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Computational study on the conformations of gambogic acid

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ABSTRACT

The conformations of gambogic acid were studied using force fields, MM3*, AMBER*, MMFFs and OPLS2005, and B3LYP methods. In a model molecule, only the MM3* and AMBER* methods produced the same number of conformers as B3LYP, generating two conformations for rings 1 and 2, and a single conformation for rings 3 and 4. The preferred conformations of these rings are maintained in a conformer of the actual gambogic acid generated using the AMBER* and B3LYP methods. Although this calculated conformer matches well with the crystal structure, it shows that H43, C25═C26 and C30═C31 bonds may be misassigned in the crystal structure.

1. Introduction

Gambogic acid (Figure 1) is a natural product isolated from gamboge, the resin from the *Garcinia hanburryi* tree in Southeast Asia. Recently, it has been found that this molecule has potent anti-cancer activities both *in vitro* and *in vivo* [1–7]. In addition, the derivatives of gambogic acid, such as gambogic amide, may also have a potential role in treating neurodegenerative disease [8]. Due to its important biological functions, there has been interest in elucidating the chemical properties and structure of gambogic acid.

Gambogic acid is composed of several rings including an intriguing polycyclic 4-oxatricyclo-[4.3.1.0]decan-2-one system, which was also found in other products isolated from *Garcinia* sp. [9,10]. The total synthesis of several compounds that contain such a ring system was reported by Nicolaou and co-workers [11–14]. The structural analysis of gambogic acid was first reported in 1965 using NMR spectroscopy [15]. Later, in 2001, the crystal structure of gambogic acid in the form of a pyridine salt was published [16], which provides detailed three dimensional information on this molecule. Although these studies aid our understanding of the properties and structure of gambogic acid, its conformational flexibility, in particular that of the ring systems, is not clear. Recently, a study on the conformations of a similar compound, morellic acid (Figure 1), using the MMFF94 force field and the B3LYP method was reported [17]. However, the conformations of the rings were not discussed. In this study, we have performed a detailed conformational search on gambogic acid, taking care to establish which force field method was best for this task. Selected conformers were further optimized using density functional theory (DFT) and compared with the reported X-ray crystal structure.

2. Computational methods

The force field and DFT calculations were performed using the MacroModel [18] and Gaussian 09 [19] programs, respectively. For the conformational search, four force fields, MM3*, AMBER*, MMFFs and OPLS2005, as implemented in MacroModel, were used. Selected conformers generated from these force fields were further optimized using the B3LYP hybrid density functional [20–22] with the 6-31G(d,p) basis set. Frequency calculations were performed at the same level to confirm that the obtained geometries are minima on the potential energy surface and to get zero-point vibrational energy (ZPVE) corrections. Relative energies were obtained by performing single point calculations at the B3LYP/6-311+G(2df,p) level of theory based on the above optimized geometries and corrected with ZPVE obtained at the B3LYP/6-31G(d,p) level. For the model compound, geometries were also optimized using the cc-pvtz basis set [23,24]. Due to its larger size, on the actual gambogic acid molecule only the 6-31G(d,p) basis set was used for geometry optimization.

3. Results and discussion

3.1. The conformations of a model molecule

Gambogic acid (Figure 1) has several exocyclic groups which contain a number of carbon–carbon single bonds. The free rotation of these bonds results in a large number of conformers. For

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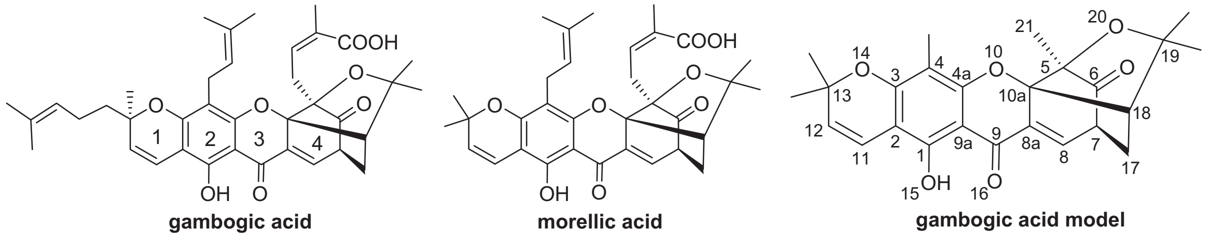

gambogic acid **morellic acid** **gambogic acid model**

Figure 1. A schematic illustration of the structures of gambogic acid, morellic acid and a simplified model of gambogic acid.

simplicity, we first substituted all the alkyl exocyclic groups by methyls (Figure 1). For this simplified model, the OPLS2005 force field yields eight conformers, while both MM3* and AMBER* yield four conformers and only two conformers were found using the MMFFs force field. In addition, some of the conformers lie very close in energy. All the conformers and their relative energies are summarized in Table 1. The minimized structures of the eight conformers obtained from the OPLS2005 field (**1**–**8**) are shown in Figure 2. The conformations of each of the rings are analyzed below.

