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Synthesis of DL-Alanine Hollow Tubes and Core-Shell Mesostructures

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Abstract: Three double hydrophilic block copolymers were used as crystal-growth modifiers of DL-alanine to generate amorphous precursor nanoparticles that undergo subsequent mesoscopic transformation to core-shell mesostructures and hollow tubes with quadratic cross-sections. The growth sequence can be stopped at various stages so that a series of intermediates between amorphous core- and crystalline-shell particles and tubes can be obtained. Time-dependent conductivity, TEM, SEM, and environmental scanning electron microscopy (ESEM) measurements were used to obtain a better understanding of the crystallization process, and a formation mechanism for the generation of the tubes is proposed. Na_2SO_4, NaCl, and $NaNO_3$ as salts differ in their influence on the crystallization behavior of alanine by changing the solubility of alanine and by decreasing the stability of the intermediate particles. Core-shell mesostructures that formed in the dissolution–recrystallization process were captured as the transformation rate was decreased by the addition of copolymers or salts. Hollow tubes with quadratic cross-sections are the final product of the transformation process.

Keywords: alanine · amorphous materials · copolymers · mesoscopic transformation · self-assembly

Introduction

The control of crystallization processes is one of the most important techniques in the preparation, purification, and application of solid substances and has been a focus of chemistry for a long time. Conventional crystallization processes are no longer considered to be exclusively a solution-mediated lattice formation from ions or molecules. An aggregation-mediated crystallization via mesoscopic building units seems to be relevant in many cases.[1] For example, mesoscale assembly and transformation take place for inorganic crystalline solids, such as iron oxides,[2] cerium oxide,[3] copper oxalates,[4] and copper oxides.[5] Often, the first precipitated species is an amorphous precursor, which subsequently undergoes mesoscopic transformation. Such amorphous precursors even seem to be relevant for biomineral formation,[6] and can be observed at the early stage of biomineralization (e.g., in sea urchin embryo spiculogenic cells).[7] Thus, polymer-controlled mineralization has rapidly developed into a promising field.[8] Double hydrophilic block copolymers (DHBCs)[9,10] have been developed and used as directing agents for the synthesis of inorganic materials with complex higher-order hierarchical structures.

An especially fascinating class of crystals assembled by mesoscale transformation are the so-called mesocrystals, which are colloidal crystals with nonspherical and perfectly aligned building units.[11,12] Both inorganic and organic mesocrystals, such as calcium carbonate and amino acids, were recently synthesized by our group.[11,13] However, the exact mechanism of their formation is yet unknown. Thus, model systems are considered as suitable to investigate these structure-formation mechanisms and also to learn about complex biomineralization mechanisms. For that, morphosynthesis of amino acid crystals seems to be an appropriate choice, as additional control parameters, such as chirality or molecular dipole moments, can be used for crystallization control. The control of crystallization of these polar organic molecules by DHBCs appears to be well suited to study this effect. Moreover, relevant parameters for the self-assembly of nanoparticles and the nature of the forces aligning the primary nanoparticles might be elucidated. In this study, we show that DHBCs can be used to induce the formation of nanoparticles of DL-alanine, which undergo self-assembly and subsequent mesoscopic transformation to core-shell and hollow alanine rods. Three DHBCs with different functional segments were used as polymeric additives to study the crystallization process of DL-alanine: 1) a poly(ethylene

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glycol)$_{3000}$-oligopeptide conjugate with [(L-glutamic acid)-(L-glutamic acid)-(L-serine)]$_3$ as peptide sequence (PEG-EES),[14,15] 2) a poly(ethylene glycol)$_{5000}$-*block*-poly(ethylene imine)$_{1200}$ in which the PEI-block was modified with (arabino-hexonic acid)$_{500}$ (PEG-PEI/AHA),[16] and 3) poly(ethylene glycol)$_{5000}$-*block*-poly(ethylene imine)$_{1200}$ with an (L-histidine)$_{300}$ modified PEI-block (PEG-PEI/H) prepared as described previously.[16] Moreover, the effect of different anions, such as SO_4^{2-}, Cl^-, and NO_3^- was studied in the crystallization process to obtain further insight into the mechanism of crystallization.

