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COMMUNICATION

Racemic compound versus conglomerate: Concerning the crystal chemistry of the triazolylketone, 1-(4-chlorophenyl)-4,4-dimethyl-2-(1H-1,2,4-triazol-1-yl)pentan-3-one.

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Abstract. The triazolylketone discussed in this paper crystallises from racemic solutions as a conglomerate. Here, we report the ternary phase diagram confirming the conglomerate behaviour of this molecule. Through computation we also explore the underlying reasons for the absence of a racemic compound in this system and the evident epitaxial crystallisation leading to crystals of almost racemic compositions but which retain the crystal structure of the pure enantiomer.

The use of crystallisation as a means of separating enantiomers of chiral molecules remains an active area both for research and process development (1). In the research arena the relationship between molecular structure and phase behaviour is an outstanding problem which impacts on both product and process development (2). For example in racemic systems experiment shows that there is a great tendency (90%) to form racemic crystals as opposed to conglomerates of single enantiomers (3). This situation hinders the use of crystallisation alone as a widespread separation technique and indeed its molecular origins remain elusive. The enhanced stability of the racemic compound is often equated to the additional entropy of demixing in the solid state (which imposes a free energy penalty

of c.a.0.5 kcal mol⁻¹) required for forming the conglomerate (4). However this can hardly be the full story since in the world of polymorphism the existence of metastable forms is common and yet in chiral systems the existence of metastable conglomerates seems to be rare (5). In the process chemistry arena there is much interest in combining crystallisation of pure enantiomer crystals with chemically induced racemisation in order to maximise yields (6) and in recent years the discovery of 'Viedma Ripening' in conglomerate slurries has been seen as a potential for process enhancement (7,8).

In this paper we return to the crystallisation of a triazolylketone molecule ((4-chlorophenyl)-4,4-dimethyl-2-(1H-1,2,4-triazol-1-yl)pentan-3-one), hereafter CITAK, first reported in 1989 (9) to crystallise as a conglomerate and to be susceptible to base induced racemisation. This original work described the crystal structure (10), the single crystal enantiomeric purity (11) as well as a combined (9) crystallisation and racemisation process yielding a product with 97% chiral purity. More recently the additional application of attrition and temperature cycling has shown how such a process may be modified to give increased yield and enhanced optical purity through Viedma ripening (12, 13).

In this current study we attempt to address a number of features of this material and its crystallisation. First we reprise the crystal chemistry of CITAK, Figure 1, and its 2-fluoro derivative which are both in the CSD (SEYPUH (14) and DIVTEH respectively). Secondly we report the ternary phase diagrams of CITAK by way of confirming the conglomerate behaviour of this system. Thirdly we explore through computation the underlying reasons for the absence of a racemic compound in this system and the evident epitaxial growth first reported in ref 11 and leading to crystals having almost racemic compositions but which retain the crystal structure of the pure enantiomer.

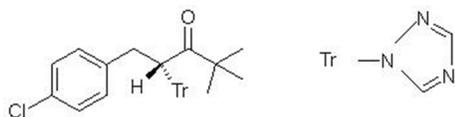


Figure 1 Molecular structure of CITAK.

