

Article

Functionalized Polyphenols: Understanding Polymorphism of 2-Chloro-3',4'-Diacetoxy-Acetophenone

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Abstract

We report here an in-depth study concerning the synthesis, NMR, and X-ray structure determination of two new polymorphs of 2-chloro-3',4'-diacetoxy-acetophenone. A new, ecologically friendly method of synthesis in the solid phase, as well as a suitable method for protecting hydroxyl functionality, is presented. The ¹H- and ¹³C-NMR spectra as well as the single crystal X-ray diffraction studies proved unambiguously the structure of the compounds: the two polymorphs of 2-chloro-3',4'-diacetoxy-acetophenone and 2-chloro-3'-hydroxy-4'-acetoxy-acetophenone. The polymorph I crystallizes in the monoclinic P21/c space group, while polymorph II crystallizes in the Sohnke P212121 space group of the orthorhombic system, with no interstitial solvate molecules. Significant differences were observed in the supramolecular interactions in the crystal structure of the two polymorphs. Polymorph I is characterized as a parallel packing of weakly interacting supramolecular layers oriented in the 1 1 0 plane. The crystal structure of polymorph II is much more complex: each molecule is interconnected through 12 (twelve) hydrogen bonds with 9 (nine) adjacent symmetry-related molecules. The monoacetoxy derivative 2-chloro-3'-hydroxy-4'-acetoxy-acetophenone 3 crystallizes in the monoclinic *P*2₁/*c* space group, with one molecule in the asymmetric unit.

Keywords: polymorphism; 2-chloro-3',4'-diacetoxy-acetophenone; 2-chloro-3'-hydroxy-4'-acetoxy-acetophenone; supramolecular interactions; hydroxyl functionality protecting; ecologically friendly; polyphenols



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1. Introduction

Crystal polymorphism is an important phenomenon of solid-state chemistry that consists of the ability of a substance to crystallize in at least two crystalline forms, differing by molecular conformation, crystal packing, or both [1,2]. Polymorph compounds display different physical, chemical, and biological properties, such as melting point, color, solubility, dissolution rate, density, hardness, morphology, stability, and bioavailability, including efficacy and toxicity [1–6]. Therefore, crystal polymorphism has numerous and fascinating applications in various fields of activity, including the pharmaceutical industry, agriculture, materials science (dyes and pigments, batteries, optoelectronic devices), etc. [1,2,7–14]. Polyphenols are natural and/or synthetic compounds with phenyl rings substituted by

more than one hydroxyl group (-OH). There are many ways in which polyphenols are classified, the most general one being in three main categories: phenolic acids, flavonoids, and non-flavonoids [15]. Naturally occurring polyphenols are considered secondary bioactive compounds derived from plant sources [16,17], while synthetic polyphenols are obtained by synthesis [17–19]. Whether they are natural or synthetic compounds, polyphenols possess a wide range of beneficial actions for human health, including high antioxidative properties, antimicrobial, anticancer, and antiviral activity, as well as antihypertensive, neuroprotective, and immunomodulatory properties [20–29]. This is why polyphenols are of great interest in the pharmaceutical industry, beauty products, dietary supplements, and food industry (almost in all segments, from processing to food preservation) [17,24,28,30]. In continuation of our research in the field of biologically active natural and functionalized polyphenols [31–34] and their polymorphism properties [35], and keeping in mind protecting the hydroxyl functionality for further transformation, we present herein a new case of polymorphism for the 2-chloro-3',4'-diacetoxy-acetophenone molecule.

2. Materials and Methods

2.1. Materials

2-Chloro-3',4'-dihydroxy-acetophenone, acetic anhydride, and solvents were purchased from Merck and Sigma-Aldrich and used as received without any further purification processes. The uncorrected melting points were obtained using an A. Krüss Optronic Melting Point Meter KSPI. Commercial silica gel plates 60 F254 (Merck Darmstadt, Germany) were used for analytical thin-layer chromatography, which was then observed under UV light (max = 254 or 365 nm). The NMR spectra were recorded using an Avance III 500 MHz spectrometer from Bruker, Vienna, Austria, which operates at 125 MHz for ^{13}C and 500 MHz for ^1H . Chemical shifts were given as parts per million (ppm), coupling constants (J) in Hz, and delta (δ) units. Single crystal X-ray diffraction data for compound **3** were collected on an Oxford-Diffraction XtaLAB Synergy, Dualflex, HyPix diffractometer using Cu K α radiation, while, for **polymorph I** and **polymorph II**, the data were collected on an XCALIBUR Eos CCD diffractometer equipped with graphite-monochromated Mo K α radiation. Unit cell determination and data integration were carried out using the CrysAlisPro package from Oxford Diffraction [36]. The structures were solved with the SHELXT program using the intrinsic phasing method and refined by the full-matrix least-squares method on F^2 with SHELXL [37,38]. Olex2 was used as an interface to the SHELX programs [39]. Non-hydrogen atoms were refined anisotropically. Hydrogen atoms were added in idealized positions and refined using a riding model. Selected crystallographic data and structure refinement details are provided in Table 1, along with the corresponding CIF-files (see also **Supplementary Materials**, CCDC no. 11491, 2481078, and 2481079). The supplementary crystallographic data can be obtained free of charge via www.ccdc.cam.ac.uk (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

Table 1. Crystal data and details of structure refinement.

	Compound 3 (1149)	Polymorph I (6731)	Polymorph II (6732)
Emp. formula	$\text{C}_{10}\text{H}_9\text{ClO}_4$	$\text{C}_{12}\text{H}_{11}\text{ClO}_5$	$\text{C}_{12}\text{H}_{11}\text{ClO}_5$
Fw	228.62	270.66	270.66
T [K]	293	293	293
Space group	$P2_1/c$	$P2_1/c$	$P2_12_12_1$
<i>a</i> [Å]	4.77080(10)	12.5751(11)	6.6155(3)

Table 1. Cont.

