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Structure, thermal and spectral study of 16α,17-epoxypregn-4-ene-3,11,20-trione monohydate

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Abstract

16α,17-epoxypregn-4-ene-3,11,20-trione is an important steroid intermediate in synthesis of many hormone pharmaceuticals, such as cortisone acetate and betamethason. It does not dissolve in water, but the single crystals grown from acetone with some water shows evident hydration behavior. The thermal analyses by DSC and TG-DTA and the IR spectra characterization of the anhydrous and hydrous crystals were performed and compared. The hydrate was also proved by IR spectral and thermal analyses. Single crystal structure of the hydrate indicates one water molecule per host molecule is included into the host lattice. The incorporation of water molecules does not change the crystal cell dimensions significantly, except for some increment of the cell along the axis *b*. In the crystal cell, two steroid molecules are linked through the water molecules as a bridge by forming two different hydrogen bonds. The incorporation of one water molecule makes some conformation changes of the molecules in the crystal unit cell.

Keywords: Crystal structure; 16α,17-epoxypregn-4-ene-3,11,20-trione; X-ray diffraction; FTIR spectra; Thermal analysis

1. Introduction

16α,17-epoxypregn-4-ene-3,11,20-trione (in this paper, it is titled as compound (1), see Fig. 1) is an important steroid intermediate in synthesis of many hormone pharmaceuticals, such as cortisone acetate and betamethason [1]. It was first prepared from 11α-hydroxy-16α,17-epoxyprogesterone by oxidation with chromium trioxide by Peterson et al. [2]. The anhydrous single crystal structure of the title compound has been reported in our previous work [3]. The anhydrous single crystal was grown from chloroform–methanol mixture. The crystal structure shows the compound (1) crystallizes in orthorhombic $P2_12_12_1$ space group. No evident hydrogen bond was observed due to the lack of the hydrogen-bond donor (HBD) in the molecule of the compound (1). But when the crystals are grown from its acetone solution with some water, the single crystals show some solvation behavior. This behavior was first observed when the DSC thermogram shows an evident endothermal peak before melting. At the first, the polymophic transformation was considered, as the solvate between the acetone and title compound was unreasonable due to the lack of the hydrogen-bond donor in both two molecules. This inspires our interest to further investigation.

In this paper, the single crystal of the hydrate of compound (1) was grown and characterized using single crystal X-ray diffraction, Fourier Transform Infrared Spectroscopy (FTIR) and thermal analysis technology (DSC and TG-DTA). The comparison between the hydrous and anhydrous crystals of compound (1) was also performed. The experimental results make certain that one water molecule per host molecule is incorporated into the unit cell. The cell dimension change slightly when the water molecule is incorporated, with some increment along crystal axis *b*. Along the *b* direction, the molecules of the host molecules are linked by the water molecule through two different hydrogen bonds, forming the hydrogen-bond bridge. This leads to different crystal packing modes and to different hydrogen bonding schemes. The water molecules distributes between the crossed layers and not easy to escape from the lattice. So the hydrate of the compound (1) is stable at ambient conditions, and DSC

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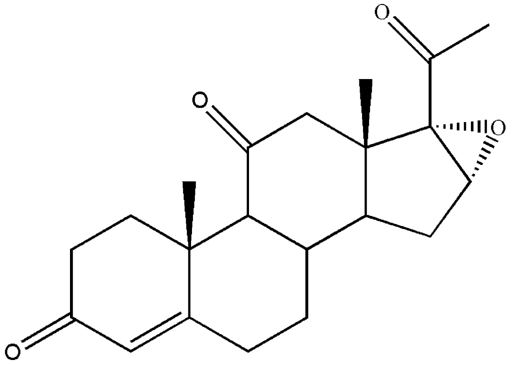

Fig. 1. The chemical structure of 16α,17-epoxypregn-4-ene-3,11,20-trione, compound (1).

thermal analysis indicates the hydrate decomposes at about 420 K.

2. Experimental

2.1. Materials and preparation of single crystal

16α,17-epoxypregn-4-ene-3,11,20-trione, $C_{21}H_{26}0_4$, was prepared in our laboratory by oxidation 11α-hydroxy-16α,17-epoxyprogesterone (provided by Tianjin Tianyao Pharmaceutical Co. Ltd, China). The latter samples was dissolved in pyridine and treated with chromium trioxide at room temperature overnight. The product was chromatographed on silica gel and recrystallized from acetone–hexane three times. The melting point determined by Differential Scanning Calorimeter (DSC) is 465.5 K, its purity is better than 99.0%, determined by HPLC.

