Indirect determination of lutetium by differential pulse anodic stripping voltammetry at a hanging mercury drop electrode

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Abstract: Lutetium has been determined by differential pulse anodic stripping voltammetry in an acidic solution containing Zn-EDTA. Lutetium (III) ions liberated zinc (II), which was preconcentrated on a hanging mercury drop electrode and stripped anodically, resulting in peak current linearly dependent on lutetium (III) concentration. Less than 0.4 ng mL^{-1} lutetium could be detected after a 2 min deposition.

Keywords: Lutetium • Zn-EDTA complex • Indirect determination • Differential pulse anodic stripping voltammetry

1. Introduction

Although lutetium has no large scale practical uses, investigations into lutetium (III) and its complexes for applications such as a new generation of cardiovascular and oncology drugs [1], PET scanner scintillation crystals [2] and catalysts [3] have increased in the last few years. In addition, ^{177}Lu (III) and radiopharmaceuticals labeled with this radionuclide are increasingly being used [4].

^{177}Lu (III) is ideally suited for radiotherapeutics due to its physicochemical behavior and because it can be easily obtained in a pure form. Its relatively long half life of 6.71 days allows time to bond the isotope to biological compounds and purify the radiopharmaceutical. ^{177}Lu emits a medium energy β$^-$ particle (E$_{\beta max}$ = 497 keV) with a maximum range of ~ 2 mm, making it effective for smaller tumours and micrometastases. Furthermore, the presence of a γ-photon (E$_\gamma$ = 208 keV) permits simultaneous evaluation of the targeting efficiency, allowing imaging and dosimetry together with the therapy.

^{177}Lu can be produced by irradiation of a natural (2.6% ^{176}Lu) or enriched (in ^{176}Lu) Lu$_2$O$_3$ target by thermal neutrons in a nuclear reactor [5]. Although the specific activity of ^{177}Lu itself is reasonably high, there is always non-radioactive Lu present. In order to determine the specific activity of ^{177}Lu (III)-containing samples it is necessary to know the concentration of non-radioactive Lu (III), i.e. the total Lu concentration.

We have recently investigated membrane extraction of ^{177}Lu (III) from aqueous solutions at very low concentrations [6] for the separation of free ^{177}Lu (III) and its labeled compounds. To investigate Lu (III) transport across the membrane, an analytical method to determine very low [Lu (III)] was needed. Differential pulse anodic stripping voltammetry (DPASV) potentially offers this possibility.

Voltammetric stripping analysis has long been recognized as a powerful technique for trace metal detection, especially in environmental samples.

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A mercury film or a hanging mercury drop electrode have been most frequently employed to achieve high reproducibility and sensitivity. Their excellent performances are due to their unique ability to preconcentrate target metals during the accumulation step [7].

Although europium gives a well developed differential pulse polarographic (DPP) peak at a mercury electrode [8] and cerium has been determined by cathodic stripping voltammetry at a graphite electrode [9], the very negative half wave potential of almost all lanthanides makes their voltammetric determination very difficult [9]. Two indirect voltammetric methods have been proposed to circumvent this problem. One is a displacement reaction between the metal ions and the EDTA or DTPA chelate of metal ions such as zinc or cadmium, which form less stable complexes and give well developed polarographic peaks [10,11]. Another method is the formation of a lanthanide complex with a reducible organic dye, and its subsequent determination [12].

The aim of this work was to investigate the determination of trace quantities of lutetium (III) by indirect voltammetry using the Zn-EDTA complex.

2. Experimental

2.1. Reagents
A stock standard solution ($1.2 \cdot 10^{-3}$ M) Lu (III) was prepared by dissolving a precisely weighed amount of $LuCl_3$ (Sigma-Aldrich) in water. More dilute solutions of Lu (III) were prepared by dilution with water.

Standard 0.015 M Zn (II) was used to prepare working solutions ($3 \cdot 10^{-3}$, $3 \cdot 10^{-4}$, and $3 \cdot 10^{-5}$ M). Stock 0.062 M disodium-EDTA in water was prepared by dissolving a precisely weighed amount of the dry compound. It was standardised by complexometric titration against dried primary standard calcium carbonate.