	Compound 3 (1149)	Polymorph I (6731)	Polymorph II (6732)
<i>b</i> [Å]	20.7983(4)	13.4660(10)	12.0609(5)
<i>c</i> [Å]	10.6313(2)	7.5855(7)	16.0245(7)
α [°]	90	90	90
β [°]	98.077(2)	97.174(9)	90
γ [°]	90	90	90
<i>V</i> [Å ³]	1044.42(4)	1274.45(19)	1278.58(9)
<i>Z</i>	4	4	4
ρ_{calcd} [g cm ^{−3}]	1.454	1.411	1.406
μ [mm ^{−1}]	3.202	0.309	0.308
Crystal size [mm]	0.15 × 0.10 × 0.05	0.35 × 0.05 × 0.05	0.30 × 0.30 × 0.02
2 θ range	8.502 to 133.168	3.264 to 50.042	4.226 to 50.022
Refls. collected	6150	7170	7594
Indep. Refls., <i>R</i> _{int}	1852, 0.0266	2237, 0.0388	2261, 0.0323
Data/rests./params.	1852/0/138	2237/0/165	2261/0/165
GOF	1.066	1.014	1.078
<i>R</i> ₁ , <i>wR</i> ₂ (all data)	0.0416, 0.1189	0.0744, 0.1822	0.0503, 0.0903
Flack parameter	−	−	0.01(4)
CCDC no.	2482798	2481078	2481079

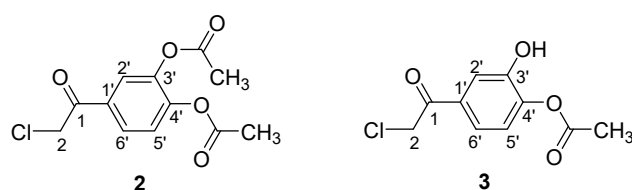
2.2. Methods

The acetylation of hydroxyl groups from 2-chloro-3',4'-dihydroxy-acetophenone with acetic anhydride took place as follows: in a 25 mL round-bottom flask, 1 mmol of 2-chloro-3',4'-dihydroxy-acetophenone and 3 mmol of acetic anhydride were added under solvent-free conditions. This mixture was homogeneously mixed by stirring (magnetic stirrer) and maintained at 60 °C using an oil bath. After 3 h, the reaction was complete. The liquid reaction mixture was then cooled down to room temperature, and a white precipitate formed. According to the TLC, the white precipitate is a mixture of 2 compounds.

a) If the precipitate is washed twice with diethyl ether, than filtered off and the compounds are separated by flash chromatography column on silica (CH₂Cl₂–MeOH = 99:1), after crystallization from methylene chloride (the crystals were grown up by slow evaporation at 20 degrees), the two polymorphous compounds are obtained (they were fully characterized by NMR and X-ray).

b) If the precipitate is dissolved in a small amount of methylene chloride, than filtered off and the compounds are separated by flash chromatography column on silica (CH₂Cl₂–MeOH = 99:1), after crystallization from methylene chloride (the crystals were grown up by slow evaporation at 20 degrees), the diacetylated 2-chloro-3',4'-diacetoxy-acetophenone **2** and the monoacetoxy derivative 2-chloro-3'-hydroxy-4'-acetoxy-acetophenone **3** are obtained (they were fully characterized by NMR and X-ray).

Scheme 1 presents the chemical structure with atom numbering for compounds **2** and **3**.



Scheme 1. Atom numbering for 2-chloro-3',4'-diacetoxy-acetophenone **2** and 2-chloro-3'-hydroxy-4'-acetoxy-acetophenone **3**.

2-chloro-3',4'-diacetoxy-acetophenone **2**.

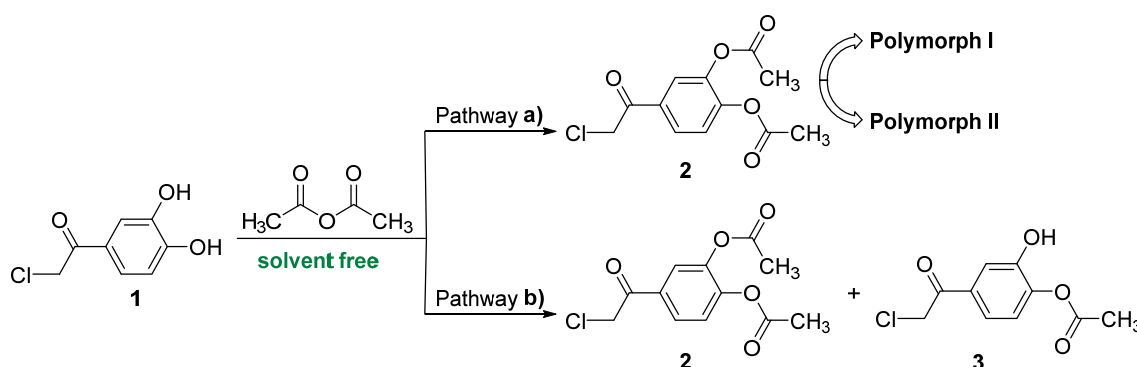
Polymorph **I** was obtained as white prism crystals, η = 63%, m.p. = 103–104 °C.

Polymorph **II** was obtained as white plate crystals, η = 12%, m.p. = 132–133 °C. ^1H NMR (500 MHz, CDCl_3 , δ , ppm): 2.31 (3H, s, methyl protons of acetoxy from 3' position), 2.32 (3H, s, methyl protons of acetoxy from 4' position), 4.66 (2H, s, methylene protons from 2 position), 7.35 (1H, d, J = 8.5 Hz, H-6'), 7.81 (1H, d, J = 0.2 Hz, H-2'), 7.87 (1H, dd, J = 8.5 Hz, J = 0.2 Hz, H-5'); ^{13}C NMR (125 MHz, CDCl_3 , δ , ppm): 20.68 (carbon from methyl group of acetoxy from 4' position), 20.79 (carbon from methyl group of acetoxy from 3' position), 45.82 (carbon from methylene group from 2 position), 124.15 (C-5'), 124.20 (C-2'), 127.17 (C-6'), 132.65 (C-1'), 142.60 (C-3'), 146.83 (C-4'), 167.67 (C from ester C=O from 3' position), 168.06 (C from ester C=O from 4' position), 189.33 (C from ketone C=O from 1 position).

2-chloro-3'-hydroxy-4'-acetoxy-acetophenone **3** was obtained as white plate crystals, η = 21%, m.p. = 135–136 °C. ^1H NMR (500 MHz, CDCl_3 , δ , ppm): 2.40 (3H, s, methyl protons of acetoxy from 4' position), 4.63 (2H, s, methylene protons from 2 position), 6.07 (1H, s, proton from OH from 3' position), 7.08 (1H, d, J = 6 Hz, H-6'), 7.77 (2H, m, H-2' and H-5'); ^{13}C NMR (125 MHz, CDCl_3 , δ , ppm): 21.09 (carbon from methyl group of acetoxy from 4' position), 45.69 (carbon from methylene group from 2 position), 117.71 (C-6'), 123.78 (C-2'), 127.69 (C-4'), 128.34 (C-5'), 138.53 (C-1'), 152.46 (C-3' from 3' position of aromatic ring), 169.05 (C from ester C=O from 4' position), 189.24 (C from ketone C=O from 1 position).

3. Results and Discussions

Initially, we tried to obtain our new compound 2-chloro-3',4'-diacetoxy-acetophenone **2** using a literature procedure applied in related cases [40], by treating 2-chloro-3',4'-dihydroxy-acetophenone **1** with acetic anhydride (AcAc) and using sodium hydroxide as the base, but we were unsatisfied with the reaction yield (less than 50%) and reaction conditions (use of toxic sodium hydroxide, long reaction time). This is why we tried different catalysts and reaction conditions, and, finally, we found an excellent setup procedure under solvent-free conditions, as we described above in the Materials and Methods Section, Scheme 2.



