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Disappearing polymorphs and the role of reaction by-products: the case of sulphathiazole

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Abstract

A combined modelling and experimental strategy has been applied to the problem of reaction by-product influence on the appearance of sulphathaizole polymorphs from aqueous solution. From pure aqueous solution after 24 h the most stable phase, form IV was isolated. This work shows for the first time that a reaction by-product, ethamidosulphathiazole, from the final hydrolysis stage at concentrations as low as 1 mol.% stabilises the metastable modification, form I. In the presence of 1.0–0.5 mol.% forms II and III are stabilised. Only at concentration below 0.5 mol.% does the transformation proceed to form IV as in the pure solution. The role of the impurity was accounted for from an analysis of the respective hydrogen bond networks and crystal morphologies of each phase.

Keywords: Polymorphism; Reaction by-product; Sulphathiazole; Phase transformation

1. Introduction

The phenomenon of polymorphism, whereby a molecule can adopt more than one crystal structure is well known in both inorganic and organic crystal chemistry. In the pharmaceutical and speciality chemical industries it is of vital importance in the context of patent protection, process development and product specification (Bryn et al., 1996). In terms of developing a robust process for isolating polymorphic materials a purely structural approach is limited since it neglects the role of kinetics in determining the appearance of polymorphic structures (Cardew and Davey, 1982). This was recognised by Ostwald (1899) in his famous rule of stages which states that upon crystallisation a system will initially adopt the crystal structure which leads to the smallest loss in free energy and that these crystals will subse-

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quently transform stepwise to the most stable crystal structure.

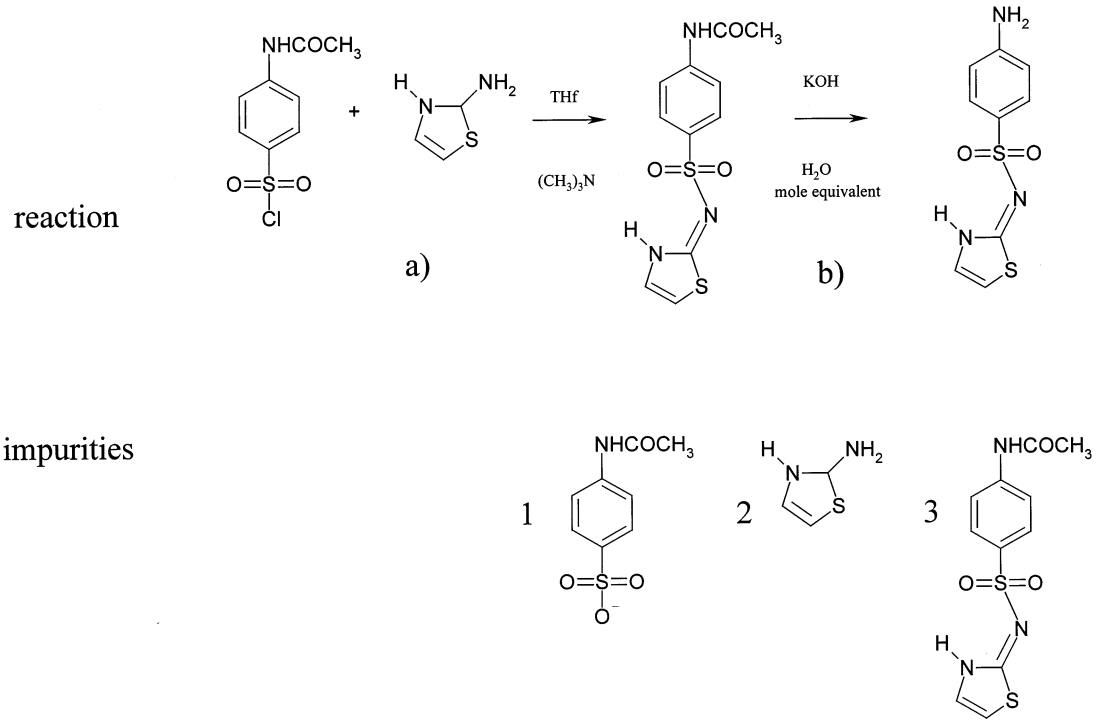
Since our ability to manipulate the kinetic processes of nucleation and growth in polymorphic systems is poor (Davey et al., 1997), the consequence of this is that the level of process control is limited. This is highlighted by the issue of so called 'disappearing polymorphs' (Dunitz and Bernstein, 1995), i.e. the sudden appearance of a new structure or the unexplained disappearance of an existing one. Such a sudden, unexplained, switch during production would have obvious disastrous consequences.

