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Prediction of spectral (IR and UV-Vis) and structural properties of active substance 3-(carboxymethyl)-3-hydroxypentanedioic acid (CMHPDA) and its complex with gallium-67 radioisotope ^{67}Ga-3-(carboxylatomethyl)-3-hydroxypentanedionate (^{67}Ga-CMHPDA)

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Abstract: During the present research study, the structural, spectral, electronic and optical properties of the 3-(carboxymethyl)-3-hydroxypentanedioic acid (CMHPDA) molecule and its complex with gallium-67 radioisotope ^{67}Ga-CMHPDA are investigated by density functional theory (DFT) computations with B3LYP/6-31+G(d,p) method in gas phase at room temperature. The gallium-67 radioisotope is calculated by Lanl2DZ level of theory. The natural bond orbital (NBO) population analysis is used to understanding the nature of bonds in the designed nuclear compound. The quantum chemical properties such as frontier molecular orbitals (HOMO and LUMO) energy and the energy gap are also calculated and studied. The theoretical electronic spectrum of gallium-67-CMHPDA gives bands at 270, 283 and 289 nm.

Keywords: CMHPDA, DFT study, Gallium-67 radionuclide, Nuclear medicine, Radiopharmaceutical, Reactivity, Stability..

Introduction

Medicinal radio-compounds or radiopharmaceuticals are a group of pharmaceutical drugs which have radioactivity [1]. The nuclear medicines can be used as diagnostic and therapeutic agents [2-4]. Radiopharmaceuticals emit radiation themselves, which is different from contrast media which absorb or alter external electromagnetism or ultrasound [5-8]. The main group of these compounds is the radioisotopes used to diagnose dysfunction in body tissues [9]. The imaging field has changed completely over the past few years and molecular imaging has dramatically become more important for diagnostic purposes in the medical world [10].

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A radiopharmaceutical or nuclear medicine makes molecular processes in the body visible to detect diseases processes early and enable a targeted treatment [11-13]. The techniques like positron emission tomography (PET) or single photon emission computer tomography (SPECT) cover this area [14-16]. These techniques are also able to illustrate tumor metabolism, that being a tumor's response to specific treatment, much sooner than a computed tomography (CT) or magnetic resonance imaging (MRI) [17-20].

A gallium imaging (also called gallium scan) is a type of nuclear medicine test that uses either a gallium-67 (^{67}Ga) or gallium-68 (^{68}Ga) radiopharmaceutical to obtain images of a specific type of tissue, or disease state of tissue [21-23]. The gamma emission of gallium-67 is imaged by gamma camera, while the positron emission of gallium-68 is imaged by positron emission tomography (PET) technique [24]. In the

