Geometry, tautomerism and non-covalent interactions of the drug halofuginone with carbon-nanotubes and γ-Fe₂O₃ nanoparticles: A DFT study

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Abstract: Halofuginone is a potential anti-malarial drug, which could exist as three possible tautomers. Herein, using density functional theory (DFT), and handling the solvent effects with the PCM model, the tautomerism of halofuginone was investigated. Intramolecular H-bonds play an important role in the stability of the tautomers. The conformer H₁a is the most stable. Non-covalent interactions of the H₁a conformer with the armchair (5,5) single-wall carbon nanotubes and γ-Fe₂O₃ nanoparticles were explored in several manners. The most stable form of them was determined. The intermolecular H-bonds play a substantial role in the energy behavior of the interaction between γ-Fe₂O₃ nanoparticles and halofuginone.

Keywords: halofuginone; DFT; PCM; tautomerism; γ-Fe₂O₃ nanoparticles; carbon nanotubes.

INTRODUCTION

In the 1960s, a number of analogues of febrifugine, such as halofuginone, were synthesized in the USA.1–4 Halofuginone is a synthetic derivative of quinazolinone alkaloid febrifugine. Febrifugine has been used to treat fever and malaria for more than 2000 years. In 1967, the drug halofuginone was designed and synthesized by the American Cyanamid Company. Its commercial name is stenorol.5,6

Halofuginone is used as an anti-coccidial feed additive,7,8 and was specifically shown to be an effective drug in malaria, cancer, fibrosis and inflammatory diseases.9–11

Nowadays, DFT methods are comprehensively used in many areas of computational chemistry, such as geometry optimization, spectroscopic assignments, drug science, investigations on the kinetics and mechanism of the chemical reactions, etc.12–23 To date, the geometry and crystal structure of halofuginone

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have not been determined and therefore, a comprehensive computational investigation on the properties of halofuginone is of major importance. In this work, the molecular geometry and tautomers of halofuginone were investigated using valuable DFT approaches.

Because of the increasing use of nanotechnology in many areas especially in the drug delivery, exploring the interaction of nanoparticles with different molecules is of great importance. The covalent and non-covalent interactions of various molecules with the carbon nanotubes and iron-oxide nanoparticles have been theoretically investigated. Herein, the non-covalent interactions of halofuginone with the carbon nanotubes and γ-Fe₂O₃ nanoparticles were theoretically explored using DFT methods.

THEORETICAL METHODS

In this work, all calculations were performed using the Gaussian 03 software package and the B3LYP functional of the density functional theory (DFT). The 6-311+G(d,p) basis set was used for an investigation of geometry optimization and tautomerism of the halofuginone molecule. Its interaction with the iron-oxide nanoparticles was investigated by employing the B3LYP and 6-31G(d) basis sets for all of the atoms except for the Fe atoms, where the LANL2DZ basis sets was used with effective core potential (ECP) functions. On the other hand, the interaction of halofuginone with a carbon-nanotube was investigated at the B3LYP/6-31G(d) level. The armchair (5,5) single wall carbon nanotube (SWCNT), comprising 150 atoms (16.6 Å length), was used.

The solvent effects in aqueous solution were considered using the sophisticated Polarized Continuum Model (PCM). All of the geometries were fully optimized. The optimized geometries were confirmed to have no imaginary frequency, except for the transition state (TS), which has only one imaginary frequency of the Hessian. Zero-point corrections were considered in the evaluation of the energies. The Chemcraft 1.7 program was used for preparation of the figures.

RESULTS AND DISCUSSION

Molecular geometry

A molecule of the halofuginone drug could exist as three possible tautomers, the geometries of which were fully optimized in aqueous solution. The H1 tautomer of halofuginone has two different conformers, H1a and H1b (Fig. 1). In the optimized geometry of H1a, there is an intramolecular hydrogen bond between the O2 and H7 atoms. Since, the H1a conformer is more stable than the H1b one.

Going from the H1a conformer to the H2 tautomer, the H7 proton transfers from C11 atom to the O2 atom of the carbonyl group via an intermolecular proton transfer (IPT). Therefore, the C10–O2 bond length increases from 121.3 to 134.2 pm, while the C10–C11 bond length reduces from 149.7 to 134.3 pm in the H2 conformer. Additionally, the hybridization of the C11 atom changes from sp³ in the H1a tautomer to sp² in the H2 tautomer. The C10–C11–C12 and
C10–C11–H6 angles are 118.8 and 107.7° for the H1a conformer, which are 125.5 and 117.9° in the H2 tautomer, respectively.

