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## Article

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# How accurate X-ray data are needed to obtain reliable order of stability for polymorphs?

## The case study of *p*-hydroxyacetophenone polymorphs.

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### Abstract:

Technical progress in crystallographic instruments allows contemporary crystallographers to more routinely conduct excellent quality low-temperature diffraction measurements. As a result, even crystal structures that have been extensively studied at ambient conditions start to reveal their more complex nature. The importance of low-temperature measurements is discussed based on the new, modulated structures found for polymorphs of 4'-hydroxyacetophenone (HAP). Diffraction data for this polymorphic system have been collected in the temperature range from 40K to 330K. At 123K form II of HAP appears to be a new, commensurately modulated structure with a modulation vector  $q = [0.4, 0.0, 0.0]$ . The structure can be solved and refined with 10 molecules in the asymmetric unit. Further decrease of temperature to 40K resulted in a discovery of a new, incommensurately modulated phase with four independent molecules in the  $P2_1$  monoclinic space group with modulation vector  $q = [0.37, 0.17, 0.0]$ . Consequences of modulation for the relative stability of polymorphs will be discussed.

**Keywords:** 4-hydroxyacetophenone, polymorphs, relative stability

## 1. Introduction

Polymorphism is the ability of a solid material to exist in more than one form of crystal structure. As it was shown in many cases, different polymorphic forms can exhibit different physicochemical properties and bioactivity. Around 30% of drugs exist in more than one polymorphic form<sup>1</sup>, and as those forms may differ in solubility and other important physicochemical properties, it is crucial to identify and characterize all polymorphic forms. Moreover, it is desired to gain knowledge about relative stability of polymorphic forms of a given substance. Experimentally, the relative stability of polymorphs can be obtained from calorimetric measurements or from solubility measurements.

There are also many theoretical studies which are focused on investigating relative stability of polymorphic structures, showing that differences in Gibbs free energies between polymorphic forms can be extremely small. For example, according to study by Nyman and Day conducted for 508 organic polymorphic systems over half of polymorph pairs are separated by less than 2 kJ/mol<sup>2</sup>. Therefore, if a given theoretical method is capable of predicting the relative stability in agreement with experiment for a wide range of polymorphic systems such a method should be considered as highly accurate.

Very often, starting point for such calculations are structures obtained from the Cambridge Structural Database (CSD), which are subsequently optimized. In such a case it is important to know, whether a given structure contains disorder or modulation, as all those features affect crystal stability. Up to now, anisotropic atomic displacement parameters (ADPs) are not stored in the official release files, therefore it is difficult to judge the quality of the structure.

This leads to a few important questions: How good X-ray data do we need in order to use them as an input for calculations of relative stability of polymorphs? How subtle structural details one needs to know for the studied polymorphic structures? And how many of those subtle details are overlooked in data deposited in the CSD?

In 2001 the CSD contained around 250,000 structures. Currently, in June 2019, the CSD has reached 1,000,000 structures. Nowadays X-ray diffractometers are much more advanced than 20-30 years ago. They have higher brilliance sources, micro sources,

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3 rotation anodes, and more sensitive faster 2D detectors. Moreover, there is a huge  
4 progress in data reduction and integration software as well. It has several consequences:  
5 we can collect data faster to higher resolutions than it was possible 30 years ago, and we  
6 can process them better. Additionally, there are several charge density models available,  
7 among them Transferable Aspherical Atom Model (TAAM)<sup>3, 4</sup> or Hirshfeld Atom  
8 Refinement (HAR)<sup>5-7</sup> that exceed the accuracy of the widely used Independent Atom  
9 Model (IAM). All of the above models can be applied during data refinement in order to  
10 obtain geometry parameters closer to optimized or neutron structure. Therefore, in  
11 principle, XRD data collected now, should be more accurate than those collected 20-30  
12 years ago. Unfortunately, it doesn't necessarily mean that data collected now and  
13 deposited in the CSD are more accurate, and there are several reasons for it.  
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24 First of all, software currently used for data reduction and integration is automated, to  
25 such a degree that one may solve and refine structure without even looking at diffraction  
26 frames. In consequence, as was already discussed by Andrew Bond<sup>8</sup>, many structures are  
27 measured, solved and refined by researches with limited experience in crystallography.  
28 As a result, some effects, such as diffuse scattering, disorder, or modulation, might simply  
29 be overlooked.  
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36 Secondly, even if crystal quality allows for a collection of high resolution, it is not done  
37 due to the lack of time. Unfortunately, common practice is to cut the data to lower  
38 resolution in order to obtain better statistics after refinement. In consequence, some  
39 subtle, but still important, features might be missed.  
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45 Thirdly, an important issue is the temperature of the data collection. More than a half of  
46 structures, deposited in the CSD were measured at room temperature only. As at room  
47 temperature it is difficult to obtain high resolution X-ray data for organic samples small  
48 disorders or modulations can be neglected due to high temperature factors. An interesting  
49 system, for which we already show, how important it is to conduct measurements not  
50 only at room temperature is gallic acid monohydrate<sup>9</sup>. A polymorph of GAM was the  
51 target of structure prediction in the fifth blind test (CSP target XXI, CSD reference codes  
52 KONTIQ037 and KONTIQ056), yet it was the only system that could not be predicted  
53 within the three most likely structures by any of the fourteen participating research  
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3 groups. The measurements, which were conducted later on, demonstrate that the  
4 structure is commensurately modulated at 10 K and disordered at higher temperatures,  
5 and that disorder gives substantial stabilization of the structure.  
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10 Therefore, we may claim that disorder, higher  $Z'$ , and modulations will contribute to Gibbs  
11 free energies of given polymorphic forms. In the case of polymorphs, where differences  
12 between both forms are below a few kJ/mol, neglecting such subtle structural details in  
13 the process of prediction of phase transition temperature may lead to incorrect stability  
14 order at given conditions.  
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20 In this contribution we will focus on the results obtained for a small, rigid system, namely  
21 4'-hydroxyacetophenone (HAP). Up to now, there are two known polymorphic forms of  
22 HAP. Both forms crystallize concomitantly, and according to calorimetric study by  
23 Bernardes et al.<sup>10</sup>, they are enantiotropically related – phase transition from stable at low  
24 temperature form II to form I occurs at around 351 K<sup>10</sup>. Recently, the phase transition  
25 temperature was estimated from adiabatic calorimetry measurements to be around 300  
26 K<sup>11</sup>. In the CSD, there are deposited structures of HAP polymorphs from 150 K and 298 K.  
27 Herein, we will present structures of HAP measured below 150 K. Our investigations  
28 demonstrate that form II of 4'-hydroxyacetophenone at 100 K is commensurately  
29 modulated and after lowering temperature to 40K we observe that structure is  
30 incommensurately modulated. X-ray and neutron diffraction data for both forms were  
31 collected in 100K. For form II of HAP weak peaks from modulation are observed from  
32 neutron diffraction data, similarly as from X-rays. Later on, we will discuss importance of  
33 the ADPs, as their direction and size at room temperature can indicate some interesting  
34 effects, such as modulations, disorders occur when the temperature will be sufficiently  
35 low. At the end, we will try to answer the question: is it really crucial, to be aware of such  
36 small structural differences between polymorphs?  
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## 52 **2. Methods**

