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# Investigation on oxidation states of rhenium in Re-HEDP

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**Abstract** The oxidation states of rhenium in Re-HEDP (hydroxyethylidene diphosphonate) were measured by the methods of extraction and potentiometric titration. The oxidation state of rhenium in Re-HEDP was mostly +4 valence, and the Re(Ⅳ)-HEDP was oxidized to Re(Ⅴ)-HEDP when it was titrated by $I_3^-$ at pH 2.0. In the reduction system of Vc+$Sn^{2+}$, $ReO_4^-$ was only reduced by $Sn^{2+}$, but Vc was oxidized earlier than $Sn^{2+}$ when it was titrated by $I_3^-$.

**Keywords** Rhenium, HEDP (hydroxyethylidene diphosphonate), Oxidation state

**CLC number** O614.432

## 1 Introduction

Two radioisotopes of rhenium, $^{186}$Re and $^{188}$Re, were considered as promising nuclides for tumor therapy,[1,2] for their excellent nuclear properties (emitting β particles with moderate energy and γ photons adapted for imaging). The complexes of Tc-diphosphonate (MDP, HEDP (hydroxyethylidene diphosphonate), etc.) have been widely used for imaging of bone cancer. Both rhenium and technetium belong to B(Ⅶ) in periodic table of the elements, and possess similar chemical properties, so the complexes of Re-diphosphonate are also hopeful therapeutic radiopharmaceuticals and have been used for bone cancer treatment in clinic.

Because rhenium has manifold valence states, and HEDP is a bidentate ligand, complexes with different constitutions or structures exist in the system of Re-HEDP correspondingly, causing the difference in the aspect of biological properties and clinical effect.[3] It is of great importance to measure the oxidation states of rhenium in Re-HEDP for evaluating the biological behavior of $^{186}$Re($^{188}$Re)-HEDP and for exploring the quantitative structure activity relationship of rhenium radiopharmaceutics.

In this paper, the oxidation states of rhenium in Re-HEDP and the influential factors were investigated by potentiometric titration[3, 4] and extraction.[4]

## 2 Experimental

### 2.1 Materials

$K_2Cr_2O_7$ was recrystallized from water, and 8-hydroxyquinoline (oxine) was recrystallized from ethanol. $^{186}$Re was purchased from China Institute of Atomic Energy. HEDP was synthesized in our laboratory and its structure was confirmed by element analysis, MS, IR and NMR. Stannous chloride and other reagents were of analytic grade.

### 2.2 Apparatus

Model FJ2021 γ-radiation immunity counter (National 262 Factory) and Model FH-1304 scaler (Beijing Nuclear Instrument Factory) were used for radioactive measurement.

### 2.3 Titration of standard $I_2$ solution

$I_2$ was dissolved in KI solution, and titrated by standard $Na_2S_2O_3$ solution.

### 2.4 Extraction analysis of Re (Ⅴ)

2.9 mL of 3.0 mol/L boric acid in saturated $Na_2SO_4$ and 3.0 mL of 0.4 mol/L oxine in chloroform solution were added to 0.1 mL of $^{186}$Re-HEDP solution.[1, 5] This mixture was vibrated for a certain time and then the water phase was separated from the organic phase. The radioactive counts of both phases were measured and the extraction efficiency and the

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content of Re (Ⅴ) were calculated.

### 2.5 Potentiometric titration of $Sn^{2+}$ and Vc

The pH of $^{186}$Re-HEDP solution was adjusted to a given value, then $Sn^{2+}$ or Vc was titrated by standard $I_3^-$ solution, and the titration terminal point was determined by measuring the electric potential.

## 3 Results and discussion

### 3.1 Re (Ⅴ) extraction

It was reported that $ReO^{3+}$ can form with oxine a complex which dissolves in chloroform, and Re (Ⅴ) can be analyzed by extracting the complex in the chloroform phase.[4] The relationships of extraction efficiency with extraction time and with pH were shown in Fig.1 and Fig.2, respectively. The extraction reached equilibrium when extraction time was 40 min and upwards. The extraction efficiency increased with the increase in pH value of the extraction solution. When the pH was more than 6.0, the extraction efficiency tended to a fixed value as given in Fig.2. Therefore, the optimal condition for extraction of Re (Ⅴ) is pH of 6.0-6.5 and extraction time of no less than 40 min.

