THE UNIVERSITY of EDINBURGH

Edinburgh Research Explorer

A new polymorph of metacetamol

Citation for published version:
Pulham, C, Nichol, G, Boldyreva, EV & Coster, PL 2015, 'A new polymorph of metacetamol', *CrystEngComm*. https://doi.org/10.1039/c5ce00910c

Digital Object Identifier (DOI):
10.1039/c5ce00910c

Link:
Link to publication record in Edinburgh Research Explorer

Document Version:
Peer reviewed version

Published In:
CrystEngComm

General rights
Copyright for the publications made accessible via the Edinburgh Research Explorer is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy
The University of Edinburgh has made every reasonable effort to ensure that Edinburgh Research Explorer content complies with UK legislation. If you believe that the public display of this file breaches copyright please contact openaccess@ed.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.

OPEN ACCESS

Download date: 12. Oct. 2024

CrystEngComm

Accepted Manuscript

This is an *Accepted Manuscript*, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this *Accepted Manuscript* with the edited and formatted *Advance Article* as soon as it is available.

You can find more information about *Accepted Manuscripts* in the Information for Authors.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard Terms & Conditions and the Ethical guidelines still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this *Accepted Manuscript* or any consequences arising from the use of any information it contains.

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/crystengcomm

Please do not adjust margins

Journal Name

ARTICLE

A New Polymorph of Metacetamol

Lindsay McGregor[a,b], Denis A. Rychkov[b,c], Paul L. Coster[a], Sarah Day[e], Valeri A. Drebushchak[b,d], Andrei F. Achkasov[b], Gary S. Nichol[a], Colin R.Pulham[a], Elena V. Boldyreva[b,c]

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

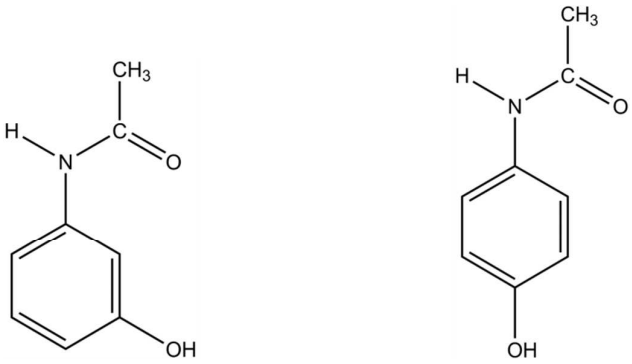
Metacetamol is a structural isomer of the widely used drug paracetamol and is being considered as a promising alternative to the latter because of its lower toxicity. Due to the importance of the well-known polymorphism ofparacetamol, an investigation of the polymorphism of metacetamol was successfully undertaken. A new polymorph of metacetamol has been discovered and extensively characterised using a variety of analytical techniques (IR- and Raman spectroscopy, UV-visible optical spectroscopy, X-ray powder and single-crystal diffraction, TGA and DSC). A procedure for the reliable and reproducible preparation of the new polymorph is described. Its properties and crystal structure are compared with those of the previously known polymorph, as well as with those of paracetamol.

Introduction

Polymorphism in molecular crystals is an important area of research due to increasing interest within the pharmaceutical industry. A change in crystalline structure can cause properties to differ between polymorphs, and these may have either beneficial or detrimental effects on a drug's method of action[1]. Polymorphism is also an important issue for the protection of intellectual property [2,3], and so for all of these reasons a complete description of all possible polymorphs is now recommended by Federal Food and Drug Administration (FDA) regulations[4].

Paracetamol provides an example of a popular and widely used Active Pharmaceutical Ingredient (API) that can exhibit polymorphism. Three polymorphs of this compound have been obtained at ambient pressure, and all have different physical properties that are related to the differences in crystal structures[5–7]. The monoclinic form I is the thermodynamically stable form at ambient pressure[8], whereas the denser orthorhombic form II becomes thermodynamically stable at high pressure[9–11]. Two additional polymorphs were recently reported to form reversibly at very high (above 8 GPa) pressures[12]. Among the drawbacks of paracetamol for medical applications is its hepatotoxicity[13–16]. There is evidence that an isomeric compound, metacetamol (N-acetyl-meta-aminophenol)[17] (Scheme 1), is significantly less toxic[18–21], although recent studies[23] make this statement questionable reporting that metacetamol may also be hepatotoxic like paracetamol. Although various biological studies have been published for metacetamol[22–24], nothing has yet been documented on the potential presence of polymorphic forms. Only one form has been described; its crystal structure has been solved[17], but no studies of its vibrational spectra or thermal properties have been reported.

The aim of this study was to investigate the polymorphism of metacetamol. In this work it was shown that another polymorph, form II, can be obtained from the melt in a reproducible manner. The bonding and stability of metacetamol form II was investigated thoroughly in relation to its crystal structure using a variety of relevant techniques, including thermal analysis and calorimetry, vibrational spectroscopy, UV-Visible spectroscopy, and X-ray diffraction.



Scheme 1: Molecular structures of metacetamol (left) and paracetamol (right) containing the same characteristic functional groups

Experimental

[a] School of Chemistry and Centre for Science at Extreme Conditions, The University of Edinburgh, King's Buildings, David Brewster Road,, Edinburgh, EH9 3FJ, Scotland, UK
[b] REC-008, Novosibirsk State University, Pirogova, 2, Novosibirsk, 630090, Russia,
[c] Institute of Solid State Chemistry and Mechanochemistry, Kutateladze, 18, Novosibirsk, 630128, Russia,
[d] V.S. Sobolev Institute of Geology and Mineralogy of the Russian Academy of Sciences, Pr. Ak. Koptyuga, 3, Novosibirsk, 630090, Russia
[e] Diamond Light Source, Harwell Science & Innovation Campus, Didcot, Oxfordshire, OX11 0DE, UK.
† Footnotes relating to the title and/or authors should appear here.
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

CrystEngComm Accepted Manuscript

Please do not adjust margins

Materials

Metacetamol was purchased from Sigma-Aldrich (form I) and was used after recrystallization from water. Depending on the procedure, purified single crystals or polycrystalline samples of form I were obtained. Form II was produced from recrystallized form I using procedures described later in the text.

Characterisation

X-ray powder diffraction. All polycrystalline samples were examined using a Bruker GADDS diffractometer: Cu Kα radiation (λ = 1.5418 Å), $5.0^{o} \leq 2\Theta \leq 46.0^{o}$, graphite monochromator, with an operating potential of 40 keV and a current of 40 mA. All data were obtained in reflection mode in a flat-plate configuration with a scanning time of 120 s per frame. In addition to laboratory experiments, X-ray powder diffraction data were recorded on Beamline I11[25] at the Diamond Light Source using monochromatic radiation of wavelength 0.82562 Å from a sample of finely ground form II contained in a 0.7 mm borosilicate-glass capillary.

Single-crystal diffraction. Single, colourless plate-shaped crystals of metacetamol were obtained by slow cooling of a hot, aqueous, saturated solution of metacetamol capped with an immiscible layer of hexadecane. Thin, plate-like crystals formed at the interface of the aqueous and organic phases. A suitable crystal (0.65 × 0.50 × 0.05 mm^3) was selected and mounted on a MITIGEN holder in Paratone oil on an Agilent Technologies SuperNova diffractometer. The crystal was maintained at T = 120.0 K during data collection. Using Olex2,[26] the structure was solved with the ShelXS[27] structure solution program, using the Direct Methods solution method. The model was refined with ShelXL[27] using Least Squares minimization.

