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Polymorphism and Conformerism in Chalcones

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Herein two solid state phenomena have been observed in two chalcones. Firstly, polymorphism has been found in the (E)-1-(2-aminophenyl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (1). This compound crystallizes with only one conformer 10 rather than three in the known reported structure. In the polymorphs, the conformation of phenyl ring bonded to carbonyl differs slightly. The intermolecular hydrogen bonding from NH₂ is the main interaction responsible for polymorphism. Our polymorph is assembled only with weak 15 N—H $\bullet \bullet \bullet \pi$ interactions instead of strong N—H $\bullet \bullet \bullet O$ and N—H●●●N ones observed in the known structure. DFT calculations reveal that the three conformers of the known polymorph deviate from the minimum energy conformation which is adopted in our crystal form to compensate the 20 absence of strong intermolecular contacts. Second, conformerism is reported for (E)-1-(3-hydroxyphenyl)-3-(4nitrophenyl)prop-2-en-1-one (2). Three crystallographically independent molecules are found in the structure of 2: two of them are similarly planar with an anti conformation around 25 the single bond between the carbonyl and α carbons while the third one is twisted, with its phenyl ring bonded to carbonyl rotated by ca. 60° besides presenting a syn conformation corresponding around the rotatable bond. Both conformational features are related to the crystal packing, 30 allowing for accommodation of twisted molecules onto the

layers made up of hydrogen bonded planar molecules. Furthermore, our potential energy surfaces indicate that planar and twisted conformations of phenyl ring bonded to carbonyl are not compatible with syn and anti conformations 35 of chalcone skeleton.

Introduction

Chalcones are important natural compounds possessing a wide range of bioactivities. They can be also synthetically obtained and 40 used as intermediates of analogues with improved pharmacological profiles.¹⁻⁷ Chalcone denomination indicates the presence of a 1,3-diarylpropenone minimal framework, even though the possibility of attaching substituents at their aromatic

rings is a recipe of getting new compounds of this class with 45 tuned biological properties.⁸⁻¹⁰

In this study, two interesting solid state behaviors have been

observed as the substitution pattern in aryl moieties of two chalcone derivatives. First, polymorphism,¹¹⁻¹³ the ability of a compound to exist in more than one crystal structure, is reported

50 for (E)-1-(2-aminophenyl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (hereinafter compound 1, Figure 1). This compound has crystallized here in the monoclinic space group $P2_1/c$ as well as in its antecedent crystal phase,¹⁴ even though its asymmetric unit accommodates only one molecule rather than three ones as occurs 55 in the antecedent structure. In addition, similar conformations are found in the two crystal forms, which exhibit a typical case of packing polymorphism. Second, conformerism, the ability of a compound to exist in more than one conformation into a crystal structure, is reported for (E)-1-(3-hydroxyphenyl)-3-(4-60 nitrophenyl)prop-2-en-1-one (hereinafter compound 2, Figure 1). It has been synthesized previously,¹⁵ but its crystal structure has not been elucidated thus far. There are three crystallographically independent molecules in its centrosymmetric triclinic unit cell. Two of them are similar in conformation, with a same planarity 65 feature and conformation into the chalcone open-chain. The third molecule is twisted, with its phenyl ring at position 1 rotated by ca. 60° relative to the 3-phenylpropenone mean plane. Likewise, its propenone conformation differs from that of the two other planar molecules for a rotation of ca. 180° around the rotatable 70 bond within this open-chain. Furthermore, single-molecule calculations using Kohn-Sham Density Functional Theory (B3LYP) have helped us to understand the role of intermolecular interactions in allowing multiple crystal structures of 1 and variable conformations of 2.



Fig. 1 Chemical representation of 1 and 2 with phenyl ring labeling scheme.

Materials and methods

Synthesis and crystallization

⁵ Chalcone derivatives were synthesized according protocol described previously in the literature.¹⁶ Briefly, a solution of 3,4,5-trimethoxybenzaldehyde (392.4 mg, 2 mmol) and *o*-aminoacetophenone (270.5 mg, 2 mmol) was prepared in 8.0 mL of ethanol. Next, an amount of 1.0 mL of 24% sodium hydroxide ¹⁰ in water at 10 °C was added to this solution. After stirring overnight at room temperature, 10% HCl was added until pH 3. The solid of **1** was filtered and recrystallized from another isopropyl alcohol solution. After 7 days upon standing at room temperature in the dark, block-shaped single crystals of **1** in its ¹⁵ new Form II were grown on bottom and walls of the glass crystallizer. The same procedure was carried out to synthesize and crystallize compound **2**. However, the initial solution was prepared with 4-nitrobenzaldehyde (302.4 mg, 2 mmol) and *m*-hydroxyacetophenone (272.5 mg, 2 mmol).

