Journal of Radioanalytical and Nuclear Chemistry, Vol. 262, No. 3 (2004) 563–567

Production of ^{177}Lu by neutron activation of ^{176}Lu

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(Received March 10, 2004)

Production of the radiopharmaceutical nuclide ^{177}Lu, by direct thermal neutron activation of ^{176}Lu, poses a discrepancy between experimentally measured and theoretically predicted activities. It was found that in the irradiation at the pneumatic transfer tube ('Rabbit') of the IRR-1 reactor, the exper./theor. ratio was 1.858±0.051. This ratio was determined also by comparing the activities of ^{177}Lu and ^{176m}Lu. The significant deviation of ^{176}Lu from the 1/v behavior explained this disagreement. The ratio exper./theor. is the Westcott $g(T_n)$-factor and was used to yield the neutron temperature $T_n = 311\pm8$ K.

Introduction

The lanthanide radionuclide ^{177}Lu is available commercially for research and investigational purposes as a diagnostic and radiotherapy agent in the treatment of several malignant tumors. The nuclear properties of ^{177}Lu are advantageous compared to other therapeutic radionuclides, e.g., ^{90}Y, which is paired with an antibody or peptide by the same techniques as ^{177}Lu. The maximum β^- energy 498.3 keV of ^{177}Lu[1] and the 130 keV average, provide a short range of 0.25 mm, which is effective in destroying small malignant tumors, but with less damage to healthy cells. Another advantage of ^{177}Lu is the low exposure by gamma-rays, due to the low energy and emission probability of the main transitions: 112.950 keV, (6.17±0.07)% and 208.366 keV, (10.36±0.07)%.[1] This gamma-emission is suitable for direct imaging by gamma scintigraphy cameras, thus eliminating the need for a surrogate such as ^{111}In. Another advantage is the relatively longer and more convenient half-life of 6.647±0.004 days.[1]

The radionuclide ^{177}Lu can be produced, either directly by the thermal neutron activation ^{176}Lu(n_{th},γ)^{177}Lu, or indirectly by the reaction ^{176}Yb(n_{th},γ)^{177}Yb. The product ^{177}Yb ($T_{1/2} = 1.911\pm0.003$ h) decays by β^- to ^{177}Lu. The drawback of this production modality is that it requires a chemical separation of ^{177}Lu from the ^{176}Yb target, resulting in excessive amounts of time, complexity and expense. In the direct production, the long-lived interference ^{177m}Lu ($T_{1/2} = 160.44\pm0.06$ d)[1] is also produced, but in a very small quantity in comparison to ^{177g}Lu (ground state).

A theoretical calculation, i.e. prediction, of the ^{177}Lu activity produced directly from ^{176}Lu, was based on the 1/v (v is the neutron velocity) behavior of the radiative capture cross section of ^{176}Lu in the thermal neutron region. Data used in the prediction were the neutron radiative capture cross section $\sigma_\gamma^0 = 2090\pm70$ b at the neutron velocity $v_0 = 2200$ m·s^{-1} and the radiative capture resonance integral $I_\gamma = 1087\pm40$ b, both of ^{176}Lu.[2] Other data needed for the calculation were the thermal and epithermal neutron fluxes, the atom% concentration of ^{176}Lu in the lutetium, the mass and the molecular weight of the lutetium chemical compound (e.g., Lu_2O_3), Avogadro's constant, the irradiation time and the half-life of ^{177}Lu. In preliminary irradiations it was found that the experimental, i.e., measured, activity of ^{177}Lu was nearly 1.9 times greater than the theoretical, i.e., predicted, value. Direct production data of ^{177}Lu in another reactor showed that the ratio between experimental and theoretical yields was 1.66.[3] The ratio exper./theor., which is uniquely relevant to the thermal neutron energy distribution in the irradiation facility, must be included in designing an irradiation for a requested activity of the therapeutic radionuclide ^{177}Lu.

The purpose of the present work was to verify and explain the ratio between experimental and theoretical activities of ^{177}Lu, as produced directly by the reaction ^{176}Lu(n_{th},γ)^{177}Lu.

