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Molecular Packing and the Structure of Nuclei.

Roger Davey

Content: 1. Does the nucleus have the same packing as the mature crystal?
2. What do the results of single crystal XRD tell us about nucleation and structure?

Clusters/monolayers/fossil relics/24dihydroxybenzoic acid/trimesic acid/

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The Volmer solution: Classical Nucleation Theory

Equilibrium in supersaturated homogeneous solution

monomers, dimers, tet

Is the packing of the nucleus the same as the crystal?
From the packing of the crystal can we learn anything about the structure of the nucleus?

Critical nucleus

crystal

Formation and Growth of critical nuclei

Thermodynamics Kinetics

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Linking crystallography to nuclei

Kinetische Behandlung der Keimbildung in übersättigten Dämpfen
Von R. Becker und W. Döring
Annalen der Physik. 5. Folge. Band 24. 1935

The next three paragraphs are devoted to the origin of crystal nuclei. For this the general thermodynamic considerations are valid as for liquid drops. A kinetic calculation of the magnitude of K for crystals was first performed by Kaischew and Stranski. This important study provides us with the impetus for the following work. We will use the strongly idealised crystal model, also used by K and S, following that of Kossel – which is composed of cubic building blocks.

$$J = K \cdot e^{-\frac{\sigma F_n}{kT}}$$

2) R. Kaischew u. I. N. Stranski, a. a. O., ferner *Ztschr. f. phys. Chem. (A)* 170. S. 295. 1934.

Cf. HMT crystal structure. Dickinson and Raymond JACS 1923 45 22-29

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Extended to - nuclei have the same packing as the mature crystal.

α PABA (AMBAC07) and β PABA (AMBAC08)

α p-aminobenzoic acid

β p-aminobenzoic acid

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Dense Liquid Precursor for the Nucleation of Ordered Solid Phases from Solution

Peter G. Vekilov
Department of Chemical Engineering, University of Houston, Houston, Texas 77204

CRYSTAL GROWTH & DESIGN
2004 VOL. 4, NO. 4 671-685

Density and order

Figure 1. The formation of crystals, whereby a highly ordered phase emerges from a disordered medium, is often viewed as one of the miracles of nature, i.e., one of the most difficult problems to tackle, top. Even the simple picture given by the classical nucleation theory that the crystal starts with a tiny ordered nucleus, bottom, is extremely informative.

Figure 11. A schematic illustrating the formation of ordered crystals can be seen as a result of the superposition of a density and a structure fluctuations. The schematic corresponds to locations on the phase diagram just below the L-L' binodal as shown in the diagram between the liquid and the L-L' coexistence line, the critical liquid nucleus size is indicated, i.e., no density fluctuations can lead to a long lifetime cluster. At locations between below the L-L' spinodal line, any density fluctuation leads to a stable long lifetime cluster.

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Are there clusters? A classic often repeated experiment.

Evidence of Molecular Cluster Formation in Supersaturated Solutions of Citric Acid

Phil. Mag. 1969, 161, 1075-1077

By J. W. MULLIN and C. L. LECl

Department of Chemical Engineering, University College London, Torrington Place, London, W.C.1

Concentration gradients developed in quiescent aqueous citric acid solutions kept under isothermal conditions

Initial concentration at all three positions c S	Concentration after time, t						Solution temp. (°C)	Time t (hours)
	Top†		Middle†		Bottom†			
2-247 1-055	2-244 1-053	2-253 1-057	2-263 1-061	2-264 1-412	22-6	71	28-2	70
2-568 1-303	2-531 1-372	2-546 1-381	2-604 1-412	2-767 1-413	25-0	71	25-0	71
2-716 1-384	* *	2-721 1-387	2-652 1-182	2-336 1-185	25-2	336	30-0	92
2-624 1-173	2-500 1-131	2-616 1-169	2-336 1-185	2-336 1-185	25-2	336	25-2	336
2-336 1-185	2-303 1-168	2-333 1-183	1-553 0-714	1-553 0-714	28-5	158	28-5	158
†1-553 0-714	1-553 0-714	1-553 0-714	1-553 0-714	1-553 0-714				

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MANCHESTER 1824 Experiment repeated in 1991 - same

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Chemical Engineering, Printed in Great Britain

2509/92 \$1.00 + 0.00
2 Program Press Ltd

Cluster size from sedimentation estimated at 16nm diameter. Supported by EM.

Fig. 2. Electron micrograph of the upper part of solution II; the replica was prepared after quenching a drop of solution in liquid nitrogen.

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MANCHESTER 1824 And again!