Scheme 2. Reaction pathway between 2-chloro-3',4'-dihydroxy-acetophenone and acetic anhydride under solvent-free conditions.

We wish to point out that our method of synthesis has some undeniable advantages: solvent-free conditions, no catalyst, higher conversions of substrates in short reaction time, mild reaction temperature, no side reactions, high atom economy (86.47%), and a good environmental factor ($\text{Ef} = 775 \text{ kg waste / kg product}$).

Our surprise came in the separation and purification process of the compounds when, after the flash chromatography, we obtained **2** (two) compounds. Initially, the separation and purification took place after procedure **b**). After crystallization from methylene chloride, the diacetylated 2-chloro-3',4'-diacetoxy-acetophenone **2** (m.p. = 103–104 °C, major,

yield 63%) and the monoacetoxy derivative 2-chloro-3'-hydroxy-4'-acetoxy-acetophenone **3** (m.p. = 135–136 °C, minor, yield 21%) were obtained. The ^1H - and ^{13}C -NMR spectra confirm the structures and are presented in Figures 1 and 2 and Table 2.

As we can see in Figure 1 and Table 2, in the ^1H -NMR spectra, the relevant signals for the structure are the two methyl groups from the acetoxy moiety and the methylene groups between the carbonyl ketone group and the chlorine atom.

Table 2. The main ^1H - and ^{13}C -NMR data of compounds **2** and **3**.

H/C	$\text{H}_{3'}$ (from CH_3)	$\text{H}_{4'}$ (from CH_3)	H_2 (from CH_2)	H (from OH)	-	-
	$\text{C}_{3'}$ (from CH_3)	$\text{C}_{4'}$ (from CH_3)	C_2 (from CH_2)	-	C, of C=O from 3'	C, of C=O from 4'
2	2.31	2.32	4.66	-	-	-
	20.79	20.68	45.82	-	167.67	168.06
3	-	2.40	4.63	6.07	-	-
	-	21.09	45.68	-	-	169.05

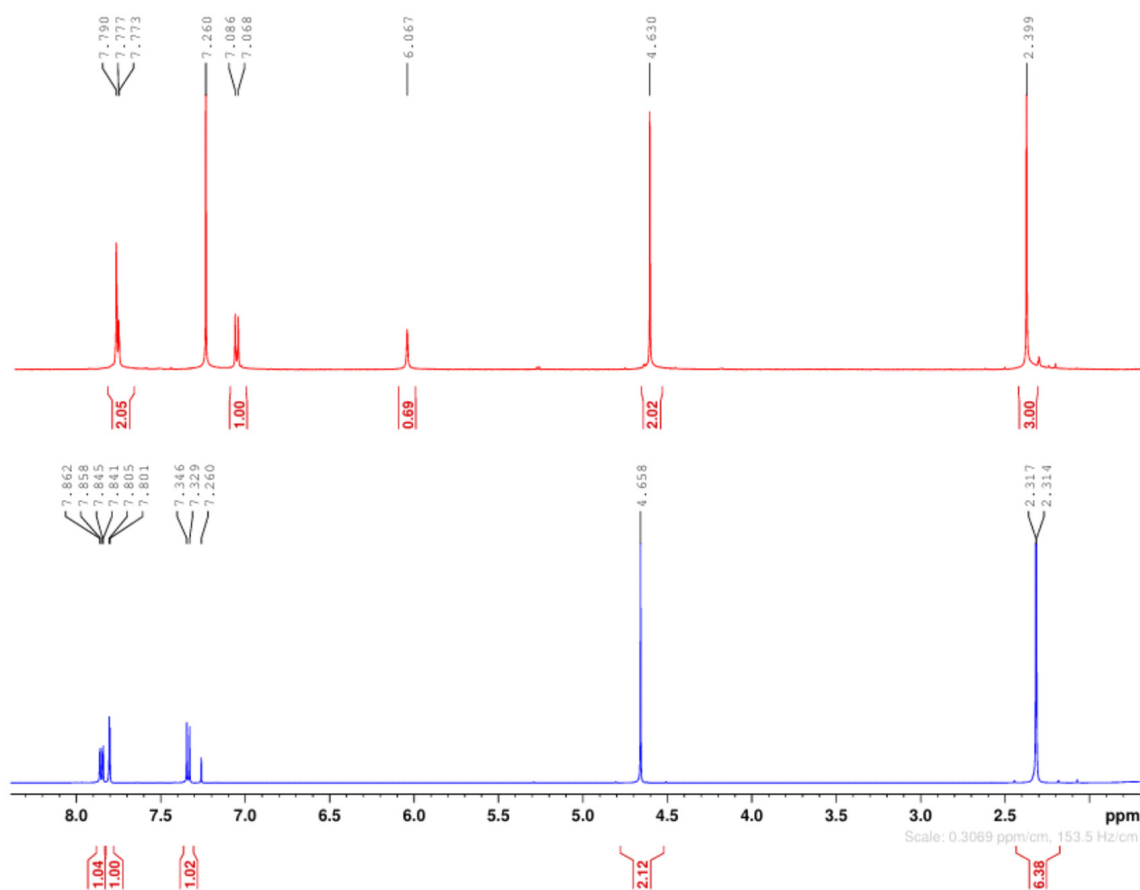


Figure 1. Superposed ^1H -NMR spectra of 2-chloro-3',4'-diacetoxy-acetophenone (**down**) and 2-chloro-3'-hydroxy-4'-acetoxy-acetophenone **3** (**up**).

