Crystallization of a Salt of a Weak Organic Acid and Base: Solubility Relations, Supersaturation Control and Polymorphic Behavior

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Control of crystallization processes for organic salts is of importance to the pharmaceutical industry as many active pharmaceutical materials are marketed as salts. In this study, a method for estimating the solubility product of a salt of a weak acid and weak base from measured pH-solubility data is described for the first time. This allows calculation of the supersaturation of solutions at known pH. Ethylenediammonium 3,5-dinitrobenzoate is a polymorphic organic salt. A detailed study of the effects of pH, supersaturation, and temperature of crystallization on the physical properties of this salt shows that the desired polymorph may be produced by appropriate selection of the pH and supersaturation of crystallization. Crystal morphology is also controlled by these crystallization conditions.

Introduction

Crystallization is used extensively as a purification and isolation process both on a laboratory and an industrial scale. It is well-known[1] that the conditions under which a solid is crystallized can affect its physical properties with factors such as temperature, agitation speed, solvent, addition of seed crystals being used routinely to control the size, morphology, purity, and polymorphic form.[2,3] Consequently, much academic and industrial work has been devoted to studies of nucleation and crystal growth, predominantly of neutral molecules from solution. However, due to a range of potential formulation problems, such as chemical and physical stability, mechanical properties, and solubility issues, it is very common to isolate and formulate active pharmaceutical materials in the form of salts. A wide range of salts[4] can be formed from an active acid or basic compound, and a salt screen[5] is frequently carried out to determine which salt has the best overall properties for production purposes. Given this general situation, it is perhaps surprising that studies of crystallization processes have not yet been extended to include organic salts nor the general principles of crystallization applied to the design of suitable processes for isolating this class of material.

Some general guidelines are usually applied commercially. For example, both high throughput salt screens[6] and large-scale salt isolations[7] are carried out by addition of a stoichiometric equivalent of the salt forming acid or base to the neutral compound in solution. A range of common solvents are used. It is also accepted that there must be a difference of at least 2 units between the pK_a values of the neutral compound and the salt former.[7] In general, an in-depth study of the pH-solubility behavior of the salt in potential solvents is not carried out.

Some studies have been reported for neutral compounds forming salts with strong acids or bases. For example, Sacchetti[8] derived equations for the solubility of a salt of a weak base with strong mono-, di-, and triprotic acids. There do not appear, however, to be any studies of the salts of weak acids with weak bases in which solid forms have been isolated under well-defined conditions of pH, supersaturation, and temperature. This is particularly important for the robust definition of a process aimed at isolating a product with a consistent size distribution, morphology, and crystal structure. The latter phenomenon of polymorphism has assumed particular importance in recent years[9] in the light of increased pressure to define reproducible processes and to have robust intellectual property cover.

In this paper, we have attempted to address many of these issues for the salt of a weak acid and a weak base. First, we discuss the formal definition and expression of solubility in such a system. We then use the Cambridge Crystallographic Database to highlight the number of crystal structures of polymorphic organic salts available in the public domain. From this group of materials, a candidate for experimental study was selected. Its pH-solubility profile has been measured and the dependence of its crystal morphology and polymorphic form in crystallization from aqueous solution over a range of pH and supersaturation values at two temperatures investigated.

Solubility Relationships and Supersaturation

For neutral molecules, solubility is defined as the mass of material that can be dissolved in a known volume or mass of liquid under given conditions of temperature and pressure. The solubility of a salt of a weak acid and weak base, however, is more complicated to define since it will depend on the species of acid and base in solution under a given set of conditions. This speciation depends on both solvent and pH and can be calculated from measured pK_a values of the acid and base. Thus, for the salt [$BH_2.A_2$] made from a weak acid, AH, and dibasic base, B, the solubility can be defined as the sum of the concentrations of B in all its possible forms. This amount must,