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Chemical Engineering Science, V, Printed in Great Britain

2509/92 \$1.00 + 0.00
2 Program Press Ltd

Mesocrystal

60nm spheres?

The findings suggest that the natural shape of the crystalline nucleus might be that of an aggregate of solute clusters observed in solution and that the nucleus is already present even in subsaturated solutions.

Fig. 4. Section through a citric acid monohydrate crystal. Many 60 nm aggregates are arranged in a direction of crystal, and an opening space is closely packed by a "homogeneous" crystal zone.

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Phys. Chem. Chem. Phys., 2003, 5, 4998-5000

A. Molecular crystallization

Supersaturated solution \rightarrow Amorphous NPs $\xrightarrow{[NP]^n[Ala]^m[Nuclei]}$ Single crystal

B. Mesoscale assembly

Amorphous NPs $\xrightarrow{[NP]^n[Ala]^m[Nuclei]}$ Mesocrystal $\xrightarrow{\text{Recrystallization (Temperature dependent)}}$ Single crystal

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Phys. Chem. Chem. Phys., 2003, 5, 4998-5000

Using a novel plug flow reactor for the *in situ*, simultaneous, monitoring of SAXS and WAXD during crystallisation from solution

Relative time to appearance of SAXS and WAXS scattering for the 10wt% precipitation of 2,6-dibromo-4-nitroanal

Key: — SAXS, — WAXS

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Figure 4 Schematic illustration of nucleation pathways. **a** Nucleation via a planar critical cluster. Stage I, single molecules in the solution; the lack of any significant concentration of dimers, trimers, and so on, has been shown by static and dynamic light scattering^{25,29}. Stage II, a few molecules at the corners of a polygon. Stage III, linear array. Stage IV, a quasi-planar critical cluster with (110) orientation, similar to structures seen in Figs 1 and 2; molecules belonging to the second layer are shown in a lighter shade. Stage V, microcrystal faceted by (111) planes; the (110) layers that stack up to form this crystal are delineated by lighter and darker contours. **b** Nucleation via a compact critical cluster³⁰.

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Scheme 1

monoform amphiphiles, and chainlike hydrocarbons.

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Crystalline Thin Film Architectures at the Air-Liquid Interface Chemical Reviews, 2001

A Multilayer Formation of Amphiphilic Molecules

So there is significant evidence to suggest that small numbers of molecules can adopt mature packings. Also evidence of other things going on – meso crystals.

Water air
water

alkanol Cholesterol

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MANCHESTER 1824 **If you believe then you can ask questions about cluster stability.**

Robert B. Hammond, Klimentina Pencheva and Kevin J. Roberts* Faraday Discuss., 2007, 136, 91–106 | 91

cluster energy, kcal/mol

cluster size

minimized clusters
● stable structure
▲ meta-stable structure

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MANCHESTER 1824 **PROCEEDINGS OF THE PHYSICAL CHEMISTRY B LETTERS**

2005, 109, 19550–19552
Published on Web 10/04/2005

Simulation of Energetic Stability of Faceted L-Glutamic Acid Nanocrystalline Clusters in Relation to Their Polymorphic Phase Stability as a Function of Crystal Size

R. B. Hammond, K. Pencheva, and K. J. Roberts*

cluster energy, kcal/mol

cluster size

minimized clusters
● alpha
■ beta

Toward S Understa
Isabelle Weis

MANCHESTER 1824 **If you believe then....**

Scheme 2

(a) $nA \rightleftharpoons (A_n)_\alpha \rightleftharpoons (A_n)_\beta \rightarrow \{A_n\}_\alpha$

(b) $nA \rightleftharpoons (A_n)_\alpha \xrightarrow{\text{Inhibitor}} \{A_n\}_\alpha$
 $nA \rightleftharpoons (A_n)_\beta \rightarrow \{A_n\}_\beta$

More of this later.

() = nucleus ; { } = crystal

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MANCHESTER 1824 **Some thoughts from crystallographers: Fossil Relics - structures with high Z'**

Benzophenone, Z' = 1

Diphenylamine, Z' = 8

Does high Z' tell us anything about nucleation?

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MANCHESTER 1824 **CHEMICAL COMMUNICATIONS**

DOI: 10.1021/CS300004K
Chem. Rev. 2015, 115, 2895–2933

at a particular transition temperature.* In the context of metastable crystals, we have described notional metastable polymorphs that do not readily transform into a (perhaps undiscovered) thermodynamic form, as a “fossil relic” of the fastest growing crystal nucleus.^{22b,45b} To us at least, this is an appealing piece of language because it implies that such a crystal is in some sense trapped in a state derived from its formation conditions as a result of either some kind of solution or melt aggregation or some stability or structure of the precritical crystal nucleus. Such strong kinetic trapping is one possible factor in the formation of metastable polymorphs, which might show strong directional intermolecular interactions without being as burdened by the increasing importance of close packing as the nucleus, and ultimately crystal, grows larger. It has been pointed out that because little is known about the structure of the crystallization nucleus, this kind of term is almost impossible to confirm or refute,^{22a} a view we have considerable sympathy with.

