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Conformational investigation of benzylhydroxamamide, its oxotechnetium(V) complexes and determination of their reaction energies

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Abstract

The structures of benzylhydroxamamide (BHam, LH) conformers, deprotonated (L^-) species and their technetium complexes have been obtained by geometry optimizations using Hatree–Fock at different basis sets and density functional theory calculations at B3LYP/6-31G(d) level of theory. Two hydroxyimino and ten hydroxyamino conformers of BHam have been found. Conformational pathways of all stable BHam conformers and their oxo-Tc(V) complexes have been investigated. The tautomerization between hydroxyimino and hydroxyamino tautomers is an endothermic reaction, with $\Delta H^o = 7.38$ kcal/mol and its equilibrium constant $\log K = -5.70$, at 298.15 K. The stabilization energies of oxo-Tc(V) complexes existing as $[(LH)_2TcO]^{+3}$, $[L_2TcO]^+$ of C_2 and $[L_2TcO]^+$ of C_{2v} conformers have been determined at HF/3-21G level of theory. The optimized geometry of hydroxyimino tautomer is the most stable species and shows good agreement with X-ray crystallographic data.

Keywords: Benzylhydroxamamide; BHam; Hydroxyimino; Hydroxyamino; Technetium complex; Ab initio; Density functional techniques

1. Introduction

Many amino oxime compounds have been used as ligand forming complexes with ^{99m}Tc as radiopharmaceutical reagent for the medical purposes. Hexamethylpropylene amine oxime (HMPAO) has been known as a ligand chelating with ^{99m}Tc as radiomedical reagent using in SPECT images applications for brain treatments [1,2]. The conformational isomers of HMPAO have been first time investigated by theoretical approach [3]. Due to hydroxamamide (Ham) derivatives comprise a typical chelating moiety containing both nitrogen an oxygen donor atoms, they easily form stable ^{99m}Tc complexes at room temperature. Ham derivatives with various substituents such as benzylhydroxamamide (BHam), p-toluylhydroxamamide (pTHam), p-chlorobenzylhydroxamamide (pCLHam) and α-naphthylhydroxamamide (NAPHam) were prepared for ^{99m}Tc complexes and analyzed using HPLC [4]. More ever, many Ham derivatives have exhibited biological activities [5]. They have been tested for pharmacological properties and found to be bactericidal, fungicidal and local anaesthetics [6]. The Ham compounds were widely investigated using and H-NMR spectroscopy and the structure of pCLHam was obtained using X-ray diffraction [7]. BHam is one of the most interesting compound of Ham derivatives which plays important role in treatment of diseases and of which ^{99m}Tc complex has been used as radiopharmaceutical reagent. The electronic structure of oxo-Tc(V)-based radiopharmaceuticals containing a variety of donor ligands were also evaluated using density functional techniques [8]. For more understanding on BHam conformations and their complexation with technetium metal ion, the structural information of BHam and their related species could be more investigated. In present work, the geometrical investigation of BHam conformers and their oxo-technetium(V) complexes has been, theoretically attempted using ab initio Hartree–Fock and DFT calculations. The optimized structures are compared to their experimentally determined crystal structures.

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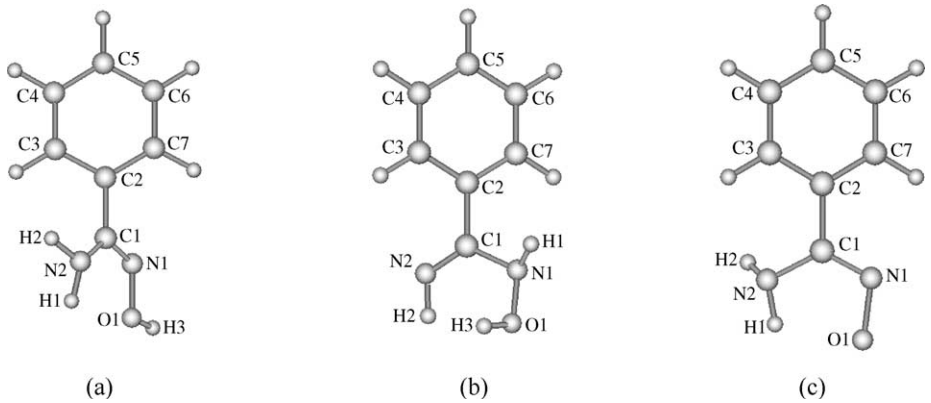

Fig. 1. Atom label for structures of (a) hydroxyimino, (b) hydroxyamino tautomers and (c) deprotonated BHam species.

