Polymorphism in Molecular Crystals: Stabilization of a Metastable Form by Conformational Mimicry

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Abstract: A combined modeling and experimental strategy has been applied to the problem of stabilisation of a metastable conformational polymorph. For the first time additives have been successfully selected which by virtue of their conformation are able to selectively inhibit the appearance of the stable β polymorph of L-glutamic acid and hence stabilize the metastable α structure.

Introduction

Polymorphism, the ability of a molecule to adopt more than one crystal structure, is fundamental to solid state chemistry[1] and is found in many classes of molecular materials, for example, triglycerides, saturated and unsaturated fatty acids, alkanes, aromatic π-bonded systems, amino acids, carboxylic acids, and amides. It is thus of importance across a wide range of industries including pharmaceuticals, healthcare, agrochemicals, pigments, dyestuffs, and foods. Recent developments in computational techniques coupled with increased appreciation and parameterization of intermolecular interactions have led to the availability of commercial software for the prediction of polymorphic crystal structures from molecular structures.[2−4] In terms of the development of robust processes for isolating polymorphic materials a structural approach, however, is limited since it neglects the vital role of kinetics in determining the appearance of polymorphic structures, a factor which Ostwald recognized almost a century ago in his famous Law of Stages.[5,6] Technologically this is crucial since these structural variants exhibit different physical properties which are reflected in crystal morphology, optical characteristics, mechanical properties, and chemical reactivity. Thus solid−liquid separation, comminution, solubility, particle flow, and formulation characteristics will all be polymorph dependent.[7,8] In some instances this allows polymorphism to be exploited such that the structure with properties appropriate for a particular formulation is isolated. In other cases the isolation of a new polymorph can threaten product specifications and radically change the status quo in the patent arena as in the recent case of Zantac.[9] Despite this our ability to manipulate the kinetic processes occurring during crystallization of polymorphic systems is extremely poor and limits the level of process control available in high performance specialty chemical production. A recent analysis by Bernstein and Dunitz[10] has highlighted this issue by documenting a number of so-called "disappearing polymorphs", i.e., sudden appearances of new structures or the unexplained disappearances of existing ones. Such examples are almost certainly mirrored (although not documented) by industrial practice and one can only speculate at the disastrous consequences of a sudden unexplained switch of polymorph during the isolation of a high value specialty product.

Previous work aimed at controlling the polymorphic outcome from crystallization processes has shown, on the one hand, how impurity induced twinning can inhibit a solid state transformation and hence lead to the kinetic stabilization of a metastable polymorph[11] and, on the other hand, how additives may be used to inhibit the nucleation of unwanted polymorphic structures in crystallization from solution.[12,13] The design of additives for the latter application was facilitated by gross differences in symmetry, one of the polymorphs belonging to a centric and the other to a noncentric space group. The current work explores further the use of additives in polymorph control by addressing the issue of conformational polymorphism.[14] The results presented here, on L-glutamic acid, demonstrate, for the first time, the possibility of designing additive molecules to selectively inhibit the crystallization of the more stable polymorph on the basis of conformational recognition, allowing kinetics to dominate the crystallization process and leading to the stabilization of a metastable phase.

Ostwald's Law of Stages, L-Glutamic Acid, and Design Strategy

Ostwald's Law of Stages[5] states simply that "when leaving an unstable state, a system does not seek out the most stable

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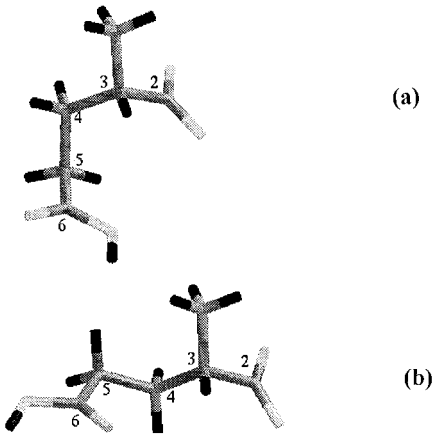

Figure 1. The conformation of L-glutamic acid in (a) the α and (b) the β crystal structure. The torsions τ_1 and τ_2 are defined by carbons 2,3,4,5 and 3,4,5,6, respectively and have values of 59.3 and 68.3° in the α structure and −171.5 and −73.1° in the β structure.