Previous work has highlighted the role that additives have in controlling the outcome from crystallisation processes. These range from impurity induced twinning which is capable of inhibiting the solid-state transformation of terephthalic acid (Davey et al., 1994), to pre-selected additives capable of inhibiting the nucleation and growth of unwanted polymorphs. In one case a polymeric derivative was used to control the appearance of the centric form of 3-*N*-ethamido-4-*N*-pyrolidino nitrobenzene over the non-centric form (Staab et al., 1990). In another example differences in molecular conformation were used to isolate the metastable α-form of L-glutamic acid (Davey et al., 1997).

The work reported here explores further the role of additives in controlling polymorph appearance by addressing the role that reaction by-products might play in this context. Sulphathiazole has been chosen as a model compound for this study since it is relatively easy to synthesise in the laboratory and exhibits a complex polymorphic behaviour, with four reported structures (Blagden et al., 1998).

2. Sulphathiazole: synthetic chemistry

The general synthetic route to sulphathiazole (Kapoor, 1993) is shown in Scheme 1, which also includes the possible reaction by-products. This is



Scheme 1. Typical synthetic route to sulphathiazole, with possible by-products.

Table 1
Crystallographic data

	Polymorph I	Polymorph II	Polymorph III	Polymorph IV
Space group	$P2_1/c$	$P2_1/c$	$P2_1/c$	$P2_1/n$[a]
a (Å)	10.554	8.235	17.570	10.867
b (Å)	13.220	8.550	8.570	8.543
c (Å)	17.050	15.580	15.583	11.456
β (°)	108.06	93.67	112.93	88.13
Cell volume (Å^3)	2261.3	1093.2	2162.0	1063.0
No. of molecules in asymmetric unit	2	1	2	1
Calculated density	1.50	1.55	1.57	1.60
Packing coefficient[b]	0.72	0.75	0.75	0.77

[a] Space group converted from $P112_1/n$ to $P12_1/n1$ for this paper.
[b] Packing coefficient defined according to Kitagiarodsky.

a typical route to sulphamide compounds and involves an amine substitution of an ethamidobenzenesulfonyl chloride, (stage a), followed by the hydrolysis of the ethamido group to the aniline functionality, (stage b). This final hydrolysis stage was carried out in an aqueous medium, consequently for this study only crystallisation from water was considered. The possible reaction by-products shown in Scheme 1 (as molecules 1, 2 and 3) are considered for their potential as crystallisation modifiers in the sulphathiazole system.

3. Sulphathiazole: crystal chemistry, polymorphism and probable reaction by-product effects

The crystal chemistry of the four polymorphic forms of sulphathiazole is well documented (Kruger and Gafner, 1971, 1972; Babilev et al., 1987). The numbering used here follows our previous work (Blagden et al., 1998) and relates to ref codes in the Cambridge Crystallographic Data Base, with: form I, *suthaz01*; form II, *suthaz* and *suthaz03*; form III, *suthaz02*; and form IV, *suthaz04*. Table 1 summarises the crystallographic data of the four reported forms. In a previous study hydrogen bond network analysis was used to explore the structural differences between the polymorphs (Blagden et al., 1998). This led to the appreciation of the similarities between structures II, III, and IV, and highlighted the uniqueness of form I. Briefly, it is now evident that form I consists of two, independent, interwoven hydrogen bonded chain networks, one a two-dimensional network and the other three-dimensional. Forms II, III and IV, on the other hand, are based on a single dimeric chain network packed into sheets. The three unique motifs are shown in Fig. 1a (form I), Fig. 1b (forms II and III) and Fig. 1c (forms III and IV). It is the difference in the hydrogen bonding at the aniline moiety which particularly distinguishes form I from the other three polymorphs as this contact gives rise to a significant difference in the hydrogen bonding usage on the fastest growing face of form I compared to the other forms (Blagden et al., 1998). In form I only one aniline hydrogen is utilised while in forms II, III and IV both are used.