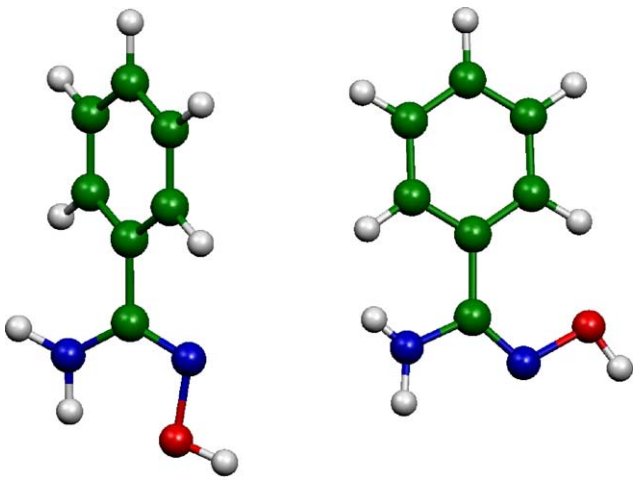

Fig. 2. B3LYP/6-31G(d) optimized structures of hydroxyimino form of BHam as neutral isomers and their relative energies which compared to most stable isomer (IE), in kcal/mol.

2. Computational details

The geometry optimizations of all conformations were computed by Hartree–Fock (HF) and density functional theory (DFT). Density functional calculations have been performed with the Becke's three parameters hybrid functional using the Lee, Yang and Parr correlation functional (B3LYP) [9,10] with different basis sets. Hydroxyimino and hydroxyamino conformers of the benzylhydroxamamide were initially searched using potential energy surface (PES) scan with HF/3-21G method. The HF/3-21G structures were fully reoptimized at the HF/6-31G(d) and B3LYP/6-31G(d) levels. The structure of oxo-Tc(V) complexes of neutral and deprotonated BHam and all related species were optimized using HF/3-21G method. All geometry optimizations were performed with the frequencies zero-point energy corrections. All calculations were performed with the GAUSSIAN 03 program [11]. The MOLDEN 3.7 program [12] was utilized to display molecular structures

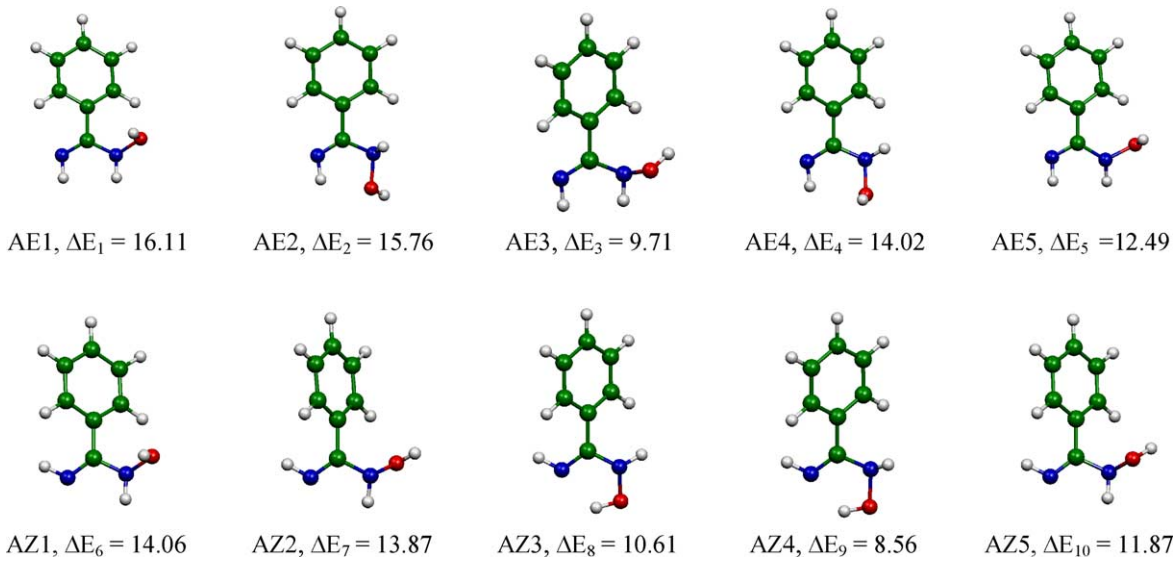

Fig. 3. B3LYP/6-31G(d) optimized structures of hydroxyamino tautomers of BHam and their relative energies compared to most stable conformer (IE), in kcal/mol.

Table 1
B3LYP/6-31G(d) structures of neutral BHam conformers, specified by dihedral angles of ϕ(C1–N1–O1–H3), ψ(C2–C1–N1–O1), $^{\theta}$(C3–C2–C1–N1) and ω(C2–C1–N2–H1)

Isomers	ϕ	ψ	θ	ω
Hydroxyimino conformers				
IE[a]	174.722	178.910	150.000	163.340
IZ	177.943	0.560	131.140	163.050
Hydroxyamino tautomers				
AE1	51.911	40.550	−159.390	−177.830
AE2	110.054	−34.330	−136.130	−177.250
AE3	115.768	168.640	−160.360	−176.820
AE4	−120.742	51.920	−154.930	−177.490
AE5	−57.311	168.140	−157.900	178.500
AZ1	56.422	46.170	−152.010	7.380
AZ2	116.903	−45.870	−121.950	−0.570
AZ3	−10.348	−167.180	−132.050	2.040
AZ4	3.665	172.660	146.640	4.990
AZ5	−123.773	52.440	−146.700	5.950

[a] Most stable structure.