Toward S Understa
Isabelle Weis

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A kinetically favoured crystal, with many molecules in the asymmetric unit, may be a fossil relic of the crystal nucleus of a more stable polymorph.

The structural landscape¹ that is encountered during the crystallisation of a molecular solid from solvent could be considered to begin with solvated molecules, which associate *via* supramolecular synthons² to give growth units,³ followed by nucleation and finally the appearance of metastable (kinetic) crystals that yield eventually to more stable (thermodynamic) polymorphs.⁴ Many aspects of this process are still in the realm of conjecture, although there have been some attempts to monitor directly the early stages of crystallisation.⁵ From the crystallographic viewpoint the very occasional appearance of large unit cells, possibly with solvent incorporated in the structure and the presence of multiple molecules in the asymmetric unit ($Z' > 1$) is reflective of 'frozen' or interrupted crystallisation.⁶ Accordingly, the intermediate stages

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stable 1-L. To use Steed's terminology,⁸ 1-H is a fossil relic of the crystal nucleus of 1-L.

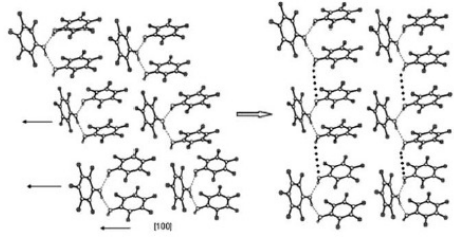


Fig. 3 A mechanism for synthon evolution, 1-H \rightarrow 1-L. Shearing of trimers along [100] would form the putative O-H...O bonds shown in bold, completing the infinite (O-H...O-H...)_n chain which is characteristic of 1-L.

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Extreme example

Angewandte Chemie

Angew. Chem. Int. Ed. 2005, 44, 2515-2520

Structure Elucidation

Structural Studies of the System Na(saccharinate)-*n*H₂O: A Model for Crystallization¹⁰

Rahul Banerjee, Prashant M. Bhatt, Michael T. Kirchner, and Gautam R. Desiraju*

Crystallization may be viewed as a supramolecular reaction, with nucleation likened to the transition state. The formation of a crystal from solution exemplifies a shift of the enthalpy-entropy balance. From the entropy-dominated situation in solution, order enters the putative crystal through the formation of a liquidlike cluster of solvent and solute.^[10]

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Crystallography and Frozen-in Transition States

362 atoms, 238 non-hydrogen atoms in the crystallographic asymmetric unit.

The fundamental problem here is that we are trying to infer nanoscale information from a crystal that contains many billions of unit cells. The nucleus may well trap in some high energy conformations or use an unsatisfactory H-bond motif but why would it keep repeating this over and over during subsequent growth?

Figure 4. Crystal structure of dihydrate 1 (Na pink, O red, N blue, S yellow, C grey, H cream). The regular regions are on the left side, and the angular regions are on the right. Note the finite supramolecular cube arrangement. The saccharin residues are numbered.

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The growth problem will never go away but this doesn't mean that we can't get insight from crystallography as long as we have enough data.

- *dihydroxybenzoic acid* crystallising from toluene and chloroform.
- *trimesic acid* crystallising from DMSO.

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Dihydroxybenzoic acid

Acta Cryst. (1994). C50, 1622-1626

γ -Resorcylic Acid, its Monohydrate and its Pyridinium Complex

MARIA GDANIEC AND MIROSLAW GILSKI

Faculty of Chemistry, A. Mickiewicz University, 60-780 Poznań, Poland

GLEB S. DENISOV

Institute of Physics, St Petersburg State University, 198904 St Petersburg, Russia

(Received 14 October 1993; accepted 17 January 1994)

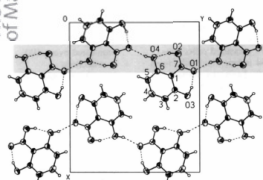


Fig. 1. View of the crystal packing of (I) along [001] showing the hydrogen-bonded chains of alternating σ - and π -bond cooperativity. Hydrogen bonds are shown by dotted lines. Displacement ellipsoids are plotted at the 50% probability level.

