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Electrolytic reduction of Re(VII) using a flow type electrolysis cell and its possibility of radiopharmaceuticals application

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The electrochemical properties of perrhenate were studied in hydrochloric acid solution via cyclic voltammetry by disk glassy carbon electrode. The electroreduction of perrhenate was performed at a constant potential -0.33 V (vs. Ag/AgCl) with a potentiostat by a flow type electrolysis cell. It was found that the change of rhenium ion concentration before and after electrolysis was negligible. This means almost no rhenium or rhenium oxides were deposited on the carbon fiber electrode during the electroreduction. The rhenium ion solution changed from colorless into yellow-brown after electrolysis process. UV-Visible spectrophotometry was used to characterize the oxidation states of Re before and after electrolysis. Some obvious peaks were detected after electrolysis, indicating that Re(VII) was reduced to Re(V). The complex behavior and stability of Re(V)-HEDP were discussed for the purpose of electroreduction of Re(VII) or Tc(VII) on radiopharmaceuticals production.

Keywords: Perrhenate, Electroreduction, Absorption spectra, Radiopharmaceuticals production

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I. INTRODUCTION

In recent years, ^{99m}Tc and ^{188}Re have been widely employed in radioimmunotherapy [1–3]. ^{99m}Tc(V)-DMSA (dimercaptosuccinic acid) and ^{188}Re(V)-DMSA can be selectively taken up in bone metastases in patients with prostate cancer [3]. As a new radiopharmaceutical, ^{188}Re(Sn)-HEDP can localize in skeletal metastases and emit beta particles that may be beneficial for therapeutical [4]. However, $KTcO_4$ and $KReO_4$ cannot be labeled directly with interested complexes as radiopharmaceuticals since they form as anion in buffer solution. The labeling procedure is realized only when Tc(VII) and Re(VII) are reduced to low valence states (I, III, IV and V) and form as cation. Up to now, chemical reduction methods are common ways in radiopharmaceuticals production. Stannous chloride [5–7] is used as the reducing regent. When it reduces ^{99m}Tc and ^{188}Re, it can company with radioactive drugs into human organisms. As stannous chloride is toxic, this method of processing radioactive drugs is harmful to the organisms. In addition, it can be easily oxidized in air, which limits its reduction efficiency. Also oxidation states in reduction of Re(VII) and Tc(VII) by stannous chloride are still undetermined [8, 9].

If the chemical reducer for radiation therapy can be replaced by electrochemical reduction process with a flow type electrolysis cell, drug safety of the radioimmunotherapy can be improved and the chemical toxicity can be decreased. In fact, electrochemical reduction technology was chosen to reduce Re(VII). Hindman *et al.* [10] studied electrolytic reduction of perrhenate in hydrochloric acid of different concentrations, but they did not connect the result with radiopharmaceuticals preparation. Dadachova *et al.* [11] studied electrolytic reduction of carrier-free ^{188}Re in 7 M hydrochloric acids, yet stability of the reduced Re(V) with DMSA was only 40 min, thus limiting application of the Re electroreduction in radiation therapy. These results indicate that Re(VII) could be reduced to lower oxidation states by electroreduction technology. However, ordinary electrolytic cell may not fit for relatively short half-life therapeutic radionuclide used in radiopharmaceuticals. With a high efficient electrolytic cell, short half-life therapeutic radionuclide could be employed into radiation therapy.

The high efficiency of electrolytic cell has been confirmed by Wei *et al.*, for up to 90% reduction of Ce(IV) [12] and much higher efficiency of Tc(VII) reduction than ordinary electrolytic cell [13]. This cell was featured by the specific design of the anode and cathode, which can prevent oxidation of the reduced rhenium by the anode. In this paper, we investigate the feasibility of reducing perrhenate to prepare Re-labeled compounds using high efficiency electrolytic cell. The irreversible reduction behavior of Re(VII) is investigated in 1 M hydrochloric acid. Stability of the reduced Re with HEDP is discussed. Stable Re(VII) isotopes, being of similar chemical properties with the radioactive Re(VII) isotopes, are used. Also, Re and Tc are in the same main group in the periodic table, stable Re isotope can be used as a surrogate for further studies on radioactive Re and Tc productions [14].