Results and Discussion

The unmodified crystallization of DL-alanine from supersaturated solution in the absence of additives results in needlelike crystals, as reported by Lahav et al.[17] Herein, the PEG–peptide conjugate (PEG-EES) was used as a polymeric additive in the alanine crystallization process. This is composed of a poly(ethylene glycol) block with $M_n = 3000$ and a small oligopeptide segment sequenced as [(L-glutamic acid)-(L-glutamic acid)-(L-serine)]$_3$ ((EES)$_3$).[14,15] The addition of 3.3 g L^{-1} PEG-EES to the DL-alanine crystallization mixture results in a fast crystallization process and large amounts of colorless precipitate were formed within 3 h. Figure 1 shows the SEM image of the DL-alanine crystals obtained. Needle-like alanine samples with hollow or tubular characteristics, a main axis longer than 100 μm, and a tube diameter of about 1–1.5 μm were observed. A high-magnification image of the DL-alanine tube shown in the inset of Figure 1 suggests that the tubes have well-facetted prismatic morphology with a relatively uniform wall thickness of 80–120 nm and quadratic cross-sections. The hollow tubes are morphologically similar to hollow CaF_2 tubes that were formed in ionic-liquid emulsions,[18] however, they were less defined than the hollow rods reported here and their formation mechanism was yet unclear. The prismatic morphology of the alanine particles indicates that the tubes are presumably single crystalline, grow along the *c* direction, and exhibit the [210] planes on their sides. This can be illustrated by a computer-generated morphology, as shown in Figure 2, according to the work of Lahav et al.[17]

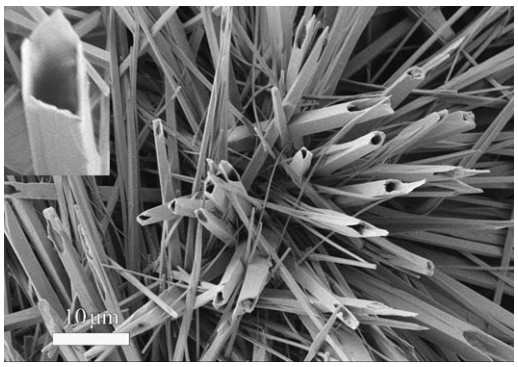

Figure 1. SEM image of DL-alanine tubes formed under supersaturated conditions in the presence of 3.3 g L^{-1} of block copolymer PEG-EES at RT for 3 h.

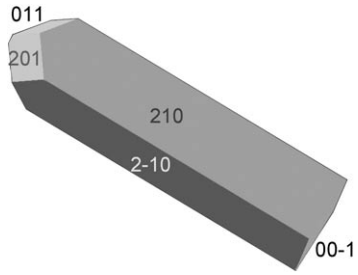

Figure 2. A computer-drawn morphology of DL-alanine crystals, according to Lahav et al.[17]

The X-ray diffraction pattern of the DL-alanine tubes is consistent with the orthorhombic structure of DL-alanine (Figure 3). The reflex intensity of the (410) peak is, however, much higher than that of the default orthorhombic DL-alanine crystals, and the reflex intensities of (400) and (112) are much smaller. This observation already indicates the presence of an altered crystallization process.

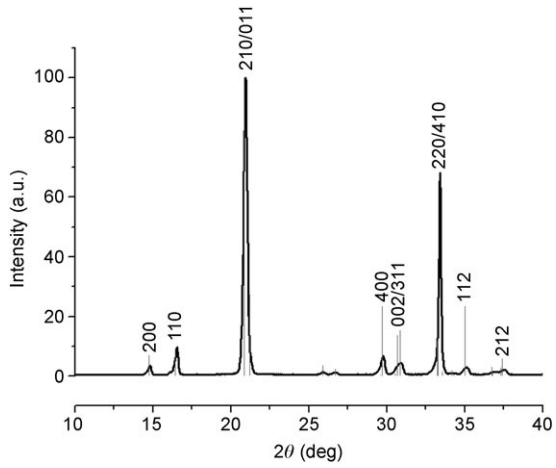

Figure 3. XRD pattern of DL-alanine tubes obtained in supersaturated solution in the presence of PEG-EES. Vertical lines are the theoretical XRD patterns of DL-alanine.