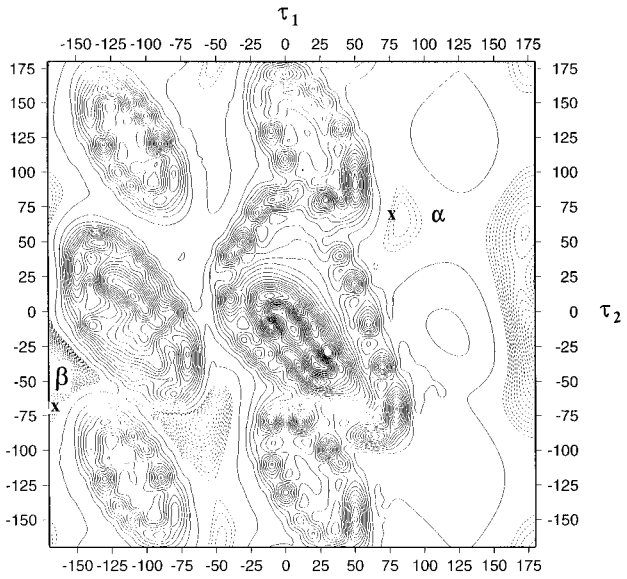

Figure 2. The calculated conformational map for L-glutamic acid with torsions τ_1 and τ_2 as defined in Figure 1. The location of α and β conformers are indicated. The TRIPOS force field was used, and the contour details are as follows: dashed lines −4.0 to +5.0 kcal/mol with contour spacing of 0.5 kcal/mol; solid lines +5.0 to +200 kcals/mol with contour spacing of 10 kcal/mol.

state, rather the nearest metastable state which can be reached with loss of free energy". It has been shown previously that this law has no general proof, rather it is a special case of nucleation and growth in a polymorphic system.[6] For a system in which two polymorphs, I and II, exist, adherence to this law requires that the initial mass fraction of crystals of form I in the product is close to unity. This is only true when the product of the crystal nucleation rate, J, and the kinetic coefficient for crystal growth, k, is lower for II, the more stable phase,[6] viz.

$$J_{II}k_{II}^{3} \ll J_{I}k_{I}^{3}$$

This suggests that the appearance of different structures may be influenced by additives designed to interfere selectively with either the nucleation or growth rates of a particular phase.

In the case of L-glutamic acid two polymorphs are known, designated α and β. The crystal structures are both orthorhombic, $P2_12_12_1$, with $a = 1.0282$, $b = 0.8779$, $c = 0.7068$ nm and $a = 0.5159$, $b = 1.730$, $c = 0.6948$ nm, respectively,[15,16] and crystals form with distinct rhombic and needle-like morphologies. Molecules crystallize in their zwitterionic state with molecular packing of both forms dominated by intermolecular hydrogen bonding[17] and electrostatic interactions, the most significant difference residing in the molecular conformations adopted in the two structures. These are shown in Figure 1 which defines the two torsions, τ_1 and τ_2, and shows the relatively extended conformation from the β structure compared to the more twisted α conformer.

The phase diagram for the L-glutamic acid−water system has been measured previously[18] and is known to be monotropic with the β form the more stable at all measured temperatures. In agreement with Ostwald's Law it is known that crystallization results in the initial nucleation and growth of the metastable α phase at all temperatures. If these α crystals are separated from their mother liquor immediately after crystallization, the dry crystals are indefinitely stable: there is evidently no solid state route to the β structure. If no separation is performed, however, a solvent-mediated transformation takes place[18−20] in which α crystals dissolve and β crystals grow from the mother liquor in a process whose rate increases with temperature.[18]

The overall objective of this work has been to select additives which by virtue of their *conformation* are able to selectively inhibit the crystallization of β and hence control the polymorphic outcome of L-glutamic acid crystallization yielding only α crystals. The strategy for achieving this objective has involved three separate tasks: firstly, simple conformational analysis aimed at establishing both the extent to which selected additives are likely to mimic α and β conformations and the degree to which the growth of L-glutamic acid itself is limited by the populations of appropriate conformers; secondly, the identification of the fastest growing faces of α and β crystals since to stabilize the α phase an additive must selectively bind to and inhibit at least the fastest growing faces of β crystals without affecting the fast growing faces of α crystals; and thirdly, an experimental protocol for testing the potency of additives in stabilizing the α polymorph relative to the more stable β structure.

