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

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Abstract

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.

Full Text

Preamble

Electrolytic Reduction of Re(VII) Using a Flow-Type Electrolysis Cell and Its Potential for Radiopharmaceutical Applications

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

Keywords: Perrhenate, Electroreduction, Absorption spectra, Radiopharmaceuticals production
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Introduction

In recent years, 99mTc and 188Re have been widely employed in radioimmunotherapy [1–3]. 99mTc(V)-DMSA (dimercaptosuccinic acid) and 188Re(V)-DMSA can be selectively taken up in bone metastases in patients with prostate cancer [3]. As a new radiopharmaceutical, 188Re(Sn)-HEDP can localize in skeletal metastases and emit beta particles that may be therapeutically beneficial [4]. However, KTcO4 and KReO4 cannot be directly labeled with target complexes as radiopharmaceuticals since they exist as anions in buffer solution. The labeling procedure is only realized when Tc(VII) and Re(VII) are reduced to lower valence states (I, III, IV, and V) and form cations. To date, chemical reduction methods are commonly used in radiopharmaceutical production, with stannous chloride serving as the reducing agent [5–7].

When stannous chloride reduces 99mTc and 188Re, it accompanies the radioactive drug into human organisms. Since stannous chloride is toxic, this method of processing radioactive drugs is harmful to organisms. Additionally, it can be easily oxidized in air, which limits its reduction efficiency. Furthermore, the oxidation states resulting from reduction of Re(VII) and Tc(VII) by stannous chloride remain undetermined [8, 9].

If the chemical reducer for radiation therapy could be replaced by an electrochemical reduction process using a flow-type electrolysis cell, drug safety in radioimmunotherapy could be improved and chemical toxicity could be reduced. Electrochemical reduction technology has been selected to reduce Re(VII). Hindman et al. [10] studied electrolytic reduction of perrhenate in hydrochloric acid of different concentrations, but they did not connect their results to radiopharmaceutical preparation. Dadachova et al. [11] studied electrolytic reduction of carrier-free 188Re in 7 M hydrochloric acid, yet the stability of the reduced

Re(V) with DMSA was only 40 minutes, thus limiting application of Re electroreduction in radiation therapy. These results indicate that Re(VII) could be reduced to lower oxidation states by electroreduction technology. However, ordinary electrolytic cells may not be suitable for therapeutic radionuclides with relatively short half-lives used in radiopharmaceuticals. With a high-efficiency electrolytic cell, short half-life therapeutic radionuclides could be employed in radiation therapy.

The high efficiency of such electrolytic cells has been confirmed by Wei et al., achieving up to 90% reduction of Ce(IV) [12] and much higher efficiency of Tc(VII) reduction than ordinary electrolytic cells [13]. This cell featured a specific design of the anode and cathode that could 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 a high-efficiency electrolytic cell. The irreversible reduction behavior of Re(VII) is investigated in 1 M hydrochloric acid, and the stability of the reduced Re with HEDP is discussed. Stable Re(VII) isotopes, having similar chemical properties to radioactive Re(VII) isotopes, are used. Since Re and Tc are in the same main group in the periodic table, stable Re isotopes can serve as surrogates for further studies on radioactive Re and Tc production [14].

II. Experimental

Potassium perrhenate (KReO4), 1-hydroxyethylidene-1,1-diphosphonic acid (HEDP), potassium thiocyanate (KSCN), sodium hydroxide (NaOH), and cesium chloride (CsCl) were commercial reagents of analytical grade.

Cyclic voltammetry experiments were performed at 298 K in a conventional three-electrode system using a flow-type electrolysis cell (HX-201; Hokuto Denka, Ltd.) as shown in [Figure 1: see original paper]. 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).

The cathode consisted of glassy carbon fibers in a cylindrical column of Vycor glass (a porous silica glass), which served as both the cathode compartment and separator. Sample solution containing 1 mM Re(VII) was prepared by diluting Re(VII) stock solution with 1 M HCl and introduced into the Vycor glass column by peristaltic pump at a flow rate of 0.8 cm^3/min. Electroreduction was carried out at a potential of -0.33 V (vs. Ag/AgCl) with a potentiostat. The concentration of Re ions before and after electrolysis was determined by 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).

Experiments were conducted using an electrochemical workstation CorrTest™

model CS1350 equipped with electrochemical testing and analysis tools Version 4.3 software. All experiments using Re solutions were carried out under nitrogen protection.

III. Results and Discussion

A. The Cyclic Voltammogram

The cyclic voltammogram of KReO4 in 1 M HCl at 298 K with a scan rate of 25 mV/s is shown in [Figure 2: see original paper]. Three reduction peaks and two oxidation peaks were observed in the scanning potential range of −0.9 to 1.3 V (vs. Ag/AgCl). On the negative-going forward scan, the first peak located at approximately 0.8 V was due to solvent reduction. The second peak observed at approximately −0.33 V corresponded to the reduction of Re(VII) to a lower oxidation state of Re [15]. At the reduction peak of approximately −0.9 V, bubbles appeared on the working electrode surface, indicating that hydrogen ion reduction 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 corresponded to oxidation of the low oxidation state of Re [16]. The oxidation peak at 1.3 V was due to oxygen evolution, as described by Eq. (2). Clearly, the cyclic voltammogram of Re(VII) in 1 M HCl provided the redox behavior of Re(VII) and demonstrated the possibility of reducing Re(VII) to low oxidation states by direct electrolysis from hydrochloric acid.

$$2H^+ + 2e^- \to H_2,$$

$$2H_{2O} - 4e^- \to O_2 + 4H^+.$$

B. Electrolytic Reduction

Based on the cyclic voltammogram of 1 mM Re(VII) in 1 M HCl, potentiostatic electroreduction experiments of the same Re solutions were conducted at a fixed potential of −0.33 V using a flow-type electrolysis cell. The resulting cathodic currents during electrolysis are shown in [Figure 3: see original paper].