On the basis of this hydrogen bonding difference it is now possible to examine in more detail the molecular structure of the possible reaction by-products 1, 2, and 3, shown in Scheme 1, in order to assess which are most likely to interact specifically with the crystallisation of the polymorphic forms of sulphathiazole. It is clear from such an examination that the ethamido precursor, 3, exhibits the closest molecular similarity to the final product. In this sense it fulfils the usual criteria for crystallisation modifying additives in that it is a derivative of both the conformational and functional features of the host (Staab et al., 1990; Davey et al., 1997). Fig. 2 shows the fastest growing faces of forms I and IV (Blagden et al.,

1998) with molecule 3 located in lattice sites. It is clear from Fig. 2a that on the {010} face of form I the ethamido derivative can enter the growing surface and take part in the hydrogen bond network through its sulphoxide oxygen, thiazole hydrogen, and imine nitrogen. This leaves the surface capable of accepting the next layer of sulphathiazole molecules through hydrogen bonding to the single aniline hydrogen. The ethamido group can be accommodated without disrupting the structure and hence this by-product is indistinguishable from sulphathiazole and crystallisation of form I can proceed undisturbed. For form IV on the other hand, Fig. 2b,

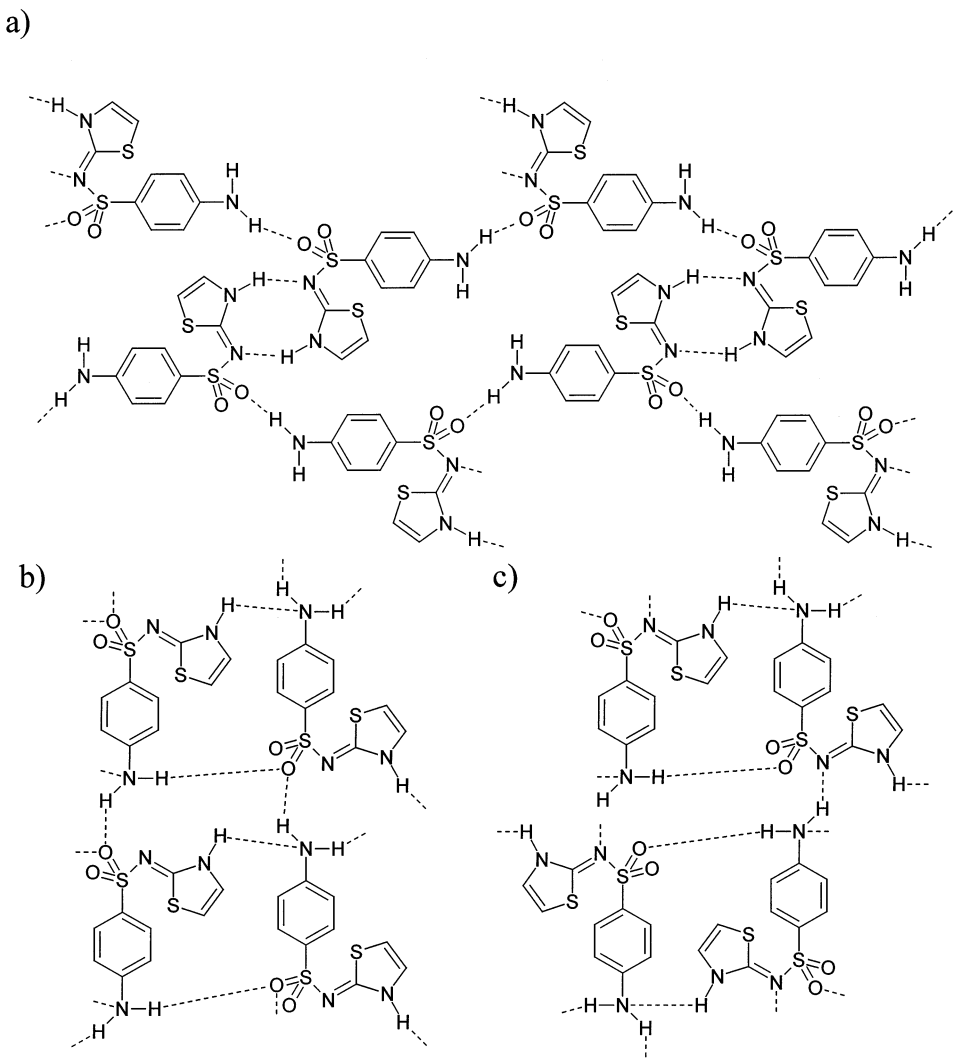


Fig. 1. (a) Schematic of the chain network common to both the two- and three-dimensional network in form I. Schematic of the two types of dimer chain dimer chain contacts (b) the dimer chain dimer chain contacts in form II, and III, (c) dimer chain common to forms III, and IV.