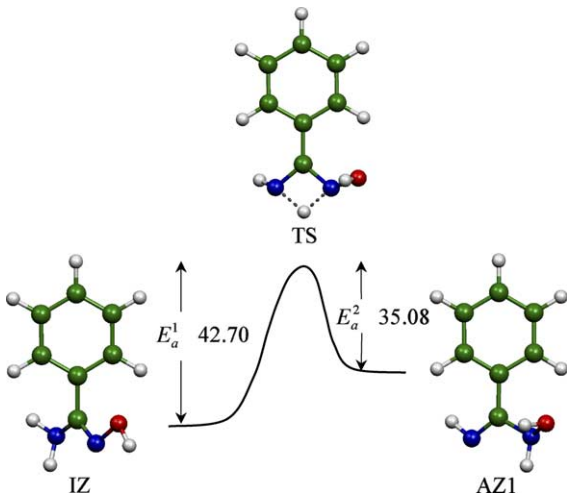

Fig. 5. Tautomerization between hydroxyimino reactant (IZ conformer) and hydroxyamino product (AZ1 conformer) via transition state (TS). The forward and backward activation energies have been corrected for ZPE at B3LYP/6-31G(d) level, in kcal/mol.

and observe the geometry convergence of ab initio calculations via the Gaussian output files. The molecular graphics of all species were generated with the MOLEKEL program [13].

The standard enthalpy ΔH^O and Gibbs free energy changes ΔG^O of interconversion reactions between BHam conformers have been derived from frequency calculations at B3LYP/6-31G(d) level. The reaction entropy ΔS^O of interconversion were evaluated by a thermodynamic equation $\Delta S^O = (\Delta H^O - \Delta G^O)/T$. The rate constant $k(T)$ derived from transition state theory was computed from Gibbs free energy of activation $\Delta^{\ddagger}G^O$, by

$$k(T) = \frac{k_B T}{hc^o} e^{-\Delta^{\ddagger} G^O / RT}.$$

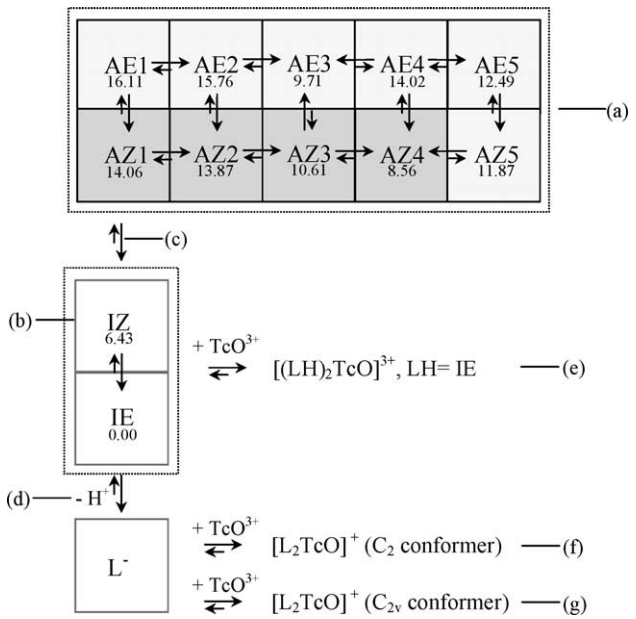

Fig. 4. Integrated pathways of isomerization between (a) hydroxyamino conformer, (b) IZ and IE hydroxyimino conformers, (c) tautomerization between IZ and AZ1 tautomers, (d) deprotonation of BHam, (e) complexations of $[(LH)_2TcO]^{3+}$ (f) $[L_2TcO]^{+}$, C_2 conformer and (g) $[L_2TcO]^{+}$, C_{2v} conformer. The numbers shown in boxes are relative energies derived from B3LYP/6-31G(d) calculations, in kcal/mole.

Table 2
Thermodynamic quantities of interconversion reactions between neutral BHam conformers, derived from B3LYP/6-31G(d) calculations