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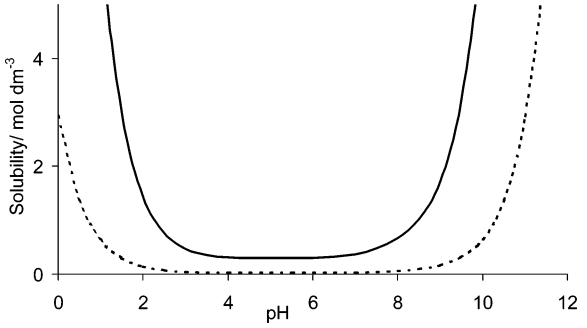

Figure 1. Typical pH-solubility profiles for a salt [$BH_2.A_2$] of a weak acid, HA, and weak base, B with — $K_{sp} = 0.1$ mol^3 dm^{-9} and - - - $K_{sp} = 0.0001$ mol^3 dm^{-9}. $K_a = 3$, $K_{a1} = 9$, and $K_{a2} = 7$.

of course, be balanced with a stoichometrically equivalent amount of A.

Combining the appropriate acid−base equilibria and mass-balance relationships, it is now possible to write

$$BH_2^{2+} \leftrightarrow BH^+ + H^+; K_{a1} = [BH^+][H^+]/[BH_2^{2+}] \quad (1a)$$

$$BH^+ + H^+ \leftrightarrow B + 2H^+; K_{a2} = [B][H^+]/[BH^+] \quad (1b)$$

$$AH \leftrightarrow A^- + H^+; K_a = [A^-][H^+]/[HA] \quad (1c)$$

to describe the ionization of the acid and base together with

$$\text{solubility} = [BH_2^{2+}] + [BH^+] + [B] = {}^1/_2([AH] + [A^-]) \quad (2)$$

for the overall solubility of the salt.

Using eqs 1a−1c, quantifying the species in solution in terms of the dissociation constants of the acid, K_a, and base, K_{a1} and K_{a2}, together with the solution pH, allows eq 2 to be rearranged to

$$\text{solubility} = \left\{\frac{1}{4}K_{sp}\left(1 + \frac{K_{a2}}{[H^+]} + \frac{K_{a1}K_{a2}}{[H^+]^2}\right)\left(\frac{[H^+]}{K_a} + 1\right)^2\right\}^{1/3} \quad (3)$$

in which K_{sp} is the solubility product of the salt. At equilibrium, the solubility product defines the maximum concentrations of the ions of the salt in solution

$$K_{sp} = [A^-]_{eq}^2[BH_2^{2+}]_{eq} \quad (4)$$

Taking typical values of K_a, K_{a1}, and K_{a2} of 3, 7, and 9 and values of K_{sp} of 0.1 mol^3 dm^{-9} and 0.000 1mol^3 dm^{-9}, eq 3 takes the form shown in Figure 1. Clearly reducing K_{sp} lowers the solubility and the curve has a smaller gradient at high and low pH. The solubility is at a minimum between pH 5 and 6 as nearly all of the salt exists in its ionized forms at these values and the solubility is limited by the solubility product. As the pH increases, the acid remains in its ionized form but the base is deprotonated according to eqs 1a and 1b, and overall there are then fewer ions of the salt in solution. The ionic product then becomes less than the solubility product and more ions of the salt can be dissolved. The same applies as the pH is decreased, the concentration of diprotonated ions of the base remains constant but the acid converts to its neutral, protonated form, eq 1c, and again the ionic product is less than the solubility product and more salt can dissolve. This argument assumes that the solubility of free acid and base in water are sufficient, for no precipitation of the free acid or base to occur at low or high pH, respectively.

Equations 3 and 4 assume that the solutions are dilute and behave ideally. At high pH values, solutions have high ionic strengths, and this may not be a valid assumption. Consequently, activity coefficients for the species in solution must be calculated from the known ionic strength. This can be done using eq 5 in which I is the ionic strength and z the ionic charge.