II. EXPERIMENTAL

Potassium perrhenate ($KReO_4$); 1-hydroxyethylidene-1, 1-diphosphonic acid (HEDP); potassium thiocyanate (KSCN), sodium hydroxide (NaOH), cesium chloride (CsCl) were commercial reagents of analytical grade.

The experiments of cyclic voltammetry were performed at 298 K in a conventional three-electrode system, with a flow type electrolysis cell (HX-201; Hokuto Denka, Ltd.) as shown in Fig. 1. The working electrode was a disk glassy carbon electrode (Φ 2 mm), the counter electrode was a platinum disk electrode (Φ 2 mm), and the reference electrode was a KCl-saturated Ag/AgCl reference electrode (0.197 V vs. standard hydrogen electrode).

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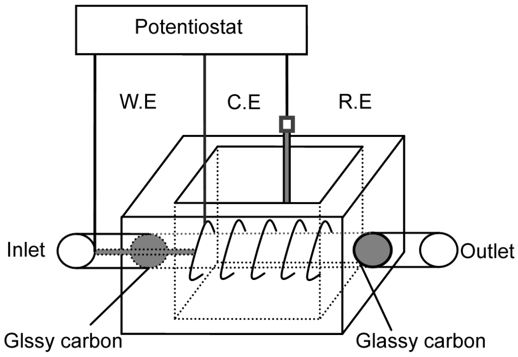

Fig. 1. The flow type high-efficient electrolysis cell.

The cathode was glassy carbon fibers in a cylindrical column of Vycor glass (a porous silica glass), which acted as both cathode compartment and separator. Sample solution containing 1 mM Re(VII) was prepared by diluting Re(VII) stock solution with 1 M HCl solution and was introduced into the Vycor glass column by peristaltic pump at the flow rate of 0.8 cm^3/min. The electroreduction was carried out at a potential −0.33 V (vs. Ag/AgCl) with a potentiostat. The concentration of Re ions before and after electrolysis was determined by an inductively coupled plasma atomic emission spectrometry (ICP-AES, ICP-7510, Shimadzu, Japan). The Re ion solution was analyzed by UV-Visible spectrometer (UV-3600, Shimadzu, Japan) and infrared spectrum analyzer (EQUINOX55, BRUCK).

The experiments were conducted by an electrochemical workstation CorrTestTM model CS1350 equipped with electrochemical testing and analysis tools Version 4.3 software. All the experiments using Re solutions were carried out under nitrogen protection.

III. RESULTS AND DISCUSSION

A. The cyclic voltammogram

The cyclic voltammogram of $KReO_4$ in 1 M HCl at 298 K with scan rate of 25 mV/s is shown in Fig. 2.

Three reduction peaks and two oxidation peaks could be seen in the scanning potential range of −0.9∼1.3 V (vs. Ag/AgCl). On the negative-going forward scan, the first peak located at ca.0.8 V was due to the solvent reduction. The second peak observed at ca.−0.33 V corresponded to the reduction of Re(VII) into a lower oxidation state of Re [15]. The reduction peak at ca.−0.9 V, bubbles appeared on the working electrode surface, which meant that the reduction of hydrogen ions had begun, as described in Eq. (1). On the positive-going reverse scan, the appearance of a weak oxidation peak at a potential of 0.5 V was the oxidation of the low state of Re [16]. As for the oxidation peak at 1.3 V, it was the overflow of the oxygen, as described by Eq. (2). Obviously, the cyclic voltammogram of Re(VII) in 1 M HCl provided the redox behaviors of Re(VII) and the possibility of reduction of Re(VII) into low oxidation states by direct electrolysis from hydrochloric acid.