The supporting electrolyte was 0.2 M $NaClO_4$ in 0.05 M pH 5.4 sodium acetate buffer. The pH was adjusted by the addition of 0.2 M HCl.

All chemicals were of analytical-reagent grade, obtained from Merck. Deionized water was supplied from a Milli-Q water purification system.

2.2. Instrumentation
A 797 VA Computrace analyser (Metrohm, Switzerland) was used for all voltammetric measurements, controlled by 797 VA Computrace software ver. 1.2. A Metrohm Multimode mercury electrode served as a working electrode, typically in the hanging mercury drop electrode (HMDE) mode. A Pt rod was the auxiliary electrode and an Ag/AgCl/KCl (3 M) double junction electrode with ceramic diaphragm was the reference electrode, to which all potentials refer.

Prior to electrochemical measurements dissolved oxygen was removed by a 5 minute purge with suprapure nitrogen. A new Hg drop with surface area of 0.30 mm² was made and the stirrer was simultaneously switched on (2000 rpm). Zn was deposited with stirring at -1.200 V for 10 to 120 s followed by a 10 s rest time. Then scanning was initiated with the parameters: initial potential – 1.200 V, end potential – 0.500 V, pulse amplitude 0.050 V, pulse time 0.04 s, sweep rate 0.010 V s⁻¹.

A Metrohm model 744 pH meter with a combined glass pH electrode and temperature sensor was used for pH measurements.

2.3. Procedure
A 25 mL aliquot of supporting electrolyte (0.2 M $NaClO_4$ in 0.05 M pH 5.4 sodium acetate buffer) was placed in the voltammetric cell. Then an aliquot of a Zn (II) working solution ($3 \cdot 10^{-3}$ – $3 \cdot 10^{-5}$ M) was added to reach the desired concentration (in the range $3 \cdot 10^{-5}$ – $8 \cdot 10^{-7}$ M) and enough EDTA was added to form the Zn-EDTA complex. The peak current due to free Zn (II) dissociated from the complex was measured as a blank.

Then an aliquot of Lu (III) solution was added, the cell was purged with nitrogen for 60 s, and the new voltammogram measured. An equivalent amount of Zn (II) liberated from Zn-EDTA increased the peak current. The current was corrected for the blank. Calibration graphs (peak current vs. Lu (III) concentration) were evaluated by least-squares linear regression.

All measurements were performed at 25 ± 2°C.

3. Results and discussion

There are only a few reports on the voltammetric determination of lanthanides [8,9].

We tried to perform direct voltammetric determinations of lutetium (III) using the following supporting electrolytes: 3 M KCl, 1 M KSCN, 0.1 M disodium oxalate, 0.1 M disodium EDTA and 0.5 M disodium tartrate. On the hanging mercury drop electrode, only a poorly defined catalytic hydrogen wave was obtained using KCl as supporting electrolyte. This peak cannot be used for quantitative analysis.

Berge and Drescher [10] proposed an indirect voltammetric method to determine lanthanides (such

as lanthanum, neodymium, samarium, dysprosium and lutetium) via Zn-EDTA or Zn-DTPA complexes. The method is based on the difference between the stability constants of Zn-EDTA ($K = 3.8 \cdot 10^{16}$) or Zn-DTPA ($K = 4 \cdot 10^{18}$) and lanthanide-EDTA (e.g. for Lu-EDTA, $K = 1.1 \cdot 10^{19}$; for Lu-DTPA, $K = 4 \cdot 10^{22}$). Because lutetium (III) forms a more stable EDTA complex than zinc (II), added lutetium (III) liberates an equivalent amount of Zn (II), which can be easily measured.

Zinc gives a well developed DPASV peak in 0.2 M NaClO$_4$ / 0.05 M pH 5.4 sodium acetate buffer as supporting electrolyte, with a peak potential, E$_p$, at -0.995 V. Fig. 1 presents the decrease in Zn (II) peak current with EDTA addition, due to complexation. The residual peak, from dissociation of the complex formed with equimolar EDTA, served as a blank.