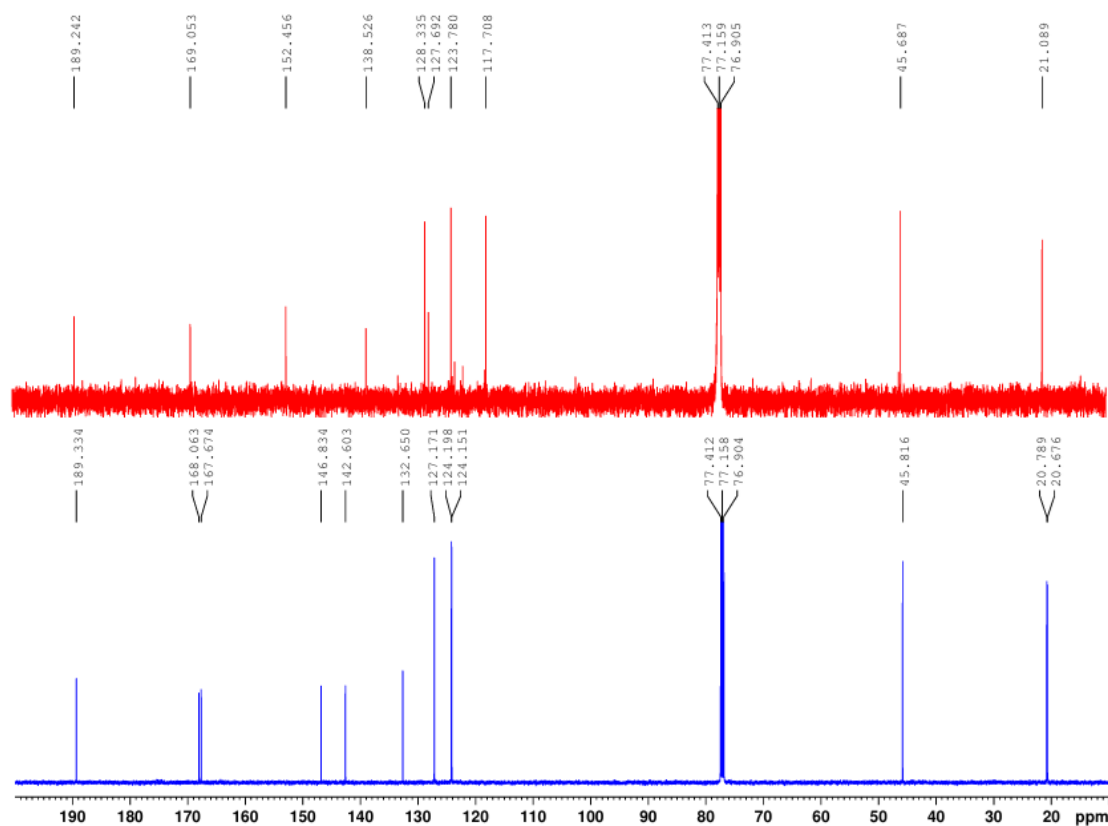


Figure 2. Superposed ^{13}C -NMR spectra of 2-chloro-3',4'-diacetoxy-acetophenone (down) and 2-chloro-3'-hydroxy-4'-acetoxy-acetophenone 3 (up).

In compound 2's spectra (Figure 1, down), the two methyl groups from the acetoxy moiety appear at 2.31 ppm (protons of CH_3 from position 3') and 2.32 ppm (protons of CH_3 from position 4'), respectively, as 6 (six) equivalent protons. The methylene protons appear at 4.65 ppm as a singlet. These findings are in accordance with the structure of 2-chloro-3',4'-diacetoxy-acetophenone 2. In compound 3's spectra (Figure 1, up), the situation changes completely: we found only a methyl group from the acetoxy moiety at 2.40 ppm and 3 (three) equivalent protons. The methylene protons appear at 4.63 ppm (as a singlet), and at 6.07 ppm, a supplementary broad singlet appears, which could be assigned to the proton from the hydroxyl moiety. These findings are in accordance with the structure of the monoacetoxy derivative 2-chloro-3'-hydroxy-4'-acetoxy-acetophenone 3 from Scheme 1.

The ^{13}C -NMR spectra are also in accordance with the considerations found above, and the differences in the spectra are even more profound. As Figure 2 and Table 2 reveal, in the ^{13}C -NMR spectra, the relevant signals for the structure are the two carbons from the methyl groups and the two carbons from the carbonyl ester groups of the acetoxy moiety. In compound 2's spectra (Figure 2, down), the two carbons from the methyl groups appear at 20.79 ppm (carbon of CH_3 from position 3') and 20.68 ppm (carbon of CH_3 from position 4'), respectively. The two carbons from the carbonyl ester groups of the acetoxy moiety appear at 168.06 ppm (C from ester $\text{C}=\text{O}$ from 4' position) and 167.67 ppm (C from ester $\text{C}=\text{O}$ from 3' position), respectively. These findings are also in accordance with the structure of 2-chloro-3',4'-diacetoxy-acetophenone 2. In compound 3's spectra (Figure 2, up), the situation changes again completely: we found only a carbon from the methyl group of the acetoxy moiety at 21.09 ppm (carbon of CH_3 from position 4') and a single carbon from the carbonyl ester group of the acetoxy moiety at 169.05 ppm (C from ester $\text{C}=\text{O}$ from 4' position). These findings are also in accordance with the structure of the monoacetoxy

derivative 2-chloro-3'-hydroxy-4'-acetoxy-acetophenone **3** from Scheme 1. The remaining signals are also in accordance with the proposed structures.

If the separation and purification took place after procedure **a**), after crystallization from methylene chloride, polymorph **I** (m.p. = 103–104 °C) and polymorph **II** (m.p. = 132–133 °C) can be obtained (according to the ^1H -, ^{13}C -NMR-, and X-ray spectra).

The X-ray spectral analysis of the monocystal also proved the structure of the compounds: the two polymorphic structures of 2-chloro-3',4'-diacetoxy-acetophenone **2** [polymorph **I** (with the m.p. = 103–104 °C) and polymorph **II** (with the m.p. = 132–133 °C)] and 2-chloro-3'-hydroxy-4'-acetoxy-acetophenone **3** (with the m.p. = 135–136 °C).

The results of the single crystal X-ray diffraction study for polymorphs **I** and **II** are illustrated in Figure 3, while the geometric parameters are summarized in Table S1 (see **Supplementary Materials**). According to X-ray crystallography, the reported structures represent two polymorphs of 2-chloro-3',4'-diacetoxy-acetophenone. Polymorph **I** crystallizes in the monoclinic $P2_1/c$ space group ($\rho_{\text{calcd}} = 1.411 \text{ g/cm}^3$), while polymorph **II** crystallizes in the Sohncke $P2_12_12_1$ space group of the orthorhombic system ($\rho_{\text{calcd}} = 1.406 \text{ g/cm}^3$). In both structures, the asymmetric part of the unit cell comprises one molecule without interstitial solvate molecules.

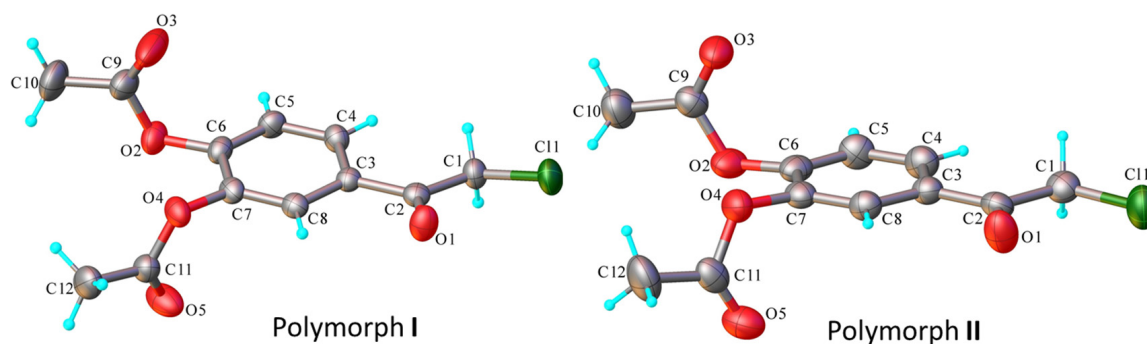


Figure 3. X-ray molecular structure of polymorphs **I** and **II** with atom labeling and thermal ellipsoids at 40% probability level.