Crystal Data. Chemical formula: C8H9NO2, M_r = 151.16, monoclinic, $P2_1$ (No. 4), a = 7.6202(8) Å, b = 19.010(3) Å, c = 10.1116(8) Å, α= 90.388(8)°, V = 1464.8(3) $Å^3$, T = 120.0 K, Z = 8, Z' = 4, λ (CuK_α) = 1.5418 Å, 16412 reflections measured, 5281 unique (R_{int} = 0.0888) which were used in all calculations. The final wR_2 was 0.3430 (all data) and R_1 was 0.1078 (I > 2(I)).The poor quality of the very fragile and highly labile crystals accounts for the high values of R_{int} and R_1.

Differential Scanning Calorimetry (DSC). Calorimetric measurements were performed using a DSC-204 (Netzsch). Samples (9 mg of several small single crystals) were loaded into standard aluminium crucibles and covered with a lid, but not sealed. The heating rate was set to 6 K/min and the cooling rate was varied from 3 to 12 K/min, using liquid nitrogen as a cooling agent.

Infrared Spectroscopy. FTIR ATR spectra were recorded using a DigiLab Excalibur 3100, Varian spectrometer equipped with a MIRacle ATR accessory in the range 600–4000 cm^{-1} with a resolution of 2 cm^{-1}. A LinkamFTIR600 Stage, from Linkam Scientific Instruments Ltd, was used in conjunction with heater TMS 94 for the variable-temperature experiments. Heating was performed at 5 K / min, with subsequent cooling at 2 K / min and (optional) retention at high (313 K) or ambient temperatures. A series of measurements was recorded either under an N_2 atmosphere, or on air with different levels of relative humidity. Further details are described in the section on Results and Discussion. Harmonic frequencies for the IR spectrum of the gas-phase minimum structure of form I metacetamol were calculated using the Gaussian 09 program[35] with B3LYP/6-31+G(d,p) and MP2/6-31G(d) levels of theory (see Figure S.3.).

Raman Spectroscopy. Raman spectra were recorded using a LabRAM HR 800 spectrometer from HORIBA JobinYvon with a CCD detector. For spectral excitation, the 488 nm line of an Ar^+ laser was used with a beam size of ~1 µm on the surface of the sample and a power of ~8 mW. All data were collected using a Raman microscope in backscattering geometry. For the sample of form I, polarization was used along the mm and ll directions. Form II was examined without using polarized radiation as it could only be studied as a polycrystalline sample.

UV-Vis Optical Spectroscopy. UV-VIS spectra were recorded using a Cary 60 UV-Vis spectrophotometer from Agilent Technologies, equipped with Agilent Cary 60 REMOTE DRA MVIDEO solid state auxiliary unit. All spectra were recorded in the range 200-800 nm with a resolution of 2 nm at a scan rate of 600nm/min.

Chromatography. Chromatographic analysis of the samples was performed using an HPLC Agilent 1200 equipped with a Zorbax SB-C18 (2.1x150mm, 3.5 µm) column used in conjunction with DAD (H_2O-MeOH (30%-100%, 2-22')) and a GC-MS Agilent GC 6890 equipped with a MSDetector 5973N. Chromatography studies (HPLC and GC-MS) were performed to check the purity of metacetamol form I samples after recrystallisation from water and for form II after its preparation as described below. For all samples the purities proved to be greater than 99%.

Results and Discussion

Preparation of form II

Trial crystallisation studies from solution using common solvents (water, acetone, ethanol, ethyl acetate, THF, dioxane) produced only form I of metacetamol. From previous research it was known that form II of *paracetamol* could be produced under certain conditions from the melt [5] and so our studies on metacetamol also focused on the melt. A sample of form I was placed into a melting point apparatus (BÜCHI M-560) and heated to just above the reported melting point of 422 Kat a rate of 5 K/min until all traces of solid material had disappeared. The sample was then cooled down to 298 K at a rate of approximately 5 K/min. It was observed that the sample sub-cooled to give an optically transparent glass. On heating this glass a rate of 5 K/min, the glass was observed to crystallize at ~360 K to give a polycrystalline solid which subsequently melted at ~403 K. The difference of ~20 K in the melting points strongly suggested the existence of new polymorph that has significantly lower lattice energy. In order to produce larger quantities of this new form (henceforth denoted form II), a scaled-up experiment was conducted using a Petri dish (diameter of 50 mm, 10 mg of sample) and a hotplate. However, this method was

CrystEngComm Accepted Manuscript

 This journal is © The Royal Society of Chemistry 20xx

Please do not adjust margins

unsuccessful as the heating-cooling process was difficult to control, and invariably resulted in the formation of form I (identified by PXRD). Nevertheless, this experiment did confirm that the heating process did not result in thermal decomposition of the sample. In the next series of experiments a sample (100 mg) was heated in a sealed glass vial in an oil bath (up to 428 K at a rate of 2 K/min, followed by cooling to ambient temperature at an average rate of 0.5 K/min). The heating of the sample was uniform, in order to minimise the likelihood of unwanted seeds of the undesirable form I, and contact with airborne contaminants was minimised. This method proved to be successful in producing form II as a polycrystalline powder, but it failed to produce single crystals. By using a programmable sublimation apparatus (BÜCHI B-585), form II was also successfully and reproducibly obtained, as heating and cooling rates were readily controlled (heating to 430 K at a 5 K/min and cooling at 0.4 K/min). Contact with air was also reduced using this apparatus as the experiment was performed under reduced pressure (16 mbar) in this device using a vacuum pump (BüCHI V-700) with vacuum controller (BüCHI V-850). No sublimation was observed under these conditions. Both methods produced a polycrystalline material. UV/Visible spectra of the samples of solid forms I and II recorded without grinding were essentially identical (Supp. Figure S1).

Thermogravimetric analysis (TGA) of samples of both forms I and II showed negligible mass loss up to the melting point (Fig. 1,a), confirming that form II is not a solvate and that no significant thermal decomposition had occurred.

Form I obtained by recrystallisation from aqueous solution contained about 1.4 % mass of solvent inclusions, as estimated from the presence of a small peak at ~273 K in the DSC curves (Fig. 1,b) combined with the TG data (Fig 1,a), which can be interpreted as melting of frozen inclusions of crystallisation liquor in the crystals. This is a very low value compared with many other organic crystals grown from solution [28].The presence of solvent inclusions is important to consider when discussing the stability of crystalline material on storage. It has been shown previously for paracetamol that these inclusions trigger the phase transformation of paracetamol II into paracetamol I on storage at ambient conditions and on heating[29]. On the contrary paracetamol II grown from the melt without solvent inclusions, melts without showing a polymorphic transition[8].The DSC trace shown in Fig. 1,b shows that form I of metacetamol melts at approximately 420.5 K. On cooling the melt at 6 K/min, a substantial degree of sub-cooling was observed until an exothermic recrystallisation peak was observed over the range 363 - 340 K. On reheating, a melting peak was observed at 400 K, corresponding to the melting point of form II. These results are in agreement with the optical observations of samples in the melting-point apparatus, and indicate that form II crystallizes from the sub-cooled melt.

