Thick target yield measurement of $^{211}$At through the nuclear reaction $^{209}$Bi($\alpha$,2n)

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Abstract. Radionuclide Therapy (RNT) and Radioimmunotherapy (RIT) are potentially of great interest for cancer therapy. In many therapeutic applications alpha emitters should be much more effective than already-approved beta emitters due to the short range and high linear energy transfer of alpha particles. $^{213}$Bi is an important alpha emitter already used in clinical trials but the half-life of this radioisotope is short (46 minutes) and so its use is limited for certain therapies. $^{211}$At is potentially very interesting for medical purposes because of its longer half-life of 7.2 hours, and suitable decay scheme. We have studied the cyclotron-based production of $^{211}$At via the reaction $^{209}$Bi($\alpha$,2n), this production route probably being the most promising in the long term. The energy dependence of thick target yields and the reaction cross sections for the production of $^{211}$At and $^{210}$At were determined and found to be in good agreement with literature. The best energy to produce $^{211}$At is 28-29 MeV. The possible production of the undesired, highly radiotoxic, and long-lived alpha-emitting $^{210}$Po (138.38 days), which is produced from decay of $^{210}$At, is also discussed.

1. Introduction

Radionuclide Therapy (RNT) and Radioimmunotherapy (RIT) are promising therapeutic approaches to treat cancers that do not respond to chemotherapy and cannot be treated by surgery or classical radiotherapy. The antibody ibritumomab labeled with the high-energy $\beta$-emitter $^{90}$Y is the first compound for RIT that has been granted market approval [1,2] for treatment of Non Hodgkin’s Lymphoma. However, for this use there is an appreciable mismatch between the range of the $\beta$-particles emitted by $^{90}$Y, up to 12 mm in human tissue, and the dimension of the target tissue, which is individual cells. In this case the choice of the radioisotope has been determined by its broad availability and affordable cost, even though it is not the ideal candidate for the purpose of single cell destruction. Radioisotopes with different properties are required for therapy in order to adjust the range of particles emitted to the size of the tumor, the metastasis or micrometastasis to be treated. Combination radionuclide therapy shows improved therapeutic efficacy, for example $^{177}$Lu and $^{90}$Y-
labeled molecules can be combined according to the dimension of the tumour [3]. For small metastases, residual disease or killing single cancer cells alpha-emitting radionuclides are expected to be the most suitable since they combine short range of several cell diameters with a high linear energy transfer. Among the most promising alpha-emitting radioisotopes $^{213}$Bi has the advantage of being available in a hospital setting via a $^{225}$Ac/$^{213}$Bi generator [4]. However, the application range of $^{213}$Bi with a half-life of 46 minutes is probably limited to locoregional applications [5,6] or the treatment of blood borne cancers [7].

Astatine-211 has gained considerable interest for cancer treatment because its half-life of 7.2 hours matches better with the biological half-life of most carrier molecules envisaged for RNT and RIT and would therefore be suitable for applications that require longer times for uptake. Moreover its decay scheme exhibits practically 100% yield for the emission of $\alpha$-particles, with very low intensity gamma emissions [8,9]. It combines a high linear energy transfer (LET) of 130 eV/nm, with a short range of around 70 $\mu$m. The emission of Auger electrons contributes significantly to the dose to tissue in the nanometer range [10], adding to the desired therapeutic effect in targeting single cancer cells. However, the production of $^{211}$At via the nuclear reaction $^{209}$Bi($\alpha$,2n)$^{211}$At requires compact cyclotrons, larger than the common mini cyclotrons used for production of PET radioisotopes, that can accelerate alpha particles to an energy in the region of 28-29 MeV. This production route is nevertheless preferable to $^7$Li ion bombardment of $^{209}$Bi, producing $^{211}$Rn via the ($^7$Li,5n) reaction, that decays into $^{211}$At [11], or other heavy ion beam methods, or proton induced spallation, that require even more expensive or rare equipment.