The conductivity of the supersaturated DL-alanine solution with PEG-EES decreased quickly during the first 30 min, followed by a slow decrease during the subsequent precipitation period, indicating a rapid particle nucleation prior to the slow crystallization (Figure 4). Dynamic light scattering (DLS) confirmed that the primary building blocks that formed directly after the mixing and cooling process are particles with an average hydrodynamic radius of about 30 nm. Aggregates with sizes of about 240 nm appeared quickly within approximately 10 min during the early stage, as could be deduced from the DLS measurements.

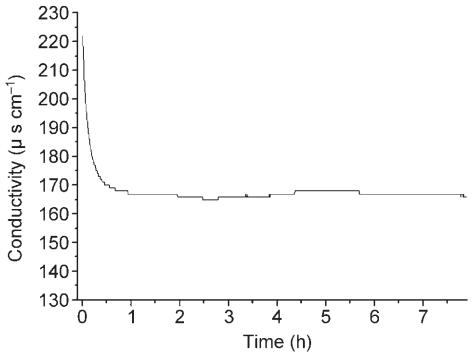

Figure 4. Time-dependent conductivity of the synthesis of the supersaturated DL-alanine aqueous solution in the presence of 3.3 g L^{-1} PEG-EES.

If the concentration of PEG-EES was reduced to 0.67 g L^{-1}, the rate of crystallization of DL-alanine decreased and the formation of a smaller amount of precipitate was observed after 3 h. For this concentration of PEG-EES, one-dimensional core-shell mesostructures with a size of about 200 nm and a distinct inner section filled with aggregated particles was observed (Figure 5a). The sectional size of the one-dimensional core-shell structure is about 2–4 μm and the length reaches more than 100 μm. It is supposed that the

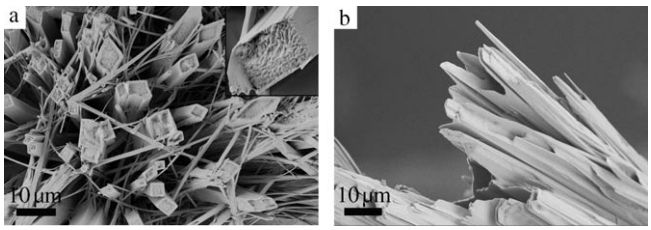

Figure 5. SEM images of one-dimensional DL-alanine core-shell structures synthesized at RT for 3 h in the presence of PEG-EES (a), and DL-alanine hollow tubes after the inner amorphous nanoparticles were dissolved (b). The concentration of copolymer was 0.67 g L^{-1}.

shells consist of DL-alanine, crystallized in an orthorhombic morphology, whereas the particles in the center of the core-shell structure correspond to amorphous intermediates. Unfortunately, the separate investigation of the crystalline shell and the amorphous interior by application of selected-area electron diffraction techniques (SAED) was not possible because the alanine crystals decompose rapidly under the electron beam. Therefore, a partial dissolution method was applied to verify the hypothesis of a crystalline shell and an amorphous interior. Because an amorphous structure is usually less stable, a dissolution faster than that of the crystalline material should occur.[19] For that, a glass substrate with the core-shell mesostructures was inserted into water for several seconds. After removal from the water, a partial dissolution of the alanine occurred, as verified by an SEM image (Figure 5b, three seconds water extraction). Most of the spherical, amorphous structures in the interior of the tubes were indeed dissolved, and clean hollow tubes were obtained, confirming our hypothesis of an amorphous, more soluble core and a crystallized shell.

Further decrease of the PEG-EES additive concentration to 0.17 g L^{-1} leads to a mixture of needles and tubular aggregates, which is stable even after 9 h crystallization time. As all processes are slowed down significantly due to lower additive concentrations, it is not surprising to find tubes even more extensively filled with amorphous intermediates. Therefore, lowering of the polymer concentration enables the visualization of the early stages of the crystallization and morphogenesis processes.

