PRODUCTION OF SHORT-LIVED RADIOISOTOPES FOR MEDICAL APPLICATIONS USING HIGH-ENERGY
REACTIONS AT JULIC

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Abstract

The advantages of high energy nuclear reactions for the production of some special short-lived carrier-free radionuclides for application in nuclear medicine are outlined. The routine production of ^{11}C (T = 20.3 min), ^{123}I (T = 13.3 h) and ^{28}Mg (T = 21.1 h) at the Jülich Isochronous Cyclotron JULIC via the ^{12}C(p,pn)^{11}C-, ^{127}I(d,6n)^{123}Xe(β^+,EC)^{123}I- and ^{27}Al(α,3p)^{28}Mg-reaction, respectively, is described. Some areas of fast labelling and its applications are given.

1. Introduction

Interest in the application of cyclotron-produced short-lived carrier-free radionuclides in nuclear medicine and other life sciences is constantly increasing. The main advantages of the use of such radionuclides, particularly of neutron deficient isotopes which do not emit β^-, lie in their short half-lives, suitable γ-ray energies and their weightless carrier-free nature. Due to the short half-lives the radiation dose to the patients is small and the measurements can be repeated, if necessary. This results are in better statistical accuracy which leads to better diagnostic information. The γ-rays and/or annihilation radiation generally associated with these radionuclides penetrate the tissues and can be easily detected externally. These nuclides are therefore very suitable for in-vivo studies, not only for localisation and function diagnostics but also for studying in-vivo pharmaco kinetics. If the nuclides are applied carrier-free, and hence practically weightless, they do not disturb the biological equilibrium of the living organism and even toxic substances can be applied. Due to these advantageous properties one strives to introduce short-lived cyclotron-produced radioisotopes, either directly or in the form of labelled molecules, to the routine biological and clinical applications.

The application of such radionuclides depends to a great extent on the availability of suitable cyclotrons. Some of the important isotopes like ^{11}C, ^{13}N, ^{18}F and ^{52}Fe are in general produced routinely in low-energy compact cyclotrons which are often attached to medical centres. However, there are some medically important nuclides, in particular ^{123}I, which can be produced in high yields and good purity easier via high-energy nuclear reactions. Therefore, in many places high-energy cyclotrons, which were originally planned for physical experiments only, are increasingly used also for the production of some special isotopes. This is also the case with the high-energy isochronous cyclotron JULIC at KFA Jülich. The relatively small beam currents available in such a machine, however, exclude its universal utilization as a production cyclotron. Nonetheless, it is very suitable for producing via high-energy nuclear reactions some nuclides, and we want to report on the production of ^{11}C, ^{123}I and ^{28}Mg. High energy reactions should also be useful for the production of neutron deficient bromine-isotopes such as ^{75}Br, ^{76}Br and ^{77}Br via Br(d,xn)Kr(β^+,EC)Br reactions, particularly because these bromine isotopes are becoming important in nuclear medicine as an substitute label for the less strongly bounded iodine.

2. Carbon-11

For the production of radiopharmaceuticals labelled with the 20.3 min ^{11}C one attempts, by choosing suitable target materials, to obtain reactive ^{11}C-labelled intermediates which are formed in very fast hot atom reactions between the recoiling carbon atom and the target material[1]. These
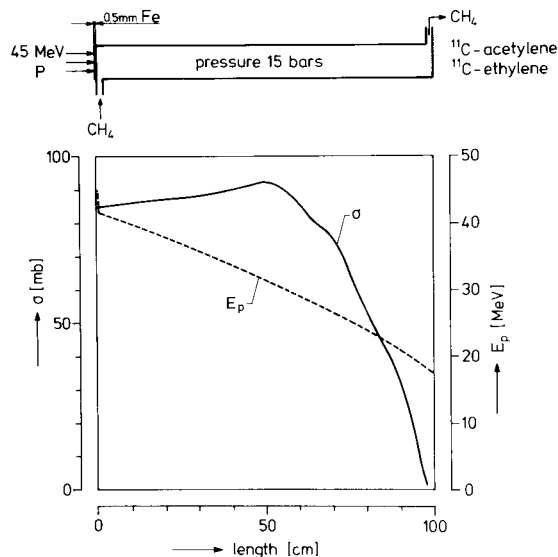

Fig. 1 Schematic diagram of target and irradiation conditions for the production of carbon-11 via the reaction ^{12}C(p,pn)^{11}C. The cross section σ[4,5]) and the absorption of the protons in the target is shown as a function of the target length.

intermediates then serve as starting materials for the production of radiopharmaceuticals via classical methods of synthesis[2]) followed by purification and quality control.

