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# Electrochemical separation and purification of yttrium-86

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**Summary.** For quantitative determination of *in vivo* dosimetry of $^{90}$Y-labeled radiotherapeuticals by means of PET, the positron emitting analogue yttrium-86 was produced at a low energy ("medical") cyclotron *via* the known $^{86}$Sr$(p,n)^{86}$Y reaction. Using 200 mg of $^{86}SrCO_3$ (enrichment 95.6%) and protons of 15.1 MeV energy, average yields of $^{86}$Y of $48 \pm 8$ MBq/μA h were produced. After dissolution of $^{86}SrCO_3$ in 3 ml of 0.6 N $HNO_3$, $^{86}$Y was deposited in a simple and highly efficient electrochemical two-step procedure onto a platinum cathode at 450 mA ($= 20$ mA/cm$^2$). The isotope was finally removed from the electrode by 100–300 μl of 0.5–1.0 N HCl or 0.3–0.6 N $HNO_3$ resulting in an overall recovery of $88 \pm 6$% (corrected for decay). Up to 1 GBq of $^{86}$Y with high radionuclidic and radiochemical purity were obtained after a 2.5 h irradiation and a radiochemical separation time of 2 h. An ICP/AES analysis of the separated fraction showed a very small amount of strontium ($< 0.1$ ppm). The chemical purity of $^{86}$Y, essential for efficient labeling, was successfully demonstrated by means of complex formation with DOTA and a DOTA-conjugated peptide, exhibiting labeling yields higher than 98%.

## Introduction

As yttrium-86 is a positron emitter ($T_{1/2} = 14.7$ h, $I_{\beta^+} = 33\%$, $E_{\beta^+,\max} = 1.2$ MeV), it is very well suited for assessing the biodistribution of $^{90}$Y pharmaceuticals and the individual dose applied therapeutically by $^{90}$Y labeled antibodies with PET [1–3]. The radionuclide can be produced *via* the $(p,n)$- or $(d,2n)$-processes on enriched $^{86}$Sr and the $(^3\mathrm{He},2n)$- or $(\alpha,3n)$-reactions on natural rubidium [4]. At a small-sized cyclotron only the $(p,n)$-process is applicable, with the additional advantage of producing less radionuclidic impurities. Here, highly enriched $^{86}SrCO_3$ was irradiated, yielding the nuclide *via* the $^{86}$Sr$(p,n)^{86}$Y nuclear reaction. For an efficient labeling a high purity of $^{86}$Y after separation from $^{86}$Sr is mandatory. The radiochemical separation previously described was based on a combined co-precipitation and ion exchange purification process [5]. In order to facilitate the production, it was the aim of this study to develop a faster and technically easier separation procedure for $^{86}$Y, yielding $^{86}$Y in highest quality. Electrodeposition of carrier-free radioactive rare earth nuclides onto a small tungsten cathode was described in 1974 [6]. Recently, the electrochemical deposition of radionuclides of superheavy elements in dependence on electrode material and deposition potential was investigated [7]. An electrochemical method, based on a procedure developed at Mainz [8, 9] to isolate $^{90}$Sr from a mixture of $^{90}$Y and $^{90}$Sr (c.a.) electrochemically, appeared very promising for isolating and purifying $^{86}$Y.

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## Experimental

### Materials

Strontium-86 was supplied by Chemotrade, Germany, with an isotopic enrichment of 95.6% (Sr-87: 1.1%; Sr-88: 3.3%) in the chemical form of strontium carbonate. Less than 475 ppm of metal impurities like Na, Mg, Al, Ca, Fe and Ba in total were certified. Nitric acid and hydrochloric acid were obtained from Fluka in the highest available purity (TraceSelect) and diluted with MilliQ-water. $NH_4OAc$, acetone, ascorbic acid and Tween 20 were from Fluka. DOTA (1,4,7,10-tetraazacyclododecane-N,N′,N″,N‴-tetraacetic acid) was purchased from Strem Chemicals and DOTA-lanreotide (DOTA-(D)$\beta$-Nal-Cys-Tyr-(D)Trp-Lys-Val-Cys-Thr-$NH_2$, molecular weight 1483 g/mol [10]) was a kind endowment of the Research Center Seibersdorf, Austria. Buffer solutions were stored over Chelex 100 (Biorad) to remove traces of bi- or trivalent metal cations. The platinum electrodes (99.99% Pt) were obtained from Degussa, Germany. Highly pure yttrium-90 was provided by PNNL (Hanford) specified with less than 380 μg/Ci of metal impurities in total. All materials used for electrolyses and labeling were washed with concentrated nitric acid, rinsed with MilliQ-water and dried before use.