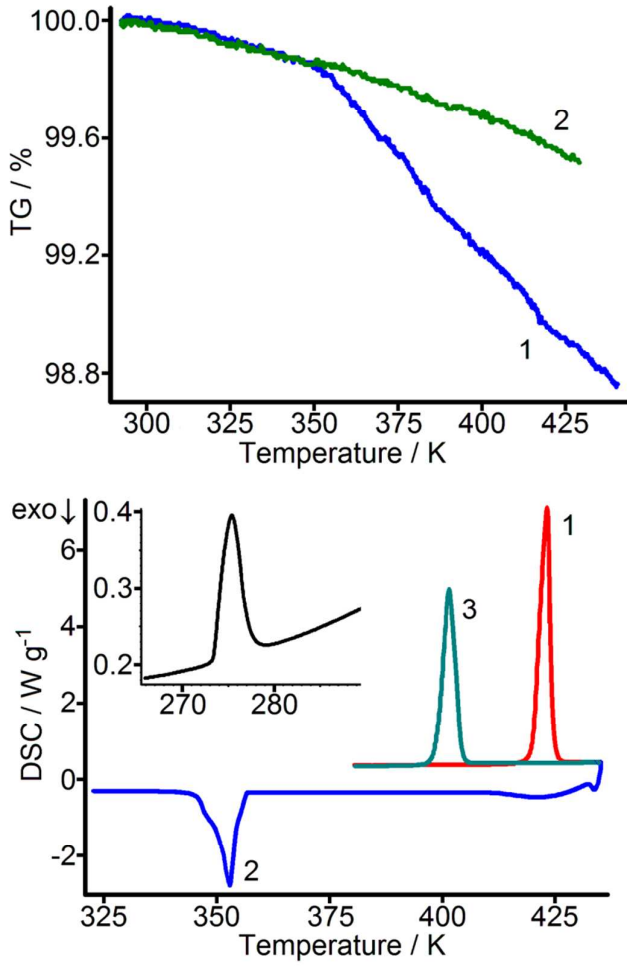


Figure 1: a) TGA of recrystallised Form I (1) and Form II from the melt (2), showing the mass loss in Form I, accounted for by mother liquor inclusions and, b) Graph showing cyclic heating of recrystallised form I from the 1st heat cycle(1) which melts at 420 K, recrystallisation upon cooling (2), then the melting of new form II at much lower temperature (400 K) during the 2nd heating cycle (3); cooling rate of 6K/min. Insert illustration represents a DSC signal from solvent inclusion (a small peak at 273K).

X-ray powder diffraction studies

Fig. 2 shows the diffraction patterns recorded for (1) a lightly ground sample of form I (2), a lightly ground sample of form II crystallised from the melt, and (3) a sample crystallised from the melt using the sublimation apparatus as described above with no grinding or mixing.

CrystEngComm Accepted Manuscript

Please do not adjust margins

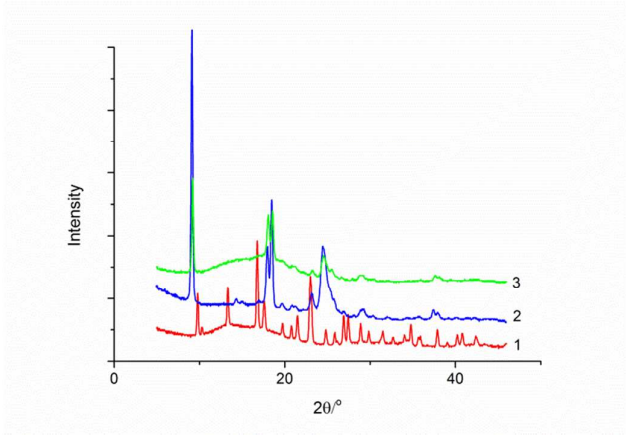


Figure 2: Powder diffraction patterns obtained for (1) a lightly ground sample of Form I, (2) Form II crystallized from the melt and then lightly ground, and (3) a sample of Form II obtained using the sublimation apparatus. (3). Plots are off-set along the y-axis for clarity.

The diffraction pattern of the film produced using the sublimation apparatus was similar to that measured for the lightly ground sample obtained from the melt, and both patterns are clearly different from form I. Furthermore, these experiments demonstrate that form II can be prepared without contamination from form I. The higher background scattering observed in pattern (3) is caused by the presence of amorphous material that has not recrystallised. The observed differences in peak intensities between patterns (2) and (3) can be explained by preferred orientation associated with sample (3)

Using the procedure developed for preparing pure samples of form-II from the melt, it was possible to collect X-ray powder diffraction data on Beamline I11 [25] at the Diamond Light Source (see Experimental Section above). The diffraction pattern recorded at 298 K is displayed in Fig. 3 and is in broad agreement with those obtained from the laboratory instrument. On account of the exceptionally high resolution available from this instrument, it was possible to index this pattern using the program DASH[30] to a monoclinic cell (a = 7.80 Å, b = 19.12 Å , c = 10.16 Å, β = 90.43°, V = 1515 Å^3), with the most probable space group being $P2_1$ based on systematic absences. This would therefore imply a value of Z' = 4, based on the volume occupied per molecule. Unfortunately, it was not possible to solve the structure using DASH, possibly because the pattern is dominated by only a few prominent peaks.

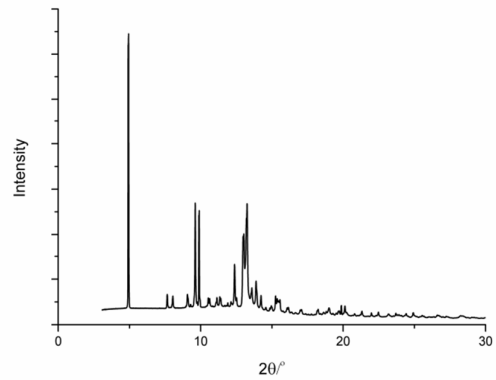


Figure 3: Powder diffraction patterns obtained for Metacetamol Form II collected at 298 K on Beamline I11 using monochromatic radiation of wavelength 0.82562 Å at the Diamond Light Source.