As can be seen from the overlay diagram presented in Figure 4, the conformation of the two molecules is very close except for the chloroacetyl fragments, which exhibit insignificant but opposite deviation from the mean plane of the aromatic ring. The acetoxy groups in both polymorphs, due to steric overcrowding, are almost perpendicular with respect to the aromatic rings. The values of the dihedral angles between the two planar fragments are in the range of $86.7(4) \div 89.2(2)^\circ$ and $81.23(1) \div 89.22(1)^\circ$ for **I** and **II**, respectively.

In order to reveal the structural distinctions of the two polymorphs, apart from the geometric characteristics of individual molecules, analyzing the supramolecular interactions in the crystal is also crucial. Therefore, the short intermolecular contacts in crystals **I** and **II** were thoroughly analyzed. Seeing that there are no conditions for classical hydrogen bonding, only $\text{C-H}\cdots\text{O}$ and $\text{C-H}\cdots\text{Cl}$ interactions are expected to determine the crystal packing motifs. The geometric parameters of the H-bonds are summarized in Table 3. It is noteworthy noting that no π - π stacking arrangements were revealed in the polymorph structures of **I** and **II**. This arises from the steric hindrance caused by the opposite orientation of two acetoxy groups relative to the aromatic ring.

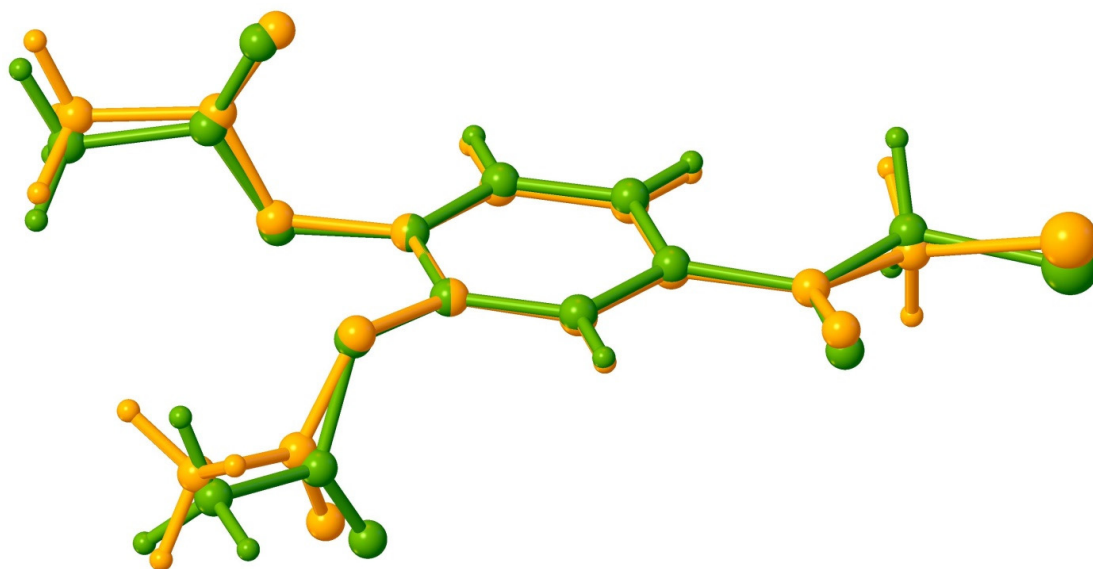


Figure 4. Overlay of polymorph I (yellow) and polymorph II (green).

Table 3. Hydrogen bond parameters.

Polymorph I					
D-H...A	$d_{D-H}/\text{\AA}$	$d_{H-A}/\text{\AA}$	$d_{D-A}/\text{\AA}$	$\angle DHA/^\circ$	Symmetry code
C1-H...O5	0.97	2.49	3.461(6)	175.1	$x, 1.5 - y, 0.5 + z$
C1-H...O1	0.97	2.57	3.332(6)	135.7	$x, 1.5 - y, -0.5 + z$
C8-H...Cl1	0.93	2.94	3.648(4)	134.0	$1 - x, -0.5 + y, 1.5 - z$
Polymorph II					
C1-H...Cl1	0.97	2.93	3.533(4)	121.1	$-0.5 + x, 1.5 - y, 1 - z$
C1-H...O5	0.97	2.54	3.401(5)	148.3	$1 - x, 0.5 + y, 0.5 - z$
C1-H...O4	0.97	2.63	3.512(5)	150.6	$1 + x, y, z$
C4-H...O3	0.93	2.59	3.289(5)	132.3	$1 + x, y, z$
C5-H...O1	0.93	2.57	3.423(5)	151.9	$1 - x, 0.5 + y, 0.5 - z$
C10-H...O2	0.96	2.59	3.379(5)	140.0	$-0.5 + x, 1.5 - y, -z$
C12-H...Cl1	0.96	2.95	3.700(5)	135.9	$0.5 - x, 1 - y, -0.5 + z$
Compound 3					
C1-H...Cl1	0.97	2.83	3.769(2)	163.8	$1 + x, y, z$
O3-H...O4	0.82	1.97	2.785(2)	175.8	$1 + x, 1.5 - y, z - 0.5$
C1-H...O2	0.97	2.39	3.362(3)	176.0	$x - 1, 1.5 - y, z - 0.5$
C5-H...O4	0.93	2.60	3.289(2)	131.4	$1 + x, 1.5 - y, z - 0.5$
C8-H...O2	0.93	2.65	3.464(3)	146.7	$x - 1, y, z$

As indicated by the data from Table 3, in the crystal structure of polymorph I, there are two short intermolecular contacts C-H...O, involving carbonyl O1 or acetoxy O5 atoms as acceptors, which are responsible for assembling the molecules into one-dimensional supramolecular arrays (Figure 5).

The third short intermolecular contacts C-H...Cl (Table 3) occur within the 2D supramolecular layer (Figures 6 and 7), which represents the main structural modules formed in crystal I. Thus, the crystal structure of polymorph I can be characterized as a parallel packing of weakly interacting supramolecular layers oriented in the 1 1 0 plane.