Experimental

Lutetium oxide

Two samples of lutetium oxide Lu_2O_3 (Aldrich, Product No. 20366-1, Milwaukee, WI), of 99.99% chemical purity, were prepared for irradiation in the reactor. The masses of the samples L1 and L2 were 6.6544 and 4.6498 mg, respectively. The samples were irradiated separately at the pneumatic transfer tube ('Rabbit') of the IRR-1 reactor, at the 5 MW operating power. Each irradiation time was 1 minute.

The atomic abundance of ^{176}Lu in Lu was analyzed by ICP-MS and found to be 2.62±0.04%, in good agreement with the adopted value 2.59±0.02% of natural lutetium.[4] This analysis was performed because lutetium compounds, enriched or depleted in ^{176}Lu, are commercial materials for production of ^{177}Lu in radio-

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0236–5731/2004/USD 20.00

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Kluwer Academic Publishers, Dordrecht

pharmaceuticals, or in lutetium oxyorthosilicate (LSO) scintillators, respectively. Hence, ^{176}Lu in the samples is not enriched or depleted and the composition of lutetium (oxide) is natural.

Gold–aluminum wires

Two wires of gold alloyed with aluminum (Reactor Experiments, Sunnyvale, CA) were irradiated to determine the neutron flux in the Rabbit by the cadmium ratio method. The mass concentration of gold in the wires was 0.1124%. The mass of the bare wire (Aub) was 3.6389 mg and the wire inserted into a cadmium sleeve (AuCd) was 4.4853 mg. The wires were irradiated separately and each irradiation time was 10 minutes.

Samples were irradiated in the sequence Aub, L1, L2, and AuCd, to average and achieve a representative neutron flux. The exact times of the ends of irradiations (EOI) were recorded.

Calibration of detection efficiency

The detection efficiency of the Ge detector (Ortec, Model No. GEM-60195, Oak Ridge, TN) was performed by a reliable set of point gamma-ray standards at a distance of 20 cm from the detector capsule. The set covers the energy range of 59.5 to 1332.5 keV.

Measurements

The irradiated samples were measured at the 20 cm geometry. Because of their small size (less than 5 mm), they can be regarded as point sources. Each sample was measured at least 3 times.

Results and discussion

Detection efficiency

The detection efficiency, versus gamma-ray energy, is shown in Fig. 1. Fitting a function was performed by the software Genie-2000 (Canberra, Meriden, CT). The calibration curve of the detection efficiency is given by the polynomial:

$$\log(\varepsilon) = \sum_{i=-1}^{i=n} a_i \left(\frac{1}{E}\right)^i \qquad (1)$$

where ε (in counts/gamma-ray) is the detection efficiency and E (in keV) is the gamma-energy. The present polynomial ($n=4$) is called linear, because logarithms are not used in the energy side of Eq. (1). This polynomial was chosen by finding the minimum χ^2, i.e., the sum of squared relative deviations, between measured and calculated values of various fitting functions. Equation (1) was used to calculate the detection efficiency for E<276 keV. In the energy range E>276 keV, the straight line:

$$\ln(\varepsilon) = a + b\ln(E) \qquad (2)$$

was fitted by linear regression.

Neutron flux

The detection efficiency of the 411.8 keV gamma-rays of ^{198}Au was calculated by Eq. (2) and found to be 0.002328±0.000010 counts/gamma-ray. The thermal ϕ_{th} and epithermal ϕ_{epi} neutron fluxes (in n·cm^{-2}·s^{-1}) were derived from Eq. (2) that give the measured activity A_0 (in Bq) of ^{198}Au in the two wires Aub and AuCd, corrected for dacay to the EOI:

$$A_0(\text{Aub}) = \frac{1}{M} N_A m_1 a \left(0.8862\sigma_\gamma^0 \phi_{th} + \frac{I_\gamma \phi_{epi}}{15.2}\right) \left[1 - \exp(-\lambda t_i)\right] \qquad (3)$$

$$A_0(\text{AuCd}) = \frac{1}{M} N_A m_2 a \frac{I_\gamma \phi_{epi}}{15.2} \left[1 - \exp(-\lambda t_i)\right] \qquad (4)$$