### 53 **2.1 Crystallization**

54 Crystals of form I were grown by slow evaporation of solvent from a saturated ethanol  
55 solution of this substance over the course of several days at the room temperature (23°C).  
56 form II was crystallized according to the procedure reported by Kulkarni et al<sup>12</sup>. Slow  
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3 evaporation at room temperature from the ethyl acetate solution at a concentration below  
4 250 mg/mL was performed in a small sample vial. After approximately 48 hours crystals  
5 of good quality and suitable size were chosen for X-ray diffraction measurements.  
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## 8 9 **2.2. Single crystal X-ray diffraction measurements**

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11 Single crystal X-ray diffraction data of form I and II were collected on the Agilent  
12 Technologies SuperNova diffractometer with MoK $\alpha$  source at 40K, 100K, 123K, 150K, 200  
13 K and room temperature. Additionally, for form II we collected data at 330K. Data  
14 reduction was done using CrysAlis RED software<sup>13</sup>. The structure was solved with direct  
15 methods and then successive least-square refinements were carried out based on full-  
16 matrix least-squares on F<sup>2</sup> using the SHELX program<sup>14</sup>. Structures are deposited in the  
17 CSD, with deposition numbers CCDC 1910394-1910408. The modulated structures were  
18 refined in JANA program package<sup>15</sup>. The structure from 40 K was integrated as  
19 pseudomorphed twin related by two-fold axis along the direction [1 0 0]. For structure  
20 refinement the model found for the 100K phase was used as a starting point after  
21 transformation to the subgroup P2<sub>1</sub>. As the number of observed reflections is extremely  
22 small, we have used a rigid body approximation of the HAP molecule to describe four  
23 molecules in the asymmetric unit. For crystallographic details see Table 1 in Supporting  
24 Materials. As it was shown that from TAAM refinement it is possible to obtain more  
25 accurate atomic positions and ADPs than from routine IAM<sup>16</sup>, TAAM refinements were  
26 conducted using the MoPro package<sup>17</sup>. Multipole population parameters were derived  
27 from the UBDB<sup>3</sup> with the aid of the LSDB program<sup>4</sup>. Thermal expansion plots were  
28 generated in PASCAL program<sup>18</sup>.  
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## 44 **2.3. Neutron diffraction measurements**

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46 The neutron experiments were performed on the Time-of-Flight (TOF) single crystal Laue  
47 diffractometer (SXD)<sup>19</sup> at ISIS (Chilton, UK). The data were collected at 100K. The  
48 integration process was carried out with the SXD2001<sup>20</sup> program. The structure was then  
49 refined using JANA with the single batch of wavelength and extinction-corrected  
50 reflections<sup>15</sup>.  
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## 2.4. Computational details

### 2.4.1. Energy Frameworks

Interaction energy between molecular pairs has been calculated with CE-B3LYP/6-31G(d,p) model implemented in CrystalExplorer17<sup>21, 22</sup>. This allowed for a construction of energy frameworks, which display pairwise energies in the crystal as cylinders proportional in size to the magnitude of the interaction energy. All calculations were based on experimental structures deposited in the CSD (deposition numbers CCDC 686778 -686781).

### 2.4.2 CRYSTAL17 computations

#### *Lattice and total energies*

All calculations of lattice energy were performed with a CRYSTAL17 code<sup>23, 24</sup>. The structures were optimized with the dispersion corrected PBE0-D3(BJ) hybrid functional<sup>25</sup> and the TZP basis set developed by Ahlrichs and co-workers<sup>26</sup>. The unit cell parameters were fixed with lattice parameters determined from the X-ray diffraction experiments at a given temperature, allowing only the atomic coordinates to vary during optimization. We tested the performance of PBE0 functional in combination with two dispersion correction schemes – D2[5] and D3(BJ)<sup>27, 28</sup>. To further validate our results we ran calculations at the B3LYP-D3ABC/TZP level of theory on the dispersion-scaled HF-3c optimized geometries, an approach recently proposed by Ugliengo and co-workers<sup>29</sup>.

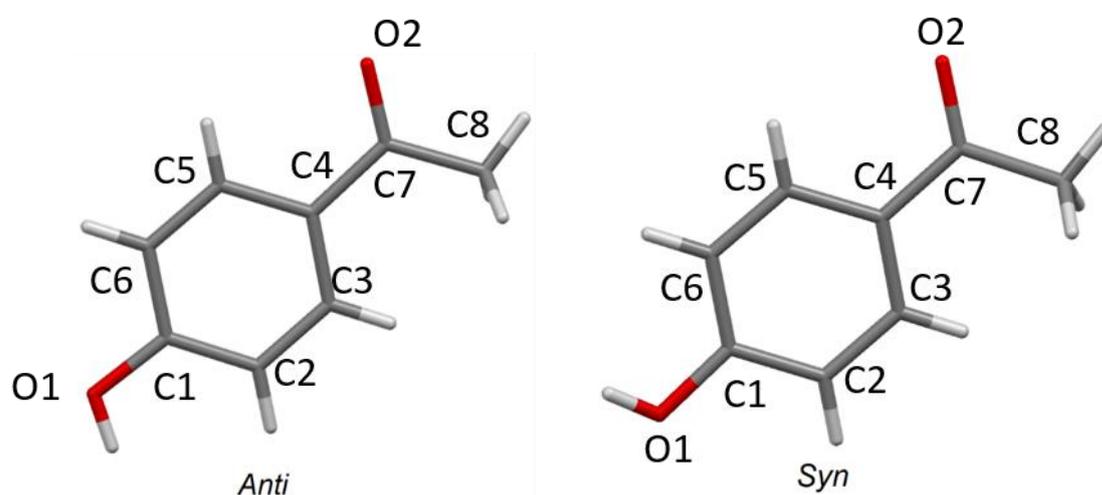
#### *Frequency calculations and ADPs estimation*

Similarly to lattice energy calculations, geometry optimization (only atomic coordinates) and  $\Gamma$  point frequency calculations were conducted in CRYSTAL17. Calculations were performed with B3LYP<sup>30</sup> functional and 6-31G(d,p) basis set. Obtained frequencies were utilised to calculate ADPs at 100K, as it was proposed by Madsen et al.<sup>31</sup>

### 3.1 Results and discussion: Structures from X-ray diffraction data and Energy Frameworks

Structures of both polymorphic forms of HAP have been previously described<sup>10</sup>. We provide a table with all crystallographic details from our experiments and detailed in the Supporting Information.

Form I and II of HAP are conformational polymorphs. In respective polymorphic forms molecules of HAP differ mainly in the orientation of the hydroxyl group with respect to the carbonyl group. In the monoclinic form I there is only one molecule in the asymmetric unit, which adopts E conformation (*anti*), whereas in form II, there are two molecules that both adopt Z conformation (*syn*).



