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Unexpected Low Temperature Behaviour of Piroxicam Monohydrate

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Pharmaceutical compounds can crystallise in different polymorphic forms with the same chemical composition; a phenomenon that has been studied for almost 200 years,[1] and remains a major issue in the pharmaceutical industry. Additional problems arise from solvated crystal forms, which incorporate one or more types of solvent from the crystallisation medium into the crystal.[2] In the special case of water incorporation, the crystal form is called a hydrate. Pharmaceutical hydrates, which can vary widely in both composition and stability, are simultaneously favoured and feared. Hydrates exhibit the lowest solubility in water of all crystal forms of a compound and hence hydrate formation can seriously influence the bioavailability and thus the safety and efficacy of a medication.[3] As a result there is considerable current interest in the study of water clusters in crystalline hydrates.[4] Hydrated crystal structures also shed light on the fundamental nature of homomeric interactions between water molecules and heteromeric interactions between water and host molecules in molecular solids.[4b, 5] With the help of modern diffraction techniques and computational studies, these interactions can now be accurately structurally characterised,[6] making essential information available for *ab initio* crystal structure prediction of hydrates.[7]

We have focussed on the neutron structural characterisation of a range of pharmaceutically relevant hydrates.[5b, 8] As part of this study we have investigated piroxicam (PIR, Figure 1), which is a non-steroidal anti-inflammatory drug (NSAID) used in the

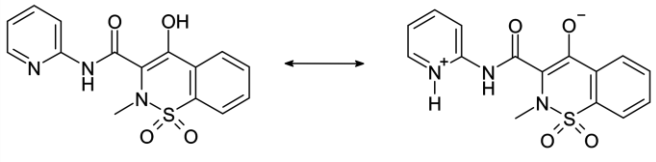

Figure 1. Molecular structure of piroxicam in its neutral and zwitterionic forms.

treatment of chronic pain in rheumatoid arthritis and osteoarthritis. PIR is listed in both the European[9] and the US Pharmacopoeias,[10] and is reported to exist in three different unsolvated crystal forms,[11] a monohydrate,[12] and several multi-component crystals and salt forms.[13] Our interest lies mainly in the interaction of water of crystallisation with the host molecule in the monohydrate structure. We now report accurate hydrogen atom positions for PIR monohydrate derived from neutron diffraction data as well as the substance's remarkable behaviour on cooling. Precise atomic coordinates for all atoms, including hydrogen, may be used in non-empirical lattice energy calculations in order to fully understand the hydrogen bonding network and the structural and energetic context of the included water.[14] With this approach, the 3D network in the crystal structure can be deconstructed *in silico* in order to obtain interaction energies for structural motifs, such as hydrogen bonds, π-stacking and van der Waals interactions.

Piroxicam monohydrate crystals were studied using the Laue thermal neutron diffractometer KOALA[15] at ANSTO (Australian Nuclear Science and Technology Organisation). For experimental details please refer to the ESI. After cooling a large single crystal (*ca*. 0.5 mm^3) from 120 K to 22 K at 180 K h^{-1}, we observed an undesirable and marked splitting in the diffraction peaks, which normally would have resulted in the abortion of the experiment assuming degradation of the crystal. This kind of phenomenon is an all-too-common occurrence in low temperature single crystal structure determination. It is generally assumed to arise from degradation of the sample due either to a destructive phase transition or cracking caused by anisotropic contraction inducing strain at crystal fault lines. Nonetheless, data collection was commenced and remarkably the peaks coalesced within 11

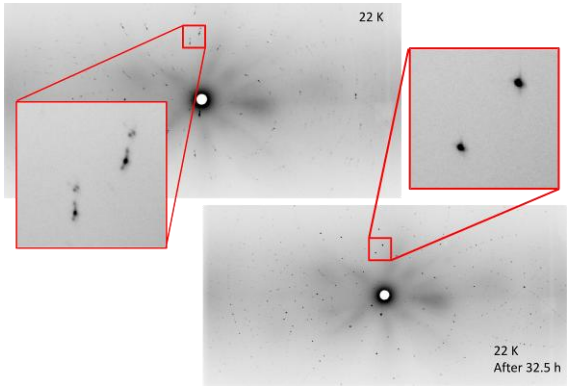

Figure 2. Neutron Laue diffraction patterns recorded for a single piroxicam monohydrate sample at 22 K at different time intervals in the same orientation.

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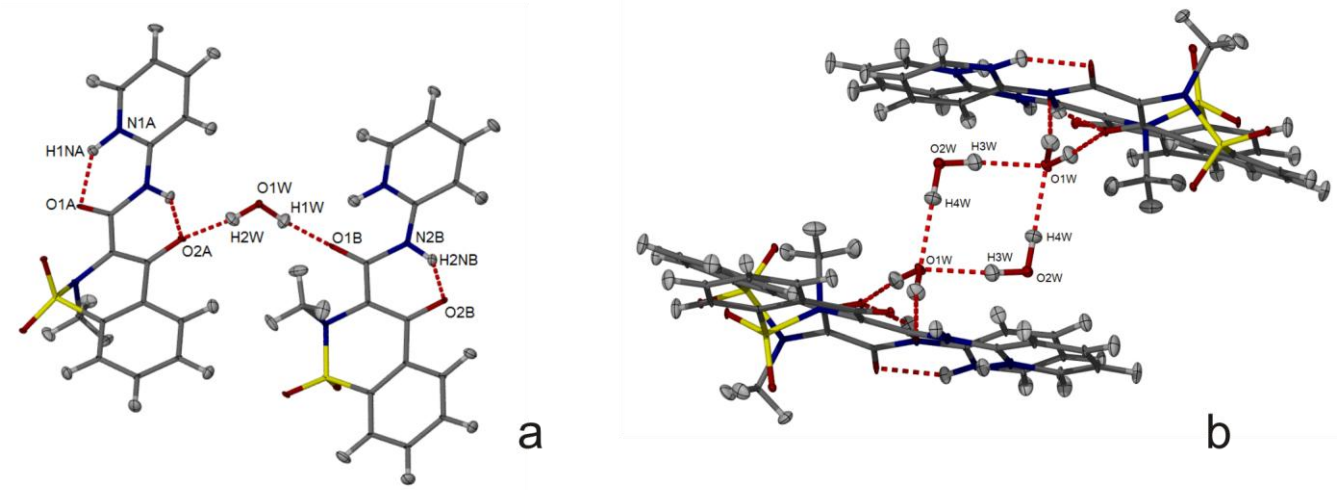

Figure 3. Packing motif of piroxicam monohydrate derived from neutron diffraction. (a) Two piroxicam molecules are bridged by a water molecule and (b) tro of these are connected by two further water molecules to form a sandwiched water tetramer. Atomic displacement ellipsoids are drawn at 50% probability.