In comparison with the H1a conformer, in the H3 tautomer, the H5 proton transfers from the C9 atom to the O2 atom of the carbonyl group via an IPT. Since the C10–O2 bond length enlarges from 121.3 to 152.4 pm, the C9–C10 bond length decreases from 135.3 to 133.9 pm in the H3 tautomer. The C9–C10–C11 and C10–C11–H5 angles are 114.8 and 52.1° for the H1a conformer, which are 120.5 and 22.7° in the H3 tautomer, respectively. These angles confirm that the hybridization of the C9 atom changes from sp³ in the H1a conformer to sp² for the H3 tautomer.

In this work, the tautomerism of the halofuginone drug was investigated using valuable computational methods, which are useful in theoretical investigation of chemical reactions. The relative energies of the optimized species are gathered in Table I. As could be seen, the H1a species is the most stable tautomer of halofuginone in aqueous solution.

There are three different tautomeration reactions for the three tautomers of halofuginone. The transition states of the H1a → H2, H1a → H3 and H2 → H3 tautomerization reactions are named as TSH1a-H2, TSH1a-H3 and TSH2-H3, respectively. In aqueous solution, the Gibbs energy change (ΔG) difference between the most stable conformer H1a with the H2 and H3 tautomers are 42.15 and 48.11 kJ mol⁻¹, respectively. Using the equation \( K = \exp(-\Delta G / RT) \), the amounts of the H2 and H3 tautomers were predicted to be negligible in aqueous solution.
solutions of halofuginone. The high barrier energies and large $\Delta G$ values demonstrate that conformer H1a is the kinetically and thermodynamically the most probable tautomer of halofuginone in aqueous solution.

### TABLE I. The relative energies (kJ mol$^{-1}$) and the relative Gibbs energy change (kJ mol$^{-1}$) for the tautomerization reaction of halofuginone in the PCM model

<table>
<thead>
<tr>
<th>Species</th>
<th>Relative energy</th>
<th>Relative Gibbs energy change</th>
</tr>
</thead>
<tbody>
<tr>
<td>H1a</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>H1b</td>
<td>12.26</td>
<td>19.53</td>
</tr>
<tr>
<td>H2</td>
<td>37.04</td>
<td>42.15</td>
</tr>
<tr>
<td>H3</td>
<td>42.25</td>
<td>48.11</td>
</tr>
<tr>
<td>TSH1a-H2</td>
<td>282.04</td>
<td>–</td>
</tr>
<tr>
<td>TSH1a-H3</td>
<td>257.72</td>
<td>–</td>
</tr>
<tr>
<td>TS H2-H3</td>
<td>330.61</td>
<td>–</td>
</tr>
</tbody>
</table>

**Non-covalent interactions of the halofuginone with the nanoparticles**

Nowadays, nano-compounds are useful in many areas especially in drug delivery.$^{24-32,40-43}$ Herein, the non-covalent interaction of the H1a conformer of halofuginone with a carbon-nanotube and a magnetic $\gamma$-Fe$_2$O$_3$ nanoparticles have been investigated using the DFT methods.

The armchair (5,5) single wall carbon nanotube (SWCNT) was used as a model for a carbon-nanotube. The optimized geometry of the SWCNT is shown in Fig. 2. The H1a conformer could interact with the SWCNT in different manners. Herein, two possible interactions between H1a and the SWCNT were investigated. These interactions, named as NANO-CNT1 and NANO-CNT2, optimized geometries, are shown in Fig. 3.

![Fig. 2. Optimized geometry for the investigated SWCNT.](image)

In the optimized geometry of the NANO-CNT1 form, the aromatic rings of H1a are parallel with respect to the SWCNT. The minimum distance between the H1a species and the SWCNT is about 400 pm. In the optimized geometry of the NANO-CNT2 form, the H1a is like a cap on the SWCNT. The Br and Cl substitutions are closer to the SWCNT than in the NANO-CNT1 form. The nearest atoms of the halofuginone molecule to the carbon atoms of the SWCNT are shown in Fig. 3.
The computed electronic energies for the investigated species together with the binding energies are gathered in Table II. The binding energy could be defined as:

$$\Delta E = E_{(\text{NANO-CNT}^*)} - (E_{(\text{H1a})} + E_{(\text{SWCNT})})$$

where $E_{(\text{NANO-CNT}^*)}$, $E_{(\text{H1a})}$ and $E_{(\text{SWCNT})}$ are the electronic energies of the investigated species, either NANO-CNT1 or NANO-CNT2 forms, the H1a conformer and free SWCNT, respectively.
As could be seen, the NANO-CNT2 form involves more binding energy than the NANO-CNT1 form by 1.53 kJ mol\(^{-1}\). Thus, NANO-CNT1 is the more stable and favorable form for non-covalent interaction of halofuginone with SWCNT.