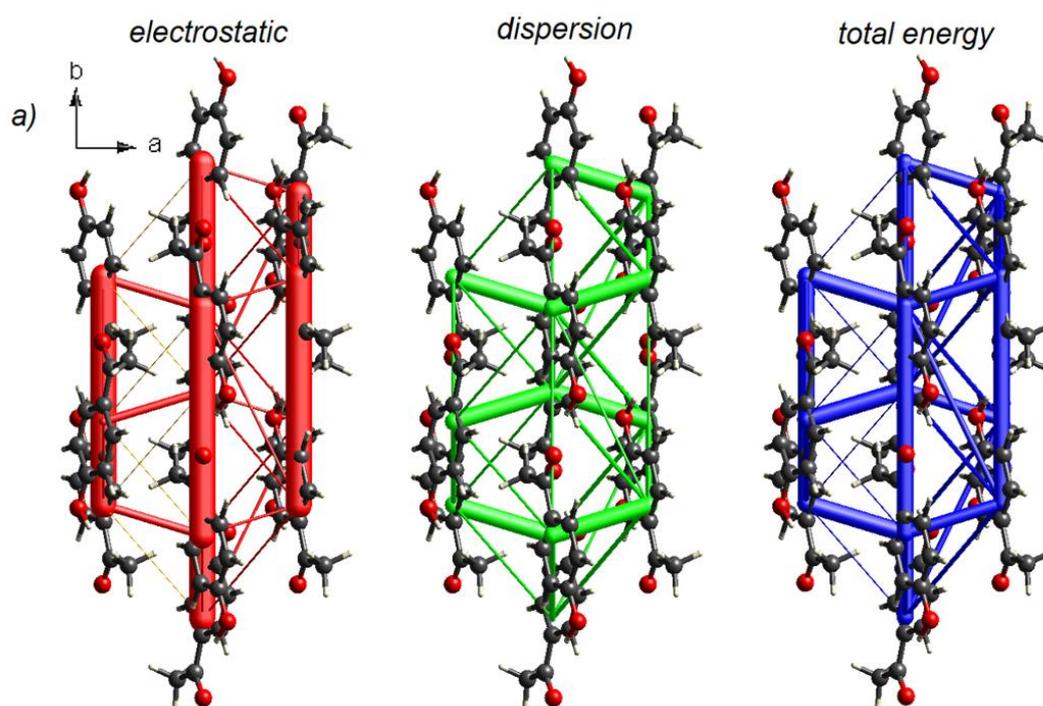
**Figure 1.** Molecular conformations of HAP form I (*anti*) and HAP form II (*syn*)

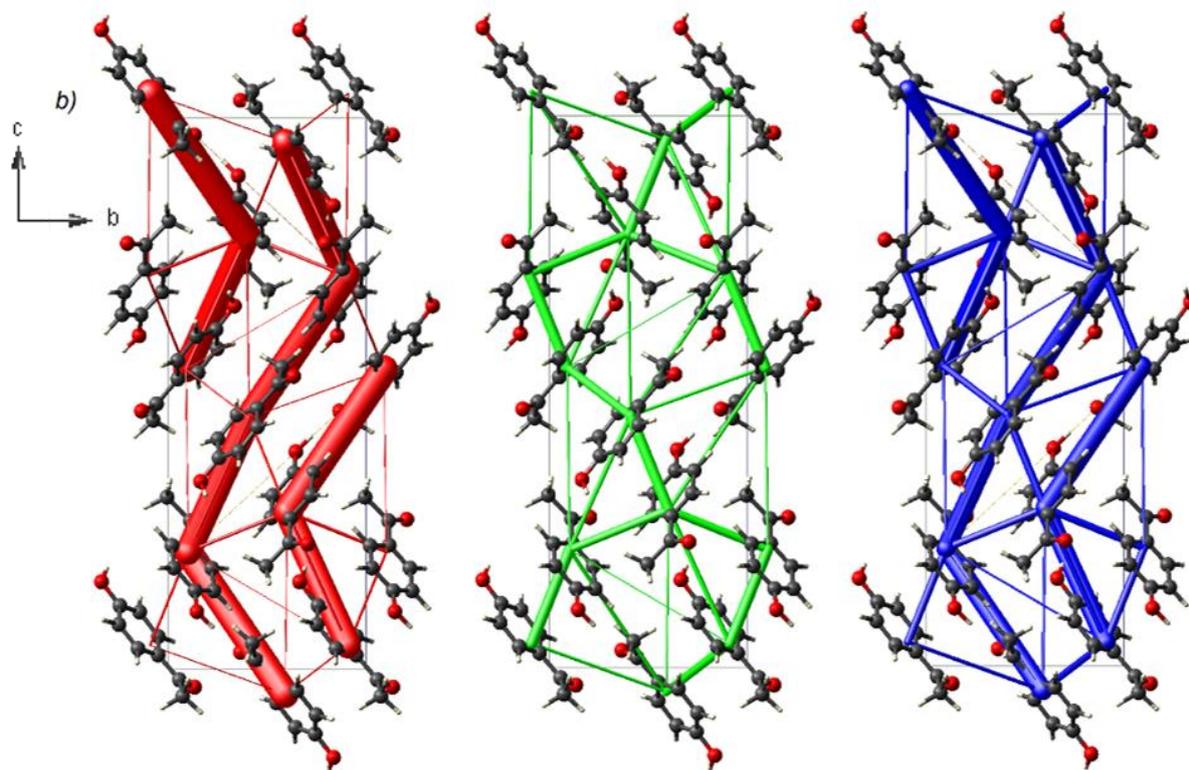
Despite the difference in conformation, both polymorphs form “head-to-tail” chains via hydrogen bonding between the hydroxyl group of one molecule (donor) and the carbonyl group of an adjacent molecule (acceptor). However, the different conformation of hydroxyl group leads to either linear chains (form I) or helical chains (form II).

To better understand structural differences in this polymorphic system we used the energy framework analysis<sup>22</sup>. This tool helps to visualize interaction energies governing molecular packing in the crystal lattice. In the case of HAP polymorphs the main structural motif, *i.e.* chains of hydrogen bonds, is clearly reproduced through a coulombic interaction (see **Figure 1**). In both polymorphs, hydrogen bonded chains in third direction are connected via dispersion interactions. However, the precise values of interaction energies

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3 reveal the differences between the two polymorphs. In the HAP I, stacking interaction  
4 between two molecules from chains separated by 3.745 Å has the highest contribution to  
5 the total energy with the value of -35 kJ/mol and is dominated by dispersion forces.  
6 Slightly lower energy (-24 kJ/mol) is observed for the chains separated by 3.940 Å. The  
7 second strongest interaction (-32 kJ/mol) in this crystal structure is the one observed for  
8 hydrogen bonded dimers in chains and has mostly electrostatic character.  
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14 The opposite situation was observed for the HAP II where two strongest interactions  
15 (-45kJ/mol and -44kJ/mol) were found among hydrogen bonded dimers and have mainly  
16 coulombic character. In contrast to HAP I, the stacking interaction between chains of  
17 hydrogen bonding is significantly weaker and its total energy equals -18kJ/mol.  
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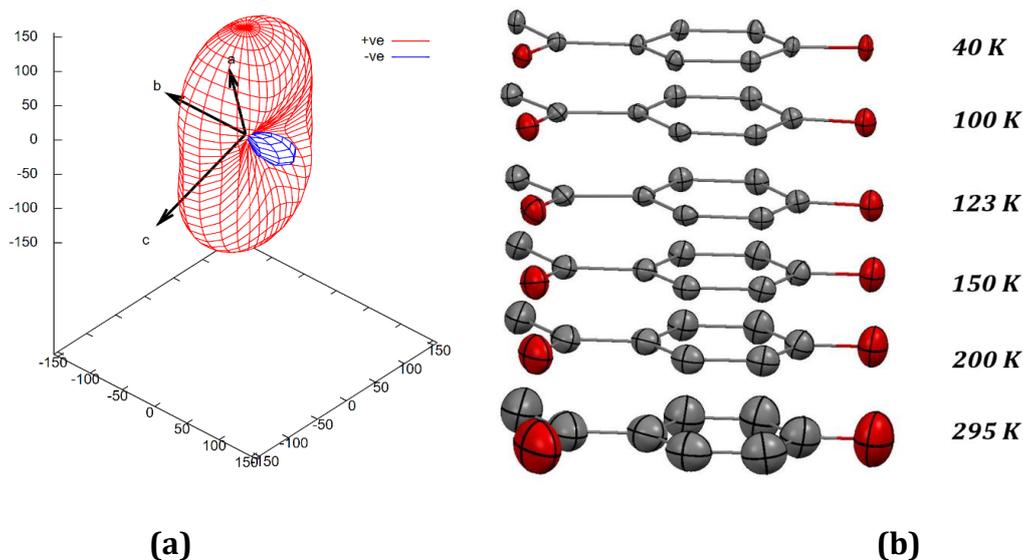
**Figure 2.** Energy framework diagrams of a) HAP I and b) HAP II polymorphs. Interactions below 1 kJ/mol energy threshold have been omitted for the clarity. The tube size was set at 100 for all presented figures enabling direct comparison of the respective dispersion (green) and electrostatic (red) contributions to the total intermolecular energies (blue).

