

PREPARATION OF ^{186}Re AND ^{188}Re WITH HIGH SPECIFIC ACTIVITY BY THE SZILARD-CHALMERS EFFECT

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SUMMARY

^{186}Re and ^{188}Re are regarded as the best radionuclides used for radiotherapy and radioimmunotherapy. We are attempting to prepare ^{186}Re and ^{188}Re with high specific activity by the Szilard-Chalmers effect. A series of rhenium complexes were synthesized and then irradiated with thermal neutrons (neutron flux: 10^{12} n/sec/cm²) for 1 hour. The recoiled radioactive rhenium atoms were separated from the target by stripping the dichloromethane solution of irradiated rhenium compound with an aqueous solution. Various aqueous stripping agents were tested. In the case of $\text{ReN}(\text{S}_2\text{CNEt}_2)_2$, an enrichment factor of 210 and a chemical yield of 36% were achieved. The product was in pure perrhenate form with specific activity of 0.72 GBq/mg Re (19.5 mCi/mg Re).

Keywords: *Szilard-Chalmers reaction/rhenium-186,188*

INTRODUCTION

^{186}Re and/or ^{188}Re -labeled radiopharmaceuticals developed rapidly in the recent years because of their appropriate half-life, emission of energetic beta particles

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and gamma rays with suitable energy for SPECT or gamma camera, and versatile coordination chemistry [1, 2]. The ^{186}Re labeled monoclonal antibodies have proven to be effective in radioimmunotherapy of human metastatic carcinoma [3]. For radioimmunotherapy, the labeled radionuclide must be carrier-free or at least in a state of very high specific activity. The bombardment of ^{186}W with proton or deuteron beam in a cyclotron can produce carrier-free ^{186}Re [4], but very expensive enriched ^{186}W target has to be employed. If an easily available natural tungsten target is used, ^{186}Re is obtained along with other rhenium radioisotopes, such as ^{181}Re , $^{182\text{m}}\text{Re}$, $^{182\text{g}}\text{Re}$, ^{183}Re and ^{184}Re simultaneously produced by (p, xn) reactions. Recently, we used 28.5 MeV protons to bombard natural $\text{Al}_2(\text{WO}_4)_3$ targets and found the activity of ^{186}Re accounted for only a small fraction of the total activity [5].

^{186}Re and ^{188}Re may be produced by the irradiation of natural rhenium with thermal neutrons in a nuclear reactor. Due to the limited neutron capture cross-section of ^{185}Re and ^{187}Re (110 barn and 70 barn, respectively) in the irradiated Re target a large amount of stable isotopes will be present, which are impossible to be removed by any routine chemical separation procedure. Therefore, the specific activity of the ^{186}Re and ^{188}Re is bound to be very low. A possible way to increase greatly the specific activity of the (n, γ) reaction products, ^{186}Re and ^{188}Re , would be the method based on the well-known Szilard–Chalmers effect [6]. Thus the radioactive rhenium may be easily separated from the target, yielding ^{186}Re and ^{188}Re in a state of high specific activity. Although a high neutron flux reactor is needed in order to obtain a product with very high specific activity, in the preliminary study we may use reactors with lower neutron flux, $10^{12}\text{--}10^{13}$ n/s/cm².

Herr [7] first studied the hot-atom chemistry of rhenium compounds consisting of potassium perrhenate, potassium hexachlororhenate(2-) and rhenium trichloride. Since then, a large amount of inorganic and carbonyl compounds of rhenium have been studied with the emphases on the hot atom reaction mechanism. Recently, Albetro [8-10] and his coworkers reported a very attractive result in the enrichment of radioactive Re by Szilard–Chalmers effect.

They irradiated pentamethylcyclopentadienyl-tri-oxo-rhenium (Cp^*ReO_3) with a neutron flux of 10^{15} n/s/cm² for 2 hr, dissolved the target in benzene and separated out the inorganic rhenium by liquid/liquid extraction or column chromatography. In one experiment they obtained a product with specific activity as high as 133 GBq/mg (3.6 Ci/mg). However, in another experiment the specific activity of the product was only 370 MBq/mg (9.9 mCi/mg). Their results indicate that Szilard-Chalmers effect does work in the preparation of 186 , ^{188}Re with high specific activity. Prompted by their results we synthesized a series of stable rhenium complexes other than Cp^*ReO_3 and carried out a similar study. We report the results in this paper.

