Research Article

16 α -Hydroxyfriedelin and 3-Oxo-16-methylfriedel-16-ene as Building Blocks: Crystal Structure and Hirshfeld Surfaces Decoding Intermolecular Contacts

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Received 30 April 2013; Accepted 13 August 2013

Academic Editors: L. R. Gomes and P. R. Raithby

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In this paper the importance of C–H...O intermolecular hydrogen bonds and van der Waals forces in crystal packing stabilization of 16 α -hydroxyfriedelin (**1**) and 3-oxo-16-methylfriedel-16-ene (**2**) is described. Compound **1** is a natural product isolated from the hexane extract of *Salacia elliptica* branches, whereas compound **2** is obtained from compound **1** after dehydration accompanied by methyl migration of C-17 to C-16. The single-crystal X-ray diffraction experiments for **1** and **2** were carried out at 150 K, and the crystallographic study demonstrated that these compounds crystallize in noncentrosymmetric space groups, with **1** showing an orthorhombic P2₁2₁2₁ space group and **2** a monoclinic P2₁ one. Compounds **1** and **2** are composed of five fused six-membered rings presenting a chair conformation, except for the central ring of **2**, which adopts a half-chair conformation. In addition, the intra- and intermolecular parameters were studied using CCDC MOGUL analyses and Hirshfeld surfaces.

1. Introduction

Terpenes are well-known secondary metabolites occurring in many plants specimens [1]. This compound class has been widely investigated due to its biological properties, as, for example, antituberculosis [2], nematostatic effects [3], anticancer [4], anti-HIV [5], and anti-inflammatory [6]. The terpenoids derivatives studied here belong to pentacyclic triterpenes (PCTT) class and they are known as 16 α -hydroxyfriedelin (**1**) and 3-oxo-16-methylfriedel-16-ene (**2**).

The triterpene **1** was isolated from the hexane extract of *Salacia elliptica* branches and its derivative 3-oxo-16-methylfriedel-16-ene (**2**) was obtained after dehydration accompanied by methyl migration [7]. In a previous report

Duarte et al. [7] elucidated the stereochemistry of **1** and **2** using 2D-NMR (NOESY) spectroscopy and mass spectrometry (GC-MS), as well as the ¹³C-NMR.

As part of our ongoing study on X-ray diffraction applied to establish the structural details of pentacyclic triterpenes [8–12], in this paper, we report the crystal structure of the triterpene 16 α -hydroxyfriedelin (**1**) and its derivative 3-oxo-16-methylfriedel-16-ene (**2**). The X-ray diffraction (XRD) studies of triterpenes have received a meaningful use in order to access both the intra and intermolecular geometry correctly, giving an unambiguous structure determination. Here, we investigate the role of the main intermolecular interactions in the stabilization of the solid state architecture of the **1** and **2** PCTT derivatives building blocks.

Structure of 16 α -hydroxyfriedelin (**1**) Structure of 3-oxo-16-methylfriedel-16-ene (**2**)

SCHEME 1: The rings of the molecules **1** and **2** should be labeled as A, B, C, D and E. (Ring A = C1, C2, C3, C4, C5 and C10); (Ring B = C5, C6, C7, C8, C9 and C10); (Ring C = C8, C9, C11, C12, C13 and C14); (Ring D = C13, C14, C15, C16, C17 and C18) and (Ring E = C17, C18, C19, C20, C21 and C22).

2. Experimental Part

2.1. Single Crystal and X-Ray Diffraction Studies. The needle-like single crystals of compounds **1** and **2** were obtained by slow evaporation of the methanol/hexane mixture (1:1 v/v) at room temperature. Crystal diffraction data were collected at 150 K on an Enraf-Nonius Kappa-CCD Diffractometer using MoK α radiation (0.71073 Å) monochromated by graphite. The final unit cell parameters were based on all reflections. Data were collected made using the COLLECT program [13]; integration and scaling of the reflections were performed with the HKL Denzo-Scalepack system of programs [14].

The structure was solved by direct methods using the program *SHELXS-97* [15] and refined by full-matrix least square on F^2 with the program *SHELXL-97* [15] considering anisotropic temperature factors for all atoms except for hydrogen atoms that had their positional parameters fixed stereochemically and refined with riding model [15]. Hydrogen atoms of the CH and CH₂ groups were set as isotropic with a thermal parameter 20% greater than the equivalent isotropic displacement parameter of the non-hydrogen atoms to which each one is bonded. This percentage was set to 50% for the hydrogen atoms of the CH₃ and OH groups.

The compounds **1** and **2** are both chiral and crystallize in noncentrosymmetric space groups. However, the Flack parameter [16] was not refined during X-ray crystallographic analysis since the most electron-rich atom is the oxygen, which does not have an anomalous scattering large enough (using MoK α radiation) to permit determination of the absolute structure using X-ray diffraction. In this way the Friedel opposites were averaged before refinement cycles.

