# ORIGINAL PAPER

# Orthorhombic Polymorphs of 1-Phenyl-3-(3-Hydroxyphenyl)-2-Propen-1-One

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Abstract Chalcones, 1,3-diphenyl-2-propene-1-ones, exist naturally and synthetically, and are characterized by the linkage of two aromatic rings joining a three carbon  $\alpha$ - $\beta$ -unsaturated carbonyl entity. We report the observation of two new polymorphs of a hydroxy chalcone, C<sub>6</sub>H<sub>5</sub>-CO-CH=CH-C<sub>6</sub>H<sub>4</sub> (m-OH), identified as a result of a Claisen-Schmidt synthesis and manual screening technique. One polymorph of this compound has been reported previously and exists in the monoclinic system, space group P2/n, with unit cell parameters a = 13.295(6) Å, b = 5.659(2) Å,  $c = 16.144(8) \text{ Å}, \beta = 109.73(5)^{\circ}, V = 1143.3(9) \text{ Å}^3$ , and Z = 4. Two crystalline forms (II and III) reported herein, are polymorphs of the reported monoclinic form (I). Form II exists in the orthorhombic system, space group  $Pca2_1$ , with unit cell constants a = 11.631 (2) Å, b = 13.163 (3) Å, c = 7.3977 (14) Å, V = 1132.6 (4) Å<sup>3</sup>, and Z = 4. Form III also crystallizes in the orthorhombic system, however in space group Pbca, with unit cell parameters a = 11.8100(8) Å, b = 7.4075(5) Å, c = 25.8729(19) Å,  $V = 2263.4(3) \text{ Å}^3$ , and Z = 8. Variations in the hydrogen bonding connectivity help to distinguish these two forms from the monoclinic, whereas crystal packing differentiates

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the two orthorhombic forms. The conformation of the C=C (C2-C3) is *E* for both orthorhombic forms.

**Keywords** X-ray single crystal structure · Chalcone · Polymorphs · 1,3-diphenyl-2-propen-1-one · Hydroxyl derivatives of chalcones

## Introduction

Chalcones, chemically 1,3-diaryl-2-propene-1-ones, are structurally simple compounds that exist naturally in petal pigments and have also been observed in the fruit, bark, nut, and root of a variety of plants, such as the Angelica and Glycyrrhiza found in Africa, Asia, and South America [1]. They are also readily synthesized via Claisen–Schmidt condensation of appropriately substituted acetophenone and benzaldehyde under acidic, basic, or solvent-free conditions [2]. Structurally they are characterized by the linkage of two aromatic rings joining a three carbon  $\alpha$ - $\beta$ -unsaturated carbonyl, or "enone" moiety. This molecular scaffold serves as a unique template in a variety of synthetic modifications, and provides an ideal framework as precursors for the synthesis of heterocyclic compounds such as flavonoids and other chemical analogs, such as curcumin [3].

Natural and synthetic based chalcones have attracted much attention in recent years as a result of their ubiquity and extensive use in a number of pharmacological and biological applications. Documented reports of derivatives and analogs of these benzylideneacetophenone suggest activities as antitumorogenic [4, 5], anti-Parkinsonism activities [6], antifungal [7, 8], and anti-tuberculosis [9, 10] agents. Moreover, more recent indications as anti-HIV and food and drug preservative usages have also been evaluated [11].

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This paper documents the observation and crystal structures of two new polymorphic modifications of *l-phenyl-3-(3-hydroxyphenyl)-2-propen-1-one* C<sub>6</sub>H<sub>5</sub>–CO–CH=CH–C<sub>6</sub>H<sub>4</sub>(*m*-OH). The monoclinic form, herein referred to as Form I, previously reported by Turowska-Tyrk et al. is also briefly discussed [12]. The two orthorhombic polymorphs identified in this work are novel forms and, to the best of our knowledge, have not yet been reported in the literature. Slight variations in the molecular geometry, specifically, the planarity orientation of the hydroxyl proton, differentiates the monoclinic and orthorhombic forms, and variation in crystal packing help to distinguishes the two orthorhombic polymorphs.

# Experimental

Commercially available starting materials were used to produce the chalcone based derivatives. These materials were accepted based on vendor certificate of analysis (CoA) data and used without further purification. The synthesis was conducted using a modified version of a Claisen–Schmidt condensation as reported by B. N. Acharya et al. [13]. These reactions are frequently referenced in organic synthesis for the formation of carbon–carbon bonds.

