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Research Article

Preparation, characterization and biodistribution of a new technetium-99 m nitrido complex with 2-methoxyisobutylisonitrile and comparison with ^{99m}Tc–MIBI

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Summary

The preparation of complex ^{99m}TcN–MIBI was carried out using two alternative procedures that led to the formation of the complex with high radiochemical purity (> 90%). The partition coefficient, electrophoresis and cationic resin exchange experiments showed that the ^{99m}TcN–MIBI is a lipophilic and neutral complex, the structure of this complex is six-coordinate distorted octahedral, its composition may be [^{99m}TcNCl$_2$(MIBI)$_3$], and the optimized geometry of this complex was calculated by using Gaussian 98 for Window (G98W) program. The biodistribution of ^{99m}TcN–MIBI shows high myocardial uptake and good target/non-target ratios in mice at early post-injection time, for 5 min post-injection the heart-to-blood, heart-to-lungs and heart-to-liver ratios are 3.18, 1.72 and 1.42, respectively. In respect of the relatively good rations after 5 min and the rapid clearance from non-target, the complex ^{99m}TcN–MIBI may be suitable for instant myocardial imaging. In

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addition, the lyophilized kit enables the convenient preparation of this complex for clinical use. Based on these promising properties, ^{99m}TcN–MIBI should be a new potential myocardial perfusion-imaging agent. Copyright © 2002 John Wiley & Sons, Ltd.

Key Words: myocardial perfusion imaging agent; radiopharmaceuticals; ^{99m}TcN–MIBI; biodistribution; charge properties; ^{99m}TcN core

Introduction

In recent years, many successful efforts have been devoted to the synthesis of technetium-99 m radiopharmaceuticals containing the $[^{99m}Tc(V)\equiv N]^{2+}$ core.[1,2] This core constitutes another characteristic functional moiety, in which the Tc^{5+} ion is multiply bonded to a nitride nitrogen atom (N^{3-}). The resulting arrangement of atoms exhibits a very high chemical stability towards both oxidation–reduction reactions involving the technetium ion and pH variations. This suggests that the Tc≡N multiple bonds would allow the facile variation of the other ancillary ligands coordinated to the metal center and hence make possible the fine tuning of the biological properties of the resulting compounds.[3]

So far, a number of ^{99m}TcN tracer agents with promising biological characteristics have been developed. For example, *bis* (*N*-ethoxy, *N*-ethyl dithiocarbamato) nitrido technetium-99 m complex $[^{99m}TcN(NOEt)_2]$ exhibits high myocardial uptake in humans and shows a behavior similar to that of thallium-201 as it undergoes redistribution in myocardial ischemic patients under stress/rest conditions.[3,4]. It is currently under preliminary clinical evaluation as a tracer for myocardial perfusion.

Isonitrile compounds are σ donor and π acceptor ligands that can be utilized in developing stable metallic complexes.[5] We thus prepared a new technetium-99 m nitrido complex: ^{99m}TcN–MIBI (MIBI = 2-methoxyisobutylisonitrile, $CH_3OC(CH_3)_2\ CH_2–N\equiv C$), and to analyse the characterization and biological properties of the newly formed complex.

Experimental

Materials

The isonitrile ligand MIBI was donated by Beijing SHIHONG Pharmaceutical Center, People's Republic of China. The nitride

nitrogen atoms (N^{3-}) donor, S-methyl dithiocarbazate (MDTC, $H_2NNHC(=S)SCH_3$), was synthesized under the following procedure.[6]

(a) $H_2NNH_2 + CS_2 + KOH \rightarrow H_2NNHC\ (=S)\ SK$,

(b) $H_2NNHC\ (=S)\ SK + CH_3I \rightarrow H_2NNHC\ (=S)\ SCH_3$.

The product MDTC was obtained as white crystals with 70% yield. M.P.: 81–83°C, ν/IR (cm^{-1}): 3260(-NH), 3200(–NH_2), 1510(δNH), 1155(C–N), 1006(C=S).