The dependence of Zn (II) peak current on added EDTA for different initial zinc concentrations and deposition times are shown in Fig. 2. Linear dependence was obtained for different ranges of zinc concentration. For the straight lines a, b, c and d, the correlation coefficients are -0.9989, -0.9993, -0.9995 and -0.9999, respectively. It is clear that the deposition time must be chosen depending on the initial zinc concentration.
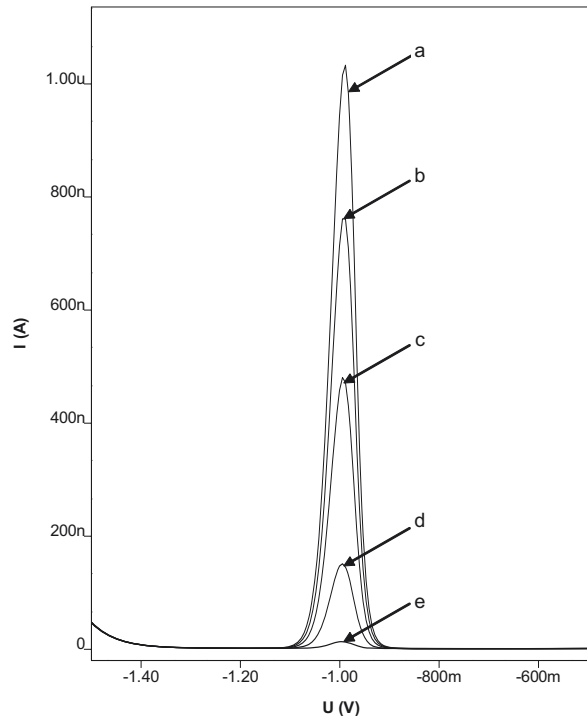
The indirect voltammetric method using Zn-EDTA formed in the voltammetric cell was applied to the determination of lutetium from $7.3 \cdot 10^{-6}$ to $1.2 \cdot 10^{-9}$ M.

Fig. 3 shows the increase in zinc peak current with lutetium addition. The initial concentrations of Zn (II) and EDTA were $8.2 \cdot 10^{-7}$ M. The concentration range of Lu (III) was from $1.2 \cdot 10^{-9}$ to $7.3 \cdot 10^{-8}$ M. The addition of $3 \cdot 10^{-6}$ M lutetium solution was followed by a 60 s nitrogen purge. After this time displacement was complete. Deposition time was 120 s. Similar voltammograms were obtained for different lutetium concentration ranges.
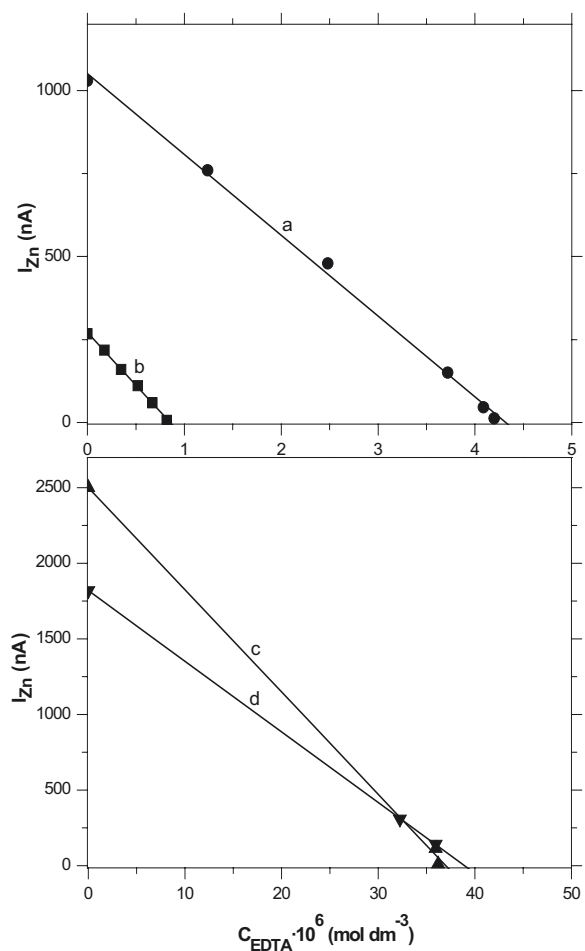

