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Rapid communication

Enhanced production possibility of the therapeutic radionuclides ^{64}Cu, ^{67}Cu and ^{89}Sr *via* (*n*, *p*) reactions induced by fast spectral neutrons

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Summary. Spectrum averaged cross sections for the ^{64}Zn(n, p)^{64}Cu, ^{67}Zn(n, p)^{67}Cu and ^{89}Y(n, p)^{89}Sr reactions were measured using a 14 MeV *d*(Be) neutron source. In each case a clean radiochemical separation was performed and the radioactivity of the product was determined *via* high-resolution γ-ray spectrometry or anticoincidence β^- counting. The cross sections are three to five times higher than with a fission neutron spectrum. It is postulated that at an intense fast spectral neutron source, *e.g.* a spallation source, it would be advantageous to use an (n, p) reaction: GBq amounts of ^{64}Cu and ^{67}Cu could be produced in one hour irradiation and of ^{89}Sr in about one day irradiation.

1. Introduction

Over the last decade internal therapy using radionuclides has been gaining considerable significance [cf. 1,2]. The radionuclides of interest include β^-, α and Auger electron emitters. Most of them are produced at nuclear reactors [cf. 3], although in recent years the use of cyclotrons has also been enhancing [cf. 4,5]. In reactor production, most commonly the (n, γ) process is utilized which, however, leads to a product of low specific activity, unless it decays to a daughter nuclide which is of high specific activity. A few examples are: ^{124}Xe(n, γ)^{125}Xe $\rightarrow$ ^{125}I, ^{130}Te(n, γ)^{131m,g}Te $\rightarrow$ ^{131}I, ^{186}W(n, γ)^{187}W(n, γ)^{188}W $\rightarrow$ ^{188}Re. In certain other cases where this parent/daughter system is not applicable, resort is made to an (n, p) reaction. A few examples are: ^{32}S(n, p)^{32}P, ^{64}Zn(n, p)^{64}Cu, ^{67}Zn(n, p)^{67}Cu, ^{89}Y(n, p)^{89}Sr. The cross sections of those reactions averaged over a fission neutron spectrum are, however, generally low [cf. 6], so that the expected product yield too is often low. Nonetheless, ^{32}P and ^{89}Sr, produced *via* the (n, p) reaction, are commercially available.

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In this work we considered it worthwhile to investigate the formation of ^{64}Cu ($T_{1/2} = 12.7$ h) , ^{67}Cu ($T_{1/2} = 61.9$ h) and ^{89}Sr ($T_{1/2} = 50.5$ d) *via* the (n, p) reactions on ^{64}Zn, ^{67}Zn and ^{89}Y with 14 MeV *d*(Be) breakup neutrons. The radionuclide ^{64}Cu has the advantage of combining therapy with positron emission tomography (PET), the radionuclide ^{67}Cu emits low-energy β^- particles and has an ideal half-life for therapy, and ^{89}Sr is a pure β^- emitter. Considerable experience is available in this institute with regard to the characterization of *d*(Be) breakup neutrons and their use in cross section measurements [cf. 7–11]. It is felt that, as far as the (n, p) reaction is concerned, the 14 MeV *d*(Be) neutrons may to a first approximation give a cross section comparable to that with other fast spectral neutrons, *e.g.* spallation neutrons. The measured data should therefore reflect whether a spallation neutron source would be superior to a fission reactor for the production of therapeutic radionuclides *via* the (n, p) reaction.

2. Experimental

2.1 Neutron source and irradiations

The *d*(Be) neutron source installed at the compact cyclotron CV28 consists of a disk shaped metallic Be (19.7 mm diam., 1.9 mm thick, 98% purity) embedded into a 2 mm thick copper holder, which is cooled with water. The neutron energy spectra and yields of such a target, investigated as a function of deuteron energy have been reported earlier [11]. For irradiation the target material ZnO (99.9%, Heraeus Feinchemikalien und Laborbedarf) or Y_2O_3 (99.99%, Hicol b.v.-chimicals) was pressed into a pellet (20 mm diam., 4 mm thick) and put inside an Al-capsule for protection. A set of high purity Al, Fe and Ni foils was put on both ends of the capsule. The sample was then placed in the 0° direction at a distance of 1 cm from the neutron source. Irradiation of the Be-target was done with 14 MeV deuterons for 2 to 11 h at a beam current of 5 μA; the neutrons generated thereby activated the various samples.

2.2 Monitor reactions

In order to monitor the integrated neutron flux density three nuclear reactions, namely $^{27}Al(n, \alpha)^{24}Na$, $^{56}Fe(n, p)^{56}Mn$ and $^{58}Ni(n, p)^{58}Co$, were used. The excitation functions of those monitor reactions were taken from the Activation File [cf. 12] and therefrom the average cross section for the neutron spectral distribution reported in Ref. [11] was obtained. The average integrated neutron flux during the irradiation was then calculated using the average cross section and the measured activity of the product. It was found to be about 7×10^{10} n/s cm^2 at a distance of 1 cm from the source. The flux degradation in an average sample of 0.6 cm thickness was about 32%.