Conformational Analysis

As a guide to the likely populations of molecules in α and β conformations, conformational analyses of L-glutamic acid and additives employed were carried out at the molecular mechanics level using both DREIDING[21] and TRIPOS[22] force fields. Published default parameters were used[21,22] together with AM1[23] charges. The resultant conformational minima were validated using semi empirical molecular orbital calculations within MOPAC.[23] In the case of L-glutamic acid conformational space, as defined by the torsions τ_1 and τ_2 (defined in Figure 1), was searched in 10° steps from 0 to 350°. The resulting map, Figure 2, demonstrates that molecular conformations corresponding to

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Table 1. Conformational Data[a] for L-Glutamic Acid and Additive Molecules

molecule	$\Delta E_{torsion}$ between α and β conformers (kcal mol^{-1})	% in α conformation
L-glutamic acid	−0.2	45
glutaric acid	1	80
2-methylglutaric acid	1.5	90
transglutaconic acid	−7.5	0

[a] Calculated using DREIDING force field.

the α and β structures represent energy minima[24] connected by a low energy pathway involving rotation mostly around τ_1. Large areas of conformational space are unavailable, and it is clear that while the α conformation lies in a localized minimum the β conformation lies in valley running parallel to the τ_2 axis allowing it torsional freedom in this region at little energetic expense. The carboxylate groups of the additive molecules were fixed according to the α and β conformations and rotation around τ_1 and τ_2 employed to transform molecules between conformations. The torsional energy was monitored, and the barrier heights in each direction were estimated in order to evaluate the difference in torsional energy between forms. The results of this analysis are shown in Table 1 where the relative Boltzmann populations of the two conformational states have also been estimated. In the case of the L-glutamic acid zwitterion the β conformation is the more stable with an activation barrier of 2.6 kcal mol^{-1} for transforming α to β. This is consistent with the known solution chemistry of the system[25] and the crystallization characteristics discussed above in which it thus seems that conformational barriers are unlikely to be rate limiting and hence that molecules joining a growing surface of either phase are those already in the appropriate conformation. This is an important conclusion since it gives credence to the notion that additive selectivity may be based on conformational mimics of the two forms.

Additive Selection

The additives were selected on the basis of the morphological data which defined the fastest growing faces of each form (see below) and comprised four 1,5-dicarboxylic acids: glutaric ($HOOC(CH_2)_3COOH$), 2-methylglutaric ($HOOCCH(CH_3)(CH_2)_2COOH$), transglutaconic ($HOOCCH_2(HC{=}CH)COOH$), and trimesic (1,3,5-benzenetricarboxylic acid) acids, judged to have increasingly rigid conformations. Table 1 summarizes the results of the simple conformational analyses described above. These are consistent with this judgment, indicating the preference of glutaric and 2-methylglutaric acids for the α conformation, while decreased torsional flexibility imposed by the double bond predisposes transglutaconic acid to the β conformation. In the case of trimesic acid the rigid nature of the aromatic link precludes rotation along τ_1 so that the α conformation is inaccessible, and, as shown in Figure 3, trimesic acid mimics closely the β conformation. This is supported by Table 2 which compares the distances between carbon and oxygen atoms in the carboxylate groups of trimesic acid, taken from the crystal structure[26] with the equivalent distances in the two glutamic acid conformers. Thus, the overall predictions of the effects of these additives, based on the extent to which they are able to mimic the α and β conformations, are that glutaric and 2-methylglutaric acids should show minimal selectivity between the polymorphs with a possible preference for the α form, while transglutaconic and trimesic acids which are present exclusively in the β conformation should selectively inhibit the crystallization of the β phase, thus stabilizing the metastable α structure. Trimesic acid is expected to show an enhanced effect compared to transglutaconic acid both due to its increased torsional rigidity and its aromatic ring which will offer a greater steric barrier to crystal growth.