Activity coefficients, γ, are calculated according to eq 5 for the anion of the acid, γ_A, the diprotonated base γ_B and the hydrogen ions γ_H in solution[10]

$$-\log \gamma_i = 0.5z_i^2\left(\frac{I^{1/2}}{1 + I^{1/2}} - 0.3I\right) \quad (5)$$

This allows calculation of the solubility with corrections for the activity of the ions in solution as shown in eq 6

$$\text{solubility} = \left\{\frac{1}{4}K_{sp}\left(1 + \frac{K_{a2}}{[H^+]\gamma_H} + \frac{K_{a1}K_{a2}}{[H^+]^2\gamma_H^2}\right)\left(\frac{[H^+]\gamma_H}{K_a} + 1\right)^2\right\}^{1/3} \quad (6)$$

The solubility product in eq 6 must be written in terms of the activities of the acid, a_{A^-}, and the base, $a_{BH_2^{2+}}$, rather than concentrations, eq 7

$$K_{sp} = a_{A^-}{}^2 a_{BH_2^{2+}} = [A^-]^2\gamma_A{}^2[BH_2^{2+}]\gamma_B \quad (7)$$

The key driving force for crystallization, the supersaturation, of a solution of a salt [$BH_2.A_2$] can be calculated from the solubility product according to eq 8[11]

$$\text{supersaturation} = \ln\left(\frac{[A^-]^2\gamma_A{}^2[BH_2^{2+}]\gamma_B}{K_{sp}}\right) \quad (8)$$

In eq 8, [A^-] and [BH_2^{2+}] are the actual concentrations of these ions in the crystallizing solution.

In the work reported here, we have accordingly used measured solubility-pH data and known pK values together with eq 6 to estimate values of K_{sp}. These estimates have then been included with actual concentrations to calculate and perform crystallization experiments at desired supersaturation values.

It is noted that in an earlier study Leclercq and Jacques[12] presented related equations for the amount of precipitated 1:1 diastereomeric salts. The focus of their work, however, was on maximizing chiral recovery rather than exploring the more general issues of crystallization control developed here.

Selection of a Suitable Candidate

The Cambridge Structural Database[13] version 5.25 (November 2003) was searched using the program Conquest to find the number of structures of different types of polymorphic organic salts in the public domain. A list of FDA approved salt forming counterions was used,[4] and the search terms entered were the name of the salt-forming ion and the words "polymorph" and "form". Organometallic complexes, solvates, and hydrates were excluded. Results (Figure 2) were limited to salts with two different components, one of which was the named salt-forming ion and the other an organic ion. The 3D coordinates for at least one of the polymorphs had been determined in all cases. Halide salts were the most frequently occurring polymorphic organic salts, making up 58% of the polymorphic organic salts in the CSD, and there are very few (only 18%) polymorphic salts in the database where both ions are organic.

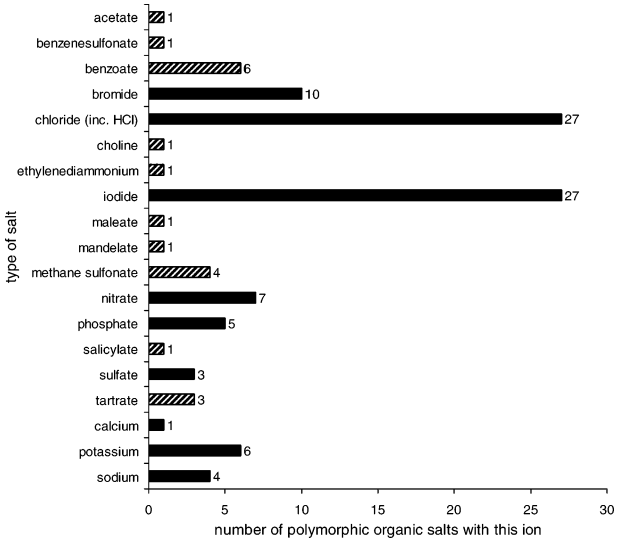

Figure 2. Polymorphic salts found in a search of the Cambridge Structural Database. Black areas indicate salts where one of the ions is organic, and hatched areas indicate that both of the ions of the salt are organic.