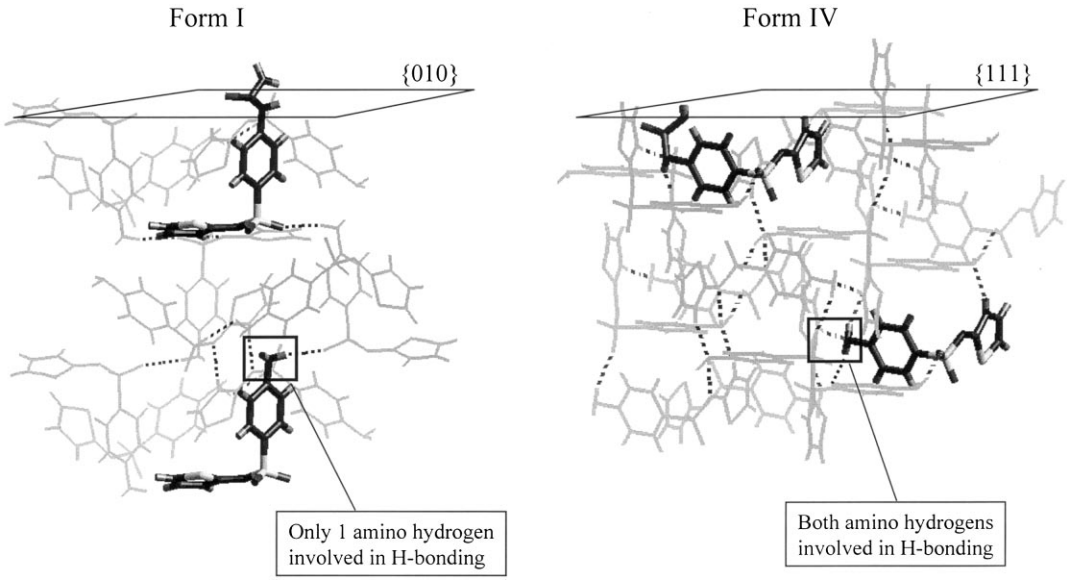


Fig. 2. Possible binding interaction of ethamidosulphamide in the fastest growing faces of (a) form I and (b) form IV.

the ethamido derivative must enter the fast growing {111} face utilising its single aniline hydrogen and a sulphoxide oxygen to take part in the hydrogen bonding network. Unlike form I a second aniline hydrogen is needed for hydrogen bonding to the next layer of sulphathiazole as growth proceeds and its replacement by the ethamido group will prevent hydrogen bond formation and provide a steric barrier to inhibit crystallisation. A similar argument pertains to additive inclusion in the fast growing faces of forms II and III which also demand two aniline hydrogens. This suggests that the appearance of the different polymorphs may be selectively influenced by the presence of this ethamido by-product.

4. Experimental section

In order to test this prediction the following protocols were used for the crystallisation of sulphathiazole from aqueous solution, the synthesis of the ethamido by-product 3, and assessing the influence of this molecule on polymorph appearance.

4.1. Crystallisation protocol

Using previous literature procedures (Babilev et al., 1987; Blagden et al., 1998) as a guide, an experimental methodology was developed in which crystallisation from aqueous solution was achieved by cooling a 22 g/dm^3 aqueous solution of sulphathiazole (ex Aldrich) from 100 to 25°C over 1 h and leaving to stand unstirred at 25°C for 24 h.