where M is the atomic weight 196.96655±0.00002 g·mol^{-1} of gold,[5] N_A is Avogadro's constant (6.02214199±0.00000047)·10^{23} mol^{-1},[6] m_1 and m_2 are the masses (in g) of the bare and cadmium covered wires, respectively, a is the mass fraction 1.124·10^{-3} of gold in the wire, σ_γ^0 is the neutron radiative capture cross section 98.65±0.09 b of gold at 2200 m·s^{-1},[2] I_γ is the radiative capture resonance integral 1550±28 b of gold,[2] λ (in s^{-1}) is the decay constant of ^{198}Au ($T_{1/2}$ = 2.69517±0.00021 d),[7] t_i (in s) is the irradiation time, and the value of 0.8862 is:

$$0.8862 = \frac{\sqrt{\pi}}{2} = 1/\frac{\int_0^\infty v^3 \exp\left[-\left(\frac{v}{v_0}\right)^2\right] dv}{\int_0^\infty v^2 \exp\left[-\left(\frac{v}{v_0}\right)^2\right] dv}$$

and the value of 15.2 is:

$$15.2 = \int_{0.5}^{2\cdot10^6} \frac{1}{E} dE$$

(E in eV) are averaging coefficients of σ_γ^0 and I_γ in the thermal (Maxwell-Boltzmann) and epithermal neutron energy regions. In the thermal region, the 1/v-law is fulfilled for gold, and in the epithermal region, the neutron flux shows a 1/E dependence.

Measured activities of samples, corrected for decay to the EOI, are given by:

$$A_0 = \frac{R}{\varepsilon P_\gamma}\exp(\lambda t_d) \quad (5)$$

where R (in cps) is the net count-rate of the gamma-peak at the beginning of the measurement, ε (in counts/gamma-ray) is the detection efficiency, P_γ (in gamma-rays/disintegration) is the emission probability of the gamma-ray and t_d is delay between the EOI and start of the measurement.

Neutron fluxes and the cadmium ratio were found to be:

$$\phi_{th} = (1.280\pm0.015)\cdot10^{12}\ \mathrm{n\cdot cm^{-2}\cdot s^{-1}}$$
$$\phi_{epi} = (2.187\pm0.042)\cdot10^{11}\ \mathrm{n\cdot cm^{-2}\cdot s^{-1}}$$
$$Cd.R. = 6.017\pm0.066$$

In an independent experiment, based on the production of ^{239}U and ^{143}Ce in the irradiation of uranium, the thermal flux was $1.270\cdot10^{12}$ n·cm^{-2}·s^{-1}, i.e., in very good agreement with the present value. The epithermal flux was then $1.834\cdot10^{11}$ n·cm^{-2}·s^{-1}, i.e., lower than the present value, and accordingly, the other $Cd.R. = 6.93$ was higher than the present one. The contribution of epithermal neutrons to the production of activity is dependent on the ratio $(I_\gamma/15.2)/(0.8862\sigma_\gamma^0)$ and the ratio of thermal to epithermal fluxes, which is about 6 in the 'Rabbit'. In many applications, the epithermal contribution is much smaller than the thermal.

Activity of ^{177}Lu

The predicted, i.e., theoretical, activity of ^{177}Lu was calculated by the measured neutron fluxes, using Eq. (3) with values relating to ^{176}Lu and ^{177}Lu. Here, m_1 (in g) is the mass of an irradiated Lu_2O_3 sample, $a = 2(0.0259\pm0.0002)$ is the atomic abundance of ^{176}Lu nuclei in Lu_2O_3 molecules, σ_γ^0 and I_γ are given above, λ (in s^{-1}) is the decay constant of ^{177}Lu ($T_{1/2}$ is given above), $t_i = 60$ seconds is the irradiation time, and $M = 397.9322\pm0.0022$ g·mol^{-1} is the molecular weight of Lu_2O_3.[5]

The experimental activity of ^{177}Lu was measured by monitoring the two most abundant gamma-rays, at energies (emission probabilities) 112.950 keV (0.0617±0.0007) and 208.366 keV (0.1036±0.0007).[1] An expanded region of the spectrum, showing the two gamma-rays is given in Fig. 2. Detection efficiencies at these energies, and activities at the EOI, were calculated by Eqs (1) and (5), respectively. Results are given in Table 1.

