the value $\bar{\sigma} = 235$ mbarn between 0.5 and 6.3 MeV, a value which might be in agreement with the result obtained from the excitation function established by WOHLLEBEN *et al.*[19]

$^{12}C(d, n)^{13}N$

We have experimentally determined a mean cross-section of 7.5 mbarn between 0 and 6.3 MeV, in close

agreement with the value that can be deduced from the yield curves obtained by KRASNOV *et al.*[21] and from the excitation function established by BRILL *et al.*[22]

$$^{14}N(p, \alpha)^{11}C$$

From the excitation curve of NOZAKI *et al.*,[23] a mean cross-section of 70 mbarn between 3 and 8 MeV can be computed. This value is near the cross-section that we have experimentally determined ($\bar{\sigma}$ = 78 mbarn between 3 and 8 MeV).

Yields

The ionization chamber is of the IG 12 (20th Century Electronics Ltd) type, filled with argon to a pressure of 20 atm. Its sensitivity to γ radiation of 0.4 to 1 MeV is from 35 to 50 times better than that of a same chamber under the pressure of 1 atm. The deep cavity delimitates an important range where the response is $1.64.10^{12}$ μCi/A and does not vary beyond a 1% range.

The absolute activity of the flowing gases is measured on a volume of 10 cm^3 in a spiral copper tube whose floor-space is within 4 × 4.5 cm ϕ. It is also possible to draw the decay curve without using geometry corrections. The ionization chamber currents are fed to a d.c. amplifier (Keithley Type 601 C) having a 14 Ω input impedance with a 20 pF shunt. The voltage obtained at a high resistance (10^6 to 10^{11} Ω) is amplified. Radioactive concentrations are expressed in mCi cm^{-3} and flows of activity in mCi sec^{-1}.

The radioactive concentrations were verified by measurement with Ge–Li on a sample taken with the help of a syringe at the end of the gas line.

Decay curves can also be analyzed in order to remove the radioactive contaminating substances having different periods. They confirm partly the results of chromatography with much more sensitivity for very short half-lives.

All the experimental results are gathered in Tables 2, 3 and 4 for the 3 preparation groups [$^{15}O_2$, $C^{15}O_2$, $C^{15}O$], [$^{13}N_2$, $^{13}N_2$ solution, $^{13}NH_3$ solution] and [$^{11}CO_2$, ^{11}CO].

These yields are obtained with specified beam currents and can therefore be increased by increasing the current; the windows stand firm perfectly at 40 μA. This remark is not valid for nitrogen isotonic solutions, which depend on the gas preparation technique, partial pressure in the bubble to be dissolved and their maximum solubility.

The gas flow rates have been calculated by a mathematical model of the system and were tested in practice with a view to yield the highest radioactive concentrations.[18]

TABLE 2. Production of ^{15}O-labelled molecules: parameters of production, radiochemistry of the target and of the preparation circuit, yields and impurities

Synthetized molecule	gaseous $^{15}O_2$	gaseous $C^{15}O_2$	gaseous $C^{15}O$
Nuclear reaction	$^{14}N(d, n)^{15}O$	$^{14}N(d, n)^{15}O$	$^{14}N(d, n)^{15}O$
Physical state of the target	gas	gas	gas
Parameters of irradiation			
Target current, μA	10.5	10.5	10.5
Particle energy			
initial, MeV	7	7	7
on the target, MeV	6.3	6.3	6.3
Windows			
material	HAVAR	HAVAR	HAVAR
thickness, μ	5.9	5.9	5.9
Collimator diameter, mm	20	20	20
Material of the irradiation cell	Stainless Steel	Stainless Steel	Stainless Steel
Carrying gas			
Nature	96%N_2–4%O_2	97.5%N_2–2.5%O_2	98%N_2–2%O_2
Pressure in the cell, kg cm^{-2}	0.54	0.61	0.54
Flow rate, cm^3 sec^{-1}	8.33	8.33	8.33
Furnaces			
Nature		charcoal	charcoal
Temperature, °C		400	900
Purpose		$Co \rightarrow CO_2$	$O_2 + 2C \rightarrow 2CO$
Traps			
Nature,	soda-lime		soda-lime
Trapped molecules	NO_2, CO_2, O_3 charcoal, N_2O silicagel, H_2O		NO_2, CO_2, O_3
Yields			
mCi cm^{-3}	0.26	0.22	0.08
mCi sec^{-1}	2.2	1.8	0.66
Impurities			
Cold chromatography	CO_2(<1/20%)	H_2, O_2	H_2, O_2, H_2O
Radiochromatography		$C^{15}O$(0.3%), $^{15}O_2$ (0.3%), $^{13}N_2$(0.3%)	$^{13}N_2$(0.3%)
Ge–Li	^{11}C(0.0076%)	$^{13}N_2$(0.3%)	

TABLE 3. Production of ^{13}N labelled molecules: parameters of production, radiochemistry of the target and the preparation circuit, yields and impurities

