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Journal of Organometallic Chemistry 693 (2008) 1822–1828
Journal of Organometallic Chemistry
www.elsevier.com/locate/jorganchem

Preparation and biological evaluation of ^{99m}Tc-CO-MIBI as myocardial perfusion imaging agent

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Received 28 December 2007; received in revised form 31 January 2008; accepted 5 February 2008
Available online 9 February 2008

Abstract

^{99m}Tc-Sestamibi has been playing an important role in the cardiac imaging for the last decades. Previously, we reported that $[^{99m}Tc(CO)_3(MIBI)_3]^+$ demonstrated a significant location in myocardium with a lower liver uptake as compared with ^{99m}Tc-Sestamibi. In this work, we found that new $[^{99m}Tc(CO)_2(MIBI)_4]^+$ could be prepared with high radiochemical purity. The inter-transformations between $[^{99m}Tc(CO)_3(H_2O)(MIBI)_2]^+$, $[^{99m}Tc(CO)_3(MIBI)_3]^+$, and $[^{99m}Tc(CO)_2(MIBI)_4]^+$ were investigated and biodistribution was performed to evaluate the $[^{99m}Tc(CO)_2(MIBI)_4]^+$ as a myocardial perfusion imaging agent. The results showed that one more CO was replaced by MIBI slowing down the pharmacokinetics. The structure characterization was performed on their corresponding rhenium complexes, and the results indicated that there were differences between ^{99m}Tc-CO-MIBI and Re-CO-MIBI in preparation and hydrophobic characteristics.

Keywords: Tricarbonyl technetium; MIBI; Myocardial imaging

1. Introduction

Myocardial perfusion imaging with radiotracers plays a very important role in the evaluation of patients with coronary artery disease in clinical practice [1–10]. ^{99m}Tc(I)-Sestamibi (shown in Fig. 1) and ^{99m}Tc(V)-Tetrofosmin have been widely used in clinics for decades, but neither of them meets the requirements of an ideal myocardial perfusion imaging agent. Their high liver uptake and slow clearance from it make it very difficult to interpret the heart activity in the inferior and left ventricular wall [1–8,10–13]. The complexes in lower oxidation state have been widely studied for the development of new imaging agents. One-step synthesis of $[^{99m}Tc(CO)_3(H_2O)_3]^+$ by direct reduction of $^{99m}TcO_4^-$ with sodium borohydride in aqueous solution was firstly developed by Alberto et al. [14]. The $^{99m}Tc(CO)_3$ core possesses many excellent features, such as its small volume and kinetic inertness, and the three coordinated water in this complex could be easily replaced by other ligands. Some crown-ether-containing cationic ^{99m}Tc(I)-tricarbonyl radiotracers developed by Liu et al. showed significant localization in myocardium [15,16]. Our previous studies also showed that the water molecules in $[^{99m}Tc(CO)_3(H_2O)_3]^+$ could be replaced by two or three 2-methoxy-isobutyl-isonitrile molecules (MIBI) under different reaction conditions. Biodistribution in mice showed the proposed $[^{99m}Tc(CO)_3(MIBI)_3]^+$ could accumulate in heart rapidly post injection (p.i.) with faster liver washout than ^{99m}Tc-Sestamibi [17,18].

In this work, we studied the inter-transformation of ^{99m}Tc(I)-CO-MIBI complexes, and found that one CO molecule in $[^{99m}Tc(CO)_3(MIBI)_3]^+$ could be further substituted by one MIBI molecule forming $[^{99m}Tc(CO)_2(MIBI)_4]^+$. Previous works indicated that $[^{99m}Tc(CO)_3(MIBI)_3]^+$ had a significant location in myocardium and lower liver uptake as compared with $[^{99m}Tc(CO)_3(H_2O)(MIBI)_2]^+$ [18]. To evaluate the newly prepared

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doi:10.1016/j.jorganchem.2008.02.006

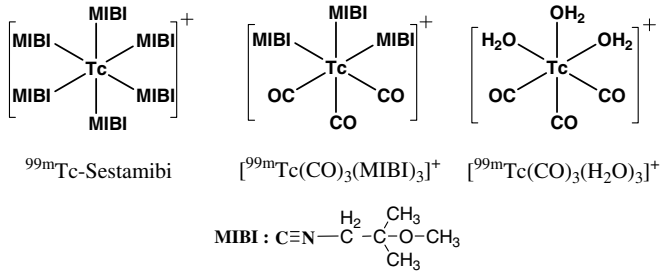


Fig. 1. The structure of ^{99m}Tc-Sestamibi, $[^{99m}Tc(CO)_3(MIBI)_3]^+$, and $[^{99m}Tc(CO)_3(H_2O)_3]^+$.

$[^{99m}Tc(CO)_2(MIBI)_4]^+$ which possesses more MIBI molecules, the biodistribution of $[^{99m}Tc(CO)_2(MIBI)_4]^+$, and $[^{99m}Tc(CO)_3(MIBI)_3]^+$ in normal mice was performed simultaneously.