A solution of acetophenone (1.00 g, 8.32 mmol) and 3-hydroxybenzaldehyde (1.27 g, 8.32 mmol) dissolved in methanol (3.95 g) was added to a flask containing sodium methoxide in methanol (25 wt%, 7.19 g, 33.29 mmol). The resulting mixture was stirred overnight at room temperature. The reaction was neutralized using dilute acid and the resulting crude product was collected by filtration. Recrystallization in methanol followed by slow overnight cooling afforded compound **1** (Form II) as a yellow solid.

Two additional polymorphic modifications were also noted, Forms I and III. Form III, is produced by recrystallization of Form II in ethanol, DMA and DMF. This polymorph is generated by equilibration of Form II in a variety of organic and aqueous based mixtures such as methanol, ethyl acetate, DMSO, H<sub>2</sub>O, H<sub>2</sub>O/ACN, and MeOH/H<sub>2</sub>O (5:1) at RT  $^{\circ}$ C. It is also readily observed through slurry of Form II in acetone. The monoclinic polymorph, Form I, is reportedly observed as a result of recrystallization in a methanol–water (5:1) mixture; however, we are only able to isolate Form I, in an acicular crystal habit, by recrystallization of Form II in toluene.

X-ray diffraction intensity data from two plate-like crystals, corresponding to polymorphs II and III, were measured at 296 (2) K using a Bruker SMART APEX diffractometer (Mo K $\alpha$  radiation,  $\lambda = 0.71073$  Å) [14]. The raw area detector data frames were reduced and corrected for absorption effects with the SAINT<sup>+</sup> and

SADABS programs [14]. Final unit cell parameters were determined by least-squares refinement of approximately 3,000 reflections from the corresponding data set. Direct methods structure solution, difference Fourier calculations and full-matrix least-squares refinement against  $F^2$  were performed with the SHELXTL software package [15].

The molecular structure of  $C_6H_5$ –CO–CH=CH– $C_6H_4$ (*m*-OH), forms II and III, with assigned atom-numbering scheme is illustrated in Fig. 1. The conformation of C2–C3 is *E* for all orthorhombic forms, which is characteristic to these compounds. An overlay of the simulated diffraction patterns of all observed polymorphs of *1-phenyl-3-*(*3-hydroxyphenyl*)-*2-propen-1-one* is given in Fig. 2. The experimental X-ray pattern of forms I, II, and III consistent with the corresponding simulated X-ray pattern, calculated using atomic coordinates, and is therefore indicative of a single crystalline phases for all observed polymorphs. A summary of the crystallographic data is provided in Table 1 and selected bond lengths and bond angles are



Fig. 1 Molecular structure of compound 1,  $C_6H_5$ -CO-CH=CH- $C_6H_4$  (*m*-OH), with atomic numbering scheme. Displacement ellipsoids drawn at the 50% probability level. Form III is shown, form II is essentially identical



Fig. 2 Overlay of simulated X-ray diffraction patterns of  $C_6H_5$ -CO-CH=CH- $C_6H_4$  (*m*-OH) polymorphs I, II, and III

Table 1 Crystal data and structure refinement for polymorphs I, II and III

Polymorph	I <sup>a</sup>	II	III
Empirical formula		$C_{15}H_{12}O_2$	
Formula wt.		224.25	
CCDC No.	209763	825808	825010
Temperature (K)	293(2)	296(2)	296(2)
Wavelength (Å)	0.71073	0.71073	0.71073
Crystal system, space group	Monoclinic, P2/n	Orthorhombic, Pca2 <sub>1</sub>	Orthorhombic, Pbca
Unit cell dimensions			
a (Å)	13.295(6)	11.631(2)	11.8100(8)
$b(\mathring{A})$	5.659(2)	13.163(3)	7.4075(5)
<i>c</i> (Å)	16.144(8)	7.3977(14)	25.8729(19)
β (°)	109.73(5)		
Volume (Å <sup>3</sup> )	1143.3(9)	1132.6(4)	2263.4(3)
Z, calculated density (Mg/m <sup>3</sup> )	4, 1.303	4, 1.315	8, 1.316
F (000)	472	472	944
Crystal dimensions (mm)	$0.40\times0.10\times0.08$	$0.42 \times 0.32 \times 0.08$	$0.30 \times 0.22 \times 0.04$
$\Theta$ Range for data collection (°)	$\Theta_{\rm max} = 26$	1.55–25.02	1.57-25.02
Limiting indices	$\begin{array}{l} -16 \leq h \leq 16, \\ -6 \leq k \leq \ 4, \ -19 \leq l \leq 19 \end{array}$	$\begin{array}{l} -13  \leq  h  \leq  13, \\ -15  \leq  k  \leq  15,  -8  \leq  l  \leq  8 \end{array}$	$\begin{array}{l} -14 \leq h \leq 14, \\ -8 \leq k \leq 8,  -30 \leq l \leq 30 \end{array}$
Reflections collected/unique	6517/2214	10714/1090	21080/1997
Data/restraints/parameters	2214/-/203	1090/1/158	1997/0/158
Goodness-of-fit on F2	0.93	1.051	1.051
R indices (all data)	$R_1 = 0.134, wR_2 = 0.133$	$R_1 = 0.0370, wR_2 = 0.0710$	$R_1 = 0.0679, wR_2 = 0.1044$
R indices $[I > 2\sigma (I)]$	$R_1 = 0.059, wR_2 = 0.113$	$R_1 = 0.0319, wR_2 = 0.0682$	$R_1 = 0.0460, wR_2 = 0.0949$