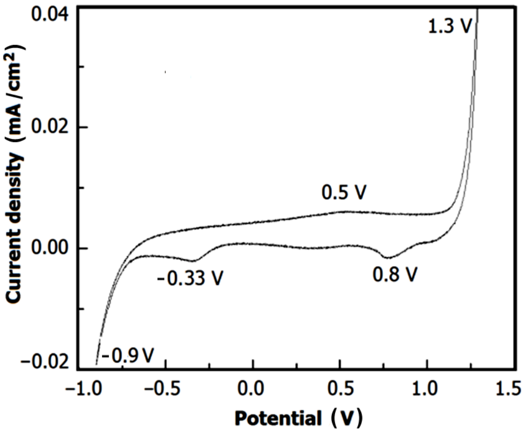

Fig. 2. Cyclic voltammogram of 1 mM $KReO_4$ in 1 M HCl at 298 K; Scan rate: 25 mV/s (Unit: Potential, V vs. Ag/AgCl).

$$2H^+ + 2e^- \rightarrow H_2, \tag{1}$$

$$2H_2O - 4e^- \rightarrow O_2 + 4H^+. \tag{2}$$

B. Electrolytic reduction

According to the cyclic voltammogram of 1 mM Re(VII) in 1 M HCl, the potentiostatic electroreduction experiments of the same Re solutions were conducted at a fixed potential of −0.33 V by a flow type electrolysis cell. The concluded cathodic currents during electrolysis were shown in Fig. 3.

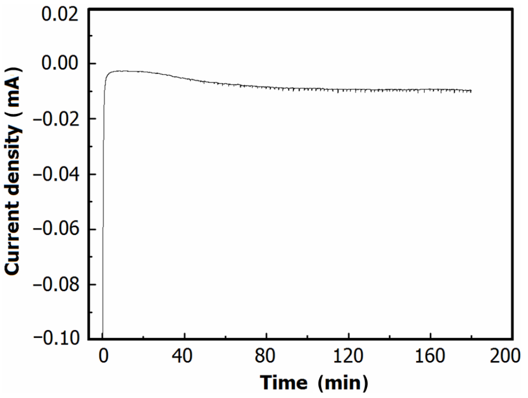

Fig. 3. Current in electrolysis of Re solution. [Re] = 1 mM; [HCl] = 1 M; flow rate: 0.8 cm^3/min; Potential: −0.33 V (vs. Ag/AgCl).

According to Méndez *et al.* [17], the possibility of electroreduction mechanisms of Re(VII) in aqueous solution was considered as follows: When the current was relatively low at the first 20–30 min, an initial amount of low oxidation states of rhenium formed by direct electron transfer, as described in

Eqs. (3)– (5). Then the current increased to an almost constant value, probably due to the adsorption of perrhenate on the glassy carbon electrode surface followed by a reduction reaction assisted through the participation of H_{ad} to yield the low oxidation state of Re, as described in Eqs. (6) and (7). This means that the electroreduction of Re(VII) stably continued on in the 1 M hydrochloric acid.

The possible electroreduction reactions [17–19] were (E^{θ} is the standard electrode potential)

$$\mathrm{ReO_4^-} + 2\mathrm{H}^+ + \mathrm{e}^- \rightarrow \mathrm{ReO_3} + \mathrm{H_2O} \quad E^{\theta} = 0.760\,\mathrm{V}, \tag{3}$$

$$\mathrm{ReO_4^-} + 4\mathrm{H}^+ + 3\mathrm{e}^- \rightarrow \mathrm{ReO_2} + 2\mathrm{H_2O} \quad E^{\theta} = 0.510\,\mathrm{V}, \tag{4}$$

$$\mathrm{ReO_4^-} + 8\mathrm{H}^+ + 7\mathrm{e}^- \rightarrow \mathrm{Re} + 4\mathrm{H_2O} \quad E^{\theta} = 0.363\,\mathrm{V}, \tag{5}$$

$$\mathrm{H}^+ + \mathrm{e}^- \rightarrow \mathrm{H_{ad}}, \tag{6}$$

$$\mathrm{ReO_4^-} + 3\mathrm{M}-\mathrm{H_{ad}} + \mathrm{H}^+ + 3\mathrm{e}^- \rightarrow \mathrm{M}-\mathrm{ReO_2}\cdot 2\mathrm{H_2O}. \tag{7}$$

From these reactions, the possible final products of electroreduction of Re(VII) were ReO_3, ReO_2 or Re. However, the Re solution concentration before and after electroreduction measured by ICP-AES did not support this conjecture. The concentrations of Re solution before and after electrolysis were measured at 186.4 ppm and 186.0 ppm, respectively, and the difference was negligibly slight. This means that there were hardly any ReO_3, ReO_2 or Re deposited on the carbon fiber electrode during the electrolysis.