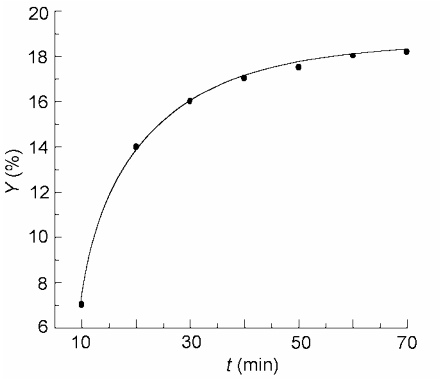

**Fig.1** Relationship between extraction time and extraction yield.

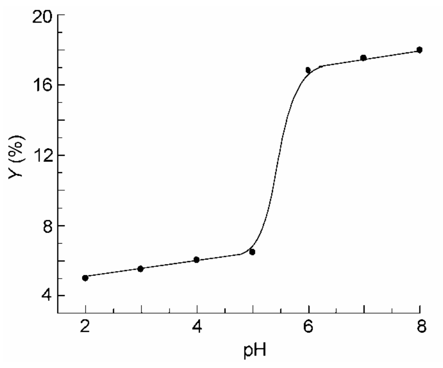

**Fig.2** Influence of pH value on extraction yield.

### 3.2 Potentiometric titration of $Sn^{2+}$ and Vc

The potential curves which occured when the unreacted $Sn^{2+}$, Vc and Vc+$Sn^{2+}$ were titrated by standard $I_3^-$ solution were shown in Fig.3, Fig.4 and Fig.5, respectively. There were two abrupt turning points in Fig.5. The quantity of $I_3^-$ needed in the first turning point was equal to that for titrating equal quantity of Vc solely. The quantity of $I_3^-$ needed in the second turning point was equal to that for titrating equal quantity of $Sn^{2+}$ solely. The transferred electron number per mole rhenium, *n*, in the process of reduction of $ReO_4^-$ by $Sn^{2+}$ or Vc was calculated according to the following equation:

$$n = \frac{2[V(\mathrm{RE})\,C(\mathrm{RE}) - V(\mathrm{I_2})\,C(\mathrm{I_2})]}{V(\mathrm{ReO_4^-})C(\mathrm{ReO_4^-})} \qquad (1)$$

where *V* (RE) and *C* (RE) are the volume and concentration of the reducing agent $Sn^{2+}$ or Vc (titrated by standard $I_3^-$ solution); $V(ReO_4^-)$ and $C(ReO_4^-)$ are the volume and concentration of $ReO_4^-$; $V(I_2)$ and $C(I_2)$ are the volume and concentration of the $I_3^-$ needed in the terminal point of the titration.

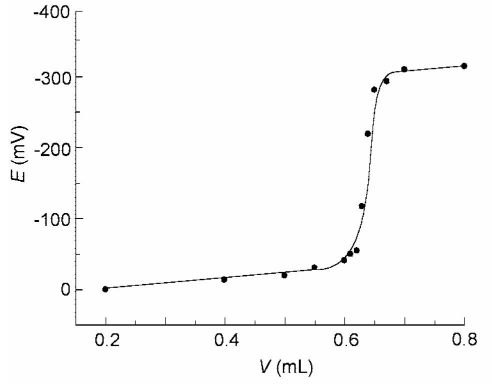

**Fig.3** Potential curve of $Sn^{2+}$ titrated by iodine.

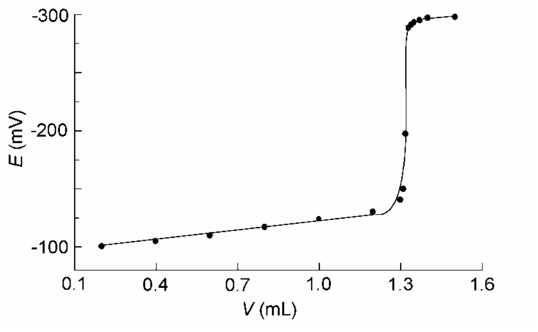

**Fig.4** Potential curve of Vc titrated by iodine.

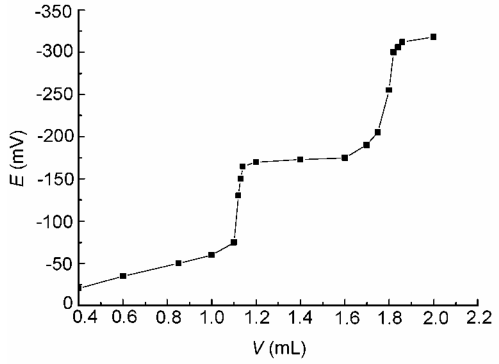

**Fig.5** Potential curve of Vc+$Sn^{2+}$ titrated by iodine.

### 3.3 Preparation of Re-HEDP

The influence of different reducing agents on the yield of Re-HEDP was shown in Table 1. The yield was higher than 95% in each of the three systems.