Reactions	$\Delta H^{O,a}$	$\Delta G^{O,a}$	$\Delta S^{O,b}$	K
Hydroxy imino conformers				
IE ⇌ IZ	6.40	6.43	-8.84×10^{-5}	1.87×10^{-5}
Tautomerization				
IZ ⇌ AZ1	7.38	7.78	-1.34×10^{-3}	1.98×10^{-6}
Hydroxy amino tautomers				
AE1 ⇌ AE2	0.27	0.61	-1.14×10^{-3}	3.54×10^{-1}
AE2 ⇌ AE3	6.19	5.72	1.57×10^{-3}	6.16×10^{-5}
AE3 ⇌ AE4	−4.38	−4.20	-6.06×10^{-4}	1.23×10^{3}
AE4 ⇌ AE5	1.62	1.39	7.45×10^{-4}	9.43×10^{-2}
AE1 ⇌ AZ1	2.09	2.01	2.69×10^{-4}	3.34×10^{-2}
AE1 ⇌ AZ2	2.21	2.41	-6.76×10^{-4}	1.69×10^{-2}
AE2 ⇌ AZ1	1.81	1.39	1.41×10^{-3}	9.44×10^{-2}
AE2 ⇌ AZ2	1.93	1.80	4.61×10^{-4}	4.77×10^{-2}
AE2 ⇌ AZ3	5.27	4.87	1.34×10^{-3}	2.61×10^{-4}
AE3 ⇌ AZ2	−4.26	−3.93	-1.10×10^{-3}	7.74×10^{2}
AE3 ⇌ AZ3	−0.92	−0.85	-2.25×10^{-4}	4.23
AE3 ⇌ AZ4	1.22	1.01	6.84×10^{-4}	1.80×10^{-1}
AE4 ⇌ AZ3	3.47	3.35	3.81×10^{-4}	3.42×10^{-3}
AE4 ⇌ AZ4	5.60	5.22	1.29×10^{-3}	1.45×10^{-4}
AE4 ⇌ AZ5	2.16	2.10	2.02×10^{-4}	2.84×10^{-2}
AE5 ⇌ AZ4	3.98	3.82	5.45×10^{-4}	1.54×10^{-3}
AE5 ⇌ AZ5	0.55	0.71	-5.43×10^{-4}	3.01×10^{-1}
AZ1 ⇌ AZ2	0.12	0.40	-9.45×10^{-4}	5.05×10^{-1}
AZ2 ⇌ AZ3	3.34	3.08	8.80×10^{-4}	5.46×10^{-3}
AZ3 ⇌ AZ4	2.14	1.86	9.09×10^{-4}	4.25×10^{-2}
AZ4 ⇌ AZ5	−3.44	−3.11	-1.09×10^{-3}	1.95×10^{2}

[a] In kcal/mole.
[b] In kcal/mole K.

The equilibrium constant K at 298.15 K and 1 atmosphere were evaluated by equation $\Delta G^{O} = -RT \ln K$ [14].

3. Results and discussion

Labeled atoms of two typical tautomers of hydroxyimino and hydroxyamino and a deprotonated form BHam conformer are shown in Fig. 1. Two hydroxyimino and ten hydroxyimino tautomers obtained by geometry optimizations using HF/3-21G, HF/6-31G(d) and B3LYP/6-31G(d) calculations are shown in Fig. 2 and Fig. 3, respectively. The most stable conformer (IE) of hydroxyimino form is more stable than the another tautomer (IZ) by 6.43 kcal/mol. Different geometry between IE and IZ conformers mainly caused by dihedral angle of ψ(C2–C1–N1–O1) whose atoms are labeled in Fig. 1, as shown in Table 1. The stable hydroxyamino tautomers of BHam comprise five E and five Z typical conformers, indicated by dihedral angles of ψ(C2–C1–N1–O1) of Table 1, and the most stable structures for E and Z typical conformations are AE3 and AZ4 conformers, respectively (see Fig. 3). Conformational interconversions of hydroxyimino, hydroxyamino, deprotonated forms of BHam and complexes with oxo-technetium(V) cation are presented by the integrated pathways as shown in Fig. 4. Interconversion between IZ and AZ1 is a tautomerization reaction and its transition state (TS) has been found. The reaction rate of tautomerization of $k(298.15\ \mathrm{K}) = 1.98 \times 10^{-6}$ has been obtained. The forward and backward activation energies for the tautomerization are 42.70 and 35.08 kcal/mol as indicated in Fig. 5.

Table 3
Relative energies of BHam conformers derived from their total energies at different theoretical levels

Conformer/methods	ΔE[a]				
Hydroxyimino conformers	*IE*	*IZ*			
HF/STO-3G	0.00	4.23			
HF/3-21G	0.00	5.79			
HF/6-31G(D)	0.00	7.03			
B3LYP/6-31G(D)	0.00	6.43			
Hydroxamino conformers	*AE1*	*AE2*	*AE3*	*AE4*	*AE5*
HF/STO-3G	17.76	13.53	13.40	12.32	15.46
HF/3-21G	20.63	18.97	11.30	17.44	17.27
HF/6-31G(D)	15.84	15.23	8.58	13.14	12.19
B3LYP/6-31G(D)	16.11	15.76	9.71	14.02	12.49
	AZ1	*AZ2*	*AZ3*	*AZ4*	*AZ5*
HF/STO-3G	16.32	14.43	13.40	12.32	12.32
HF/3-21G	19.24	16.94	16.65	14.10	15.52
HF/6-31G(D)	13.32	12.52	11.95	9.73	10.60
B3LYP/6-31G(D)	14.06	13.87	10.61	8.56	11.87

[a] Relative energies compared to energy of IE conformer (most stable species), all energies have been corrected for ZPE at specified levels of theory, in kcal/mol.