4.2. Inhibitor preparation

Following Kapoor (1993), ethamidosulphathiazole was prepared according to the following modified literature procedure. A mixture consisting of $NaHCO_3$ (2.4 g), amino thiazole (3 g) in THF (50 cm^3) and water (100 cm^3) was added dropwise to a mixture of ethamido benzylthionlychloride (6.9 g) in THF (110 cm^3) and held at reflux for 4 h. This mixture was left to cool to 30°C and water (300 cm^3) was slowly added to obtain a fine initial precipitate. This initial precipitate was collected by filtration, then discarded as it contained the unreacted precursors. The resulting filtrate was then reduced to half its original volume by rotavaporation. The desired product

was isolated by filtration, and subsequently recrystallised twice from THF. It was characterised using DSC, IR and ^{1}H NMR.

4.3. Assessing the influence of additive on polymorph appearance

The desired amount of additive was always added to the aqueous sulphthiazole solutions (22 g/dm^3) prior to crystallisation. The appearance of polymorphic forms and their interconversion was monitored by taking samples of crystal slurry at given time intervals up to a maximum crystallisation time of 24 h. These samples were studied in situ by optical microscopy and forms assigned from their known morphologies (Blagden et al., 1998). In some experiments the crystals were separated for powder XRD analysis in order to check for the presence of form I (unique peak at $2\theta = 11°$). Phase compositions were estimated to within $\approx 5\%$ by combining the microscopic and powder XRD data. It is noted that in general, morphology alone is not a reliable method of polymorph identification. For this reason it is always important to use a secondary mode of analysis, such as XRD as discussed here.

5. Results

Both the morphology and abundance of forms I, II, III and IV from pure solution and from solutions containing varying amounts of additive were analysed.

5.1. Pure solution

Fig. 3 shows a time-lapse sequence of micrographs from a typical crystallisation experiment carried out in pure aqueous solution The initial precipitation, Fig. 3A, (10–30 s after the onset of cooling) was dominated ($>90\%$) by needle shaped crystals of form I. After 4 h, Fig. 3B, form I had almost all disappeared (some thin partially dissolved needles remain) and a mixture of II (small cubes), III (elongated hexagons) and IV (regular hexagons) was present with form IV being the dominant phase ($>60\%$). The final micrograph in Fig. 3C shows the situation after 24 h with the transformation to form IV complete. This experimental data confirms that Ostwald's rule of stages (Ostwald, 1899) applies to sulphathiazole precipitated from aqueous solution and indicates that the stability of the polymorphs does increase in the order: $\mathrm{I} \rightarrow \mathrm{II} \rightarrow \mathrm{III} \rightarrow \mathrm{IV}$.

5.2. The effect of the by-product

To test the predication that the ethamido by-product would influence the crystallisation behaviour of sulphathiazole in aqueous solution, a series of impurity loaded samples (10, 5, 2, 1, 0.75, 0.5, 0.1, and 0.01 mol.%) were crystallised following the above protocol. Micrographs of the sulphathiazole products crystallised in the presence of 10, 1, and 0.01 mol.% (all after 24 h) are shown in Fig. 4A–C respectively. It is clear from these data that while a pure solution yields only form IV after 24 h, in a solution containing 10 mol.% of additive (Fig. 4A) only form I crystallises. In

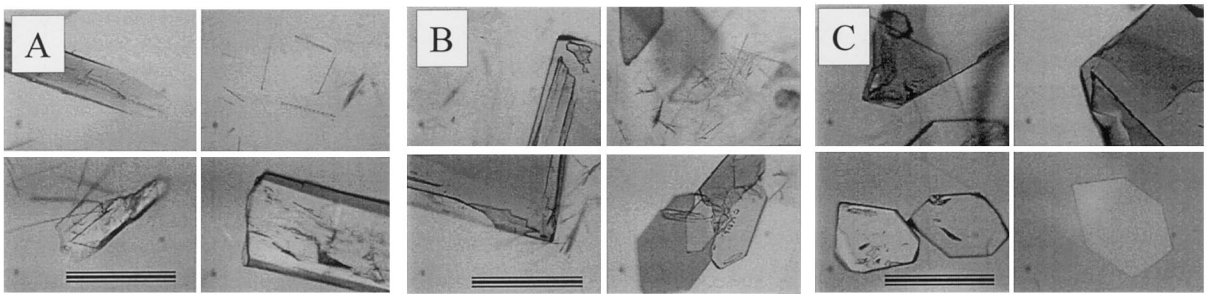


Fig. 3. Micrographs of a pure aqueous solution after (A) 10–30 s, (B) after 4 h, and (C) after 24 h. All micrographs bar 100 μm.