### Production of yttrium-86

At the cyclotron of the PET Center Tübingen (PETtrace, General Electric Medical Systems) protons were accelerated to an energy of 16.5 MeV. The proton energy to be effective on the target material was determined in two test experiments resulting in values of 15.0 and 15.1 MeV by irradiating a foil of natural copper (0.025 mm) using the nuclear processes $^{63}$Cu$(p,n)^{63}$Zn and $^{63}$Cu$(p,2n)^{62}$Zn as monitoring reactions [11, 12]. Under the applied target conditions, complete absorption of the protons within the $^{86}SrCO_3$ target

was achieved ($E_p = 15.1 \rightarrow 0$ MeV). Production runs lasted 90 min to 150 min using a beam current of 10 μA.

For irradiating $^{86}SrCO_3$ a target system to be described elsewhere was used allowing the beam to enter the target material at an angle of 10° or 15° related to the beam axis. 200 mg of $^{86}SrCO_3$ were pressed on an aluminium backing over an area of 3.0 $cm^2$ resulting in a thickness of 67 $mg/cm^2$.

### Electrolytic separation

After irradiation the target material was dissolved in 3 ml of 4% $HNO_3$ (0.6 N) in a cylindrical beaker (30 mm diameter, 80 mm height). After dilution with 47 ml of highly pure MilliQ-water the pH of the solution was between 2.5 and 3.0.

To remove oxygen and carbon dioxide, argon was bubbled through the solution for 15 min, while the solution was heated to 50 °C and stirred by means of a magnetic stirring bar. Two platinum plate electrodes (10 mm × 60 mm) were plunged and fixed in the solution 3 mm apart from each other. The electrolytic deposition was performed during 60 min with a constant current of 450 mA at 50 °C. During electrolysis a strong evolution of gas was observed, as expected when electrolyzing an acidic aqueous solution, where hydrogen and oxygen are formed. The yttrium-86 was electrodeposited on the cathode. Subsequently, the electrodes were removed from the electrolysis cell while having the voltage turned on. The electrode containing $^{86}Y$ was washed with 10 ml of acetone and transferred to a second beaker filled with 50 ml of 0.003 N $HNO_3$ of pH 2.5, heated to 50 °C and argon bubbled through earlier for 15 min. By changing the polarity the electrode was used as an anode with a platinum wire (1.0 mm diameter) as the new cathode 3 mm apart from the Pt plate anode. Electrolysis was performed for 20 min at 50 °C. During this process $^{86}Y$ was removed from the platinum plate and deposited onto the platinum wire. After 20 min the electrodes were removed from the cell under voltage which was turned off after removal from the solution. The platinum wire with the deposited $^{86}Y$ was washed with 10 ml of acetone. Finally, $^{86}Y$ was removed from the cathode by means of 100–300 μl of 0.5–1.0 N HCl or 0.3–0.6 N $HNO_3$.

### Analyses

Assay of radioactivity was performed by $\gamma$-ray-spectroscopy using a HPGe detector, a multichannel analyzer and Wingamma 3.0 software (GSA, Germany). Yttrium-86 was mainly identified by the following gamma lines: 627.8 keV (32.6%), 1076.7 keV (82.5%), 1153.2 keV (30.5%) [13]. The radionuclidic impurity of major importance was $^{86m}Y$ ($T_{1/2} = 48$ min), which was identified by its photopeak at 208.1 keV (93.6%). Other radioyttrium isotopes identified were $^{88}Y$ [$T_{1/2} = 106.6$ d, 898.1 keV (92.7%) and 1836.1 keV (99.35%)] and $^{87}Y$ [$T_{1/2} = 3.35$ d, 484.72 keV (92.2%)], measured between 4 and 7 days after EOB.