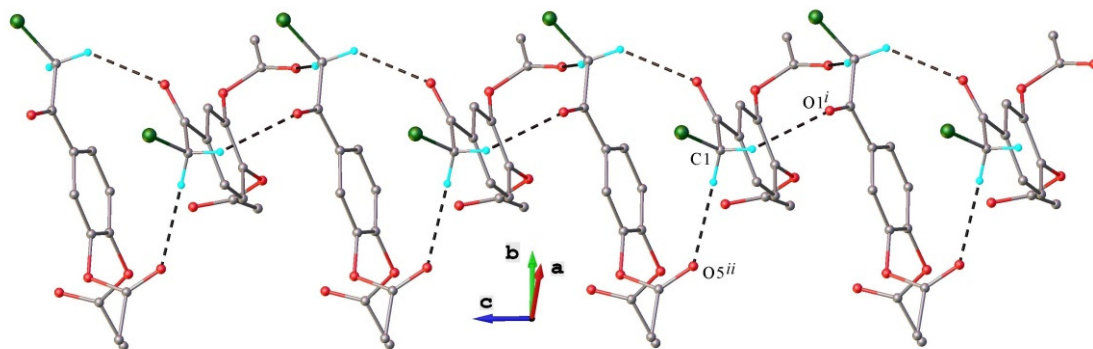


Figure 5. View of 1D supramolecular assembly in crystal structure of polymorph **I** showing role of C-H $\cdots$ O hydrogen bonding. Non-relevant H atoms are not shown for clarity.

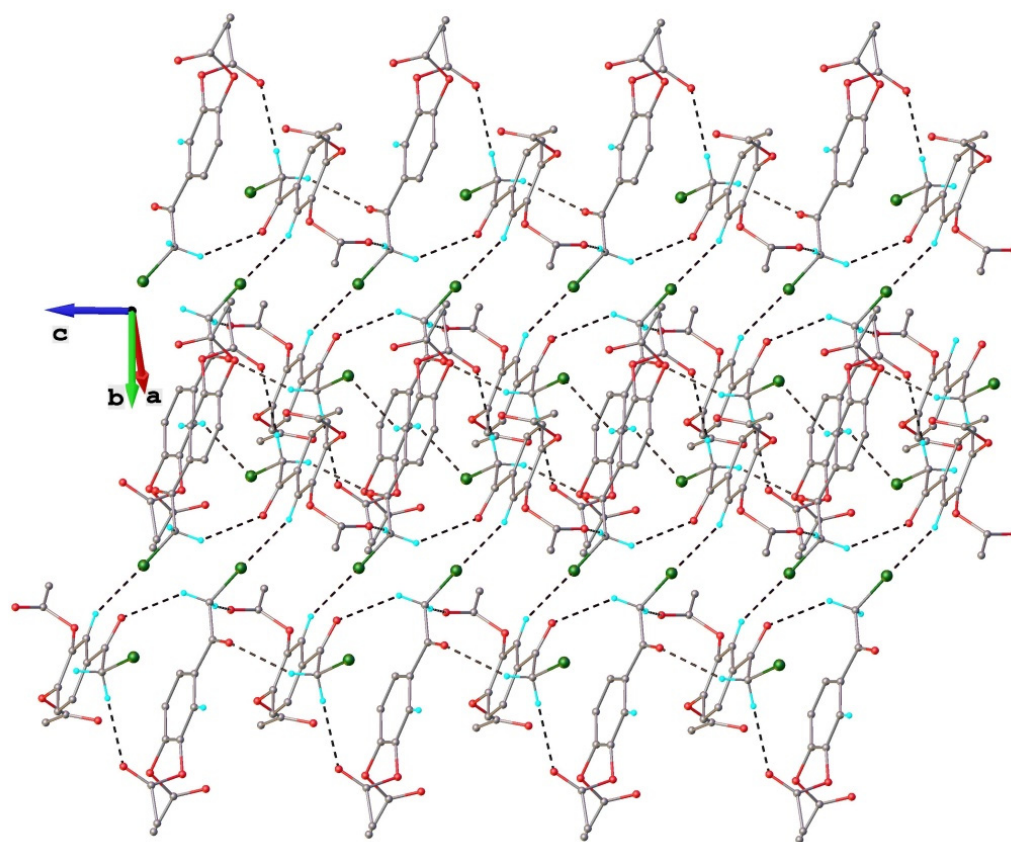


Figure 6. View of two-dimensional supramolecular layer in crystal structure of polymorph **I**.

When comparing the crystal structures of polymorphs **I** and **II**, it can be seen that in the latter case, the number of short intermolecular contacts is much higher (Table 3). Further analysis of the crystal packing did not reveal the presence of common structural modules specific to both crystals **I** and **II**. Indeed, as can be observed from Figure 8 illustrating the multitude intermolecular interactions exhibited by the isolated molecule in the crystal structure of polymorph **II**, each molecule is interconnected through twelve hydrogen bonds with nine adjacent symmetry-related molecules.

This specific structural module influences crystal packing, which determines the assembly of a quite dense and complex three-dimensional supramolecular network, as illustrated in Figure 9.

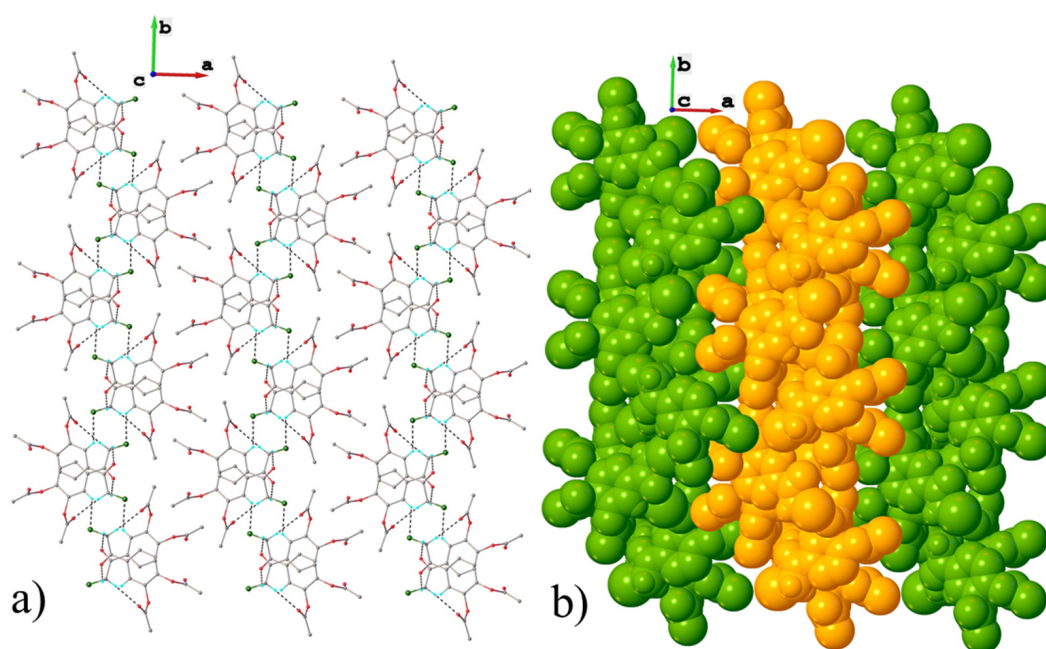


Figure 7. (a) Projection of crystal structure along a axis showing parallel packing of 2D layers in polymorph I; (b) sphere packing representation in polymorph I.