Preparation of ^{99m}TcN–MIBI complex[3]

The preparation of ^{99m}TcN complex was carried out using the following two procedures:

Method 1 (*Liquid formulation*). One milliliter of saline containing $^{99m}TcO_4^-$ (activity ranging from 1.85 to 185 MBq) was added to a vial containing 0.05 mg of $SnCl_2 \cdot 2H_2O$ and 1.0 mg of MDTC dissolved in 1.0 ml of HCl (0.1 mol l^{-1}). The resulting solution was heated at 100°C for 10–15 min and then cooled to room temperature. The pH of the solution was raised to 5.0–6.0 by adding 0.2 ml of a sodium phosphate buffer (pH = 7.0) and 0.1 ml of an ethanol solution containing 1.0 mg of the MIBI ligand was added. The formation of the final complex occurred at 100°C for 10–15 min.

Method 2 (*Lyophilized formulation*). One milliliter of saline containing $^{99m}TcO_4^-$ (activity ranging from 1.85 to 185 MBq) was added to a vial containing 0.05 mg of $SnCl_2 \cdot 2H_2O$, 18 mg of the sodium salt of citrate and 1.0 mg of MDTC in a freeze-dried form. The resulting solution was heated at 100°C for 10–15 min and then 0.1 ml of an ethanol solution containing 1.0 mg of the MIBI ligand was added and the reaction vial maintained at 100°C for 10–15 min.

Preparation of ^{99m}Tc–MIBI complex

Two milliliters of saline containing $^{99m}TcO_4^-$ (activity ranging from 1.85 to 185 MBq) was added to a vial containing 0.1 mg of $SnCl_2 \cdot 2H_2O$ dissolved in 1.0 ml of HCl (0.1 mol l^{-1}). Then 0.1 ml of an ethanol solution containing 1.0 mg of the MIBI ligand was added and the resulting solution was heated at 100°C for 10–15 min.

Radiochemical analysis

The radiochemical purity (RCP) of the final complexes, including ^{99m}TcN–MIBI and ^{99m}Tc–MIBI, were evaluated by TLC

chromatography. The chromatography analyses were performed on polyamide film with acetonitrile as mobile phase. $^{99m}TcO_2 \cdot xH_2O$ and $[^{99m}Tc{\equiv}N]^{2+}_{int}$ are retained at the origin, R_f values for $^{99m}TcO_4^-$ are about 0.3–0.5, and the ^{99m}Tc complexes, including ^{99m}Tc–MIBI and ^{99m}TcN–MIBI, are moved at the solvent front.

HPLC analysis

Reversed-phase high-pressure liquid chromatography (HPLC) experiments were performed using a Waters System with dual 515 HPLC pump system and LB509 Radioflow detector (EG&G BERTHOLD). The column (SHIMADZU Shim-pack VP-ODS, spherical silica particle size $4.6 \pm 0.3\,\mu m$, $150 \times 4.6\,mm^2$ ID) was eluted at a flow rate of 1.0 ml/min according to the procedures described in Table 1. Analysis was accomplished using method 1 for the samples of complexes ^{99m}TcN–MIBI and $[^{99m}Tc{\equiv}N]^{2+}_{int}$, the analysis for the samples ^{99m}Tc–MIBI and ^{99m}TcN–MIBI was using method 2.

Octanol/water partition coefficient

The lipophilicity of ^{99m}TcN–MIBI and ^{99m}Tc–MIBI complexes with a radiochemical purity of at least 95% was determined following this method: by partitioning the complexes between 1-octanol and water (the pH of this octanol/water system is about 7) and counting the activity (cpm) in both phases in a test tube. The test tube is vortexed at room temperature for 1 min and then centrifuged at high speed for

Table 1. The procedures of HPLC analysis (gradient systems)[a]

	Time (min)	Flow rate (ml min−1)	Injection volume (μl)	A (%)	B (%)	C (%)	Samples
Method 1	0.10	2	10	80	20	—	
	4	2	10	30	70	—	^{99m}TcN–MIBI
	8	2	10	5	95	—	$[^{99m}Tc{\equiv}N]^{2+}_{int}$
	10	2	10	0	100	—	
	20	2	10	0	100	—	
Method 2	0.10	1	15	80	—	20	
	8	1	15	30	—	70	^{99m}TcN–MIBI
	16	1	15	0	—	100	^{99m}Tc–MIBI
	25	1	15	100	—	0	
	30	1	15	100	—	0	

[a] A = 0.01 mol/l $NaHCO_3$; B = methanol; C = acetonitrile.