Programs included in the WinGX package [17] were used to prepare materials for publication. The programs MERCURY [18] and ORTEP-3 [19] were used to generate the molecular graphics. The intramolecular parameters were

analyzed using MOGUL [20], a knowledge base of molecular geometry derived from the CSD (Cambridge Structural Database) [21], which gives a rapid access to information on the preferred values of bond lengths, valence angles, and acyclic torsion angles. Structure data files of compounds **1** and **2** are deposited at Cambridge Crystallographic Data Centre (CCDC 936437 and 936625 for **1** and **2**, resp.). Summary of crystal, data collection procedures, structure determination methods, and refinement results are summarized in Table 1.

The CrystalExplorer 2.1 program [22] was used to generate the Hirshfeld surfaces and the finger print plot of **1** and **2**. The Hirshfeld surfaces are used to define the intermolecular environment of molecules within the crystal. Thus, it allows us to explore the properties of each intermolecular contact in the solid state of the chemical component [23–25]. Interesting information is obtained from the 2D-fingerprint graphics, which is constructed by the plot of d_e versus d_i (d_e = external distance, the distance between the calculated Hirshfeld surface and the nearest atom of an adjacent molecule; d_i = internal distance that is defined as the distance from the nearest nucleus internal to the calculated Hirshfeld surface). The 2D-fingerprint also provides the percentage of each contact that is useful to compare the occurrence of intermolecular interactions of the triterpenes derivatives studied here.

3. Results and Discussion

The X-ray crystallographic analyses of compounds **1** and **2** were performed, confirming the structures previously established by the NMR data [7]. The crystal structure of each compound presents only one molecule in the asymmetric unit. The ORTEP diagrams of **1** and **2**, including the atom labeling, are shown in Figure 1. The PCTT derivatives **1** and **2** crystallize in the noncentrosymmetric space groups

TABLE 1: Crystal data, data collection details, and structure refinement results for compounds **1** and **2**.

	1	2
Molecular formula	C ₃₀ H ₅₀ O ₂	C ₃₀ H ₄₈ O ₁
Formula weight	442.70	424.78
Crystal system	Orthorhombic	Monoclinic
Space group	P2 ₁ 2 ₁ 2 ₁	P2 ₁
Unit cell dimensions	$a = 13.6119(10) \text{ \AA}$ $b = 6.3245(2) \text{ \AA}$ $c = 29.260(2) \text{ \AA}$	$a = 13.2220(12) \text{ \AA}$ $b = 6.2492(8) \text{ \AA}$, $\beta = 106.03(2)^\circ$ $c = 15.6054(19) \text{ \AA}$
Volume	2519.0(3) Å ³	1237.3(2) Å ³
Z	4	2
Density (calculated)	1.167 Mg/m ³	1.140 Mg/m ³
Absorption coefficient	0.070 mm ⁻¹	0.066 mm ⁻¹
F(000)	984	472
Crystal size	0.07 × 0.07 × 0.78 mm ³	0.05 × 0.08 × 0.63 mm ³
Theta maximum	2.99 to 25.36°	3.63 to 25.41°
Reflections collected	14414	4392
Completeness to theta	98.1%	98.5%
Independent reflections	2629 [R(int) = 0.1900]	2464 [R(int) = 0.1235]
Data/restraints/parameters	2629/0/290	2464/1/280
Goodness of fit on F ²	0.996	1.042
Final R indices [I > 2σ(I)]	R1 = 0.0599, wR2 = 0.1181	R1 = 0.0737, wR2 = 0.1352
R indices (all data)	R1 = 0.1169, wR2 = 0.1414	R1 = 0.1354, wR2 = 0.1568
Largest diff. peak and hole	0.251 and -0.256 e·Å ⁻³	0.182 and -0.201 e·Å ⁻³

FIGURE 1: ORTEP-3 view [7] of the molecular structure of **1** and **2**, with displacement ellipsoids being drawn at the 50% probability level. The hydrogen atoms are shown as spheres of arbitrary radii.

P2₁2₁2₁ (orthorhombic) and P2₁ (monoclinic), respectively. The MOGUL [20] analysis points out that all geometric parameters agree well with the expected values reported in the literature, including the PCTT previously published by us [8–12]. Selected bond lengths of **1** and **2**, compared with MOGUL results, are represented in Table 2. Only compound **1** presents the bond length C16–O2 corresponding to the hydroxyl group [value of 1.437(5) Å], which is longer than the C3=O1 carbonyl group with values of 1.212(5) and 1.209(3) Å for **1** and **2**, respectively. The C16–O2 and C3=O1 values represent an evidence of single and double bonds, respectively, considering the MOGUL results [20] and related

C–O and C=O bond lengths of PCTT derivatives, such as lupeol [8], 30-hydroxy-lup-20(29)-en-3-one and (11α)-11-hydroxy-lup-20(29)-en-3-one (**2**) [9]. In **2**, C16 and C17 atoms are separated by 1.341(6) Å, as expected, based on the sp² hybridization. This is an evidence of dehydration of compounds **1** to **2**, to form a C16=C17 double bond.