Experimental. CITAK was prepared by a patented method (13, 15). Samples of the product ketone were washed sequentially with up to 2 litres of water to remove residual base from the product as it was anticipated that this may catalyse racemisation during subsequent thermal analysis. All solvents methanol, toluene, acetonitrile, and nitromethane were spectroscopic grade and obtained from Sigma-Aldrich. Melting points were determined using a Mettler Toledo DSC 30 instrument controlled by a Mettler TC15 complete with a liquid nitrogen cooling system with data analyzed by STARE software v.610. A start temperature of 30 °C and heating rates of 5 and 10 °C/min were used up to a final heating temperature of 155 °C. Sample masses between 2 and 8 mg were used. Solution spectra were recorded using a Mettler Toledo ReactIR 4000 fitted with a diamond composite and analysed using Nicolet's OMNIC software. Optical microscopy was performed using a Zeiss Axioplan 2 polarizing microscope and Linksys image capture software. The ternary diagram was measured at 25 °C in methanol using the tie-line methodology described previously (16) and some selected compositions were checked using chiral HPLC. For HPLC, a few mg of the sampled solid was dissolved in 1 ml of ethanol of which 20 µl was injected. The separation was carried out on a Chiralcel OC column (250mm x 4.6 mm). A solution of 5 % ethanol in heptane was used as a mobile phase; the flow rate was 1.5ml min⁻¹. The enantiomers were detected at 8 and 10 min. ($\lambda_{\text{detector}} = 227 \text{ nm}$). Single crystal diffraction was performed at 100K on an Oxford Xcaliber2 diffractometer with MoK α radiation and a graphite monochromator using an Oxford Cryosystems Cryostream 700 to maintain the temperature. The data were collected and processed using CryalisPro software. Structure solution was carried out using Shelxs97 and refined against F² for all reflections by full matrix methods in Shelxl97 (17). Crystals of both the pure enantiomer and racemate were grown by evaporation from a saturated 3:1 w/w water methanol mixture at room temperature.

Computation. The energetics of epitaxial interactions between appropriate crystal blocks was calculated by optimising the position and orientation of one component (overlayer) onto a defined surface of the other (substrate) using a differential evolution optimisation algorithm (18). The average interaction energy between all the molecules of the substrate and all molecules of the overlayer was calculated using the non-bonding terms of the Drieding force field and atomic point charges (19) and was minimised during the optimisation process (20). The substrate was defined as two unit

cells of the R-enantiomer extended along the *b*-axis, while the epitaxial overlayer was a single unit cell of either R or S. The location of this overlayer utilised three parameters (*u, v, w*) defined relative to the surface to be optimised (Figure 2), while the rotation was about the three Euler indices of the cell (θ, ϕ, γ). The control parameters of the differential evolution (*K* (recombination level), *F* (mutation level), *Gmax* (maximum number of generations), *Np* (population size)) were set to 0.9, 0.7, 2000, 60 respectively, while the boundary conditions were adjusted depending on the substrate studied.

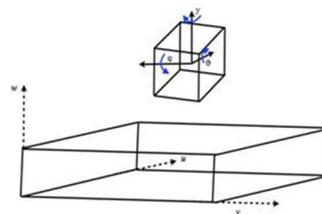


Figure 2 Definition of the six optimisation parameters

Crystal structure predictions were carried out to investigate the potential for racemic compound formation for this system. Gavezzotti's Prom program (21) was selected for this application as it generates trial crystal structures through the clustering of molecules by sequential application of symmetry operations of a selected space group. A molecular model of the R enantiomer was constructed from the known crystal structure of CITAK with the hydrogen atoms placed in calculated positions. The molecular geometry was then fixed and the space group P2₁2₁2₁ tested to check that the methodology reproduced the known pure enantiomer structure. P-1, P2₁/c, C2/c were then explored in order to generate potential racemic compounds. Trial structures were sorted to remove duplicates and the energy minimised by the simplex procedure with the lattice energies calculated using the UNI forcefield (22). The process was repeated until a unique set of structures was generated. The determined structures were then processed in Oprop (23) to calculate density and lattice energies using the Williams forcefield (24).