Colorless rhombic plate single crystals suitable for X-ray diffraction were obtained by slow natural evaporation of solution in acetone (with some water) at room temperature. The acetone was purchased from Tianjin Chemical Reagent Co., China, analytical grade, without any treatment.

2.2. Crystal structure determination and refinement

A suitable colorless crystal of compound (1) monohydrate was mounted on a glass fiber. All measurements were made on a Rigaku R-axis RAPID IP Area Detector diffractometer with graphite monochromated Mo Kα radiation. The data were collected at a temperature of 293(2) K to a maximum 2θ value of 54.96°. 18,441 reflections were collected with the index ranges $-9<h<9$, $-12<k<12$, $-31<k<32$. An empirical absorption correction was applied.

The structure was solved by direct-methods using SHELXS-97 [4] and anisotropic displacement parameters were applied to non-hydrogen atoms in a full-matrix least-squares refinement based on F^2 using SHELXL-97 [5]. Hydrogen atoms of water were obtained from different maps and refined isotropically. All other hydrogen atoms were located in geometric positions and included with a riding model. Atomic scattering factors were taken from the International tables for Crystallography [6]. Bruker SHELXTL was used to prepare molecular graphics.

2.3. Differential scanning calorimetry (DSC) and TG-DTA thermal analysis

DSC curves of the samples (4 mg) were recorded by a thermal analysis system (NETZSCH DSC 204, Germany). Following calibration with indium and lead as standards, about 5 mg samples were heated at 10 K/min in aluminum pans under a nitrogen atmosphere.

A Rigaku thermal gravimetric analyzer (TG-DTA) was used to calculate percentage weight changes. About 4.8 mg of the sample was weighted into a platinum pan and heated from 300 to 800 K at a rate of 10 K/min, under a static nitrogen atmosphere.

2.4. Infrared spectral analysis

Fourier transform infrared (FTIR) spectra were recorded in the range 400–4000 cm^{-1} using a Nicolet 560 IR spectrophotometer (4 cm^{-1} resolution) with reference to a potassium bromide pellet.

3. Characterization

3.1. Single crystal structure analysis

The structure of the anhydrous crystals of the compound (1) has been reported in our previous study [3]. The compound has a typical steroid conformation with three six-membered rings and one five-membered ring denoted A, B, C and D, respectively. Ring A has a 1α-sofa conformation, and rings B and C are in nearly perfect chair conformations. The presence of the three-membered ring constrains the five-membered D ring to have a 14α-envelope conformation as described by Goubitz et al. [7]. The carbonyl group on C20 nearly eclipses the C13–C17 bond. The C13–C17–C20–O4 torsion angle is 7.4(4)°. The overall conformation is similar to the parent molecule 11α-hydroxy-16α,17-epoxyprogesterone [8]. The title compound crystallizes in the orthorhombic space group $P2_12_12_1$, similar to 11α-hydroxy-16α,17-epoxyprogesterone.

A summary of crystallographic data, experimental details and refinement results for the hydrate of compound (1) are given in Table 1. And the fractional atomic coordinates and equivalent isotropic displacement coefficients are listed in Table 2. The molecular structure of 16α,17-epoxypregn-4-ene-3,11,20-trione as observed in the crystal structure of its hydrate, is shown in Fig. 2. The molecular structure of the hydrous crystal of compound (1) is similar with its anhydrous crystal. But the incorporation of water modified