EXPERIMENTAL

Material and Irradiation

Bis(diethyldithiocarbamato)nitrodorhenium(V) [$\text{ReN}(\text{S}_2\text{CNET}_2)_2$], μ -oxo-bis[bis(ethyldithiocarbamato)oxorhenium(V)] [$\text{Re}_2\text{O}_3(\text{S}_2\text{CNET}_2)_4$], μ -oxo-bis[bis(diethyldithiocarbamato)(phenylimino)rhenium(V)] [$[\text{Re}(\text{NPh})(\text{S}_2\text{CNET}_2)_2]_2\text{O}$] [6], tetra-*n*-butylammonium octachlorodirhenate(III) [$(\text{n-C}_4\text{H}_9)_4\text{N}]_2\text{Re}_2\text{Cl}_8$] [7], bis[chlorobis(propionato)rhenium(III)] $\text{Re}_2\text{Cl}_2(\text{O}_2\text{CC}_2\text{H}_5)_4$ [8], bis[chlorobis(benzoato)rhenium(III)] $\text{Re}_2\text{Cl}_2(\text{O}_2\text{CC}_6\text{H}_5)_4$ [9], and bis[chloro(acetato)(trichloroacetato)rhenium(III)] $\text{Re}_2\text{Cl}_2(\text{O}_2\text{CCH}_3)_2(\text{O}_2\text{CCCl}_3)_2$ [10] were prepared according to the corresponding references and characterized by IR, UV-Vis, and elemental analysis. The structures of some compounds are shown in Fig. 1.

The structure of $\text{Re}_2\text{O}_3(\text{S}_2\text{CNET}_2)_4$ and $[\text{Re}(\text{NPh})(\text{S}_2\text{CNET}_2)_2]_2\text{O}$ are similar to $\text{ReN}(\text{S}_2\text{CNET}_2)_2$ but with a bridging oxygen atom between two rhenium atoms. The Re atom in these compounds is bonded by O, N or another Re atom via a double bond (Re=O in $\text{Re}_2\text{O}_3(\text{S}_2\text{CNET}_2)_4$, Re=NPh in $[\text{Re}(\text{NPh})(\text{S}_2\text{CNET}_2)_2]_2\text{O}$), a triple bond (Re≡N in $\text{ReN}(\text{S}_2\text{CNET}_2)_2$), or a quadruple bond (Re≡Re in $[(\text{n-C}_4\text{H}_9)_4\text{N}]_2\text{Re}_2\text{Cl}_8$, $\text{Re}_2\text{Cl}_2(\text{O}_2\text{CC}_2\text{H}_5)_4$, $\text{Re}_2\text{Cl}_2(\text{O}_2\text{CC}_6\text{H}_5)_4$ and $\text{Re}_2\text{Cl}_2(\text{O}_2\text{CCH}_3)_2(\text{O}_2\text{CCCl}_3)_2$), forming a very stable Re=O, Re=NR, Re≡N or Re≡Re core. The samples in triplicate (80~100 mg) were sealed in polyethylene capsules, and activated in the miniature reactor at China Institute of Atomic Energy (CIAE) with a thermal neutron flux of 10^{12} n/s/cm² for 1 hour.