Table 4
Data for most stable neutral BHam conformer (IE form) optimized at different energy levels

Structural data	Exp[a]	HF/STO-3G	HF/3-21G	HF/6-31G(d)	B3LYP/6-31G(d)
Neutral form					
Bond distances (Å)					
N1–O1	1.435	1.465	1.416	1.390	1.420
N1–C1	1.290	1.270	1.290	1.260	1.290
O1–H3	–	0.960	0.990	0.940	0.960
N2–H1	–	0.990	1.020	0.990	1.010
N2–H2	–	0.990	1.020	0.990	1.000
N2–C1	1.356	1.270	1.440	1.480	1.370
C1–C2	1.482	1.480	1.500	1.390	1.480
C2–C3	1.393	1.380	1.390	1.380	1.400
C3–C4	1.381	1.380	1.380	1.380	1.390
C4–C5	1.370	1.380	1.380	1.380	1.390
C5–C6	1.378	1.380	1.380	1.380	1.390
C6–C7	1.395	1.380	1.380	1.380	1.390
C2–C7	1.386	1.380	1.390	1.390	1.400
Bond angles (°)					
N2–C1–C2	118.5	117.785	117.380	117.260	119.24
N1–C1–C2	117.1	117.720	118.480	118.070	117.210
N1–C1–N2	124.4	124.490	124.030	124.620	123.520
C1–N1–O1	109.8	108.680	110.370	111.040	109.110
C1–C2–C3	119.8	120.560	120.690	120.480	121.380
C2–C3–C4	120.6	120.150	120.270	120.41	120.653
C3–C4–C5	119.0	120.060	120.160	120.19	120.140
Dihedral angles (°)					
N2–C1–C2–C3	36.8	30.480	17.640	30.330	31.760
C1–N1–O1–H3	–	173.910	179.860	179.990	179.720
N2–C1–N1–O1	4.4	2.830	4.410	4.500	0.770
N1–C1–N2–H1	–	−0.790	−15.160	−11.94	−18.540
N1–C1–N2–H2	–	−160.860	−133.490	−146.700	−167.870

[a] X-ray data from Ref. [7].

The transition structure for the tautomerization has been confirmed by the imaginary frequency of $-1842.58\ \mathrm{cm}^{-1}$ of the molecular vibration. The standard enthalpy, Gibbs free energy, entropy change and equilibrium constant of interconversion reactions of BHam conformers derived from the B3LYP/6-31G(d) calculations are tabulated in Table 2.

The relative energies of neutral BHam conformers compared to IE (the most stable conformer) were derived from the total energies at different theoretical levels as shown in Table 3. The structural data for IE conformer obtained by geometry optimizations at different methods of calculations are shown in Table 4. As comparison of the most accurate structural data, the B3LYP/6-31G(d) optimized geometry of IE conformer shows the bond distances, bond angles and dihedral angles that are close to the X-ray structural data [7] as 1.420/1.435 Å for N1–O1, 1.290/1.290 Å for N1–C1, 1.37/1.356 Å for N2–C1 bonds, 119.24/118.5° for N2–C1–C2 bond angle and 31.760/36.8° for N2–C1–C2–C3 dihedral angle. The geometrical data for the most stable deprotonated form BHam of either HF/STO-3G, HF/3-21G, HF/6-31G(d) or B3LYP/6-31G(d) optimized structures are not much different as reported in Table 5. The N1–C1, C2–C3 bonds, N2–C1–C2, N1–C1–N2 bond angles