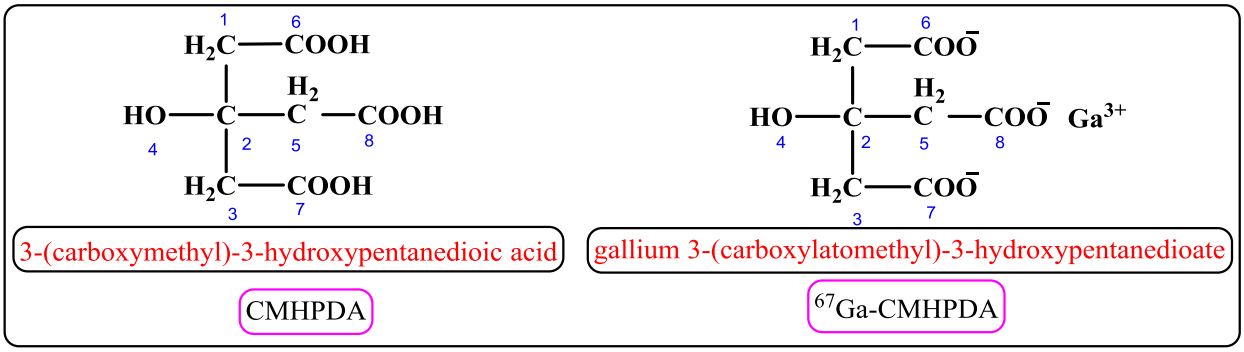
past, the gallium scan was the gold standard for lymphoma staging, until it was replaced by PET using fludeoxyglucose (FDG) [25]. Gallium imaging is still used to image inflammation and chronic infections and it still sometimes locates unsuspected tumors as it is taken up by many kinds of cancer cells in amounts that exceed those of normal tissues. Thus, an increased uptake of gallium-67 may indicate a new or old infection, an inflammatory focus from any cause, or a cancerous tumor [26-28]. It has been suggested that gallium may bind to lactoferrin (it is contained within leukocytes) and be transported to sites of inflammation, or binds to lactoferrin released during bacterial phagocytosis at infection sites and remains due to binding with macrophage receptors [29]. Gallium-67 also attaches to the siderophore molecules of bacteria themselves, and for this reason can be used in leukopenic patients with bacterial infections (here it attaches directly to bacterial proteins, and leukocytes are not needed). Uptake is thought to be associated with a range of tumor properties including transferring receptors, anaerobic tumor metabolism and tumor perfusion and vascular permeability [30]. Gallium-67 citrate injection is a most important member of this group of radiopharmaceuticals. This nuclear medicine is used to help doctors in diagnosis of various types of cancer such as Hodgkin's disease, lymphoma, or lung cancer [31-33]. Finding of new gallium-67 attached radiopharmaceuticals can be helped us more in detecting of these diseases. The active substance 3-(carboxymethyl)-3-hydroxypentanedioic acid (CMHPDA) is a chemical compound similar to citric acid. So, its gallium-67 radiopharmaceutical can be a good analogue of gallium-67 citrate nuclear medicine with novel properties. Here, prediction of spectral and structural properties, reactivity and stability of gallium-67-CMHPDA will be performed by theoretically methods.

Results and discussion

Scheme **1** shows the molecular structure of 3-(carboxymethyl)-3-hydroxypentanedioic acid (CMHPDA) molecule and its complex with gallium-67 radioisotope ^{67}Ga-CMHPDA. During the present study, the structural and spectral (IR, UV-Vis and CD) properties, reactivity and stability of the mentioned compounds are discussed. It is necessary to say that all our findings have been done based on the theoretically methods.

Structural properties of CMHPDA and ^{67}Ga-CMHPDA compounds:

The 3-(carboxymethyl)-3-hydroxypentanedioic acid (CMHPDA) and ^{67}Ga-3-(carboxylatomethyl)-3-hydroxypentanedionate (^{67}Ga-CMHPDA) compounds were optimized by B3LYP/6-31+G(d,p) computational method. The Lanl2DZ basis set was used to compute the gallium atom.



Scheme 1: The molecular structures of CMHPDA compound and its complex with gallium-67 radionuclide.

The optimized structures have been shown in Figure **1**. The bond lengths, bond angles and bond orders (B.O.) data of CMHPDA molecule and its complex with gallium-67 radionuclide (^{67}Ga-CMHPDA) have been listed in Table **1**. The C1-C2 and C1-C6 bond lengths of the CMHPDA molecule are 1.556 Å and 1.513 Å, while these bond lengths in the ^{67}Ga-CMHPDA complex are 1.592 Å and 1.538 Å. When the CMHPDA molecule is labeled with gallium-67 radionuclide, the C1-C2 bond length increases and C1-C6 bond length decreases. The bond orders data shows that the C1-C2 bond of the CMHPDA molecule is stronger than the ^{67}Ga-CMHPDA compound. In

contrast, the C1-C6 bond is strong in the CMHPDA molecule.

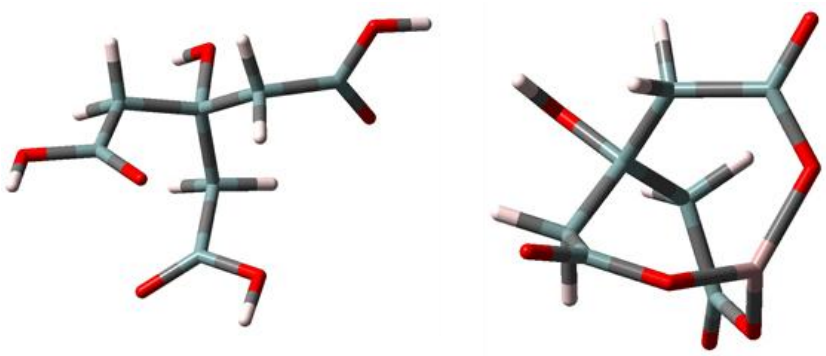


Figure 1: The optimized structures of CMHPDA compound and its complex with gallium-67 radionuclide.