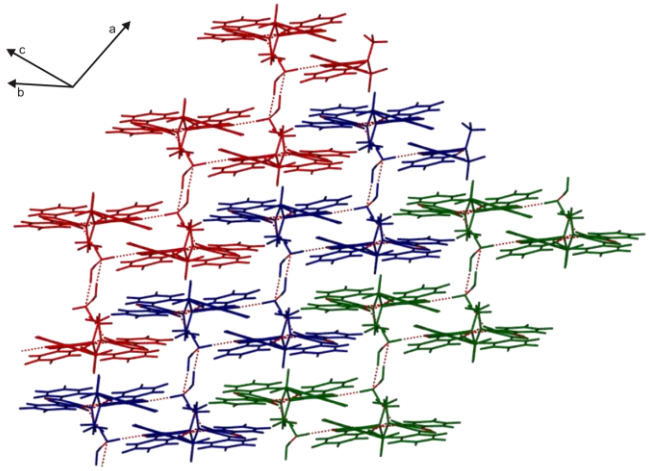

Figure 4.Packing of water tetramers into chains and thence layers; different colours show different continuous hydrogen bonded chains.

hours to give a diffraction pattern consistent with an essentially single crystalline sample (see Fig. 2 and ESI Fig. S1). The splitting of the diffraction pattern was not observed for a single crystal of the same crystallisation batch, which was covered in fluorosilicone oil during preparation for low temperature neutron diffraction. We attribute this difference to the thermal conductivity of the covering oil.

X-ray diffraction data collected at room temperature and 120 K, as well as neutron diffraction data collected at room temperature, 120 K and 22 K showed that the known monohydrate was present in all cases excluding the possibility of a first order phase transition (see ESI Table S2). If a phase transition is not responsible for the observed reversible splitting behaviour, an alternative explanation may be a strong anisotropy in the unit cell contraction during cooling and thus strain on the crystals. This hypothesis is strengthened by the fact that crystals used in both the neutron and X-ray experiments show no splitting when they are covered in oil evening out thermal gradients within the crystal and quickly transmitting changes in temperature from the surrounding medium into the crystal. Thus, the splitting could be caused by thermal strain, however, subsequent relaxation of the split crystal into a single crystal is surprising and suggests significant resilience of the crystal in strongly hydrogen bonded molecular solids. As a result it is possible to elucidate the full neutron structure to high precision.

The monohydrate structure is in the zwitterionic form comprising two intramolecular hydrogen bonds in the piroxicam molecule. Two host molecules are bridged by one water molecule (O1W) hydrogen bonding to the deprotonated hydroxyl oxygen atom O2A and the amide carbonyl O1B (Figure 3a, Table S3). Two of these core motifs are connected by the second crystallographically independent water molecule, which hydrogen bonds to the O1W atom of both bridging water molecules and thus forms a water tetramer ‘sandwiched’ between four piroxicam molecules (Figure 3b). The hydrogen bonds donated from the water molecule O2W are 2.00(1) and 1.94(2) Å in length, considerably longer than those donated by the O1W water at 1.87(1) and 1.796(6) Å, respectively, at room temperature. Each sandwich then connects with another through two hydrogen bonds per piroxicam molecule from the amide carbonyl O1A to the amide H2NB-N2B and from the second deprotonated hydroxyl oxygen O2B to the protonated pyridyl nitrogen atom N1A-H1NA. Interestingly, these hydrogen bonds result in the formation of infinite chains of sandwiches along (101), which do not have strong interactions (hydrogen bonds) with each other (Figure 4).

The accurate atomic coordinates obtained from the neutron diffraction experiments were submitted to non-empirical lattice energy calculations[14] to assign interaction energies to the hydrogen bonds found in the crystal network (see ESI Table S4). The hydrogen bonds donated by the O1W water molecule yield the strongest interactions with energies of -33.7 and -28.6 kJ mol^{-1}. Those involving the O2W water are less stabilising with -26.9 and -23.3 kJ mol^{-1}, which is consistent with the longer distance. The hydrogen bonds connecting the sandwiches only account for an energy of -19.0 kJ mol^{-1} each and are thus considerably weaker than those involving water molecules, but since four of these hydrogen bonds connect the sandwiches, their sum is one of the major stabilising factors of the crystal structure.

It appears possible that the chains, stabilised by the strong hydrogen bonds involving water and the charge-assisted hydrogen bonds between the host molecules, can contract in isolation to each other. If this happens in an unsynchronised