10 min. A 0.2 ml aliquot of both phases is pipetted into another test tube with adequate care to avoid cross contamination between the phases, and counted in a well counter. The partition coefficient, P, was calculated using the following equation: P = (cpm in octanol − cpm background)/(cpm in water − cpm background). The partition coefficient was measured several times and the mean value was taken as the final partition coefficient of the complex to be determined.

Electrophoresis

Under the same condition, for two complexes ^{99m}TcN–MIBI and ^{99m}Tc–MIBI, electrophoresis was performed concurrently on chromatography paper strips ($10 \times 1\,cm^2$) impregnated with the electrolyte solution and at a potential difference of 150 V. The analyses were run for different times (90–210 min), the developed electrophoresis strips were left to dry, and each of them was divided into three parts (cathode, origin and anode). The radioactivity of each part was determined by a well counter, then the relative percentage of radioactivity distribution of each part was calculated.

Cationic resin exchange experiments

$n \times V$ ml (1.85–7.40 MBq) of the purified complex solution was taken in n vials, respectively, then the solutions in the vials were adjusted to different pHs by using concentrated hydrochloric acid (pH < 2.0). After that, $n \times W$ g of cationic resins were added to corresponding n vials, respectively. The vials were stirred at room temperature for 30–60 min and then 4×0.1 ml water phase of each vial in different test tubes, and counted in a well counter. The pH of each solution was determined by a potable pH meter. The distribution coefficient, D, was calculated using the following equation: $D = V\,(S_0\text{-Se})\,/(\text{Se} \times W)$, in the equation, S_0 is the average specific activity of two contrast solutions, that is no-resin-added samples; Se is the specific activity of resin-added equilibrium solution. Then plot the lines of lg$D$-pH for ^{99m}TcN–MIBI and ^{99m}Tc–MIBI, respectively.

Biological distribution studies

In vivo distribution studies of these ^{99m}Tc complexes were carried out in mice (average weight about 20 g, obtained from Animal Center of

Beijing Medical University). ^{99m}Tc complex (about 740 MBq in 50 µl solution) was injected through the tail vein. The mice were sacrificed at different times (5–60 min post-injection) and the organs of interest were weighed and counted in an NaI well-type counter. The %ID/g in each organ and blood was calculated by comparing its activity with appropriate standards of injected dose (ID).

Calculation of configuration for ^{99m}TcN–MIBI complex

The program Gaussian 98 for Window (G98W)[7] was employed for the calculation and Hartree–Fock energy was minimized on the basis set STO-3G*. The Gaussian input files (*.gjf) were created by using CS Chem3D Ultra® software. And the complex $[Tc(CO)_3(TBI)_3]^+$ was used to verify the reliability of the methods. The calculation result of this complex was consistent with the crystal structure. The mass of Tc atom was auto-set to 1 in G98W, so the thermodynamics parameters of complex could not be calculated.

Results and discussion

Preparation of ^{99m}Tc complexes

The complexes were prepared using $SnCl_2 \cdot 2H_2O$ reduction of pertechnetate. The RCP of the final complexes, including ^{99m}TcN–MIBI and ^{99m}Tc–MIBI, were evaluated by TLC chromatography and HPLC chromatography and ranged between 90% and 98%. The preparation of ^{99m}TcN–MIBI was carried out using two alternative procedures. The first method was based on the reaction of $^{99m}TcO_4^-$ with S-methyl dithiocarbazate, $H_2NNHC(=S)SCH_3$, in the presence of $SnCl_2 \cdot 2H_2O$ and HCl. In this reaction, the species $H_2NNHC(=S)SCH_3$ plays the role of an efficient donor of nitride nitrogen atoms (N^{3-}) and $SnCl_2 \cdot 2H_2O$ behaves as the reducing agent.[3,8] The preparation of ^{99m}TcN–MIBI was carried out in two steps. In the first step, the reaction of $^{99m}TcO_4^-$ with S-methyl dithiocarbazate led to the formation of a mixture of intermediate, reduced complexes all containing the terminal Tc≡N multiple bond. The complete chemical characterization of these intermediate species was not accomplished. Then, the ^{99m}TcN–MIBI was prepared by ligand exchange reaction with the mixture of intermediate. In the second method, the complex ^{99m}TcN–MIBI was obtained as freeze-dried formulation. So it was