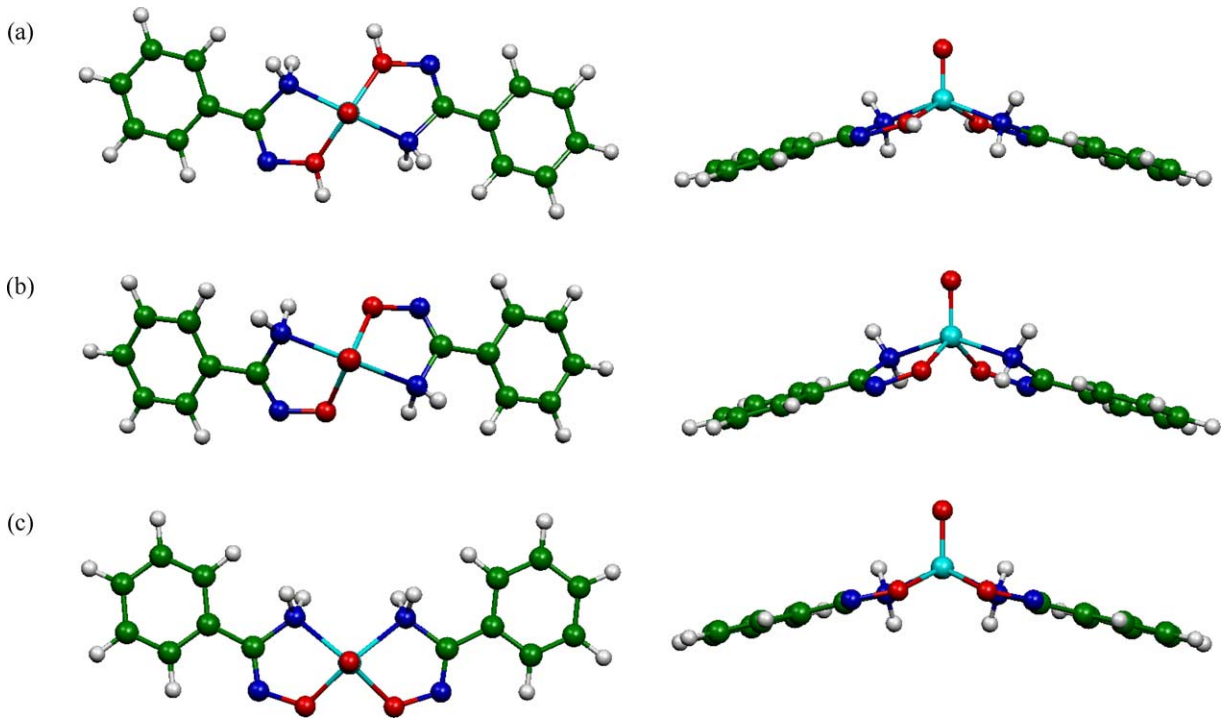

Fig. 6. Top and side views of HF/3-21G optimized structures of oxo-Tc(V) complexes with (a) hydroxyimino tautomer, (b) deprotonated BHam C_2 conformer and (c) C_{2v} conformer.

and N1–C1–N2–H1 dihedral angle of the B3LYP/6-31G(d) optimized structure are obviously different from the others. However the structural data obtained from the calculations are quite different from the X-ray crystallographic data which belongs to the crystal structure of neutral BHam. Nevertheless, data for B3LYP/6-31G(d) optimized structure of IE conformer is in best agreement with X-ray geometrical data. The HF/3-21G optimized structure of oxo-Tc(V) complexes with neutral, protonated Bham in forms of $[(LH)_2TcO]^{+3}$, $[L_2TcO]^+$ of C_2 and $[L_2TcO]^+$ of C_{2v} conformers as shown in Fig. 6, are also compared to the X-ray structural data of BHam as shown in Table 6. The relation of all reactions and the corresponding energies can be presented as the reaction pathways as shown in Fig. 7.

The reaction energies of deprotonation and preorganization of different forms of BHam and complexation of various BHam conformers derived from the HF/3-21G calculation with correction for ZPE are reported in Table 7. These reaction energies are related as a following formula:

$$\Delta E^n_{\text{binding}} = \Delta E^n_{\text{complex}} + 2\Delta E^n_{\text{preorg.,L}} + \Delta E^n_{\text{preorg.,M}}$$

where $\Delta E^n_{\text{binding}}$ and $\Delta E^n_{\text{complex}}$ are the binding and complexation energies of the nth complex formation between two identical species of BHam and one TcO^{3+} ion. $\Delta E^n_{\text{preorg.,L}}$ and $\Delta E^n_{\text{preorg.,M}}$ are the preorganization energies of the nth BHam and the nth TcO^{3+} ion, respectively. Thermodynamic properties of complexation of two different BHam conformers and TcO^{3+} ion, derived from HF/3-21G calculation with correction for ZPE are

Table 5
Data for deprotonated BHam conformer optimized at different energy levels

Structural data	Exp[a]	HF/STO-3G	HF/3-21G	HF/6-31G(d)	B3LYP/6-31G(d)
Bond distances (Å)					
N1–O1	1.435	1.373	1.370	1.283	1.305
N1–C1	1.290	1.280	1.280	1.283	1.330
N2–H1	–	1.010	1.010	1.000	1.030
N2–H2	–	1.010	1.010	1.000	1.020
N2–C1	1.356	1.440	1.440	1.430	1.430
C1–C2	1.482	1.450	1.450	1.460	1.440
C2–C3	1.393	1.390	1.390	1.390	1.410
C3–C4	1.381	1.380	1.380	1.380	1.390
C4–C5	1.370	1.380	1.380	1.380	1.390
C5–C6	1.378	1.390	1.390	1.390	1.400
C6–C7	1.395	1.370	1.370	1.370	1.380
C2–C7	1.386	1.400	1.400	1.410	1.420
Bond angles (°)					
N2–C1–C2	118.5	117.600	117.600	118.560	120.330
N1–C1–C2	117.1	121.290	121.290	119.972	120.170
N1–C1–N2	124.4	121.060	121.060	121.410	119.470
C1–N1–O1	109.8	115.220	115.220	117.740	115.503
C1–C2–C3	119.8	121.240	121.150	121.260	121.370
C2–C3–C4	120.6	121.060	120.890	121.380	121.440
C3–C4–C5	119.0	120.780	120.760	120.980	121.060
Dihedral angles (°)					
N2–C1–C2–C3	36.8	5.810	5.810	4.200	3.040
N2–C1–N1–O1	4.4	2.040	2.040	2.590	3.210
N1–C1–N2–H1	–	13.350	13.350	9.900	−2.776
N1–C1–N2–H2	–	−101.520	−89.850	−101.620	−115.330

[a] X-ray data from Ref. [7].

