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Simulation of Energetic Stability of Facetted L-Glutamic Acid Nanocrystalline Clusters in Relation to Their Polymorphic Phase Stability as a Function of Crystal Size

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A molecular modeling approach is used to study the stability of different polymorphic forms of L-glutamic acid through building and optimizing molecular clusters of different sizes and shapes with the latter corresponding to the predicted crystal growth morphologies. The results reveal that the initially nucleating (according to Oswald rule) metastable (α) form is the more energetically stable form at small cluster sizes of ca. 200 molecular units, whereas the stable (β) form is more stable when the cluster size is larger.

The formation of metastable polymorphic phases represents a topical area for current research in solid-state chemistry reflecting its status as a useful exemplar for understanding molecular recognition and self-assembly. Polymorphism is also an area of significant industrial and commercial importance because of its impact on the performance of commercial product formulations, notably those associated with variation in pharmaceutical bioaviability due to polymorphic transformations. This latter area has also affected litigation related to the protection of commercial intellectual property, e.g., that associated with patent extension and bypassing.[1]

The interrelationship between crystal formation kinetics and polymorphic form has been the subject of long-standing debate. Oswald's rule of stages[2] proposes that the least thermodynamically stable polymorphic forms should be those that are initially created, reflecting the lower energy penalty associated with their formation. A theoretical interpretation of this rule was given by Stranski and Tomanow[3] who showed that, more often then not, metastable phases have higher nucleation rates, providing the crystallizing system is not too far below the phase transformation point. Ostwald's rule would suggest that there should be a thermodynamic driving force such that a metastable phase would subsequently transform to a more stable phase. This could take place either via an enantiotropic (solid-state) or a monotropic (solvent-mediated) phase transformation process until eventually the ultimate, stable phase is attained. Such effects, of course, depend on the compound in question and the nature of the crystallizing environment (solvent choice, reactor hydrodynamics, equipment design, process conditions, etc.). It is also well-known that metastable polymorphic forms are often created under nonideal crystallizing conditions, notably those associated with fast crystal growth rates where the solute supersaturation can be expected to be rather high. Such observations have led to metastable polymorphic phases being referred to as kinetic forms, reflecting the fact that their nucleation and growth rates tend to be higher than those for the more stable phases. However, which of these two stages associated with the crystallization process, i.e., nucleation or growth, plays the dominant role in the formation of a metastable polymorphic phase is not clear at this time.

Although classical homogeneous nucleation theory has always assumed solute clustering prior to nucleation,[4] it has been only recently that detailed experimental evidence has been provided indicating that significant solute ordering takes place within the solution prior to nucleation and crystal growth.[5] Yau and Velkov[6] have supported this by observing apoferritin nucleation clusters. The structure of such prenucluation clusters has been the subject of much debate. In this respect, it is, perhaps, a rational assumption that within a supersaturated solution the solute molecules would be likely to aggregate, hence forming embryonic prenucleation clusters which might be expected to be similar structurally to those associated with the still-to-be-formed crystals.[7] Yau and Velikov confirmed this for the above case of apoferritin in which the arrangement of the constituent molecules was found to be identical to that known to exist within the crystal structure associated with the microscopic protein crystals. Other authors, however, believe that such nuclei clusters might well differ substantially from the eventual crystalline phase in both composition and structure.[8,9] For example, it has been proposed that the nuclei might not even be crystalline but rather exhibit a disordered, liquidlike molecular aggregate structure[9] having no defined long-range 3-D order.

In particular, for polymorphic systems, it might be expected that embryos for all the known polymorphic forms could, perhaps, simultaneously exist within the solution phase. Such clusters on a molecular basis might be expected to mimic the crystal chemistry of the eventual phase developed,[10] i.e., that molecular ordering within the nucleus could be expected to act as a self-assembly template for the subsequent growth of the resulting polymorphic phase. So far, however, there is to our knowledge no experimental evidence to prove this hypothesis.

Hence, this short communication considers the proposition that, of the two potential rate-limiting processes, it is nucleation that forms the key stage in directing the formation of metastable