However, it was found that the colorless Re solution became yellow-brown after electroreduction, indicating the formation of the Re(V) species [10, 11], which confirmed that Re(VII) had been reduced.

C. UV-visible spectroscopy

Figure 4 shows the absorption spectra of 1 mM Re in 1 M HCl solution before and after electroreduction. There was no visible absorption peak for Re(VII) between 300 nm and 600 nm. For Re solution after electroreduction, a large adsorption peak appeared around 450 nm [10]. This peak was assigned to Re(V). This confirmed that the Re(VII) was reduced to Re(V). According to Refs. [8, 9], the Re(V) species might be $ReO(Cl)_4^-$ or $Re(Cl)_6^-$. In order to characterize the Re reduced structure (ReO_3^+ or Re^{5+}), 0.5 M cesium chloride was added into the reduced Re solution and there was no precipitation. As described in Ref. [8], only $Re(Cl)_6^-$ can react with cesium chloride resulting in precipitation. The Re(V) species after electrolysis was probably $ReO(Cl)_4^-$.

KSCN solution was added into the solution to confirm the oxidation states of Re. The absorption spectra were recorded. The reduced solution (after electrolysis) stayed yellow-brown with the addition of KSCN solution, whereas the initially colorless solution without electrolysis turned into very light purple. This observation agreed with the reported results [11, 13]. The absorption spectra are shown in Fig. 5. A sharp peak around 350 nm assigned to the absorption of $Re^{V}O(SCN)^{4-}$ appears with a shoulder peak around 450 nm corresponding to $ReO(Cl)_4^-$. It means that a part of the ReO_3^+ was complexed with thiocyanate ions.

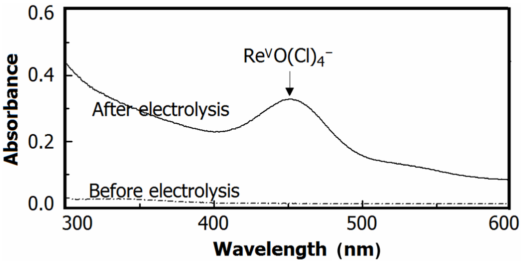

Fig. 4. Absorption spectra of Re solution before and after the electrolysis. Concentrations: [HCl] = 1 M.

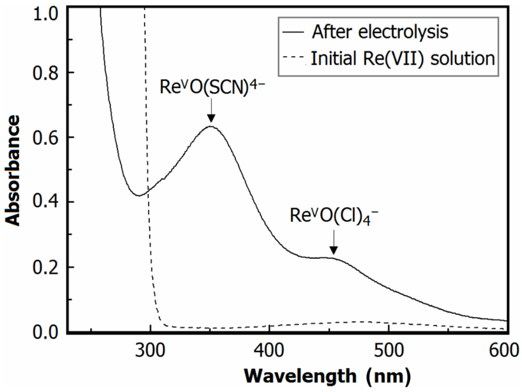

Fig. 5. Absorption spectra of Re solution modified with KSCN. Concentration: [HCl] = 1 M; [KSCN] = 0.1 M.

One day after the reduction, the reduced solution stayed yellow-brown in color. In order to confirm the stability of the reduced Re solution, the absorption spectra of reduced Re solution were measured 6 and 24 h after reduction of the solution (Fig. 6). The peak around 450 nm was observed 24 h after the reduction, indicating that the reduced Re solution remains stable in the hydrochloric acid for at least one day.