Single crystal X-ray diffraction analysis

Block-shaped single crystals of 1 and 2 were selected and mounted on a k-goniostat of an Enraf-Nonius Kappa-CCD 25 diffractometer. Room temperature diffraction intensities were collected using graphite-monochromated MoKa X-ray beam through φ - ω scans and κ offsets. The X-ray diffraction frames were recorded using the program COLLECT,¹⁷ and reduction and scaling of the raw dataset were performed with HKL Denzo-30 Scalepack.¹⁸ The structures were solved by direct methods with SHELXS-97.¹⁹ The models were refined by the full-matrix least squares method on F^2 with SHELXL-97,¹⁹ with anisotropic thermal parameters for non-hydrogen atoms. Hydrogens were placed in idealized positions after their identification in the 35 difference Fourier map. Next, they were refined with fixed individual isotropic displacement parameters $[U_{iso}(H) = 1.2U_{eq}]$ $(C_{sp}^{2} \text{ or } N) \text{ or } 1.5U_{eq} (C_{sp}^{3} \text{ or } O)]$ using a riding model with bond lengths of 0.82 Å (O–H), 0.86 Å (N–H), 0.93 Å (C_{sp}^2 –H), or 0.96 Å (C_{sp}^{3} —H). Crystal data of compounds 1 (Form I¹⁴ and ⁴⁰ Form II) and **2** are shown in Table 1. The programs MERCURY²⁰

and ORTEP-3²¹ were used to generate artworks. The distribution of the most relevant torsion angles describing conformational features of both compounds was searched for chalcone structures deposited in the Cambridge Structural Database (CSD,²² version 45 5.36 of November 2014 with May 2015 update) using the

ConQuest²³ tool and afterwards analyzed with MERCURY.²⁰

Theoretical calculations

- ⁵⁰ Full geometry optimizations were performed starting from the X-ray structures of **1** [Form I¹⁴ and Form II (this study)] and **2**. Relaxed potential energy curves and surface scan were performed for the most relevant molecular dihedral angles in order to rationalize the polymorphism and conformerism found in the
- ⁵⁵ compounds studied here. All electronic structure calculations were performed with the GAMESS suite of programs²⁴ using the Density-Functional Theory (DFT)²⁵ with the Becke, threeparameter, Lee-Yang-Parr (B3LYP)^{26,27} exchange-correlation

function (mixing Becke²⁸ Slater exchange, Lee-Yang-Part²⁹
correlation functional, and exact exchange from Hartree–Fock theory³⁰). The diffuse Augmentated Polarization Consistent using a valence double-ζ polarizatoion quality (APC1)³¹ basis set, optimized to DFT, was employed in the calculations (DFT/B3LYP/APC1). The calculations were performed in ⁶⁵ Methano cluster placed in the Laboratory of Theoretical and Computational Chemistry at the Institute of Chemistry of the Federal University of Goiás. The calculation of a single point on the relaxed potential energy surface of the compound 1 was parallelized into 6 cores in an AMD Phenom II X6 2.8 GHz ⁷⁰ processor took about 5 days. Each point in the relaxed potential curves of compound 2 took about 3 day with the jobs parallelized into 4 cores in an Intel Core i7 2.8 GHz CPU.

 Table 1. Crystal data and refinement statistics for the crystal forms of

 75 compound 1 and for compound 2.

	Form I of 1^{14}	Form II of 1	2
structural formula	$C_{18}H_{19}NO_4$	$C_{18}H_{19}NO_4$	$C_{15}H_{11}NO_4$
fw	313.34	313.34	269.25
crystal dimensions (mm ³)	0.40/0.20/0.14	0.20/0.12/0.05	0.22/0.19/0.09
cryst syst	monoclinic	monoclinic	triclinic
space group	$P2_{1}/c$	$P2_{1}/c$	<i>P</i> -1
Ζ	12	4	6
<i>T</i> (K)	100	298(2)	298(2)
<i>a</i> (Å)	14.8537 (3)	12.713(16)	11.620(3)
b (Å)	20.5009 (4)	8.649(11)	13.232(3)
<i>c</i> (Å)	19.5952 (3)	15.231(19)	13.981(3)
α (°)	90	90	105.7760(10)
β (°)	127.043 (1)	103.798(15)	90.626(2)
γ (°) $V(\lambda^3)$	90 4762.78 (16)	90 1626(4)	112.7210(10) 1891.8(7)
calculated density (Mg/m ³)	1.311	1.280	1.418
absorption coefficient (mm ⁻¹)	0.093	0.091	0.104
θ range for data collection (°)	1.64 - 27.50	1.65 - 25.62	3.05 - 26.38
h range	-16 to 19	-11 to 15	-14 to 14
k range	-26 to 23	-8 to 10	-16 to 16
l range	-25 to 22	-18 to 18	-17 to 17
data collected	48,383	9,480	14,210
unique reflections	10,835	3,061	7,547
unique reflections with $I > 2\sigma(I)$	6,967	2,187	4,457
symmetry factor (R_{int})	0.0479	0.0269	0.0481
$\theta_{\rm max}$ completeness (%)	99.0	99.6	97.5
F (000)	1992	664	840
parameters refined	631	211	544
goodness-of-fit on F^2	1.023	1.030	1.050
R_1 factor for $I > 2\sigma(I)$	0.0645	0.0402	0.0673
wR2 factor for all data	0.1244	0.1168	0.1936
largest diff. peak (e/Å ³)	0.289	0.156	0.615
largest diff. hole $(e/Å^3)$	-0.243	-0.128	-0.230
CCDC deposit number	845,518	1,436,382	1,436,383

