Linking solution chemistry to crystal nucleation: the case of tetrolic acid

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The application of FTIR spectroscopy to concentrated solutions of tetrolic acid shows, for the first time, a direct relationship between molecular self association in solution and H-bonded motifs in the subsequently crystallised solid phases.

The process of crystal nucleation from liquids is central to the disciplines of physical chemistry and materials science and to the processing of a wide range of consumer products from foods, through pharmaceuticals to polymers. Despite this, surprisingly little is known about the molecular self assembly processes that surround the nucleation event and in particular the link between solution speciation, molecular aggregation and the nature of intermolecular interactions in the resulting crystal. This gap in understanding is particularly evident in systems which exhibit crystal polymorphism, when small changes in solvent choice and crystallisation conditions can yield a new crystal structure.[1] In this communication we report the application of Fourier Transform Infrared–Attenuated Total Reflection Spectroscopy (FTIR-ATR) to the study of this problem. In the past, infrared spectroscopy has been well utilised as a means of confirming molecular structure and exploring solvent–solute interactions. This earlier work[2–4] was performed on relatively dilute solutions, using transmitted radiation and predates advances in ATR technology developed over the last decade. These are the now routinely available robust ATR crystals and *in situ* probes. While the latter have found significant application in online crystallisation monitoring[5] they do not appear to have been used to infer chemical information concerning the species present in solution at the time of nucleation.

In the work reported here we have studied the simple carboxylic acid, tetrolic acid, $CH_3C{\equiv}CCOOH$. This acid has two polymorphic forms: α based on a classic dimer motif and β based on an H-bonded catemeric chain. The dimer form has been reported to be triclinic, space group $P\bar{1}$, while the catemer form is monoclinic, space group $P2_1$.[6] These two structures are seen in Fig. 1. According to the original work of Bengiat and Leiserowitz, it was found that both forms crystallised simultaneously from pentane solution.[7] In a solvent screen we found that, at room temperature, polymorphically pure samples of the metastable α form could be reproducibly recovered by evaporation of a chloroform solution and of the stable β form from ethanolic solution.

Solid state spectra were recorded on an Atavar 360 ESP spectrometer with a Germanium ATR crystal in conjunction with Nicolet's OMNIC software. For solution spectra a Mettler Toledo ReactIR 4000 with a diamond composite ATR crystal was used. Following earlier studies[8,9] we have employed two major IR absorption bands to indentify different H-bonded motifs. One is the –C=O anti-symmetric stretch which appears in the range 1740–1660 cm^{-1} varying with the extent of hydrogen bonding. The other is the –OH···O– out of plane wag which appears in the range 960–875 cm^{-1} and typifies the carboxylic acid dimer.

Fig. 2 shows the solid state spectra of the two forms. The dimeric α form is characterised by a –C=O antisymmetric stretch at 1671 cm^{-1} together with the hydroxyl out of plane wag at 918 cm^{-1}. In the catemeric β form, the –C=O stretch is split between 1697 cm^{-1} and 1632 cm^{-1} and, as expected there is no dimer peak in the 900 cm^{-1} region. This behaviour mirrors earlier studies of formic and oxalic acid polymorphs which also exhibit both dimer and catemeric forms.[2,10]

Solution spectra were then recorded in near saturated ethanolic and chloroform solutions at 20 °C. These are shown in Fig. 3, where it is clear that in chloroform solution (3 M), not only is the –C=O peak at 1687 cm^{-1}, typical for an H-bonded band, observed but also the broad peak centred on 911 cm^{-1} can be seen, characteristic of the carboxylic acid dimer. In the ethanolic solution (8 M), on the other hand, while the –C=O peak is at 1687 cm^{-1}, again typically H-bonded, the 900 cm^{-1} peak is absent indicating that dimers are not present in this solution.