Synthetized molecules	gaseous $^{13}N_2$	dissolved $^{13}N_2$	gaseous $^{13}N_2$	dissolved $^{13}N_2$	$^{13}NH_3$
Nuclear reaction	$^{12}C(d,n)^{13}N$	$^{12}C(d,n)^{13}N$	$^{12}C(d,n)^{13}N$	$^{12}C(d,n)^{13}N$	$^{12}C(d,n)^{13}N$
Physical state of the target	gas	gas	thick target of charcoal	thick target of charcoal	gas
Parameters of irradiation					
Target current, μA	20	20	40	20	15
Particle energy					
initial, MeV	7	7	12.5	12.5	7
on the target, MeV	6.3	6.3	12.03 (50%) 5.1 (50%)		6.3
Windows					
material	HAVAR	HAVAR	HAVAR	HAVAR	HAVAR
thickness, μ	5.9	5.9	5.9	5.9	5.9
Target holder	—	—	Molybdenum, 70 μ thick 100 × 100 mesh lattice		
Collimator diameter, mm	25	25	25	25	20
Material of the irradiation cell	st. steel	st. steel	st. steel	st. steel	glass
Carrying gas					
Nature	CO_2(N48)	CO_2(N48)	He(N56)	CO_2(N48)	CH_4
Pressure in the cell, kg cm^{-2}	0.68	0.68	0.05	0.05	not very > P.A.
Flow rate, cm^3 sec^{-1}	1.2	1.2	1	1	16.7
Furnaces					
Nature		CuO	CuO	CuO	
Temperature, °C		800	800	800	
Purpose		oxydation of CH_4	$CO \rightarrow CO_2$, oxydation of CH_4		
Traps					
Nature, trapped molecules	Cu coil, $^{13}NO_2$	Cu coil, $^{13}NO_2$	Mg $(ClO_4)_2$, H_2O soda-lime, HCN, CO_2	$Mg(ClO_4)_2$, H_2O	soda-lime, HCN
Yields					
mCi cm^{-3}	0.060	0.29	1	1	0.5
mCi sec^{-1}	0.072		1		(20 min of bubbling)
Impurities					
Cold chromatography	N_2(1500 ppm)–H_2–CH_4 (traces)		CH_4 (traces)		
Ge–Li					$HC^{13}N$(~2%)

TABLE 4. Production of ^{11}CO and $^{11}CO_2$: parameters of production, radiochemistry, yields and impurities

Synthetized molecules	gaseous $^{11}CO_2$	gaseous ^{11}CO
Nuclear reaction	$^{14}N(p, \alpha)^{11}C$	$^{14}N(p, \alpha)^{11}C$
Physical state of the target	gas	gas
Parameters of irradiation		
Target current, μA	15	15
Particle energy		
initial, MeV	8.5	8.5
on the target, MeV	8	8
Windows		
material	HAVAR	HAVAR
thickness, μ	5.9	5.9
Collimator diameter, mm	25	25
Material of the irradiation cell	st. steel	st. steel
Carrying gas		
Nature	99.9%N_2(A52)–0.1% O_2 (A48)	
Pressure in the cell kg cm^{-2}	0.53	0.53
Flow rate, cm^3 sec^{-1}	1.4	1.4
Furnaces		
Nature	CuO	Zinc
Temperature, °C	800	390
Purpose	$CO \rightarrow CO_2$	$CO_2 \rightarrow CO$
Traps		
Nature	$Mg(ClO_4)_2$ at both sides of the target, H_2O	$Mg(ClO_4)_2$ at both sides of the target, H_2O
Trapped molecules		soda-lime at the end of the purification line, CO_2
Yields		
mCi cm^{-3}	0.18	0.15
mCi sec^{-1}	0.25	0.2
Impurities		
Cold chromatography	O_2(0.1%)	H_2
Radiochromatography	$^{14}O_2$ (6%)	
Ge-Li	$^{14}O_2$ (6%)	

Conclusion

The routine production of ^{11}C, ^{13}N and ^{15}O was designed and realized at the Cyclotron Research Center of Liège University.

Simple labelled molecules in gas (O_2, $C^{15}O$, $C^{15}O_2$, $^{13}N_2$, ^{11}CO, $^{11}CO_2$) or in solution ($^{13}N_2$ isotonic solution, $^{13}NH_3$) are available with specific activities which equal or even exceed the best results of the literature.

The yields of gaseous $^{13}N_2$ obtained thanks to a new target conception are especially favourable.

Besides the contribution of original techniques, improvements to the working parameters were obtained; the use of a mathematical model for the optimization of the flow rates in the gaseous targets is an original contribution.

The realized molecules are, *per se*, of considerable importance for medical applications. They are, furthermore, fore-runners of the labelling of more complex molecules. Two methods of organic labelling are made concrete. The biosynthetic method is used for the photosynthesis of ^{11}C-glucose. The organo–synthetic method is in the process of realization with the synthesis of highly reactive ^{11}C-labelled organic compounds, $H^{11}CN$, $H^{11}COH$, $^{11}CH_3OH$, CH_3–$^{11}COONa$, $^{11}CH{=}^{11}CH$ and $^{11}CH_3I$.

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