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Results and discussion

Conformational analysis of 1

⁵ Compound **1** is known to crystallize with three crystallographically independent molecules (Z' = 3) in a monoclinic lattice, space group $P2_1/c$.¹⁴ In fact, its crystal structure has been elucidated only in 2011 and no polymorphs thereof are known up to now. To the best of our knowledge, ¹⁰ polymorphism is rare in chalcones. Only few chalcone compounds are known to crystallize in at least two distinct solid state structures thus far due to an apparent conformational rigidity of the open-chain framework.³²⁻³⁴

Here, a true polymorph of **1** has crystallized in the same space ¹⁵ group of the antecedent crystal form but with only one molecule in its asymmetric unit (Z' = 1) instead (Figure 2). Hereinafter, this polymorph will be called as Form II. Its conformation does not differ much from those of the three molecules present in the asymmetric unit of the antecedent Form I.¹⁴ Their molecular ²⁰ backbone is almost completely planar, except for 1) the methyl moiety of methoxy in *para*-position being out of the plane passing through phenyl ring B and 2) a slight rotation on the C1– C7 bond axis connecting the *ortho*-aminophenyl ring to the central propenone core. To the best of our knowledge, searches in ²⁵ literature reveal a trend for planarity of the chalcone moiety with an *anti* conformation around C7–C8 (also called *s-cis* conformation),³⁵⁻³⁹ as found in **1**.



Fig. 2 30% Probability ellipsoid plots of **1** and **2** in the crystal forms ³⁰ elucidated in this study. Non-hydrogen atoms are arbitrarily labeled and hydrogen atoms are shown as spheres of arbitrary radii.

There are slight twists between the two least-square planes calculated through ring A (see Figure 1 for labeling scheme of chalcone rings) and through the propenone non-hydrogen atoms. ³⁵ These two planes form angles of 10.89(8)°, 18.90(7)° and 15.65(7)° in molecules A, B and C of Form I (according to numbering order given by Chantrapromma, Ruanwas and Fun¹⁴) and of 8.91(8)° in Form II. There is a still higher coplanarity between the central mean plane and ring B. The dihedral angle ⁴⁰ between them is 2.64(9)°, 7.48(6)° and 3.12(10)° in molecules A, B and C of Form I and 5.73(5)° in Form II. The values of torsions around C9–C10 bond axis connecting these two frameworks also describe their coplanarity. They measure close to either 0° or 180° (Figure 3) in all molecules of the two polymorphs.



Fig. 3 Distribution of chalcones in the Cambridge Structural Database (CSD)²² for the C8—C9—C10—C11 torsion. Colored lines highlight the values found in **1** and **2** for this torsion.

In order to assess these planarity features in chalcones, we have also performed a search in the CSD restricted to compounds bearing the 1,3-diarylpropenone moiety and compared to structures investigated here. In this sense, the torsions C6—C1—C7—C8 and C8—C9—C10—C11 were chosen to describe the scoplanarity between phenyl rings A and B and the central propenone core of 1. In Figures 3 and 4, histograms exhibit how 607 structures of chalcones found in the CSD are distributed for these two torsion angles. This structure number includes chalcones with any (or without) substituent in both phenyl rings 60 (gray bars). The distribution of a subset composed with 151 structures having either N or O atoms bonded to C2 is also displayed for torsion C6—C1—C7—C8 in Figure 4 (red bars).

It is observed that both torsions lie close to either 0° or 180° for the most of chalcones, revealing a tendency of coplanarity between phenyl rings A and B and propenone in that compounds. However, the most of chalcones possessing a potential hydrogen bonding donor substituent in C2 is present with C6—C1—C7— C8 in the range from 0° to 18° (ca. 60%, 90 out of 151 structures), as occurs in all molecules of 1 known thus far (see the values found in 1 in both crystal forms highlighted in Figure 4). This torsion stays in the upper range from 162 to 180° only in ca. 16% (24 out of 151) of all those chalcones. Therefore, the assembly of a $S_1^1(6)$ motif hinders the conformational freedom around C1—C7 bond axis so that only slight bents are observed in the most of these *ortho*-substituted chalcones. The rotation of approximately 180° is frequently hindered when N or O atoms is bonded to C2 due to formation of such intramolecularly hydrogen-bonded cycle.



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Fig. 4 Distribution of chalcones in the CSD²² for the C6—C1—C7—C8 and O1—C7—C8—C9 torsions. Colored lines highlight the values found in **1** for these torsions.