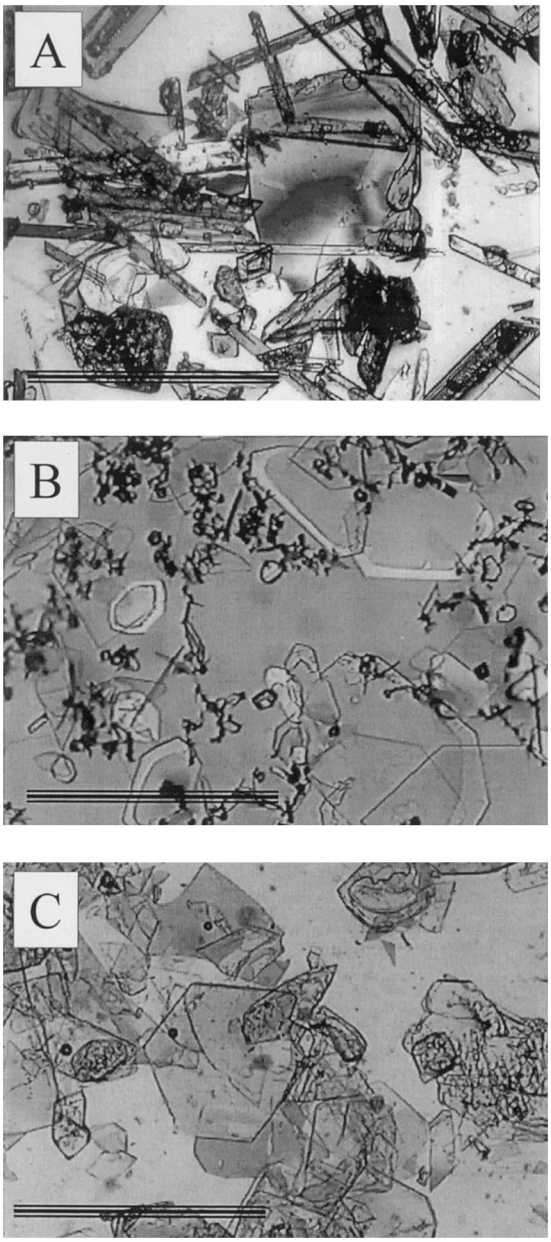


Fig. 4. Micrographs of (A) 10 mol.%, (B) 1 mol.% and (C) 0.01 mol.% additive doped aqueous solutions after 24 h. All micrographs bar 100 μm.

the range 1–0.5 mol.% of impurity a mixture of the four polymorphs was obtained comprising ca. 40% form IV, 40% form I and 20% composed of forms II and III. The 0.01 mol.% sample was

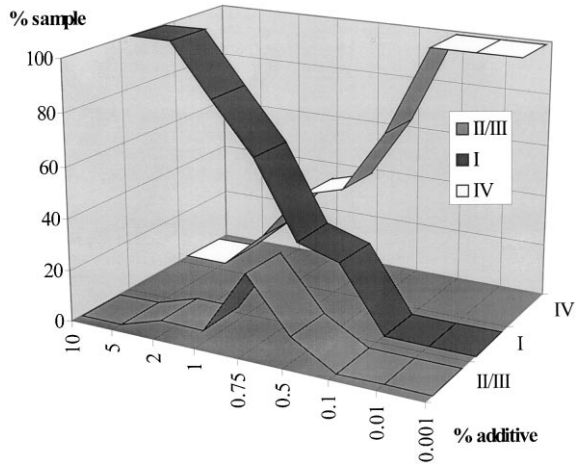


Fig. 5. Concentration of additive vs % of polymorph present, data was obtained from the micrographs and powder XRD.

identical to the pure system, yielding 100% form IV. Fig. 5 shows the data graphically using Excel. Overall it is clear from these experiments that the activity and selectivity expected of the ethamido by-product is matched by the experimental data.