Table 1
Basic crystallographic data, data collection and refinement parameters

Empirical formula	$C_{21}H_{26}O4\ H_2O$
a	7.530(1) Å
b	9.853(2) Å
c	25.276(5) Å
V	1875.4(7) $Å^3$
Z	4
D (calc)	1.277 Mg m^{-3}
Crystal system	Orthorhombic
Space group	*P*212121
Formula Weight	360.43
μ(Mo Ka)	0.090 mm^{-1}
F(000)	776
Crystal dimensions	0.65×0.4×0.35 mm
Diffractometer and radiation used	Rigaku R-axis Rapid diffractometer Mo Kα radiation, $\lambda = 0.71073$ Å
Scan technique	Oscillation scans
Range of *h*, *k* and *l*	−9→9, −12→12, −31→32
Total number of reflections measured	18441
θ range	3.15–27.48°
No. of independent reflections (Rint)	4288(0.0290)
No. of observed reflections	3729
Criterion for observed reflections	$I > 2\sigma(I)$
Absorption correction	Empirical
Refinement method	Full-matrix least-squares on F^2
Function minimized	$\omega = 1[\sigma^2(F_o^2) + (0.0819P)^2 + 0.1533P]$ Where $P = (F_o^2 + 2F_c^2)/3$
Parameters refined	244
Value of *R*	0.0411
Value of *wR*	0.11945
Goodness-of-fit on F^2	0.991
Max. and min. heights in final Dr map	0.158, −0.211 $Å^3$
Source of atomic scattering factors	International tables for crystallography (Vol. C)
Programs used	SHELXS-97, SHELXL-97, Bruker SHELXTL

Table 2
Atomic coordinates and equivalent isotropic displacement coefficients U_{eq} for compound (1) $U_{eq} = (1/3)\, \Sigma i\, \Sigma j U_{ij} a_i^* a_j^* a_i a_j$

	x	*y*	*z*	U_{eq}
C1	0.0182(2)	−0.0440(2)	−0.09705(7)	0.0438(3)
C2	−0.0042(2)	−0.0494(2)	−0.15692(7)	0.0499(4)
C3	−0.1665(3)	−0.1248(2)	−0.17230(7)	0.0552(4)
C4	−0.3159(2)	−0.1181(2)	−0.13611(7)	0.0526(4)
C5	−0.3127(2)	−0.0536(2)	−0.08987(6)	0.0418(3)
C6	−0.4797(2)	−0.0377(2)	−0.05840(7)	0.0528(4)
C7	−0.4552(2)	−0.0785(2)	−0.00065(7)	0.0499(4)
C8	−0.3016(2)	−0.0033(2)	0.02518(6)	0.0393(3)
C9	−0.1311(2)	−0.0283(1)	−0.00802(6)	0.0358(3)
C10	−0.1450(2)	0.0118(1)	−0.06754(6)	0.0374(3)
C11	0.0349(2)	0.0246(2)	0.02035(7)	0.0429(3)
C12	0.0582(2)	−0.0204(2)	0.07701(7)	0.0481(4)
C13	−0.1100(2)	0.0121(2)	0.10853(6)	0.0430(3)
C14	−0.2682(2)	−0.0553(2)	0.08078(6)	0.0400(3)
C15	−0.4155(2)	−0.0526(2)	0.12278(7)	0.0489(4)
C16	−0.3128(3)	−0.0810(2)	0.17283(7)	0.0524(4)
C17	−0.1233(2)	−0.0467(2)	0.16422(7)	0.0478(4)
C18	0.0047(3)	−0.0131(2)	0.20740(8)	0.0643(5)
C19	−0.0044(4)	−0.0913(3)	0.25764(9)	0.0782(7)
C20	−0.1604(3)	0.1667(2)	−0.07546(8)	0.0530(4)
C21	−0.1340(3)	0.1675(2)	0.11294(8)	0.0565(4)
O1	−0.1807(3)	−0.1837(2)	−0.21459(7)	0.0980(7)
O2	0.1436(2)	0.0964(1)	−0.00074(5)	0.0597(4)
O3	−0.1831(2)	−0.1868(1)	0.16604(5)	0.0536(3)
O4	0.1170(3)	0.0718(2)	0.19900(8)	0.1019(7)
O1W	0.0640(4)	−0.2293(3)	−0.29449(9)	0.0884(9)

the packing of the molecules. So this paper is focus on the change of the arrangement and packing of the steroid molecules in the unit cell when the water molecule incorporates into the unit cell. The comparison of basic crystal structure data of hydrous and anhydrous crystal of compound (1) are listed in Table 3.

The crystal packing of compound (1) is shown in Fig. 3 in a projection along the orthorhombic axis *y*. The steroid molecules are oriented roughly parallel to the *ac* plane, thus forming a layer-type packing. This is also can be seen from Fig. 4. The water molecules are incorporated in such a way that they form hydrogen bond bridges between pairs of steroid molecules. There are no direct contacts between these steroid molecules, so the contact between the adjacent steroids molecules along *c* direction is entirely due to solvent-mediated hydrogen bonds.