The development of technetium complexes as potential radiopharmaceuticals is facilitated by the use of rhenium, the group VIIB congener of technetium. Rhenium generally produces complexes with similar physical and biodistribution properties to those of technetium and is often used as a non-radioactive alternative to technetium for large-scale synthesis and structural characterization [19,20]. In this work, the corresponding Re-CO-MIBI complexes were also prepared and characterized.

2. Experimental

2.1. Materials and methods

All chemicals were purchased from Aldrich and Acros. Pure CO gas was purchased from National Research Center for CRM'S. $K_2[BH_3CO_2]$ and $[Re(CO)_3(H_2O)_3]Br$ were prepared according to the literature [21,22]. $Na^{99m}TcO_4$ was obtained from a commercial $^{99}Mo/^{99m}Tc$ generator, Beijing Atomic High-tech Co. MIBI kit vials (containing 1.0 mg of $Cu(MIBI)_4BF_4$, 0.15 mg of $SnCl_2 \cdot 2H_2O$, 1.0 mg of L-cysteine hydrochloride monohydrate, 2.6 mg of sodium citrate and 20.0 mg of mannitol) and $Cu(MIBI)_4BF_4$ were obtained as gifts from Beijing Shihong Pharmaceutical Center. $Cu(MIBI)_4BF_4$ was synthesized according to the literature [23]. HPLC analyses were performed on a Shimadzu SCL-10AVP system which consisted of a binary pump with on-line degasser, a model SPD-10 Avp UV detector operating at a wavelength of 254 nm and a Packard 500 TR series flow scintillation analyzer. The samples were analyzed on a C-18 Alltech alltima column (5 μM, 250 × 4.6 mm). HPLC separation was performed on Alltech semipreparative HPLC system which consisted of a binary pump with on-line degasser, a linear UVIS 201 detector operating at wavelength of 254 nm. The rhenium sample was separated on a semi-preparative Kromasil RPC-18 (10 μM, 250 × 10 mm). HPLC eluting condition A: gradient mixtures of 0.1% trifluoroacetic acid in water (solvent A) and 0.1% trifluoroacetic acid in CH_3CN (solvent B) (0–28 min, 10–90% solvent B, and 28–40 min, 90–90% solvent B, 1 mL/min); HPLC eluting condition B: aqueous 0.05 M TEAP (triethylammonium phosphate) buffer, pH 2.25 (solvent A), MeOH (solvent B) (0–3 min, 0% solvent B, 3–6 min, 0–25% solvent B, 6–9 min, 25–34% solvent B, and 9–20 min, 34–100% solvent B, 1 mL/min). Infrared (IR) spectra were recorded on a Nicolet AVATAR 360 IR spectrometer. Mass spectra were collected on a Micromass QTOF mass spectrometer. Proton nuclear magnetic resonance (NMR) spectrum was performed on an Avance 500 MHz NMR apparatus (Bruker).

2.2. Preparation of $[^{99m}Tc(CO)_3(H_2O)_3]^+$

$[^{99m}Tc(CO)_3(H_2O)_3]^+$ intermediate was prepared as previously described [24]. Briefly, 2 mL of $^{99m}TcO_4^-$ from a commercial generator (10 mCi) was added to a 10 mL vial containing potassium boranocarbonate (3 mg), sodium potassium tartrate tetrahydrate (6.7 mg), and potassium tetraborate pentahydrate (5.5 mg). The solution was heated for 15 min in boiling water under N_2. After cooling down to room temperature, the sample was analyzed on TLC and HPLC.

2.3. Preparation of $[^{99m}Tc(CO)_3(H_2O)(MIBI)_2]^+$, $[^{99m}Tc(CO)_3(MIBI)_3]^+$, and $[^{99m}Tc(CO)_2(MIBI)_4]^+$

A MIBI kit was added to $[^{99m}Tc(CO)_3(H_2O)_3]^+$ intermediate reaction vial and the pH value was adjusted to definite pH value 1.0 for $[^{99m}Tc(CO)_3(H_2O)(MIBI)_2]^+$, 10.0 for $[^{99m}Tc(CO)_3(MIBI)_3]^+$ and 13.0 for $[^{99m}Tc(CO)_2(MIBI)_4]^+$) using 0.1 N hydrochloride solution or sodium hydroxide solution. Then the reaction mixtures were heated in boiling water (15 min for $[^{99m}Tc(CO)_3(H_2O)(MIBI)_2]^+$ and $[^{99m}Tc(CO)_3(MIBI)_3]^+$, and 60 min for $[^{99m}Tc(CO)_2(MIBI)_4]^+$). After cooling down to room temperature, samples were filtered (2 μm) and analyzed on HPLC. The radiochemical purity was examined by HPLC with gradient mixtures of 0.1% trifluoroacetic acid in water (A) and 0.1% trifluoroacetic acid in CH_3CN (B) (0–28 min, 10–90% B, and 28–40 min, 90–90% B, 1 mL/min).