## 3.2. Structures of HAP from multi-temperature measurements

**3.2.1 Structure of HAP I.** The structure of HAP form I measured at 40K, 100K, 123K and the room temperature (295K) stays in agreement with the previously reported structure from 150K. Structure from 100 K, obtained from neutron diffraction measurements, differ from X-ray structure mainly by X-H bond lengths. The most pronounced differences are observed for O-H...O hydrogen bonding.

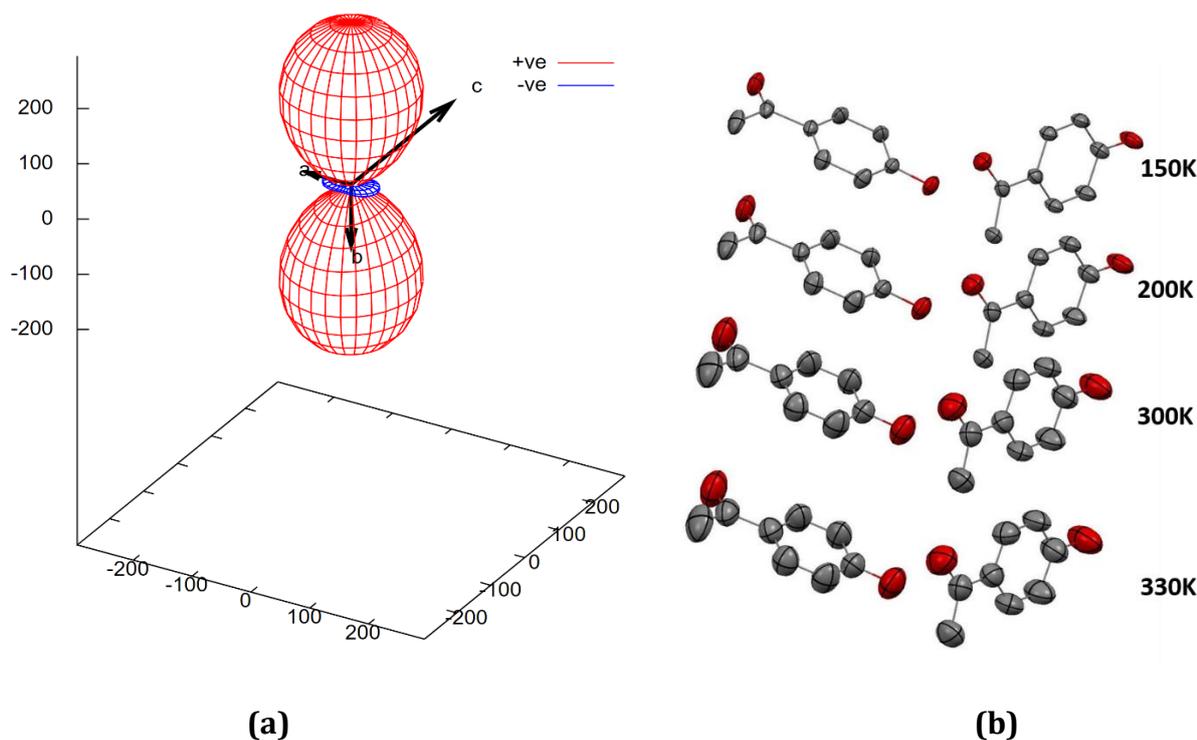
While the temperature is raised, as expected, the cell volume increases (from 681 Å<sup>3</sup> in 40K to 714 Å<sup>3</sup> in 295K). The thermal expansion tensor is plotted in the **Figure 3a**. We can clearly observe, that cell dimensions **a** and **c** are increasing while temperature is increased, whereas in **b** direction the situation is opposite. By looking into energy frameworks and by analysing interactions in **a**, **b** and **c** directions, one can easily explain this phenomenon: along **b** direction HAP molecules form chains via hydrogen bonding. In this direction interactions are the strongest and the most directional, therefore thermal expansion is negative. Such correlations of thermal expansion of a unit cell with interactions strength in different directions were studied already for many different systems *e.g.*<sup>32, 33</sup>, herein we present how easy it is to correlate thermal expansion with interactions strength in different directions *via* energy frameworks analysis.

As expected, ADPs are getting larger while the measurement temperature is growing (**Figure 3b.**) Interestingly, carbon atoms' ADPs on both sides of the ring, although look almost spherical, especially at higher temperatures exhibit slightly different size and orientation – those situated on the same side as oxygen from the acetic group are smaller and elongated in the bond direction, whereas those placed on the other side of the ring perpendicular to the ring plane.



**Figure 3. (a)** Unit cell thermal expansion tensor for **HAP I** **(b)** comparison of ADPs from different temperatures for **HAP I**.

**3.2.2. HAP II at liquid nitrogen temperature.** In the case of HAP II, initial results of diffraction measurements at 123K, 150 K, 200 K, 300 K, 330 K indicated, as in the case of HAP I, that the structure is identical to the previously known structure. The thermal expansion tensor is completely different in comparison to the one observed for the first polymorph - in the case of HAP II it is negative in *a* and *c* directions, and large, positive in *b* direction. Once again, such shape of thermal expansion tensor can be explained by analysis of intermolecular interactions and energy frameworks. In *b* direction, structure is the most susceptible for changes, as in this direction the interactions are the weakest: from energy frameworks (**Figure 2b**), we can clearly state, these chains of hydrogen bonds are affecting *a* and *c* directions, whereas in *b* direction we observe less directional and significantly weaker in this case stacking interactions. In the **Figure 4b**, we present thermal evolution of ADPs.