The two hydrogen atoms of the water can form two different hydrogen bonds with the O1 of one steroid molecule and O4 of another steroid molecule of the compound (1), respectively. The hydrogen bonding information in the crystal packing is given in Table 4. The two hydrogen bonding are not in same strength, as is presented in Table 4, for O1W–H2W···O1 hydrogen bond, the *D–H* distance is 0.85(4) and *H···A* distance is 1.92(4) Å, while in the hydrogen bonding of O1W–H1W···O4, the D–H distance is 0.68(4) and H···A distance is 2.23(4) Å. The total hydrogen bond length of O1W–H2W···O1 (2.771(3) Å) is shorter than that of the O1W–H1W···O4 (2.865(3) Å). The angle of O1W–H2W···O1 is 175(3)°, which is more closed to 180° compares with that of O1W–H1W···O4 (155(4)°). This indicates the hydrogen bonding of O1W–H2W···O1 has more strength. This may be explained by discussing the electronegativity of the hydrogen bond acceptors. There is a double bond –C=C– at the adjacent position of the carbonyl –C(4)=O(1), owing to the p-electron conjugation effect, the oxygen atom O1 has more electronegativity, so the interaction between O1 and H2w is more strong and more stable.

The water molecules are trapped in interstitial voids, and are not free to leave. So the hydrate is stable at room temperature. Except the hydrogen bonding along the *z* direction, the main interaction between the steroid molecules are Van de walls forces. Along the *x* direction, the steroid molecules, as well as the water molecules, forms a zigzag chain in the crystal, as is shown in Fig. 5.

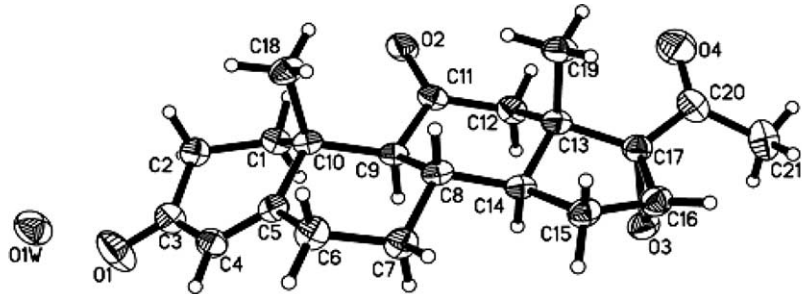

Fig. 2. Molecular structure of compound (1) as observed in the crystal structure. Displacement ellipsoids are drawn at 30% probability level.

Table 3
Comparison of basic crystal structure data of hydrous and anhydrous crystal of compound (1)

	Hydrous crystal of compound (1)	Anhydrous crystal of compound (1)
Crystal system	Orthorhombic	orthorhombic
a	7.530(1) Å	7.536(1) Å
b	9.853(2) Å	9.900(2) Å
c	25.276(5) Å	23.288(4) Å
V	1875.4(7) $Å^3$	1737.6(5) $Å^3$
Z	4	4
Crystal density	1.277 mg m^{-3}	1.309 mg m^{-3}

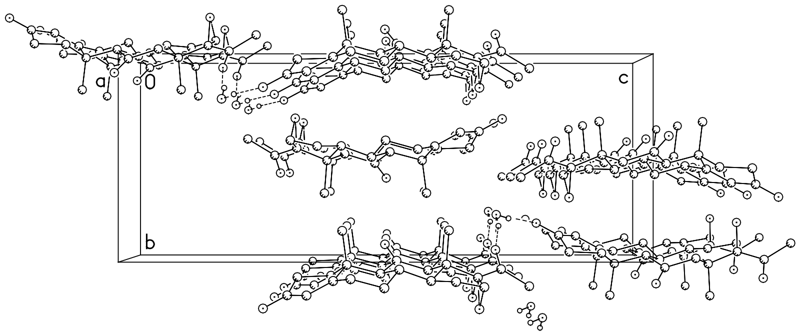

Fig. 3. The molecular packing of the hydrate of the compound (1), view along *a* axis. The dash line indicates the hydrogen bond.