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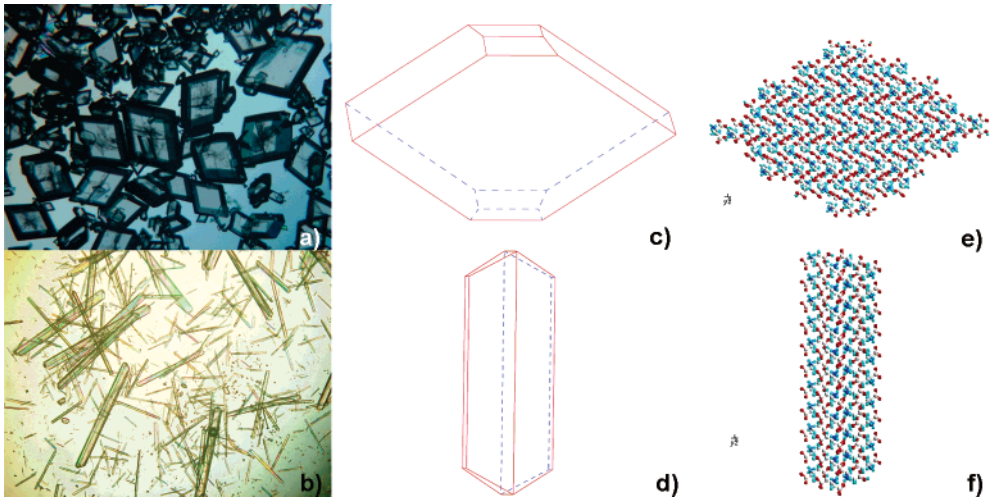

Figure 1. Experimentally observed (aqueous solution at ca. 2 wt %) crystals for (a) α-form L-glutamic acid reveals a prismatic shape, while (b) β-form is needlelike. Morphological simulations of the crystal morphology of (c) α- and (d) β-forms are in good agreement with the experimental observations. Shaped molecular clusters for (e) α- and (f) β-forms.

polymorphic forms. This supposition draws down on the basic kinetic laws associated with homogeneous solution nucleation in which the critical cluster size r^* needed for a molecular nucleation embryo to develop into a stable crystalline structure is given by[4]

$$r^* = \frac{2\gamma\nu}{kT\sigma^2} \tag{1}$$

where σ is the supersaturation, γ is the interfacial specific surface energy, ν is the molecular volume, k is the Boltzman constant, and T is the absolute temperature.

Inherent in this hypothesis is that at high supersaturation the critical cluster size would be expected to be small, and vice versa. Hence, an attractive proposition is to consider whether, at the small molecular cluster sizes associated with the formation of metastable polymorphic forms, the metastable phase might, in fact, be more thermodynamically stable than the stable form. Such a proposition is, of course, difficult to verify experimentally, given the lack of measurement techniques capable of characterizing crystal size and crystallographic order at the nanocrystalline-scale sizes expected to be important at nucleation. Hence, in this study, we have sought to test this hypothesis via the use of molecular modeling and minimization techniques to study the relative thermodynamic stability of molecular clusters assessed as a function of cluster size. In this modeling approach, we have considered the clusters to have a defined crystal shape based upon the material's crystal growth form as can be predicted using morphological modeling techniques via the attachment energy model.[11] This hypothesis, i.e., that the critical nucleus might be shaped, has also previously been suggested by a number of authors.[6,7,12] It is also noteworthy that the modeling approach adopted in this study does not include entropic effects, albeit a factor which should not be too significant for such a low molecular weight system, nor does it take into account the effects of solution binding at the cluster surfaces or surface reconstruction effects which may also play an important role. The molecular clusters are assumed to have the same internal molecular arrangement as those involved in the crystal structures of the known polymorphic forms. This model is then confronted with an examination of the relative stabilities of the α and β polymorphic forms of L-glutamic acid.

L-Glutamic acid is often used as a representative pharmaceutical compound, albeit one having a comparatively simple molecular structure with a crystal structure having both undirected van der Waals and directed hydrogen intermolecular bonds.[13] L-Glutamic acid crystallizes in one of two polymorphic forms, the metastable α-form and the stable β-form.[14,15] Crystallization of L-glutamic acid from aqueous solution reveals that the metastable α-form crystallizes at high cooling rates whereas the stable β-form crystallizes at lower cooling rates.[14] A polymorphic monotropic solvent-mediated transformation mechanism has been previously reported.[14,16,17] The two phases show contrasting crystal morphologies; the metastable α-form crystallizes as prisms (Figure 1a), while the stable β-form crystallizes with a needlelike shape (Figure 1b). Lattice energies, which were calculated using the Momany force field[18] following relaxation of the hydrogen atom positions and calculation of the partial electronic charges using *MOPAC* within the MNDO formalism[19] were found to be −41.23 kcal/mol and −42.69 kcal/mol, respectively, in good general agreement with the experimentally observed polymorphic stabilities and the known sublimation enthalpies for representative amino acids.[20]