Table 1 shows that the activities derived from the measurements of the 112.950 keV gamma-ray are slightly lower than those of the 208.366 keV gamma, but they agree within ±σ. The estimated uncertainties at 112.950 keV are slightly higher than at 208.366 keV. A possible explanation is the detection efficiency at 112.950 keV, i.e., in the 'knee' region of the detection efficiency curve (Fig. 1). Calibration standards are rare in the 'knee', and therefore the polynomial fitted by Eq. (1) can introduce there significant deviations between calculated and true efficiencies.

Table 1 shows that the experimentally measured activity of ^{177}Lu is greater than the theoretically predicted by the ratio 1.858±0.051 (average over the 2 energies).

The ratio experimental/theoretical

In the neutron activation of ^{176}Lu, the isomer ^{177m}Lu (level 970.175 keV, 160.44±0.06 d half-life)[1] is produced with a 2.8±0.7 b cross section.[2] The isomeric transition abundance is 21.4% and the β$^-$-decay (78.6%) to excited levels of ^{177}Hf leads to the 208.366 keV gamma-ray with $P_\gamma = 57.4\%$. Because the activity of the isomeric state is negligible ($5.55\cdot10^{-5}$ of the ground state) it cannot explain the ratio exper./theor.

For many nuclide targets in (n_{th},γ) reactions, the radiative capture cross section in the thermal neutron energy region obeys the 1/v-law. The ultimate monitor ^{198}Au deviates slightly (<1%) from this behavior. On the other hand, the nuclide ^{176}Lu is an exception, because it deviates significantly from the 1/v-law[8] and the deviation is due to the strong (~14000 b) resonance at 0.141 eV.[9] In this case, the WESTCOTT convention[10] is applicable and the WESTCOTT $g(T_n)$-factor, that depends on the neutron temperature T_n, is an estimate of the deviation from a pure 1/v behavior. The $g(T_n)$-factor is given in:

$$\sigma_\gamma = \sigma_\gamma^0\frac{\sqrt{\pi}}{2}g(T_n) \quad (6)$$

where σ_γ is the cross section averaged over the Maxwell-Boltzmann distribution and σ_γ^0 refers to $T_0 = 293.2$ K ($E_0 = kT_0 = 0.0253$ eV, $v_0 = 2200$ m·s^{-1}).

The present measurements show that $g(T_n) = 1.858\pm0.051$. Experimental and calculated values of the g-factor for ^{176}Lu agree very well[11] and show a linear relationship in the interval 200 to 500 K. Using Fig. 15.2.6 in Reference 11, the present $g(T_n)$ value corresponds to $T_n = 311\pm8$ K. In the operating IRR-1 reactor, the moderator water temperature is 35 °C, i.e., in very good agreement with the measured value 311 K. Hence, ^{176}Lu is a suitable nuclide for obtaining information about the temperature in neutron activation.

Natural lutetium consists of (97.41±0.02)% ^{175}Lu[4], which follows the 1/v-law in the thermal region.[9] Neutron activation of ^{175}Lu ($\sigma_\gamma^0 = 16.2\pm0.5$ b and $I_\gamma = 550\pm30$ b),[2] leads to the product ^{176m}Lu which decays with a half-life of 3.664±0.019 hours.[12]

The activity of ^{176m}Lu can be determined by its 88.361 keV gamma-ray, with $P_\gamma = (8.902\pm0.442)\%$.[12] In

this case, the WESTCOTT $g(T_n)$-factor is equal to 1. Hence, the ratio of experimental activities, of ^{177}Lu relative to ^{176m}Lu, divided by the corresponding ratio of theoretical activities is equal to $g(T_n)$.