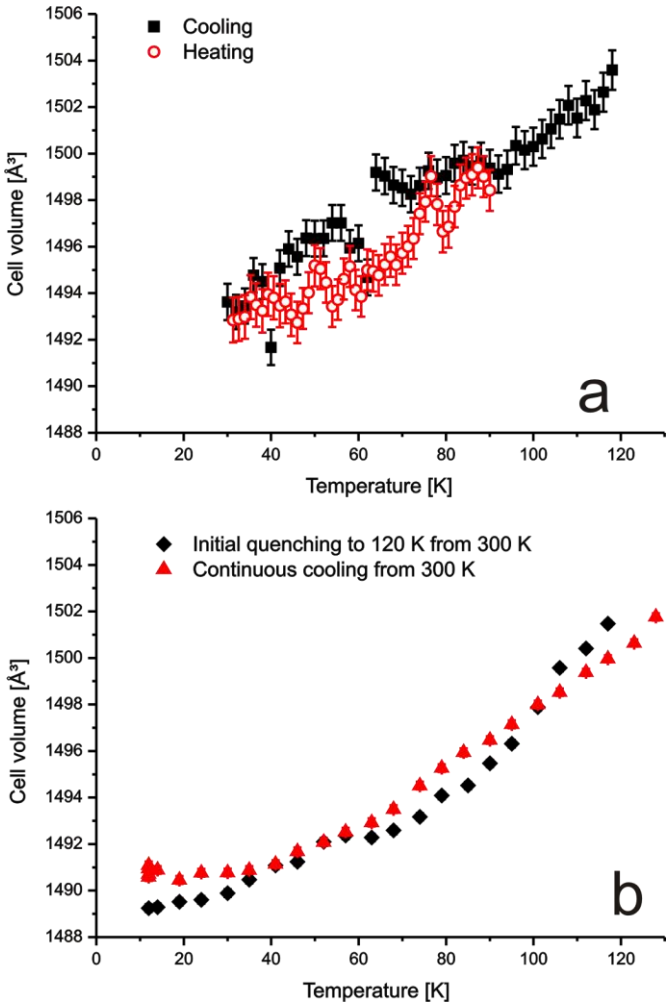

Figure 5. Volume of PIR monohydrate as a function of temperature as measured by (a) single crystal X-ray diffraction and (b) by powder X-ray diffraction. Error bars for the powder diffraction experiment are smaller than symbols.

manner, for example because of a temperature gradient across the crystal, it could lead to considerable strain in the crystal resulting in the separation of crystalline domains, apparent as peak splitting in the neutron diffraction images, without causing irreversible damage to the single crystal. Annealing at low temperature leads to the relaxation of the crystal and a synchronisation of the domains into a single crystal. This crystal strain, however, was not observable for ground samples, on which a powder X-ray diffraction strain analysis was performed by quench cooling from room temperature to 22 K at a rate of 360 K h^{-1}, *i.e.* the maximum cooling rate possible on the instrument to maximise temperature stress of the sample. Once the final temperature was achieved, powder X-ray diffractograms were recorded continuously over 25 h and subsequently analysed for crystal strain changes by modelling the peak shapes against those of highly crystalline, strain-free CeO_2 (see ESI Figure S5). It is very likely that the temperature strain is more pronounced in the bigger crystals used for single crystal X-ray and neutron diffraction.

In comparison to the monohydrate, single crystal neutron diffraction experiments of the thermodynamically stable anhydrous polymorph form I did not show peak splitting during cooling on the KOALA instrument. The resulting accurate atomic coordinates were also submitted to PACHA calculations. Interestingly, this structure consists of piroxicam dimers connected through two hydrogen bonds from the sulfonyl oxygen O3 to the amide nitrogen H2N-N2 (see ESI Figure S6). This hydrogen bond energy is -11.4 kJ mol^{-1}, by far the strongest interaction in the crystal structure but considerably weaker than the stabilising forces in the monohydrate. Thus the structure may well be more flexible towards temperature gradients, as the dimers can contract and relax without influencing their neighbouring dimers.

During the investigation of the possible causes for the splitting of PIR monohydrate single crystals a temperature–controlled measurement was undertaken to unambiguously eliminate the possibility of a mechanically destructive phase transition in the monohydrate. During this experiment we observed unusual thermal behaviour. Thermal treatment of the crystalline sample causes a memory effect, which can be observed in the subsequent behaviour upon cooling/heating. A single crystal was quenched from room temperature to 120 K by placing it in the pre-cooled cryostream. Subsequently, the sample was cooled to 30 K at 5 K h^{-1} and the unit cell dimensions were monitored by continuously collecting diffraction patterns and refining the peak positions to give a unit cell every 2 K during this cooling experiment. Plotting the cell volume *vs.* the temperature (Figure 5a black squares) reveals the expected overall shrinking of the unit cell with decreasing temperature. This decrease seems to follow a linear slope, which is surprising as the contraction of the unit cell has been reported to level off with decreasing temperature for other compounds.[16] The step between 65 and 60 °C is due to an experimental artefact. A subsequent heating cycle from 30 K to 90 K at 5 K h^{-1} of the same sample shows a slight hysteresis of the unit cell volume which is attributed to the relaxation of the β angle during the time the crystal was held at 30 K. This indicates that despite the low cooling rate, the relatively large single crystal used for the neutron experiment is not in equilibrium during the temperature ramp.

A powder X-ray diffraction experiment was undertaken to examine this relaxation effect within a powder sample of small crystallite size. The sample of PIR monohydrate, carefully ground to minimise the crystal size without inducing phase transition, was sieved (80 µm) onto a zero background silicon disc coated with vaseline and submitted to a temperature programme continuously cooling from room temperature (*ca.* 300 K) to the minimum temperature of 12 K at a cooling rate of 15 K min^{-1}. The linear unit cell contraction was not observed in this experiment (Figure 5b, triangles), verifying that it is a feature of the large crystal size. In a subsequent experiment, the same powder sample was quenched from room temperature to 120 K at a cooling rate of 360 K min^{-1}, a cooling rate comparable to that a crystal would be exposed to when placed directly in a precooled cryo-stream on a single crystal diffractometer. This quenched sample was then cooled to the final temperature of 12 K with a cooling rate of 15 K min^{-1} (Figure 5b, diamonds). Surprisingly, the two cooling cycles (continuously and quenched) show distinct differences. For the continuously cooled sample the unit cell volume decreases in a continuous and smooth fashion to a temperature of about 50 K, below which the contraction of the cell volume levels off and stays approximately constant below 35 K. The quenched sample, however, reveals a cell volume that is larger than that found for the continuously cooled sample. This result corresponds well to the behaviour found in cooling the single crystal sample, indicating that after quenching, piroxicam monohydrate is in a non-equilibrium state. During the subsequent cooling of this

initially quenched sample, the unit cell volume contracts more quickly than that of the continuously cooled powder, but levels off at about 70 K. Between 70 K and 50 K the cell volume stays nominally unchanged but continues to decrease below 50 K and levels off again below 25 K. Surprisingly, the final cell volume of the initially quenched sample lies below that of the continuously cooled one. It is obvious that the cooling history of the sample induces a kinetically controlled memory-effect, similar to that observed in amorphous materials.[17]

After both the continuous and the quenched cooling cycle, the powder was heated up to room temperature at a heating rate of 15 K min^{-1} while diffractograms were continuously collected (ESI Figure S7). Both cell volume *vs*. temperature curves start from the respective final cell volumes measured in the respective cooling cycle and follow parallel slopes converging at higher temperatures until they are identical above 135 K. Up to this temperature, the initially quenched sample reveals the smaller cell volumes indicating that the memory-effect remains in the sample over a considerable temperature range.