5.3. Solvent mediated transformations: Ostwald's rule and impurity effects

The data reported above (Fig. 3) confirm previous data (Blagden et al., 1998) and demonstrate that the crystallisation of sulphathiazole from water appears to follow Ostwald's rule of stages, with form I appearing initially followed by the stepwise transformation, via polymorphs II and

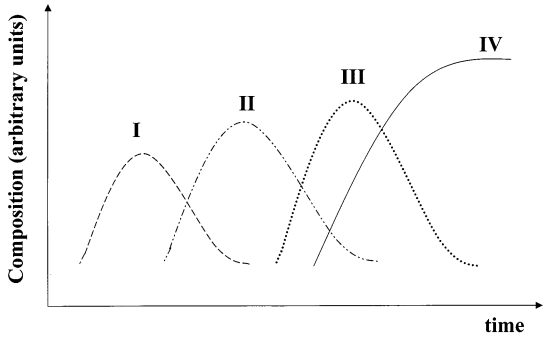


Fig. 6. Representation of relative transformation of form I, II, III and IV with additive concentration.

III, to the most stable form IV. This process is shown schematically in Fig. 6.

As shown previously (Cardew and Davey, 1982), this can only be true when the product of the nucleation rate (J) and the growth rate coefficient (k^3) for the various forms follow their thermodynamic stability. Thus it seems likely that the stability of sulphathiazole polymorphs in pure solution follows their relative densities (Table 1) and that:

$$J_I k_I^3 > J_{II} k_{II}^3 > J_{III} k_{III}^3 > J_{IV} k_{IV}^3$$

In this context the effect of the ethamido derivative would be to inhibit the nucleation and growth of forms II, III and IV thus kinetically stabilising form I. It must be recognised that the inhibiting role would be sensitive to additive loading. At high additive loadings the product of the nucleation rate and the growth rate coefficient of form I would then be the same as for a pure system with those of the other forms being decreased:

$$J_I k_I^3 \gg J_{II} k_{II}^3 \approx J_{III} k_{III}^3 \approx J_{IV} k_{IV}^3$$

with only form I appearing. At intermediate impurity loadings, the product of the nucleation rate and the growth rate coefficient of form I would again be the same as for a pure system with those of forms II and III being decreased but similar and form IV reduced further relative to the other forms:

$$J_I k_I^3 > J_{II} k_{II}^3 \approx J_{III} k_{III}^3 \gg J_{IV} k_{IV}^3$$

leading to the partial transformation of form I to forms II and III. At low impurity levels the nucleation rates and the growth rate coefficients of all the forms would be comparable to those in pure solution, consequently the system would transform according to Ostwalds rule of stages.

6. Discussion

The experimentally observed effectiveness of the ethamido by-product in stabilising form I reflects its predicted discrimination between the hydrogen bond networks of form I and the other forms. This selectivity was shown to be possible through the differences in hydrogen bonding contacts along the fastest growing faces of form I compared to forms II, III and IV. In form I, the fastest growing face contains a two dimensional network, whose structure and orientation requires only one aniline hydrogen whereas, in forms II, III and IV the fastest growing faces contain a hydrogen bond sheet network which requires two aniline hydrogen bond contacts. On this basis it is clear that the by-product can enter the surface of form I unnoticed but once in the growing surfaces of forms II, III, and IV it offers a steric and enthalpic barrier to further growth hence the observed selectivity.

7. Conclusions

A number of important conclusions may be drawn from this work. First, the experimental results mirror well the predicted by-product effects on the transformation of form I to the other phases, through preferential inhibition of the growth of forms II, III, and IV. Second it has shown for the first time that a reaction by-product can play a powerful role in determining the polymorphic outcome of a crystallisation process. This has significant implication for process development in the pharmaceutical industry where route selection procedures and continual process improvement will often take place without any regard being given to how these might alter the by-product spectrum and hence the polymorph selectivity of the process.

Overall, it has been shown that the combination of crystal morphology (as an indication of the link between kinetics and structure), and the hydrogen bond network analysis of the different polymorphs affords a new and powerful approach to understanding and controlling polymorph appearance and stability in the presence of impurities.

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