2.4. Biodistribution of $[^{99m}Tc(CO)_3(MIBI)_3]^+$ and $[^{99m}Tc(CO)_2(MIBI)_4]^+$

The pH values of freshly prepared $[^{99m}Tc(CO)_3(MIBI)_3]^+$ and $[^{99m}Tc(CO)_2(MIBI)_4]^+$ were adjusted to 7.4, and 0.1 mL of the resulting solution (20–25 μCi) was injected into the tail vein of male ICR mice (18–22 g). The mice were sacrificed by decapitation at specific time points post injection. The organs of interest were excised and weighed, and the radioactivity was measured using a Wallac WIZARD 1470 automatic Gamma counter (PerkinElmer, USA). The biodistribution of radiotracer in each tissue sample was expressed as a percentage of the injected dose per gram of wet tissue weight.

2.5. Synthesis of $[Re(CO)_3(MIBI)_3]^+$ and $[Re(CO)_2(MIBI)_4]^+$

$[Re(CO)_3(H_2O)_3]Br$ (51 mg, 130 μmol) was dissolved in water (6 mL). One equivalent of $AgNO_3$ was added and the precipitate (AgBr) was filtered. $Cu(MIBI)_4BF_4$ (57 mg, 95 μmol) was added to the rhenium solution and the pH value was adjusted to 1.0 for $[Re(CO)_3(MIBI)_3]^+$ and 10.0–13.0 for $[Re(CO)_2(MIBI)_4]^+$. The mixtures were heated for 35 min in boiling water and neutralized. After the samples were filtered (0.2 μm), they were analyzed on HPLC and mass spectroscopy. $[Re(CO)_3(MIBI)_3]^+$ was purified by HPLC and the collected fraction was evaporated in vacuo. IR (KBr, cm^{-1}): 2982 (m), 2242 (m), 2214 (s), 2059 (vs), 1995 (vs), 1198 (m). ^1H NMR (500 MHz, D_2O): δ 1.18 (s, 18H), 3.19 (s, 9H), 3.83 (s, 6H). MS (ESI) m/z: 610.