possible for ^{99m}TcN–MIBI to be used in clinics conveniently. By using these two methods described above the final complex ^{99m}TcN–MIBI was obtained in high yield (more than 90%).

The *P* (partition coefficient) values for the partition of ^{99m}TcN–MIBI and ^{99m}Tc–MIBI between 1-octanol and water determined on the final products with a radiochemical purity of > 95% were 33.71 ± 1.75 and 28.35 ± 0.28 ($n = 4$), respectively.

HPLC analysis

Figure 1(a) and 1(b) show HPLC radio-chromatograms of $[^{99m}Tc{\equiv}N]^{2+}_{int}$ and ^{99m}TcN–MIBI, respectively, and indicate that the intermediates

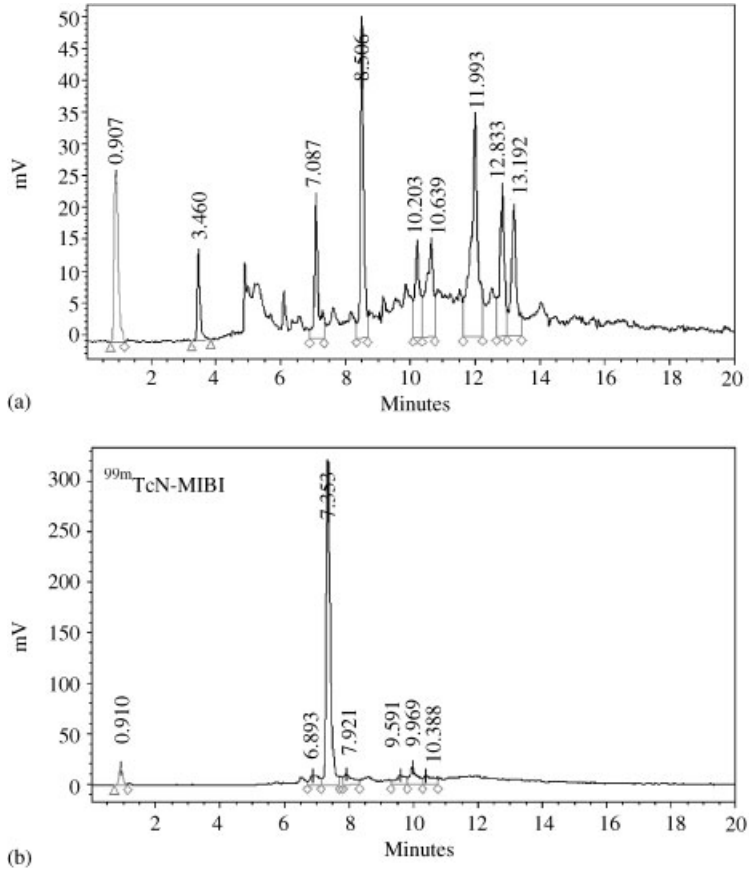

Figure 1. (a) HPLC radio-chromatograms of $[^{99m}TcN]^{2+}_{int}$ intermediate by using method 1 for gradient elution and (b) of ^{99m}TcN–MIBI by using method 1 for gradient elution