The availability of appropriate cyclotrons is a major drawback for medical research in order to fully explore the potential of $^{211}$At in cancer therapy and to prepare clinical trials with the most promising compounds [12,13]. Therefore considerable effort has gone into the optimization of the production and extraction of $^{211}$At from cyclotron irradiated targets [14,15,16]. The production principle is basically understood. The reaction $^{208}$Bi($\alpha$,2n)$^{211}$At has to be performed with an alpha particle energy of about 28 to 29 MeV in order to stay just below the threshold of the reaction $^{209}$Bi($\alpha$,3n) that produces $^{210}$At with a half-life of 8.1 h, which subsequently decays into the undesired alpha-emitting $^{210}$Po ($T_{1/2} = 138.38$ d) [17,18,19]. This means that the maximum reaction cross-section of about 1000 mbarn for the reaction $^{209}$Bi($\alpha$,2n)$^{211}$At is not suitable for production because it is reached at a slightly higher energy of about 30 MeV. Another problem is related to the low melting point (271.3°C) and low thermal conductivity (7.9 Wm$^{-1}$K$^{-1}$) of the bismuth target and the high volatility of the astatine that could cause evaporation losses during production. This has caused a large scatter of experimental yield data, that seem however to converge towards saturation yields around 400 MBq/µA [15,16] when using thin bismuth layers on a thin substrate with good thermal conductivity, actively water cooled from the back side, and irradiated at glancing angle.

In this study the possible production of $^{210}$Po by the direct reactions $^{209}$Bi($\alpha$,t)$^{210}$Po, $^{209}$Bi($\alpha$,dn)$^{210}$Po and $^{209}$Bi($\alpha$,2np)$^{210}$Po having thresholds of 14.83 MeV, 21.08 MeV and 23.31 MeV respectively has been taken into consideration [9]. Several alpha particle irradiations of bismuth below the threshold of the production of $^{210}$At were carried out for this purpose, and the irradiated samples were analysed by $\alpha$-spectrometry to check for any significant $^{210}$Po production.

The excitation functions of the reaction $^{209}$Bi($\alpha$,2n)$^{211}$At reported in the literature [17,18,19] are in good agreement as shown in figure 1. In addition, the theoretical excitation function calculated with the evaporation code ALICE-91 is in good agreement with the experimental values (figure 1). Using these experimental and theoretical values, the thick target yields of both $^{211}$At and $^{210}$At through the reaction $^{209}$Bi($\alpha$,2n) and $^{209}$Bi($\alpha$,3n) respectively have been calculated, using SRIM-2003 for the stopping power. The yields are calculated as:
where $N_v$ is the number of target atoms for the desired reaction per unit volume, $I$ is the beam intensity, $\lambda$ is the radioactive constant of the produced isotope ($\lambda = \ln(2)/T_{1/2}$), $t$ is the duration of the irradiation, $E_p$ is the beam energy, $E_{th}$ is the reaction threshold energy, $\sigma(E)$ is the excitation function and $dE/dx(E)$ is the stopping power of the target material.

\[
A = N_v \cdot I \cdot (1 - e^{-\lambda t}) \cdot \int_{E_{th}}^{E_p} \sigma(E) \cdot \left(\frac{dE}{dx}(E)\right)^{-1} \cdot dE
\]  

(1)

Figure 1. Experimental excitation functions of the reactions $^{209}$Bi($\alpha$,2n)$^{211}$At and $^{209}$Bi($\alpha$,3n)$^{210}$At reported in the literature, together with those calculated with the ALICE-91 code.

2. Materials and methods

The alpha particle irradiations were performed with the Scanditronix MC-40 cyclotron of the Joint Research Centre (Ispra, Italy). This machine is able to accelerate four different ions: alphas, helium-3, protons and deuterons. The maximum energy for protons and alphas is about 39 MeV, for deuterons about 19.5 MeV and for helium-3 about 53 MeV. For these studies the bismuth targets were irradiated with $\alpha$-particles in the energy range 15.5 – 34.5 MeV both to construct the yield versus energy curve and to check for production of $^{210}$Po below the threshold of $^{210}$At production, through the direct reactions ($\alpha$,t), ($\alpha$,dn) and ($\alpha$,2np). A beam current of 0.5 $\mu$A was used for all the irradiation runs.