In many cases $^{11}CO_2$ and ^{11}CO serve as intermediates. These species generally are produced via the reaction $^{14}N(p,\alpha)^{11}C$ by employing a degraded proton energy of 13 MeV[3]). At the Jülich Isochronous Cyclotron the reaction $^{12}C(p,pn)^{11}C$ is more suitable and particularly useful for the production of carrier-free ^{11}C-acetylene. Using methane, propane or cyclopropane as target material carrier-free ^{11}C-acetylene with radiochemical yields between 30 to 50 % is obtained as recoil product. We use a methane flow gas target whose length and also the gas pressure are so adjusted that the maximum yield, as expected from the excitation functions[4,5]), is obtained (cf. fig. 1). With 45 MeV protons we obtain yields of about 0.1 mCi/μAmin ^{11}C-acetylene. At the same time some ^{11}C-ethylene and other products are also formed[6]). A chemical separation of the ^{11}C-acetylene from the other products is easily achieved via gas chromatography[7]). Acetylene labelled with ^{11}C is employed for the production of lithium-acetylide, a useful compound to introduce the acetylene group, e.g. for labelling of steroids.

3. Iodine-123

3.1 Methods of Production

Due to its suitable nuclear properties, the 13.3 h ^{123}I has several advantages[8]) over ^{131}I which has till now been very commonly employed for medical purposes. Several methods are available for the production of ^{123}I, a summary of which has already been given by us[9]). The application of high-energy cyclotrons for the production of ^{123}I via spallation reactions has the following advantages in comparison to the use of low-energy compact cyclotrons:
1) Target material employed is elementary iodine or its compounds which are much cheaper than the highly enriched tellurium or antimony isotopes needed for production using a compact cyclotron.
2) The thickness of the target can be chosen such that the energy of the incident particles is degraded to the optimum energy depicted by the excitation functions. By this way higher yields can be achieved.
3) The production of ^{123}I via the decay of the first formed ^{123}Xe avoids the formation of the undesired ^{124}I activity. Furthermore, it allows the application of the so called "excitation" or "decay-induced labelling" which makes use of the reactive daughter ions formed in the decay of ^{123}Xe for direct labelling or for the production of reactive iodination reagents[10]).

At the high-energy machines ^{123}Xe is generally produced via the reaction $^{127}I(p,5n)^{123}Xe$ at $E_p \sim 55$ MeV. Since the

maximum proton energy available at JULIC is 45 MeV, the above reaction is not ideal for our machine. We therefore make use of the reaction $^{127}I(d,6n)^{123}Xe$[11]). A calculation using the excitation functions of the two reactions shows that the latter reaction gives ^{123}I yields slightly lower than the former reaction[11,12]). Using an incident deuteron energy of 78 MeV, a target thickness corresponding to the degradation of E_d by 14 MeV and the ^{123}Xe precursor decay time of 6.7 h, we get ^{123}I yields of 8 mCi/μAh. The level of impurities then amounts to <0.2 % ^{125}I and <0.02 % ^{121}Te.

Some preliminary experiments have also been carried out on the production of ^{123}I via $^{127}I(\alpha,8n)^{123}Cs(\beta^+)^{123}Xe(\beta^+,EC)^{123}I$. The ^{123}I yield appears to be lower than that via the $^{127}I(d,6n)^{123}Xe(\beta^+,EC)^{123}I$ reaction. However, under certain circumstances the $(\alpha,8n)$ reaction may serve as a supplementary method of production of ^{123}I at JULIC.

At present the demand for ^{123}I is much greater than its availability. A network of collaborating cyclotrons seems necessary to decrease the burden of an individual place and at the same time garantee a broader distribution.

3.2 Target Arrangements

We make use of two target arrangements. In the first one, which has already been reported[11]), NaI powder is irradiated in the external beam and the radioactive xenon is swept off on-line by a helium stream. The second target arrangement has been developed to make use of the high-intensity internal beam. This, however, produces ^{123}Xe in batches. A view of this target system is shown in fig. 2. The target material (NaI)
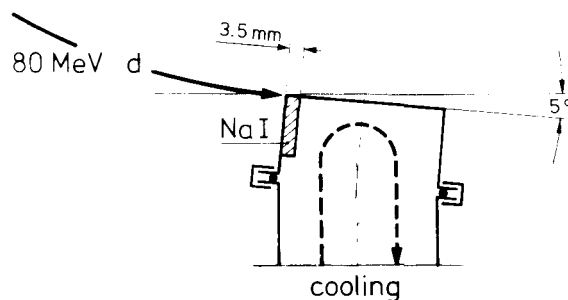
Fig. 2 Schematic diagram of the arrangement of the internal batch target for production of ^{123}I via the reaction $^{127}I(d,6n)^{123}Xe(\beta^+,EC)^{123}I$.