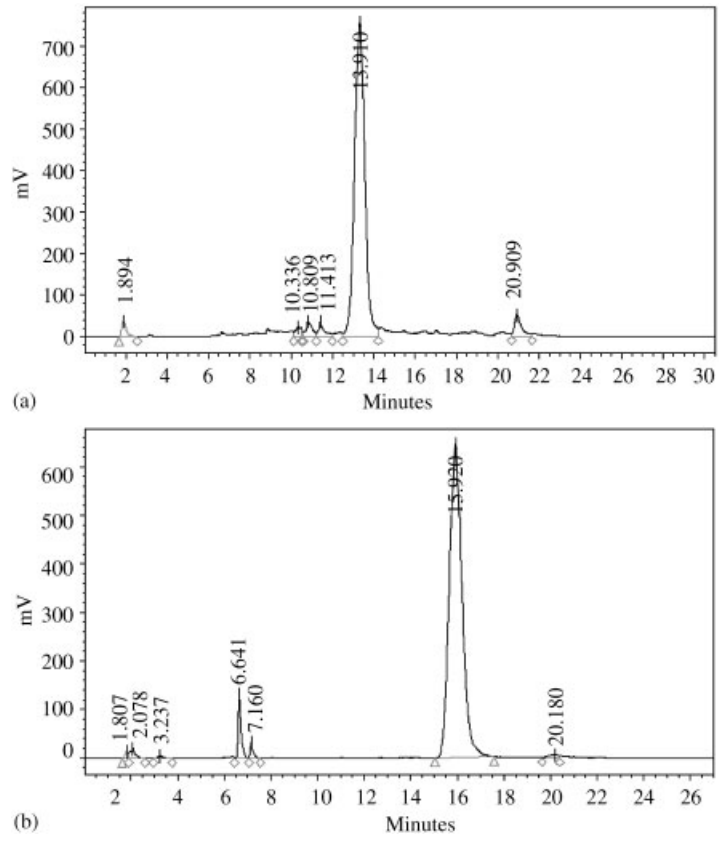

Figure 2. (a) HPLC radio-chromatograms of ^{99m}TcN–MIBI by using method 2 for gradient elution and (b) of ^{99m}Tc–MIBI by using method 2 for gradient elution

were composed of several species. However, it was found that all the complexes composing the mixture underwent facile substitution reactions with the ligand MIBI to give the same final product ^{99m}TcN–MIBI in high yield (>90%). It is very similar to the preparation of ^{99m}TcN(L)$_2$ [L = R^1(R^2)NCS$_2$] in the literature (3).

In order to validate the formation of ^{99m}TcN–MIBI (were not ^{99m}Tc–MIBI), we compared the ^{99m}TcN–MIBI with ^{99m}Tc–MIBI by using HPLC analysis under the same conditions. The results of HPLC analysis shown in Figure 2(a) and 2(b) indicate that the retention time for ^{99m}TcN–MIBI (R_t = 13.3 min) and ^{99m}Tc–MIBI (R_t = 15.9 min) differs significantly. According to Figure 2(a) and 2(b), it was found that there is no ^{99m}Tc–MIBI produced during the preparation process of ^{99m}TcN–MIBI.

Table 2. The conditions and results of electrophoresis for ^{99m}Tc–MIBI and ^{99m}TcN–MIBI

Complexes	*R* (%)			V/V	t (min)	Support medium	Solution medium
	Anode	Origin	Cathode				
^{99m}Tc–MIBI[a]	0.23	3.71	96.05		90	Acetate film	A[b]
^{99m}Tc–MIBI[a]	1.70	2.85	95.45	150	110–150	Fibrous paper	B
^{99m}Tc–MIBI[c]	0.28	1.13	98.67		210	Fibrous paper	C
^{99m}TcN–MIBI[a]	0.55	78.80	20.65		90	Acetate film	A[b]
^{99m}TcN–MIBI[a]	3.50	71.55	24.95	150	110–150	Fibrous paper	B
^{99m}TcN–MIBI[c]	9.03	76.53	14.40		210	Fibrous paper	C

[a] $n = 2$.

[b] Electrolyte A: 0.04 mol/l sodium barbiturate solution was adjusted to pH 6.0 using 1 mol/l HCl; B: 1/15 mol/l phosphate buffer, pH 6.4; C: V (B solution): V (0.9%NaCl): V (95% ethanol) = 1:2:2.

[c] $n = 3$.

In Figure 2(a) and 2(b), there are some small peaks before or after the main peak, maybe they are $^{99m}TcO_4^-$, $^{99m}TcO_2 \cdot xH_2O$ or other radioimpurities. Compared to the main peak, they can be omitted due to the small integral area.