Table 1: Bond lengths, bond angles and bond orders data of CMHPDA compound and its complex with gallium-67 radionuclide.

Bonds	Bond length (Å)		Bond order (B.O.)		Bond angle	Angle (degree)	
	CMHPDA	^{67}Ga-CMHPDA	CMHPDA	^{67}Ga-CMHPDA		CMHPDA	^{67}Ga-CMHPDA
C1-C2	1.556	1.592	0.969	0.971	C2-C1-C6	116.091	121.920
C1-C6	1.513	1.538	0.982	0.976	C1-C6=O6	124.638	121.898
C2-O4	1.436	1.438	0.926	0.939	C1-C6-O6	112.752	117.331
O4-H	0.967	0.969	0.731	0.727	O6=C6-O6	122.608	120.743
C1-H	1.095	1.090	0.900	0.878	C1-C2-C5	112.319	114.726
C6=O6	1.215	1.206	1.748	1.791	C1-C2-O4	107.766	105.325
C6-O6	1.351	1.361	1.062	1.037	H-C1-H	109.746	105.457
O6-H	0.973	-	0.695	-	C6-O6-Ga	-	118.387
O6-Ga	-	1.762	-	0.410	O6-Ga-O8	-	116.775

Also, we can see that the C6=O6 and C6-O6 bond lengths decreases and increases, respectively, when the molecule make complex with gallium-67 radioisotope. On the other hand, the O-Ga-O bond angle (116.8 degree) indicates angle deviation 3.2 degree from the planar triangular structure, because the CMHPDA molecule is a tridentate ligand. So, the gallium core of the ^{67}Ga-CMHPDA compound doesn't show the planar geometry.The natural bond orbitals (NBOs) population analysis data have been listed in Table **2**.

Table 2: Natural bond orbitals (NBOs) analysis data of ^{67}Ga-CMHPDA compound**.**

Bonds	Occupancy	Population/Bond orbital/Hybrids
σ(Ga-O6)	1.93108	8.53% Ga ($sp^{2.24}$), 91.47% O6 ($sp^{3.45}$)
σ(C6=O6)	1.99526	34.24% C6 ($sp^{1.93}$), 65.76% O6 ($sp^{1.39}d^{0.01}$)
π(C6=O6)	1.98790	31.87% C6 ($sp^{99.99}d^{0.51}$), 68.13% O6 ($sp^{99.99}d^{1.13}$)
σ(C6-O6)	1.99226	31.49% C6 ($sp^{2.64}d^{0.01}$), 68.51% O6 ($sp^{1.84}$)
σ(C1-C6)	1.98336	52.05% C1 ($sp^{3.04}$), 47.95% C6 ($sp^{1.61}$)
σ(C1-C2)	1.97666	49.65% C1 ($sp^{2.81}$), 50.35% C2 ($sp^{2.80}$)

σ(C1-H1)	1.97179	64.83% C1 ($sp^{3.06}$), 35.17% H1 (s)
σ(C2-O4)	1.98879	34.38% C2 ($sp^{3.89}d^{0.01}$), 65.62% O4 ($sp^{2.42}$)
σ(O4-H4)	1.98743	75.61% O4 ($sp^{3.61}$), 24.39% H4 (s)