Single crystal X-ray diffraction study

On account of the difficulties associated with solving the structure from X-ray powder diffraction data, attempts were made to grow single crystals of form II from a selection of common solvents. All of these attempts failed and so a different approach was adopted that was based on work described by Capes and Cameron in which the metastable orthorhombic form of paracetamol was obtained by the phenomenon of "contact-line crystallisation"[31]. A similar approach has also been used to grow single crystals of the highly metastable β-form of RDX[32]. In both cases, single crystals of the metastable forms grew at a solvent-air interface. In the current study, we modified this procedure to create an interface between water and hexadecane –a high-boiling, water-immiscible liquid. An aqueous solution of metacetamol (saturated at ~70 °C) was heated to its boiling point in order to remove any possible seed crystals of form I. Whilst still hot, a layer of hexadecane was added to the vial, and on cooling to ambient temperature thin, plate-like crystals formed at the interface of the aqueous and organic phases. Provided that the crystals of form II were retained in the crystallisation medium in a sealed vial, they appeared to be stable for a period of several days. However, if agitated in an open vial, they rapidly transformed to form I.The crystals were mechanically very fragile and rapidly transformed to form I unless they were handled very carefully. The crystals also diffracted poorly and hence the quality of the diffraction data was not optimum. Nevertheless, it proved possible to solve the structure in space group $P2_1$ using direct methods. The poor quality of the intensity data is quite obvious on inspection of a displacement ellipsoid plot: all ellipsoids are oriented in the same direction and all are quite significantly prolate. A strong similarity restraint (RIGU in ShelXL) was used to prevent several atoms from becoming non-positive definite during anisotropic refinement. The possibility of twinning was investigated, but we could not integrate the data assuming the crystal to be twinned as the reflections were too smeared out to identify a definitive second component. Integration using the option "follow significant sample movement" gave a significantly better refinement.

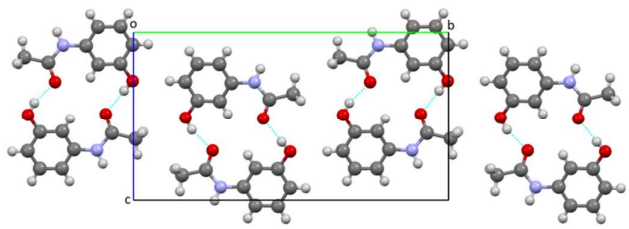
CrystEngComm Accepted Manuscript

This journal is © The Royal Society of Chemistry 20xx

The calculated powder diffraction pattern based on the model obtained from the single-crystal diffraction matched well the experimental patterns obtained for polycrystalline samples (Fig. 3), confirming that the bulk material obtained from the melt is the same form as the single crystals grown at the water/hexadecane interface.

The crystal structure of metacetamol form II is remarkable (Fig. 4). In contrast to form I[17] or to any of the polymorphs of paracetamol[5–7], the molecules are not linked as infinite chains, but instead form dimers via O-H...O hydrogen bonds between the phenolic -OH and the amide O=C groups.

a)



b)

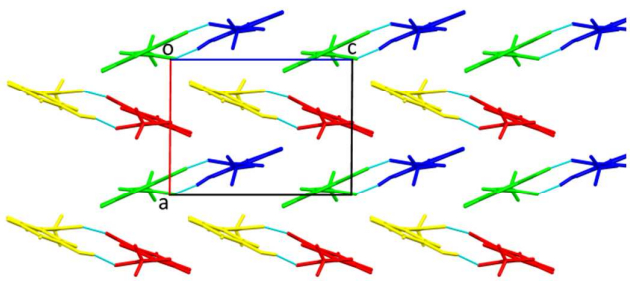


Fig.4. a) Representation of structural motifs in the structure of metacetamol II along a axis, b) along b axis. Hydrogen bonds are shown by dashed lines.

Using graph-set notation to describe the H-bonded motifs in form I, metacetamol molecules form $C^2_2(6)$, $C^2_2(14)$, $C^4_4(20)$ chains and large $R^6_6(32)$ rings involving 6 molecules, while form II contains only $R^2_2(16)$rings (formally $R^2_2(16)$>a>b and $R^2_2(16)$>c>d due to the inequivalence of pairs of dimers**)‡.** The dimers are not linked to other dimers by any hydrogen bonds, but instead pack to form a herring-bone arrangement along the a and *c*-axis with an angle of 46° between the aromatic rings. The structure can also be described as zigzag motif of non-connected metacetamol molecules along the *a*-axis and wavy lines of dimers along *b*-axis. Unlike in form I, the N-H bond of the amido-group is not involved in any significant interaction with neighboring molecules because of the formation of dimers.

Table 1. Hydrogen bond geometries of metacetamol form I and II (Å, °) at 120 K

Form	D-H...A	D...A Distance	D-H...A Angle
I	O2-H2O...O1(i)	2.628(1)	165.98
I	N1-H1N...O2(ii)	2.953(1)	169.61
II	O21-H21...O2(iii)	2.69(1)	166.0
II	O1-H1...O22(iii)	2.68(1)	160.4
II	O31-H31...O12(iv)	2.67(1)	169.5
II	O11-H11...O32(iv)	2.67(1)	159.6

Symmetry codes: (i) 2-x,1-y,-1/2+z; (ii) 3/2-x,-1/2+y,1/2+z; (iii) x,y,1+z; (iv) x,y,z. Atom numbering according to structure files from CCDC. Form I at 120 K is a Private communication to the CCDC (CCDC # 825236, S.L. Huth, T.L. Threlfall, M.B. Hursthouse, University of Southampton, Crystal Structure Report Archive , 542, 2008; DOI: 10.3737/ecrystals.chem.soton.ac.uk/542).

Hydrogen bonds are described in Table 1, showing that different types of H-bonds are present in two forms of metacetamol - N-H..O and O-H..O bonds in form I versus only O-H..O bonds in form II. Another peculiarity is that H-bonds in form II between and within dimers are slightly different (table 1). The formation of dimers *via* H-bonds became possible because metacetamol molecule has different stereochemical structure in the new form II than in previously reported polymorph I: the O-H and C=O groups are in a cis position in II but in a trans position in form I. Packing densities were calculated and compared for both structures. They are practically equal, if compared at the same temperature. The volume per molecule of in Form II is 183 $Å^3$ corresponding to a density of 1.371 g/cm^3 at 120 K. Form I has a volume per molecule of 182 $Å^3$, corresponding to a density of 1.378 g/cm^3 at 120 K. The densities being practically the same, one can suppose that form II is metastable because of weaker directional intermolecular interactions, such as hydrogen bonds. It is well known that even denser forms of molecular crystals can be less stable, if denser packing actually results in weaker or fewer hydrogen bonds. Such an effect has been observed for the polymorphs of paracetamol, where the denser form is less stable at ambient pressure[8,33].

Polymorph II of metacetamol belongs to high Z' crystal structures. Pseudosymmetry is frequently encountered in such cases and it seems to be also present here [for (010) layers slightly distorted p 2_1/c 1 1 layer group symmetry with Z'=1]. Additionally, this pseudosymmetry can most probably be related to the crystal twinning.