- ¹⁰ Moreover, the main intramolecular characteristic changed in the crystallographically independent molecules of **1** is in the rotation on the C1–C7 bond axis. Although subtle, this rotation is responsible for different ring A conformations. If central propenone mean plane is taken as reference, the NH₂ group can ¹⁵ be either on the same (molecules B and C of Form I and that of
- Form II) or on the opposite (molecule A of Form I) side of the out-of-plane methyl moiety (Figure 5). In order to describe this conformational feature, the values of the chosen torsion on the C1–C7 bond axis (C6–C1–C7–C8) are shown in Figure 4. One
- ²⁰ can see that this torsion in molecule A of Form I has opposite sign of that in all other molecules of **1**. Even so, the two observed ring A conformations are compatible with the formation of the intramolecular hydrogen bonding between amine and carbonyl moieties. Simultaneously, the other hydrogen of NH₂, which is
- ²⁵ not involved in $S_1^1(6)$, can be directed towards a hydrogen bonding acceptor in the lattice in both ring A conformations. In other words, the intramolecular non-covalent contact is formed in both conformations, assembling a $S_1^1(6)$ ring, meanwhile the

ortho-aminophenyl moiety can be slightly rotated to interact ³⁰ intermolecularly with neighbors in the lattice.

Concerning conformation around the rotatable C7-C8 bond, compound 1 adopts an anti conformation in both crystal forms, with the torsions C1-C7-C8-C9 and O1-C7-C8-C9 measuring close to 180° and 0°, respectively. This conformation 35 is preferred over the syn one (also called s-trans conformation) which has higher energy in most cases due to the steric hindering between the two hydrogens at C9 and at an ortho-position of ring A.35,36 For the last torsion, 85% of all chalcones found in the CSD (516 out of 607) are in 0-18° range, as observed for the 40 crystallographically independent molecules of 1 in its Form I and in that of Form II. Only ca. 6% (35 out of 607) are in the 162-180° range for O1-C7-C8-C9, which features a syn conformation around C7-C8. Contrary to distribution of the torsion on C1-C7, which is affected by the presence of a N or O 45 substituent in the 2-position of phenyl ring A, this orthosubstitution is not related to either syn or anti conformations around C7-C8. The distribution for O1-C7-C8-C9 in the chalcones subset with either N or O atom bonded to C2 follows that of general chalcones with any (or without) substituent in 50 phenyl rings.

At last, the conformation of the three methoxy groups is similar among the crystallographically independent molecules of Form I and II (Figure 5). All molecules are present with their non-hydrogen methoxy atoms in the plane crossing through the ⁵⁵ ring B, except for the methyl carbon of *para*-methoxy group. In fact, the conformation of the last groups differs negligibly for molecules of **1**.



Fig. 5 Superposition of crystallographically independent molecules of 1 $_{60}$ and 2 in the crystal forms elucidated in this study and also in the known Form I¹⁴ of 1.

Crystal packing analysis of 1

The crystal packing of 1 is stabilized only with weak intermolecular contacts in its Form II. The amine moiety is a nons classical hydrogen bonding donor to π -system of ring A, giving rise to one-dimensional chains along the [010] direction through N1—H1a•••Cg_(ring A) interactions (Figure 6a). Face-to-edge C— $H \bullet \bullet \bullet \pi$ interactions between rings A and B (C5—H5 \bullet \bullet Cg_{(ring} _{B)} and C17—H17b•••Cg_(ring A)) are also responsible for the 10 assembly of weakly stabilized supramolecular chains in Form II of 1 (Figure 6b). Geometry of these contacts is shown in Table 2.

In fact, the intermolecular hydrogen bonding donation from amine moiety is the main responsible for polymorphism in 1. All molecules are classical hydrogen bonding donors in Form I, 15 either to methoxy oxygens or to amine nitrogen. Molecules A and C are assembled into a centrosymmetric tetramer through classical hydrogen bonding donation from their amine moiety to amine nitrogen and *para*-methoxy oxygen of each others, respectively. Molecules B are hydrogen bonded to themselves 20 through their amine and 5-methoxy groups (Figure 7). On the other hand, in the polymorph described here, the amine moiety is intermolecularly involved only in weak N—H $\bullet \bullet \pi$ interactions.

reported in organic crystal structures and biomolecules.⁴⁰⁻⁴⁸ For instance, these non-classical hydrogen bonds are commonly found in protein structures being responsible for their folding and 35 maintenance through close packing between amine/amide and chains.43-45 Concerning polymorphism aromatic side phenomenon, the role of N—H $\bullet \bullet \pi$ interactions in the ability of the E-isomer of 2-fluoro-N'-(3-fluorophenyl)benzimidamide to assemble different crystal forms has been recently investigated by 40 Dey and Chopra.48 When one hydrogen atom of the amine group is not able to interact in strong N-H•••N interaction upon fast evaporation from a hexane solution of the compound, N- $H \bullet \bullet \pi$ contact is accessorily assembled to guarantee crystal lattice stability. On contrary, whether the solvent is slowly 45 evaporated, both hydrogens of NH₂ are involved in classical N bonds.48 hydrogen Here, H●●●N however, N---- $H \bullet \bullet \bullet \pi$ interactions are the main intermolecular contacts in crystal Form II of 1 since neither N—H●●●N nor N—H●●●O hydrogen bonds are found in its crystal packing. In conclusion, 50 these weak contacts are the primary intermolecular interactions in our polymorph while they work together with classical N-H•••N hydrogen bonds in the precedent polymorph described