The strontium content of the $^{86}Y$ solutions after the first and second electrolysis was determined by ICP/AES with a detection limit of 0.1 ppm Sr (Institut Prof. Dr. Jäger, Tübingen, Germany). For this purpose, 200 mg of natural $SrCO_3$ were electrolyzed without preceding irradiation. In the first series of three individual experiments only one electrolysis was performed. Afterwards, the platinum plate cathode was washed with exactly 5 ml of 2% $HNO_3$ and the strontium content of the solution was determined. In the second series both electrolyses ($n = 3$) were carried out and finally the platinum wire cathode was rinsed with 5 ml of 2% $HNO_3$ and analyzed for strontium.

For the analysis of $^{86}Y$ labeled products thin layer chromatography (tlc) was applied, using silica gel plates (Merck, Germany): $^{86}Y$-DOTA 10% $NH_4OAc$ aq./MeOH = 1 : 1, $R_f = 0.46$. $^{86}Y$-DOTA-lanreotide 0.1 N citrate buffer pH 5, $R_f = 0$.

### Recovery of $SrCO_3$

For recovery of $^{86}Sr$ the acidic solution after the first electrolysis was used. Upon precipitation of strontium carbonate with ammonium carbonate, the $^{86}Sr$ was recovered almost quantitatively as $^{86}SrCO_3$ [5]. After filtration the product was washed with dilute $(NH_4)_2CO_3$, water and acetone. It was finally dried at 120 °C for 12 h and subsequently used for further irradiations.

### Labeling reactions

For testing the labeling efficiency of $^{86}Y$ the acidic $^{86}Y$ solution was evaporated to dryness and 0.2 M $NH_4OAc$ was added. For labeling experiments, a concentration of 100 kBq of $^{86}Y$ in 50 μl of solution was prepared.

### DOTA

A stock solution of DOTA was prepared containing $1.03 \times 10^{-5}$ g/ml of DOTA in water, resulting in a 100 000 fold excess of DOTA in 50 μl of the solution (1.3 nmol) compared to 100 kBq of $^{86}Y$ in 50 μl ($1.3 \times 10^{-5}$ nmol). 50 μl of this DOTA solution was reacted with 50 μl of $^{86}Y$ at 37 °C for 30 min and analyzed with tlc. Additionally, the DOTA solution was diluted in such a way that the molar ratio of DOTA to $^{86}Y$ was 1 : 10 000, 1 : 5000, 1 : 2500, 1 : 1000, 1 : 100, 1 : 10, 1 : 1 and the reactions were performed in the same way. For comparison the same set of experiments was repeated using highly pure $^{90}Y$ of 23 kBq ($1.3 \times 10^{-5}$ nmol)/50 μl.

### DOTA-lanreotide

A solution of 100 μg of DOTA-lanreotide in 200 μl of 0.2 M $NH_4OAc$, pH 7, was freshly prepared. 400 to 600 MBq of $^{86}Y$ in 70 μl of 0.05 M HCl were added and the resulting solution was heated at 100 °C for 20 min. After cooling, the solution was diluted with 400 μl of the acetate buffer. Subsequently, 2 ml of a mixture of 0.15 M NaCl (pH 7), 0.2 M ascorbic acid and 0.1% Tween 20 were added and the solution was passed through a 0.22 μm Millipore filter for sterile filtration.

## Results and discussion

### Radionuclide production

Yttrium-86 was produced at beam currents up to 10 μA with irradiation times between 10 min and 2.5 h. The average production yield at EOB was $48 \pm 8$ MBq/μA h.

At EOB the main radionuclidic impurities were $^{86m}$Y (400% related to $^{86}$Y), $^{87}$Y (0.5%) and $^{88}$Y (0.03%), respectively. In [5] a 15 min irradiation in the proton energy range of $E_p = 14 \rightarrow 10$ MeV resulted in 280% $^{86m}$Y, 0.4%–0.5% $^{87}$Y and 0.02%–0.03% $^{88}$Y at EOB. Due to the high activity of the 48 min $^{86m}$Y the target was taken out of the holder usually 90 min after EOB in order to keep radiation exposure minimized. As nuclear medical application did not start earlier than 4 hours after EOB, the radiation dose due to radionuclides other than $^{86}$Y was significantly minimized.