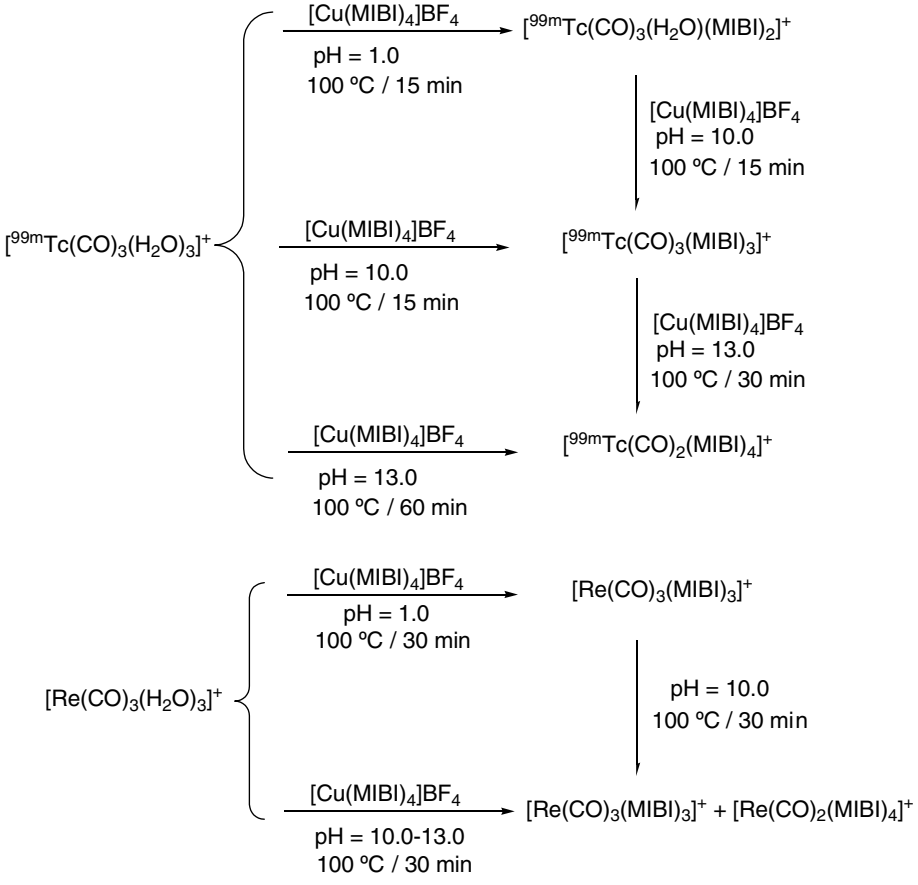
3. Results and discussion

3.1. Preparation of $[^{99m}Tc\text{-}CO\text{-}MIBI]^+$

The preparations of three cationic complexes are shown in Scheme 1. First, $[^{99m}Tc(CO)_3(H_2O)_3]^+$ was prepared with high labeling yield and radiochemical purity (RCP > 95%) measured by TLC and HPLC. Only two water ligands were replaced by two MIBI ligands forming $[^{99m}Tc(CO)_3(H_2O)(MIBI)_2]^+$ at pH 1.0 as shown in Fig. 2A. The third water ligand could not be replaced even with longer heating time. $[^{99m}Tc(CO)_3(H_2O)(MIBI)_2]^+$ was totally converted to $[^{99m}Tc(CO)_3(MIBI)_3]^+$ by adjusting the pH value to 10.0 and heating for another 15 min. $[^{99m}Tc(CO)_3(MIBI)_3]^+$ could also be directly prepared by exchanging three water ligands with three MIBI ligands when pH value was 10.0. Heating for 15 min in boiling water was enough for all the three water ligands to be exchanged and the RCP was higher than 98% as shown in Fig. 2B. Some tetra-substituted product, $[^{99m}Tc(CO)_2(MIBI)_4]^+$ (ca. 5–10%), was determined when extending the heating time from 15 min to 30 min. Once $[^{99m}Tc(CO)_3(MIBI)_3]^+$ was formed, it could not be changed back to $[^{99m}Tc(CO)_3(H_2O)(MIBI)_2]^+$ by adjusting the pH value to 1.0 and heating for 30 min at 100 °C.

$[^{99m}Tc(CO)_2(MIBI)_4]^+$ was prepared under more basic condition (pH 13.0) with extended heating time (60 min) from $[^{99m}Tc(CO)_3(H_2O)_3]^+$ as shown in Fig. 2(C). $[^{99m}Tc(CO)_2(MIBI)_4]^+$ could also be prepared from $[^{99m}Tc(CO)_3(MIBI)_3]^+$ with less heating time (30 min) at the pH value of 13.0.

The pH value played an important role in the ligand-exchange reactions. The first and second water molecules could be easily exchanged by MIBI. However, the third



Scheme 1. Preparations and inter-transformations of the ^{99m}Tc(I), Re (I).