In the present work, the ratio of theoretical activities at the EOI was 0.0555±0.0025. The main contributions to the uncertainty come from the uncertainties of the two cross sections σ_γ^0, i.e., 2090±70 and 16.2±0.5 b. Average resonance integrals divided by the ratio $\phi_{th}/\phi_{epi} = 5.853$ are small compared with average thermal cross sections, and therefore, their contributions to the total uncertainty are negligible. The contributions by saturation factors of irradiation and isotopic abundances may also be neglected.

The experimental activity of ^{176m}Lu, in samples L1 and L2, at the EOI, as well as the ratios of experimental activities of ^{177}Lu (Table 1) to ^{176m}Lu, and the ratio of experiment to theory, are given in Table 2.

Table 1. Theoretical and experimental activities of ^{177}Lu in neutron activation of ^{176}Lu

Sample	A_0 (theor.), $\times 10^4$ Bq	A_0 (exper.), $\times 10^5$ Bq		A_0 (exper.)/A_0 (theor.)	
		112.950 keV	208.366 keV	112.950 keV	208.366 keV
L1	9.013 ± 0.327	1.657 ± 0.074	1.695 ± 0.065	1.838 ± 0.106	1.881 ± 0.100
L2	6.298 ± 0.229	1.127 ± 0.051	1.208 ± 0.046	1.790 ± 0.103	1.917 ± 0.100
Average ± standard uncertainty:				1.813 ± 0.074	1.899 ± 0.071

Table 2. Experimental and theoretical ratios of activities of ^{177}Lu and ^{176m}Lu

Sample	A_0 (exper.), ^{176m}Lu $\times 10^6$ Bq	Ratio (exper.)		Ratio (exper.)/Ratio (theor.)	
		112.950 keV	208.366 keV	112.950 keV	208.366 keV
L1	1.602 ± 0.110	0.1034 ± 0.0084	0.1058 ± 0.0083	1.864 ± 0.172	1.908 ± 0.172
L2	1.078 ± 0.074	0.1046 ± 0.0086	0.1121 ± 0.0088	1.886 ± 0.176	2.021 ± 0.182
Average ± standard uncertainty:				1.875 ± 0.123	1.961 ± 0.125