is pressed in a water-cooled well and closed by an air tight screw cap. In order to avoid the absorption of the beam in the material of the cap the whole assembly is tilted by 5^0 to the direction of the beam. At the end of the irradiation the target is released and transferred to the laboratory area where it is opened in an air tight system and the

irradiated NaI dissolved in a small amount of water. ^{123}Xe formed is then removed by streaming in helium and after letting it pass through drying traps it is collected in a vacuum apparatus[9]) and diluted with some inactive xenon. 2 ml ampoules containing about 50 µl of O.01 N NaOH solution are then filled with xenon which is allowed to decay. Using this system yields of 80 mCi ^{123}I per run at 10 µA can be achieved.

3.3 Production and Quality Control of Na^{123}I

After xenon has decayed for about 7 h the ampoule is warmed up for 5 - 7 minutes at 100 ^{0}C and then opened whereby xenon is allowed to escape. High pressure liquid and thin layer chromatographic analyses show that more than 98 % of the ^{123}I separated is present as iodide, the remaining part being iodate. Experience has shown that the carrier-free iodine species are expectedly very sensitive to the surrounding medium and therefore characterization of species under conditions of the analytical quality control is meaningless. A stabilization of the species can be achieved either by adding a reducing agent ($S_2O_3^-$) or by introducing a few µg of iodide carrier. At Jülich about 50 to 100 mCi ^{123}I are produced per week routinely, an amount which is much too small to satisfy even the demands of the State of Nordrhein-Westfalen.

3.4 Production of ^{123}I-labelled Compounds

In our institute a large number of biomolecules have been labelled with ^{123}I. The direct xenon gas exposure technique is especially suitable for iodine-halogen exchange in molten or liquid systems. A very valuable extension of the labelling technique is provided by the decay of ^{123}Xe in a crystalline matrix of KIO_3. This reagent appears to be extremely reactive, especially for labelling of aromatic systems[10]). The purification of the labelled molecules is carried out via high pressure liquid chromatography.

In collaboration with the Institut für Medizin of the KFA Jülich as well as other medical institutes the ^{123}I-labelled compounds are used for various purposes, e.g. saturated and unsaturated iodofatty acids for investigations of heart muscle metabolism; o-, m- and p-iodohippuric acid for kidney function studies; monoiodotyrosine, mono-iodothyronine and monoiodoinsuline for metabolic studies; monoiodinated fibrinogene for diagnosis of the vein thrombosis; mono-iodinated hepatitis antibody for antibody-antigene investigations etc. All these applications have been carried out so far using ^{125}I and ^{131}I. The ^{123}I label, however, is a considerable improvement. Due to its suitable nuclear properties, larger amounts of activity can be applied. This together with the ideal γ-ray energy of 159 keV gives rise to much better and more informative pictures.

4. Magnesium-28

^{28}Mg is the only radioisotope of this element whose half-life (T = 21.1 h) is long enough to enable its use in the life sciences. It can be produced through various nuclear reactions, a summary of which has already been given by us[9]). In general ^{28}Mg of low specific activity is produced in nuclear reactors and of high specific activity via the ^{26}Mg(t,p)^{28}Mg reaction. Our excitation function measurements on the ^{26}Mg(α,2p)^{28}Mg reaction show (cf. fig. 3) that the ^{28}Mg yields are appreciable. High specific activity, however, can be achieved only by employing isotopically enriched ^{26}Mg as target material which makes the process of production rather costly.
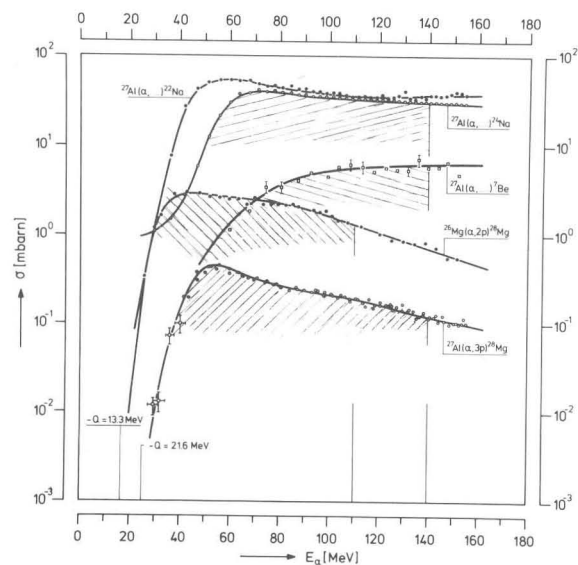
Fig. 3 Excitation functions of nuclear reactions leading to ^{28}Mg and to the contaminants ^{22}Na, ^{24}Na and ^{7}Be.