<sup>a</sup> Turowska-Tyrk et al. [12]

shown in Table 2. Crystal structure data for the monoclinic form is transcribed from a previous assignment [12].

#### **Results and Discussion**

The monoclinic form, Form I, has been identified and is reported in the literature. Form I adopts the space group P2/n with unit cell parameters a = 13.295(6) Å, b =5.659(2) Å, c = 16.144(8) Å,  $\beta = 109.73(5)^{\circ}$ , V =1143.3(9) Å<sup>3</sup>, and Z = 4 [12]. In Form I, hydrogen bonding links molecules into a discrete dimeric structure where the two molecules are related by an inversion center.

Form II exists in the orthorhombic crystal system. Space groups  $Pca2_1$  and Pbcm were indicated by the pattern of systematic absences in the intensity data. The acentric group,  $Pca2_1$ , was confirmed by obtaining a reasonable and stable solution and refinement, and verified by ADDSYM program implemented in PLATON [16–18], which found no missed symmetry elements. The asymmetric unit consists of one molecule and non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms bonded to carbon were placed in geometrically idealized positions and included as riding atoms, with d (C–H) = 0.93 Å and

Table 2 Select bond lengths (Å) and bond angles (°) for polymorphs I, II and III

Polymorph	I <sup>a</sup>	Π	III			
C(1)–O(1)	1.224	1.223(2)	1.227(2)			
C(1)–C(2)	1.476	1.470(3)	1.470(3)			
C(1)-C(10)	1.473	1.493(3)	1.490(2)			
C(2)–C(3)	1.325	1.322(2)	1.316(2)			
C(3)–C(4)	1.456	1.462(3)	1.462(2)			
C(4)–C(5)	1.386	1.393(3)	1.389(2)			
C(4)–C(9)	1.387	1.395(3)	1.395(2)			
C(5)-C(6)	1.381	1.386(3)	1.381(2)			
C(6)–O(2)	1.366	1.364(2)	1.361(2)			
C(6)–C(7)	1.386	1.381(3)	1.380(3)			
C(8)–C(9)	1.372	1.373(3)	1.374(3)			
C(10)-C(15)	1.383	1.388(2)	1.388(3)			
C(10)–C(11)	1.400	1.390(3)	1.390(3)			
C(11)-C(12)	1.383	1.383(3)	1.381(3)			
C(12)-C(13)	1.373	1.368(3)	1.371(3)			
C(13)-C(14)	1.370	1.375(3)	1.373(3)			
C(14)-C(15)	1.364	1.382(3)	1.380(3)			

Bond distances for form I refer to the atom numbering scheme used for forms II and III

<sup>a</sup> Turowska-Tyrk et al. [12]

Polymorph	D-HA	D-H	НА	DA	D—HA
I <sup>a</sup>	O(2)-H(2A)O(1)#1	1.032	1.753	2.775	170
II	O(2)-H(2A)O(1)#1	0.87(2)	1.91(2)	2.752(2)	160(3)
III	O(2)-H(2A)O(1)#1	0.92(3)	1.87(3)	2.784(2)	170(2)

Table 3 Geometries of hydrogen bond, for polymorphs I, II and III (Å, °)

<sup>a</sup> Turowska-Tyrk et al. [12]

 $U_{\rm iso,H} = 1.2U_{\rm eq~C}$ . The hydrogen atom bonded to oxygen (H2A) was located in a difference map and refined freely. Because of the absence of any atoms heavier than oxygen in the crystal, Friedel opposites were merged during refinement and the absolute structure could not be reliably determined.