The importance of N—H $\bullet \bullet \pi$ interactions has been well





Fig. 6 The crystal packing of 1 in its Form II (this study) is featured by 25 presence of chains assembled with (a) N—H $\bullet\bullet$ and (b) C—H $\bullet\bullet$ π interactions. The centrosymmetric dimer formed in this structure through C—H••• π interactions is shown in (c). The term Cg denotes the centroid calculated through the phenyl ring carbons. The measurements refer to hydrogen...Cg distance. Only hydrogens involved in the shown contacts 30 are displayed.

55 Fig. 7 Crystal packing in the known Form I of 1 showing two hydrogen

bonded tetramers made up of molecules A and C and their intercalation through a hydrogen bonded chain of molecules B (the framed chain grows onto the circled region as the drawing projection). Only hydrogens involved in the shown contacts are displayed.

DFT analysis of 1

Aiming to rationalize the polymorphism phenomenon of compound 1, the minimum energy conformations were computed 65 through a relaxed potential energy surface (PES) scan for the dihedral angles on the C1-C7 and C7-C8 bond axes (C6-C1-C7-C8 and O1-C7-C8-C9). These two dihedral angles were forced to assume constrained values ranging from -20° to 20°, with variable step increments considered in the DFT 70 calculations. Computational methods have been much explored nowadays to understand how different molecular geometries of a compound can occur in crystal structure and which are the

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Compound	$D - H \cdot \cdot \cdot A$	D—H (Å)	$H \cdot \cdot \cdot A(Å)$	$D \cdot \cdot \cdot A(A)$	$D - H \cdot \cdot \cdot A(^{\circ})$
1 N1-H1bO1 N1-H1aCg _(ring A) ⁱ	N1-H1bO1	0.86	1.97	2.612(3)	131
	0.86	3.18	3.999(4)	160	
	C5-H5Cg _(ring B) ⁱⁱ	0.93	2.88	3.633(4)	139
	C17-H17bCg _(ring A) ⁱⁱⁱ	0.93	3.48	3.846(5)	105
2	O1a-H1aO2b ^{iv}	0.82	2.03	2.848(3)	174
O1b-H1bO2 a^{iv} O1c-H1cO1 b^{v} C12a-H12a CgC _(ring A) ^{vi}	0.82	1.90	2.719(3)	176	
	0.82	2.04	2.844(2)	166	
	0.93	2.97	3.726(3)	139	

⁵ energetic spent and barrier to their interconvertion.⁴⁹⁻⁵² Besides such knowledge, these theoretical approaches allow for the prediction of forbidden geometries and additional minimum energy points.⁵³

The PES shown in Figure 8 was built by the cubic spline 10 interpolation of the electronic energies after optimization of all internal coordinates at the DFT/B3LYP/APC1 level of theory, except those defining the two constrained dihedral angles. In this picture, we can see two minimum energy conformers whose energies differ for about 0.0387 kJ mol⁻¹. This is a small energy 15 difference facilitating the inter-conversion between them in gas phase and even in solution,⁵⁰ mainly taken into account a low energy barrier to convert the most stable conformer into the local minimum energy point $[0.0877 \text{ kJ mol}^{-1}]$, which is the energy difference between the global minimum and the transition state 20 (TS)]. These two minimum energy conformers are featured by the $S_1^{(6)}(6)$ motif which can be slightly twisted towards opposite sides of the overall chalcone mean plane. This is achieved through synchronous rotations on both C1-C7 and C7-C8 bond axes, as can be seen in the similar signs and values of C6-25 C1-C7-C8 and O1-C7-C8-C9 dihedral angles in each minimum energy conformation (see below and in Figure 8). Moreover, an interesting finding comes from comparison between the two minimum energy geometries and the molecular conformations found in its crystal forms. The global minimum 30 has C6-C1-C7-C8 and O1-C7-C8-C9 torsion angles measuring -7° and -5°, which are values very close to the

experimental ones found in the polymorph described here (-9.1(2)° and -10.5(3)°). In fact, Form II is remarkably similar to the global minimum energy molecule from a conformational ³⁵ point of view with a root mean square deviation (RMSD) for the coordinates of their non-hydrogen equivalent atoms of 0.0934 Å.