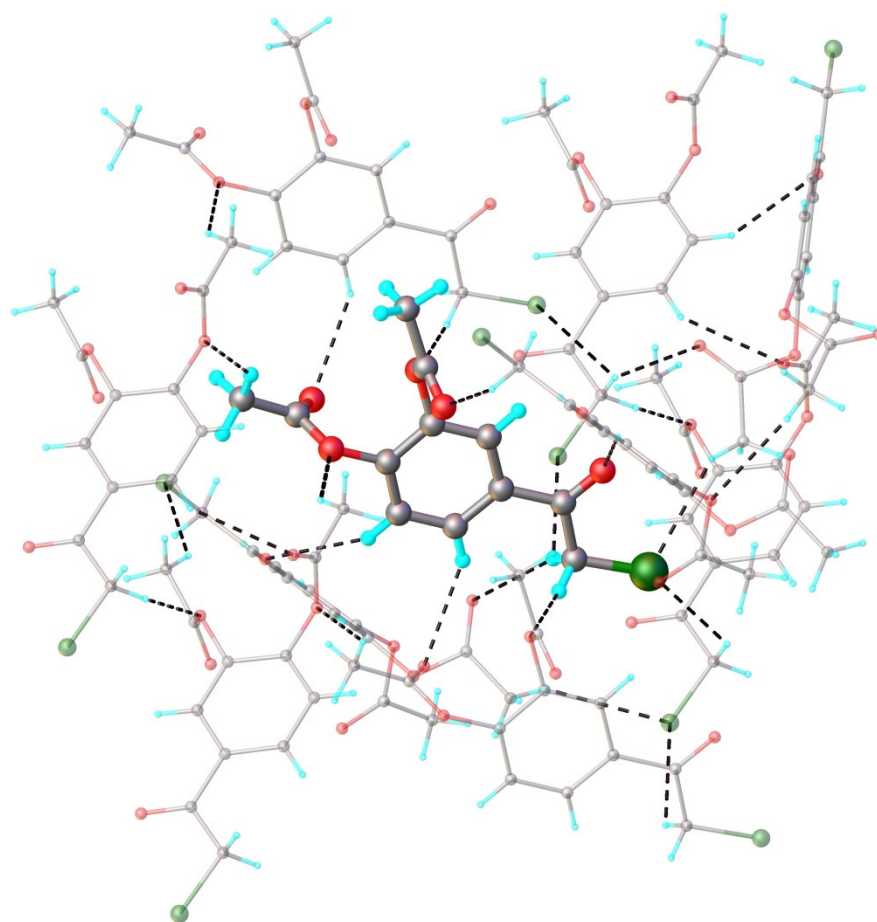


Figure 8. Fragment of crystal structure showing role of C-H...O and C-H...Cl hydrogen bonding in crystal structure of polymorph II. Symmetry generated molecules are drawn with faded colors.

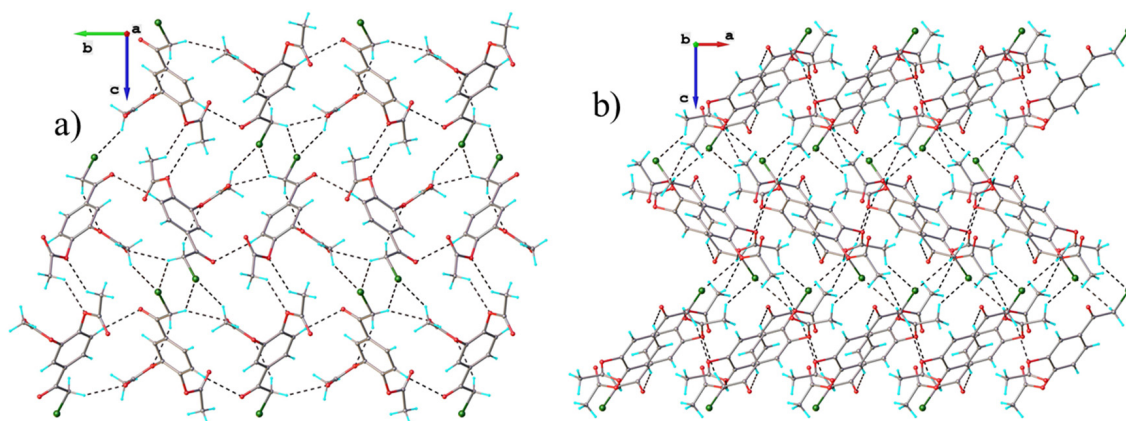


Figure 9. Projection of crystal structure in crystal structure of polymorph II: (a) along *a*; (b) along *b*.

The monoacetoxy derivative 2-chloro-3'-hydroxy-4'-acetoxy-acetophenone **3** crystallizes in the monoclinic $P2_1/c$ space group, with one molecule in the asymmetric unit. There are no interstitial solvent molecules in the crystal. The molecular structure of compound **3** is illustrated in Figure 10. As can be observed, the acetoxy group, due to steric overcrowding, is in nearly perpendicular orientation with respect to the main part of the molecule, which adopts essentially planar configuration. The absolute value of the C6-C7-O1-C9 torsion angle is $95.4(2)^\circ$. There are two contacts between the molecules in the adjacent stacks that are shorter than the sum of the van der Waals radii. In the absence of π - π stacking interactions, the crystal packing of compound **3** is mostly driven by the system of O-H $\cdots$ O and C-H $\cdots$ O contacts that are shorter than the sum of van der Waals radii, which organize the adjacent molecules into two-dimensional supramolecular layers in parallel arrangement to the 0 1 0 plane, as shown in Figure 11. The geometric parameters of the hydrogen bonds are listed in Table 3. The shortest contacts, C10-H10b $\cdots$ Cl1ⁱ (H $\cdots$ Cl1 = 3.110 Å, C $\cdots$ Cl = 3.647 Å, $\angle$ CHCl = 116.9° , symmetry code (i) $-x, y - 0.5, 1.5 - z$) and Cl1 $\cdots$ Cl1ⁱ (Cl $\cdots$ Cl = 3.737 Å, symmetry code (i) $-x, 2 - y, 1 - z$), between the molecules in the adjacent layers, which exceed the sum of van der Waals radii, indicate that the crystal structure is built from the parallel packing of the discrete 2D supramolecular network, as shown in Figure 12.