Table 6
Data for BHam structure in $[(LH)_2TcO]^{3+}$, $[L_2TcO]^{+}$ (C_2) and $[L_2TcO]^{+}$ (C_{2v}) complexes optimized at HF/3-21G level of theory

Structural data	Exp[a]	$[(LH)_2TcO]^{3+}$	$[L_2TcO]^{+}$ (C_2)	$[L_2TcO]^{+}$ (C_{2v})
Bond distances (Å)				
N1–O1	1.435	1.556	1.430	1.427
N1–C1	1.290	1.280	1.250	1.250
O1–H3	–	0.970	–	–
N2–H1	–	1.020	1.010	1.010
N2–H2	–	1.020	1.010	1.010
N2–C1	1.356	1.490	1.480	1.490
C1–C2	1.482	1.430	1.470	1.470
C2–C3	1.393	1.400	1.380	1.380
C3–C4	1.381	1.370	1.380	1.380
C4–C5	1.370	1.390	1.380	1.380
C5–C6	1.378	1.380	1.380	1.380
C6–C7	1.395	1.370	1.370	1.370
C2–C7	1.386	1.400	1.390	1.390
Bond angles (°)				
N2–C1–C2	118.5	119.040	118.480	118.260
N1–C1–C2	117.1	122.140	123.180	124.110
N1–C1–N2	124.4	118.810	118.320	117.620
C1–N1–O1	109.8	108.650	114.720	115.730
C1–C2–C3	119.8	121.390	121.430	122.040
C2–C3–C4	120.6	119.670	120.010	120.280
C3–C4–C5	119.0	119.800	120.040	119.880
Dihedral angles (°)				
N2–C1–C2–C3	36.8	25.330	12.800	0.100
C1–N1–O1–H3	–	178.120	–	–
N2–C1–N1–O1	4.4	9.960	0.330	−2.580
N1–C1–N2–H1	–	102.010	109.910	117.330
N1–C1–N2–H2	–	−143.630	−129.469	−125.630

[a] X-ray data from Ref. [7].

reported in Table 8. The complex formations of $[(LH)_2TcO]^{+3}$, $[L_2TcO]^{+}$ of C_2, $[L_2TcO]^{+}$ of C_{2v} are the spontaneous reactions of which ΔG^o are −605.56, −1197.7 and −1175.26 kcal/mol, respectively. Their formations are

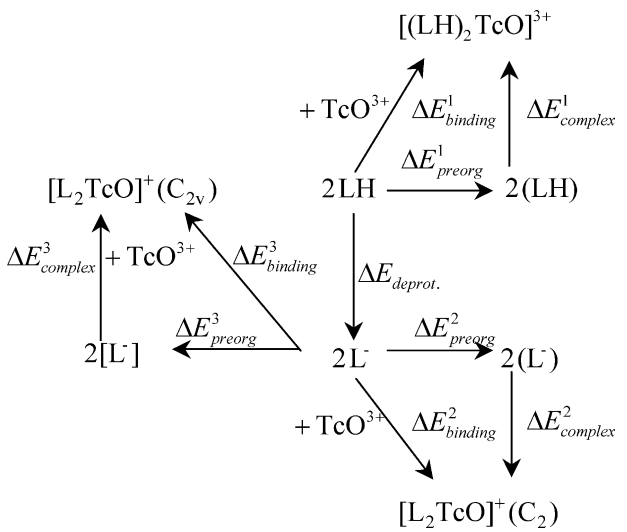

Fig. 7. Deprotonation, preorganization of the most stable conformers of Bham and their oxo-Tc(V) complexes.

Table 7
Reaction energies of deprotonation and preorganization of different forms of BHam and complexation with oxo-Tc(V) ion, derived from the HF/3-21G calculations with correction for ZPE

Reactions		Relative energies[a]
		HF/3-21G
Deprotonation:		
	$LH \overset{\Delta E_{preorg}}{\rightleftharpoons} L^- + H^+$	383.05
Preorganization:		
Neutral BHam	$LH \overset{\Delta E^1_{preorg}}{\rightleftharpoons} (LH)$	28.71
Deprotonated Bham C_2	$L^- \overset{\Delta E^2_{preorg}}{\rightleftharpoons} (L^-)$	22.51
Deprotonated Bham C_{2v}	$L^- \overset{\Delta E^3_{preorg}}{\rightleftharpoons} [L^-]$	22.73
TcO^{3+} in $[(LH)_2\ TcO]^{3+}$	$TcO^{3+} \overset{\Delta E^{1'}_{preorg}}{\rightleftharpoons} (TcO^{3+})$	0.68
TcO^{3+} in $[L_2\ TcO]^{+}$ (C_2)	$TcO^{3+} \overset{\Delta E^{2'}_{preorg}}{\rightleftharpoons} \{TcO^{3+}\}$	3.40
TcO^{3+} in $[L_2\ TcO]^{+}$ (C_{2v})	$TcO^{3+} \overset{\Delta E^{3'}_{preorg}}{\rightleftharpoons} [TcO^{3+}]$	2.55
Complexations:		
Neutral Bham	$2LH + TcO^{3+} \overset{\Delta E^1_{binding}}{\rightleftharpoons} [(LH)_2TcO]^{3+}$	−568.58
	$2(LH) + (TcO^{3+}) \overset{\Delta E^2_{complex}}{\rightleftharpoons} [(LH)_2TcO]^{3+}$	−626.68
Deprotonated BHam C_2 conformer	$2L^- + TcO^{3+} \overset{\Delta E^1_{binding}}{\rightleftharpoons} [L_2TcO]^{+}$	−1170.07
	$2(L^-) + (TcO^{3+}) \overset{\Delta E^2_{complex}}{\rightleftharpoons} [L_2TcO]^{+}$	−1218.48
Deprotonated BHam C_2v conformer	$2L^- + TcO^{3+} \overset{\Delta E^1_{binding}}{\rightleftharpoons} [L_2TcO]^{+}$	−1147.40
	$2[L^-] + (TcO^{3+}) \overset{\Delta E^2_{complex}}{\rightleftharpoons} [L_2TcO]^{+}$	−1195.41