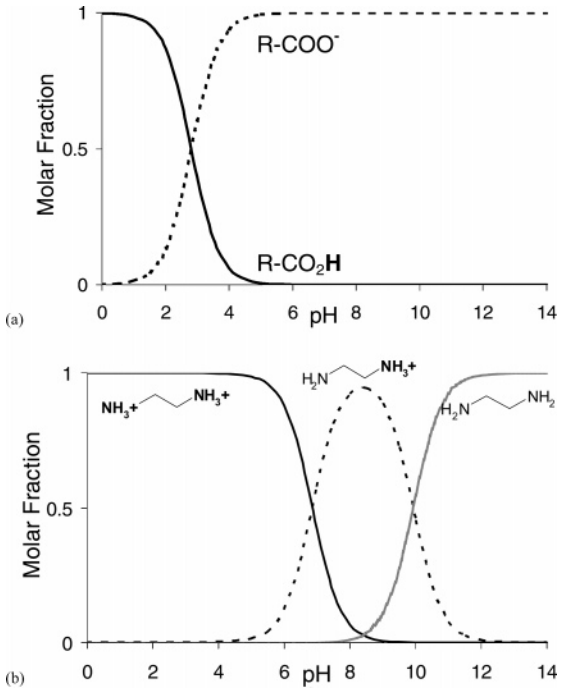

Figure 3. Solution speciation of (a) 3,5-dinitrobenzoic acid at 25 °C showing the relative amounts of protonated (—) and unprotonated (- - -) acid at each pH value and (b) ethylenediamine at 25 °C showing the relative amounts of diprotonated (black line), monoprotonated (dotted line), and unprotonated (gray line) base present at each pH value.

From these data, we selected the 2:1 salt of 3,5-dinitrobenzoic acid with ethylenediamine, ethylenediammonium 3,5-dinitrobenzoate,[14,15] as the subject of our experimental study. It has a number of attractive features: the acid and base are available commercially; the pK_a values are known (3,5-dinitrobenzoic acid in water at 25 °C and 50 °C are 2.82[16] and 3.07[17] respectively and for ethylenediamine pK_{a1} is 6.86[18] at 25 °C and 6.33 at 50 °C and pK_{a2} is 9.92[18] at 25 °C and 9.00 at 50 °C); it is of low toxicity; it has two polymorphic modifications. The speciation profiles for 3,5-dinitrobenzoic acid and ethylenediamine are shown in Figure 3. As a free acid, 3,5-dinitrobenzoic acid has very low aqueous solubility.[19] As inferred from Figure 3, below pH 4 the solubility of the acid decreases rapidly as the majority

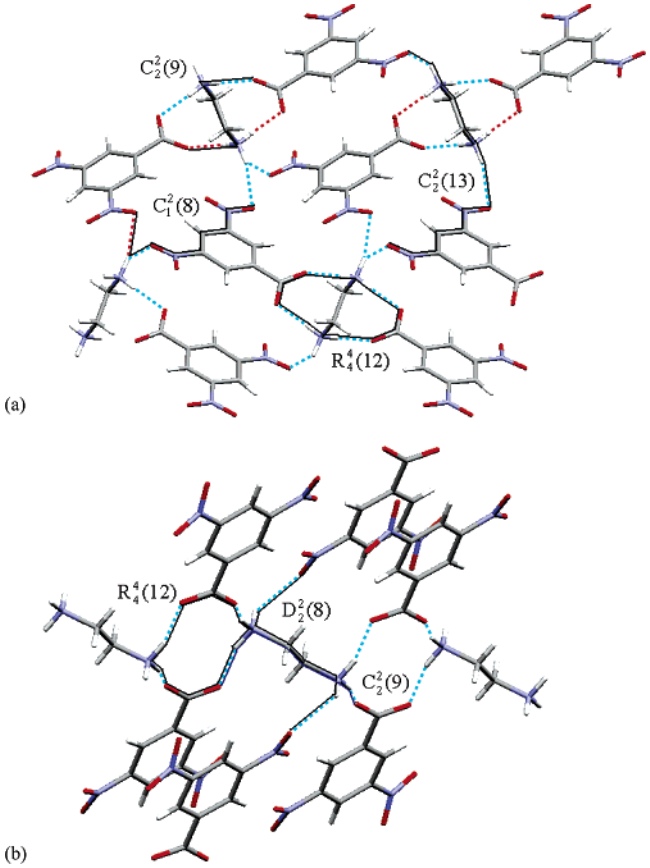

Figure 4. Crystal structure diagrams showing hydrogen bonding motifs for (a) the monoclinic form and (b) the triclinic form.