Vibrational spectroscopy

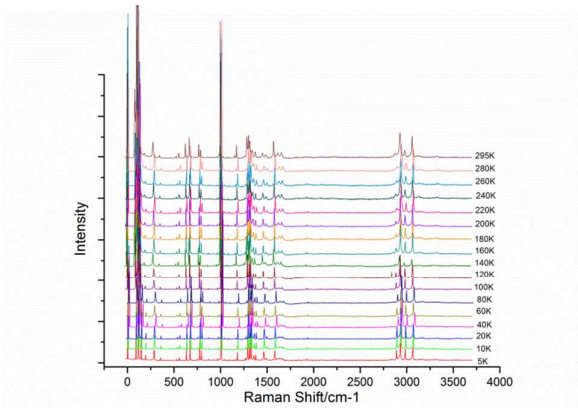
Vibrational spectroscopy provided complementary insight into the properties of the hydrogen bonds in the new polymorph. Raman spectra recorded for both forms on cooling from 295 K to 5 K in steps of 20 K are shown in Figure 5.The main difference between the spectra of the two forms in the higher wavenumber ranges in the positions of the N-H stretching modes (3325 cm^{-1} for form I and 3400 cm^{-1} for form II at 295 K). This is consistent with the crystal structure of form II in which the N-H groups are not involved in any

CrystEngComm Accepted Manuscript

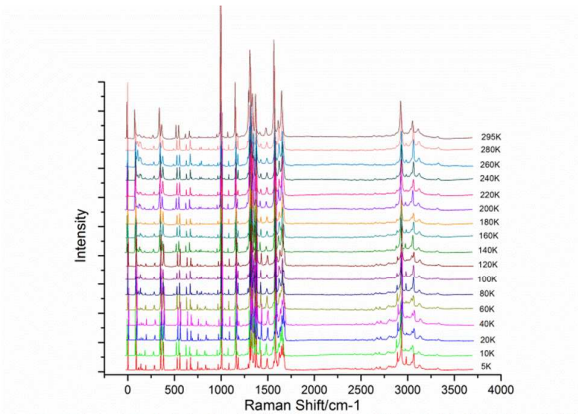
Please do not adjust margins

hydrogen bonds. Slight differences in the O-H..O vibrational modes were also observed - bands at 3104cm^{-1} and 3123 cm^{-1} for forms II and I, respectively. Differences in the low wavenumber range below 1000 cm^{-1} can also be discerned, thereby providing an additional means of distinguishing the two forms[34]. The Raman spectra collected at variable temperature show that no phase transitions occur on cooling either Form I or Form II (Fig.5).

a)



b)



c)

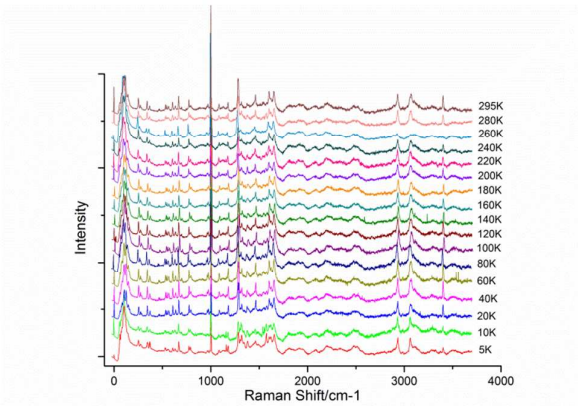
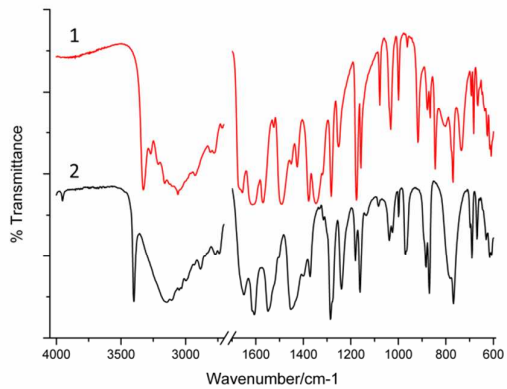


Figure 5: a), b) polarized Raman spectra of Form I single crystals in two different directions (*ll* and *mm* respectively) and, c) Raman spectra of Form II without polarization (polycrystalline sample).

Infrared spectroscopy was used to complement the Raman spectroscopic studies, in particular to follow the vibrations of the NH-groups. A large difference in the spectra in this region was observed for metacetamol I and II. A band at 3327 cm^{-1} (298 K) in the spectrum of form I (Figure 6 a,b) could be assigned to the N-H stretching mode, when compared to the gas phase spectra calculated in Gaussian09[35] (DFT, B3LYP 6-31+G(d,p) and MP2, 6-31G(d)) (see Supporting Information). A similar peak is present in the spectrum of form II (Figure 6 a,b), but both its position (3398 cm^{-1}) and intensity are changed, in agreement with the fact that the NH-group is no longer involved in a H-bond

a)



b)

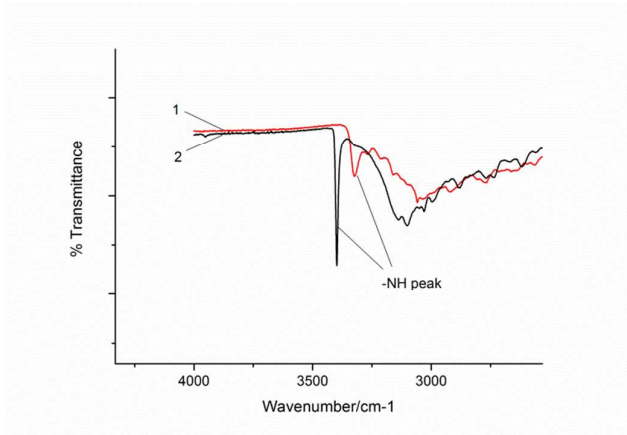


Figure 6: a) IR spectra for Form I (1) and Form II (2); b) Expanded region showing the difference in N-H stretching modes between the two forms.

The range between 1350-1550 cm^{-1} contains several modes that could be assigned to combined frequencies of δ_{CNH} with υ_{Ph} and υ_{CO} by analogy with paracetamol[36]. Displacement of these bands also correlates with the change in vibration of the NH-group due to the absence of H-bonds. Another difference present in the "fingerprint region" of IR spectra (below 1000 cm^{-1}) results in the disappearance of bands at 743 cm^{-1}, 844 cm^{-1} and 918 cm^{-1} in the spectra of form II. Assignment of OH-vibrations is very complicated and the origin of bands at 3269$_{(w)}$ cm^{-1}, 3209$_{(w)}$ cm^{-1} and 3161$_{(w)}$ cm^{-1} in the spectra of form I is not clear, bearing in mind that the O-H...O distances from the X-ray data are very close in both forms. Another

CrystEngComm Accepted Manuscript

This journal is © The Royal Society of Chemistry 20xx

peculiarity for metacetamol II was discovered - the appearance of the band at 3952cm^{-1} (probably, a combination band), which was not observed in the spectra of metacetamol I, which can also be explained by the change in N-H group bonding. In general, with the exception of the NH-vibrations, the IR-spectra of both forms of metacetamol are very similar, thus providing evidence that vibrations of other functional groups are not affected much by the change in molecular packing

Transitions between metacetamol forms I and II

In order to follow the transition from form I to the melt followed then by recrystallizsation to form II *in situ*, we used IR-spectroscopy and DSC. The characteristic peak associated with the N-H stretching mode observed at 3325 cm^{-1} in the infrared spectrum of form I was no longer visible in the spectrum of the melt (Fig.7). Instead, a broad absorption over the region 3000-3500 cm^{-1} was observed. When the experiment was carried out under dry N_2, no crystallizsation of the melt was observed upon cooling or upon subsequent storage at 298 K for up to 12 hours. By contrast, when air was allowed to diffuse slowly into the container, crystallisation of melt into form II at 298 K occurred after approximately one hour and this resulted in the appearance of the N-H stretching mode at 3400 cm^{-1}, characteristic of form II (Fig. 7).