2.3 Radiochemical separations

The separation of ^{64}Cu and ^{67}Cu was done by solvent extraction with copper-dithizone [13, 14]. The irradiated ZnO pellet was dissolved in conc. HCl and evaporated to dryness. The residue was taken up in 1 M HCl and the copper isotopes produced were extracted with 0.01% dithizone in CCl_4 in a 1 : 1 ratio. The separation, when done without carrier, needed no more than three extractions. If a small amount of Cu carrier was added, more extraction steps were needed. By shaking the organic solution in a 1 : 10 ratio with 7 M HCl mixed with H_2O_2 (*ca.* 5 vol %) the complex could be destroyed and the copper transferred to the aqueous phase. After washing with CCl_4 the aqueous phase was concentrated and analysed *via* γ-ray spectrometry. The separation yield was determined radiometrically (by comparing the ^{67}Cu activity before and after separation) and was about 86%.

In studies on ^{89}Sr a radiochemical separation was absolutely necessary since it is a pure β^- emitter. The carrier added $Y(OH)_3$ precipitation method used earlier [15] did not give satisfactory results. A modified method was therefore developed. To the irradiated Y_2O_3 pellet (weighing about 4 g) 30 mg $SrCO_3$ carrier was added and the mixture dissolved in conc. HCl. The acid was evaporated and the residue taken up in 0.1 N EDTA at pH 12. Slowly 1 M H_2SO_4 was added until pH 3.5 was reached and $SrSO_4$ precipitation started. The solution was heated for two hours and then cooled to room temperature. The precipitate was filtered and washed with 0.1 N Na_2SO_4 and water. The deposit was dissolved in 16 M HNO_3 and extracted with TBP for additional cleaning [16]. The final product was sedimented on a 0.1 mm thick Al foil as a thin layer for β^- counting. The chemical yield was about 40% and was determined *via* neutron activation analysis after the completion of the experiment.

2.4 Measurement of radioactivity

The radioactivity of the pure β^- emitter ^{89}Sr was determined using an anticoincidence gas flow proportional counter (Berthold). Thin samples of about 11 mm diameter were prepared and covered by thin plastic foils for protection. The self-absorption within the sample was below 1%. Since counting was started about 3 weeks after the irradiation, the ^{90}Y formed had decayed out.

Any possible contamination from ^{88}Y and ^{86}Rb was checked *via* γ-ray spectrometry and absorption measurements. In all measurements at least 10 000 counts were accumulated so that the error in the counting statistics was below 1%. Measurement was done over a period of about six months and the decay curve was carefully analysed. In each case only the 50.5 d ^{89}Sr was observed. From extrapolation the count rate at EOB was obtained.

The radioactivity of the irradiated monitor foils was assayed *via* γ-ray spectrometry using a HPGe-detector (Ortec) and of the separated Cu fractions using a Ge(Li)-detector (Canberra). All samples were placed at a distance of at least 10 cm from the detector. For measurement of the annihilation photons of the ^{64}Cu positrons, a chamber made of 2 mm thick copper was used to guarantee a small volume at a defined distance for the particles to annihilate. Peak area analysis was done using the software Gamma Vision, Version 5.10. The area under the annihilation peak was determined manually. For characterization of the monitor reaction products ^{24}Na, ^{56}Mn and ^{58}Co, well established decay data were used. The activity of ^{67}Cu was determined relative to the 184.6 keV γ-ray (48.7%). In the case of ^{64}Cu the annihilation decay curve was carefully analysed and the contribution of the 12.7 h component was determined; it amounted to $> 99\%$. The intensity of the annihilation radiation was adopted as 38%. The count rate of each product was extrapolated to EOB by using the respective half-life.

2.5 Calculation of cross sections and estimation of errors

The count rate of each product (at EOB) was converted to absolute activity by introducing corrections for the emission probability of β^-- or γ-ray, detector efficiency and chemical yield. The efficiencies of the detectors were determined experimentally using well calibrated β^-- and γ-ray sources (supplied by Amersham International and PTB Braunschweig).

Cross sections were calculated using the well-known activation equation. For this purpose the absolute activities of the products (see above) and the average neutron flux density derived *via* the monitor reactions were used.

The uncertainties in the cross sections arose from the following principal sources: counting statistics (1%–2%), β^-- and annihilation radiation decay curve analysis (5%), detector efficiency (γ-counting: 5%, β^--counting: 12%), sample mass ($< 1\%$), decay constants (1%–3%), average neutron flux (15%), chemical yield (8%). The total uncertainty in each cross section value was obtained by combining all the individual uncertainties in quadrature. For measurement of ^{64}Cu *via* annihilation radiation the total uncertainty amounted to 19% and for measurement of ^{89}Sr *via* β^- counting to 22%. The measurement of ^{67}Cu was done using γ-ray spectrometry and the total uncertainty in the cross section was estimated as 17%.