**Table 1** Influence of different reducing agents on the preparation of Re-HEDP

| Reducing agent | Hydrolyzing rhenium (%) | Labeling efficiency (%) |
|---|---|---|
| Vc | 2.1±0.2 | 95.7±0.8 |
| $Sn^{2+}$ | 2.7±0.3 | 95.2±0.5 |
| Vc+$Sn^{2+}$ | 0.8±0.2 | 97.3±0.6 |

### 3.4 Oxidation states of rhenium in Re-HEDP

Relationships of unreduced $ReO_4^-$, Re (Ⅴ) and the average oxidation state of rhenium in different reaction conditions were shown in Table 2. Unreduced $ReO_4^-$ was analyzed by radioactive paper chromatography, Re (Ⅴ) by extraction and the average oxidation state of rhenium $(7-n)$ by potentiometric titration. For rhenium, the valence electron is $5d^56s^2$. Assume that $ReO_4^-$ is reduced to +5 valence at first, then reduced to +4, +3 valence further, the percentages of Re (Ⅳ) and Re (Ⅲ) were calculated as follows:

$$7-n=7\times X(\mathrm{ReO_4^-})+5\times X(\mathrm{Re(Ⅴ)})+4\times X(\mathrm{Re(Ⅳ)})+3\times X(\mathrm{Re(Ⅲ)}),$$

$$100\%=X(\mathrm{Re(Ⅴ)})+X(\mathrm{Re(Ⅳ)})+X(\mathrm{Re(Ⅲ)})+X(\mathrm{ReO_4^-}) \qquad (2)$$

where $(7-n)$ is the average oxidation state of rhenium of reduced $ReO_4^-$; $X(ReO_4^-)$, $X$ (Re (Ⅴ)), $X$ (Re (Ⅳ)) and $X$ (Re (Ⅲ)) are the molar percentage of $ReO_4^-$, Re (Ⅴ), Re (Ⅳ) and Re (Ⅲ) valence in the system, respectively.

**Table 2** The average oxidation state of rhenium in Re-HEDP

| Reaction pH | Reducing agent | Titration pH | $n$ | 7-$n$ | Re(Ⅴ) (%) |
|---|---|---|---|---|---|
| 2.5±0.1 | Vc | 4.0±0.1 | 3.01±0.02 | 3.99 | 1.9±0.2 |
| 2.5±0.1 | $Sn^{2+}$ | 4.0±0.1 | 2.93±0.04 | 4.07 | 2.7±0.1 |
|  |  | 2.0±0.1 | 3.04±0.03 | 3.96 | 2.3±0.3 |
|  |  |  | 1.97±0.05 | 5.03 | 95.6±0.4 |
| 2.5±0.1 | Vc+$Sn^{2+}$ | 4.0±0.1 | 3.14±0.07 | 3.86 | 2.4±0.3 |
|  |  | 2.0±0.1 | 3.08±0.06 | 3.92 | 2.1±0.4 |
|  |  |  | 2.04±0.03 | 4.96 | 96.7±0.7 |

When the titration pH was 4.0, the transferred electron number was about 3.0 and the average oxidation state was about 4.0. The Re (Ⅴ) percentage was lower than 3.0%, and the yield of Re-HEDP was more than 95%. So the valence of rhenium in Re-HEDP was +4 at that time.

At the titration pH 2.0, there were two abrupt turning points in the potential curve when $Sn^{2+}$ served as the reducing agent. The first point was the terminal point of excessive $Sn^{2+}$ titrated by $I_3^-$. The transferred electron number in the second point was about 1 less than that in the first one.

There were two abrupt turning points in the potential curve with titration pH of 4.0 in the reaction system of Vc+$Sn^{2+}$. The quantity of $I_3^-$ needed in the first point was equal to that for titrating the added Vc solely. The quantity of $I_3^-$ needed in the second point was equal to that for titrating the unreacted $Sn^{2+}$. The transferred electron number was calculated according to the second point. The result showed that $ReO_4^-$ was only reduced by $Sn^{2+}$ and Vc was oxidized earlier than $Sn^{2+}$ when it was titrated by $I_3^-$, and that Vc had a function of anti-oxidation.

While the titration pH was 2.0 in the reaction system of Vc+$Sn^{2+}$, there were three abrupt turning points in the potential curve. The first point was the terminal point of Vc titrated by $I_3^-$, and the second one as the terminal point of excessive $Sn^{2+}$ titrated by $I_3^-$. The transferred electron number in the third point was about 1 less than that in the second point.

For different reaction system with titration pH value of 2.0, the quantity of Re (Ⅴ) by the extraction analysis after the titration by $I_3^-$ was close to the yield of Re-HEDP, so the final point was the result of Re(Ⅳ)-HEDP oxidized to Re (Ⅴ)-HEDP by excessive $I_3^-$. It was simultaneously shown that Re(Ⅳ)-HEDP was easily oxidized to Re (Ⅴ)-HEDP in strong acidic medium, while comparatively stable in weak acidic medium.

## 4 Conclusions

The oxidation state of rhenium in Re-HEDP was +4 valence as the reaction pH is 2.5. In the system of Vc+$Sn^{2+}$, $ReO_4^-$ was only reduced by $Sn^{2+}$, but Vc was oxidized earlier than $Sn^{2+}$ when it was titrated by $I_3^-$, thus affirming the antioxidation function of Vc. The stability of rhenium in different oxidation states was related to the system's acidity. While Re (Ⅳ)-HEDP was easily oxidized to Re (Ⅴ)-HEDP in strong acidic medium, it was comparatively stable in weak acidic medium.

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