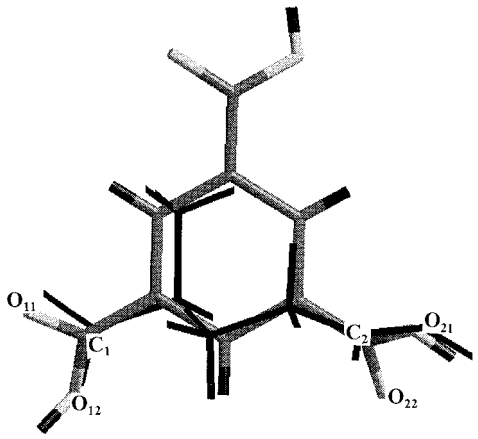

Figure 3. Comparison of trimesic acid and β glutamic acid conformations. Distances between labeled atoms are given in Table 2.

Table 2. Geometric Comparison of Carboxylate Separations in Trimesic and l-Glutamic Acids[a]

molecule	$-C_1\cdots C_2-$ distance (nm)	$-O_{11}\cdots O_{21}-$ distance (nm)	$-O_{12}\cdots O_{22}-$ distance (nm)
Trimesic acid	0.5	0.71	0.488
α-L-glutamic acid	0.382	0.575	0.335
β-L-glutamic acid	0.469	0.664	0.479

[a] See Figure 3 for atom numbering.

Experimental Section

Using previous work as a guide[18,19] experimental protocols were developed in which crystallization from aqueous solutions yielded crystals of the two polymorphic forms either as pure phases or mixtures. Thus pure α was prepared by seeding a 20 g/L aqueous solution at 18 °C, pure β was obtained by unseeded crystallization of a 35 g/L aqueous solution at 38 °C, and a mixture of forms was obtained from a 45 g/L solution crystallized at 48 °C. Crystallizations were carried out in thermostated glass vessels at the isoelectric pH (3.2) both unstirred and with gentle (magnetic) stirring. Additives (ex Sigma and Aldrich) were added prior to crystallization. For all the compositions used, the starting solutions were supersaturated with respect to both phases, and, as expected, in all experiments α was the first phase to appear. In order to assess the ability of additives to stabilize the α structure the overall α ⇒ β transformation times were estimated at both 38 and 45 °C by sampling and using combined X-ray diffraction and optical microscopy.[18] A few transformation experiments were performed in an unstirred temperature controlled microscope cell in order to observe the process *in situ*.

Large (1 mm) crystals of each form were grown from unstirred solutions, and their morphologies were determined by a combination of X-ray oscillation photography and optical goniometry in order to define the crystal surfaces of interest and determine the morphological effects of additives.

Results

Pure Morphologies: Identification of Fastest Growth Directions. Figure 4a,b shows examples of α crystals grown at 18 °C and β crystals grown at 38 °C. α Crystals always grew as single well-formed rhombs, whilst β crystals tended to nucleate and grow as clusters of fragile needles. The indexed morphologies are shown diagrammatically and allow the