Figure 2. Dependence of Zn (II) peak current on added EDTA for different initial [Zn (II)] and deposition times (t$_{dep}$) : (●) [Zn] = $4.2 \cdot 10^{-6}$ M, t$_{dep}$ = 90 s; (■) [Zn] = $8.2 \cdot 10^{-7}$ M, t$_{dep}$ = 120 s; (▲) [Zn] = $3.6 \cdot 10^{-5}$ M, t$_{dep}$ = 30 s; (▼) [Zn] = $3.6 \cdot 10^{-5}$ M, t$_{dep}$ = 10 s. Supporting electrolyte: 0.2 M NaClO$_4$ in 0.05 M pH 5.4 sodium acetate buffer; deposition potential: -1.200 V; sweep rate: 10 mV s^{-1}.

Figure 1. Differential pulse anodic stripping voltammograms of Zn (II), [Zn] = $4.2 \cdot 10^{-6}$ M, with progressive addition of EDTA. [EDTA] (M): 0 *(a)*, $1.2 \cdot 10^{-6}$ *(b)*, $2.5 \cdot 10^{-6}$ *(c)*, $3.7 \cdot 10^{-6}$ *(d)*, $4.2 \cdot 10^{-6}$ *(e)*. Supporting electrolyte: 0.2 M NaClO$_4$ in 0.05 M pH 5.4 sodium acetate buffer; deposition potential: -1.200 V; deposition time: 90 s; sweep rate: 10 mV s^{-1}.

Calibration graphs for $(1 - 7.3) \cdot 10^{-6}$ M Lu (III), for two applied deposition times (Fig. 4), show that the Zn (II) peak current is linearly dependent on added
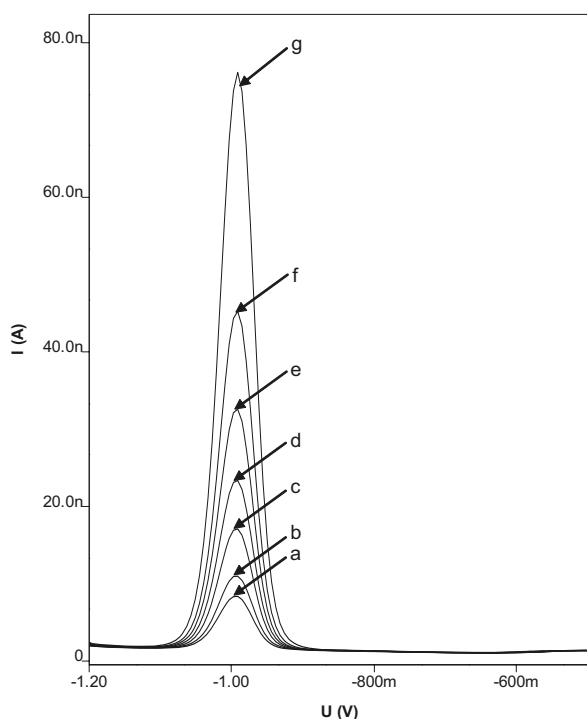
Figure 3. Differential pulse anodic stripping voltammograms of Zn (II) obtained by simultaneous addition of Lu (III). [Lu] (M): 0 *(a)*, 1.2·10⁻⁹ *(b)*, 4.9·10⁻⁹ *(c)*, 9.8·10⁻⁹ *(d)*, 1.9·10⁻⁸ *(e)*, 3.7·10⁻⁸ *(f)*, 7.3·10⁻⁸ *(g)*. Initial [Zn-EDTA] was 8.2·10⁻⁷ M. Supporting electrolyte: 0.2 M NaClO₄ in 0.05 M pH 5.4 sodium acetate buffer; deposition potential: -1.200 V; deposition time: 120 s; sweep rate: 10 mV s⁻¹.

lutetium concentration when the ratio [Zn-EDTA] / [Lu] ≥ 4. Our investigations found no upper limit to the [Zn-EDTA] : [Lu] ratio, i.e., a larger amount of Zn-EDTA can be added to a sample with an unknown [Lu (III)].