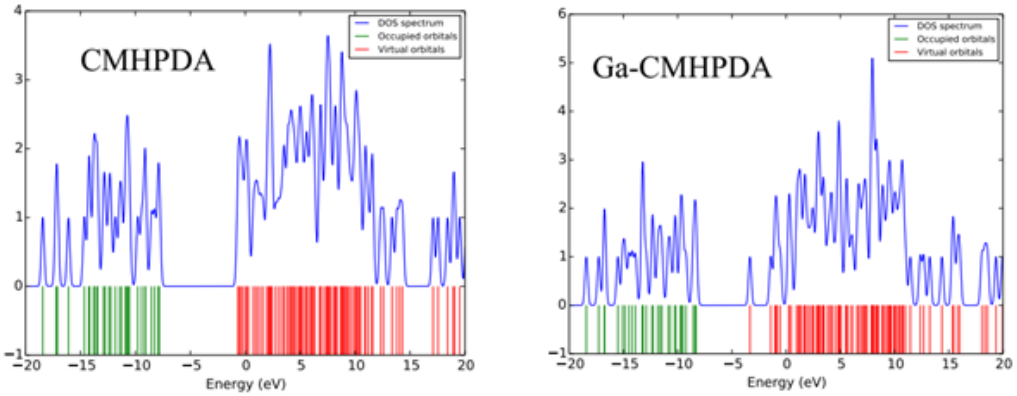


Figure 2: The density of states (DOS) graphs of CMHPDA compound and its complex with gallium-67 radionuclide.

It can be seen from the NBO data that the gallium-67 isotope participates with $sp^{2.24}$ hybrid in construction of the Ga-O bond, while we know the hybrid of an element in a planar triangular geometry is sp^2. So, the gallium core of our compound has the geometry between planar triangular and tetrahedral structures.
Table **3** shows the charges on the atoms of CMHPDA compound and its complex with gallium-67 radionuclide. The comparison between compounds indicates that the negative charges on C1 and O6 atoms reduce when the CMHPDA makes complex with gallium-67 radionuclide. In contrast, the gallium-67-CMHPDA compound has more positive charge on C6 atom than the CMHPDA molecule. Also, the H4 atom of gallium-67 labeled compound has more acidic property due to the more positive charge on this atom.

Reactivity prediction of CMHPDA and ^{67}Ga-CMHPDA compounds:

As we know the frontier molecular orbitals (FMOs) can help us in good understanding the nature of organic and inorganic chemical compounds [34-36]. The highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) are very important parameters as a measure of relative stability and reactivity [37].

Table 3: The charges on the atoms of CMHPDA compound and its complex with gallium-67 radionuclide.

Atoms	CMHPDA	^{67}Ga-CMHPDA
Ga	-	0.962
C1	-0.386	-0.165
H1	0.150	0.190
C6	0.162	0.178
=O6	-0.412	-0.375
-O6	-0.387	-0.358
C2	0.415	0.389
O4	-0.519	-0.537
H4	0.346	0.362

The energies of the frontier molecular orbitals of the CMHPDA molecular structure and its complex with gallium-67 radioisotope have been listed in Table **4**. A large HOMO-LUMO energy gap has been associated

with high stability of structures. It can be seen from the data that the amount of this energy for the CMHPDA and gallium-67-CMHPDA compounds is 7.15 eV and 4.97 eV, respectively. So, the gallium-67 labeled compound has more reactivity and low stability than the CMHPDA molecule. The density of states (DOS) graphs of the compounds under study show that the LUMO energy of ^{67}Ga-CMHPDA is less than the CMHPDA molecule. So, this radioisotope-labeled compound likes more the nucleophilic reactions. This happens due to the nature of gallium atom.

Table 4: The frontier molecular orbitals energies data of CMHPDA compound and its complex with gallium-67 radionuclide.

Compounds	HOMO (eV)	LUMO (eV)	GAP (eV)
CMHPDA	-7.81	-0.66	7.15
^{67}Ga-CMHPDA	-8.30	-3.33	4.97

Spectral study of CMHPDA and ^{67}Ga-CMHPDA compounds:

Chemical analysis and identification of real structure of radiopharmaceuticals are more difficult due to the low half time of the radioisotopes [38-41]. So, the theoretical spectral study of nuclear medicines can give us important information about their structures. During this part of the article, UV-Vis and IR spectra of the studied compounds will be discussed. The UV-Vis spectra of CMHPDA compound and its complex with gallium-67 radionuclide have been shown in Figure **3**.