Electrophoresis

The conditions and results of electrophoresis are shown in Table 2.

^{99m}TcN–MIBI complex did not migrate from the point of application during electrophoresis at all conditions, while ^{99m}Tc–MIBI complex migrated towards the cathode. The results indicated that the ^{99m}TcN–MIBI complex is neutral and that the ^{99m}Tc–MIBI complex is positively charged.

Cationic resin exchange experiments

In the linear equation $\lg D = C + x$ pH, the value of slope (x) is equal to the net charge of the experiment complex. The results of cationic exchange experiment show that the net charge of ^{99m}Tc–MIBI is one (Figure 3, $x = 0.99$), while ^{99m}TcN–MIBI is neutral (Figure 4, $x = 0.04$). The results of cationic resin exchange experiments have agreed to that of electrophoresis.

According to the result of octanol/water partition coefficient experiment, the partition coefficient values for ^{99m}TcN–MIBI and ^{99m}Tc–MIBI were 33.71 ± 1.75 and 28.35 ± 0.28, respectively. Because

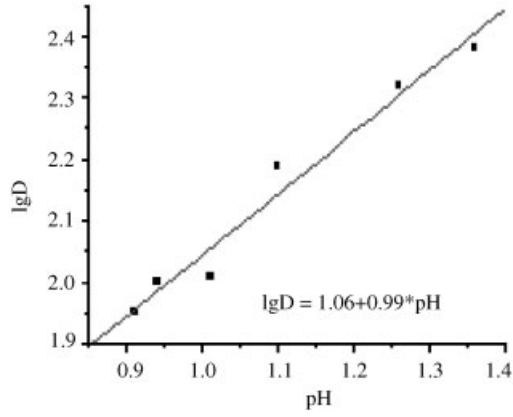

Figure 3. The logarithm of *D* as a function of pH for ^{99m}Tc–MIBI

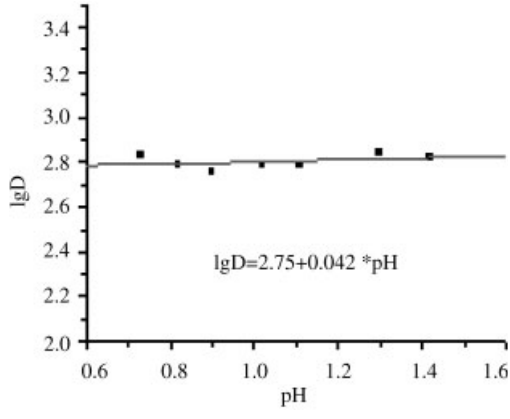

Figure 4. The logarithm of *D* as a function of pH for ^{99m}TcN–MIBI

they have similar lipophilic properties the adsorption of solid medium cannot affect the experiment results. Both the methods in this study have all shown that the ^{99m}TcN–MIBI complex is neutral. The ^{99m}TcN core synthesized following the reported method [3,7] was determined to be $[^{99m}Tc(V)\equiv N]^{2+}$, bears two positive charges. Therefore, it must have two chloro ligands in the composition of ^{99m}TcN–MIBI to neutralize the positive charge of ^{99m}TcN core.

Most $[Tc(V)\equiv N]^{2+}$ complexes are either five-coordinate square pyramidal or six-coordinate distorted octahedral. In the case of square pyramidal and octahedral complexes, the strong axial ligand field induced by the nitrido ligand results in a low energy, essentially non-bonding, d_{xy} orbital.[1] According to this conclusion, 20% of the

^{99m}TcN–MIBI complex migrated towards the cathode (Table 2) and it can be interpreted as follows: ^{99m}TcN–MIBI is a six-coordinate distorted octahedral complex. The chloro ligand in the *trans* position can be cleaved partly during the electrophoresis due to the strong *trans* influence of the nitrido ligand, so the cationic species $[^{99m}TcNCl(MIBI)_3]^+$ was formatted and migrated towards the cathode.

Biological distribution studies

The biodistribution of ^{99m}Tc–MIBI and ^{99m}TcN–MIBI in mice is shown in Tables 3 and 4, respectively.