TABLE II. The electronic and binding energies of the optimized geometries for the non-covalent interactions of the H1a conformer with the SWCNT in aqueous solution

<table>
<thead>
<tr>
<th>Species</th>
<th>Electronic energy, Hartree</th>
<th>Binding energy, kJ mol(^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>SWCNT</td>
<td>-4966.2215459</td>
<td></td>
</tr>
<tr>
<td>H1a conformer</td>
<td>-4041.828239</td>
<td></td>
</tr>
<tr>
<td>SWCNT+ H1a conformer</td>
<td>-9008.083114(^a)</td>
<td></td>
</tr>
<tr>
<td>NANO-CNT1</td>
<td>-9008.0843194</td>
<td>-3.16</td>
</tr>
<tr>
<td>NANO-CNT2</td>
<td>-9008.0849021</td>
<td>-4.69</td>
</tr>
</tbody>
</table>

\(^a\)Sum of electronic energies of the free SWCNT and the H1a conformer

In addition, non-covalent interaction between nano-magnetic \(\gamma\)-Fe\(_2\)O\(_3\) particles and the H1a conformer of halofuginone was investigated theoretically. Previously, a model was presented for \(\gamma\)-Fe\(_2\)O\(_3\) nanoparticles based on a Fe\(_6\)(OH)\(_{18}\)(H\(_2\)O)\(_6\) ring cluster. This model has good consistency with the experimental data, such as the vibration frequencies and bond lengths \(^{29,31,32}\) This model was employed in this research. The geometry of the used model for \(\gamma\)-Fe\(_2\)O\(_3\), shown in Fig. 4, was fully optimized.

![Fig. 4. Optimized geometry of the \(\gamma\)-Fe\(_2\)O\(_3\) nano-particle.](image)

For the investigation of the non-covalent interactions of the H1a conformer with the \(\gamma\)-Fe\(_2\)O\(_3\), the proposed geometry of this tautomer in the presence of the \(\gamma\)-Fe\(_2\)O\(_3\) was optimized in three different forms. These forms are named NANO-Fe1 to NANO-Fe3 and their optimized geometries are shown in Fig. 5. In the
NANO-Fe1 form, the H1a conformer is close to the SWCNT via the carbonyl and hydroxyl group. Three intermolecular hydrogen bonds are seen in Fig. 5. Two of them are between the oxygen atom of the drug and the hydrogen atoms of the H2O and the –OH ligands of the nano-particle. The lengths of these H-bonds are 176.9 and 214.2 pm. The remaining one is between the hydrogen atom of the hydroxyl group and oxygen atom of the –OH ligand in the nano-particle, which is a strong H-bond (174.1 pm).

Fig. 5. Optimized geometries of three possible non-covalent interactions between the H1a species and the γ-Fe2O3 nano-particle.
In the NANO-Fe2 form, contrary to the NANO-Fe1 form, the aromatic rings are far from the SWCNT. There is only a weak hydrogen bond between H37 of the –NH group in H1a and oxygen atom of the –OH ligand of the γ-Fe2O3 nano-particle. The bond length of this hydrogen bond is 203.4 pm. In the NANO-Fe3 form, the H1a molecule is close to the SWCNT via the Cl and Br substitutions on the benzene ring. As could be seen, there is no H-bond between the drug molecule and the nano-particle. The computed distance between the H1a and nano-particle is about 300 pm.

The calculated electronic energies and binding energies are listed in Table III. As could be seen, the NANO-Fe1 form is the most stable form of the three investigated forms, which involves the greatest number of intermolecular hydrogen bonds. There are three hydrogen bonds between the carbonyl and hydroxyl groups of the drug and oxygen and hydrogen atoms of the –OH and H2O ligands of the nano-particle.