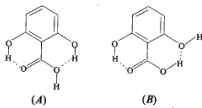
Experimental

Compound (I) was obtained by recrystallization of γ -resorcylic acid from chloroform, (II) from a methanol/water mixture and

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Comment
 γ -Resorcylic acid is one of the strongest carboxylic acids ($pK_a = 1.3$). It is also an interesting example of a molecule with two possible intramolecular hydrogen-bond systems, one with two phenolic OH groups and another with one phenolic and one carboxylic OH group involved as donors in intramolecular hydrogen bonds; these two forms, A and B, are shown in the scheme below.



(A) (B)

Solution ^1H NMR studies of this acid in the presence of bases of different proton-acceptor ability show that structure A prevails and that an intermolecular hydrogen-bond interaction with the base occurs through the carboxylic OH group (Golubev & Denisov, 1992).

at O4. Unlike the structure in solution, the molecular structure in the crystal corresponds to form B, in which one phenolic OH group acts as an intra- and the other as intermolecular hydrogen-bond donor. The

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Journal of Chemical Crystallography, Vol. 24, No. 10, 1994

Received July 26, 1994

Crystal and molecular structure of 2,6-dihydroxybenzoic acid

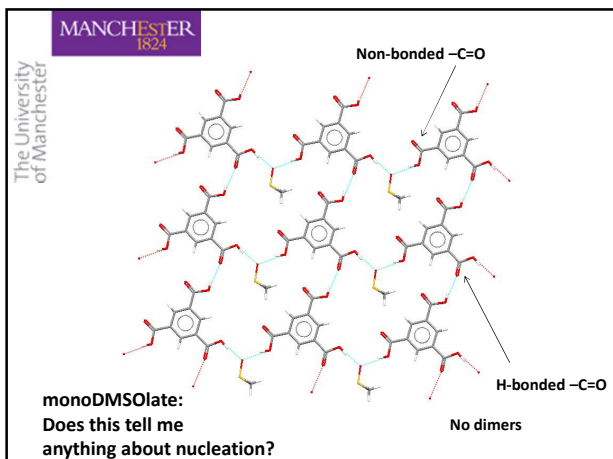
Leonard R. MacGillivray,⁽¹⁾ and Michael J. Zaworotko^(*,1)

In the solid state, benzoic acid derivatives typically self-assemble as centrosymmetric dimers.¹ During our studies into structural manifestations of π - π interactions on self-assembly of substituted pyridinium salts of 2,6-dihydroxybenzoates² we inadvertently isolated crystals of 2,6-dihydroxybenzoic acid, **1**. Despite the amount of literature concerning carboxylic acids³ we were surprised to discover that **1** has not yet been crystallographically characterized. In this note we report the crystal and molecular structure of **1**.

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9.1 mmol, 83% yield). However, recrystallization from hot toluene afforded single crystals of **1** instead of the expected salt. (mp: 162–163°C (lit. 165°C); IR: (Nujol



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Cooling crystallisation from pure DMSO 40 to 25C.

Roger J. Davey,** Monika Bryczczynska,* Ghazala Sadiq,* Geoffrey Dent* and Robin G. Pritchard*

CCDC funding

CrystEngComm, 2013, 15, 856-859

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Crystallography vs crystallisation

Most metastable form in DMSO

Monosolvate in DMSO

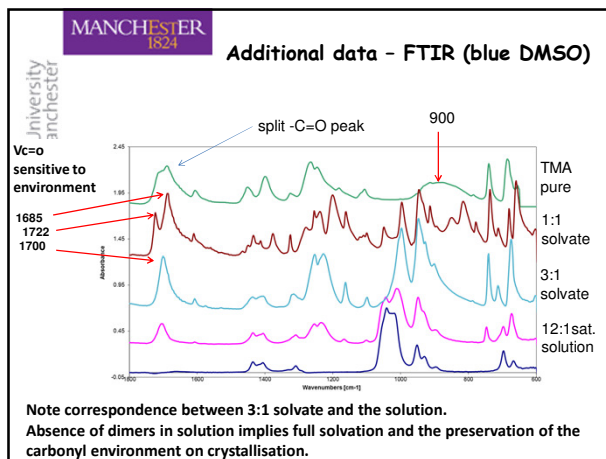
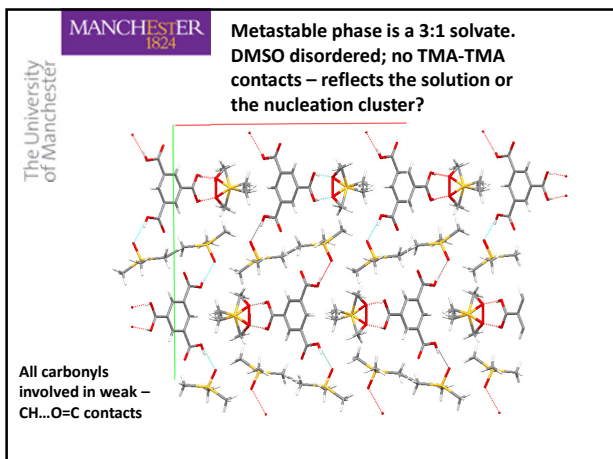
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Additional information.