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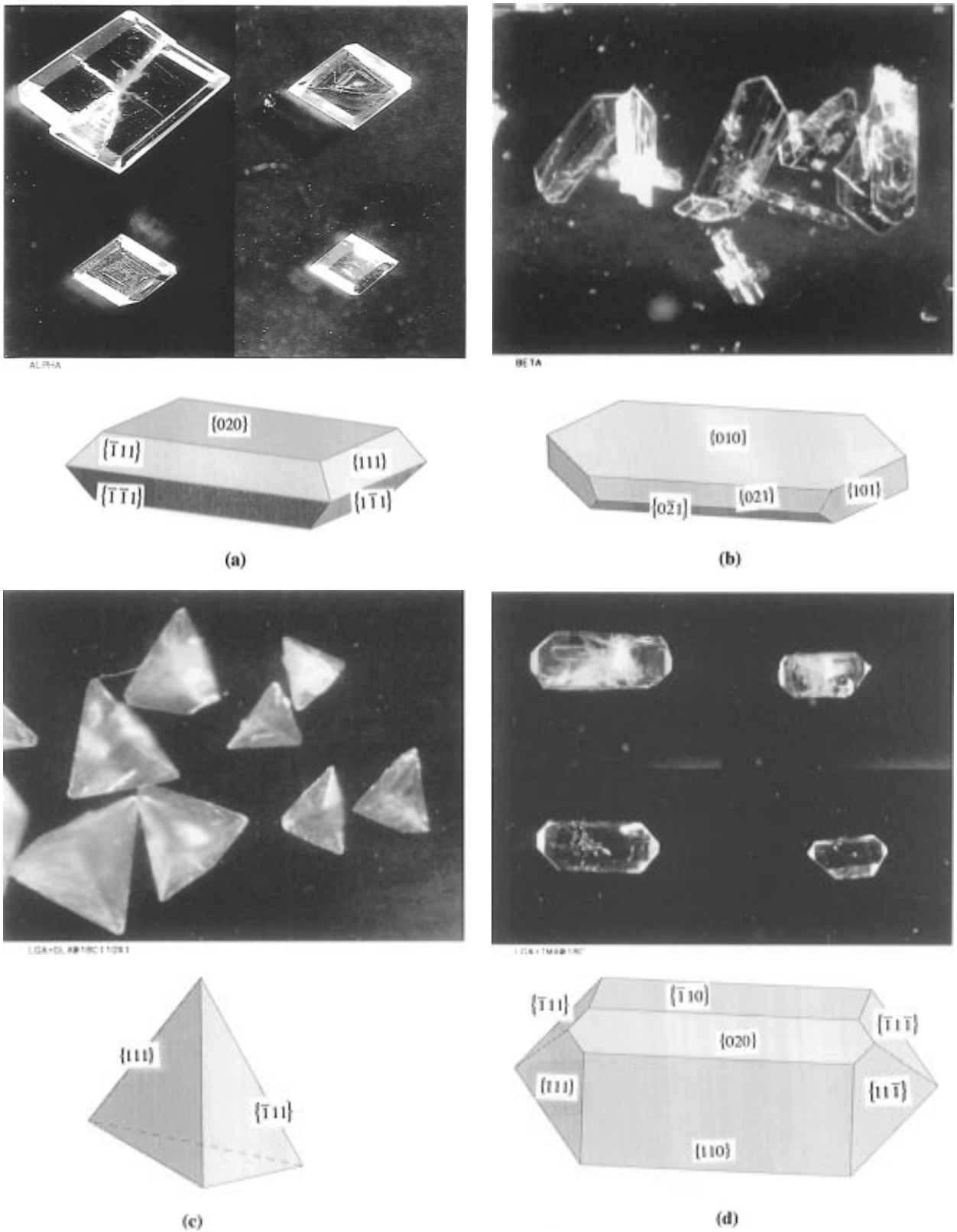

Figure 4. The morphologies (experimental and diagrammatic) of α and β crystals of L-glutamic acid: (a) α crystals grown from pure aqueous solution, (b) β crystals grown from pure aqueous solution, (c) α crystals grown in the presence of glutaric or methyl glutaric acids, (d) α crystals grown in the presence of transglutaconic or trimesic acids.

identification of the fastest growing crystallographic directions as {111} in α and {101} in β.

Conformational Discrimination and Selection of Additives. The molecular packings in these fast growing surfaces are shown in Figure 5a,b[27] and it is based on the information held within these surfaces that discriminatory additives were selected for the stabilization of the α form. This was based on the reasoning described above that to prevent the appearance of a particular polymorph it is essential to inhibit at least its fastest growth directions. In both sets of faces there are four molecular orientations with intermolecular hydrogen bonds between $-NH_3^+$, $-COO^-$, and COOH functionalities creating a two

(27) All packing diagrams were visualized using CERIUS, molecular modeling software, MSI/ Biosym Inc., Cambridge, UK.