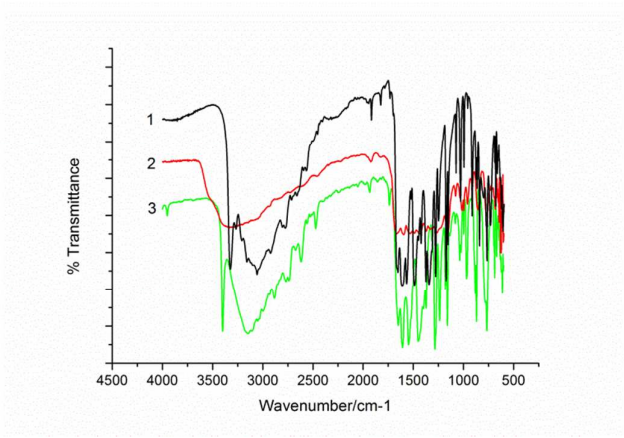


Figure 7: Infra-red spectra showing the initial transformation from Form I (1) to Form II (3), through an intermediate melt stage (2), at which the characteristic N-H stretching mode disappeared. Plots are staggered along the y-axis for clarity.

The transition to form II was also confirmed by measuring the melting temperature of the sample (399.5 K) with DSC. The effect of cooling rate was not studied during the IR experiment. The storage temperature apparently did not have any pronounced effect on the transition. On heating, form II to its melting point under dry N_2, the melt did not crystallise (instead, it remained amorphous) after cooling over a period of at least a week (the maximum observation time). After the N_2 was replaced by air, the crystallisation of the amorphous form to form II could be observed (Figure 8).

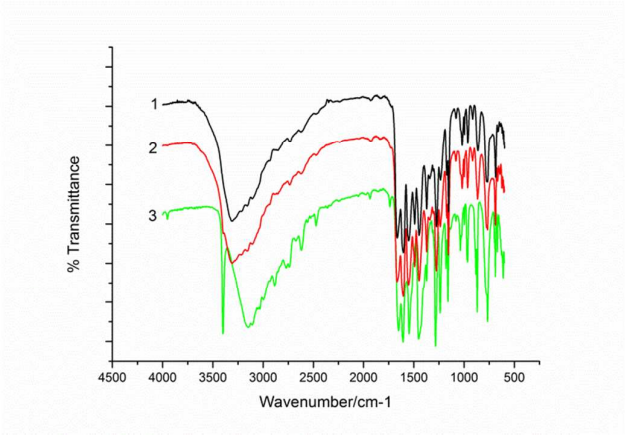
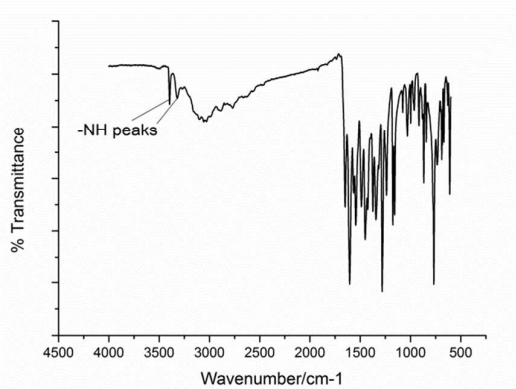


Figure 8: IR-spectra, giving evidence of a slow transformation from an amorphous phase (1, 2) to Form II (3), seen over several hours, identified by the –NH peak which begins to form at ~ 3400 cm^{-1}. Plots are staggered along the y-axis for clarity.

During the variable-temperature IR-spectroscopy experiments, the sample partially sublimed and condensed onto the glass slide covering the cell. After the experiment, this cover slide was removed and the IR-spectrum of the condensed sample was recorded. The presence of both forms of metacetamol was confirmed by the IR-spectrum (Figure 9).

a)



b)

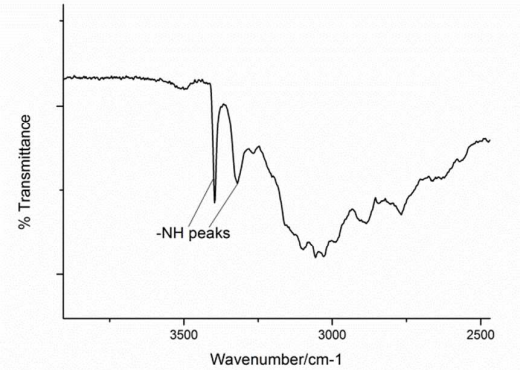


Figure 9: a) IR spectrum recorded for the upper film which shows that both Form I and Form II have crystallised in the same environment, and b) expanded region, showing that peaks from both forms are present.

CrystEngComm Accepted Manuscript

Please do not adjust margins

The sample was also inspected visually under the optical microscope, and this gave clear evidence that polycrystalline form II was present alongside crystals of form I (Figure 10). The behaviour and appearance of metacetamol form II is rather similar to that of the "elusive" paracetamol form III: both substances form drops with a large number of small crystallites radiating from the centre to borders of the drop[34]

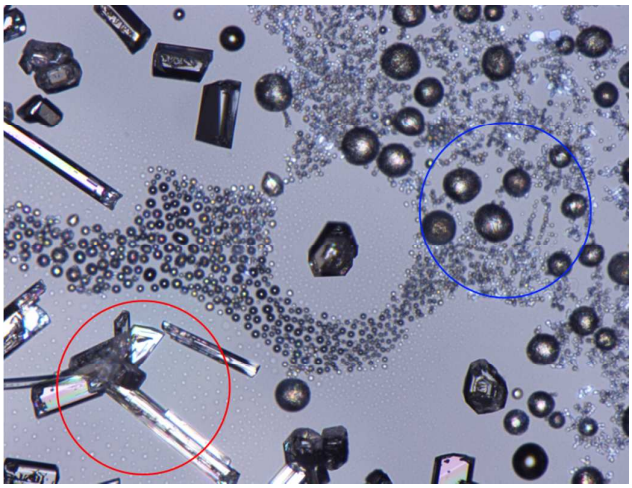
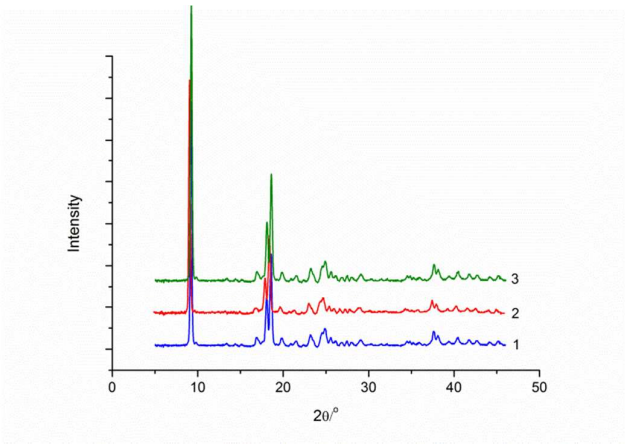


Figure 10: Optical image of the characteristic needles of Form I (circled in red), and polycrystalline Form II (circled in blue).