exists in its protonated form. Equations 2, 3, 6 and 8 are consequently only valid above pH 4; furthermore, they are also limited to below pH 9 as (see below) the acid reacts with sodium hydroxide at high pH values.

The crystal structures of both polymorphs were extracted from the database: one is monoclinic (VUJXIH01; $P2_1/c$; Figure 4a) and the other triclinic (VUJXIH; P-1; Figure 4b). The structure for the triclinic form did not have hydrogen atom positions determined, so this structure was re-solved to allow eventual comparison of the hydrogen bonding motifs in the two forms. {Crystals were grown by evaporation of an aqueous solution of ethylenediammonium 3,5-dinitrobenzoate. Diffraction patterns were recorded on an Enraf-Nonius KappaCCD low-temperature diffractometer at 150 °K.} In the triclinic structure, each benzoate ion is H-bonded to three different ethylenediamine ions with one of the aromatic nitro groups not involved in intermolecular H bonds. In the monoclinic structure, each benzoate ion interacts with four ethylenediamine ions and both aromatic nitro groups are now involved in H bonding. The benzoate ions in the monoclinic structure adopt 2 different orientations while in the triclinic structure they all lie in the $(\bar{4}12)$ plane. Graph set analysis[20] revealed, in the monoclinic form, H-bonding between carbonyl and ammonium groups to yield the motifs $R_4^4(12)$ and $C_2^2(9)$ and H-bonding between the ammonium and nitro groups in the motifs $C_1^2(8)$ and $C_2^2(13)$. In the triclinic form, the carbonyl and ammonium groups are linked in the motifs $R_4^4(12)$ and $C_2^2(9)$ and the nitro and ammonium groups in the motif $D_2^2(8)$. There is no report in the literature of the relative stability of these two forms.

One potential drawback with this material is its reported reaction with hydroxide ions at high pH to yield a red colored solution containing 2,3-dihydroxy-5-nitrobenzoic acid and

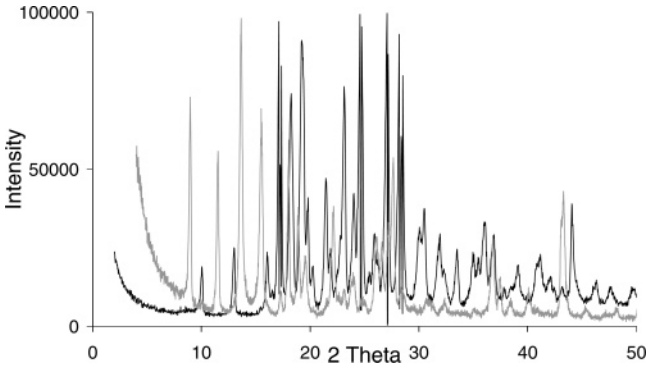

Figure 5. XRPD patterns of the monoclinic (black line) and triclinic (gray line) polymorphs.

3,3′-dinitro-5,5′-dicarboxyazoxybenzene.[21] Our experiments confirmed that this reaction did indeed take place above pH 9. To avoid this complication, experiments were restricted to pH < 8.0 at 25 °C and pH < 7.0 at 50 °C.