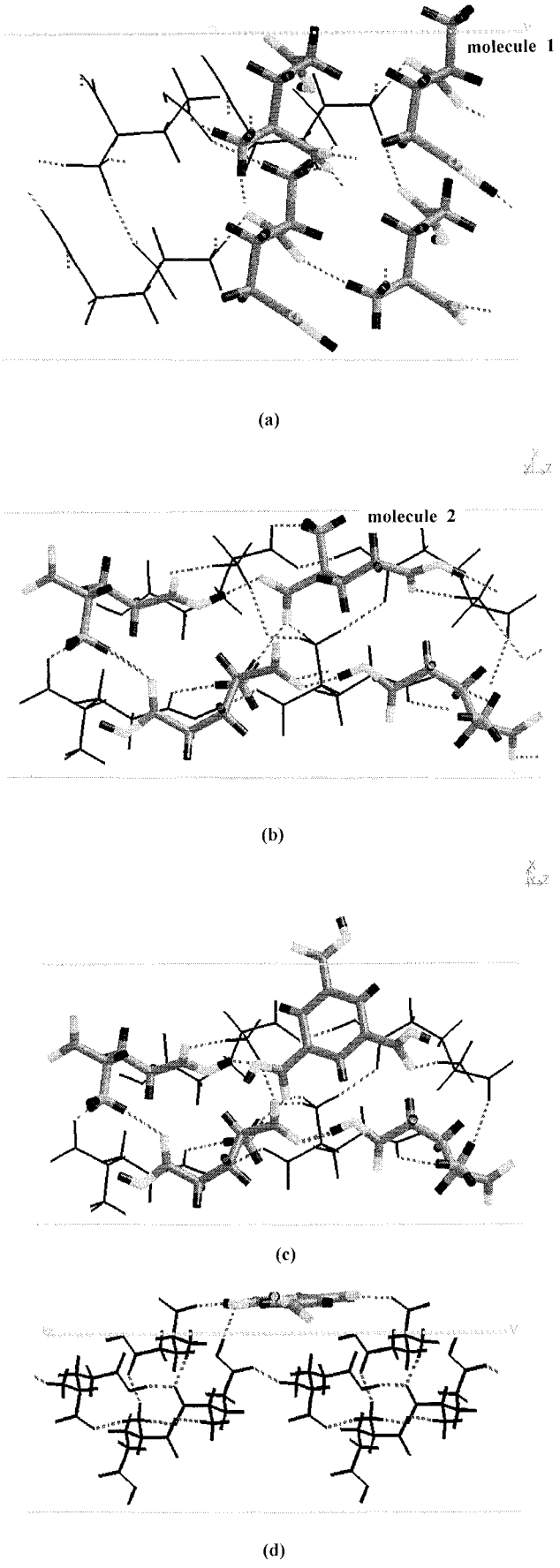

Figure 5. Molecular modeling of crystal surfaces: (a) the {111} and {$\bar{1}\bar{1}\bar{1}$} surfaces of α L-glutamic acid, (b) the {101} surfaces of β L-glutamic acid, (c) trimesic acid occupying a site on the (101) surface of β L-glutamic acid, (d) trimesic acid bound to the {110} surface of α L-glutamic acid.

Table 3. The Influence of Additives on the Appearance and Stability of the β Form of L-Glutamic Acid

additive	time for α to appear (min)	relative stability of α (−)[a]	aspect ratio of β crystals a:c (−)	length of β crystals along [001] (μm)
pure	5	1	1:4	40−45
glutaric acid	20	2	1:3	10−15
2-methylglutaric acid	30	3	1:5	10−15
transglutaconic acid	50	10	1:2	13−18
trimesic acid	35	1000	1:1	6−9

[a] The relative stability of α has been defined as time taken for 75% conversion to β in presence of additive/time taken for 75% conversion to β in pure solution.