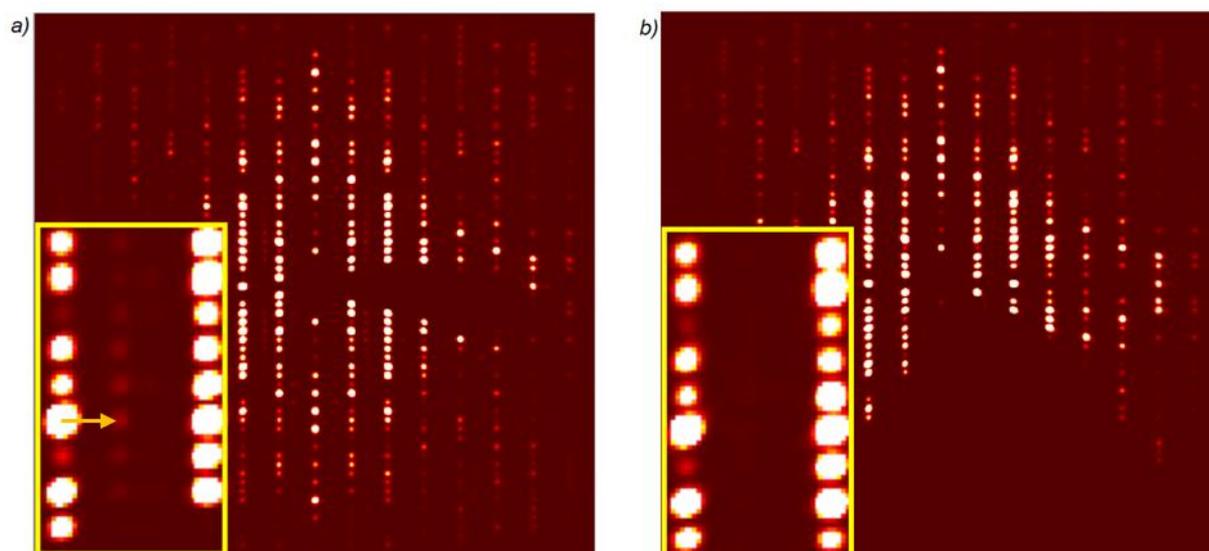
**Figure 4.** (a) Unit cell thermal expansion tensor for **HAP II** (b) comparison of ADPs from different temperatures for **HAP II**.

At 123K following standard integration and data refinement procedures, the data were refined to a reasonable R-factor value of 0.0421. Routine validation procedure performed with an *IUCr checkCIF* reported only minor alerts of a C level (namely, large U3/U1 Ratio for Average U(i,j) Tensor). However, after looking at the reconstructed precession images (**Figure 5.**) it was clear that some additional reflections, which were not observed for this polymorph at 150K, appear. In the case of 123K temperature HAPII even though it was possible to account for additional reflections during data processing and subsequently refine data collected at 123K in larger unit cells, none of the proposed solutions led to an unambiguous crystal structure. Therefore, data collection was repeated at 100K which allowed us to observe sufficient intensity to sigma ratio of additional peaks.

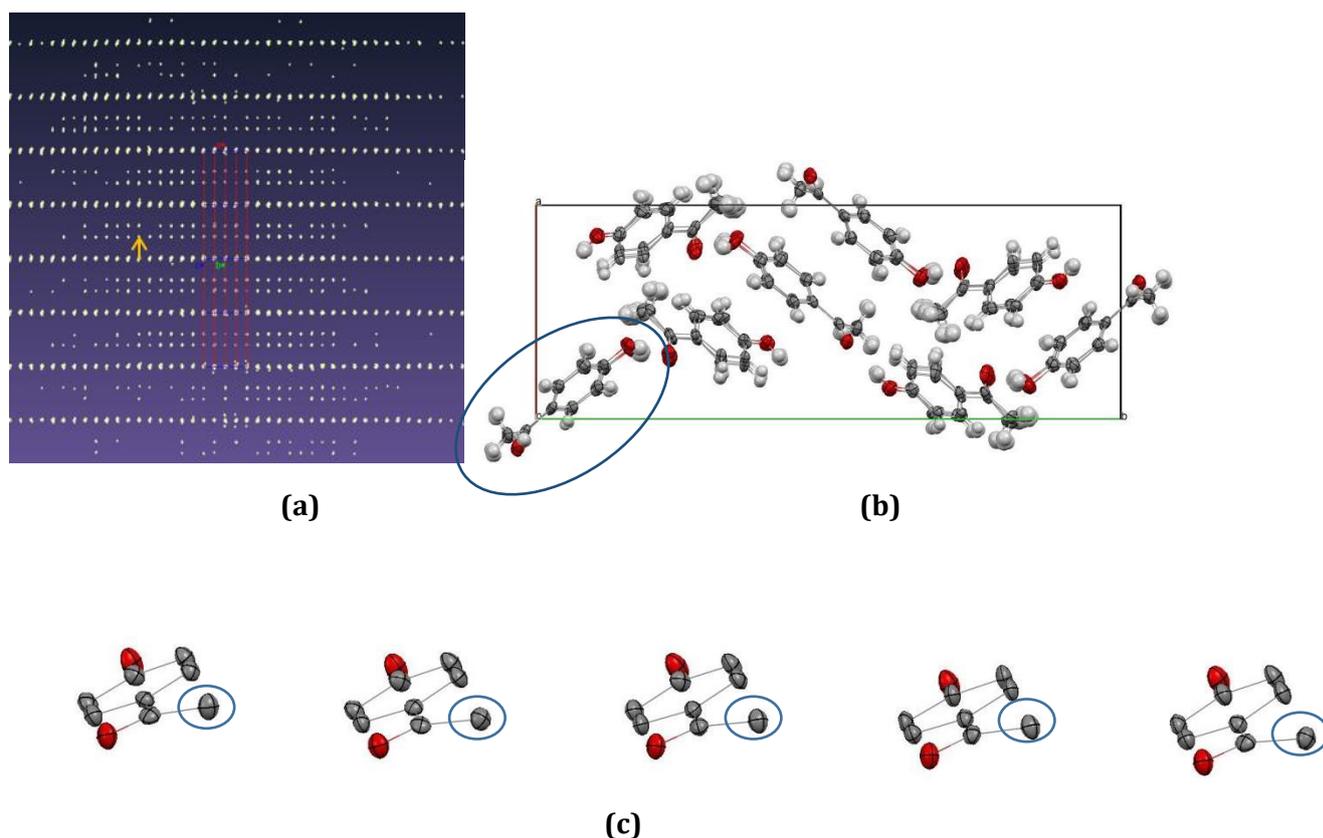
Such small satellite spots in the diffraction pattern suggest that the structure is modulated. What is the difference between a modulated structure and a perfect crystal? A perfect crystal is built by repeating the unit cell by translation along the three directions of space. In the case of modulated structures, at least in one direction, an additional periodic variation of the atomic sites (positions and/or occupancies and/or ADPs) with respect to an ideal average periodic structure occurs. When the periodicity of this