The targets were prepared by cutting a 1 cm x 1 cm piece of high purity (99.99%) bismuth foil supplied by Goodfellow, with a thickness of 0.25 mm, which corresponds to a thick target. The target was enveloped in aluminum foil (14 $\mu$m thickness) to avoid loss of activity by recoil or evaporation, due to the fact that astatine is very volatile. The energy loss of the bombarding alpha particles in the aluminum was taken into account using SRIM 2003. The target was supported in the holder by an aluminum collimator of 8 mm diameter. The beam current on the Bi was determined with a copper...
monitor foil irradiated together with the bismuth target. The thickness of the copper foil was 2.2 μm, so this layer is considered thin, with a correspondingly negligible energy loss. Ga-66, Ga-67 and Zn-65 are the products of the reaction \(^{nat}\text{Cu}(\alpha,x)\). Measuring the activity of these products and using the recommended cross section values of IAEA it is possible to calculate the current of the beam and then using it to determine the thick target yields of \(^{211}\text{At}\) and \(^{210}\text{At}\).

Both gamma and alpha spectrometry were applied in this work. A HPGe gamma spectrometer was utilized to detect \(^{211}\text{At}\), \(^{211}\text{Po}\) and \(^{210}\text{At}\), while a Si (ion implanted) alpha detector was used for the detection of \(^{211}\text{At}\), \(^{211}\text{Po}\) and \(^{210}\text{Po}\). All instruments were supplied by Ortec and the analysis was made with the GammaVision and AlphaVision programs. All spectrometers were calibrated in energy and efficiency with certified standard sources. The HPGe was calibrated in 6 different geometry positions with radioactive sources of \(^{152}\text{Eu}\) and \(^{241}\text{Am}\) for the low energy, both with an uncertainty of 2%. The Si alpha detector was calibrated in 10 different geometry positions using a certified standard source of a standard mixture of Pu, Am and Cm. The alpha and gamma emission of At and Po radioisotopes with their abundance are compiled in tables 1 and 2. These data are taken from the database of R.B. Firestone, C.M. Baglin, F.S.Y. Chu (8th edition on CD-ROM) [9].

| Radioisotopes | Gamma-ray energy (keV) | Intensity (%) |
|--------------|------------------------|---------------|
| \(^{210}\text{At}\) | 245.31 | 79.44 |
| | 527.4 | 1.14 |
| | 817.23 | 1.71 |
| | 852.66 | 1.38 |
| | 955.84 | 1.80 |
| | 1181.39 | 99.30 |
| | 1436.70 | 29 |
| | 1483.39 | 46.50 |
| | 1599.70 | 13.40 |
| | 2254.28 | 1.52 |
| \(^{211}\text{At}\) | 669.60 | 0.0035 |
| | 687.00 | 0.26 |
| | 742.64 | 0.00095 |
| \(^{210}\text{Po}\) | 803.10 | 0.0012 |
| \(^{211}\text{Po}\) | 328.12 | 0.0033 |
| | 569.702 | 0.54 |
| | 897.80 | 0.56 |

Table 1. Gamma lines with their intensities of \(^{210}\text{At}\), \(^{211}\text{At}\), \(^{210}\text{Po}\) and \(^{211}\text{Po}\)

| Radioisotope | Alpha-ray energy (MeV) | Intensity (%) |
|--------------|------------------------|---------------|
| \(^{211}\text{At}\) | 5.87 | 41.8 |
| \(^{211}\text{Po}\) | 7.45 | 98.92 |
| | 6.89 | 0.557 |
| | 6.57 | 0.544 |
| \(^{210}\text{Po}\) | 5.30 | 100 |

Table 2. Alpha lines with their intensities \(^{211}\text{At}\), \(^{210}\text{Po}\) and \(^{211}\text{Po}\)
3. Results and discussion