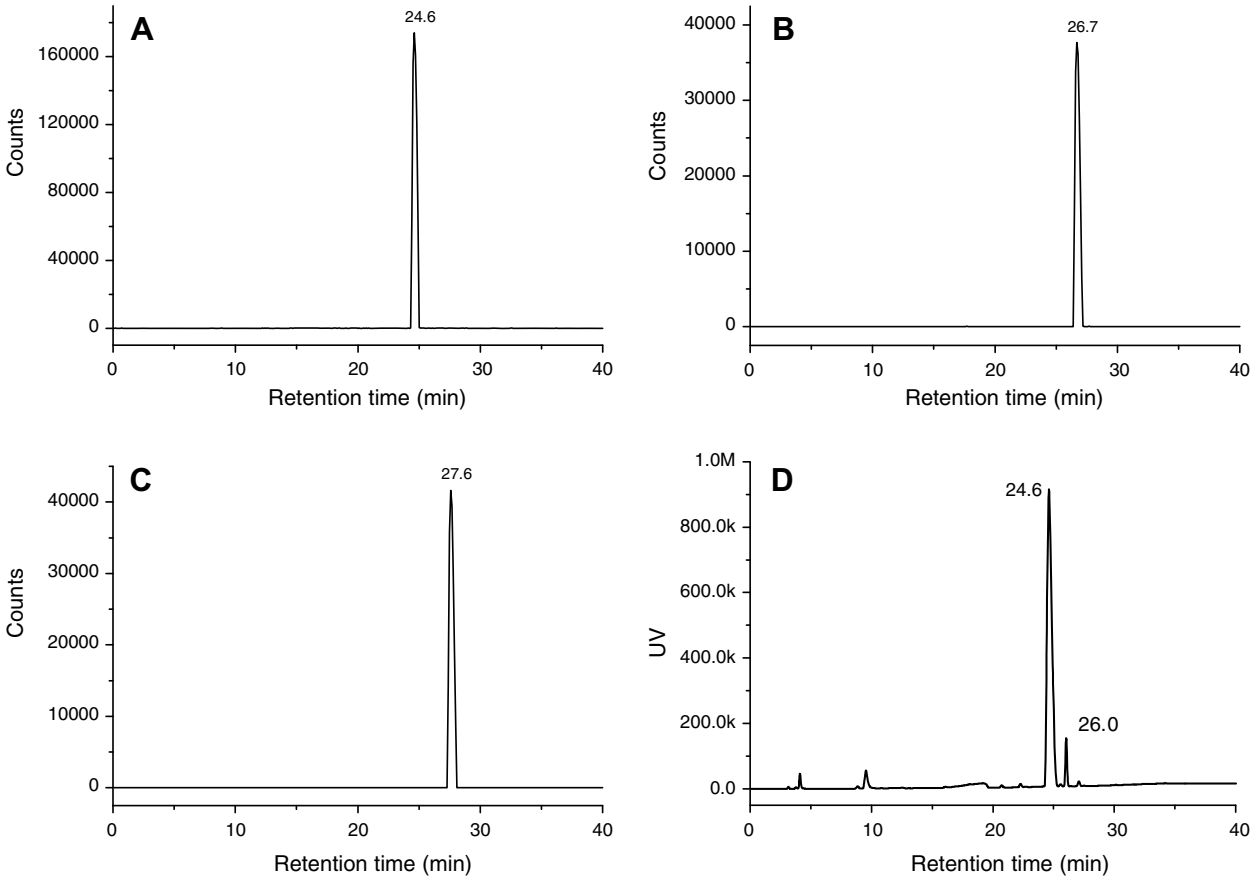


Fig. 2. The radioactivity chromatograms of ^{99m}Tc-CO-MIBI complexes and Re-CO-MIBI complexes under the eluting condition A. (A) $[^{99m}Tc(CO)_3(H_2O)(MIBI)_2]^+$ with retention time of 24.6 min; (B) $[^{99m}Tc(CO)_3(MIBI)_3]^+$ with retention time of 26.7 min; (C) $[^{99m}Tc(CO)_2(MIBI)_4]^+$ with retention time of 27.6 min. HPLC conditions see Section 2; and (D) $[Re(CO)_3(MIBI)_3]^+$ and $[Re(CO)_2(MIBI)_4]^+$ with retention times of 24.6 min and 26.0 min, respectively.

water molecule could not be fully replaced by MIBI until pH value in reaction was higher than 9.0. One CO molecule could even be replaced by one MIBI when the hydroxide ion concentration was high enough. Dyszlewski et al. have also observed that some tetra-substituted product, $[^{99m}Tc(CO)_2(MIBI)_4]^+$ or $[Re(CO)_2(MIBI)_4]^+$ (ca. 5–10%), formed during the preparation of $[^{99m}Tc(CO)_3(MIBI)_3]^+$ or $[Re(CO)_3(MIBI)_3]^+$ [25]. Usually, the CO can not be substituted by other ligand molecule owing to its strong π-back-bonding interaction. MIBI ligand, also possessing such strong π-back-bonding interaction with technetium, labilized the bond between CO and rhenium or technetium at the opposite site. So, one of the CO ligand in $[^{99m}Tc(CO)_3(MIBI)_3]^+$ or $[Re(CO)_3(MIBI)_3]^+$ was replaced by one MIBI ligand. Till now, no further replacement of CO molecule was observed under current reaction conditions in this work.

3.2. Biodistribution of $[^{99m}Tc(CO)_3(MIBI)_3]^+$ and $[^{99m}Tc(CO)_2(MIBI)_4]^+$

The results of biodistribution studies of $[^{99m}Tc(CO)_3(MIBI)_3]^+$ and $[^{99m}Tc(CO)_2(MIBI)_4]^+$ in normal mice are shown in Table 1 and Fig 3. $[^{99m}Tc(CO)_2(MIBI)_4]^+$ demonstrated lower initial heart uptake than $[^{99m}Tc(CO)_3(MIBI)_3]^+$ in the 0–60 min after injection and both of them showed slow washout from heart. At 120 min after injection, there was almost the same heart uptake of radioactivity for $[^{99m}Tc(CO)_2(MIBI)_4]^+$ and $[^{99m}Tc(CO)_3(MIBI)_3]^+$. For $[^{99m}Tc(CO)_2(MIBI)_4]^+$, the slower clearance from blood and liver caused inferior heart to blood and heart to liver ratios. However, $[^{99m}Tc(CO)_2(MIBI)_4]^+$ washed out quickly from the lungs and demonstrated less accumulation in muscle and skeleton, which is in favor of heart imaging. $[^{99m}Tc(CO)_2(MIBI)_4]^+$ with one more MIBI molecule was more hydrophobic than $[^{99m}Tc(CO)_3(MIBI)_3]^+$ as could be seen from the longer retention time on the C-18 column. But it did not accumulate in the heart quickly, and its extra MIBI molecule slowed its pharmacokinetics.

3.3. Synthesis of $[Re(CO)_3(MIBI)_3]^+$ and $[Re(CO)_2(MIBI)_4]^+$

Only $[Re(CO)_3(MIBI)_3]^+$ was obtained at pH 1.0. After purification on HPLC, its structure was confirmed by IR, ^{1}H NMR, and ESI-MS (Fig. 5). $[Re(CO)_3(MIBI)_3]^+$ showed a retention time of 21.4 min, and $[^{99m}Tc(CO)_3(MIBI)_3]^+$showed a retention time of 22.3 min under the same

Table 1
Biodistribution data of $[^{99m}Tc(CO)_3(MIBI)_3]^+$ and $[^{99m}Tc(CO)_2(MIBI)_4]^+$ in IRC mice at 5, 15, 30, 60, 120 min p.i. ($n = 3$)