The presence of air, and in particular moisture in the air, had a noticeable effect not only on the crystallisation of form II from the melt, but also on the transformation of form II to form I. This was demonstrated in an experiment in which a sample of form II was divided equally into three portions which were stored under different levels of relative humidity. Samples were monitored over a period of ~5 days, and X-ray powder diffraction patterns were measured at 24-hour intervals (Figure 11). To simulate humid conditions the sample contained in a diffractometer sample holder was placed under a jar (12 x 12 x 6 cm) alongside a vial containing ~10 ml water. Ambient relative humidity of 50-60 % conditions were achieved by leaving the loaded sample holder exposed to the laboratory atmosphere. The third sample holder was placed inside a sealed desiccator with anhydrous calcium chloride used as the dessicant. The sample stored under dry conditions remained as pure form II over the study period, but the sample stored under humid conditions, to form I within 24 hours. Sample stored at ambient humidity also undergo transition to form I but slower. In this respect, it is worth noting that a transformation of paracetamol II to paracetamol I is also facilitated in the presence of water vapour, whereas dry samples can be preserved indefinitely long [8,37].

a)



b)

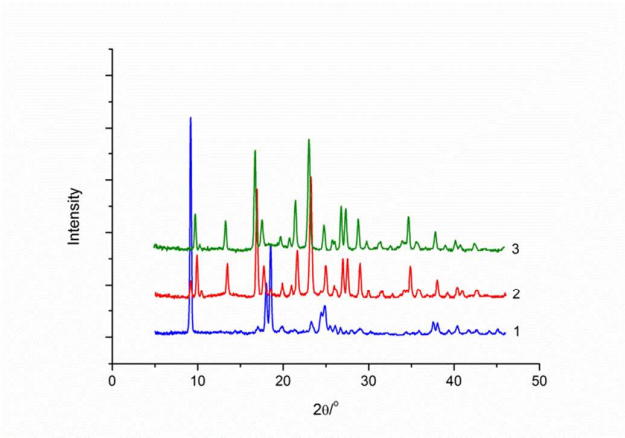


Figure 11: a) XRPD of a sample under dry conditions, showing that Form II remains stable and does not undergo any transformation after 3 days, and b) XRPD showing a transformation from Form II to Form I after 1 day, triggered by the humidity.

Conclusions

A new polymorph (Form II) of metacetamol has been identified and characterised using a range of techniques. Form II can be crystallised from the melt or at the interface of an aqueous-organic layer.

Form II exhibits a very different crystal packing from either Form I or any of the known polymorphs of paracetamol. This polymorph can be formed under certain conditions from the melt. It is highly unstable in the presence of even small amounts of water in the air, but can be preserved indefinitely long in dry atmosphere. In this respect, metacetamol II behaves similar to the orthorhombic paracetamol II. Metacetamol II melts at a significantly lower temperature than Form I and has a lower lattice energy despite having a very close density. This can be explained by consideration of its crystal structure in which metacetamol molecules form dimers linked by OH…O hydrogen bonds, whereas the N-H bonds of the amide groups are not involved in any hydrogen bonds. One would expect that Form II has a higher aqueous solubility than Form I and hence a higher bioavailability. Further studies

CrystEngComm Accepted Manuscript

This journal is © The Royal Society of Chemistry 20xx

Please do not adjust margins

would be required to test this hypothesis, and given the propensity for Form II to transform to Form I in the presence of water, such studies are likely to be challenging.

Acknowledgements

We are grateful for the support of the Year Abroad Programme of The University of Edinburgh (LMcG), the Royal Society of Edinburgh (CRP), the Ministry of Education and Science of the Russian Federation (EVB, VAD, AFA), including project 1828 (DAR), and Russian Academy of Sciences (EVB, DAR). We thank the Scottish Funding Council (SPIRIT) and the EPSRC Centre for Innovative Manufacturing in Continuous Manufacturing and Crystallisation (CMAC) for contributions towards studentships (PLC). We acknowledge the support of the Diamond Light Source for beamtime. We also acknowledge the support of the Centre of Collective Use SB RAS (NIOCH SB RAS) for assistance in chromatography analysis.

Notes and references

‡Notations of the H-bonded motifs see in [30]

1 A. Llinàs and J. M. Goodman, *Drug Discov. Today*, 2008, **13**, 198–210.

2 J. Bernstein, *Polymorphism in Molecular Crystals*, Oxford University Press, New York, 2002, vol. 14.

3 R. Hilfiker, *Polymorphism*, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, FRG, 2006.

4 Federal Register, Vol.65, N. 251, December 29, 2000, pp. 83041-83063; http://www.fda.gov/RegulatoryInformation/RulesRegulations/.

5 M. Haisa, S. Kashino and H. Maeda, *Acta Crystallogr. B*, 1974, **30**, 2510–2512.

6 M. Haisa, S. Kashino, R. Kawai and H. Maeda, *Acta Crystallogr. B*, 1976, **32**, 1283–1285.

7 M.-A. Perrin, M. A. Neumann, H. Elmaleh and L. Zaske, *Chem. Commun.*, 2009, 3181–3.

8 E. V. Boldyreva, V. A. Drebushchak, I. E. Paukov, Y. A. Kovalevskaya and T. N. Drebushchak, *J. Therm. Analys. Calorim.*, 2004, **77**, 607–623.

9 E. V. Boldyreva, T. P. Shakhtshneider, H. Ahsbahs, H. Sowa and H. Uchtmann, *J. Therm. Analys. Calorim.*, 2002, **68**, 437–452.

10 I. D. H. Oswald, I. Chataigner, S. Elphick, F. P. a. Fabbiani, A. R. Lennie, J. Maddaluno, W. G. Marshall, T. J. Prior, C. R. Pulham and R. I. Smith, *CrystEngComm*, 2009, **11**, 359-366.

11 M. Barrio, E. Maccaroni, I. B. Rietveld, L. Malpezzi, N. Masciocchi, R. Céolin and J.-L. Tamarit, *J. Pharm. Sci.*, 2012, **101**, 1073–8.

12 S. J. Smith, M. M. Bishop, J. M. Montgomery, T. P. Hamilton and Y. K. Vohra, *J. Phys. Chem. A*, 2014, **118**, 6068–77.

13 M. Topoła, M. Podawacz, M. Śliwińska-Mossoń, W. Sajewicz and H. Milnerowicz, *Curr. Issues Pharm. Med. Sci.*, 2013, **26**, 206–210.

14 C. Bunchorntavakul and K. R. Reddy, *Clin. Liver Dis.*, 2013, **17**, 587–607.

15 R. Twycross, V. Pace, M. Mihalyo and A. Wilcock, *J. Pain Symptom Manage.*, 2013, **46**, 747–55.

16 D. B. Njoku, *Int. J. Mol. Sci.*, 2014, **15**, 6990–7003.

17 L. K. Hansen, G. L. Perlovich and A. Bauer-Brandl, *Acta Crystallogr. E*, 2006, **62**, o3627–o3628.

18 B. A. Howell, S. Q. Siler and P. B. Watkins, *Toxicol. Lett.*, 2014, **226**, 163–72.

19 J. G. Kenna, *Arch. Toxicol.*, 2013, **87**, 15–8.

20 W. F. Salminen, S. M. Roberts, N. R. Pumford and J. A. Hinson, *Drug Metab. Dispos.*, 1998, **26**, 267–71.

21 W. F. Salminen, R. Voellmy and S. M. Roberts, *J. Pharmacol. Exp. Ther.*, 1997, **282**, 1533–40.

22 B. D. Stamper, T. K. Bammler, R. P. Beyer, F. M. Farin and S. D. Nelson, *Toxicol. Sci.*, 2010, **116**, 164–173.

23 M. Hadi, S. Dragovic, R. Van Swelm, B. Herpers, B. Van De Water, F. G. M. Russel, J. N. M. Commandeur and G. M. M. Groothuis, *Arch. Toxicol.*, 2013, **87**, 155–165.