[a] in kcal/mole.

all exothermic reactions of which ΔH^o are −627.17, −1219.38 and −1196.20 kcal/mol, respectively. Table 9 shows the selected vibrational frequencies and their corresponding intensities of hydroxyimino, hydroxyamino tautomers, deprotonated conformer of BHam. Due to the frequency calculations of these three most interesting conformers, the same mode of OH stretching vibration in IE (3782 cm^{-1}), IZ (3767 cm^{-1}) and its most stable tautomer AZ1 (3610 cm^{-1}) result that their corresponding vibration intensity ratio of IE to IZ and IZ to AZ1 are approximately 1.4:1.0 and 5.0:1.0, respectively.

Table 8
Thermodynamic properties of complexation between two different BHam conformers and TcO^{3+} ion, derived from HF/3-21G calculations with correction for ZPE

Reactions	$\Delta H^{o,a}$	$\Delta G^{o,a}$	$\Delta S^{o,b}$
Neutral conformer $LH + TcO^{3+} \rightleftharpoons [(LH)_2TcO]^{3+}$	−627.17	−605.56	−0.0746
Deprotonated C_2 conformer[c] $L + TcO^{3+} \rightleftharpoons [L_2TcO]^{+}$	−1219.38	−1197.70	−0.0727
Deprotonated C_2v conformer[d] $L + TcO^{3+} \rightleftharpoons [L_2TcO]^{+}$	−1196.20	−1175.26	−0.0702

[a] In kcal/mole.
[b] In kcal/mole K.
[c] Conformer in Fig. 6(b).
[d] Conformer in Fig. 6(c).

Table 9
Selected vibrational frequencies (in cm^{-1}) and intensities (km mol^{-1}) of hydroxyimino, hydroxyamino tautomers, deprotonated conformer of BHam

Species	Imaginary frequency	ν_{OH} (st.)	I_{OH} (st.)	ν_{OH} (st.)	I_{OH} (st.)	ν_{OH} (b)	I_{OH} (b)	ν_{CN} (b)	I_{CN} (b)
Hydroxyimino conformers									
IE[a]	–	3782	83	3727	36	1365	77	960	110
IZ	–	3767	57	3668	14	1367	3.7	969	29.8
TS	−1842.58i	3647	7.6	3464	1.4	1369	4.58	978	1.8
Hydroxyamino tautomers									
AE1	–	3618	8.2	3494	4.0	1368	1.3	977	1.2
AE2	–	3716	38	3522	5.5	1365	2.6	978	1.9
AE3	–	3723	48	3499	7.9	1366	0.6	982	1.0
AE4	–	3727	24	3496	2.7	1365	0.9	972	0.5
AE5	–	3561	2.2	3508	7.4	1367	1.7	981	1.1
AZ1	–	3610	3.8	3498	6.7	1367	2.8	975	0.6
AZ2	–	3724	38	3509	9.6	1365	0.8	973	1.3
AZ3	–	3574	13	3528	5.4	1350	9	972	0.6
AZ4	–	3527	21.6	3526	3.6	1350	6.8	980	1.5
AZ5		3731	26.1	3500	8.3	1364	1.2	973	0.3
deprotonated conformer									
L^-	–	–	–	3422	13.9	–	–	853	37.5

4. Conclusions

The two hydroxyimino and ten hydroxyamino conformers of BHam have been obtained by the PES method with B3LYP/6-31G(d) calculations. The tautomerization between hydroxyimino and hydroxyamino conformers is an endothermic reaction, with $\Delta H^o = 7.38$ kcal/mole and its equilibrium constant of $K = 1.98 \times 10^{-6}$ at 298.15 K. The B3LYP/6-31G(d) optimized structure of hydroxyimino tautomer of BHam is the most stable species and shows good agreement with X-ray geometry data. The geometries of technetium complexes existing as $[(LH)_2TcO]^{+3}$, $[L_2TcO]^+$ of C_2, $[L_2TcO]^+$ of C_{2v} conformers and their stabilization energies have been determined by the HF/3-21G calculation. The $[L_2TcO]^+$ of C_2 conformer is the most stable complex species that should be dominant species existing in the radiopharmaceutical reagent.

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