Time (min)	Heart	Blood	Lung	Liver	Kidney	Muscle	Spleen	Bone	Brain
$[^{99m}Tc(CO)_3(MIBI)_3]^+$									
5	15.13 ± 6.76	1.16 ± 0.09	4.43 ± 1.90	11.01 ± 1.42	51.3 ± 12.93	4.80 ± 0.70	4.73 ± 0.86	3.95 ± 1.08	0.16 ± 0.05
15	14.52 ± 1.30	0.45 ± 0.14	2.68 ± 0.83	9.86 ± 2.15	38.23 ± 2.01	4.80 ± 0.38	3.69 ± 1.10	3.08 ± 0.48	0.16 ± 0.02
30	13.09 ± 2.31	0.25 ± 0.07	2.14 ± 0.66	8.21 ± 2.79	31.57 ± 5.50	4.27 ± 0.58	3.37 ± 1.19	2.28 ± 0.37	0.16 ± 0.01
60	12.14 ± 2.08	0.15 ± 0.02	1.65 ± 0.52	7.95 ± 1.71	16.55 ± 2.14	4.88 ± 0.81	2.48 ± 0.80	2.07 ± 0.96	0.16 ± 0.01
120	12.40 ± 2.50	0.11 ± 0.01	1.46 ± 0.11	5.47 ± 0.92	16.46 ± 3.02	4.65 ± 0.43	1.24 ± 0.21	1.86 ± 0.61	0.09 ± 0.02
$[^{99m}Tc(CO)_2$ $(MIBI)_4]^+$									
5	9.08 ± 2.70	1.95 ± 0.94	3.51 ± 0.56	13.91 ± 1.06	43.65 ± 9.46	2.64 ± 0.69	3.97 ± 0.98	2.65 ± 0.96	0.14 ± 0.03
15	8.11 ± 3.05	1.29 ± 1.13	2.23 ± 0.70	13.70 ± 3.04	36.19 ± 11.51	2.64 ± 0.95	3.48 ± 1.08	2.00 ± 0.59	0.12 ± 0.03
30	8.27 ± 0.70	0.35 ± 0.04	1.40 ± 0.26	12.06 ± 4.03	30.03 ± 11.08	3.04 ± 0.60	2.75 ± 0.52	1.99 ± 0.64	0.14 ± 0.02
60	8.61 ± 1.54	0.23 ± 0.02	1.16 ± 0.13	6.61 ± 1.38	23.64 ± 8.78	3.20 ± 0.63	1.37 ± 0.06	1.52 ± 0.26	0.10 ± 0.01
120	12.02 ± 1.66	0.24 ± 0.08	1.11 ± 0.45	4.33 ± 0.72	14.52 ± 2.98	3.85 ± 0.28	0.68 ± 0.20	0.88 ± 0.31	0.06 ± 0.01

Organ uptake is expressed as the percentage of injected dose per gram (%ID/g) of wet tissue mass.

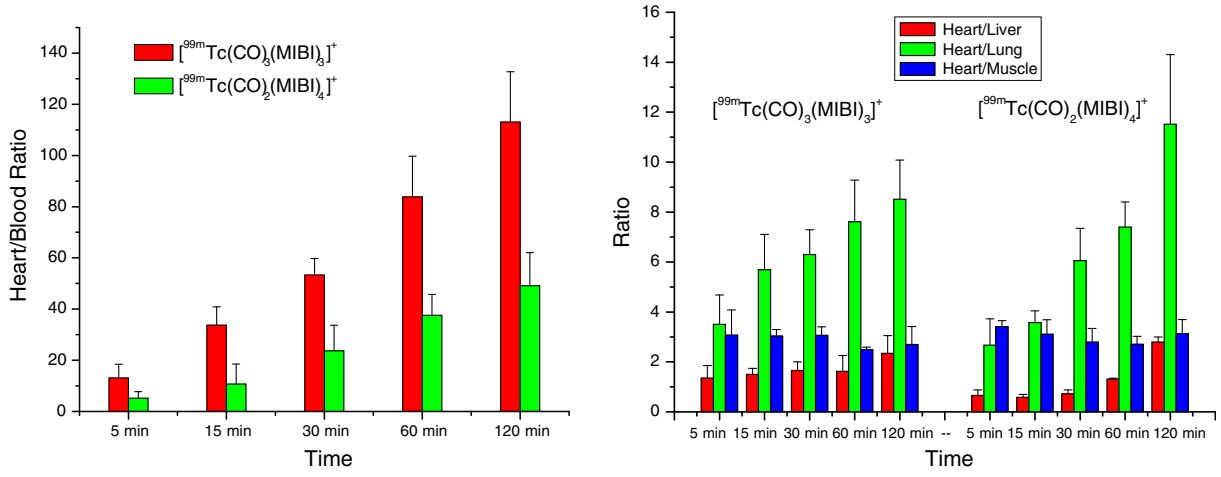


Fig. 3. Histogram representation of ratios of heart to other tissues at different time points after injection.