dimensional network parallel to the surface. It is this feature which makes conformational discrimination possible since it precludes surfaces of one conformation from accepting molecules of the other and means that the requirement for any successful additive molecule is that it should have the appropriate conformation and on entering the surface should be capable of taking part in the hydrogen bonding network with minimum disruption. To achieve this the 1,5-dicarboxylic acids described above were selected as additives. Such molecules, lacking the protonated amino group, would clearly be capable of entering the growing surfaces only in sites at which the amino group plays little or no role in the in-plane hydrogen bonding networks. For the {111} and {$\bar{1}\bar{1}\bar{1}$} surfaces of α (which comprise two sets of nonequivalent Friedel pairs) only the molecule in position 1 (Figure 5a) on the {111} faces represents such a site, while for the {101} faces of β the equivalent site is defined by molecule 2 (Figure 5b). In both sites a 1,5-dicarboxylic acid of appropriate conformation could enter the surface with its carboxyl functionalities substituting for those of glutamic acid. The missing amino group would not be noticed until the next growth layer were laid down when its absence, or substitution for a bulkier moiety, would disrupt and inhibit growth. In this way it becomes clear that the 1,5-dicarboxylic acids selected, being of increasingly rigid and β-like conformation should be able to selectively prevent the growth of β crystals and hence stabilize the α phase. Figure 5c, constructed simply on the basis of a geometric fit, illustrates the expected incorporation of trimesic acid into the (101) face of the β structure, showing how the carboxylated phenyl ring points out into the solution to disrupt the addition of further L-glutamic acid molecules and inhibit growth. Further, those additives capable of accessing α conformations should influence only {111} and not {$\bar{1}\bar{1}\bar{1}$} faces of α crystals giving rise to polar morphologies.

Experimental Verification. To test these predictions experiments were performed using the protocols described above to determine the effects of these additives on the appearance, stability, and morphologies of the individual polymorphic forms. The results of experiments performed in stirred vessels at 38 °C with 10 mol% of additive are summarized in Table 3 which records four aspects of the crystallization process: the time taken for the initial appearance of α crystals, the stability of these α crystals in terms of their rate of transformation to the β structure, the a:c aspect ratio, and size of the final β crystals. A number of factors are clear from these data.

Firstly, all these additives have some influence on the crystallization of α with nucleation delayed significantly compared to pure solution. This influence was confirmed by examining the morphologies of α crystals grown at 18 and 38 °C in the presence of the additives. As expected, with glutaric and 2-methylglutaric acids crystals developed an increasingly polar morphology. At 10 mol% they appeared as pyramids (Figure 4c), in which only one set of the Friedel opposites {111} were present. This confirms that these molecules do indeed only access the surface site indicated in Figure 5a, replacing

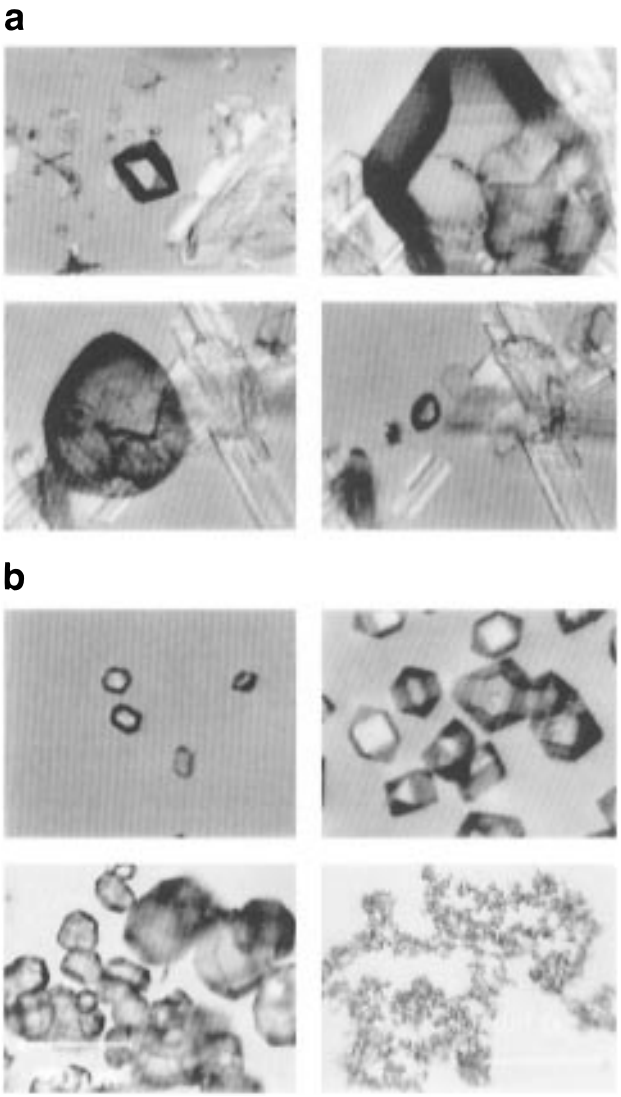

Figure 6. Time lapse micrographs of the α ⇒ β solution mediated phase transition (a) (upper left, 20 min; upper right, 90 min; lower left, 150 min; lower right, 220 min) in pure solution and (b) (upper left, 35 min; upper right, 60 min; lower left; 1 week; lower right, 3 weeks) in the presence of 10% trimesic acid.