The formation of the DL-alanine core-shell mesostructures with amorphous nanoparticles in the interior is not unique to the addition of PEG-EES. In fact, it seems to be a more general phenomenon, largely independent of the nature of the polymeric additive. To prove this, two other block copolymers PEG-PEI/AHA and PEG-PEI/H were utilized as additives. These block copolymers consists of a linear PEG with $M_n = 5000$ g mol^{-1} and a branched polyethylene imine (PEI) with a $M_n = 1200$ g mol^{-1}. The PEI block was modified either with arabino-hexonic acid (AHA; $M_n = 500$) resulting in PEG-PEI/AHA or with L-histidine (H, $M_n = 300$) leading to PEG-PEI/H. The application of these polymers was described by Wohlrab et al.[11]

If PEG-PEI/AHA was added as a polymeric additive in the crystallization of DL-alanine, only a few particles could be found in the solution even after seven days. This can be explained because PEG-PEI/AHA promotes the nucleation and crystal growth of DL-alanine to a much lesser degree than does PEG-EES. However, similar boxlike DL-alanine mesostructures with crystallized shell and an interior filled with amorphous particles were obtained (Figure 6a,b). The sides of the hollow boxes are about 8 μm in length, and the

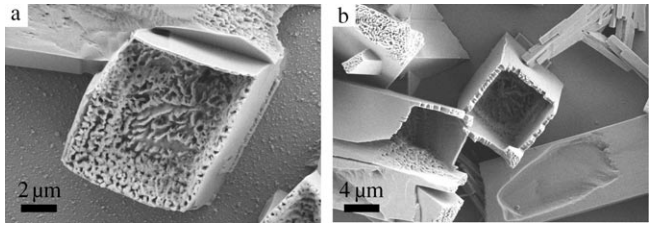

Figure 6. SEM images of the DL-alanine core-shell mesostructures synthesized at RT for 7 d in the presence of 3.3 g L^{-1} of copolymer PEG-PEI/AHA.

thickness of the walls could be determined to be about 500 nm. The surface of the walls appears very smooth, indicating that the walls crystallized in an undisturbed manner. However, some amorphous nanoparticles, as well as steps on the section of the wall, were observed. As nucleation of DL-alanine crystallization proceeds in this case over a longer time span, it is likely that this image captures different intermediate morphologies of the crystal-growth process. It could be supposed that the core-shell mesostructure in Figure 6a

finally transforms to the boxlike crystal structure shown in Figure 6b.

PEG-PEI/H was applied as a third polymeric crystal-growth modifier in a concentration of 3.3 $g L^{-1}$ while keeping the other conditions unchanged. Cubic DL-alanine particles with sizes of 3–4 μm could be obtained in solution after 9 h (Figure 7a,b). The particle shown in the inset of Figure 7a exhibits two rough faces consisting of precursor nanoparticles, whereas the other four faces appear as smooth crystal planes. The rough faces are considered to be the (001) face of the orthorhombic DL-alanine crystal structure. Hence, these mesostructures are related to the previously described structures obtained with the PEG-EES additive, although the growth in the *c* direction is limited.

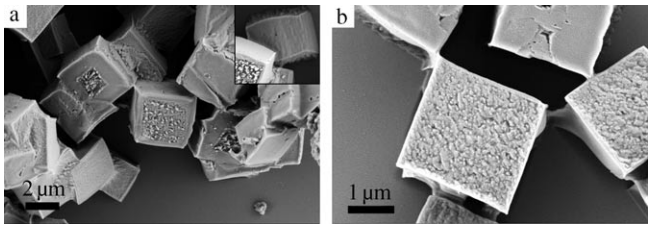

Figure 7. SEM images of DL-alanine synthesized in supersaturated alanine solution in the presence of 3.3 $g L^{-1}$ of PEG-PEI/H at RT for 9 h in the absence of salt.