Experimental Section

3,5-Dinitrobenzoic acid and ethylenediamine were obtained from Sigma Aldrich Ltd. The acid was recrystallized from ethanol before use. All experiments were carried out using deionized water. Solution pH was measured using an Accumet Basic AB15 pH meter with an Accumet glass calomel pH electrode and an ATC probe to compensate for temperature changes. X-ray powder diffraction patterns (Figure 5) of crystallized samples were measured on a Bruker D8 diffractometer between 4 and 50° 2θ with a step size of 0.015° at 0.3 s per step. Patterns were collected at room temperature with samples on a silicon wafer or copper sample holder and without prior sample preparation. Solid samples were analyzed by microscopy using a Zeiss Axioplan 2 optical microscope, and images were recorded using Linkam's Linksys image capture software. Optical micrographs were used to estimate crystal sizes. ATR−IR spectra of solids were recorded in ATR-mode on a ThermoNicolet Avatar 360 ESP spectrometer integrated with Nicolet's OMNIC software. A background spectrum was collected before each spectrum was recorded. Spectra were measured in air at room temperature. Samples were not ground before analysis.

To measure the solubility of the two forms, samples of the desired polymorph were first prepared by precipitation from mixed ethanolic solutions of 3,5-dinitrobenzoic acid and ethylenediamine. XRPD and ATR−IR spectroscopy were used to confirm the form obtained. The diffraction peaks at 10.1° and 13.1° 2θ for the monoclinic form and 9.0° and 11.5° 2θ for the triclinic form proved suitable for this, whereas in the infrared, the polymorphs can be distinguished by the bands at 1549, 1516, 1356, and 1346 cm^{-1} for the monoclinic form and at 1533, 1502, and 1344 cm^{-1} for the triclinic form. A slurry of each form of the salt in water (40 mL) was prepared at 25 and 50 °C, and its pH was adjusted by addition of sodium hydroxide solution and allowed to equilibrate in a closed, thermostated, glass vessel for a few hours with stirring. Slurry samples (1−2 mL) were removed, and the composition of the solution phase was analyzed gravimetrically. The corresponding solid form present was confirmed by XRPD or ATR−IR spectroscopy as discussed above. Data were fitted to the theoretical expressions, eqs 3 and 6 using the least-squares method in Microsoft Excel.

Controlled crystallization experiments were performed in order to investigate the relationship between temperature, pH, supersaturation, and crystal form. According to eqs 2 and 3, the solubility of the salt should increase with pH (above a minimum which occurs between the pK_a values of the acid and base). Thus, by dissolving the acid and base at high pH (the solution is held at high pH for a short period of time to minimize reaction of the acid) and then reducing the pH, the solution becomes supersaturated and crystallization occurs. In these experiments, 3,5-dinitrobenzoic acid was dissolved in sodium hydroxide solution and a solution of ethylenediamine in water was added. Concentrated (37%) hydrochloric acid was then added dropwise to adjust the pH to the desired pH value. The experiment was carried out on a 50 mL scale in a jacketed vessel with an overhead stirrer (Citenco F. H. P. Motors type LC9, speed setting 4) and baffles to ensure good mixing. The pH and amounts of 3,5-dinitrobenzoic acid and ethylenediamine used were determined by the supersaturation required. The temperature was controlled using a thermostated waterbath and kept constant throughout the experiment. All experiments were carried out at 25 and 50 °C, with a fixed stirrer speed and without seeding. Supersaturations were chosen so as to cover as wide a range as possible over the pH range 4.0−8.0 at 25 °C and 4.0−7.0 at 50 °C.

Results & Discussion

Solubility. The solubility data, measured at 25 and 50 °C for the monoclinic form, are shown in Figure 6 as a function of pH. The solubility equation (3) was fitted to the data and this gave good agreement (standard deviation of measured solubility from calculated solubility at 50 °C is 0.0041). The data were refitted using the activity coefficient correction, eq 6 and this gave a better (standard deviation at 50 °C is 0.0023) fit to the experimental data as seen in Figure 6. The least-squares method was used to fit eq 6 to the data between pH 4 and pH 8 at 25 °C and pH 4 and pH 7 at 50 °C giving solubility products of 0.000 052 $mol^3\ dm^{-9}$ and 0.000 373 $mol^3\ dm^{-9}$ at 25 and 50 °C, respectively. These values yield an enthalpy of solution, $\Delta H_s = 63.2$ kJ mol^{-1}, and an entropy of solution, $\Delta S_s = 130$ J K^{-1} mol^{-1}.