Since almost no information exists about the thermal behaviour of molecular crystals at temperatures below room temperature down to 10 K or lower, it is problematic to classify the temperature dependent behaviour of piroxicam monohydrate as either normal or abnormal. Temperature dependent X-ray diffraction, infrared or Raman spectroscopic, and calorimetric experiments of molecular crystals at temperatures above room temperature are quite common, especially in the study of phase transitions and desolvation.[6, 18] Cooling experiments, however are normally only performed for single crystal determination or for the elucidation of anticipated or known phase transitions *e.g.* in magnetic materials[19] or in spin crossover complexes.[20] The full characterisation of extraordinary thermal behaviour such as negative or zero thermal expansion also requires the detailed study of the thermal behaviour at low temperatures.[21] However, as we have shown in this study, 'ordinary' molecular crystals can also show unexpected thermal behaviour at low temperatures and indeed may retain a memory effect of their previous thermal treatment. In the case of PIR monohydrate it can be assumed that the strongly hydrogen bonded chains, as discussed above, cause this memory effect. When quenched to 120 K, these chains 'freeze' in a non-equilibrium crystal structure normally observed at temperatures closer to room temperature. Over time the chains then relax causing a concerted and overshooting contraction of the crystal resulting in an overall smaller unit cell volume than if the crystal structure is cooled in a continuous fashion with sufficient time to relax.

In conclusion, we have shown that piroxicam monohydrate shows unexpected thermal behaviour at temperatures below 120 K. The crystals exhibit a memory effect depending on their cooling history, as has been reported for amorphous materials[22] but is unprecedented for single crystals. The knowledge of the thermal behaviour in molecular crystals is important to any analytical work at low temperatures, such as X-ray and neutron diffraction or spectroscopy, but also to the engineering of low temperatures devices, which could lose intended function due to unexpected thermal behaviour. We also show that an initially split diffraction pattern due to thermal strain in a large crystal (~0.5 mm^3) can coalesce to give a single crystal diffraction pattern given sufficient relaxation time. This can be explained by the strongly hydrogen bonded, isolated chains present in the hydrate, which can contract separately from each other. It can be expected that a crystal structure stabilised by strong hydrogen bonds, as for example observed in strong hydrates, may be prone to this type of thermal behaviour.

Acknowledgements

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Keywords: lattice energy calculations · Low temperature · Piroxicam monohydrate · temperature controlled analysis · X-ray and neutron diffraction

[1] E. Mitscherlich, *Ann. Chim. Phys.* **1822**, 19, 350-419.

[2] A. Nangia, in *Encyclopedia of Supramolecular Chemistry - update, Vol. 1:1* (Eds.: J. L. Atwood, J. W. Steed), Taylor & Francis, **2007**, pp. 1-9.

[3] U. J. Griesser, in *Polymorphism* (Ed.: R. Hilfiker), Wiley-VCH, Weinheim, Germany, **2006**, pp. 211-233.

[4] a) N. S. Oxtoby, A. J. Blake, N. R. Champness, C. Wilson, *Chem. Eur. J.* **2005**, 11, 4643-4654; b) B. C. R. Sansam, K. M. Anderson, J. W. Steed, *Cryst. Growth Des.* **2007**, 7, 2649-2653; c) M. Henry, H. Bogge, E. Diemann, A. Muller, *J. Mol. Liq.* **2005**, 118, 155-162; d) S. K. Ghosh, P. K. Bharadwaj, *Angew. Chem. Int. Ed.* **2004**, 43, 4390-4390; e) R. J. Doedens, E. Yohannes, M. I. Khan, *Chem. Commun.* **2002**, 62-63.

[5] a) D. R. Turner, M. Henry, C. Wilkinson, G. J. McIntyre, S. A. Mason, A. E. Goeta, J. W. Steed, *J. Am. Chem. Soc.* **2005**, 127, 11063-11074; b) K. Fucke, K. M. Anderson, M. H. Filby, M. Henry, J. Wright, S. A. Mason, M. J. Gutmann, L. J. Barbour, C. Oliver, A. W. Coleman, J. L. Atwood, J. A. K. Howard, J. W. Steed, *Chem. Eur. J.* **2011**, 17, 10259-10271.

[6] K. Fucke, J. W. Steed, *Water* **2010**, 2, 333-350.

[7] D. E. Braun, P. G. Karamertzanis, S. L. Price, *Chem. Commun.* **2011**, 47, 5443-5445.

[8] K. Fucke, G. J. McIntyre, C. Wilkinson, M. Henry, J. A. K. Howard, J. W. Steed, *Cryst. Growth Des.* **2012**.

[9] *Pharmacopoeia Europaea 6.8*, Deutscher Apotheker Verlag, Stuttgart & Govi-Verlag GmbH, Eschborn.

[10] *United States Pharmacopoeia Vol 32*.

[11] a) M. Kuhnert-Brandstaetter, R. Voellenklee, *Fresenius' Z. Anal. Chem.* **1985**, 322, 164-169; b) F. Vrecer, M. Vrbinc, A. Meden, *Int. J. Pharm.* **2003**, 256, 3-15; c) A. R. Sheth, S. Bates, F. X. Muller, D. J. W. Grant, *Cryst. Growth Des.* **2004**, 4, 1091-1098.

[12] J. Bordner, J. A. Richards, P. Weeks, E. B. Whipple, *Acta Crystallogr. C* **1984**, C40, 989-990.