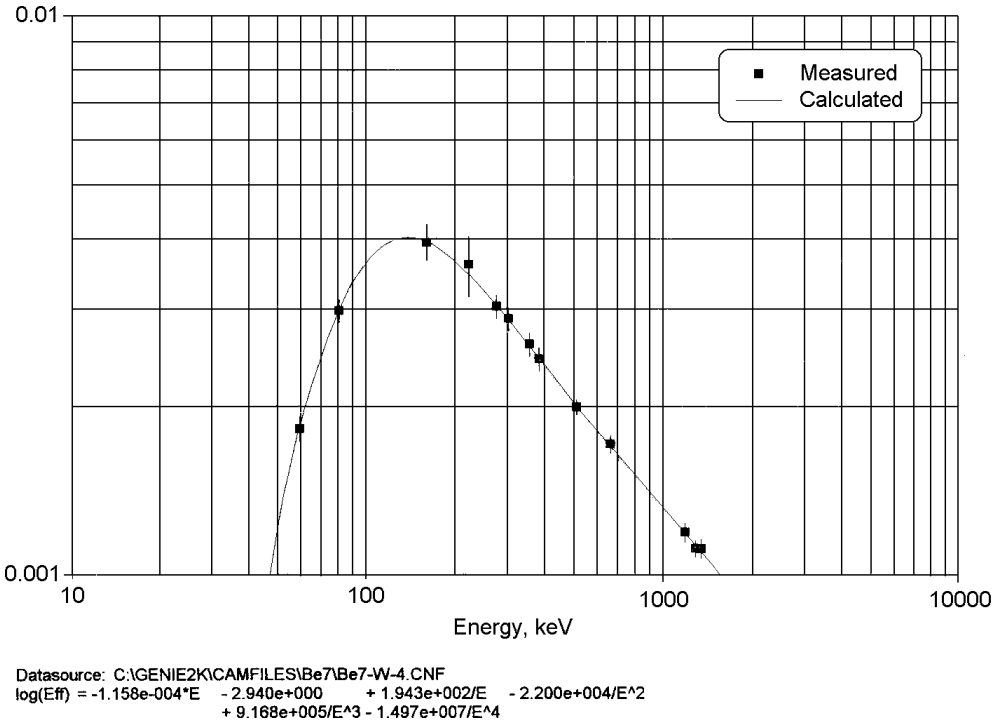

Fig. 1. Detection efficiency of the Ge detector at the 20 cm geometry

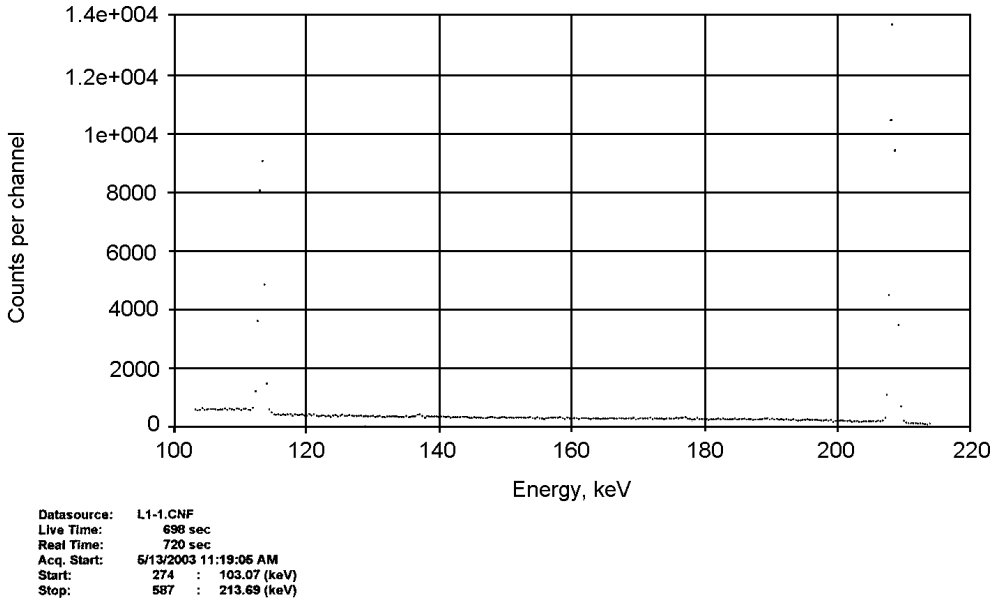

Fig. 2. Gamma-peaks at 112.950 and 208.366 keV used to determine ^{177}Lu

The ratio exper./theor., averaged over the two gamma-rays in Table 1, is 1.917±0.088. This value which was determined from the activations of ^{176}Lu (non 1/*v* target) and of ^{175}Lu (1/*v* target), agrees very well (±σ) with the WESTCOTT $g(T_n)$-factor = 1.858±0.051, as derived from the activation of ^{176}Lu alone. In this latter activation, the experimental production was compared to the theoretical, assuming the 1/*v*-law for the target ^{176}Lu.

Conclusions

The production of radiopharmaceutical nuclide ^{177}Lu by the reaction ^{176}Lu(n_{th},γ)^{177}Lu is influenced by the significant deviation of the target nuclide ^{176}Lu from the 1/*v*-law. The ratio between experimental and theoretical (assuming the 1/*v*-law) production was found to be 1.858±0.051, in the irradiation at the pneumatic transfer tube ('Rabbit') of the IRR-1 research reactor. The thermal neutron temperature can be derived from this ratio [the $g(T_n)$-factor in the WESTCOTT formalism]. In the present work, it was 311 K. The ratio of measured activities, of ^{177}Lu relative to ^{176m}Lu, both produced simultaneously in the irradiation of lutetium, was compared to the corresponding ratio of theoretical activities and yielded the $g(T_n)$-factor. The ratio of experimental to theoretical activities of ^{177}Lu, which is uniquely relevant to the thermal neutron energy distribution in the irradiation facility, must be included in designing an irradiation for a requested activity of the radiopharmaceutical nuclide ^{177}Lu.

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The assistance of Eyal ELISH in performing the ICP-MS analyses of Lu is gratefully acknowledged.

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