Two days after the reduction, the yellow-brown color faded

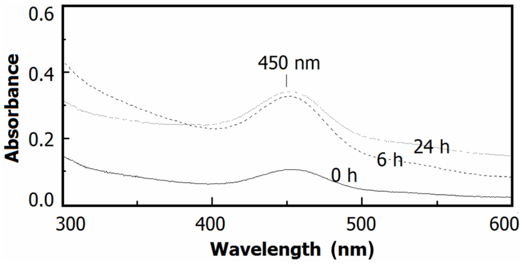

Fig. 6. Absorption spectra of electroreduced Re solution 0 h, 6 h and 24 h after electrolysis. Concentrations: [HCl] =1 M.

and black precipitation appeared in the solution. Because the Re(V) solution undergoes disproportionate to compounds of Re(VII) and Re(IV) [20], as described in Eq. (8). This black solid was presumed to be $\mathrm{ReO_2}$

$$3\mathrm{Re}^{5+} \rightarrow 2\mathrm{Re}^{4+} + \mathrm{Re}^{7+}. \tag{8}$$

D. ATR-IR Spectroscopy

In order to study the complexation properties of electrolytic reduction of rhenium with HEDP, the attenuated total reflection-Fourier transform infrared spectroscopy (ATR-IR) was used to give the specific structural information concerning the Re(V)-HEDP complexes in solution.

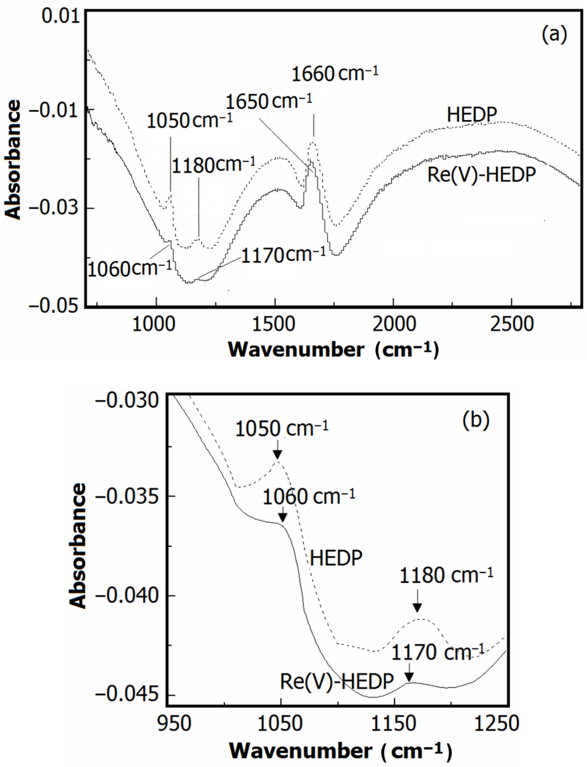

Fig. 7. ATR-IR spectra for HEDP (alone) and Re(V)-HEDP complex at 298 K and pH 4. (a) 700–2800 $\mathrm{cm^{-1}}$, (b) 950–1250 $\mathrm{cm^{-1}}$.

The ATR-IR was recorded between 4000 $\mathrm{cm^{-1}}$ and 600 $\mathrm{cm^{-1}}$. The ATR-IR spectra of Re(V)-HEDP and free HEDP ligand are shown in Fig. 7. On the basis of Ref. [21], absorption bands assigned to P=O stretching modes were observed in the 1610–1720 $\mathrm{cm^{-1}}$ region for both HEDP (alone) and Re(V)-HEDP. Absorption bands assigned to P-O asymmetric and symmetric stretching vibration modes were shown in the 1020–1210 $\mathrm{cm^{-1}}$ region for HEDP, and in the case of the complex are shifted to the bands 1030–1200 $\mathrm{cm^{-1}}$. The absorption bands in 1160–1210 $\mathrm{cm^{-1}}$ region was attributed to the (P-O)H asymmetric stretching modes, and the (P-O)H symmetric stretching modes were observed in the 1020–1110 $\mathrm{cm^{-1}}$ region for HEDP, while the (P-O)-Re(V) vibrations are observed at about 1060 $\mathrm{cm^{-1}}$(symmetric) and 1170 $\mathrm{cm^{-1}}$(asymmetric), respectively.