The radiochemical separation of $^{211}$At and $^{210}$At from the Bi target has already been outlined elsewhere (see [20] and citations therein). Figure 2 shows a typical alpha spectrum of a prepared thin layer of an alpha activated bismuth target where the alpha lines of $^{211}$At and its daughter $^{211}$Po are well resolved. The thin layer sample was obtained by drying a drop of the dissolved activated bismuth. Figure 3 shows an alpha spectrum of a purified $^{210}$Po fraction from a bismuth target where $^{210}$At was produced during an irradiation above the threshold for its production.

**Figure 2.** Typical alpha spectrum of a deposited thin layer of bismuth irradiated below the threshold for production of $^{210}$At.

**Figure 3.** Alpha spectrum of a purified Po fraction ($^{210}$Po daughter of $^{210}$At) obtained from a bismuth target irradiated above the threshold for production of $^{210}$At.
The measured thick target yields for both $^{211}$At and $^{210}$At are shown in figure 4 and compared with the literature values. Within the error margins, the experimental results of the thick target yields are in good agreement with the previously reported data. A 10% uncertainty was estimated by the propagation of the measurement uncertainties related to the beam (current, energy and irradiation time) and activities. In figure 4 the theoretical thick target yield curve using the excitation function calculated with ALICE-91 is also presented as calculated with formula given above. The experimental yields may be underestimated because of a loss of the highly volatile At [21] especially during Bi irradiation. The low thermal conductivity and melting point of Bi favor such losses.

**Figure 4.** Experimental and theoretical thick target yields of $^{211}$At and $^{210}$At through the reactions $^{209}$Bi($\alpha$,2n)$^{211}$At and $^{209}$Bi($\alpha$,3n)$^{210}$At respectively.

Figure 5 shows the energy dependency of the ratio of production of $^{210}$At to $^{211}$At. The calculated threshold energy for the reaction $^{209}$Bi($\alpha$,3n)$^{210}$At is 28.6 MeV. The curve shows that for alpha irradiation of natural bismuth at a beam energy of 30.5 MeV, the contamination of $^{211}$At with $^{210}$At would be below 0.4% in activity, already a rather low value. In fact Henriksen et al. [22] have reported that at a lower beam energy of 29.1 MeV (0.5 MeV above the theoretical $^{210}$At production threshold), the relative atomic content of $^{210}$At would be reduced to around 0.023% and that this would not represent a significant impurity in a final radiopharmaceutical product.
Figure 5. Ratio of the yield of $^{210}$At to the yield of $^{211}$At at three different alpha irradiation energies.

For irradiations above 28.6 MeV, $^{210}$Po impurity in the irradiated target material arises from the decay of $^{210}$At. In this work, four lower energy alpha irradiations (23 MeV, 21 MeV, 19 MeV and 15.5 MeV) were performed to check whether a direct production of $^{210}$Po occurs through the direct reactions ($\alpha$,t) ($\alpha$,dn) and ($\alpha$,2np), which have energy thresholds of 14.83 MeV, 21.08 MeV and 23.31 MeV respectively. The alpha spectrometry measurements made in this work did not reveal any significant and quantifiable amount of $^{210}$Po present in the irradiated material, confirming ALICE-91 calculations which resulted in extremely small cross sections for the corresponding nuclear reactions at these energies.

4. Conclusions
We have performed a series of alpha irradiations on $^{209}$Bi in order to measure the thick target yields of $^{211}$At and $^{210}$At at various energies. The experimental yields measured in this work were in good agreement with those already reported in the literature. In addition, the excitation functions calculated in this work with ALICE-91 code are also in good agreement with the published ones. The work tends to support the conclusion of G. Henricksen et al [22] that irradiation of $^{209}$Bi with an alpha beam energy above the theoretical threshold for $^{210}$At production can result in an increased $^{211}$At yield while maintaining an acceptable level of $^{210}$At/$^{210}$Po impurity.

5. References
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