3.1.1. Ring 1

Ring 1 can be viewed as a 2*H*-pyran derivative. Two possible conformations with C13 located on different sides of the C12–C11–C2–C3–O14 plane (Figure 3) were found with the MM3*, AMBER* and OPLS2005 force fields. Specifically, in conformation **A** C13 is below this plane while it is above the plane in **B**. We note that this also results in a different orientation of the two exocyclic methyl groups which are connected to C13 (see Figure 3). The MMFFs force field, however, yields only conformation **A**. We further verified these two conformations using the DFT method. Both of them were retained during DFT geometry optimization. Since the MMFFs force field failed to predict the two conformations for this ring, we judged it to be the least suitable of the methods we tested for describing the conformation of gambogic acid.

It should be noted that the energy difference between the two conformations of ring 1, **A** and **B**, is quite small. For example, conformer **1** lies only marginally lower in energy than **2** by 0.15–0.22 kJ mol^{-1} using the three force fields which predicted two conformations of ring 1 (Table 1). Furthermore, the energy difference between **1** and **2** further decreases to only 0.09 kJ mol^{-1} with an interconversion barrier of 1.1 kJ mol^{-1} at the B3LYP/6-311+G(2df,p)//B3LYP/6-31G(d,p) + ZPVE level of theory. Using a larger cc-pvtz basis set for geometry optimization, the energy difference between **1** and **2** slightly increases to 0.24 kJ mol^{-1} with an interconversion barrier of 0.9 kJ mol^{-1}. Hence, these two conformers lie very close in energy and should be able easily to interconvert.

3.1.2. Ring 2

Because ring 2 is aromatic, it always remains planar in the conformational searches. However, the hydrogen of the exocyclic –OH group may rotate toward ring 3 (conformation **C**, see Figure 3) or ring 1 (conformation **D**, see Figure 3). The former results in the formation of an intramolecular hydrogen bond between the exocyclic –OH and O16 and is, therefore, lower in energy. All the force fields yield these two conformations. However, the obtained relative energies are quite different. In the MM3*, AMBER* and OPLS2005 force fields, conformer **1** is 16.11–29.52 kJ mol^{-1} lower in energy than **6**. However, the difference increases to 53.3 kJ mol^{-1} in the MMFFs force field. Using the DFT method at the B3LYP/6-311+G(2df,p)//B3LYP/6-31G(d,p) + ZPVE level, the difference further increases to 61.6 kJ mol^{-1}. Hence, only the MMFFs force field gives a difference close to the DFT level. The other force fields significantly underestimate the importance of the intramolecular O–H $\cdots$ O hydrogen bond.

3.1.3. Ring 3

Ring 3 can be viewed as a ketone derivative of tetrahydropyran. Only the OPLS2005 force field yields two conformations while all the other force fields as well as the DFT method predict only one conformation. In the two conformations generated from the OPLS2005 force field, O12 and O16 are found above the aromatic plane of ring 2 (conformation **E**) or below that plane (conformation **F**), as shown in Figure 3. The former conformation lies ~3 kJ mol^{-1} lower in energy than the latter. However, only **E** was found using all the other force fields and the DFT method. Hence, the OPLS2005 force field failed to predict correctly the single conformation of this ring, but did find **E** to be the lowest energy conformation. It should be noted that at the B3LYP/6-31G(d,p) level, the C9–C8a–C10a–O10 and C4a–C9a–C9–O16 dihedral angles are 2.2° and 179°, respectively. Thus, ring 3 is almost planar.

3.1.4. Ring 4

For simplicity, we break ring 4 into three sub-rings: C10a–C8a–C8–C7–C6–C5, C10a–C8a–C8–C7–C17–C18 and C10a–C18–C19–O20–C5. All the force fields as well as DFT agree on the conformations of these three sub-rings. The two six-membered rings C10a–C8a–C8–C7–C6–C5 and C10a–C8a–C8–C7–C17–C18 can be viewed as cyclohexene derivatives and are both in boat conformations. The five-membered ring C10a–C18–C19–O20–C5 is a tetrahydrofuran derivative with the four atoms C18–C19–O20–C5 all in the same plane. The remaining carbon C10a lies above this plane, i.e., on the same side as the exocyclic methyl carbon C21.

It is necessary to compare the overall behavior of the four force fields on the conformational search of the model compound. The MM3* and AMBER* yield the same number of conformers as the DFT method. The MMFFs and OPLS2005 force fields, however, predict either fewer or more conformers. Thus, the conformational search for the actual gambogic acid molecule was performed using the MM3* and AMBER* force fields.

3.2. The conformation of gambogic acid

The carboxylic group of gambogic acid was chosen to be ionized as $-\text{COO}^-$ to match physiological conditions. Because this molecule contains several flexible alkyl groups, many conformers were found. For example, within a relative energy of 100 kJ mol^{-1}, 930 and 856 conformers were found using the AMBER* and MM3* force fields, respectively. Most of them correspond to the free rotation of exocyclic alkyl groups. It is not necessary to discuss all of these conformers. Only the lowest energy conformers and selected higher energy ones (Figure 4) are discussed in this Letter.

Notably, the AMBER* and MM3* force fields predict different lowest energy conformers. Specifically, the lowest energy AMBER* conformer (**A1**) has the –OH group of ring 2 hydrogen bonded with the side chain carboxylic acid group, while the lowest energy MM3* conformer (**M1**) has that –OH group hydrogen bonded with