TABLE III. The electronic and binding energies of the optimized geometries for the non-covalent interactions of the H1a tautomer and a γ-Fe2O3 nano-particle in aqueous solution

<table>
<thead>
<tr>
<th>Species</th>
<th>Electronic energy, Hartree</th>
<th>Binding energy, kJ mol⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Free nano-Fe2O3</td>
<td>–2654.5173599</td>
<td>–</td>
</tr>
<tr>
<td>H1a conformer</td>
<td>–4041.828239</td>
<td>–</td>
</tr>
<tr>
<td>Free nano-Fe2O3+ H1a conformer</td>
<td>–6606.0245989⁺</td>
<td>–</td>
</tr>
<tr>
<td>NANO-Fe1</td>
<td>–6606.0469129</td>
<td>–58.53</td>
</tr>
<tr>
<td>NANO-Fe2</td>
<td>–6606.0277126</td>
<td>–8.17</td>
</tr>
<tr>
<td>NANO-Fe3</td>
<td>–6606.0253233</td>
<td>–1.90</td>
</tr>
</tbody>
</table>

⁺Sum of the electronic energies of the proposed model for the γ-Fe2O3 nano-particle and the H1a tautomer

The binding energy is defined as:

\[ \Delta E = E_{(NANO-Fe^*)} - (E_{(H1a)} + E_{(Fe2O3)}) \]

where \( E_{(NANO-Fe^*)} \), \( E_{(H1a)} \) and \( E_{(Fe2O3)} \) are the electronic energies of one of the three NANO-Fe forms, the electronic energies of the H1a conformer of halo-fuginone and the optimized model for a free γ-Fe2O3 nano-particle, respectively. The NANO-Fe1 form involves three H-bonds, while the NANO-Fe2 form involves only one H-bond and the NANO-Fe3 form has no hydrogen bond. The intramolecular hydrogen bonds stabilize the investigated system. Since, the NANO-Fe1 form has the lowest energy value and the highest stability, it is the favorite model for the non-covalent interaction of the H1a conformer of halo-fuginone with a γ-Fe2O3 nano-particle. In aqueous solution, the NANO-Fe1 form is more stable than the NANO-Fe2 and NANO-Fe3 forms by 50.36 and 56.63 kJ mol⁻¹, respectively.
CONCLUSIONS

Halofuginone is a beneficial and effective drug in the therapy of the malaria, cancer, fibrosis and inflammatory disease. This drug could exist as three different tautomers that may be converted to each other via the IPT. In this work, their geometries as well as the kinetics of its tautomerization were evaluated using DFT methods. The PCM model was used for considering the solvent effects in aqueous solution.

In aqueous solution, H1 is the most stable tautomer of halofuginone, which has two different conformers, H1a and H1b. The H1a conformer involving an intramolecular H-bond is more stable than the H1b one.

Tautomerization of the H1a tautomer to each of the H2 and H3 tautomers progresses via IPT. These tautomerization reactions involve high activation energies, confirming that the H1a species is kinetically and thermodynamically the most favorable tautomer of halofuginone. The amount of the H2 and H3 tautomers is predicted to be negligible.

The non-covalent interactions between the armchair (5,5) single wall carbon nanotube (SWCNT) and H1a conformer of halofuginone were investigated in two different forms. The calculated binding energies show that the non-covalent interactions slightly stabilize the system.

Furthermore, non-covalent interactions of the H1a conformer with the magnetic γ-Fe2O3 nanoparticles in the proposed model were investigated in three different manners. All of three forms involve intermolecular hydrogen bonds in their optimized geometries. The most stable form is the NANO-Fe1 one. In the optimized geometry of the NANO-Fe1 form, there are three intermolecular H-bonds between the drug and nano-particle, two strong and one weak H-bond. The two carbonyl groups and hydroxyl group of the H1a species are engaged in these H-bonds. The NANO-Fe2 form involves only one weak H-bond between the –NH amine group of the H1a and oxygen atom of the –OH ligand of the γ-Fe2O3 nano-particle. The bond length of this H-bond is 2.03 Å. In the structure of the NANO-Fe3 form there is no intermolecular H-bond between the drug molecule and the investigated nano-particle, resulting in the most unstable form for non-covalent interaction.
молекулске H-везе имају значајну улогу у стабилизацији таутомера. H1a је најстабилнији конформер. Нековалентне интеракције конформера H1a са столичастом (5,5) једнозидном угљеничном наноцврстком и са γ-Fe2O3 наночестичом истраживане су на више начина. Одређен је њихов најстабилнији облик. Међумолекулске H-везе имају суштинску улогу у енергетском понасашању интеракције γ-Fe2O3 наночестице и халофугинона.

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