Therefore, the different polymeric additives do not alter the general morphogenesis scenario of dissolving amorphous particle aggregates that recrystallize into hollow tubes with quadratic cross-sections. Nevertheless, the additives certainly have a strong influence on the kinetics of the crystallization reaction (PEG-EES, 3 h; PEG-PEI/AHA, 7 d; PEG-PEI/H, 9 h) until the first precipitates are observed.

To study the possible influence of salts on the crystallization behavior of alanine in the presence of the DHBCs, the addition of three different salts, Na_2SO_4, NaCl, and $NaNO_3$, was investigated. Because it facilitates a convenient rate of crystallization that is easy to monitor, the PEG-PEI/H was used as additive. By contrast, PEG-EES would lead to a very rapid formation of crystals and PEG-PEI/AHA would result in a very slow crystallization process.

DL-alanine precipitation was highly accelerated and was complete within one day following the addition of Na_2SO_4 at a concentration of 0.1 M to the supersaturated DL-alanine solution that included 3.3 $g L^{-1}$ of PEG-PEI/H. Figure 8a shows the SEM image of cubic crystals of size 2–5 μm that were obtained as the crystallization product. Following the Hofmeister series, the SO_4^{2-} anion is a strong "salting-out" ion.[20] Thus, the solubility of organic molecules is decreased, resulting in a massive nuclei formation of DL-alanine within a few minutes. Because the concentration of DL-alanine in the solution with Na_2SO_4 is lower than that in the solution without Na_2SO_4, the crystal growth along the *c* direction is slower, resulting in the formation of cubes instead of needles.

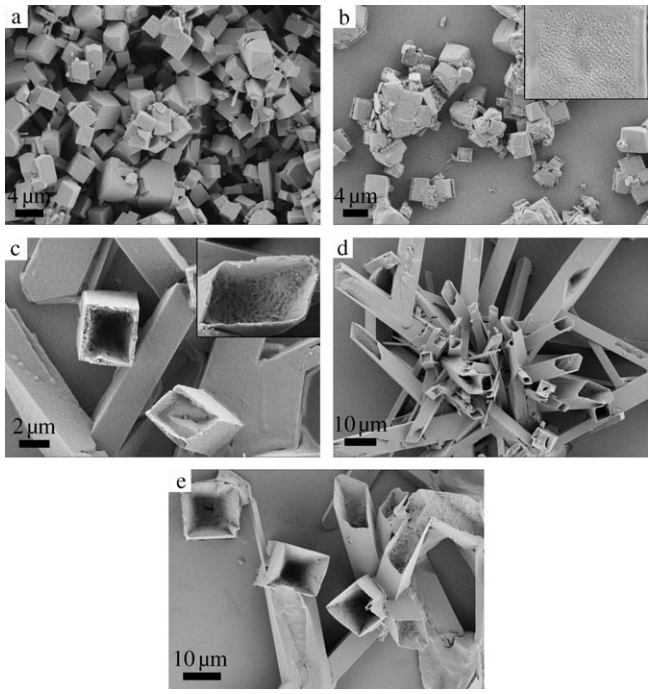

Figure 8. SEM images of DL-alanine synthesized in supersaturated alanine solution in the presence of 3.3 $g L^{-1}$ of PEG-PEI/H at RT after the addition of different salts: a) reaction time: 1 d, $[Na_2SO_4] = 0.1$ M; b) reaction time: 6 h, [NaCl] = 0.1 M; c) reaction time: 6 h, [NaCl] = 1 M; d) reaction time: 16 d, [NaCl] = 1 M; e) reaction time: 16 d, $[NaNO_3] = 1$ M.