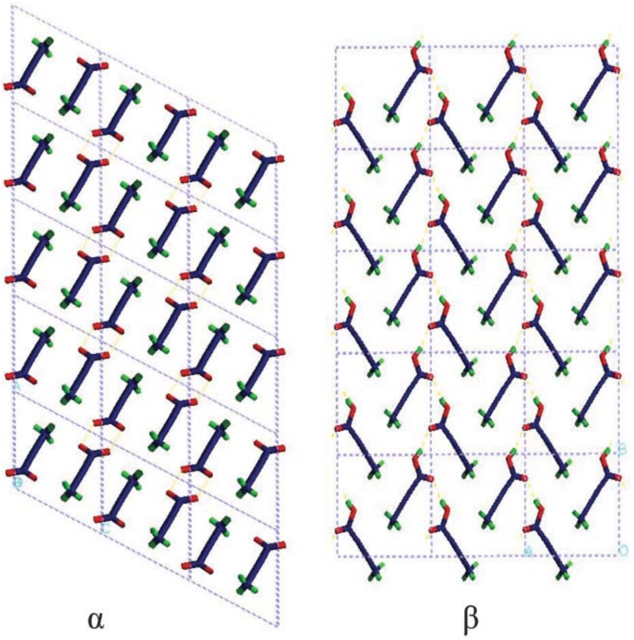

Fig. 1 Packing diagrams of α and β forms of tetrolic acid.

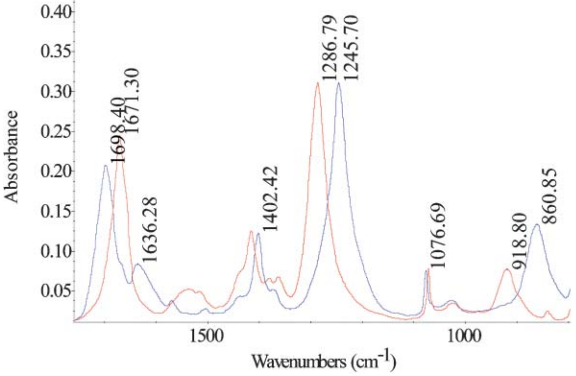

Fig. 2 Solid-state infrared spectra of α (red) and β (blue) tetrolic acid.

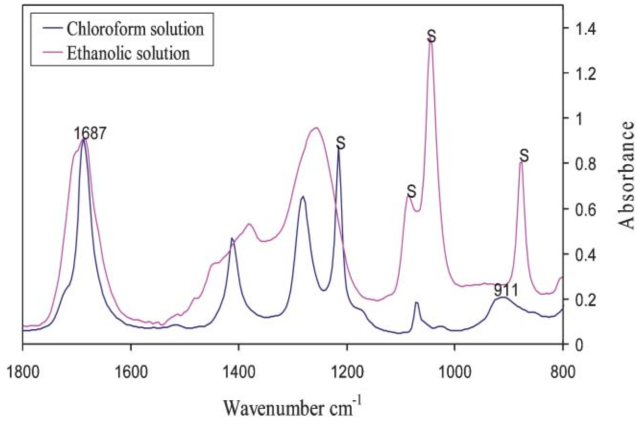

Fig. 3 Solution state spectra of tetrolic acid in chlorform (blue) and ethanol (red), all the solvent peaks have been marked with an "S".

We are thus able to see that, in this simple system, there is indeed a direct link between the assembly of molecules in solution and the solid form which crystallises. Solutions rich in dimers nucleate the α polymorph, solutions in more polar sovents in which dimer formation is disrupted nucleate the catemeric β structure. We note that this experimental result mirrors the previous molecular dynamic study of Gavezzotti *et al.*[11] who predicted the existence of dimers in carbon tetrachloride solutions which fell apart in water. While this tells us nothing about the actual process of molecular clustering it does indicate the efficacy of IR spectroscopy as an indicator of the formation of the fundamental growth units in the crystallisation event.

As a follow-up to this insight and to our previous work on discovering new polymorphs through combined prediction and experimentation,[12] we then recorded the FTIR spectrum of tetrolic acid in a number of other solvents (hexane, heptane, pentane, dichloromethane, nitromethane, THF, acetonitrile, dioxane and acetone) and found that uniquely in dioxane the –C=O stretch came unusually high, at 1710 cm^{-1} (Fig. 4), a position that appeared unaffected by dilution (pink spectra is at 0.09 M and blue at 2.93 M).