The complex ^{99m}TcN–MIBI shows high heart uptake with good heart-to-liver, heart-to-lungs and heart-to-blood ratios at early post-injection time. Compared with the prototypical isonitrile complex, ^{99m}Tc–MIBI, liver uptake at early post-injection time and the clearance rates from liver and blood, in particular, are greatly improved.

Since the complex ^{99m}TcN–MIBI washouts from heart rapidly, it makes possible the heart imaging at early post-injection time with ^{99m}TcN–MIBI and reduces the time during two successive injections that are required to be able to differentiate transient and permanent defects under exercise.

Table 3. Biodistribution of ^{99m}Tc–MIBI and ^{99m}TcN–MIBI in mice (%ID/g, $n = 3$)

Tissues	Complex	Post-injection time/min			
		5	15	30	60
Heart	A[a]	32.14 ± 0.75	27.72 ± 2.61	24.93 ± 1.56	26.83 ± 4.78
	B[a]	25.67 ± 3.79	20.30 ± 0.90	16.94 ± 1.74	10.34 ± 1.74
Liver	A	34.09 ± 0.37	36.44 ± 0.81	27.77 ± 6.84	25.88 ± 1.51
	B	18.08 ± 0.97	18.34 ± 2.40	17.06 ± 1.40	12.86 ± 0.37
Lungs	A	11.21 ± 1.43	4.56 ± 0.26	2.75 ± 0.18	2.19 ± 0.35
	B	14.93 ± 0.69	10.06 ± 0.25	6.54 ± 1.43	3.44 ± 1.16
Kidneys	A	88.85 ± 14.79	53.49 ± 2.81	52.52 ± 8.33	42.41 ± 0.35
	B	21.18 ± 4.98	18.10 ± 0.26	16.06 ± 0.70	12.81 ± 3.95
Brain	A	0.48 ± 0.02	0.29 ± 0.07	0.18 ± 0.04	0.15 ± 0.03
	B	0.69 ± 0.03	0.52 ± 0.21	0.51 ± 0.14	0.45 ± 0.16
Muscle	A	7.28 ± 0.28	6.46 ± 0.86	5.02 ± 0.56	4.89 ± 0.87
	B	5.33 ± 0.07	3.98 ± 1.12	2.88 ± 0.58	2.05 ± 0.19
Blood	A	2.51 ± 0.48	0.79 ± 0.05	0.28 ± 0.03	0.20 ± 0.01
	B	8.07 ± 2.61	5.44 ± 2.21	2.96 ± 0.34	1.78 ± 0.10

[a]A: ^{99m}Tc–MIBI, B: ^{99m}TcN–MIBI.

Table 4. Target/non-target ratios for the ^{99m}Tc–MIBI and ^{99m}TcN–MIBI complexes at 5–60 min post–injection in mice ($n = 3$)

Complexes	Post-injection time/min							
	^{99m}Tc–MIBI				^{99m}TcN–MIBI			
	5	15	30	60	5	15	30	60
Heart/liver	0.94	0.76	0.90	1.04	1.42	1.11	0.99	0.80
Heart/blood	12.80	35.09	89.04	134.15	3.18	3.73	5.72	5.81
Heart/lungs	2.87	6.08	9.07	12.25	1.72	2.02	2.59	3.01

Although it was proposed that the cation species which migrated towards the cathode during electrophoresis is $[^{99m}TcNCl(MIBI)_3]^+$, we cannot make sure which species ($[^{99m}TcNCl(MIBI)_3]^+$ or $[^{99m}TcNCl_2(MIBI)_3]$) dominates the biodistribution in mice. This question is worth studing further.

Results of calculation for ^{99m}TcN–MIBI complex

The program Gaussian 98 for Window (G98W) was employed for the calculation and Hartree–Fock energy was minimized on the basis set STO-3G*. Figures 5–7 showed the optimized geometry of ^{99m}TcN–MIBI complexes. Correlative calculation results are listed in Table 5.