Monosolvate most stable in DMSO

Needles least stable form in DMSO



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Key role of desolvation

What do we conclude? :

- In transforming from solution to trisolvate the carbonyl environment is unchanged.
- TMA can jump from solution to crystal with preservation of its co-ordination.
- DMSO makes the transition whilst retaining its liquid phase disorder.
- In solution TMA fully solvated so during nucleation removal of 9 DMSO molecules takes place

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What are the messages?

It is quite feasible for a nanocluster to have the packing of a mature crystal. But this is not guaranteed.

Using crystallography to infer structural data about the nucleus must be done with care.

To learn anything about nucleation from crystallography we need to study metastable states/solvates.

The addition of some simple characterisation of solutions can add significant insight into what's going on.

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Returning to high Z' -Crystals that don't form...conformation?

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Faraday Discussions
 OneView DOI: 10.1039/C5FD00037H

PAPER View Article Online
 View Article

Crystal nucleation from solutions – transition states, rate determining steps and complexity†

Roger J. Davey,* Kevin R. Back† and Rachel A. Sullivan‡

CRYSTAL GROWTH & DESIGN *Cryst. Growth Des.* 2012, 12, 6110–6117

Molecular Conformation and Crystallization: The Case of Ethenzamide

Published as part of a *Crystal Growth and Design* virtual special issue of selected papers presented at the 10th International Workshop on the Crystal Growth of Organic Materials (CCOM10)

Kevin R. Back,¹ Roger J. Davey,^{1,†} Tudor Grecu,¹ Christopher A. Hunter,² and Lynne S. Taylor³

Chemical Science
 EDGE ARTICLE

Can the study of self-assembly in solution lead to a good model for the nucleation pathway? The case of tolfenamic acid.‡

W. Du,^{1*} A. J. Cruz-Cabeza,^{1*} S. Woutersen,² R. J. Davey^{1†} and Q. Yin¹

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1
 Ethenzamide
 MW 165.2

2 key torsions

Will any of these be difficult to nucleate crystallise ?

Will any have multiple forms?

With multiple conformers?

Will solvent choice matter?

~13 torsions 3 chiral centres

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What's the view?

Organic Process Research & Development 2000, 4, 396–402

Crystallization and Polymorphism of Conformationally Flexible Molecules: Problems, Patterns, and Strategies

Lian Yu,* Susan M. Reutzel-Edems, and Christine A. Mitchell
 Eli Lilly and Company, Lilly Corporate Center, Indianapolis, Indiana 46285, U.S.A.

The alditol family HOCH₂(CHOH)_nCH₂OH

Mannitol, galactitol, and arabinitol – straight chain in crystal, easy to grow

Sorbitol, iditol, and xylitol – lowest energy conformation different to that seen in crystal structure, slow to crystallise

Acylanilines
 $R_1 = \text{CH}_3, \text{C}_2\text{H}_5$

Organic Process Research & Development 2009, 13, 1221–1240


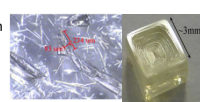
Why Do Organic Compounds Crystallise Well or Badly or Ever so Slowly? Why Is Crystallisation Nevertheless Such a Good Purification Technique?†

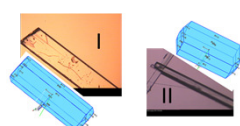
Michael B. Hursbouse, L. Susanne Huth, and Terence L. Threlfall*
 School of Chemistry, University of Southampton, Highfield, Southampton SO17 1BJ, U.K.