- Hereinafter, all RMSD values presented refer to the coordinates of equivalent non-hydrogen atoms.
- On the other hand, the three crystallographically independent ⁴⁰ molecules of Form I resemble less the global minimum energy point, with corresponding RMSD values of 0.235 Å (A), 0.163 Å (B) and 0.134 Å (C). Except for one of these three crystallographically independent molecules, they also do not resemble much the local minimum energy conformer present with
- ⁴⁵ both torsions measuring 7° (the RMSD between the molecules A, B and C of Form I and the secondary calculated stable conformer is 0.0886 Å, 0.2608 Å and 0.3071 Å). It is key to observe that in Form I the signs of these two chosen torsions do not differ only in

their values but also in their signs, indicating an unsynchronized ⁵⁰ slight twist around their bond axes, *i. e.*, there are rotations on such bond axes towards opposite sides of chalcone mean plane in Form I. This differs from both minimum energy points and Form II present with both rotations in a same direction. Such behavior can be attributed to a competition between intramolecular and ⁵⁵ intermolecular classical hydrogen bonds present in Form I, while no deviation from global minimum energy conformation is gotten in Form II because of the absence of intermolecular classical hydrogen bonds in it. In other words, strong intermolecular from ⁶⁰ the intramolecular minimum energy point in all molecules found in the asymmetric unit of Form I, while in Form II this intramolecular geometry is obligatorily adopted to compensate the loss of strong intermolecular contacts.⁵³



65 Fig. 8 Potential energy surface of compound 1 calculated at the DFT/B3LYP/APC1 level of theory around two torsion angles on the single bond axes bearing carbonyl moiety.

In summary, Form I and II are intermolecularly and ⁷⁰ intramolecularly driven, respectively. Since the calculated energy difference between the conformations found in both crystal forms is lower than energetic gain from classical hydrogen bonds in Form I (~20 kJ.mol⁻¹ *per* contact) over non-classical ones in Form II (~5-10 kJ.mol⁻¹ *per* contact), Form I is expected to be the most ⁷⁵ stable one even though deviating from global minimum energy conformation, which is in agreement with the fact that it has been reported earlier.

Conformational analysis of 2

Compound 2 has crystallized in the triclinic space group P-1 with three molecules in the asymmetric unit (Figure 2). 5 Molecules labeled as A and B are considerably planar and can be related by pseudo translation symmetry through the lattice. The phenyl rings A and B of molecule A form angles of 9.26(9)° and $7.06(8)^{\circ}$ with the central propenone mean plane, respectively, while the corresponding measurements for molecule B are 10 2.56(9)° and 1.68(10)°. These values also reveal that molecule B is a few more planar than molecule A. Inspection of the torsion angles around C1–C7 and C9–C10 bond axes connecting phenyl rings to propenone core also shows this (Figures 3 and 9). They are nearer to either 0° or 180° in molecule B than in A. In fact, 15 molecule B is not completely planar only due to a slight rotation on the N1-C13 bond axis responsible for twisting the nitro group. Nitro group of molecule A is a few less bent than that of molecule B. There is also a small rotation on the C1-C7 bond axis of molecule A of 2 similarly as occurs in all molecules of 1.



Fig. 9 Distribution of chalcones in the CSD²² for the C2—C1—C7—C8 and C1—C7—C8—C9 torsions. Colored lines highlight the values found in **2** for these torsions.

25 The distribution for the chosen C2—C1—C7—C8 and C8— C9—C10—C11 torsion in all chalcone structures found in the CSD is in agreement with this planarity feature observed in molecules A and B of **2**. Most of chalcones are featured by both dihedral angles close to 0° or 180° (Figures 3 and 9). In addition, ³⁰ the subset having either N or O atom bonded to C3 is majorly composed with C2—C1—C7—C8 near to 180°. More than 86% (51 out of 59) of the structures belonging to this subset are in 162-180° range (Figure 9), revealing that the *meta*-substituent is preferred to be positioned in the same side of carbonyl oxygen.

³⁵ However, the conformerism observed in **2** is not due to these negligible differences between molecules A and B. If these two molecules are taken as references, the third crystallographically independent molecule C is present with notable rotations on the C1–C7 and C7–C8 bond axes bearing the carbonyl group. The ⁴⁰ mean planes of ring A and propenone are twisted by 64.70(12)° as a consequence of a ca. six-fold rotation axis on the first bond. Torsion angles around C1–C7 also describe such conformation. The unusual conformation around C1–C7 of molecule C can be viewed in the bottom histogram of Figure 9. Indeed, there are few

⁴⁵ examples of general chalcones with C2—C1—C7—C8 in the central range from 18° to 153° and this is the first report of a N or O *meta*-substituted chalcone in this interval. The other rotation on the C7–C8 bond axis is still larger. The torsions around this bond measure near to 180° (O2—C7—C8—C9) or 0° (C1—C7—C8—

⁵⁰ C9) in molecule C, while there is inversion of these values in molecules A and B, *i. e.*, their O2—C7—C8—C9 and C1—C7—C8—C9 torsions are close to 0° and 180°, respectively (Figure 9). Therefore, a rotation of ca. 180° on the C7—C8 bond axis can be also described for molecule C when compared to the two others

55 (Figure 5). In other words, molecules A/B and C adopt *anti* and *syn* conformations around this rotatable bond axis, respectively. As mentioned in the conformational analysis of 1, the occurrence of both conformations around this bond is well known,³⁵⁻³⁹ but their simultaneous occurrence into a same crystal structure is not.