The Cl^- anion is found in the middle of the Hofmeister series and can be considered as neither a strong "salting out" anion nor a strong "salting in" anion. Therefore, cubic morphologies of the DL-alanine crystals can be observed (Figure 8b) that are similar to that without salt addition, as displayed in Figure 7. Nanoparticles with sizes between 37 and 62 nm are visible on the surface of the cubes, suggesting an inner amorphous, particular structure of the cube. The walls of the cubes are smooth and appear to be well crystallized, which is similar to Figure 7. Boxlike core-shell structures were obtained at NaCl concentrations of 1 M (Figure 8c). The diameters of the amorphous particles are about 70–140 nm for 1 M NaCl, which is greater than that of the precursor particles observed at 0.1 M NaCl, as seen by comparing the insets of Figure 8b and c. This was attributed to the increased ionic strength, decreasing the colloidal stability and leading to the early aggregation of the primary particles. As for all other presented examples, these boxlike core-shell mesostructures are most likely composed of a crystallized shell and amorphous core, similar to the results presented in Figures 5 and 6. The box-like DL-alanine particles grew into tubes after 16 days (Figure 8d). This longitudinal growth of the tubes is probably the result of a mass transfer process (sacrificial crystallization) of the material forming the amorphous particles in the interior of the crystallized shell. Short tubes of about 10 μm in length grew on the glass substrate within 16 days upon addition of a strong "salting-in" anion, such as NO_3^- (Figure 8e), although the

ionic strength is comparable to that in experiments with NaCl. Less DL-alanine precipitated in the solution with $NaNO_3$ than in the solution with NaCl or Na_2SO_4. This is because $NaNO_3$ increased the solubility of DL-alanine in aqueous solution so that DL-alanine precipitation occurs at a much slower rate. Although DL-alanine solubility and colloidal stability, which are coupled to the ionic strength, certainly influence the morphology of the formed mesostructures, it is impossible to predict the morphology of the formed structure from the chosen experimental conditions. However, the rate of crystallization is predictable as this corresponds to the findings for the variation of the DHBC additives, as described above.

The experiments discussed above showed that it is possible to generate hollow DL-alanine tubes from sacrificial aggregates of amorphous precursor particles under the control of polymeric additives. To investigate the underlying mechanism, a time-dependent SEM study of the species formed upon the addition of PEG-EES as polymeric additive was performed. Particles precipitated on a glass substrate could already be captured after 5–30 min in a supersaturated DL-alanine solution with 3.3 $g L^{-1}$ of PEG-EES (Figure 9a–d). Primary amorphous particles of about 20–30 nm are formed and aggregation to structures with a diameter of 200–500 nm occurred within a few minutes of mixing the reactants and cooling the solution from 65 °C to room temperature (Figure 9a). This is coincident with the DLS measurements in solution. These aggregates partially dissolve and recrystallize on the aggregate exterior to form a "seed box" and, thus, show one-dimensional morphologies with core-shell structures or ill-defined crystalline shells, which distorted under the electron beam of SEM (Figure 9b). As a consequence, smaller particles, as observed in the background of Figure 9a, are no longer detectable as background.

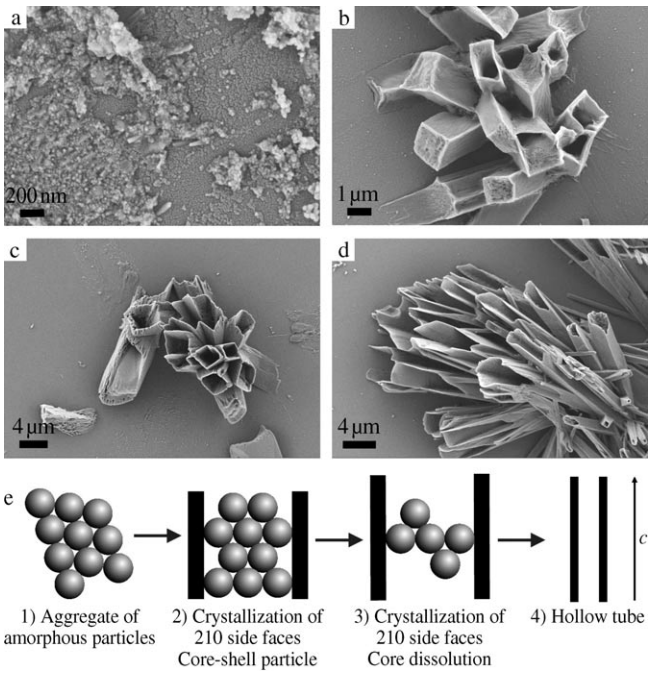

Figure 9. SEM images (a–d) of DL-alanine tubes formed in the early stage of reaction (5–25 min) in supersaturated alanine solution with 3.3 $g L^{-1}$ of block copolymer PEG-EES: a,b) 5 min, c) 15 min, and d) 25 min. The schematic graph (e) gives the formation mechanism of DL-alanine tubes.