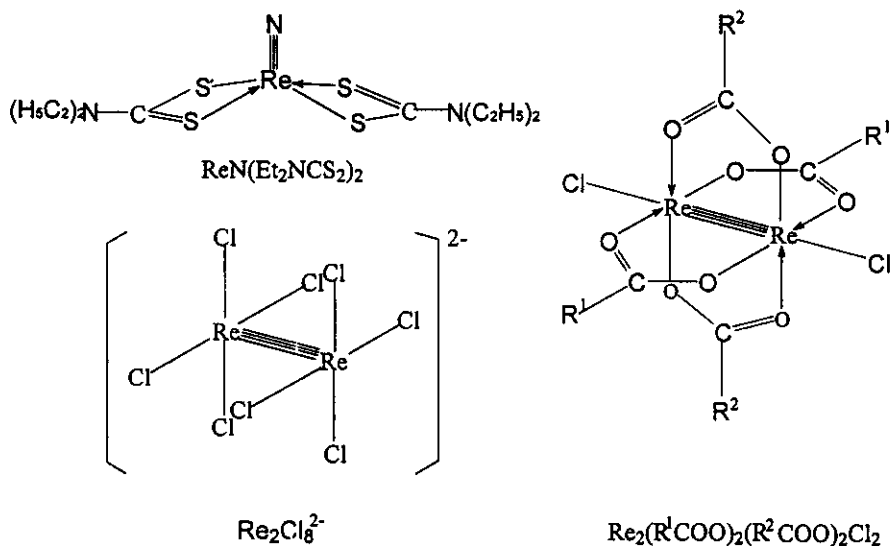


Fig.1 The structure of target compounds

Separation of Enriched ^{186}Re and ^{188}Re

The irradiated targets were dissolved in dichloromethane. Each of the resulted solutions was divided into 8 aliquots. One aliquot was used for measurement of the total activity. The other 7 aliquots were equilibrated for 2 minutes with different stripping solution. The following stripping agents were tested: sodium hydroxide (I), sodium citrate (II), sodium bisulfite (III), hydrogen peroxide (in 0.02 mol/dm³ hydrochloric acid) (IV), hydrochloric acid (V), 0.9% saline solution (VI) and pure water (VII). The concentration of the former five was 0.05 mol/dm³. These agents were chosen because they were representative reagents (basic, chelating, reducing, oxidizing, acidic and neutral), non-toxic, and did not interfere subsequent reactions. Recoiled Re atoms present in back-extractable forms entered the aqueous phase and the target compounds remained in the organic phase. The aqueous phase was further scrubbed with dichloromethane.

Analysis

The activities of the aqueous phase, the organic phase and the original organic phase were measured with a GM counter. The efficiency of this instrument was calibrated by a liquid scintillation counter beforehand. The counting

efficiency of the latter was nearly 100% because the beta particles emitted by ^{186}Re and ^{188}Re were quite energetic ($E_{\beta\text{max}}=1.07$ and 2.12 MeV, respectively). The overall yield was calculated by dividing the activity of the aqueous phase with the total activity in the original organic phase.

Radioactive rhenium in the aqueous phase was identified by both ascending paper chromatography and paper electrophoreses. In the former case a 0.9% sodium chloride was used as a mobile phase. In the latter case a 0.005 mol/dm³ hydrochloric acid was used as the supporting electrolyte and a current of 2.0 mA and a voltage gradient of 19 volts/cm was applied. The identities of the radionuclides in the aqueous phase were detected by a high-purity Ge detector that was interfaced with a Canberra 35 Plus MCA. The concentration of Re in aqueous phase was determined spectrophotometrically[11]. The solution was treated with tin(II) chloride-9% hydrochloric acid solution, and then reacted with thiourea to form a yellow complex. The absorbency was measured at $\lambda=445$ nm. The activity divided by the corresponding rhenium mass yielded its specific activity. The ratio of the specific activity of the aqueous solution to that of original organic phase before separation was the enrichment factor (E. F.) for that system.

RESULTS AND DISCUSSION

The paper chromatogram of the aqueous phase for all studied systems showed exclusively a single peak at $R_f = 0.8$, identical with $^{188}\text{ReO}_4^-$ eluted from a ^{188}W - ^{188}Re generator, indicating ReO_4^- was the only product. Electrophoretic experiments gave the same conclusion: a single species moved towards the anode. All peaks with detectable intensity in the gamma spectra of the products could be assigned to ^{186}Re and ^{188}Re .

For the production of radionuclides by the Szilard-Chalmers effect, the enrichment factor and the chemical yield are two most important parameters. The concentration of rhenium in stripping solutions are listed in Table 1. The large error in mean concentration was caused probably by three independent runs. The overall yields of the seven studied systems are listed in Table 2, and E. F. in Table 3.

Table 1 Re concentration in stripping solutions ($\mu\text{g}/\text{cm}^3$)

Neutron-irradiated Complexes	Stripping agent						
	I	II	III	IV	V	VI	VII
$\text{ReN}(\text{S}_2\text{CNEt}_2)_2$	2.37 ± 0.21	0.62 ± 0.08	2.14 ± 0.08	6.4 ± 0.17	0.59 ± 0.02	6.9 ± 0.58	5.07 ± 1.23
$\text{Re}_2\text{O}_3(\text{S}_2\text{CNEt}_2)_4$	9.33 ± 0.67	2.45 ± 0.06	99 ± 11	416 ± 39	89.9 ± 7.8	2.06 ± 0.01	1.85 ± 0.08
$[\text{Re}(\text{NPh})(\text{S}_2\text{CNEt}_2)_2]_2\text{O}$	4.17 ± 0.03	4.73 ± 0.03	3.28 ± 0.42	4.47 ± 0.82	13.4 ± 2.4	23.0 ± 1.3	6.43 ± 0.33
$[(n\text{-C}_4\text{H}_9)_4\text{N}]_2\text{Re}_2\text{Cl}_8$	11.0 ± 2.4	54.3 ± 2.6	–	2.17 ± 0.32	10.5 ± 0.9	9.27 ± 1.6	1.41 ± 0.11
$\text{Re}_2\text{Cl}_2(\text{O}_2\text{CC}_2\text{H}_5)_4$	–	–	–	253 ± 37	4.64 ± 0.28	9.65 ± 0.12	–
$\text{Re}_2\text{Cl}_2(\text{O}_2\text{CC}_6\text{H}_5)_4$	–	–	–	74.4 ± 4.9	9.67 ± 2.7	10.0 ± 0.4	–
$\text{Re}_2\text{Cl}_2(\text{O}_2\text{CCH}_3)_2(\text{O}_2\text{CCCl}_3)_2$	11.6 ± 1.6	40.2 ± 3.6	–	9.6 ± 2.1	32.6 ± 6.5	21.1 ± 3.2	29.1 ± 4.9