Attempts to measure the solubility of the triclinic form yielded irreproducible results particularly as the temperature was raised. This was found to be due to its transformation to the monoclinic form occurring during equilibration. This result is important in demonstrating the monoclinic form to be the more stable. Taking the maximum value of the solubility, as measured at 25 °C and pH 5.1 of 0.034 mol dm^{-3}, and using eq 6 the solubility product for this form was estimated to be 0.000 153 $mol^3\ dm^{-9}$.

pH Controlled Crystallization. Figure 7 shows the results of the crystallization experiments in the form of morphodromes,[22] in which both morphology and polymorphic modification are illustrated as functions of supersaturation and pH. For the data measured at 25 °C, our estimated K_{sp} values enable supersaturations (eq 8) to be given with respect to both phases. At 25 °C the metastable, triclinic form was crystallized at all pH and supersaturation values investigated (Figure 7a) even though it is apparent that for all pHs the solutions are more highly supersaturated with respect to the stable monoclinic form. Crystals formed as rectangular plates whose thickness increased with decreasing supersaturation. Characterization by X-ray diffraction indicated the slowest growth face of the plates to be {001} and the *a* axis to be the fastest growth direction. At the lower supersaturations (∼1.0), the mean length of these crystals decreased from ca. 400 to 175 μm with increasing pH, whereas at higher supersaturations, sizes were independent of pH. Crystallization times decreased and yields increased with increasing supersaturation as expected.

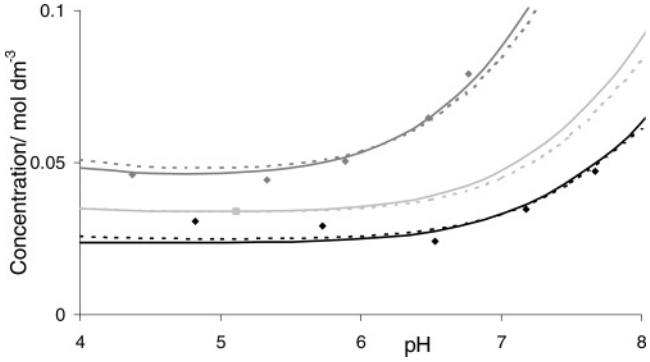

Figure 6. Solubility curves of the monoclinic and triclinic forms of the salt. Solubility of the monoclinic form at 25 °C without activity correction (dotted black line) and with activity correction (solid black line). Solubility of the triclinic form at 25 °C without activity correction (dotted light gray line) and with activity correction (solid light gray line). Solubility of the monoclinic form at 50 °C without activity correction (dotted dark gray line) and with activity correction (solid dark gray line).

At 50 °C, both polymorphic forms crystallized depending on the precise pH and supersaturation values (Figure 7b). At lower pH and higher supersaturations, the triclinic form appeared, again as rectangular plates whose thickness increased with decreasing supersaturation. However, contrary to the behavior observed at 25 °C, all pH values above 6 and lower supersaturations at 50 °C yielded, directly, the stable monoclinic form. This was confirmed by ATR−IR spectra recorded within minutes of crystallization occurring. These crystals take the form of *a*-axis prisms with sizes increasing from 105 to 700 μm as the supersaturation decreased. Our inability to measure K_{sp} for the triclinic form at 50 °C means that Figure 7b only includes supersaturation values with respect to the monoclinic form.

In terms of the polymorphic outcome in this system, it is apparent that at 50 °C the desired polymorph can be obtained by controlling both the supersaturation and pH of the solution: at pH 5 and supersaturations greater than ca. 0.5, the triclinic form is crystallized, whereas above pH 6, the monoclinic form appears. On the other hand, at 25 °C, only the triclinic form may be crystallized directly. The reason for this subtle impact of pH, temperature, and supersaturation is not clear. It is evident from evaporative experiments at room temperature that the monoclinic form is reluctant to nucleate, and we assume therefore that with increasing temperature kinetic limitations favoring the appearance of the triclinic crystals become more delicately balanced against thermodynamic factors.