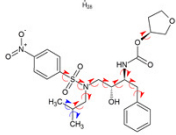

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Looking at the KNOWN FORMS

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1 pure form  16 solvates/cocrystals 

5 polymorphs: I and II are conformational 

3 solvates No pure form  

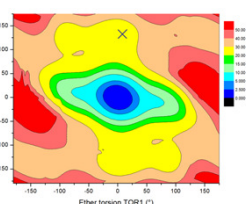
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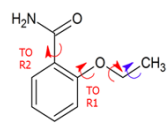
CONFORMATIONS: MOLECULE 1

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Table 2. Torsion Angles of the Ether (TOR1) and Amide (TOR2) Groups of Ethanamide in the Known Crystal Structures Containing the Molecule

co-former(s)	CSD Refcode or Deposition Number	TOR1 (deg)	TOR2 (deg)
none (single component)	CCDC 891073	6.80	119.67
gentic acid and acetic acid ²⁰	NURPOW	3.55 ^a	-9.14 ^a
gentic acid ²⁰	QUILLIF	5.55 ^b	-1.01 ^b
	QUILLIF01	-6.00 ^b	9.46 ^b
	QUILLIF02	-3.85	1.22
		-12.26	0.2
saccharin ²⁰	VUHFIO	-1.67	-6.33
	VUHFIO01	8.88	-1.67
3,5-dihydroxybenzoic acid ²¹	WUZHOP	-10.75	-2.32
	WUZHOP01	-10.79	-14.62
with acetone ²¹	WUZHAD	-8.05	-7.06
dimane ²²	WUZHJI	-8.47	-6.53
diethyl ether ²³	WUZHIL	-8.67	-6.88
toluene ²⁴	WUZHJQ	-7.55	-4.01
acetamide ²⁵	WUZHJX	7.37	6.47
ethyl acetate ²⁵	WUZHAE	7.99	6.64
paraxylene ²⁵	WUZHFI	7.25	6.11
methylane ²⁵	WUZHIM	-1.1	3.05
ethylmalonic acid ²⁵	VAKTOS	2.99	-3.07
thiourea ²⁶	VAKTOS01	-4.94	-6.17
	KTFWQA	plane, no structure available	
2,6-dihydroxybenzoic acid	CCDC 891074	1.86	3.37
3,5-dihydroxybenzoic acid	CCDC 891075	-4.83	-1.69

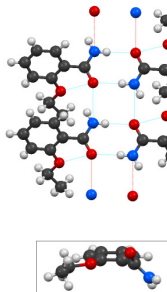
Potential energy surface 

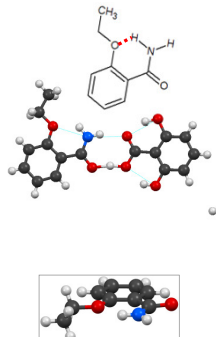


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CONFORMATIONS: MOLECULE 1

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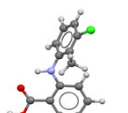
Pure form O...O contact 

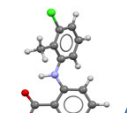
Cocrystal forms O...H-N... intramolecular contact 

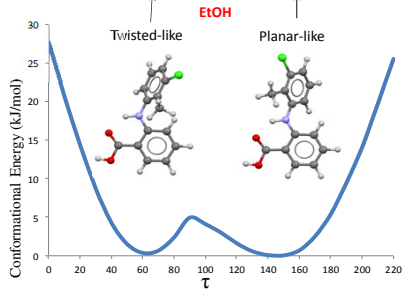
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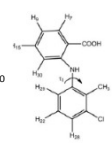
CONFORMATIONS: MOLECULE 2

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Form I (stable) Twisted-like  ETOH

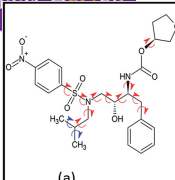
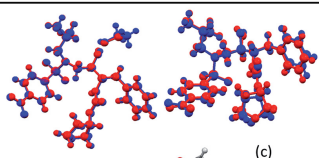
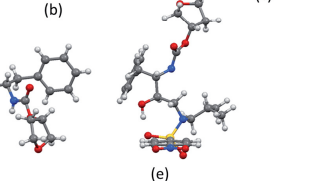
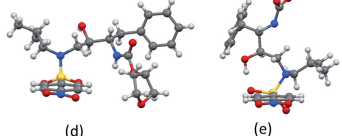
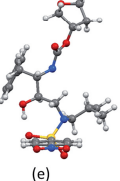
Form II (metastable) Planar-like 

Conformational Energy (kJ/mol) vs τ 



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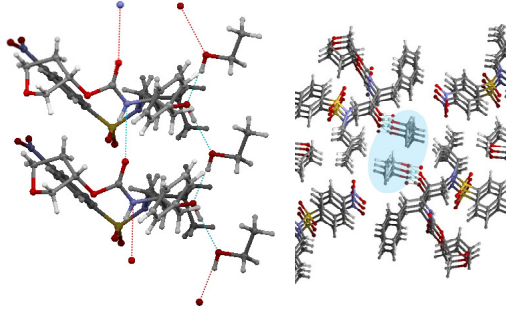
(a)  (b)  (c)  (d)  (e) 