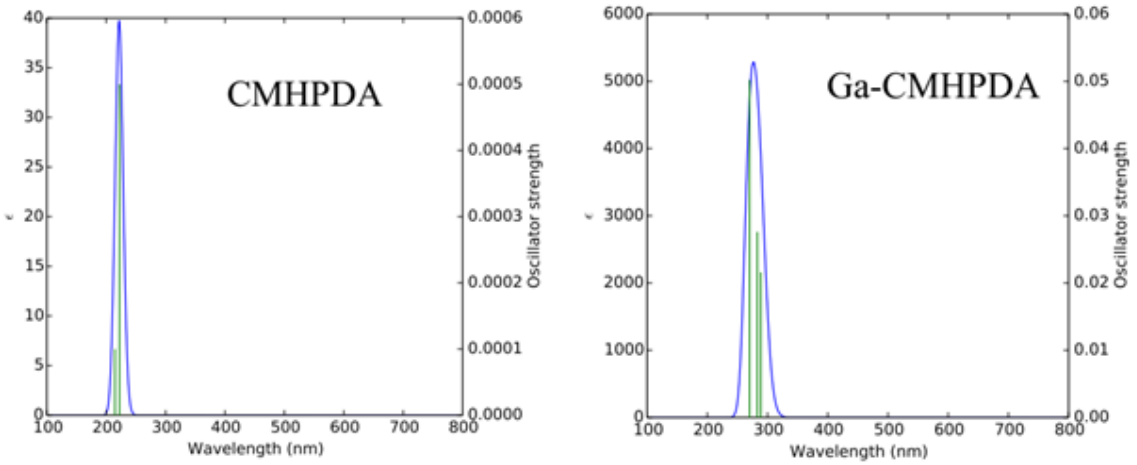


Figure 3: The UV-Vis spectra of CMHPDA compound and its complex with gallium-67 radionuclide.

CMHPDA: UV-Vis [wavelength of electronic transition (nm), energies (cm^{-1}), electronic transitions]:
a. 222.503 nm (44943.136 cm^{-1}), HOMO-1 to LUMO (27%), HOMO-1 to LUMO+1 (29%), HOMO to LUMO (11%), HOMO to LUMO+1 (12%) and HOMO-1 to LUMO+2 (5%)
b. 214.835 nm (46547.384 cm^{-1}), HOMO-2 to LUMO (55%), HOMO-2 to LUMO+1 (19%), HOMO-3 to LUMO (4%), HOMO-1 to LUMO (5%) and HOMO to LUMO (6%)
^{67}Ga-CMHPDA: UV-Vis [wavelength of electronic transition (nm), energies (cm^{-1}), electronic transitions]:
a. 288.911 nm (34612.716 cm^{-1}), HOMO to LUMO (97%)
b. 283.125 nm (35320.069 cm^{-1}), HOMO-1 to LUMO (97%)
c. 270.281 nm (36998.520 cm^{-1}), HOMO-2 to LUMO (93%)

Figure **4** shows the IR spectra of the molecular structures under study. Here, the main harmonic frequencies (cm^{-1}) of the structures are discussed.
CMHPDA: 25.023, 40.972, 55.080, 74.314, 88.458, 99.893, 150.340, 155.075, 187.841, 245.139, 274.604, 280.696, 326.211, 364.230, 416.145, 421.313,

453.400, 520.187, 532.800, 552.418, 586.817, 621.461, 639.710, 662.840, 683.282, 703.090, 723.091, 835.443, 893.009, 900.851, 909.932, 914.470, 935.721, 963.781, 1065.884, 1091.385, 1114.403, 1152.910, 1163.851, 1191.752, 1227.713, 1237.614, 1273.903, 1297.266, 1309.505, 1340.554, 1375.958, 1379.135, 1415.683, 1426.073, 1459.728, 1467.302, 1489.821, 1802.139, 1810.196, 1816.124, 3053.345, 3069.310, 3090.621, 3100.845, 3138.652, 3147.228, 3748.228, 3748.646, 3750.082, 3752.718, and 3810.016.