3. Results and discussion

The experimentally determined average cross sections of the three (n, p) reactions under consideration in this work, induced by 14 MeV d(Be) neutrons, are given in Table 1. The

Table 1. Experimentally determined average cross sections of (n, p) reactions induced by 14 MeV *d*(Be) neutrons and fission neutrons.

Nuclear reaction	Average cross section $\langle\sigma\rangle$ [mb]	
	14 MeV *d*(Be) breakup neutron spectrum[a]	Fission neutron spectrum[b]
^{64}Zn$(n, p)^{64}$Cu	132 ± 25	31.0 ± 2.3
^{67}Zn$(n, p)^{67}$Cu	5.13 ± 0.87	1.07 ± 0.04
^{89}Y$(n, p)^{89}$Sr	0.91 ± 0.20	0.31 ± 0.06

a: Values from present measurements;
b: Values from Ref. [6].

cross section is relatively high for the ^{64}Zn$(n, p)^{64}$Cu reaction but decreases rapidly with the increasing mass and charge of the target nucleus. Very conspicuous is the sharp decrease in the (n, p) cross section while proceeding from ^{64}Zn to ^{67}Zn. This isotopic effect is due to the different thresholds of the two reactions. Whereas the threshold of the ^{64}Zn$(n, p)^{64}$Cu reaction lies at 0.9 MeV [cf. 12], that of the ^{67}Zn$(n, p)^{67}$Cu reaction is at about 3 MeV [cf. 17]. The 14 MeV *d*(Be) neutron spectrum is not hard enough to excite the compound nucleus to energies much above the thresholds of the two reactions. In other words, the excitation energy is high enough to favour the (n, p) reaction on ^{64}Zn but not on ^{67}Zn. This postulate is supported by the fact that isotopic effects have not been observed in extensive measurements with 30 MeV *d*(Be) neutrons [cf. 7] and 53 MeV *d*(Be) neutrons [cf. 8], *i.e.* with neutron spectra having much longer tails and much higher mean energies. The low cross section of the ^{89}Y$(n, p)^{89}$Sr reaction with 14 MeV *d*(Be) neutrons is due to the high threshold of 5.8 MeV [cf. 15].

For comparison the average cross sections of the three (n, p) reactions under consideration induced by fission neutrons are also given in Table 1. They are recommended values [cf. 6] based on several measurements. It is obvious that the cross section of a reaction with 14 MeV *d*(Be) neutrons is 3 to 5 times higher than that with the fission neutrons.

We consider now briefly the implications of these average cross section measurements on the production of the three therapeutic radionuclides ^{64}Cu, ^{67}Cu and ^{89}Sr. As mentioned above, the yields obtained *via* reactor irradiations are low. For ^{64}Cu and ^{67}Cu production, therefore, there has been a shift towards the use of a cyclotron. For ^{89}Sr production, however, a cyclotron method is not available. The procedure used for no-carrier-added production of ^{89}Sr is still the ^{89}Y$(n, p)^{89}$Sr reaction and very long irradiations in the reactor core are needed [cf. 18]. Our measurements show that if a harder neutron spectrum is used, the yields of all the three products could be considerably improved. On the other hand, it should be emphasized that only spectral neutrons with average neutron energies above a few MeV would be useful. Thus not only thermal and breeder reactor neutrons but also Linac-based white neutron sources would not lead to much enhancement of the (n, p) reaction product yield. Evidently any of the four major quasi-monoenergetic neutron sources, *viz.* *p*(Li), *dd*, *dt* and *d*(Be), would be useful. However, to date none of those sources has been constructed with the neutron intensity comparable to that in a nuclear reactor. It is therefore meaningless to consider those sources for radionuclide production. The most realistic and promising neutron sources deserving consideration for production of the above mentioned therapeutic radionuclides appear to be a fusion reactor and a spallation neutron source. Since a fusion reactor is still rather far from realization, the utilization of a spallation neutron source appears to be most promising.

The average neutron energy of the spallation neutrons is estimated to be 3.98 MeV [cf. 19] and that of the 14 MeV *d*(Be) neutrons as 4.95 MeV. The data measured in this work are assumed to reflect to a first approximation the average (n, p) cross section values with spallation type neutrons. In fact these may be regarded as conservative estimates and the real (n, p) cross sections would possibly be higher with spallation neutrons. Since the neutron flux of a high-intensity spallation source is generally expected to be by an order of magnitude higher than that of a medium flux nuclear reactor used in radionuclide production, it is estimated that the yields of the three radionuclides under consideration would be 30 to 50 times higher with a spallation source than in a nuclear reactor. It should then be possible to obtain GBq amounts of ^{64}Cu and ^{67}Cu in one hour irradiation and of ^{89}Sr in about one day irradiation.

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