- In the CSD, the C1—C7—C8—C9 torsion measures between 153° and 180° in almost all chalcones (ca. 93%, 566 out of 607). All N/O *meta*-substituted chalcones (59) are in this range for such torsion. Molecules A and B of 2 add to this range of values, while molecule C deviated from this trend and is the first report of a
- 65 N/O meta-substituted chalcone with C1—C7—C8—C9 measuring close 0°. It is striking to observe that the presence of meta-substituents beginning with either O or N does not affect the distribution for this torsion. Red bars present a same distribution profile of gray bars. At last, ring B is coplanar to propenone mean 70 plane of molecule C of compound 2, as occurs in its other conformers and also in all molecules of 1. There is an slight angle

of $11.4(2)^{\circ}$ between this phenyl ring and the central mean plane.

Crystal packing analysis of 2

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In the crystal packing of **2**, planar molecules A and B assemble a pseudo centrosymmetric dimer through classical hydrogen bonds between their hydroxyl and carbonyl groups (Figure 10). These dimers are side-to-side packed onto (110) plane, so originating sheets which are further stacked along the [110] direction through π - π interactions. Twisted molecules C are also accommodated into the sheets, through intercalation of two pseudo centrosymmetric A=B dimers, but their phenyl ring A is pointed towards the interlayer space. This packing fashion of ss molecules C has been resulted from its conformational

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(b)

Fig. 10 (a) The layered structure of **2**. Observe that one molecule C is between two hydrogen bonded dimers made up of molecules A and B onto the layer. The molecules marked with asterisks are shown in detail in (b). The term Cg denotes centroid calculated through the phenyl ring carbons. The s measurements refer to hydrogen...acceptor atom (or Cg) distance and hydrogen bonding angle. Only hydrogens involved in shown contacts are displayed.

adaptability and allows for simultaneous intermolecular contacts. These include classical hydrogen bonding donation to hydroxyl oxygen of molecule B on an adjacent layer, C— 10 H $\bullet \bullet \bullet \pi$ interaction between its ring A π -system on an interlayer site and an aromatic CH moiety of molecule A, and π - π interactions through the pillaring of the sheets (Figure 10 and Table 2 for geometry of classical and non-classical hydrogen bonds). Therefore, this set of strong (O—H $\bullet \bullet \bullet \bullet$ O) and weak 15 (C—H $\bullet \bullet \bullet \pi$ and π - π) intermolecular contacts compensates the

¹⁵ (C—110-01, and 12-17) internitorecular contacts compensates the energy gain from both rotations on the C1—C7 and C7—C8 bond axes (see in sequence). On can see the role of weak interactions in the crystal packing of 2. Indeed, these contacts are well documented as stabilizers of organic crystal structures, ²⁰ aiding or even playing the role of stronger interactions when they are not present.^{22,42,54-56}

DFT analysis of 2

In order to understand how so distinct conformations can be assumed into the same crystal form of 2, we have also calculated PES curves for torsion angles on the same bond axes analyzed for compound 1, at the same theory level. Firstly, the C2—C1— C7—C8 dihedral angle was forced to range from 0° to 180°, with

- ³⁰ increments of 5°, followed by optimization of all atom coordinates except those of the four atoms from the chosen torsion angle. Since there are two conformations in the asymmetric unit of 2 differing for ca. 180° around C7—C8 bond axis (*syn* and *anti* conformers), the PES curve for C2—C1—
 ³⁵ C7—C8 was calculated inputting the two distinct conformers (Figure 11). For both conformations, the PES scan is featured by
- two minimum energy points, which are lower in the *anti* conformer than in the *syn* one. The lowest two minimum energy points, both of them found for the *anti* conformer, are present 40 with C2—C1—C7—C8 torsion angle measuring 20° and 170°.
- These values describe almost planar conformations of the substituted phenyl ring A relative to chalcone mean plane. Both slight deviation from complete planarity is due to steric hindrance between vicinal hydrogen atoms bonded to C8 and the carbon at
- ⁴⁵ ortho-position of ring A (C2 or C6 according to the rotation of ca. 180° around C1—C7 bond axis). The second value is the lowest minimum energy point which matches well to the experimental value in the *anti* conformers of 2 (172.4(2)° and 179.0(2)° for molecules A and B). In fact, these theoretical and experimental ⁵⁰ conformations are similar, with RMSD of 0.157 Å and 0.241 Å for crystallographically independent molecules labeled as A and
- B. The highest two minimum energy points for the *syn* conformer

have torsion values of 40° and 145° featuring twisted conformations of phenyl ring A, which are related by a ca. 180° rotation on the C1-C7 bond axis as occurs in the two minimum energy points for the anti conformer. The higher energy of the s svn conformer have been reported previously for other chalcones.^{39,57-59} Such twisted conformations are a consequence of the steric hindrance between C9-H9 moiety from olefin moiety and the CH one at ortho-position of ring A (C2-H2 or C6-H6 depending of what minimum energy point), which are 10 positioned close together in the syn conformer.^{35,36} For this less stable conformer, the second dihedral angle energetically is slightly higher than the first one. This second theoretical torsion angle is in good agreement with that observed for the experimental syn conformer (119.0(2)°). Likewise, their 15 superimposed molecular backbones are resembled (RMSD of 0.398 Å).