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3 modulation is commensurate with lattice parameters, a structure can be solved either in  
4 supercell, with larger cell and higher  $Z'$  than the average structure, or by using so-called  
5 superspace approach – with a small unit cell and modulation vector (see **Figures 5** and  
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13 The new, HAPII 100K structure appears to be commensurately modulated (abbrev.  
14 *cmHAPII*). It can be indexed in a new, larger unit cell ( $\mathbf{a}=9.0155 \text{ \AA}$ ,  $\mathbf{b}=24.4861 \text{ \AA}$ ,  
15  $\mathbf{c}=30.9055 \text{ \AA}$ ) with 10 independent molecules in the asymmetric unit. Neutron diffraction  
16 measurements at 100 K confirmed large unit cell (cell parameters  $\mathbf{a} = 8.9946 \pm 0.0067$   
17  $\text{ \AA}$   $\mathbf{b} = 24.4806 \pm 0.0167 \text{ \AA}$   $\mathbf{c} = 30.9195 \pm 0.0176 \text{ \AA}$ ), however we were not able to solve  
18 a structure based on the neutron data. Thus, below we are presenting results from  
19 refinements against X-ray data.  
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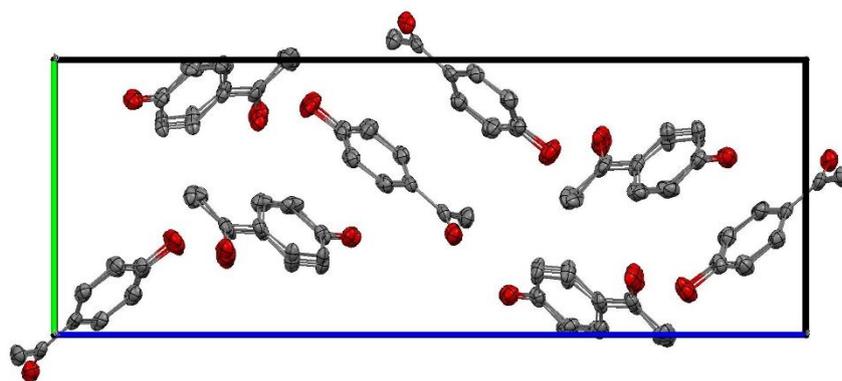
47 **Figure 5.** Reconstructed reciprocal  $h0l$  layers of the **a)** HAP II at 123K and **b)** HAP II at  
48 150K. Notice additional reflections at 123K between main reflections which are not  
49 present at 150K.  
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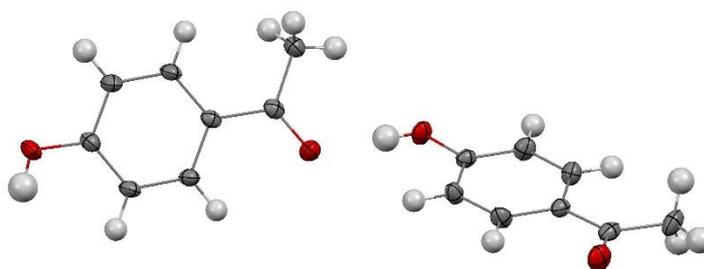
**Figure 6.** *cmHAPII* structure: **(a)** reconstruction of Ewald sphere viewed along the  $b^*$ - visible small additional satellite peaks **(b)** view of unit cell in the [001] direction **(c)** HAP molecules from asymmetric part of the unit cell view along the  $c$  axis

*cmHAPII* can be described as a supercell solution of higher temperature HAP II structure with five times more molecules and five times bigger cell volume than the base structure. As a result, the structure has a  $Z'=10$ . Description of ADPs in the structure is significantly improved as many more parameters are considered (**Figure 6 c.**)

Alternatively, the commensurately modulated structure was solved by SuperFlip<sup>34</sup> in the space group  $P2_12_12_1(\sigma00)$  with the modulation wave vector  $q$  in the superspace model of  $q = 2/5a^*$  and cell parameters  $\mathbf{a} = 6.1800 \text{ \AA}$ ,  $\mathbf{b} = 9.0200 \text{ \AA}$  and  $\mathbf{c} = 24.5060 \text{ \AA}$ . Note, owing to the standard choice of the unit cell in the orthorhombic space group the order of the base vector changes from  $(abc)$  to  $(bca)$ . To describe the modulation, in the final model continuous atomic modulation functions for displacive modulation and modulation of the anisotropic ADPs (with higher harmonic up to 2<sup>nd</sup> order) are applied to all non-hydrogen atoms. The hydrogen atoms are coupled via a riding model to their corresponding carbon/oxygen atoms.



(a)



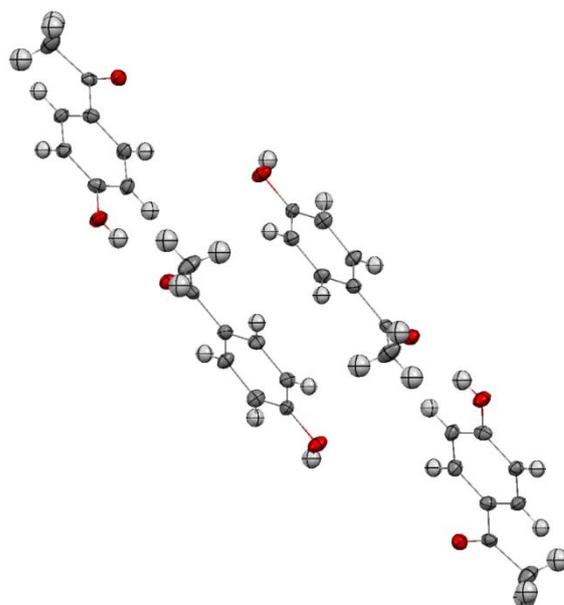
(b)

**Figure 7.** Solution with superspace approach. **(a)** approximatant structure – similar to  $Z'=10$  structure, **(b)** averaged structure – ADPs similar to  $Z'=2$  structure. See also attached movie (hap\_100K.avi)

**3.2.3. HAP II at liquid helium temperature.** Further lowering of temperature reveal that at 40 K, the HAP II structure has even more complex nature. At 40 K, in addition to satellite peaks observed along  $a^*$  axis, we observed a new set of reflections in the  $b^*$  direction. Main reflections are accompanied by first and second order satellite reflections.

In this direction, periodicity of modulation is not commensurate with cell parameters –it means, that structure is incommensurately modulated (abbrev. *imHAPII*) and can be solved only by using the superspace approach. It was possible to solve the structure in the monoclinic  $P2_1(\sigma\gamma 0)$  space group with a modulation wave vector  $q = [0.38, 0.17, 0.0]$  and 4 symmetry-independent molecules in the asymmetric unit. Cell parameters remain close to the commensurate structure with:  $a=6.1738(7)\text{\AA}$ ,  $b=8.9627(10)\text{\AA}$ ,  $c=24.516(3)\text{\AA}$ ,

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3  $\beta=89.714(9)^\circ$ . Due to not sufficient data completeness and twinned crystal structure rigid  
4 body approach was executed to diminish the number of refined parameters. Rigid body  
5 position was described with continuous displacive modulation of rotation and translation.  
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7 Additionally, ADPs were derived from TLS rigid-body analysis with two modulation  
8 function for tensor components of translation, libration and screw-rotation.  
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32 **Figure 8.** Representation of the averaged structure of HAP II at 40K viewed along *a*-axis. See  
33 also attached movie (hap\_40K.avi)  
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#### 36 37 38 39 40 41 **4. Energy calculations results**

42  
43 According to earlier investigations of relative stability of polymorphic forms of  
44 hydroxyacetophenone the thermodynamically stable form at low temperature is  
45 orthorhombic form, HAP II. Theoretical periodic *ab-initio* calculations, which we  
46 conducted are in good agreement with experimental results from calorimetry: they  
47 indicate HAP II as the more stable form (by c.a. 2-3 kJ/mol). As the phase transition from  
48 HAP II to HAP I is entropy driven, and our calculations take into account only enthalpy,  
49 we did not observe changes in stability order at room temperature.  
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56 We wanted to check, whether it will make a difference, if we use for our calculations as a  
57 starting point structure of the orthorhombic form, which contains ten molecules in the  
58 asymmetric unit, or the orthorhombic structure of HAP II with two molecules in  
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asymmetric unit. Surprisingly, obtained lattice and total energies for both  $Z'=2$  and  $Z'=10$  structures are almost the same.