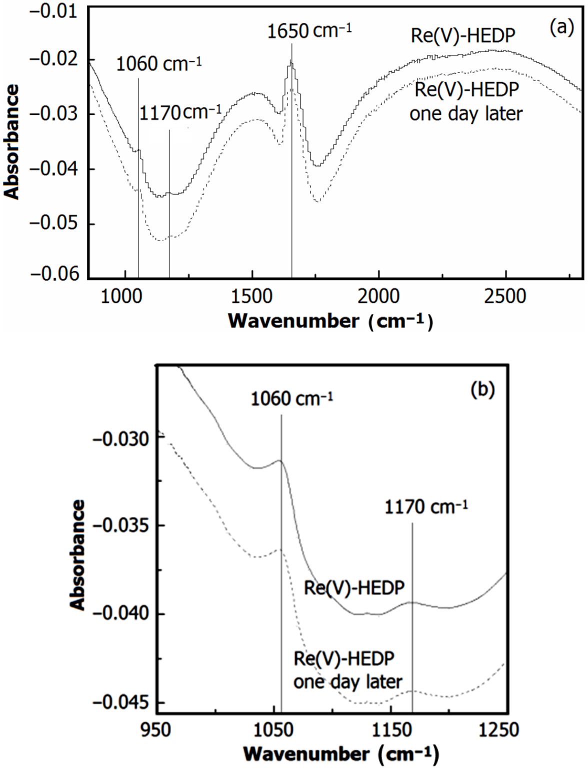

Fig. 8. ATR-IR spectra for Re(V)-HEDP complex at 298 K and pH 4 one day later. (a) wavenumber regions from 700 $\mathrm{cm^{-1}}$ to 2800 $\mathrm{cm^{-1}}$, (b) from 950 $\mathrm{cm^{-1}}$ to 1250 $\mathrm{cm^{-1}}$.

The ATR-IR absorption spectra of the Re(V)-HEDP solution (one day later) were measured (Fig. 8). One finds that the spectra are almost the same. If the Re(V) made changes in the solution of the Re(V) and HEDP, then the ATR-IR spectra of the Re(V)-HEDP one day later would differ from the Re(V)-HEDP. This confirms the stability of Re(V)-HEDP, hence the possibility of using Re(V)-HEDP in radiopharmaceuticals production.

IV. CONCLUSION

Re(VII) was electroreduced in a flow type electrolysis cell with glassy carbon as working electrode at −0.33 V (vs. Ag/AgCl) in 1 M hydrochloric acid and no Re or rhenium oxides were deposited on the working electrode. After the high-efficient electrolysis, Re(VII) was specifically reduced to its lower oxidation state: Re(V), and Re(V) solution was stable enough for several days. Also the stability of the Re(V)-HEDP solution was confirmed and it is possible to be applied in the radiation therapy.

[1] Bläuenstein P. Rhenium in nuclear medicine: general aspects and future goals. New J Chem, 1990, **14**: 405–407. DOI: 10.1002/chin.199108397

[2] Prakash S, Went M J, Blower P J. Cyclic and acyclic polyamines as chelators of rhenium-186 and rhenium-188 for therapeutic use. Nucl Med Biol, 1996, **23**: 543–549. DOI: 10.1016/0969-8051(96)00038-8

[3] Blower P J, Kettle A G, O'Doherty M J. ^{99m}Tc (V) DMSA quantitatively predicts 188Re (V) DMSA distribution in patients with prostate cancer metastatic to bone. Eur J Nucl Med, 2000, **27**: 1405–1409. DOI: 10.1007/s002590000307

[4] Maxon H R, Schroder L E, Washburn L C. Rhenium-188 (Sn) HEDP for treatment of osseous metastases. J Nucl Med, 1998, **39**: 659–663.