glutamic acid molecules by virtue of their ability to adopt α-like conformations. In the presence of transglutaconic and trimesic acids, however, α crystals displayed a morphology (Figure 4d) in which the previously unobserved {110} faces appeared. This unexpected result is consistent with the binding of these additive molecules to carboxylic acid groups of adjacent surface glutamic acid molecules whose separation (0.71 nm) can only be matched when the additive molecules adopt the β conformation. This is shown in Figure 5d for trimesic acid. Thus, on the basis of the morphological modification of α alone the expected conformational states of the additives are confirmed although their interactions with the α structure are more complex than predicted, being modified by binding to {110} surfaces.

Secondly it is clear from Table 3 that the major thesis of this study is proven, namely that additives which mimic the conformation of molecules in the thermodynamically stable structure are able to kinetically stabilize the metastable polymorph. Thus, in a pure, stirred, L-glutamic acid solution at 38 °C most of the α crystals have disappeared after 35 min to be replaced by β. This transformation time is equivalent to a relative stability of unity as defined by Table 3. With glutaric and 2-methylglutaric acids which can access both α and β conformations the selectivity between the polymorphs is limited, and this time is merely doubled. For transglutaconic and trimesic acids however, it is extended by an order of magnitude and for up to 3 weeks, respectively, as expected in view of their strong preference for the β conformation and the relatively larger steric barrier to crystal growth offered by trimesic acid. Figure 6 shows two sequences of time-lapse photomicrographs taken during the solution mediated α ⇒ β transformation in pure unstirred solution and in a stirred solution containing 10% trimesic acid. For the pure system (Figure 6a) both rhombic, α, and needle, β, crystals are present after 20 min, and the sequential photographs focus on a central α rhomb which has grown to a size of about 100 μm after 90 min. Subsequent dissolution yields the situation after 220 min in which this α crystal has reduced in size and adopted a rounded morphology typical of a dissolving crystal, while the β crystals continue to grow. When trimesic acid is present (Figure 6b), no β needles are evident even after a week. The α crystals exhibit a modified morphology with the surface rounding due to dissolution only being evidence after 1 week. The final β product crystals are shown after 3 weeks to be small isometric crystals.

In the absence of stirring the effect of trimesic acid is dramatically enhanced with no evidence of β crystals after one month. The resulting β crystals show some decrease in size but no change in morphology in the presence of glutaric and 2-methylglutaric acids, while for transglutaconic and trimesic acids the a:c aspect ratio is decreased, and the crystal sizes are significantly smaller. This confirms that, as expected (Figure 5c) these additives attack the {101} surfaces, becoming more effective with increasing conformational rigidity. The decrease in size suggests that some changes in nucleation rate have taken place. Further studies on trimesic acid showed it to be active in preventing the appearance of β crystals for 1 week at levels as low as 0.1 mol% at 38 °C, while at 48 °C a 10% loading stabilizes α for a period in excess of 3 days.

Conclusions

Overall the results mirror well the predictions and serve as a powerful demonstration of the importance of molecular recognition at crystal surfaces in determining the outcome of the supramolecular assembly process operating in polymorphic systems. The possibility of using conformational mimicry to stabilize metastable structures of conformational polymorphs has been demonstrated for the first time and offers now a powerful tool in the development of robust processes in polymorphic systems. It is particularly gratifying and an indication of the predictive power of this strategy that the additives reported here were not found by a trial and error approach: they were the only ones selected for this task. Finally, it is noted that attempts to select additives which mimic the α conformation and hence lead to direct crystallization of β and nonadherence to Ostwald's Law were unsuccessful. Despite searching the Cambridge Crystallographic Database it did not prove possible to find a molecule with sufficient rigidity to mimic only the α conformation.

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