Table 2. Radioactive yields of Szilard-Chalmers effect (%)

Neutron-irradiated Complexes	Stripping agent						
	I	II	III	IV	V	VI	VII
$\text{ReN}(\text{S}_2\text{CNEt}_2)_2$	36.2 ± 4.1	11.7 ± 1.7	4.2 ± 0.3	14.0 ± 0.5	3.4 ± 0.4	12.9 ± 1.9	13.2 ± 3.4
$\text{Re}_2\text{O}_3(\text{S}_2\text{CNEt}_2)_4$	51.2 ± 4.1	25.4 ± 1.1	10.3 ± 0.3	32.7 ± 0.7	8.3 ± 0.6	12.1 ± 0.2	9.8 ± 0.8
$[\text{Re}(\text{NPh})(\text{S}_2\text{CNEt}_2)_2]_2\text{O}$	30.2 ± 0.8	6.4 ± 0.3	0.9 ± 0.2	2.8 ± 0.7	2.1 ± 0.2	3.9 ± 0.8	1.7 ± 0.2
$[(n\text{-C}_4\text{H}_9)_4\text{N}]_2\text{Re}_2\text{Cl}_8$	5.0 ± 2.7	21.6 ± 1.6	–	4.4 ± 1.0	7.8 ± 0.4	0.8 ± 0.2	1.3 ± 0.3
$\text{Re}_2\text{Cl}_2(\text{O}_2\text{CC}_2\text{H}_5)_4$	–	–	–	91.8 ± 4.3	49.0 ± 5.4	53.4 ± 5.7	–
$\text{Re}_2\text{Cl}_2(\text{O}_2\text{CC}_6\text{H}_5)_4$	–	–	–	52.5 ± 3.9	28.5 ± 1.1	33.2 ± 1.7	–
$\text{Re}_2\text{Cl}_2(\text{O}_2\text{CCH}_3)_2(\text{O}_2\text{CCCl}_3)_2$	4.3 ± 0.4	19.7 ± 1.1	–	5.2 ± 0.3	12.3 ± 1.5	7.1 ± 0.6	5.1 ± 0.2

Note (1) The symbol “-” indicates that the target compound reacts with the stripping agent

(2) Stripping agents: I — 0.05 mol/dm³ NaOH . II — 0.05 mol/dm³ sodium citrate. III — 0.05 mol/dm³ NaHSO₃. IV — 0.05 mol/dm³ H₂O₂+0.02 mol/dm³ HCl . V —0.05 mol/dm³ HCl. VI — 0.9% saline. VII — pure water

Table 3 Enrichment factors of Szilard-Chalmers effect

Neutron-irradiated Complexes	Stripping agent						
	I	II	III	IV	V	VI	VII
ReN(S ₂ CNEt ₂) ₂	209.7 ±4.8	260.2 ±3.5	27.1 ±3.0	30.1 ±1.8	78.4 ±7.0	25.6 ±1.6	35.9 ±0.3
Re ₂ O ₃ (S ₂ CNEt ₂) ₄	72.9 ±0.7	138.8 ±3.2	1.4 ±0.2	1.1 ±0.3	1.3 ±0.4	78.2 ±1.8	70.4 ±3.3
[Re(NPh)(S ₂ CNEt ₂) ₂] ₂ O	85.2 ±1.4	15.9 ±0.8	3.2 ±0.3	7.4 ±0.5	1.9 ±0.5	2.0 ±0.4	3.1 ±0.2
[(n-C ₄ H ₉) ₄ N] ₂ Re ₂ Cl ₈	5.2 ±1.9	4.8 ±0.6	-	24.1 ±2.0	9.0 ±1.2	1.1 ±0.2	11.2 ±3.3
Re ₂ Cl ₂ (O ₂ CC ₂ H ₅) ₄	-	-	-	6.8 ±1.3	195.7 ±9.1	101.5 ±9.6	-
Re ₂ Cl ₂ (O ₂ CC ₆ H ₅) ₄	-	-	-	12.2 ±1.7	53.8 ±16.6	59.1 ±7.5	-
Re ₂ Cl ₂ (O ₂ CCH ₃) ₂ (O ₂ CCCl ₃) ₂	5.3 ±1.2	6.9 ±1.0	-	7.9 ±2.1	5.5 ±1.7	4.8 ±1.1	2.7 ±0.9