Conclusions

A search of the Cambridge Structural Database identified ethylenediammonium 3,5-dinitrobenzoate, a salt of a weak acid

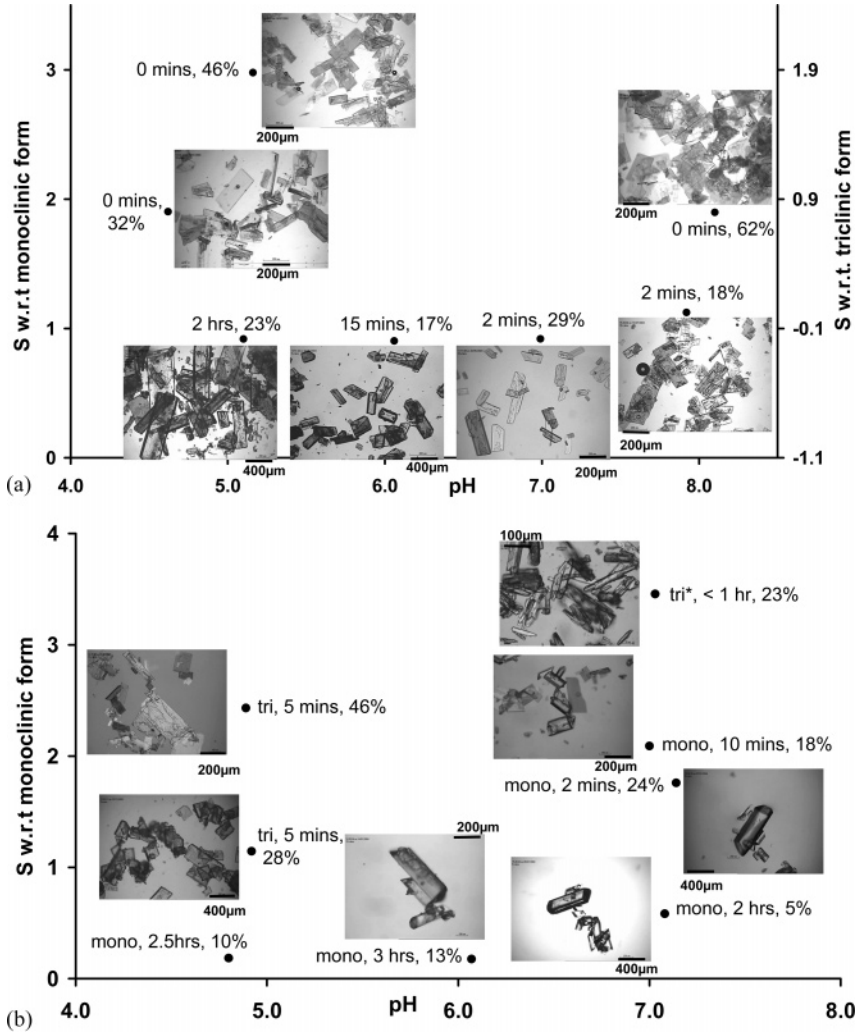

Figure 7. Graphs showing crystals grown as a function of pH and supersaturation of crystallization at (a) 25 °C and (b) 50 °C. Images were recorded on filtration of the product after 3 h stirring following crystallization: numbers are crystallization time and percentage yield. In (b) the label tri indicates a sample of the triclinic form, tri* is a sample of the triclinic form but a side reaction occurred in this crystallization, and mono indicates crystallization of the monoclinic form.

and a weak base, as candidate for this study. A method for estimating the solubility product of an organic salt from measured solubility versus pH data has been derived and, for the first time, used to interpret experimental data. Using this information, it is possible to separate the effects of pH, temperature, and supersaturation on the crystallization of this salt. In particular, it has been shown that altering the pH of crystallization independently of other factors can be used to control the polymorphism and morphology of the crystals produced.

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Supporting Information Available: Derivation of eq 3. Crystal structure of triclinic ethylenediammonium 3,5-dinitrobenzoate (CIF file). This material is available free of charge via the Internet at http://pubs.acs.org.

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