Through inspection of the PES curve for the *syn* conformer shown in Figure 11, it is possible to see that both ring A planar conformations are not compatible with such conformation around ²⁰ C7—C8 bond axis because of higher molecular energy values for the C2—C1—C7—C8 torsion measuring close to 0° or 180°. In the same way, twisted ring A conformations have higher molecular energies than planar ones in the *anti* conformer. One can observe this seeing that the minimum energy points of one ²⁵ curve are not minimal in the other.



Fig. 11 Potential energy scans around C2–C1–C7–C8 torsion angle starting from *syn* (blue curve) and *anti* (green curve) conformers of compound 2.

Another interesting conclusion can be drawn from the PES curve for a torsion on the C7—C8 bond axis. This chosen dihedral angle was C1—C7—C8—C9, which was rotated with steps of 5° in the 0-180° range using the experimental *syn* ³⁵ conformer as starting geometry (Figure 12). This last PES was also calculated constraining only the coordinates of atoms enclosing the torsion angle with further optimization of all other atomic coordinates. As result from this DFT calculation, two minimum energy conformations have been outputted with C1—⁴⁰ C7—C8—C9 measuring 25° and 175°. These values are similar to those of the experimental molecules with *syn* and *anti* conformation around this bond axis. Furthermore, these two theoretical minimum energy geometries are well superimposed to the corresponding crystal ones (RMSD of 0.749 Å (C) and 0.119 ⁴⁵ Å (A) / 0.169 (B) Å for *syn* and *anti* conformers, respectively),

indicating that twisted and planar ring A conformations are adopted upon rotation around C7—C8 bond axis. This allows us to conclude that rotation around C1—C7 bond axis defining the phenyl ring A conformation just obeys the rotation on the C7— 50 C8 bond axis determining either *syn* or *anti* conformation of chalcone skeleton.

Taken into account the moderate energy differences^{53,60} between the two minimum energy points shown in Figure 12 and between the lowest minimum energy point and the transition ⁵⁵ state, which are somewhat 4 and 20 kJ mol⁻¹, respectively, the two distinct conformations of **2** can be promptly converted into each other with small energetic spent starting from a single rotation on the C7—C8 bond axis. In turn, classical intermolecular hydrogen bonds can be assembled through ⁶⁰ alternative positioning of the hydroxyl moiety of molecule C, allowing intermolecular accommodation even with net energetic gain from this balance between intra and intermolecular driving forces. In order to optimize this balance, it is known that molecules can assume higher energy conformers in crystal ⁶⁵ structure of up to 25 kJ mol⁻¹ above the global minimum energy geometry in the gas phase.⁵³

This study adds to the field in the line that simple molecules bearing the important chalcone scaffold can assemble into different crystal structures, keeping its backbone a few changed, 70 or, on a contrary thought, they can be present into a same crystal structure with very different conformations. Both phenomena arose from the balance between inter and intramolecular energies, being the latter probed in this study using DFT. In both cases, any deviation from the most stable conformer is compensated by 75 intermolecular stabilization. We hope that similar correlated experimental-theoretical investigations can be carried out with other chalcone-based compounds in order to know better the extension of these supramolecular and conformational adaptabilities into this compound class.



Fig. 12 Potential energy scan around C1–C7–C8–C9 torsion angle starting from *syn* conformer of compound **2**.

Conclusions

We have here reported two interesting solid state phenomena ⁸⁵ in two chalcones. Polymorphism has been found in **1**. This is not common in compounds owning chalcone skeleton. Even though conformation does not change much in the polymorphs, crystal packing is completely different between them, including loss of

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all classical intermolecular hydrogen bonds in the new crystal form. This unsuitable set of intermolecular hydrogen bonds in Form II is compensated by adopting the global minimum energy conformation around rotatable single bonds of the carbonyl ⁵ carbon atom. This contributes to the crystal lattice stabilization in the polymorph described here, while classical intermolecular hydrogen bonds contribute majorly in Form I whose molecules deviate from minimum energy points.

Chalcone **2** has exhibited conformerism. Its crystal structure is ¹⁰ formed with two similar and almost completely planar molecules and another one present with its 1-phenyl ring twisted by ca. 60° . It also differs from the two others in the conformation of the central propenone moiety (*syn* or *anti*). In addition, our DFT results have demonstrated that *anti*/planar and *syn*/twisted pair ¹⁵ conformations are exclusive and driven by the rotation on the bond axis connecting carbonyl and α carbons.

Therefore, we believe to have rationalized in depth molecular adaptations responsible for both phenomena described here, which will be useful for further comprehension in other ²⁰ compounds owing chalcone scaffold. The correlation between experimental and theoretical structures seems to be a suitable approach to probe the overall tendency of polymorphism and conformerism in this compound class.

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