For the Szilard-Chalmers effect of a given nuclear reaction, E. F. is principally determined by the property of the target material and the separation process. The recoil energy in $^{185,187}\text{Re}(n,\gamma)$ reactions is large enough to break the chemical bond with which Re atom is combined to the rest of a target molecule. Therefore, the secondary re-combination of the recoiled atom and the rest mother molecule will be the major process leading to the recoil atom retention. The more stable the target molecule, the less molecular fragment radicals made by neutron and gamma radiation will be. Thus the recoiled Re atoms will have higher probability to escape the "reaction cage" according to Libby's model, and a lower secondary retention can be expected. Further more, the high stability

of a target will eliminate any possible isotope exchange and prevent the direct decomposition of the target. Both of these processes would lead to lowering the product specific activity. In the present study, Re atom is bonded by a double, triple, or quadruple bond in all the target molecules. All of compounds selected as target materials in this study possess quite high stability against heat and radiation (see below) and are easy to synthesize. A proper separation protocol is also important for achievement of high E. F. From Table 3 we can see that different stripping solution gives quite different E. F. Aqueous sodium hydroxide and sodium citrate solutions are significantly superior to others in the case of rhenium (V) dithiocarbamate target. Binuclear rhenium (III) compounds $\text{Re}_2\text{Cl}_2(\text{O}_2\text{CC}_2\text{H}_5)_4$ and $\text{Re}_2\text{Cl}_2(\text{O}_2\text{CC}_6\text{H}_5)_4$, are decomposed by aqueous alkaline solutions or pure water. But they are stable to the stripping agents containing chloride anion. Hydrochloric acid is the best stripping agent for these target materials. Sodium bisulfite gives the worst results, probably due to its strong reducing ability. It seems that a good stripping agent must neither decompose the target molecule, nor reduce Re(VII) to lower oxidation states.

In conclusion, aqueous sodium hydroxide solution and sodium citrate solution are the best choices for the production of radiorhenium from neutron-irradiated $\text{ReN}(\text{S}_2\text{CNEt}_2)_2$. The former gave an E.F. of 210 and an overall yield of 36 %, resulting in a specific activity of 0.72 GBq/mg (19.5 mCi/mg). If radiorhenium was not separated from the target, the specific activity was only 3.43 MBq/mg (0.092 mCi/mg) and the theoretical specific activity in this condition was 6.83 MBq/mg (0.185 mCi/mg), higher than we actually obtained. The difference may be attributed to the lower neutron flux than the nominal. The volume of dichloromethane used for dissolving targets also remarkably affects the E. F. A higher E. F. could be obtained when a less quantity of solvent was used. The mechanism is not clear.

The highest specific activity we obtained is still not high enough to meet the clinic need of radioimmunotherapy. In order to get $^{186,188}\text{Re}$ products with a specific activity of >37 GBq/mg (1 Ci/mg) by using the present method, a reactor with high neutron flux of $10^{14}\sim 10^{15}$ n/s/cm² has to be used. However,

under such high neutron flux in the reactor the target must be stable in standing against the higher temperature and higher radiation dose. We have tested the thermal and radiation stability of $\text{ReN}(\text{S}_2\text{CNET}_2)_2$, $\text{Re}_2\text{O}_3(\text{S}_2\text{CNET}_2)_4$ and $\text{Re}_2\text{Cl}_2(\text{O}_2\text{CC}_2\text{H}_5)_4$. These compounds were found stable below their melting point, 230, 215, and 245°C respectively. After irradiation with 1.65×10^6 Gy gamma ray dose, corresponding to a dose of one hour irradiation with neutron flux of 10^{14} n/s/cm², the decomposition was less than 0.2 percent for all these complexes. Therefore, if a 1×10^{14} n/s/cm² neutron flux is used for irradiation, a specific activity of ~ 74 GBq/mg (~ 2 Ci/mg) of the produced ^{186}Re and ^{188}Re may be expected.

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