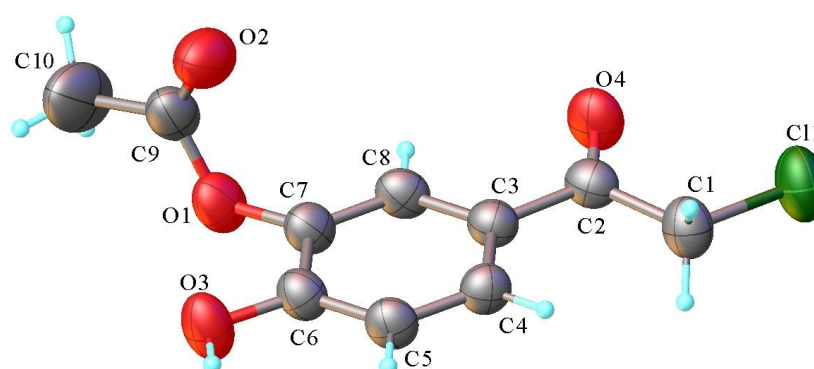


Figure 10. X-ray molecular structure of compound **3** with atom labeling and thermal ellipsoids at 50% probability level.

A possible explication for the polymorph II formation could be the in situ conversion of the monoacetoxy derivative to the diacetoxy during the crystallization process from methylene chloride.

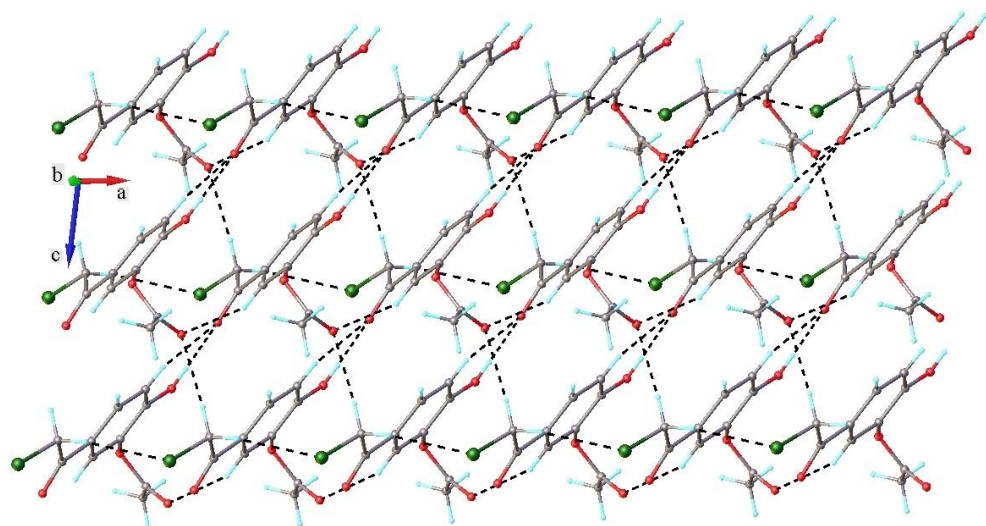


Figure 11. Crystal packing in **3** viewed along *b* axis showing role of H-bonding in formation of 2D supramolecular layer.

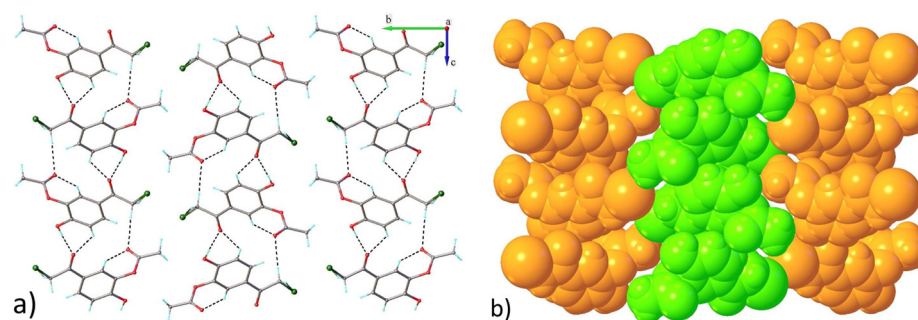


Figure 12. Projection of crystal structure **3** along *a* axis showing parallel packing of 2D layers. (a) Projection of crystal structure **3** along *a* axis showing (b) parallel packing of 2D layers.

4. Conclusions

This paper presents an in-depth study concerning the synthesis, NMR, and X-ray structure determination of two new polymorphs of 2-chloro-3',4'-diacetoxy-acetophenone. A new method of synthesis, in solid phase, for 2-chloro-3',4'-diacetoxy-acetophenone is presented. Our method has some undeniable advantages: less energetic consumption, shorter reaction time, no side reactions, high yield, no organic solvent used (reaction being in solid phase), high atom economy, and a good environmental factor. Keeping in mind the 12th principles of green chemistry, our method of synthesis could be considered ecologically friendly. This method of synthesis also has the advantage of being a facile and suitable pathway for protecting hydroxyl functionality for further chemical transformations.

According to the conditions of separation and purification, the method allows for obtaining either the two polymorphs of 2-chloro-3',4'-diacetoxy-acetophenone or the diacetoxy and the monoacetoxy derivatives of 2-chloro-3',4'-dihydroxy-acetophenone. The ^1H - and ^{13}C - NMR spectra as well as the single crystal X-ray diffraction studies proved unambiguously the structure of the compounds: the two polymorphs of 2-chloro-3',4'-diacetoxy-acetophenone and 2-chloro-3'-hydroxy-4'-acetoxy-acetophenone. The X-ray studies for polymorphs **I** and **II** reveal that the conformation of the two molecules is very close, except for the chloroacetyl fragment, which exhibits a slight but opposite deviation from the mean plane of the aromatic ring. Polymorph **I** crystallizes in the monoclinic P21/*c* space group, while polymorph **II** crystallizes in the Sohnke P212121 space group of the orthorhombic system, with no interstitial solvate molecules. Dramatic differences were

observed in the supramolecular interactions in the crystal structure of the two polymorphs. The crystal structure of polymorph **I** is characterized as a parallel packing of weakly interacting supramolecular layers oriented in the 1 1 0 plane. In the crystal structure of polymorph **I**, there are two short intermolecular contacts C-H $\cdots$ O, involving carbonyl O1 or acetoxy O5 atoms as acceptors, which are responsible for assembling the molecules into one-dimensional supramolecular arrays. The third short intermolecular contacts C-H $\cdots$ Cl occur within the 2D supramolecular layer, which represents the main structural modules formed in crystal **I**. The crystal structure of polymorph **II** is much more complex: each molecule is interconnected through twelve hydrogen bonds with nine adjacent symmetry-related molecules. This specific structural module influences crystal packing, which determines the assembly of a quite dense and complex three-dimensional supramolecular network. The monoacetoxy derivative 2-chloro-3'-hydroxy-4'-acetoxy-acetophenone **3** crystallizes in the monoclinic $P2_1/c$ space group, with one molecule in the asymmetric unit.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/cryst15090780/s1>.

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