[13] a) S. L. Childs, K. I. Hardcastle, *Cryst. Growth Des.* **2007**, 7, 1291-1304; b) H.-S. Gwak, J.-S. Choi, H.-K. Choi, *Int. J. Pharm.* **2005**, 297, 156-161; c) S. C. Hong, C. H. Yu, D. H. Cho, H. J. Shin, Y. S. Gil, *Yakche Hakhoechi* **2003**, 33, 85-89; d) P. M. Bhatt, N. V. Ravindra, R. Banerjee, G. R. Desiraju, *Chem. Commun.* **2005**, 8, 1073-1075.

[14] M. Henry, *ChemPhysChem* **2002**, 3, 561-569.

[15] Edwards, A. J. *Aust. J. Chem.* **2011**, 64, 869.

[16] a) L. Gondek, J. Przewoznik, J. Czub, Y. Tyvanchuk, A. Szytula, A. Arurlaj, *Intermetallics* **2012**, 21, 10-17; b) F. J. M. Casado, O. Fabelo, J. A. Rodriguez-Velamazan, M. R. Riesco, J. A. R. Cheda, A. Labrador, C. Rodriguez-Blanco, J. Campo, V. Sanchez-Alarcos, H. Muller, *Cryst. Growth Des.* **2011**, 11, 4080-4089; c) S. Saha, S. Singh, B. Dkhil, S. Dhar, R. Suryanarayanan, G. Dhalenne, A. Revcolevschi, A. K. Sood, *Physical Review B* **2008**, 78.

[17] a) R. Pantani, G. Titomanlio, *J. Pol. Sci. B* **2003**, 41, 1526-1537; b) F. A. Kuhnast, J. Therm. Anal. 1992, 38, 409-420.

[18] R. Hilfiker, *Polymorphism: In the Pharmaceutical Industry*, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany, **2006**.

[19] A. A. Belik, P. Naumov, J. Kim, S. Tsuda, *J. Solid State Chem.* **2011**, 184, 3128-3133.

[20] a) A. E. Goeta, J. A. K. Howard, A. K. Hughes, D. O'Hare, R. C. B. Copley, *J. Mater. Chem.* **2007**, 17, 485-492; b) A. E. Goeta, J. A. K. Howard, *Chem. Soc. Rev.* **2004**, 33, 490-500.

[21] J. S. O. Evans, *Dalton Trans.* **1999**, 3317-3326.

[22] a) J. Hadac, P. Slobodian, P. Saha, *J. Therm. Anal. Calorim.* **2005**, 80, 181-185; b) J. K. Y. Tang, P. Lee-Sullivan, *J. Appl. Polym. Sci*. **2008**, 110, 97-108; c) Y. T. Liu, B. Bhandari, W. B. Zhou, *J. Agric. Food Chem.* **2006**, 54, 5701-5717.

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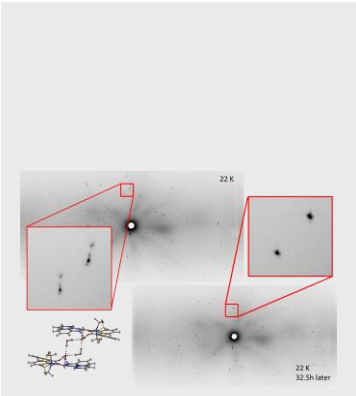
Entry for the Table of Contents

COMMUNICATIONS

The monohydrate of the anti-inflammatory drug piroxicam was found to show splitting upon cooling, which was reversible over time. In addition, the cell shows an irregular contraction over temperature and reveals a memory effect of its thermal history. The reason for these characteristics are the strongly hydrogen bonded chains present in the monohydrate, which allow the crystal domains to contract separately from each other.



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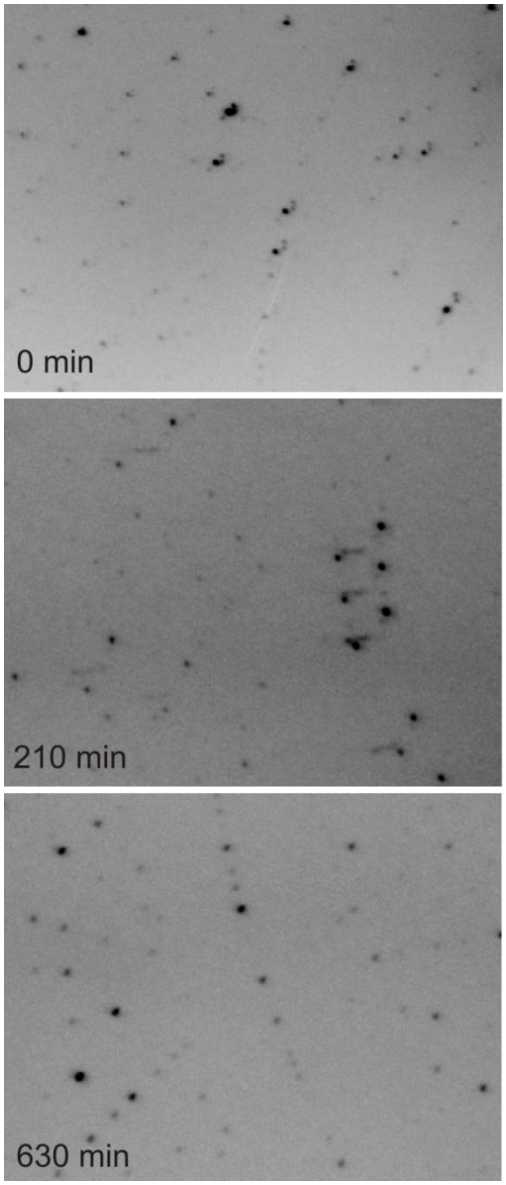


Figure S1 Neutron Laue diffraction patterns of the PIR monohydrate crystal at 22 K at different time intervals during the data collection. The first image was acquired at ϕ = -150°, the second at ϕ = -116° and the third at ϕ = -48°. The peaks are split into at least five domains in the initial image, while after 210 min the peaks show considerable coalescence with the peak centre being of higher intensity than the satellites. After 630 min the diffraction pattern is apparently completely coalesced and only shows single crystal diffraction.