[5] Steigman J, Meinken G, Richards P. The reduction of pertechnetate-99 by stannous chloride—I.the Stoichiometry of the reaction in HCl, in a citrate buffer and in a DTPA buffer. Int J Appl Radiat Is, 1975, **26**: 601–609. DOI: 10.1016/0020-708X(75)90078-2

[6] Steigman J, Meinken G, Richards P. The reduction of pertechnetate-99 by stannous chloride-II. The Stoichiometry of the reduction in aqueous solutions of several phosphorus (V) compounds. Int J Appl Radiat Is, 1978, **29**: 653–660. DOI: 10.1016/0020-708X(78)90102-3

[7] Neas R E and Guyon J C. Spectrophotometric determination of thiocyanate with rhenium. Anal Chem, 1969, **41**: 1470–1473. DOI: 10.1021/ac60280a039

[8] Maun E K and Davidson N. Investigation in the chemistry of rhenium .I. oxidation states IV, V and VII. J Am Chem Soc, 1950, **72**: 2254–2260. DOI: 10.1021/ja01161a104

[9] Crouthamel C E. Thiocyanate spectroscopy determination of technetium. Anal Chem, 1957, **29**: 1756–1760. DOI: 10.1021/ac60132a024

[10] Hindman J C and Wehner P. Electrolytic Reduction of Perrhenate.I.Studies in Perchloric, Ethanesulfonic, Trifluoroacetic and Hydrochloric Acids. J Am Chem Soc, 1953, **75**: 2869–2872. DOI: 10.1021/ja01108a023

[11] Dadachova E, Smith S V, Mirzadeh S. Electrolytic reduction of carrier-free ^{188}Re. Appl Radiat Isotopes, 1996, **47**: 289–292. DOI: 10.1016/0969-8043(95)00301-0

[12] Fang B, Iwasa S, Wei Y. A study of the Ce(III)/Ce(IV) redox couple for redox flow battery application. Electrochim Acta, 2002, **47**: 3971–3976. DOI: 10.1016/S0013-4686(02)00370-5

[13] Hoshi H, Wei Y Z, Kumagai M. Electrolytic reduction of Tc(VII) in nitric acid solution using glassy carbon electrode. J Radioanal Nucl Chem, 2004, **262**: 601–605. DOI: 0236-5731/2004/USD

[14] Deutsch E, Libson K, Vanderheyden J L. The chemistry of rhenium and technetium as related to the use of isotopes of these elements in therapeutic and diagnostic nuclear medicine. Radiolabel Mono Anti, 1986, **13**: 465–477. DOI: 10.1016/0883-2897(86)90027-9

[15] Astheimer L and Schwochau K. Electrochemical reduction of MnO4-,TcO4- and ReO4- in organic solvents. J Inorg Nucl Chem, 1976, **38**: 1131–1134. DOI: 0236-5731/2004/USD

[16] Schrebler R, Cury P, Orellana M. Electrochemical and nanoelectrogravimetric studies of the nucleation and growth mechanisms of rhenium on polycrystalline gold electrode. Electrochim Acta, 2001, **46**: 4309–4318. DOI: 10.1016/S0013-4686(01)00725-3

[17] Méndez E, Cerdá M F, Luna A M C. Electrochemical behavior of aqueous acid perrhenate-containing solutions on noble metals: critical review and new experimental evidence. J Colloid Interf Sci, 2003, **263**: 119–132. DOI: 10.1016/S0021-9797(03)00165-6

[18] Cobble J W, Jr W T S, Boyd G E. Thermodynamic properties of technetium and rhenium compounds .II. heats of formation of technetium heptoxide and pertechnetic acid, potential of the technetium(IV)-technetium(VII) couple, and a potential diagram for technetium. J Am Chem Soc, 1953, **75**: 5777–5782. DOI: 10.1021/ja01120a700

[19] Bard A J, Parsons R, Jordan J. Standard potentials in aqueous solution. New York (USA): CRC Press, 1985.

[20] Young R C and Irvine J W. Reduction of perrhenate. Chem Rev, 1938, **23**: 187–191. DOI: 10.1021/cr60074a010

[21] Jacopin C, Sawiki M, Plancque G. Investigation of the Interaction between 1-hydroxyethane-1,1'-diphosphonic Acid (HEDP) and Uranium(VI). Inorg Chem, 2003, **42**: 5015–5022. DOI: 10.1021/ic0343509