Results. Crystal chemistry. As reported previously (10), and confirmed here CITAK crystallises from racemic solutions as a conglomerate in the space group P2₁2₁2₁. As seen in Figure 3 the pure enantiomers of CITAK and 2fluoroTAK are isostructural. In both cases -CH...O= interactions run along the *b*-axes (carbon - oxygen distances 3.16 Å in SEYPUH and 3.24 Å in DIVTEH) and edge to face ring stacking contacts (centroid distances 4.92 Å in SEYPUH (*a*-axis) and 4.89 Å in DIVTEH (*c*-axis)) are present. In their original report from 1990 Davey *et al* (10) reported that prismatic crystals of SEYPUH grown from racemic methanolic solutions were elongated about their *a*-axes, presumably as a result of the stacking interaction. These crystals had the structure of the pure enantiomer but exhibited a wide range of enantiomeric purities. Optical microscopy and Laue X-ray topography of such crystals suggested that they were composed of domains of R and S (11). Single crystal XRD and microscopy during this current work has confirmed these results. A typical selection of crystals grown from racemic (Fig 4a, b and c) and pure enantiomer (Fig 4d) solutions are shown in Figure 4. Thus Fig 4a shows the 'hourglass' figures within the *a*-axis growth sectors as reported in (11) while Figures 4b and c show a form of striation and intergrowth comprising (010) layers which run parallel to the *a*-axis and along which crystals easily cleave. The crystal in Figure 4d was grown from enantiomerically

pure solutions – such crystals typically lack the hourglass and the striations and appear reasonably perfect.

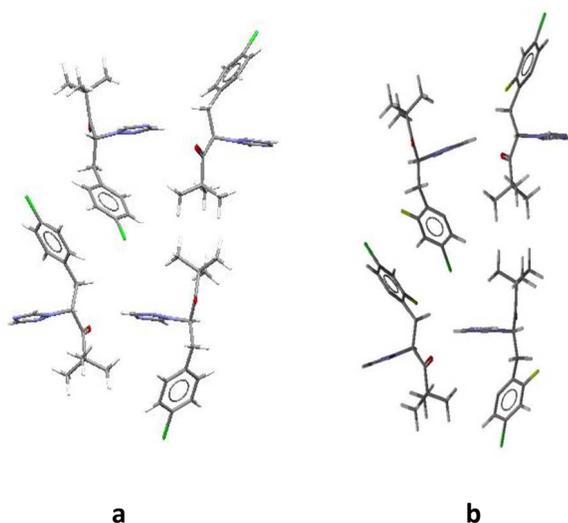


Figure 3. Structures viewed down their a- axes with b-axes horizontal: a) CITAK, SEYPUH; b) 2FluoroTAK, DIVTEH.

Single X-ray diffraction analysis showed that of 8 crystals selected only one showed strong diffraction spots with a Flack parameter of 0.18 confirming it to be almost pure R (14). All the other crystals appeared to be highly disordered.

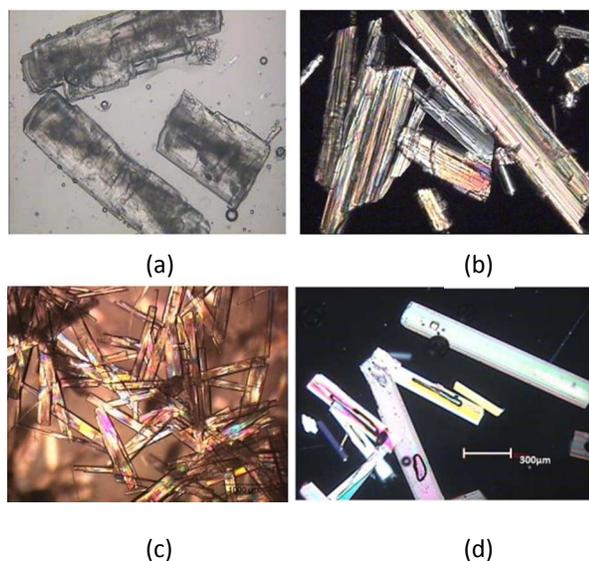


Figure 4. Crystals of CITAK grown from racemic solutions (a) showing hourglass figure within the crystal; (b) showing striations; (c) showing mass intergrowth of crystals and (d) showing CITAK grown from enantiomerically pure solution. All magnifications as in (d).