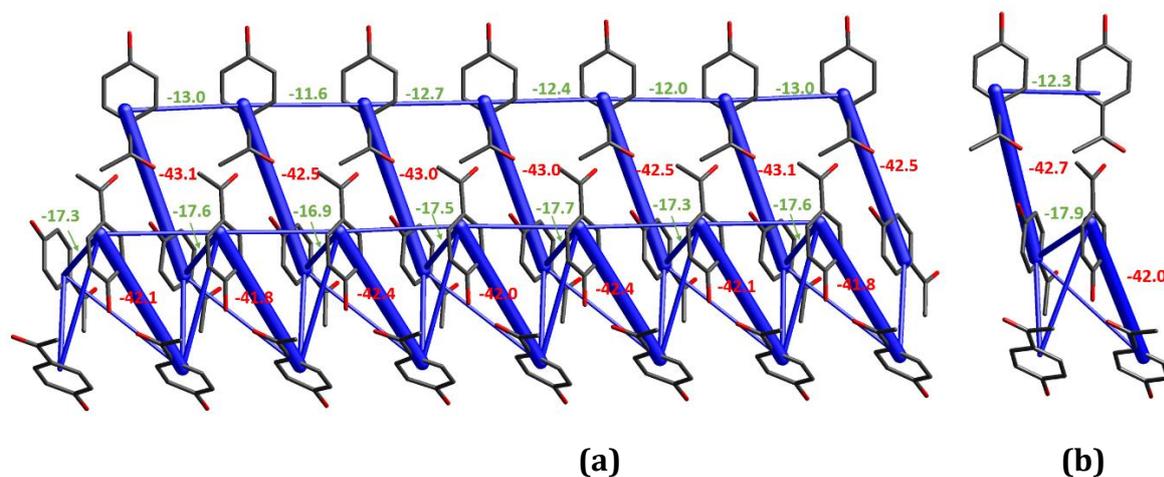
**Table 1.** Total energy per molecule and lattice energy in the brackets. All values are in kJ/mol

Computational method	PBE0-D3	PBE0-D2	B3LYP-D3ABC/VTZ/HF-3c	B3LYP-D3ABC/6-31/HF-3c
HAP I	-1207106.22 (-119.9)	-1207102.80 (-133.6)	-1207790.94 (-113.7)	-1207574.80
HAP II ( $Z'=2$ )	-1207109.18 (-127.5)	-1207105.07 (-138.9)	-1207794.50 (-119.5)	-1207579.51
HAP II ( $Z'=10$ )	-	-	-	-1207579.48
$\Delta E_{\text{HAPI-HAPII}}$	-2.96 (-7.6)	-2.27 (-5.3)	-3.56 (-5.9)	-4.71
$\Delta E_{\text{HAPII - modHAPII}}$	-	-	-	-0.03

Therefore, one may raise a question: as energies for the orthorhombic form of hydroxyacetophenone with two molecules in asymmetric unit (asu) remains the same as for ten molecules in asu, why do we observe a modulation at low temperature? In the case of modulated systems, very often modulation can be rationalised as result of a compromise between the steric demands of the molecule and the optimal arrangement of hydrogen bonding moieties<sup>35</sup>. We decided to investigate dimer interaction energies, and verify, whether due to modulation some interactions for the structure with  $Z'=10$  are becoming significantly stronger than in the case of averaged structure, with  $Z'=2$ .

From our analysis of dimer interactions energies (see **Figure 9**) we conclude that for two types of hydrogen bonds energies are almost the same as in the case of HAP II with  $Z'=2$ . In the case of  $Z'=10$  structure energies for first type of hydrogen bond vary between -42.5 and -43.1 kJ/mol and for the second type between -41.8 and -42.4 kJ/mol, and on average they are equal to energies obtained for  $Z'=2$  structure (-42.7 and -42.0 kJ/mol). We observe larger deviations from average for weak dispersive interactions (green energy values on **Figure 9**). Weak dispersive interactions between parallel

hydroxyacetophenone molecules vary between -11.6 kJ/mol up to -13 kJ/mol. We may conclude that locally, some of those weak interactions are stronger than in the case of  $Z'=2$  structure, but on the other hand some are weaker, and on average structures with  $Z'=2$  and  $Z'=10$  have almost the same electronic energy.



**Figure 9.** Comparison of energy frameworks for  $Z'=10$  (a) and  $Z'=2$  (b) structures.

Interesting discussion of similar cases, for which high temperature phase has lower  $Z'$  than the low temperature phase was presented by Steed & Steed<sup>36</sup>. For example, similarly to our case, Tröger's base derivative, undergoes a  $Z' = 1$  to  $Z' = 3$  phase transition on cooling below 130 K<sup>37</sup>. The authors suggest, that although the higher  $Z'$  structure exhibit lower energy, the more stable at higher temperatures is the  $Z'=1$  structure due to increase of entropic term with the temperature. Similarly, in our case, entropic term most probably is stabilizing structure with  $Z'=1$ .

## 5. Importance of ADPs: computed vs experimental ADPs

Experimental ADPs are prone to all experimental errors. A simple test, which should show, whether ADPs are correct, is the Hirshfeld rigid bond test. It tests whether the components of the anisotropic displacement parameters along chemical bonds are equal in magnitude. Large differences might indicate a systematic distortion of these parameters with other (unresolved) effects such as (substitutional) disorder, model or data errors and/or over-refinement. Atomic sites assigned the wrong scattering type (*e.g.* Ag versus Br) should generate 'problem signals' with this test. Data sets corrected for