For Lu (III) concentrations in the ranges of (0.5 – 9.8)·10⁻⁷ and (1 – 7.3)·10⁻⁶ M, a 30 s deposition time was most suitable. A shorter time (10 s) leads to lower sensitivity as well as larger deviations from
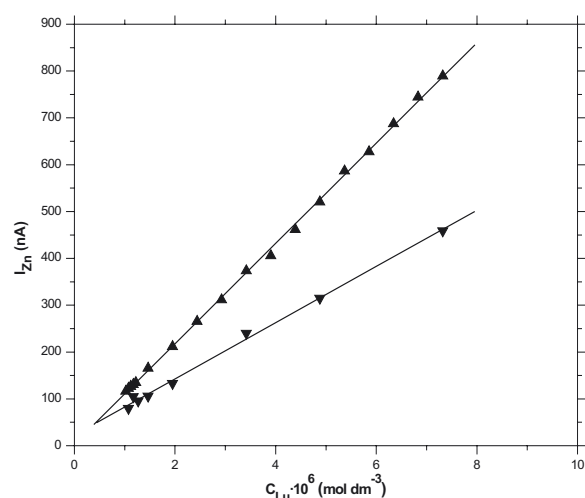

Figure 4. Dependence of Zn (II) peak current on added Lu (III) in the range [Lu] = (1 - 7.3)·10⁻⁶ M, and deposition time: (▼) 10 s; (▲) 30 s. The initial [Zn-EDTA] was 3.6·10⁻⁵ M. Supporting electrolyte: 0.2 M NaClO₄ in 0.05 M pH 5.4 sodium acetate buffer; deposition potential: -1.200 V; sweep rate: 10 mV s⁻¹.

linearity, as can be seen from Table 1.

For Lu (III) concentrations in the ranges (1.2 - 9.8)·10⁻⁸ and (1.1 - 7.3)·10⁻⁷ M the deposition time was prolonged to 90 s and the initial Zn-EDTA concentration decreased to 4.2·10⁻⁶ M. The decreased [Zn-EDTA] increases the sensitivity because the relative increase in Zn (II) current is greater when the initial [Zn-EDTA] is not too much higher than [Lu (III)]. The use of an initial [Zn-EDTA] of 10 to 100 times the expected [Lu (III)] yields an easily measurable increase of peak current from the liberated Zn (II) ions.

A further increase in sensitivity was achieved by increasing the deposition time to 120 s and by further decreasing initial [Zn-EDTA] to 8.2·10⁻⁷ M. Under these conditions the curves corresponding to [Lu

Table 1. Parameters of the calibration graphs with the applied deposition times (t$_{dep}$) for three different initial concentrations of Zn-EDTA complex (C$_{ZnEDTA}$), the 95% confidence limits for the intercept *(A)* and slope *(B)*, the correlation coefficient *(r)* and the deviation of the experimental points from the calculated straight line *(SD)*. *(S(A)* – standard deviation of intercept, *S(B)* - standard deviation of slope, t – value of Student's distribution coefficient for a confidence interval of 95% and *(n-2)* degrees of freedom).