In order to investigate the possible origin of such disorder and potential epitaxial growth and taking into account the microscopic observations of Figure 4, computational optimisations were performed as described above in which an (010) layer of either R or

S was docked onto an (010) surface of R configuration. These optimisations were carried out with fixed orientations of the overlayer (boundaries $-1 \leq \theta, \phi, \gamma \leq 1^\circ$) and reduced translational boundaries ($-2 \leq u, v \leq 2 \text{ \AA}$, $-10 \leq w \leq 20 \text{ \AA}$) since initial calculations on the R/R system indicated that it would preferentially optimise onto the (100) face due to the significantly lower energy of the interaction ($-25.3 \text{ kJ}\cdot\text{mol}^{-1}$). For the first set of optimisations the R/R pair gave an energy of $-5.5 \text{ kJ}\cdot\text{mol}^{-1}$ with final parameters of $u, v, w, \theta, \phi, \gamma$ 0.1644, 0.0831, 13.3221Å, $-0.7127, -0.6674, 0.9998^\circ$, while the S/R pairs resulted in an energy of $-6.9 \text{ kJ}\cdot\text{mol}^{-1}$ with final parameters of $u, v, w, \theta, \phi, \gamma$ 0.6482, $-4.7110, 11.9197 \text{ \AA}, -0.0037, -0.0018, -0.0478^\circ$. This lower binding energy for the R/S pair is consistent with the preferred formation of an epitaxial interface in racemic solutions and indeed this appears to explain the experimental observations. These outcomes are shown in the crystallographic projections of Figure 5. It is clear from these that the R/R pair extends the crystal lattice as expected, while the unexpected stability of the S/R pairing results from the possibility of a continuation of the C=O...H-C hydrogen bonding chain with very little concomitant disruption to the crystal packing.

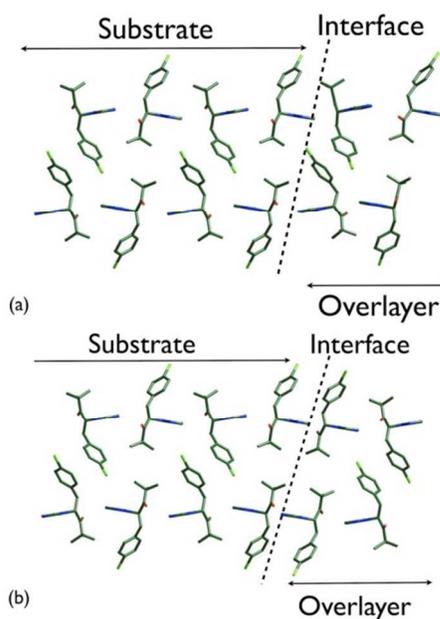


Figure 5 (a) Optimisation of an R CITAK overlayer onto (010) face of an R CITAK substrate, viewed along a-axis, (b) optimisation of S CITAK overlayer onto (010) face of R CITAK substrate, viewed down the a-axis.

To confirm the selectivity of the binding, similar calculations were performed for potential epitaxy on the (100) interface. In this case, as noted above, the R-R interface extended the lattice as expected with an interaction energy of $-25.3 \text{ kJ}\cdot\text{mol}^{-1}$; the R-S equivalent was significantly less favoured with an energy of $-11.2 \text{ kJ}\cdot\text{mol}^{-1}$. Thus only the (010) face offers competitive sites for binding S molecules onto growing R crystals, allowing molecular docking and growth of a homochiral (010) epitaxial layer. While this produces a two dimensional racemate it is evidently not able to expand in the third dimension so that a racemic compound is not observed. Similar epitaxy appears to have been observed in a number of other systems (25, 26, 27, 28)

Phase behaviour. The heat of fusion of the pure enantiomer was determined to be $33.8\text{kJ}\cdot\text{mol}^{-1}$ and the temperature of melting 424K . The measured eutectic temperature (m.p. of the conglomerate) is 394K (heat of melting $29.3\text{kJ}\cdot\text{mol}^{-1}$). The ternary phase diagram of Figure 6 shows the measured solubility of CITAK in methanol at 25°C . For the pure enantiomer this amounts to a mass fraction of 0.157 (mole fraction = 0.0187) and for the racemic composition 0.322 , very close to the expected double solubility (Meyerhoffer Rule (3)). The calculated ideal solubility of the pure enantiomer in methanol based on the thermal data is 0.0175 . The measured value is significantly higher, presumably due to solvation of the ketone by H-bonding in methanol.