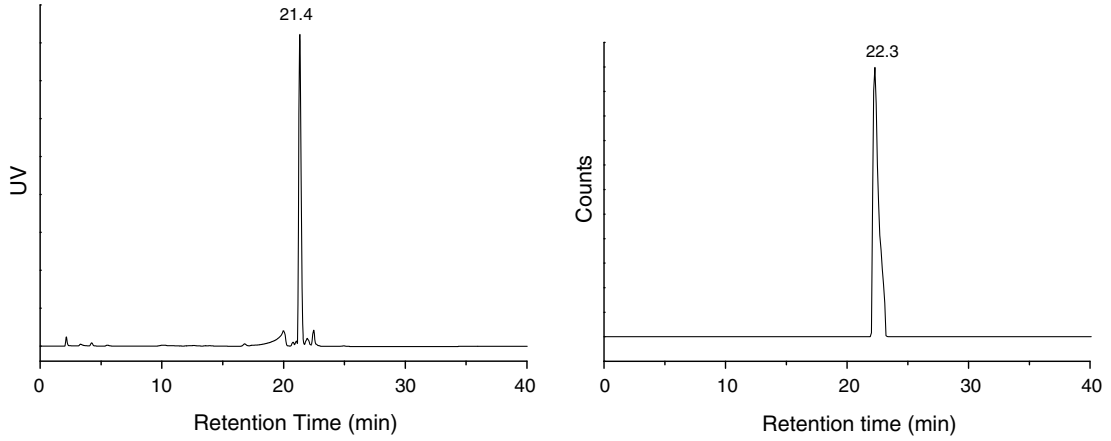


Fig. 4. The chromatograms of $[Re(CO)_3(MIBI)_3]^+$ (UV) and $[^{99m}Tc(CO)_3(MIBI)_3]^+$ (radioactivity) under the eluting condition B.

conditions as shown in Fig. 4. However, a mixture of $[Re(CO)_3(MIBI)_3]^+$ with some $[Re(CO)_2(MIBI)_4]^+$ was obtained even at the pH 14.0 as shown in Figs. 2D and 6. The mixture was analyzed by mass spectroscopy without purification as shown in Fig. 7 and species with molecular weights of 695 and 610, which were corresponding to $[Re(CO)_2(MIBI)_4]^+$ and $[Re(CO)_3(MIBI)_3]^+$, respectively, were detected. $[Re(CO)_3(MIBI)_3]^+$ was the primary product, and $[Re(CO)_2(MIBI)_4]^+$ was only in percentage of 5–10%. We tried different HPLC eluting conditions in this

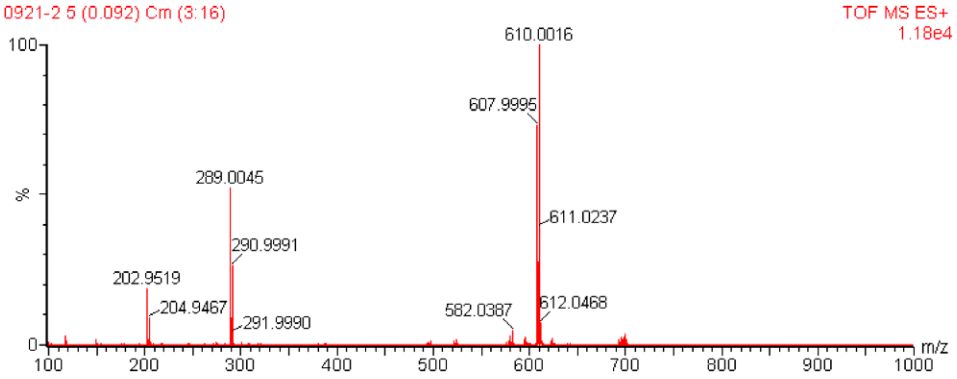


Fig. 5. ESI-MS of $[Re(CO)_3(MIBI)_3]^+$.