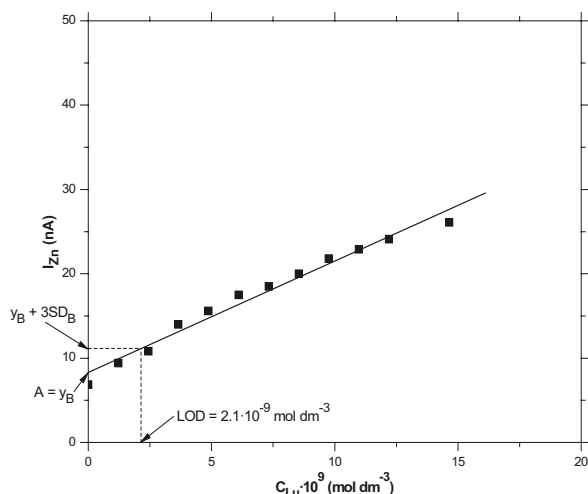| C$_{ZnEDTA}$ (mol dm⁻³)	C$_{Lu}$ (mol dm⁻³)	t$_{dep}$ (s)	A ± t$_{(n-2)}$S(A)(nA)	B ± t$_{(n-2)}$S(B)(mA dm³ mol⁻¹)	r	SD(nA)
3.6·10⁻⁵	(1 – 7.3) ·10⁻⁶	10	22.5 ± 12.2	60.1 ± 3.5	0.9983	8.5
	(0.5 – 9.8) ·10⁻⁷		0.9 ± 5.2	70.1 ± 10.1	0.9724	5.0
3.6·10⁻⁵	(1 – 7.3) ·10⁻⁶	30	3.6 ± 6.5	107.1 ± 1.6	0.9996	6.8
	(0.5 – 9.8) ·10⁻⁷		-1.2 ± 1.3	112.3 ± 2.3	0.9992	1.4
4.2·10⁻⁶	(1.1 – 7.3) ·10⁻⁷	90	7.2 ± 2.2	261.8 ± 6.5	0.9997	1.5
	(1.2 – 9.8) ·10⁻⁸		0.3 ± 0.7	321.3 ± 11.5	0.9994	0.4
8.2·10⁻⁷	(1.1 – 7.3) ·10⁻⁸	120	7.4 ± 0.9	830.6 ± 24.2	0.9991	0.7
	(1.2 – 9.8) ·10⁻⁹		1.2 ± 1.1	1444.1 ± 184.2	0.9920	0.6

Figure 5. Graphical representation of limit of detection (LOD) determination: (A) – intercept of the calibration line; y_B – calculated blank; SD_B – estimated blank standard deviation; [Lu] = $(1 - 15) \cdot 10^{-9}$ M. Initial [Zn-EDTA] was $8.2 \cdot 10^{-7}$ M. Supporting electrolyte: 0.2 M $NaClO_4$ in 0.05 M pH 5.4 sodium acetate buffer; deposition potential: -1.200 V; deposition time: 120 s; sweep rate: 10 mV s^{-1}.

(III)] ranges of $(1.2 - 9.8) \cdot 10^{-9}$ and $(1.1 - 7.3) \cdot 10^{-8}$ M were measured. The current vs. concentration dependences were linear with correlation coefficients of 0.9991 and 0.9920, respectively (Table 1).

As represented in Fig. 5, the limit of detection (LOD) [13] of lutetium (III) was $2.1 \cdot 10^{-9}$ M (0.37 µg L^{-1}, i.e. approx. 0.4 ppb in water samples). This value is significantly lower than the lowest quantification limit ($5 \cdot 10^{-7}$ M) obtained from previous indirect polarographic lanthanide determinations [9,10]. The mean relative error of ten measurements of Lu (III) at $6.1 \cdot 10^{-9}$ M was 7.3%, which gives $4.5 \cdot 10^{-9}$ M as the limit of quantitation [14].

Ions which form EDTA complexes with comparable or larger stability than Zn-EDTA will interfere; thus, this method can only be used for Lu (III) determination in an analyte without these interfering ions. Such applications are in the production of lutetium containing radiopharmaceuticals and in the production of radioactive ^{177}Lu by neutron irradiation of [176]Lu

4. Conclusion

Direct determination of Lu (III) by DPASV is not possible because the reduction potential of Lu (III) at a mercury electrode is very negative, near the decomposition potential of the supporting electrolyte.

The results show that indirect voltammetric determination of Lu (III) via Zn displacement from its EDTA complex, using 0.2 M $NaClO_4$ as the supporting electrolyte in 0.05 M pH 5.4 sodium-acetate buffer, can be used for trace Lu (III) determination. For different initial [Zn-EDTA] there is a range of [Lu (III)] for which the linear dependence of Zn (II) current vs. [Lu (III)] enables ready determination of unknown [Lu (III)]. The limit of detection is $2.1 \cdot 10^{-9}$ M.

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