## Electrolyses

The isolation of yttrium-86 was performed by means of two electrolyses in order to gain optimal purity and to have the radionuclide dissolved in a small volume of 100–300 μl as essential prerequisites for efficient labeling of biomolecules.

For the first of the two electrolytic separations the time dependence of the $^{86}$Y deposition was determined at 30, 45 and 60 min. Optimum yields of $97 \pm 2$% were obtained at 60 min (Table 1). In addition, the influence of the pH value was studied showing a clear dependence (Fig. 1). At pH between 2.5 and 3.0 nearly complete deposition ($97 \pm 2$%) occurred. When the pH was lower than 2.5 at the beginning of the electrolysis, yields clearly decreased. Similarly, pH values higher than 6 also resulted in lower $^{86}$Y yields. Consequently, it was important to maintain the pH between 2.5 and 3.0 by adding 0.6 N $HNO_3$. If necessary, pH was also adjusted during electrolysis, otherwise yields dropped dramatically to 40% and less. In [8] it had been shown that a current density of about 20 mA/cm$^2$ to be most advisable, therefore the current was adjusted to 450 mA taking the cell geometry into account. In tests using the same current density and a volume of 3 ml instead of 50 ml, yields decreased to 30%–50% indicating the importance of avoiding too high concentrations of strontium. Thus, 50 ml of electrolyte turned out to be the strontium concentration ($\leq 4.0$ mg/ml) for optimum deposition.

Bubbling of an inert gas (argon) through the solution for 15 min before and during electrolysis turned out to be necessary, as first experiments had shown that without argon bubbling, there was a thin white layer on the cathode after electrolysis, while with argon bubbling the electrode remained polished.

Since the radionuclide is thought to be obtained in the chemical form of $Y(OH)_3$ on the surface of the electrode [8], both electrodes were always removed out of the solution under voltage. Otherwise most of the activity was dissolved again.

In order to remove traces of $^{86}$Sr, eventually co-deposited on the platinum plate, the radioyttrium was removed from the platinum plate. The $^{86}$Y was re-deposited almost quantitatively (> 97%) on a platinum wire. The final isolation from the electrode was performed with 300 μl of 0.5–1.0 N, either $HNO_3$ or HCl, resulting in $93 \pm 4$% yield for the removal. If acid of a lower concentration or a smaller volume was used, less $^{86}$Y was redissolved. The results of the electrolyses are summarized in Fig. 2. In total, about $88 \pm 6$% of the produced $^{86}$Y could be isolated in a small volume of 300 μl.

The wet separation procedure described in [5] was a two-step method consisting of co-precipitation of the $^{86}$Y hydroxide with La(III) carrier added and a subsequent ion exchange chromatography for separation of the carrier and other trivalent cations. The overall time of processing the irradiated target was in the range of 3 hours.

The electrochemical procedure applied here has the advantage of avoiding any addition of carriers. Moreover, handling is easier and the entire process takes about two hours only.

**Table 1.** Dependence of yttrium-86 recovery yield on electrolysis time for the first electrolysis (pH = 2.5–3.0).

| Electrolysis time/min | 30 | 40–45 | 60 |
|---|---|---|---|
| No. of runs | 3 | 7 | 5 |
| Yield/%[a] | 47 (0.4) | 85 (3) | 97 (2) |

a: in brackets: Standard deviation.

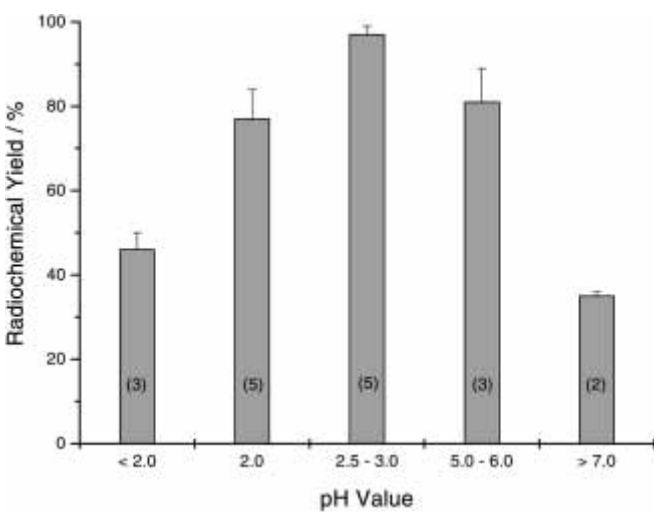


**Fig. 1.** Dependence of yttrium-86 recovery yield on pH value during first electrolysis ($t = 60$ min, No. of experiments in brackets).