This indicates a major weakening of intermolecular H-bonds in this solvent or, judging by its insensitivity to dilution, even the existence of monomeric solute species. On crystallisation we recovered, a previously uncharacterised solvate (**1**) in which the solid state –C=O stretch appeared at 1705 cm^{-1} (not shown) and which had the crystal structure shown in Fig. 5.†

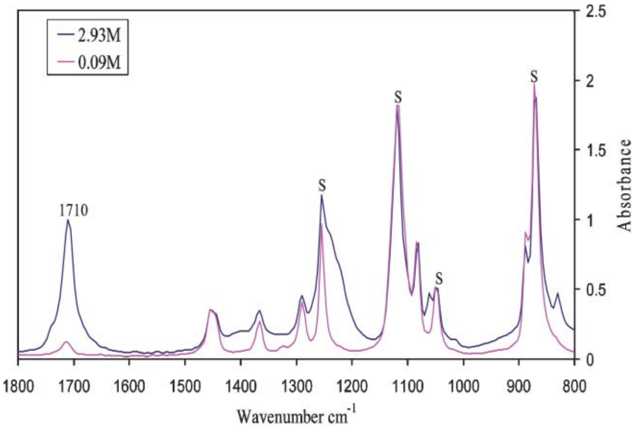

Fig. 4 Solution state spectra of dioxane in tetrolic acid, the solvent peaks have been marked with an "S".

Again there appears to be a link between the solution chemistry revealed through the IR spectrum and the crystal form isolated, with the molecule appearing monomeric in solution and a crystal structure with no intermolecular tetrolic acid H-bonding interactions.

Thus we have demonstrated, for the first time, not only the application of IR spectroscopy in understanding the relationship between solution and solid state interactions during crystallisation but also the use of *in situ* studies for the identification of potential new crystal phases.

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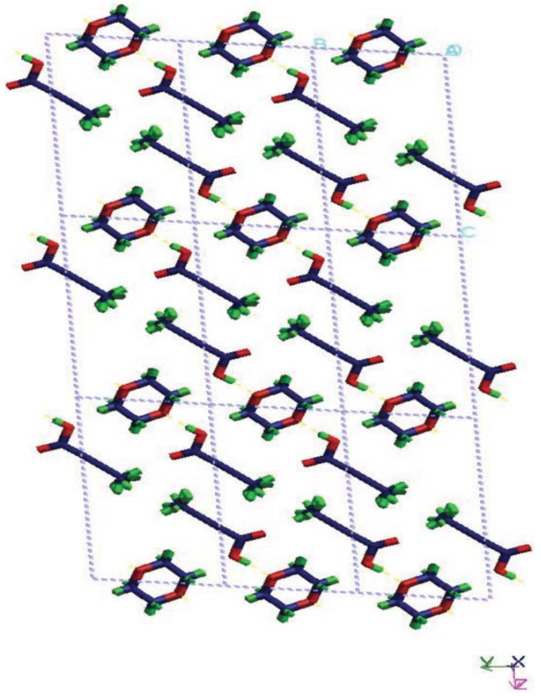

Fig. 5 The structure of tetrolic acid solvate from dioxane.

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Notes and references

† Crystal data for (**1**), $C_{12}H_{16}O_6$, M = 256.25, measured at 223 K: triclinic, unit cell parameters (Å, °): a = 4.1673(2), b = 6.5063(4), c = 12.4424 (6), α = 97.557(3), β = 92.948(3), γ = 91.670(2), $P\bar{1}$, Z = 1. μ(Mo-Kα) = 0.103 mm^{-1}. Of 1189 reflections 976 were unique (R_{int} = 0.0382) and were used in all calculations. The final $wR2$ = 0.1071 (all data), $R1[F^2 > 2\sigma(F^2)]$ = 0.0985, and goodness-of-fit on F^2, S = 1.035. CCDC 258387. See http://www.rsc.org/suppdata/cc/b4/b418603f/ for crystallographic data in .cif or other electronic format.

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