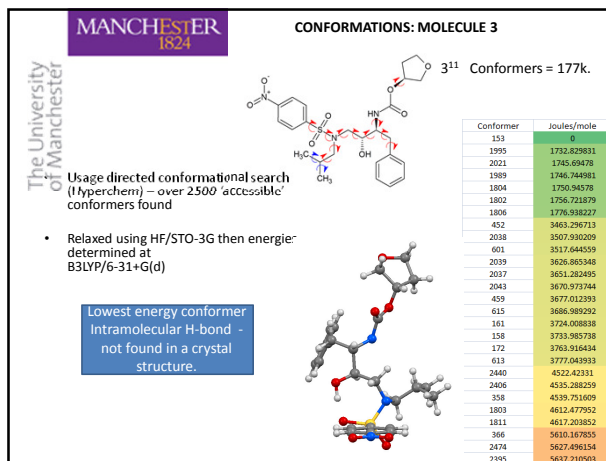
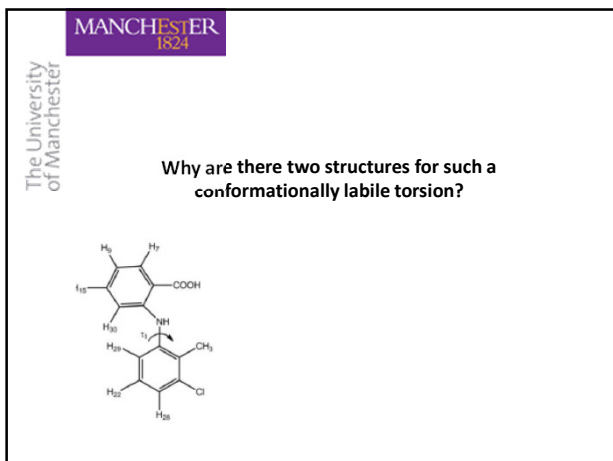
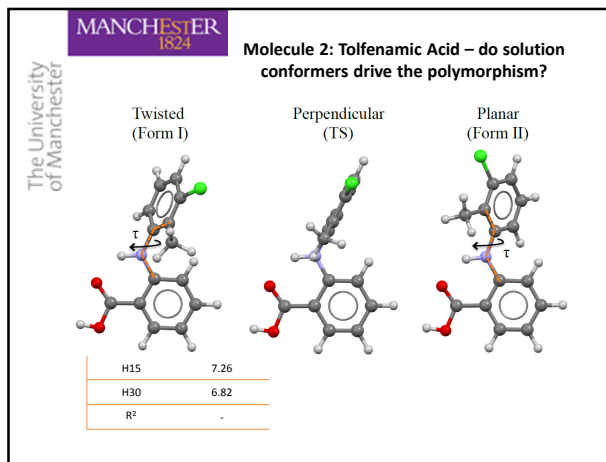
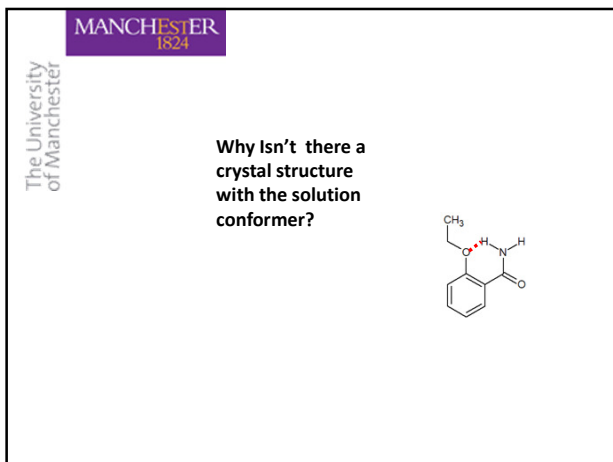
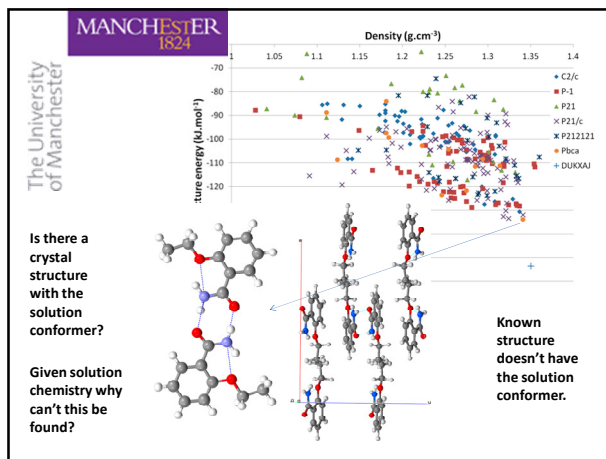
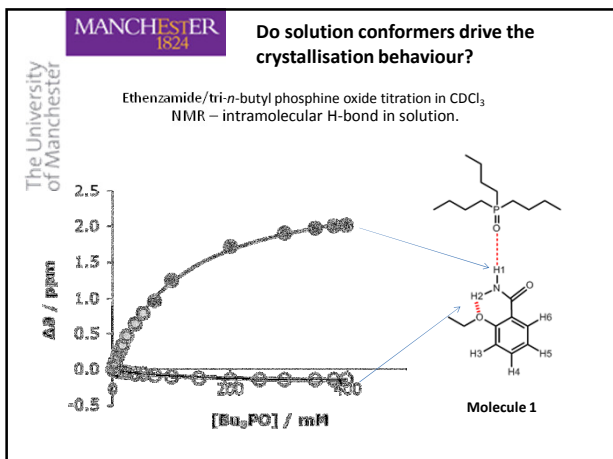
(b) An overlay of ethanolate (blue) and methanolate (red) conformations. (c) An overlay of ONSC ethanolate (blue) and hemihydrate (red) conformations. (d) ONSC-E crystal structure conformation. (e) Lowest energy structure from a Monte Carlo search.