For the production of carrier-free ^{28}Mg two reactions appear suitable: ^{27}Al(α,3p)^{28}Mg and ^{30}Si(γ,2p)^{28}Mg. At JULIC we make use of the former reaction. Since this reaction has not been well investigated over the energy range of α-particles available in our machine, we measured the excitation functions using the stacked foil technique. The results are shown in fig. 3 together with the excitation functions for the formation of the main impurities ^{24}Na, ^{22}Na and ^{7}Be. The maximum of the excitation function for the reaction ^{27}Al(α,3p)^{28}Mg lies at about 55 MeV. Optimum yields of ^{28}Mg are obtained by using incident α-particle energy of 140 MeV. The theoretically achievable ^{28}Mg activity at the end of irradiation amounts to 40 µCi/µAh. By irradiating Al with 140 MeV α-particles in the internal beam of JULIC about 3 mCi ^{28}Mg are produced per run.

The main undesired activity produced is 15 h ^{24}Na. Its contribution amounts to about 150 times that of the ^{28}Mg activity. Using a radiochemical method which employs adsorption of carrier-free ^{28}Mg on $Fe(OH)_3$ followed by anion-exchange chromatography, ^{28}Mg is obtained carrier-free in a pure form. Because of the high level of activity the chemical operations are performed in a lead cell. The level of the impurities in ^{28}Mg after chemical separation is: ^{24}Na < 0.1 %, ^{7}Be < 0.01 %.

^{28}Mg is used in studies pertaining to plant physiology and exchange processes in photosynthesis. Furthermore, medical investigations on the magnesium metabolism in small children using ^{28}Mg showed in different cases hypomagnesemia, which is generally fatal[13]). Since the symptoms of this disease are similar to those for calcium deficiency, it is probably a dark area and open fully for investigations. With a purposeful magnesium therapy the life of such small children could possibly be saved.

References

1) for a review cf.: G. Stöcklin, "Chemie heißer Atome", Verlag Chemie, Weinheim/Bergstr. (1969), and extended French edition "Chimie des Atomes Chauds", Masson et Cie (1972)

2) for a review cf.: A.P. Wolf, D.R. Christman, J.S. Fowler and R.M. Lambrecht, Proc. Symp. Radiopharm. and Labelled Compounds, IAEA, Vienna, 1 (1973) 345

3) R. Weinreich, F. Ritzl, L.E. Feinendegen, H.G. Schnippering and G. Stöcklin, Rad. and Environm. Biophys., in press

4) A.B. Whitehead and J.S. Foster, Canad.J. Phys. 36 (1958) 1276

5) J.B. Cumming, Nucl.Phys. 49 (1963) 417

6) G. Stöcklin, H. Stangl. D.R. Christman, J.B. Cumming and A.P. Wolf, J.Phys.Chem. 67 (1963) 1735

7) H.-J. Machulla and G. Stöcklin, Proc. XIIIth Intern.Ann.Meet.Soc.Nucl. Medicine, Copenhagen, (1975), in press

8) W.G. Myers and H.O. Anger, J.Nucl.Med. 3 (1962) 183

9) R. Weinreich, S.M. Qaim, H. Michael and G. Stöcklin, J.Radioanalyt.Chem., in press

10) M. El-Garhy and G. Stöcklin, Radiochem. Radioanalyt. Letters 18 (1974) 281

11) R. Weinreich, O. Schult and G. Stöcklin, Int.J.Appl.Radiat. Isotopes 25 (1974) 535

12) S.R. Wilkins, S.T. Shimose, H.H. Hines, J.A. Jungerman, F. Hegedus and G.L. DeNardo, Int.J.Appl.Radiat. Isotopes 26 (1975) 279

13) I. Lombeck, F. Ritzl, H.G. Schnippering, H. Michael, H.J. Bremer, L.E. Feinendegen and W. Kosenow, Z.Kinderheilk. 118 (1975) 249