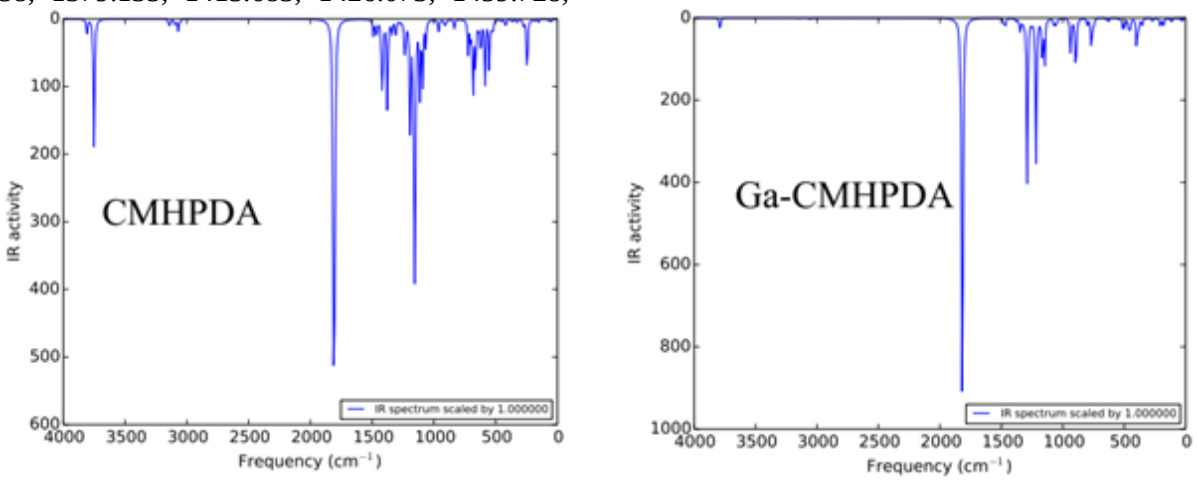


Figure 4: The IR spectra of CMHPDA compound and its complex with gallium-67 radionuclide

^{67}Ga-CMHPDA: 24.996, 38.089, 70.408, 112.077, 116.611, 135.208, 180.661, 203.167, 210.639, 265.276, 273.862, 350.654, 357.045, 381.432, 395.310, 398.740, 449.796, 461.024, 467.326, 495.169, 511.532, 547.975, 624.701, 643.580, 748.940, 762.516, 769.539, 801.236, 884.908, 892.163, 898.754, 930.049, 937.349, 938.321, 1038.698, 1055.390, 1071.477, 1146.650, 1167.153, 1216.856, 1252.626, 1289.098, 1291.394, 1317.830, 1334.706, 1347.959, 1380.844, 1464.809, 1468.826, 1479.237, 1814.261, 1818.885, 1832.316, 3043.687, 3063.084, 3066.657, 3132.598, 3143.718, 3152.839, and 3788.596.

Conclusions

Our theoretical work represents the structural and spectral properties of 3-(carboxymethyl)-3-hydroxypentanedioic acid (CMHPDA) molecule and its complex with gallium-67 radioisotope ^{67}Ga-CMHPDA. The molecular structures have been optimized in the gas phase at B3LYP/6-31+G(d,p) level of theory. The gallium-67 radioisotope was computed by Lanl2DZ level of theory. The frontier molecular orbitals (HOMO and LUMO) analysis of the structures showed that the ^{67}Ga-CMHPDA has more reactivity and low stability than the CMHPDA molecule. The theoretical electronic spectrum of gallium-67-CMHPDA gives bands at 270, 283 and 289 nm.

Computational method

During present research, all calculations were performed with using the Gaussian 03 [42] and Gauss View 5.0.8 molecular modeling software. Also, GaussSum 3.0 and ChemBioDraw Ultra 13.0 programs have been used to draw the molecular structures and their spectra. All computations performed with B3LYP functional and 6-31+G(d,p) basis set of theory. The Lanl2DZ basis set was used for the gallium-67 radionuclide. The computations were done in the gas phase at room temperature. It wasn't shown any imaginary frequency in IR computation for the molecular structures. It proves accuracy of our computations.

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