According to Méndez et al. [17], the possible electroreduction mechanisms of Re(VII) in aqueous solution were considered as follows. When the current was relatively low during the first 20–30 minutes, 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 adsorption of perrhenate on the glassy carbon electrode surface followed by a reduction reaction assisted through the participation of Had to yield the low oxidation state of Re, as described in Eqs. (6) and (7). This indicates that the electroreduction of Re(VII) proceeded stably in 1 M hydrochloric acid.

The possible electroreduction reactions [17–19] were (E is the standard electrode potential):

$$
\begin{gathered}
ReO_4^- + 2H^+ + e^- \rightarrow ReO_3 + H_{2O} \quad E^\theta = 0.760\,\mathrm{V}, \\
ReO_4^- + 4H^+ + 3e^- \rightarrow ReO_2 + 2H_{2O} \quad E^\theta = 0.510\,\mathrm{V}, \\
ReO_4^- + 8H^+ + 7e^- \rightarrow Re + 4H_{2O} \quad E^\theta = 0.363\,\mathrm{V}, \\
H^+ + e^- \rightarrow H_{ad}, \\
ReO_4^- + 3M^- + H_{ad} + H^+ + 3e^- \rightarrow M^- - ReO_2 \cdot 2H_{2O}.
\end{gathered}
$$

From these reactions, the possible final products of electroreduction of Re(VII) were ReO3, ReO2, 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, with a negligibly slight difference. This means that hardly any ReO3, ReO2, or Re were deposited on the carbon fiber electrode during electrolysis. However, the colorless Re solution became yellow-brown after electroreduction, indicating the formation of Re(V) species [10, 11], which confirmed that Re(VII) had been reduced.

C. UV-Visible Spectroscopy

[Figure 4: see original paper] 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 the Re solution after electroreduction, a large absorption peak appeared around 450 nm [10]. This peak was assigned to Re(V), confirming that 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^-. To characterize the reduced structure (ReO3^+ or Re5+), 0.5 M cesium chloride was added to the reduced Re solution, but no precipitation occurred. As described in Ref. [8], only Re(Cl)6^- can react with cesium chloride to form a precipitate. The Re(V) species after electrolysis was probably ReO(Cl)4^- or Re(Cl)6^-.

To confirm the oxidation states of Re, KSCN solution was added to the solution and the absorption spectra were recorded. The reduced solution (after electrolysis) remained yellow-brown upon addition of KSCN solution, whereas the initially colorless solution without electrolysis turned very light purple. This observation agreed with reported results [11, 13]. The absorption spectra are shown in [Figure 5: see original paper]. A sharp peak around 350 nm assigned to the absorption of ReVO(SCN)4^- appears with a shoulder peak around 450 nm corresponding to ReO(Cl)4^-. This indicates that a portion of the ReO^+ was complexed with thiocyanate ions.

To confirm the stability of the reduced Re solution, the absorption spectra were measured 6 and 24 hours after reduction ([Figure 6: see original paper]). The peak around 450 nm was observed 24 hours after reduction, indicating that the reduced Re solution remains stable in hydrochloric acid for at least one day. One day after reduction, the reduced solution stayed yellow-brown in color. Two days after reduction, the yellow-brown color faded and black precipitation appeared in the solution because the Re(V) solution undergoes disproportionation to compounds of Re(VII) and Re(IV) [20], as described in Eq. (8). This black solid was presumed to be ReO2.

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

D. ATR-IR Spectroscopy

To study the complexation properties of electrolytically reduced rhenium with HEDP, attenuated total reflection-Fourier transform infrared spectroscopy (ATR-IR) was used to obtain specific structural information concerning the Re(V)-HEDP complexes in solution.

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

The ATR-IR absorption spectra of the Re(V)-HEDP solution (one day later) were measured ([Figure 8: see original paper]). The spectra are almost identical. If the Re(V) had undergone changes in the solution of Re(V) and HEDP, then the ATR-IR spectra of Re(V)-HEDP one day later would differ from the initial Re(V)-HEDP spectrum. This confirms the stability of Re(V)-HEDP, hence supporting the possibility of using Re(V)-HEDP in radiopharmaceutical production.

IV. Conclusion

Re(VII) was electroreduced in a flow-type electrolysis cell with glassy carbon as the 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 high-efficiency electrolysis, Re(VII) was specifically reduced to its lower oxidation state Re(V), and the Re(V) solution was stable for several days. Additionally, the stability of the Re(V)-HEDP solution was confirmed, demonstrating its potential applicability in radiation therapy.

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