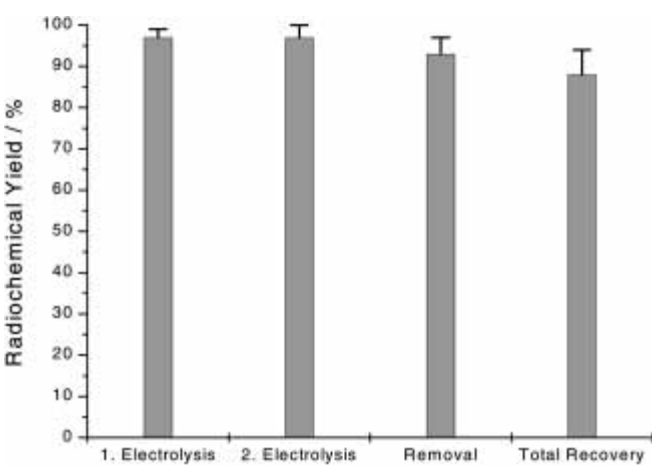


**Fig. 2.** Individual recovery yields of yttrium-86 after the electrolytic separations and the removal from the electrode ($n = 5$).

### Strontium content

The separation of *n.c.a.* yttrium from the macroscopic strontium was evaluated in a separate series of experiments. Performing an electrolysis of 200 mg of natural $SrCO_3$ following the procedure described above for the first electrolysis and washing the platinum plate cathode with 0.3 N $HNO_3$, gave a reduction of the strontium content by a factor of almost 6000 *i.e.* $23 \pm 2$ μg ($n = 3$) as determined by ICP/AES. When in a second series of experiments two electrolyses were carried out sequentially, the amount of residual strontium was reduced down to less than 0.1 ppm, the detection limit of the ICP/AES analysis.

### Formation of *n.c.a.* $^{86}$Y-DOTA complexes

The chemical purity of $^{86}$Y is essential for consecutive labeling steps of biological material. Before labeling of compounds relevant for nuclear medical application, complex formation yields with the electrolytically purified $^{86}$Y were determined using DOTA as a bifunctional ligand frequently applied in peptide labeling. Solutions were used with a 100 000 fold excess down to a stochiometric amount of DOTA in relation to $^{86}$Y. Above a molecular excess of 10 000 of DOTA the reaction was quantitative. With less DOTA the yields decreased. To value these findings, yttrium-90 from PNNL was reacted with DOTA under the same conditions. The results were practically the same as those obtained with $^{86}$Y. Thus, the product obtained by the electrolytic work-up can be considered to be very well suited for labeling DOTA conjugated peptides or antibodies. As a typical example for labeling with radioyttrium DOTA-lanreotide was taken. In case of five experiments a labeling yield of $99 \pm 1$% was found and in further studies that product could be used without additional purification.

## Conclusions

Using $^{86}SrCO_3$ yttrium-86 was produced *via* the $^{86}$Sr(p,n)$^{86}$Y process with 15.1 MeV protons and a current of 10 μA in yields of 48 MBq/μA h. An electrochemical procedure was successfully applied for separating $^{86}$Y from the irradiated $^{86}SrCO_3$. Thus, the radionuclide could easily be separated, purified and concentrated in two steps within 2 h. Up to 1 GBq of purified $^{86}$Y was obtained in an irradiation time of 2.5 h. The product was of a high chemical purity, and residual strontium content was reduced to less than 0.1 ppm. Consequently, the high purity was successfully demonstrated by labeling a DOTA-conjugated peptide in excellent yields. Therefore, $^{86}$Y, thus prepared, is thought to be very well suited for labeling compounds such as DTPA-conjugated peptides and proteins.

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