3.2. Spectral characteristics

The FTIR spectral analyses of compound (1) and its hydrate were carried out between 4000 and 400 cm^{-1}. The resulting spectrum is shown in Fig. 6. From the two IR spectra, it can be seen that the spectra of the anhydrous and the hydrous crystal of compound (1) are quite similar below the wavelength at 3400 cm^{-1}. The strong absorption

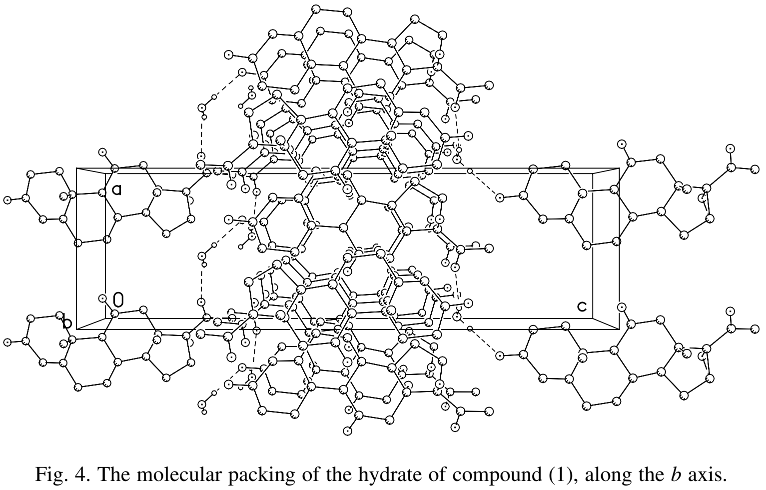

Fig. 4. The molecular packing of the hydrate of compound (1), along the *b* axis.

Table 4
Hydrogen bonding geometry for 16α,17-epoxypregn-4-ene-3,11,20-trione monohydrate (Å, °)

D–H···A	*D–H*	*H···A*	*D···A*	*D–H···A*
O1W–H2W···O1	0.85(4)	1.92(4)	2.771(3)	175(3)
O1W–H1W···O4^{i}	0.68(4)	2.23(4)	2.865(3)	155(4)

Symmetry codes: (i) $1/2-x$, $-y$, $z-1/2$

at the 1670 and 1704 cm^{-1}, indicates the existence of the carbonyl group. There are three carbonyl functions in the steroid molecules, but only two different absorption peaks are observed. The 11-C=O and 20-C=O may be overlapped and represent only one absorption at 1704 cm^{-1}, while the absorption of 3-C=O occurs at 1670 cm^{-1}, due to the effect the adjacent C=C double bond. And the middle strong absorption at 1613 cm^{-1} is due to this double –C=C– at 4 position of the steroid skeleton. A series of sharp absorption bands at 2948, 2916, 2974, 2889 cm^{-1} characterize the –C–H vibration of methyl and methylene.

The biggest difference between the anhydrous and hydrous crystals lies in the absorption between 3600 and 3200 cm^{-1} of the wave number. The IR spectrum of the hydrous crystals show a split and middle strong absorption bands between 3200 and 3600 cm^{-1}, i.e. at 3581, 3452 and 3400 cm^{-1}, which are the characteristic absorption of ν(OH) vibrations originating from the lattice water in the crystal of the compound (1) [9]. We also found an absorption at 3400 cm^{-1} in the spectrum of the anhydrous crystal, this may be owing to the minor water was captured into the anhydrous crystals of the compound.

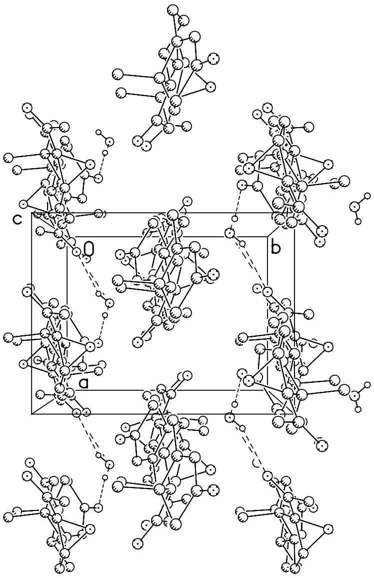

Fig. 5. The molecular packing of the hydrate of compound (1), along the *c* axis.