Among the three configurations of ^{99m}TcN–MIBI, we observed that the energy of *trans*-mer configuration is lower than that of *cis*-fac and *cis*-mer (Table 5). So the *trans*-mer configuration is the most

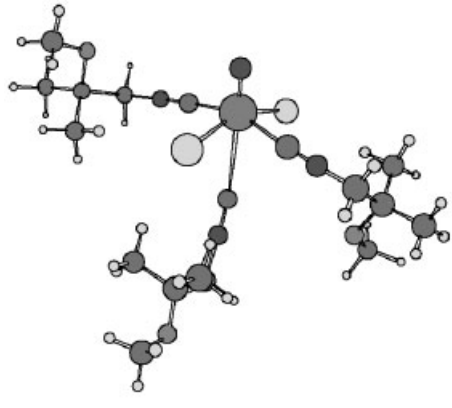

Figure 5. Optimized geometry of *trans*-mer-$[^{99m}TcN(MIBI)_3Cl_2]$

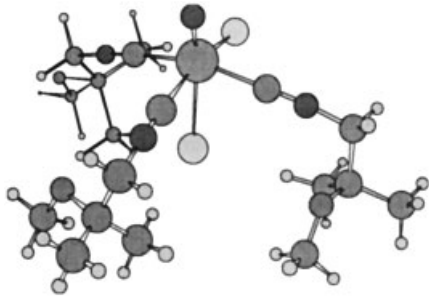

Figure 6. Optimized geometry of *cis*-mer-[^{99m}TcN(MIBI)$_3$Cl$_2$]

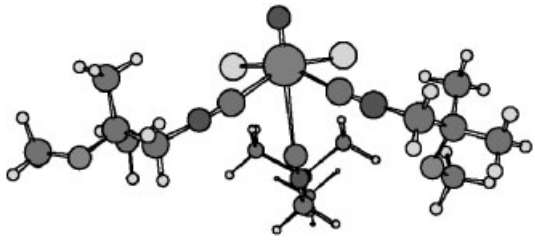

Figure 7. Optimized geometry of *cis*-fac-[^{99m}TcN(MIBI)$_3$Cl$_2$]

Table 5. Optimized results of three configurations of [TcN(MIBI)$_3$Cl$_2$][a]

	E(RHF) (a.u)	E(LUMO) (a.u)	Dipole moment (deby)
cis-fac	−6201.9567	0.24349	8.7960
cis-mer	−6201.9438	0.26467	7.0468
trans-mer	−6201.9617	0.25695	5.4225

[a]1 a.u. = 1 Hartree = 27.2116 ev.

thermodynamically stable configuration. For the *cis*-fac and *cis*-mer configuration, the -*trans* position to Tc≡N bond is taken up by the MIBI ligand. Two Cl atoms are in the plane of Tc atom. The charge of the whole molecule is zero. The optimized result of *cis*-mer configuration demonstrates the Tc–Cl bond distances are 2.552 and 2.304 Å for -*trans* position and -*cis* position. It means the interaction between Tc atom and Cl atom in -*trans* position is weaker than in -*cis* position. And an electron does not complete the entire transfer from Tc atom to Cl atom. It results in the charge of the whole molecule of *cis*-mer configuration being between 0 and +1. The *cis*-mer configuration becomes the unstable one because of the highest energy and occurs in

the least proportion. According to the above results, the charge of ^{99m}TcN–MIBI molecule is mostly zero. It is consistent with the electrophoresis experiments. The results of electrophoresis experiments indicate that about 75.63% of ^{99m}TcN–MIBI does not migrate from the origin point at all conditions.

Conclusion

The preparation of complex ^{99m}TcN–MIBI was carried out using two alternative procedures that led to the formation of the complex with high radiochemical purity (>90%). Based on the results of the experiments reported here, we concluded that the ^{99m}TcN–MIBI is a lipophilic and neutral complex, the structure of this complex is six-coordinate distorted octahedral, its composition may be $[^{99m}TcNCl_2(MIBI)_3]$, and is the most thermodynamically stable configuration, which is shown in Figure 5, is optimized by using G98W program. On the basis of the fact that it provides high myocardial uptake and good target/non-target ratios in mice at early post-injection time, we think it is worth developing this complex for clinical use. In addition, the lyophilized kit enables the convenient preparation of this complex for clinical use. Clinical trials are being conducted and will be reported in due course.

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