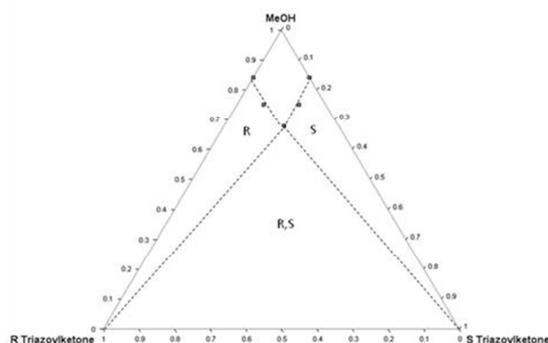


Figure 6 The ternary phase diagram of CITAK in methanol at 25°C

This was explored further using infrared spectroscopy to monitor the position of the carbonyl stretch. In the solid state this appears at 1711cm^{-1} as might be expected given the existence of the weak $-\text{CH}\dots\text{O}$ with an $-\text{H}\dots\text{O}$ distance of approximately 2.2\AA . Table 1 records the position of the carbonyl stretch in concentrated solutions of both pure enantiomer and racemate for a range of solvents. It is evident that in all cases there is no measurable difference between pure enantiomer and racemic solutions with the carbonyl band appearing at around 1720cm^{-1} as might be expected in the absence of specific TAK-TAK interactions in solution. In the case of methanol solutions a second broader band is seen peaking at 1666cm^{-1} which is consistent with the solvation of the carbonyl group through hydrogen bonding to methanol, in any event this too is both concentration and chiral purity independent but consistent with the notion that the observed enhancement in the measured solubility is due to solvation.

Solvent	Conc mol/dm ³	$\nu\text{C=O}$ (cm^{-1})
Methanol	0.09	1722, 1666 for both (R and R,S)
Methanol	0.3	1722, 1666 for both (R and R,S)
Toluene	0.09	1721 for both (R and R,S)
Acetonitrile	0.09	1719 for both (R and R,S)
Nitromethane	0.3	1721 for both (R and R,S)

Table 1 The position of the carbonyl stretch in racemic and enantiomerically pure solutions in various solvents.

Conglomerate versus Racemic Compound. Given the general propensity for racemic solutions to yield racemic compounds and the observed two dimensional epitaxial growth of CITAK it was of interest to use a limited form of structure prediction to explore possible reasons why a compound is not observed in this system. The energy landscape obtained using the methodology described above is shown as a density/energy plot in Figure 8. The lowest energy structures for R CITAK are generally obtained in the non-centrosymmetric (chiral) space group $P2_12_12_1$ and an overlay of the lowest energy structure with the experimental crystal structure confirms their similarity (Figure 9) and validates the methodology. Of the predicted racemic compound structures no energetically favourable clusters in $C2/c$ were obtained and overall it is apparent that the potential racemic compounds are energetically less favourable than the enantiomerically pure crystal. The energy difference between the best $P2_12_12_1$ and $P2_1/c$ structures is $9.1\text{kJ}\cdot\text{mol}^{-1}$, which is at the limit of the range considered to identify metastable polymorphs ($10\text{kJ}\cdot\text{mol}^{-1}$ of the global minima) (29) and well in excess of the $2\text{kJ}\cdot\text{mol}^{-1}$ needed to overcome the entropy of demixing of enantiomers. The packing of the lowest energy $P2_1/c$ solution, seen in Figure 10, lacks the $-\text{C}\dots\text{H}\dots\text{O}=\text{C}-$ intermolecular interactions observed in the experimental structure and appears to be dominated by ring stacking.