Instead, short tubes could be observed after 15 min, although core-shell mesostructures or aggregates of amorphous nanoparticles are still found (Figure 9c). One-dimensional tubular structures similar to that in Figure 1 are obtained after 25 min (Figure 9d).

At high levels of supersaturation, amorphous particles of about 20–30 nm are generated in the entire solution, and these can aggregate to form particles with a diameter 200–500 nm at the early stage. At lower levels of supersaturation of alanine, due to the initial formation of a large number of primary particles and aggregates, the nucleation rate is decreased. This can be accounted for by the strong dependence of the nucleation rate on the level of supersaturation.

These findings were not only revealed by the microscopy time series as presented above (Figure 9a–d), but were also supported by conductivity measurements, which show a strong drop in conductivity of the solution prior to the observation of macroscopic particles (Figure 4). The associated DLS observation of nanoparticles with a radius of about 240 nm already at the early reaction stage indicates the strong tendency of the primary building blocks to aggregate. The amorphous nature of the primary particles was demonstrated by the dissolution experiment (Figure 5). The conductivity remains almost constant in the second dissolution–recrystallization stage (Figure 4), and the core-shell mesostructures transform to hollow rods with crystallized walls (Figures 1 and 9b–d). In this reaction step, the amorphous particles dissolve according to the Ostwald rule of stages, and lead to a recrystallization at the exterior of the amorphous particle aggregates under the control of the negatively charged DHBC (Figure 5). The dissolution process was also proven by results of environmental scanning electron microscopy (ESEM). The intermediate amorphous core/crystallized wall mesostructures were isolated at the early reaction stage of the alanine system with 3.3 $g L^{-1}$ of block copolymer PEG-EES. This alanine intermediate sample was subjected to ESEM. The temperature was decreased to 1.2 °C under vacuum. The environment of the sample was humidified by decreasing the vacuum from 1 Torr to 4.8 Torr. Figure 10a shows the core/shell mesostructures at the early stage. Wormlike pores could be observed after 3 min (Figure 10b), which are induced by the dissolution of amorphous structures under humidity. Figure 10 provides direct evidence for core dissolution in the DL-alanine crystallization process by introducing humidity under ESEM conditions. However, recrystallization onto the exterior crystalline faces cannot take place, due to the lack of mobility and mass transport. Consequently, only a decrease in volume of the amorphous interior can be observed, due to the formation of the denser crystalline phase. Overall, the material removal/compaction becomes quite apparent. Partial beam damage to the sample was also observed; however, as the beam intensity was uniform over the entire sample, it cannot, therefore, be respon-

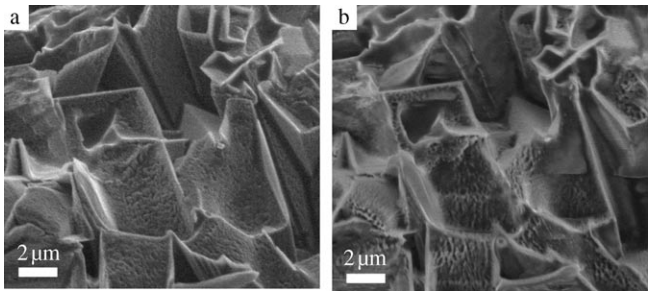

Figure 10. ESEM micrographs of the core/shell mesostructures formed in the early stage of reaction of the DL-alanine system with 3.3 gL^{-1} of block copolymer PEG-EES (a), and the partly dissolved core/shell mesostructures after 3 min of humidity exposure (b).

sible for the systematic formation of pores in the particle interior while the crystalline walls remain essentially unaffected.