24 R. P. L. Van Swelm, M. Hadi, C. M. M. Laarakkers, R. Masereeuw, G. M. M. Groothuis and F. G. M. Russel, *J. Appl. Toxicol.*, 2014, **34**, 993–1001.

25 S. P. Thompson, J. E. Parker, J. Potter, T. P. Hill, A. Birt, T. M. Cobb, F. Yuan and C. C. Tang, *Rev. Sci. Instrum.*, 2009, **80**, 075107.

26 O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard and H. Puschmann, *J. Appl. Crystallogr.*, 2009, **42**, 339–341.

27 G. M. Sheldrick, *Acta Crystallogr. A.*, 2008, **64**, 112–22.

CrystEngComm Accepted Manuscript

Please do not adjust margins

28 E. V Boldyreva, Y. Chesalov, T. N. Drebushchak, E. N. Kolesnik, Y. Kovalevskaya, I. E. Paukov, V. A. Drebushchak and B. A. Kolesov, *Phase Transitions*, 2009, **82**, 497–506.

29 M. A. Mikhailenko, *J. Cryst. Growth*, 2004, **265**, 616–618.

30 W. I. F. David, K. Shankland, J. Van De Streek, E. Pidcock, W. D. S. Motherwell and J. C. Cole, *J. Appl. Crystallogr.*, 2006, **39**, 910–915.

31 J. S. Capes and R. E. Cameron, *Cryst. Growth Des.*, 2007, **7**, 108–112.

32 D. I. a Millar, I. D. H. Oswald, D. J. Francis, W. G. Marshall, C. R. Pulham and A. S. Cumming, *Chem. Commun.*, 2009, 562–564.

33 B.A. Kolesov, M. A. Mikhailenko and E. V Boldyreva, *Phys. Chem. Chem. Phys.*, 2011, **13**, 14243–53.

34 M. Szelagiewicz, C. Marcolli, S. Cianferani and A. P. Hard, *J. Therm. Anal. Calorim.*, 1999, **57**, 23–43.

35 09 Gaussian, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, J. E. P. Jr., F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, and D. J. Fox and W. C. G. Inc.", 2009, 5.

36 E. B. Burgina, V. P. Baltakhinov, E. V. Boldyreva and T. P. Shakhtschneider, *J. Struct. Chem.*, 2004, **45**, 64–73.

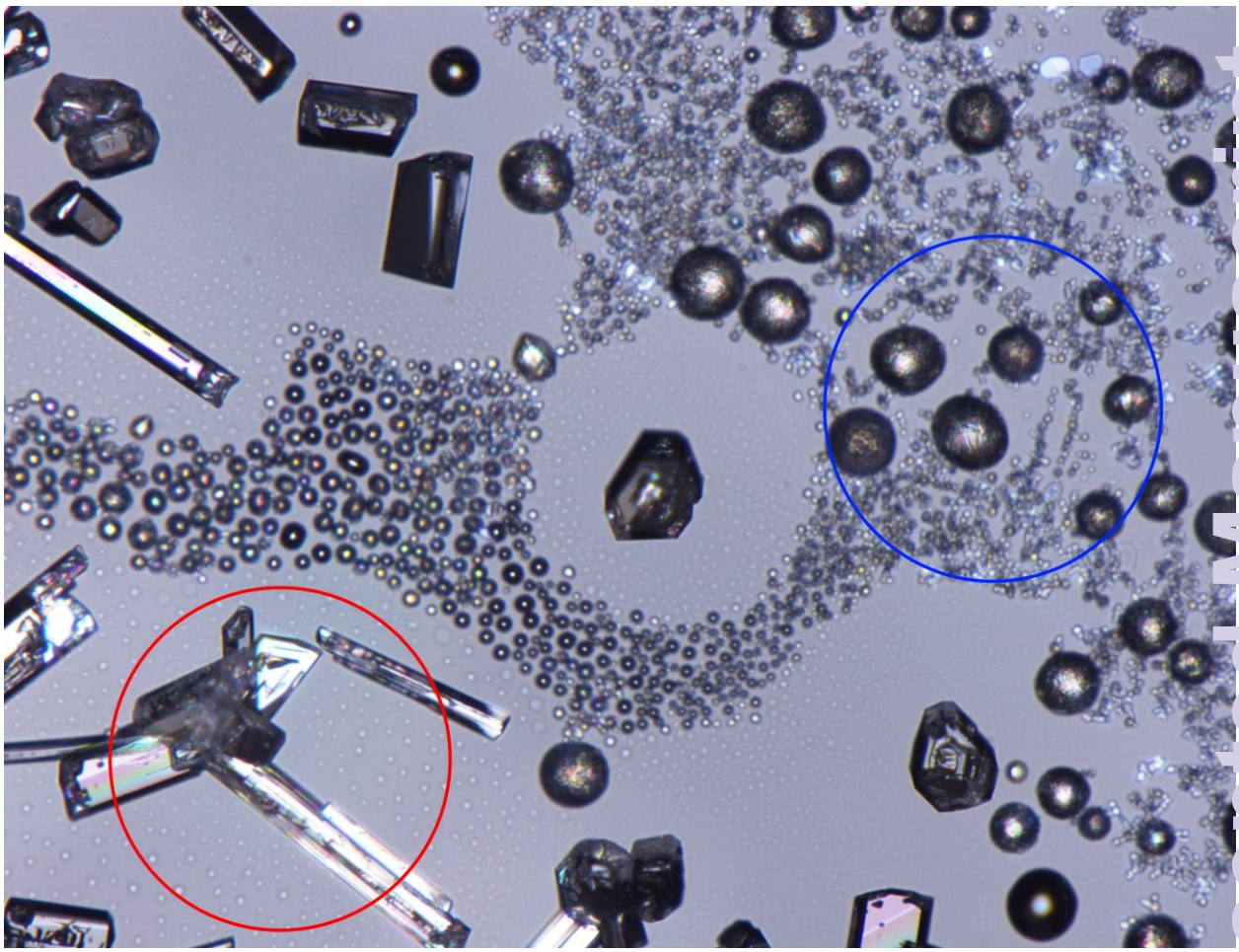
37 K. Kachrimanis, K. Fucke, M. Noisternig, B. Siebenhaar and U. J. Griesser, *Pharm. Res.*, 2008, **25**, 1440–1449.

CrystEngComm Accepted Manuscript

This journal is © The Royal Society of Chemistry 20xx

The existence of a new polymorph of metacetamol together with its properties are reported for the first time.

CrystEngComm Accepted Manuscript



CrystEngComm Accepted Manuscript