The crystal habit of the two forms was simulated via molecular modeling studies using the atom−atom approximation and the attachment energy approach[11] using the HABIT98 program.[21] The simulated morphologies reveal a good agreement with respect to the observed crystal morphologies (Figure 1c and d). The simulated 3-D morphological shapes were used to create shaped molecular clusters of different sizes using the POLYPACK program[22] (Figure 1e and d). The energies of the molecular clusters were calculated using the Cerius[2] package and again following further optimization using the Momany force field[18] with the resulting energies being plotted as a function of the cluster size for both the nonoptimized and optimized clusters and for both the polymorphic forms (Figure 2a and b). The results were fitted with a power law function which enabled calculation of cluster energy as a function of size. This revealed the metastable α-form to be energetically more stable compared to the β-form at small cluster sizes. In this, it can be seen that, at the small cluster sizes, a predominance of the metastable α-form on energetic grounds is expected, with the difference in the energy first becoming smaller as the cluster size increases with a crossover point in relative cluster energy taking place at crystal sizes with 40 and 207 molecules, respectively, for the nonrelaxed and relaxed polyhedral clusters, followed by the stable polymorphic form being expected to predominate at the larger sizes. This is further illustrated by

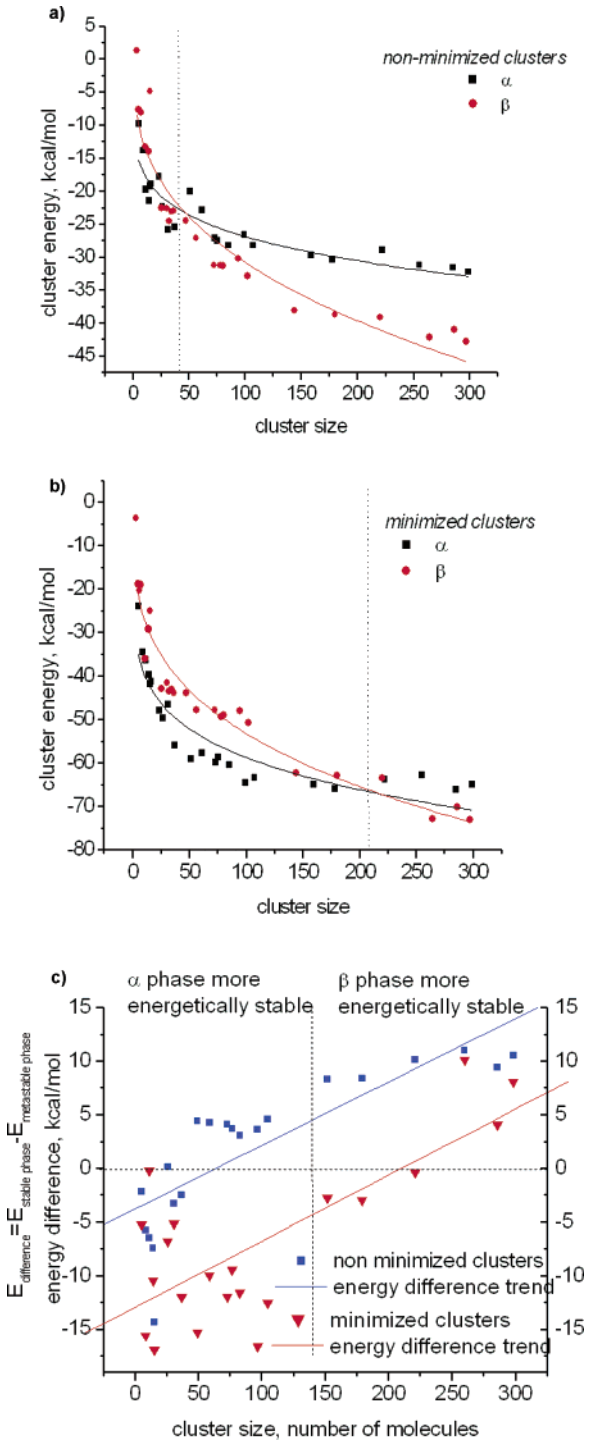

Figure 2. Energy minimization of polyhedral molecular clusters for the α and β polymorphic forms of L-glutamic acid showing that the metastable α-form is more stable at small cluster sizes: (a) nonoptimized structures; (b) optimized structures; (c) differential energies.

Figure 2c, which shows that the differential cluster energies, i.e., $E_{\text{stable}}-E_{\text{metastable}}$, increase from negative to positive with the cluster size for both the nonoptimized and optimized configurations.

Hence, in conclusion, this study reveals that for L-glutamic acid it is the metastable α-form, not the expected β-form, that should be anticipated to be the stable form at high supersaturations when the nucleation cluster size is small, and vice versa. Caution, however, is necessary in assessing the general applicability of this work, being mindful of both the base assumptions stated earlier and the lack of experimental verification so far. However, further studies are currently underway to test the more general suitability of this model to other polymorphic systems. Nevertheless, the current study is, we believe, helpful in reviewing the issues associated with deriving a unified approach for understanding the interplay between molecular, nanocrystalline, and microcrystalline properties in relation to crystallization kinetics in order to address the crystallographic science underpinning Ostwald's rule of stages.

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