According to the published crystal structure of DL-alanine (Figure 2), the (001) face of DL-alanine is positively charged and the (00$\bar{1}$) basal plane is negatively charged as the alanine molecular dipole extends along the *c* axis of the alanine rod.[17] Therefore, adsorption of the polyanion is expected to take place on the (001) face, blocking the extension of the alanine rods in the *c* direction. This is expected to be the primary means of controlling the DL-alanine hollow-rod axial ratio. More interestingly, the control of DL-alanine supersaturation, for example, by salt addition, allows for an additional kinetic tool to control the precipitation of amorphous precursor particles and the rate of the dissolution–recrystallization reaction. The overall growth mechanism deduced is summarized schematically in Figure 9e. Initially, amorphous particles aggregate (1). These particles act as a material depot and partly dissolve and recrystallize at the aggregate exterior on the observed (210) faces (2). After the early crystallization stage, this seed-box formed by four (210) faces grows along the *c* axis by classical molecule addition (3), and this process continues until the amorphous precursor particles in the interior of the forming hollow rod are used up, resulting in the finally observed hollow rod (4).

The dissolution–recrystallization mechanism of a sacrificial precursor structure was observed previously. Yu et al. reported hollow calcite spheres that grew at the expense of a sacrificial spherical vaterite core.[21] Therefore, similar dissolution–recrystallization scenarios appear to be plausible with amorphous particles, which can be generated for a large number of crystalline systems. The tube-formation mechanism by a dissolution–recrystallization process from an amorphous precursor has also been proposed in the formation of t-Se nanotubes.[22] A future related study will show that even the control of supersaturation by solvent mixtures can lead to hollow rods of various amino acids.[23] Thus, the mechanism reported here appears to be applicable to a variety of crystalline systems for the formation of hollow tubes with cross-sections deviating from the common spherical shape for nanotubes.

Conclusion

It is possible to generate hollow DL-alanine tubes with quadratic cross-sections from sacrificial aggregates of amorphous precursor particles. The growth sequence can be stopped at various stages so that a series of intermediates between amorphous-core/crystalline-shell particles can be obtained. Crystallization control can be achieved by the addition of DHBC and salt, so that a whole family of related morphologies is made available by using a single approach. We have revealed a novel mechanism for the production of hollow rods with nonspherical cross-sections, that is, the tubes are formed through a dissolution–recrystallization process from sacrificial amorphous precursor nanoparticles.

Experimental Section

Block copolymers, such as PEG-EES, PEG-PEI/AHA, and PEG-PEI/H, were used as additives to control the crystal growth of DL-alanine. PEG-EES was synthesized according to a solid-phase supported peptide synthesis by using the PAP-resin[14] and by following HBTU/NMP/piperidine protocols.[15] The structural identity of the product was confirmed by recording MALDI-TOF-MS measurements. PEG-PEI/AHA and PEG-PEI/H were synthesized by our group.[16] DL-Alanine was purchased from Aldrich. Double-distilled water was used in all experiments.

Supersaturated DL-alanine aqueous solution was obtained by cooling DL-alanine solution saturated at 65 °C to RT, that is, 3.7 g of DL-alanine was dissolved in 15 mL water at 65 °C. In a typical synthesis, 5 mg of block copolymer PEG-EES was added to a glass bottle with 2 mL supersaturated DL-alanine solution. A small glass substrate was put on the bottom of the glass bottle containing DL-alanine solution. The alanine aqueous solution was kept at RT for several hours. DL-Alanine was slowly precipitated onto the surface of the glass substrate at the bottom of the bottle and the pH of the solution did not change during the process. The glass substrate was removed from the solution either after the precipitation process was finished, or sooner, if intermediate products were to be investigated. The remnant solution on the glass substrate was removed by filter paper to prevent further alanine crystallization occurring as water evaporated from the surface of the glass substrate. The SEM measurements were performed by using a LEO 1550-GEMINI instrument. Powder X-ray diffraction (XRD) patterns were recorded by using a PDS 120 diffractometer (Nonius, Solingen) with $Cu_{K\alpha}$ radiation. The reaction intermediate mesostructures at the early stage of the alanine system were characterized by environmental scanning electron microscopy (ESEM, Quanta 600 FEG, FEI Europe).

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