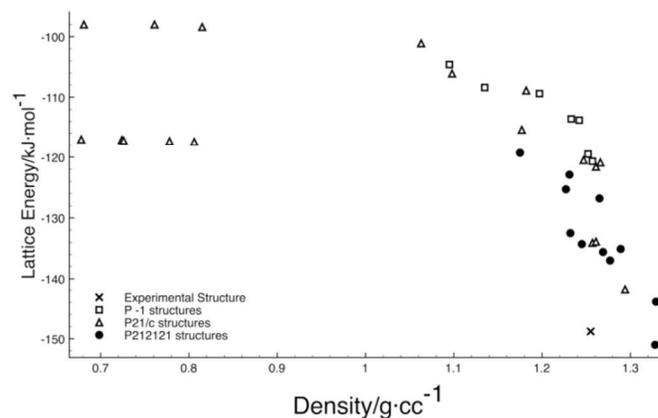


Figure 8 Energy landscape for R-CITAK structure prediction. Open shapes indicate centrosymmetric space groups and filled shapes are noncentrosymmetric space groups. The experimental crystal structure is indicated by the cross.

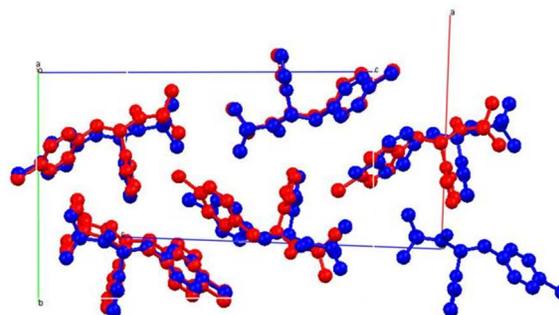


Figure 9: Overlay of the experimental crystal structure of R-CITAK (blue) with the lowest energy solution of prom calculations (red)

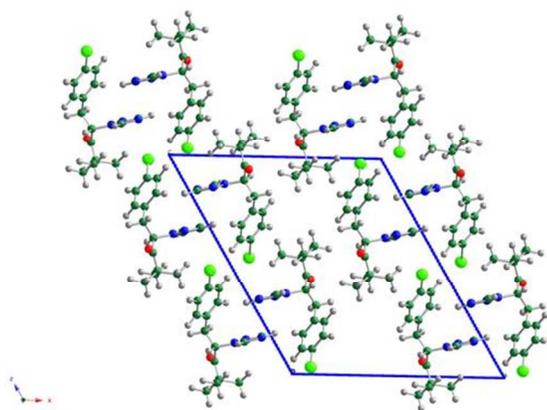


Figure 10: Packing of the lowest energy solution in P2₁/c

Conclusions. This study has returned to the case of CITAK (SEYPUH) crystallising from racemic solutions and in particular used solubility data to confirm the conglomerate behaviour of this system. Crystallisation of this molecule from racemic methanol solutions has long been known to produce crystals of low chiral purity despite the thermodynamic evidence. We have confirmed this observation and used a computational approach to demonstrate how growth normal to the (010) plane is insensitive to the chirality of the docking molecules and may lead to the formation of homochiral epitaxial layers. This results from the existence of weak hydrogen bonds which may be continued irrespective of which enantiomer docks at the surface. Finally we address the broader question of why this molecule does not form a racemic compound and through structure prediction conclude that again this is determined by the –CH...O– chain which does not appear in the predicted compound structures and evidently stabilises the conglomerate sufficiently to overcome the demixing process. Kinetically this may of course be aided by the apparent state of solvation and lack of solution phase self-association as revealed through FTIR spectra.

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References.