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Molecule 3: the solvent as a conformational auxiliary.

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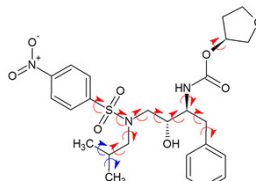




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Why does this molecule rely so heavily on the solvent? Why do none of 2500 accessible conformers form a crystal structure?



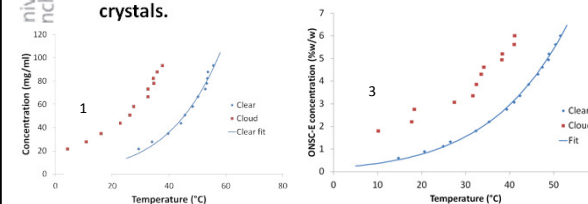
Only one conformer is found in the crystal structures. Solvent plays key role.

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Does any of this matter?

Small crystals but well defined metastable zones. Nothing unusual except (maybe) difficulty in growing large crystals.



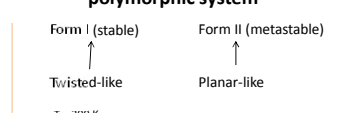
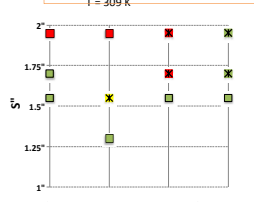
	b-axis alpha glycine [1]	ONSC	Ethenzamide
Supersaturation	0.46	1.24	1.35
Growth rate $\mu\text{m}/\text{min}$	61	0.3	0.1

56

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Tolfenamic Acid: conformation irrelevant – just like any other polymorphic system

Behaviour Unrelated to solution conformation.

- = form I, stable
- = form II, metastable
- = mixed, majority form I
- = mixed, majority form II
- = mixed, concomitant

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Faraday Discussions
 One view: DOI: 10.1039/C5FD00037H

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Crystal nucleation from solutions – transition states, rate determining steps and complexity†

Roger J. Davey,* Kevin R. Back† and Rachel A. Sullivan‡

CRYSTAL GROWTH & DESIGN *Cryst. Growth Des.* 2012, 12, 6110–6117

Molecular Conformation and Crystallization: The Case of Ethenzamide

Published as part of a *Crystal Growth and Design* virtual special issue of selected papers presented at the 10th International Workshop on the Crystal Growth of Organic Materials (CCOM10)

Kevin R. Back,¹ Roger J. Davey,^{1*} Tudor Grecu,¹ Christopher A. Hunter,² and Lynne S. Taylor³

Chemical Science

EDGE ARTICLE

Can the study of self-assembly in solution lead to a good model for the nucleation pathway? The case of tolfenamic acid.‡

W. Du,^{1*} A. J. Cruz-Cabeza,^{1*} S. Woutersen,² R. J. Davey^{1†} and Q. Yin³

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Molecular Packing and the Structure of Nuclei.
 Roger Davey

Content: 1. Does the nucleus have the same packing as the mature crystal?
 2. What do the results of single crystal XRD tell us about nucleation and structure?

Nucleation Summer School June 20-24th 2016 University of Strathclyde