Table S2 Crystallographic data of the neutron structures of PIR form I and PIR monohydrate at different temperatures

Parameter		Form I	Monohydrate		
			RT[a]	120 K	22 K[a]
Formula		$C_{15}H_{13}N_3O_4S$	$C_{15}H_{13}N_3O_4S \cdot H_2O$		
Mr [g mol^{-1}]		331.35		349.36	
λ (Å)		0.8 – 5.2		0.8 – 5.2	
Crystal system		monoclinic		triclinic	
Space group		$P2_1/c$		*P*-1	
T [K]		120	295	120	22
a [Å]		7.0366(1)	10.4734(7)	10.3484(3)	10.3124(5)
b [Å]		14.9956(3)	12.722(1)	12.7047(4)	12.7071(8)
c [Å]		13.8945(3)	12.9120(9)	12.8013(4)	12.7791(7)
α [°]		90	102.658(4)	102.748(1)	102.771(5)
β [°]		96.450(1)	99.298(4)	99.931(1)	100.040(4)
γ [°]		90	108.902(4)	108.756(1)	108.764(5)
V [Å^3]		1487.15(5)	1536.9(2)	1499.32(8)	1490.7(14)
Z		4	4	4	4
density [calc, g cm^{-3}]		1.510	1.510	1.548	1.557
F(000)		421	414	414	414
crystal size (mm^3)		1 x 1 x 1	1.5 x 1.5 x 0.7		
index ranges		0<*h*<13	0<*h*<12	0<*h*<12	0<*h*<12
		0<*k*<27	-15<*k*<14	-15<*k*<14	-15<*k*<14
		-19<*l*<18	-14<*l*<11	-14<*l*<11	-14<*l*<11
independent reflections		5747	3830	3880	3887
R(int)		0.055	0.046	0.044	0.051
refinement method			full-matrix least-squares on F^2		
data/restraints/parameters		5747/0/325	3830/0/703	3880/0/697	3887/0/691
goodness of fit on F^2		1.155	1.170	1.303	1.361
final *R* indices [$I>2\sigma(I)$]	*R*1	0.0619	0.0393	0.0391	0.0395
	*wR*2	0.1096	0.0642	0.0820	0.0856
R indices (all data)	*R*1	0.1064	0.0641	0.0536	0.0503
	*wR*2	0.1202	0.0701	0.0859	0.0885
largest diff peak		1.802	0.370	0.52	0.534
and hole [fm Å^{-3}]		-1.828	-0.469	-0.492	-0.587

[a] unit cell dimensions for the structure refinement from the Laue data were obtained from X-ray powder diffraction at the corresponding temperatures.

Table S3 Hydrogen bond of the two water molecules in PIR hydrate at different temperatures

Hydrogen bond		RT	120 K	22 K
O1W-H1W···O1B	Length (H···A) [Å]	1.874(10)	1.832(10)	1.828(10)
	Angle (D-H···A) [°]	173.2(7)	173.5(6)	173.3(5)
O1W-H2W···O2A	Length (H···A) [Å]	1.793(6)	1.786(5)	1.793(5)
	Angle (D-H···A) [°]	171.6(6)	170.9(6)	170.4(5)
O2W-H3W···O1W	Length (H···A) [Å]	2.001(11)	1.958(8)	1.948(7)
	Angle (D-H···A) [°]	175.3(7)	175.1(6)	174.9(6)
O2W-H4W···O1W	Length (H···A) [Å]	1.942(16)	1.899(9)	1.915(8)
	Angle (D-H···A) [°]	171.8(7)	171.8(6)	171.4(6)

Table S4 Hydrogen bonding energy of the PIR hydrate structures. All energies given in kJ mol^{-1}.

Hydrogen bond	RT	120K	22K
Monohydrate			
O1W-H1W···O1B	-33.7	-34.3	-35.1
O1W-H2W···O2A	-28.6	-28.4	-28.9
O2W-H3W···O1W	-26.9	-26.3	-27.8
O2W-H4W···O1W	-23.3	-24.2	-23.9
N1A-H1NA···O1B	-19.0	-19.6	-19.9
Form I			
N2-H2N···O3		-11.4	

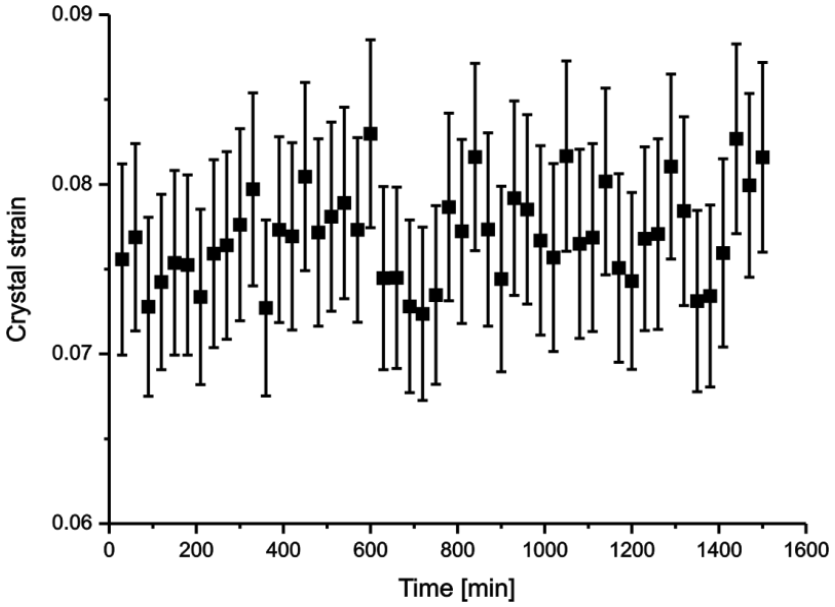


Figure S5 Strain analysis of PIR monohydrate powder by powder X-ray diffraction.