- G. Subramanian, *Chiral Separation Techniques*, 2nd edn, WILEY-VCH, Weinheim, 2003.
- A. Collins, G. Sheldrake and J. Crosby, *Chirality in Industry II – Developments in the Manufacture and Applications of Optically Active Compounds*, John Wiley & Sons, Chichester, 1997.
- J. Jacques, A. Collet, S. H. Wilen, *Enantiomers, Racemates, and Resolutions*; Krieger: Malabar, 1994.
- A. Collet, in *Problem and Wonders of Chiral Molecule*; Simonyi, M., Ed.; Akademiai Kiado: Budapest, 1990, 91-109.
- H. Lorenz, J. von Langermann, G. Sadiq, C. Seaton, R. J. Davey, A. Seide-Morgenstern, *Crystal Growth & Design* 2011, **11**, 1549-1556.
- G. Coquerel, *Preferential Crystallization*, in *Novel Optical Resolution Technologies*. 2007, Springer: Springer Berlin / Heidelberg, p. 1-51.
- W. L. Noorduin *et al.*, *J. Amer. Chem. Soc.*, 2008, **130**, 1158-1159.
- C. Viedma, *Phys. Rev. Letts*, 2005, **94**, 065504.
- S. N. Black, L. J. Williams, R. J. Davey, F. Moffat, R. V. H. Jones, D. M. McEwan, D. E. Sadler, *Tetrahedron*, 1989, **45**, 2677-2682.
- S.N. Black, L. J. Williams, R. J. Davey, *J. Phys. Chem.*, 1990, **94**, 3222-3226
- R. J. Davey, S. N. Black, L. J. Williams, *J. Cryst. Growth*, 1990, **102**, 97-102
- G. Levilain, C. Rougeot, F. Guillen, J. C. Plaquevent, G. Coquerel, *Tetrahedron:Asymmetry*, 2009, **20**, 2769-2771.
- K. Suwannasang, A.E. Flood, C. Rougeot, G. Coquerel *Cryst. Growth & Des.* 2013, **13**, 3498- 350
- For a more recent structure solution performed during the course of this work see CCDC deposition number 969515. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
- Balasubramanyan *et al*, United States Patent, 4,243,405, Jan 6, 1981
- K. Chadwick, R. J. Davey, G. Sadiq, G. W. Cross, R. Pritchard, *CrystEngComm*; 2009, **11**, 412-414.
- G.M. Sheldrick, *Acta Crystallogr. Sect. E: Struct. Rep. Online*, 2008, **64**, 112–122.
- R. Stron & K. V. Price *J. Global Opt.*, 1997, **11**, 314-359.
- Calculated by fitting to a DFT calculated electrostatic potential calculated at the PBE-D/def2-TVPP level in the program ORCA: F. Neese, *WIREs Comput. Mol. Sci.* 2011, **2**, 73–78.
- C. C. Seaton & N. Blagden *Trans. ACA*, 2004, **39**, 90-102.; A. Munroe, D. M. Croker, B. K. Hodnett, C. C. Seaton, *CrystEngComm* 2011, **13**, 5903–5907.
- Gavezzotti, A., *J. Amer. Chem. Soc.*, 1991, **113**, 4622-4629.
- G. Fillipini, A. Gavezzotti, *Acta Cryst B*, 1993, **49**, 868-880.
- A. Gavezzotti, *Z. Kristogr.* 2005, **220**, 499-510.
- D.E. Williams, D. J. Houpt, *Acta Cryst.* 1986, **B42**, 286-295.
- S. Furberg, O. Hassel, *Acta Chem. Scand.* 1950, **4**, 1020-1023.
- R. H. Martin, M. J. Marchant, *Tetrahedron* 1974, **30**, 343-345.
- B. S. Green, M. Knossow, *Science* 1981, **214**, 795-797.
- C. Gervais, S. Beilles, P. Cardinaël, S. Petit, G. Coquerel, *J. Phys. Chem. B* 2002, **106**, 646-652.
- S.L Price, *Phys. Chem. Chem. Phys.* 2008, **10**, 1996-2009.