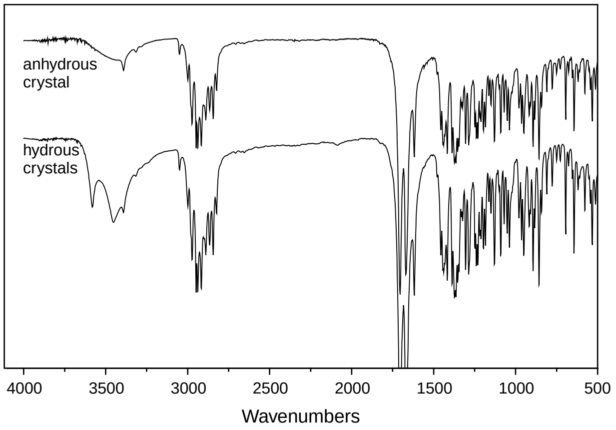

Fig. 6. The FTIR spectra of the anhydrous and hydrous crystals of compound (1).

3.3. Thermal analysis

The DSC curves of both the anhydrous and hydrous crystals of the compound (1) are shown in Fig. 7. The DSC curves of anhydrous crystals shows only one endothermal peak in the temperature range 458–468 K, indicating a melting behavior. The DSC curve of the hydrate crystals shows two endothermal peaks, the first is in the temperature range of 425–435 K and the second in the range of 458–468 K, which indicate the dehydration and melting, respectively. As the temperature of dehydration is some high to 433 K, both two forms are stable in the air at room temperature and begin to melt when the temperature up to about 460 K.

Further study for the hydrate of compound (1) was performed by using TG-DTA from a temperature of 300 K up to 780 K. The TG-DTA curves are presented in Fig. 8, two endothermal peaks are observed in the DTA curve of the hydrate crystals in the range of 420–435 and 458–468 K, respectively, which in accord with the results of the DSC determination. The TG curve (the upper curve in the Fig. 8) has a sharp decrease at the temperature of about 423 K, indicating a weight loss. The experimental mass loss value of 5.6% is in agreement with the calculated value 5.0% base

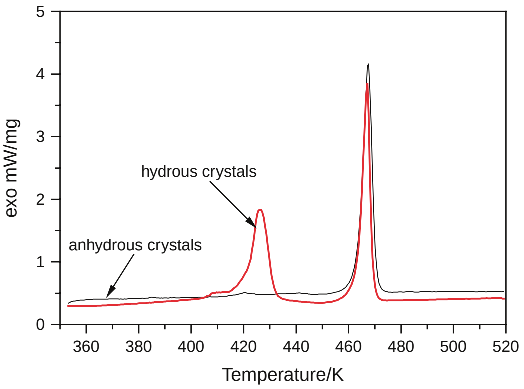

Fig. 7. DSC curves of the anhydrous and hydrous compound (1).

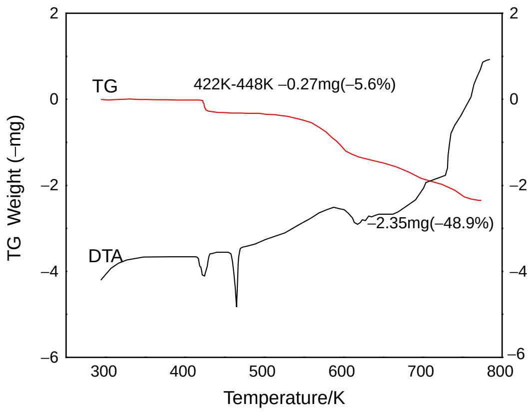

Fig. 8. TG-DTA curves of the hydrous compound (1).

on the hypothesis of dehydration of one water molecule. The DTA curve and the TG curve together proved the dehydration behavior at about 423 K. The DTA determination also shows the compound (1) began to decompose when the temperature over 470 K.

4. Conclusion

The single crystal of the monohydrate of 16α,17-epoxypregn-4-ene-3,11,20-trione was grown from its solution in acetone–water mixture. The single crystal X-ray diffraction determination indicates that one water molecule per host molecule is incorporated into the host lattice. The IR spectral of the hydrate represents evident absorption in the wave number range 3200–3600 cm^{-1}, which implies the existence crystal water. Thermal analyses by differential scanning calorimetry (DSC) and Thermal Gravimetry (TG) for the studied compound and its hydrate show both of them are stable at room temperature. And the hydrate begin to dehydrate at about 150 °C. TG curve shows 5.6% weight loss in the temperature range 420–450 K, which is in agreement with the calculated value 5.0% weight loss based on the dehydration of one water molecule.

The incorporation of water molecules does not change the crystal cell dimensions significantly, only results in some increment of the cell dimension along the axis *b*. In the crystal cell, two steroids molecules are linked through the water molecules by forming two different hydrogen-bonds. The role which the water molecule plays is just as a ‘bridge’.

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