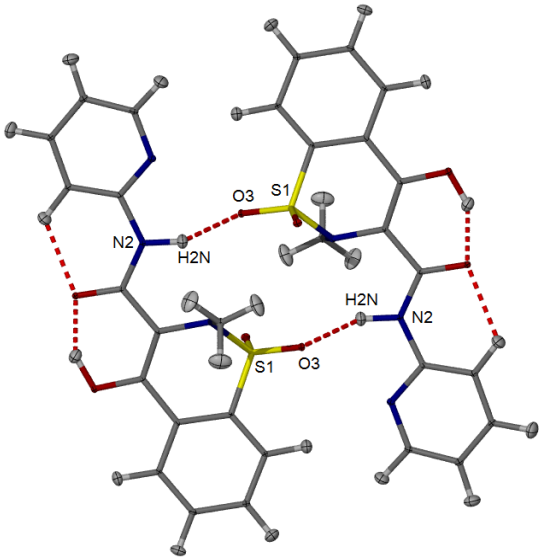


Figure S6 Basic packing motif of the anhydrous form I of piroxicam (120 K). Atomic displacement ellipsoids are drawn at 50% probability.

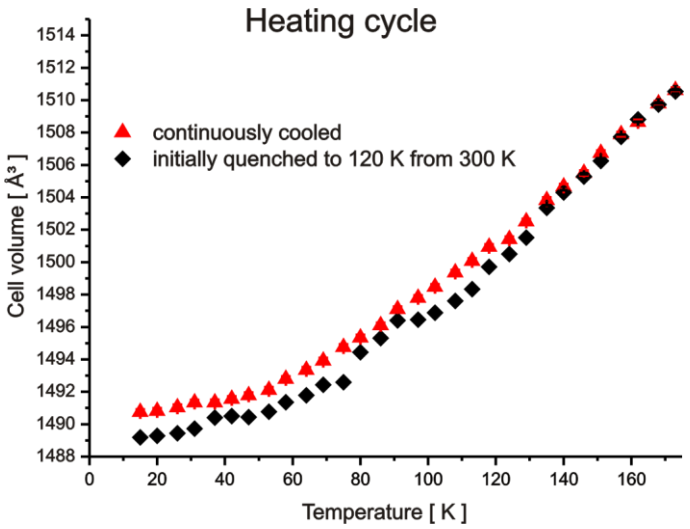
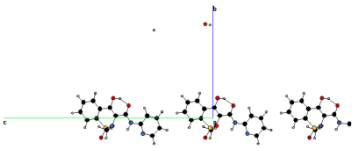


Figure S7 Heating cycle of the powder X-ray experiment. Triangles represent the sample which was continuously cooled from 300 K in the cooling cycle. Diamonds represent the sample which was initially quenched from 300 K to 120 K before commencing the cooling cycle.

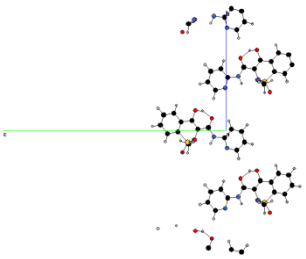
PACHA[1] analysis of Form I

3D network SE = -1834.9 kJ mol^{-1} (Z = 4)
SE_{PIR} = -423.4 kJ mol^{-1}
Network cooperativity $\Delta SE = (4*SE_{PIR} - SE_{3D})/4$ = -35.3 kJ mol^{-1} Thus highly cooperative

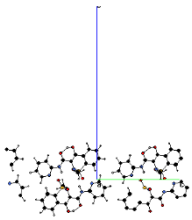
Motif 1
PIR molecule stacks along (1 0 0)
$SE_{motif\ 1}$ = -431.8 kJ mol^{-1}
$\Delta SE = SE_{PIR} - SE_{P1}$ = -8.4 kJ mol^{-1}
This is due to interactions between the S=O group of one molecule with the CH_3 group of the molecule above with an interaction distance of 2.47 Å. There are no π-stacks present, as the distance between the planes are >7 Å.



Motif 2 stacks motif 1 along (0 0 1)
$SE_{motif\ 2}$ = -863.5 kJ mol^{-1} (Z = 2)
$\Delta SE = (2*SE_{motif\ 1} - SE_{motif\ 2})/2$ = -0.1/2 = -0.05 kJ mol^{-1}
Motif 2 is neutral in the crystal packing. The contact of the hydrogen atoms is minimised by a distance of >6 Å.



Motif 3 stacks motif 1 along (0 1 0)
$SE_{motif\ 3}$ = -867.2 kJ mol^{-1} (Z = 2)
$\Delta SE = (2*SE_{motif\ 1} - SE_{motif\ 3})/2$ = -1.8 kJ mol^{-1}
This motif is slightly cooperative in the network which is due to CH-O=C interactions with a distance of 2.55 Å. This orientation however leads to repulsive interactions due to short H-H distances of 2.45 Å. Another stabilising factor is a long range CH-N interaction with a distance of 4.2 Å.



Motif 4 stacks motif 2 along (0 1 0) in supercell (1 2 1)
$SE_{motif\ 4}$ = -886.3 kJ mol^{-1} (Z = 2)
$\Delta SE = (SE_{motif\ 2} - SE_{motif\ 4})$ = -22.8 kJ mol^{-1} represents 2 hydrogen bonds, thus 11.4 kJ mol^{-1} per hydrogen bond
Highly cooperative due to the interaction of the SO_2 group with the ring NH of the next molecule. The distances of these interactions are with 3.1 and 2.2 Å not especially short for hydrogen bonds but both together result in a considerable contribution to the stability of the network.

Experimental

Single crystal X-ray diffraction

Single crystals of PIR form I and the monohydrate suitable for single crystal diffraction were grown by crystallisation from THF (form I) and water (monohydrate). The crystals were soaked in perfluoropolyether oil and mounted on a glass fiber. Crystallographic measurements were carried out at 120 K using a Bruker SMART CCD 6000 single crystal diffractometer equipped with open flow N_2 Cryostream (Oxford cryosystems) device using a graphite monochromated MoKα radiation (λ= 0.71073Å). For data reduction, the SAINT suite was used, the structures were solved with SHELXS[1] and refined with SHELXL[2]. All non-hydrogen atoms were treated anisotropically, the hydrogen atoms were located from the Fourier maps and refined isotropically.