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3 absorption effects with DELREF techniques (e.g. DIFABS, SHELXA, XABS2) often show  
4 large DELU values for bonds involving the heaviest atom.  
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7 Interestingly, in the case of both polymorphic forms of HAP at 123 K, the Hirshfeld rigid  
8 bond test is fulfilled. However, a closer look into ADPs of HAP II showed strange features  
9 that convince us to conduct theoretical computations of ADPs for both HAP forms to  
10 compare results. Due to fast increase in computer power, calculation of ADPs for  
11 molecular crystal started to be feasible. Usually, computed ADPs are compared with  
12 experimental ones (preferably from neutron diffraction experiments), in order to verify  
13 quality of theoretical calculations<sup>31, 38, 39</sup>.  
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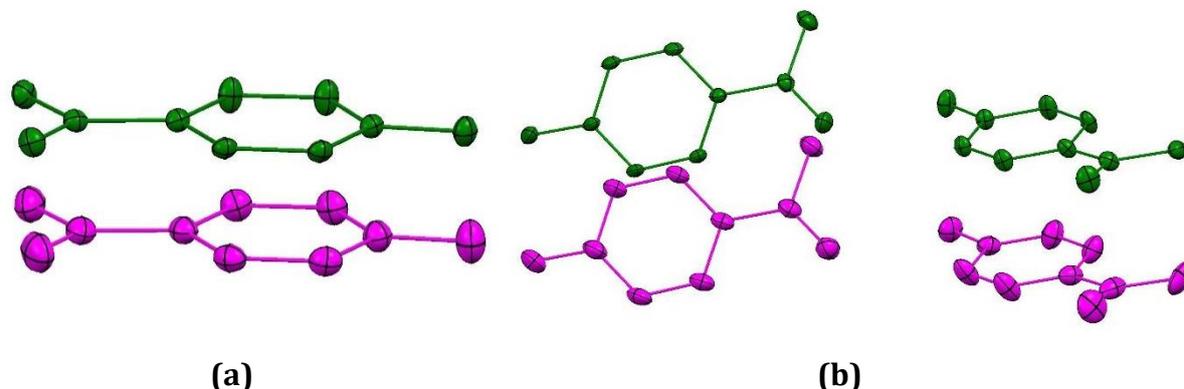
16  
17 Herein, we would like to show, that computation of theoretical ADPs to compare them to  
18 experimental ones can pinpoint some still unresolved features in the crystal structure.  
19 Without doubt, special attention should always be paid to the experimental diffraction  
20 data.  
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24 As ADPs are a mean value over the Brillouin zone, and those computed by us are based  
25 only on  $\Gamma$  point frequencies, computed ADPs would not be exactly equal to experimental  
26 ADPs. However, some features of ADPs should be preserved, and in the case of HAP I main  
27 trends are preserved – on one side of the ring ADPs are elongated in a direction  
28 perpendicular to the ring plane, whereas on the other structure, in bond direction.  
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32 From theoretical computations we even can indicate one particular vibration with low  
33 frequency ( $80\text{cm}^{-1}$ ) that is responsible for such shape of aromatic carbon atom ADPs. In  
34 the case of HAP II computed ADPs differ significantly from experimental ones (see **Figure**  
35 **10 b**). Experimental ADPs, for one of the HAP molecules, are elongated in one direction,  
36 and for the second molecule ADPs from ring seem to follow libration around C1...C4 axis.  
37 None of those features is observed in the case of computed ADPs.  
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41 Taking into account satellite peaks and, as consequence, modulation of the HAP II  
42 structure in 100K results in ADPs for averaged structure very similar to those from 150K.  
43 Thus, we may conclude that  $Z' = 2$  high temperature structure is an average structure that  
44 does not fully account for all of the small conformational differences in HAP molecule  
45 geometry in the  $Z'=10$  system. Similar conclusion was made for another interesting  
46 example, namely the complex  $[\text{Ni}(\text{OAc})(\text{PNPtBu})]\text{OT}$ , which contains one independent  
47 molecule in the asymmetric unit of the crystal structure with very large anisotropic  
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displacement parameters, and undergoes phase transition on cooling to low-temperature phase, which has six independent, well ordered molecules in the asymmetric unit <sup>40</sup>.



**Figure 10.** Anisotropic displacement parameters computed (top, green) vs experimental (bottom, magenta) **(a)** HAP I **(b)** HAP II.

## 6. Conclusions

In this contribution we present, that even such simple and well-studied structure of 4'-hydroxyacetophenone, when studied with low and ultra-low temperatures, can reveal a more complex nature. After cooling of orthorhombic form II of 4'-hydroxyacetophenone to 100 K, we obtain commensurately modulated structure, with five times more molecules in the asymmetric unit than the room temperature structure. By further lowering temperature to 40 K, the structure is becoming even more complicated, incommensurately modulated. This structure is thermodynamically stable at low temperatures as confirmed by our theoretical investigations. Consideration of additional diffraction spots and superstructure with  $Z'=10$  indicated the same lattice (or bulk) energy as  $Z'=2$  structure. It was confirmed by detailed analysis of dimer interaction energies, that in  $Z'=10$  structure some dimer interactions are stronger than in the case of  $Z'=2$  structure influencing weaker ones and on average structures exhibit almost the same electronic energy. Therefore, most probably, phase transition (HAPII > HAP I) is driven by entropy. Additionally, it is important to remember, that in the case of HAP polymorphs, as conformation of both HAP molecules for forms I and II is different, kinetics also might play a role.

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3 Both structures form head-to-tail hydrogen bonds and stacking interactions that were  
4 quantified with the aid of the energy frameworks analysis. Stable at low-temperature  
5 polymorph (HAP II) forms stronger hydrogen bond and weaker stacking interactions by  
6 the means of lower energy *syn* molecular conformation. On the contrary, the HAP I case  
7 exemplifies opposite features. Both structures illustrate a compromise between the  
8 dispersive and electrostatic forces to achieve a stable structure. Additionally, energy  
9 frameworks can help with understanding strength of interactions in given directions, and  
10 in consequence, the shape of thermal expansion tensors - indeed, in directions in which  
11 interactions are weaker thermal expansion is larger than in the case of directions in which  
12 interactions are stronger.

21 Comparison of experimentally obtained and computed ADPs reveals significant  
22 differences between ADPs in the case of HAP II. It is not an indication that theory is wrong,  
23 but it might be also that some more attention should be put to experimental data. In  
24 general, we recommend careful analyse of ADPs especially in the case of polymorphic  
25 systems as they can behave as dustbin to all experimental errors, therefore rationalization  
26 and explanation of their size and orientation are crucial for correct data analysis. In such  
27 a situation, conducting multi-temperature measurements, observing temperature  
28 evolution of ADPs and going to low and ultra-low temperatures is vital for understanding  
29 the complex solid-state chemistry. Especially in the view that polymorph relative stability,  
30 modulated and high  $Z'$  structures are still a challenge for theoretical methods and for  
31 crystal structure prediction.

42 Additionally, it is worth to remember, that the lattice energy is computed for an ideal  
43 crystal, without any disorders, incommensurate modulations, etc. Therefore, computed  
44 values might not always agree with experimental ones. Thus, in order to progress in  
45 computational sciences, not only good new functionals and dispersion corrections are  
46 needed, but also state-of-the-art low-temperature measurements! Moreover, as all data  
47 deposited in the CSD might be later utilised by other researchers, it is of great importance,  
48 even when X-ray data collection was done just to confirm the structure, to give as many  
49 details about a measurement as possible and to report all problems which occurred  
50 during structure refinement.

## Supporting Information

Supporting Information contains crystallographic details for HAP I and HAP II after TAAM refinements, the de Wolf sections for commensurate and incommensurate HAP II structure, neutron data collection details. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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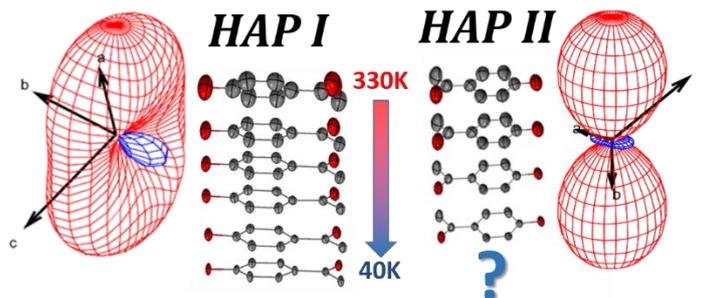
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For Table of Contents Use Only

***“How accurate X-ray data are needed to obtain reliable order of stability for polymorphs? The case study of p-hydroxyacetophenone polymorphs.”***

Marcin Sztylko, Maura Malinska, Vaclav Petricek, Matthias J. Gutmann, Anna A. Hoser



The importance of high quality, low-temperature X-ray diffraction experiments is discussed based on the new, modulated structures found for polymorph of 4'-hydroxyacetophenone (HAP)