Focusing on their ring conformations, it could be seen that in **1**, all six-membered rings, A, B, C, D, and E, have adopted a chair conformation, which is the most stable one, as observed in other PCTT crystal structures [7–10, 16]. It was also noted that the hydroxyl group linked to C-16 of the D ring was located in an equatorial position (see

FIGURE 2: Representation of the Hirshfeld surfaces (a) and the full fingerprint plots (b) of compounds 1 and 2.

FIGURE 3: The crystal packing of compounds 1 (a) and 2 (b) projected onto ac plane.

Figure 1). In the structure of 2, A, B, C, and E rings present a chair conformation, while the D ring adopts a half-chair conformation due to C16=C17 double bond.

The crystal packing of 1 and 2 is stabilized by weak intermolecular interactions. To better explore the intermolecular interactions occurring in 1 and 2, the Hirshfeld surface [20] and the corresponding two-dimensional fingerprint plots [21, 22] were used (Figure 2). In the graphics, the d -values

range from 0.8 to 3.0 Å, with color gradient from blue to red, in order to represent the proportional contribution of the (d_i, d_e) pair to the Hirshfeld surface. In both fingerprint plots the shortest distribution points (~ 1.0 Å) occur due to H $\cdots$ H contacts. Only in structure of 1 the presence of a pair of sharp spikes, which is characteristic of hydrogen bonds [24], is evident. These sharp spikes generated by O $\cdots$ H contacts occur around 1.05 Å (d_e, d_i) and 1.35 Å (d_i, d_e) in 1,

TABLE 2: Selected bond length (Å) determined for compounds **1** and **2**.

Bond length	1	2	Mogul values
C(16)–O(2)	1.437(5)	—	1.41(3)
C(3)–O(1)	1.212(5)	1.209(5)	1.22(2)
C(16)–C(17)	1.560(6)	1.341(6)	1.52(3)/1.33(3)
C(1)–C(10)	1.527(5)	1.525(6)	1.52(3)
C(1)–C(2)	1.533(6)	1.520(7)	1.52(3)
C(2)–C(3)	1.500(6)	1.485(6)	1.52(3)
C(20)–C(29)	1.540(6)	1.505(6)	1.52(3)

whereas in the fingerprint plot of the structure of **2**, the sharp spikes formed by the C–H···O intermolecular contacts are overlapped by the H···H contacts.

In the structure of **1**, the relative contributions to the Hirshfeld surface area due to H···H, O···H, C···O, C···H, and O···O intermolecular contacts are 89.9, 9.6, 0.2, 0.2, and 0.1%, respectively. Also, for compound **2** the percentage found to H···H, O···H, C···C, and O···O are 93.2, 6.1, 0.5, and 0.2%, respectively. Due to the molecule composition, **1** presenting an additional oxygen atom compared with **2**, more intermolecular contacts involving the oxygen atom in compound **1** are expected. In both structures, it seems clear that H···H intermolecular contacts represent the biggest contribution to the fingerprint plot, such as that expected for a compound class where the majority of the surface is covered by H atoms. This evidences that van der Waals forces exert an important influence on the stabilization of the packing in **1** and **2**.

Concerning the crystal packing of **1** and **2** onto the *ac* plane, a different assembly is observed (Figure 3). As shown in Figure 3(a), the molecules of **1** form a zigzag arrangement, whereas in the crystalline structure of **2**, the molecules form parallel layers (Figure 3(b)). The perspective of Figure 3 shows the organization of hydrophobic tails to form van der Waals interactions. The absence of strong intermolecular forces to stabilize the molecules in solid state and the packing characteristics may explain the difficulty in obtaining single crystals of **1** and **2** and their fragility.

4. Conclusion

The crystal structures of two PCTT derivatives named 16 α -hydroxyfriedelin (**1**) and 3-oxo-16-methylfriedel-16-ene (**2**) were determined by single crystal X-ray diffraction and compared according their intra- and intermolecular geometries. The Hirshfeld surfaces obtained for **1** and **2** show that H···H contacts are the most abundant to crystal stabilization, as expected for a molecular crystal where the majority of the surface is covered by H atoms. It was possible to probe by the Hirshfeld surfaces analyses the role of C–H···O intermolecular hydrogen bonds and van der Waals forces in crystal self-assembly of PCTT building blocks.

Acknowledgments

This work was supported by the Brazilian agencies FAPEMIG (APQ-02600-12 and PPM-00524-12), CAPES (PNPD-2007 and PNPD-2011), FINEP (Refs. 134/08 and 0336/09), CNPq (476870/2011-9 and 308354/2012-5), and FAPESP. Rodrigo S. Corrêa, thanks FAPESP for a fellowship (Grant no. 2009/08131-1).

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