Temperature controlled single crystal unit cell measurements of the monohydrate were carried out between 120 K and 30 K using a Bruker SMART CCD 1000 single crystal diffractometer equipped with an Oxford Cryosystems Helix.[3] The crystal was cooled at a rate of 5 K h^{-1} and measurements were performed continuously. The data reduction was performed using Bruker SMART and SAINT programs. SMART_reduce and MULTI_integrate are programs that have been written to control the flow of data, input and output, for the Bruker-AXS Ltd data reduction programs SMART and SAINT. SMART_reduce and MULTI_integrate modify key parameters in the input files for SMART and SAINT in an iterative process, and allow sequential data reduction to occur on successive diffraction datasets without user interaction. The datasets must be collected in a manner such that one environment variable is altered between data collections; most commonly temperature. The number of datasets that can be reduced in this manner is not limited, and allows the user to reduce such data without the danger of modifying a parameter which should remain constant throughout the extent of the experiment. Since SMART_reduce and INTEGRATE_multi only control the flow of data through well debugged industrial data reduction software, the quality of the output is not compromised, and is directly comparable with data treated in a 'standard' manner.

Powder X-ray diffraction

Low-temperature powder diffraction experiments were performed using Cu $K\alpha_1/K\alpha_2$ radiation on a Bruker d8 diffractometer equipped with a Lynxeye psd and an Oxford Cryosystems pHeniX cryostat. Samples were prepared for these experiments by grinding and sprinkling them onto a silicon disc smeared with Vaseline. Data sets were collected from 4 to 90 ° 2θ in step sizes of 0.02 ° 2θ over 20 minute time slices while cooling/warming the sample at a constant rate of 15 K h^{-1}. A first set of experiments involved cooling the sample from 300 to 12 K, warming from 12 to 300 K, quenching (at 360 K h^{-1} = 30 minutes) to 120 K and then cooling from 120 to 12 K, finally being warmed from 12 to 300 K.

Powder diffraction data were analysed using Rietveld refinement to extract the temperature dependence of cell parameters. A total of 85 parameters were refined for each data set (6 cell parameters, 44 terms of an 8^{th} order spherical harmonic preferred orientation correction, 1 thermal parameter, 4 peak shape parameters, a scale factor for piroxicam monohydrate 27 background parameters, a sample height correction, and 1 parameter to describe axial divergence). These protocols gave good fits to data over the whole temperature range, and checks were made to ensure that other parameters did not correlate significantly with the key unit-cell parameters we were trying to extract. All refinements were performed using the Topas Academic software suite controlled by local routines.[4]

A second experiment quenched the material directly to 22 K and collected continuous 30 minute scans over a period of 25 hours. These data were analysed using the protocol above, with the following exception. Peak shapes were modelled by convoluting a sample-dependent strain term onto an instrumental peak shape determined using highly crystalline CeO_2. This enabled the extraction of the changing strain within the crystallites immediately following the quenching. The strain parameter is a combination of a Gaussian and Lorentzian strain broadening terms being reported as the single value *e* as defined by Balzar.[5]

Neutron single crystal diffraction

Crystals of piroxicam were well coated in a highly viscous fluorosilicone oil, mounted to an aluminium pin and inserted into a Lindemann glass capillary affixed to the Al pin by epoxy glue. The crystal mount

was then transferred to the phi axis of the KOALA Laue diffractometer,[6] located on a thermal neutron supermirror guide at the OPAL nuclear reactor of the Australian Nuclear Science and Technology Organization, to which a bottom loading cryostat was mounted. Laue diffraction images were collected from the stationary crystal on the cylindrical image plate across a series of exposures covering a rotation of at least 204°.
PIR form I data was collected at 120K from 13 images with a rotation between images of 17° and an exposure time of 16000 seconds.
The first crystal of Piroxicam monohydrate (which gave rise to the split and subsequently coalesced images) was fixed to the Al pin using the fluorosilicone oil as adhesive, but not coating the entire crystal, and prepared furthermore as described above. The crystal was then cooled to 120 K and 18 frames were collected at 6000 seconds exposure and 17° rotation. Subsequently, the crystal was cooled to 22 K at a cooling rate of 180 K h^{-1} and 23 frames were recorded at 6000 seconds exposure and 17° rotation.
The second sample of PIR monohydrate was mounted as described above. The sample was directly cooled to 4 K at 180 K h^{-1} and the temperature then slowly raised to 22 K over 6 hours. 25 data frames were collected at 3000 seconds exposure and 11° rotation. Subsequently, the temperature was raised to 120 K recording 6 images at 3000 seconds exposure time to screen for unusual behaviour and splitting, following which an analogous data collection proceeded. Finally, the crystal was warmed up to 295 K and 25 frames were collected at 2500 seconds exposure time at the same 11° rotation interval.
The complete datasets were subsequently reduced by means of Lauegen,[7,8] and the in-house developed programs laue1, laue2, laue3 and laue4.[9] The structures were refined against the data in ShelXL[2] using the structural models obtained by X-ray single crystal diffraction as starting point.

(1) Henry, M. *ChemPhysChem*. **2002**, 3, 561 – 569
(2) Sheldrick, G. M. *Acta Crystallogr., Sect. A: Found. Crystallogr.* **2008**, *A64*, 112.
(3) Goeta, A. E.; Thompson, L. K.; Sheppard, C. L.; Tandon, S. S.; Lehmann, C. W.; Cosier, J.; Webster, C.; Howard, J. A. K. *Acta Crystallographica Section C-Crystal Structure Communications* **1999**, *55*, 1243.
(4) Coelho, A. A.; Bruker AXS: Karlsruhe, 2004.
(5) Balzar, D.; Audebrand, N.; Daymond, M. R.; Fitch, A.; Hewat, A.; Langford, J. I.; Le, B. A.; Louer, D.; Masson, O.; McCowan, C. N.; Popa, N. C.; Stephens, P. W.; Toby, B. H. *J. Appl. Crystallogr.* **2004**, *37*, 911.
(6) Edwards, A. J. *Aust. J. Chem.* **2011**, *64*, 869.
(7) Campbell, J. W. *J. Appl. Crystallogr.* **1995**, *28*, 228.
(8) Campbell, J. W.; Hao, Q.; Harding, M. M.; Nguti, N. D.; Wilkinson, C. *J. Appl. Crystallogr.* **1998**, *31*, 496.
(9) Piltz, R. O. *Acta Cryst A* **2011**, *67*.