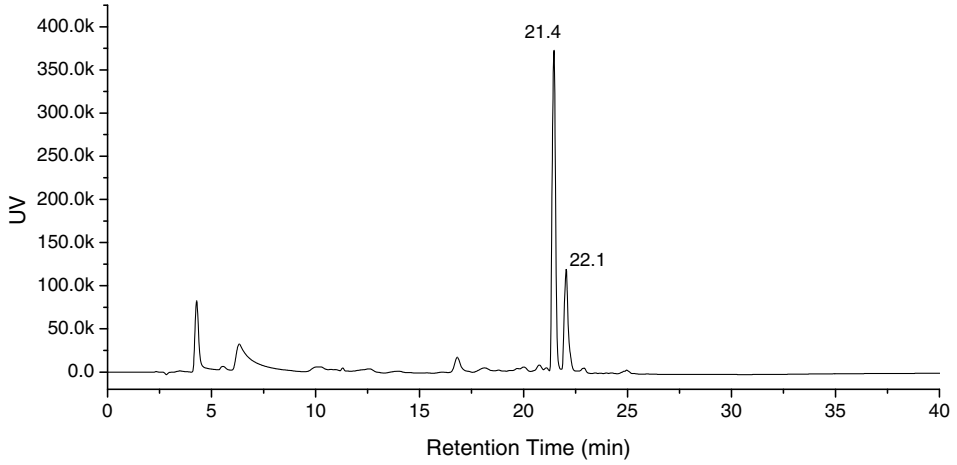


Fig. 6. HPLC chromatograms for mixture of $[Re(CO)_3(MIBI)_3]^+$ and $[Re(CO)_2(MIBI)_4]^+$ under the eluting condition B. The retention time for $[Re(CO)_3(MIBI)_3]^+$ is 21.4 min and $[Re(CO)_2(MIBI)_4]^+$ is 221 min, respectively.

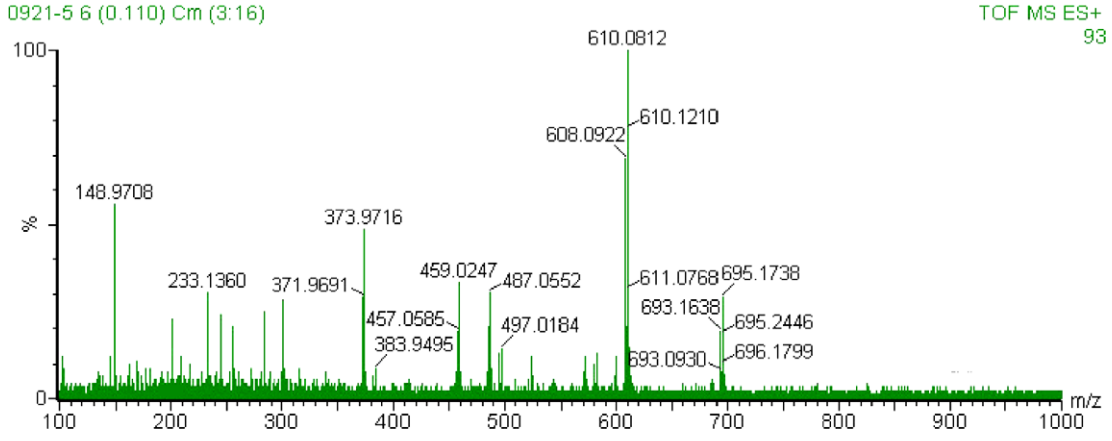


Fig. 7. ESI-MS of mixture of $[Re(CO)_3(MIBI)_3]^+$ and $[Re(CO)_2(MIBI)_4]^+$.

work and neither $[^{99m}Tc(CO)_3(MIBI)_3]^+$ nor $[^{99m}Tc(CO)_2(MIBI)_4]^+$ demonstrated matchable retention time with its corresponding rhenium complex. Technetium complexes were always washed out with longer retention times than the corresponding rhenium complexes, which indicated that technetium complexes were more hydrophobic that the corresponding rhenium complexes. These differences may be due to the different atomic radii of technetium and rhenium. Similar unmatched retention times have also been observed previously [26].

Also, unlike ^{99m}Tc-CO-MIBI, in the reaction between $[Re(CO)_3(H_2O)_3]^+$ and MIBI, only $[Re(CO)_3(MIBI)_3]^+$ was obtained under acidic condition (pH 1.0), and no $[Re(CO)_3(H_2O)(MIBI)_2]^+$ was detected. $[Re(CO)_3(MIBI)_3]^+$

could be partly converted into $[Re(CO)_2(MIBI)_4]^+$ when the pH value was readjusted to ~10.0, heating for another 30 min. $[Re(CO)_3(MIBI)_3]^+$ and $[Re(CO)_2(MIBI)_4]^+$ were both observed by heating $[Re(CO)_3(H_2O)_3]^+$ with MIBI for 35 min at the pH value of 10.0–14.0 in boiling water. $Re(CO)_3$ and $Tc(CO)_3$ demonstrated different characteristics when they reacted with MIBI.

4. Conclusion

The preparations and inter-transformations between $[^{99m}Tc(CO)_3(H_2O)(MIBI)_2]^+$, $[^{99m}Tc(CO)_3(MIBI)_3]^+$, and $[^{99m}Tc(CO)_2(MIBI)_4]^+$ were investigated. Biodistribution studies indicated that $[^{99m}Tc(CO)_3(MIBI)_3]^+$ had the most favorable characteristics as a myocardial imaging agent among them and one more CO was replaced by MIBI slowing down the pharmacokinetics. ^{99m}Tc-CO-MIBI and Re-CO-MIBI behaved differently in preparation and hydrophobic characteristics.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (No. 20471011) and Beijing Municipal Commission of Education. We also thank Beijing Shihong Pharmaceutical Center for providing MIBI kit and $Cu(MIBI)_4BF_4$.

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