Polymorph III crystallizes in the orthorhombic system in space group Pbca, as determined uniquely by the pattern of systematic absences in the intensity data. Non-hydrogen atoms were refined with anisotropic displacement parameters and the asymmetric unit consists of one molecule. Hydrogen atoms bonded to carbon were placed in geometrically idealized positions and included as riding atoms with d (C–H) = 0.93 Å and  $U_{iso,H} = 1.2U_{eq}$  C. The hydrogen atom bonded to oxygen (H2A) was located in a difference map and refined freely.

The molecular structure of this hydroxyl chalcone consists of a phenyl and a hydroxyl (phenyl) ring joined by a -C (=O–)–CH=CH entity. The dihedral angle between the {C4–C9} and {C10–C15} ring planes is 10.0°, 18.07(9)°, and 12.52 (10)° for Forms I, II and III, respectively. In the extended orthorhombic structures, molecules interact via hydrogen bonding of the carbonyl and hydroxyl groups (Table 3). These (molecular) links form infinite zigzag chains running along the crystallographic *a*-axis

direction in both compounds (Fig. 3a), which may be contrasted with that of Form I, where a molecular dimer is the repeating motif (Fig. 3b).

Although both forms II and III exist in the orthorhombic crystal system. Form II is a non-centrosymmetric packing variant of Form III. Differences in unit cell volume facilitate the distinct packing arrangements of these two polymorphs, Form II (1132.6  $Å^3$ ) possessing half the unit cell volume of Form III (2263.4 Å<sup>3</sup>). This smaller unit cell is evident when comparing the lattice parameters, where axes a and b are comparable, but the c-axes differ by half the length, as indicated in Table 1. The pattern of the hydrogen bonding is equivalent in these two structures and accounts for similarities along the crystallographic a-axis. A comparison of three adjacent symmetry-equivalent hydrogenbonded chains formed from OH-O hydrogen bonding is given in Fig. 4. Views nearly perpendicular to (upper figures) and parallel to (lower figures) a layer of chains are illustrated in Fig. 5. Adjacent chains in polymorph II  $(Pca2_1, left)$  are related by an axial translation (b axis). Adjacent chains in Form III (Pbca, right) are related by glide mirror plane symmetry. The glide plane is parallel to and bisects the layers of chains. The consequence of this glide symmetry is a repeat unit of two equivalent chains in



(a) Hydrogen bonding links molecules into infinite chains running along the crystallographic a-axis direction

(b) Hydrogen bonding links molecules into dimmer motif

Fig. 3 Hydrogen bonding scheme of polymorphs a: II and III. b: I



Fig. 4 Comparison of the crystal packing for polymorphs II and III. Views nearly perpendicular to (*upper figures*) and parallel to (*lower figures*) a layer of chains



Form III, Pbca

Fig. 5 Packing diagrams perpendicular to three adjacent layers of hydrogen bonded chains for polymorphs II and III. Views perpendicular to the propagation direction of the chains

Form III, compared to a repeat unit of one chain in Form II, and a doubling of one axial length (the c axis in form III). This packing also results in the centrosymmetric structure of polymorph III versus an acentric structure of polymorph II (Fig. 5).

Crystals of 1-phenyl-3-(3-hydroxyphenyl)-2-propen-1one can be isolated in one of three polymorphic forms. We report herein, the unique observation of the two orthorhombic forms of this hydroxy chalcone, Forms II and III. Although Form II and Form III both exist in the orthorhombic system and possess comparable plate-like morphologies, they vary in unit cell parameters, space groups, and packing, and as such are considered polymorphs. Variations in the hydrogen bonding connectivity help to distinguish these two forms from the monoclinic form I, where a dimer pattern is the repeating motif, and crystal packing differentiate the two orthorhombic forms.

# **Supplementary Material**

X-ray crystallographic data reported in this paper is deposited with the Cambridge Crystallographic Data Center as supplementary publication numbers CCDC 825010 and 825808. Copies of available material can be obtained, free of charge, on application to the Director, CCDC, 12 Union Road, Cambridge CB21EZ, UK.

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