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## Communications

### Nonphotochemical, Laser-Induced Nucleation of Supersaturated Aqueous Glycine Produces Unexpected $\gamma$ -Polymorph

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**ABSTRACT:** Supersaturated aqueous solutions of glycine exposed to intense pulses of plane-polarized laser light at 1.06  $\mu\text{m}$  unexpectedly crystallized into the polar  $\gamma$ -polymorph of glycine. Control solutions not exposed to the laser always produced crystals of  $\alpha$ -glycine, the expected and most stable form. This result suggests a new approach to polymorph control and possibly a means to produce new polymorphs.

The control of crystallization from solution has commanded considerable attention in recent years, in contexts ranging from biomineralization<sup>1</sup> to nucleation on polymer surfaces<sup>2</sup> and Langmuir–Blodgett films.<sup>3</sup> In such systems, the amplification of fluctuations plays a crucial role in determining the macroscopic outcome of the process. The initial metastable state can be greatly and nonlinearly influenced by relatively weak driving fields.<sup>4</sup> Several years ago we reported an experiment in which supersaturated solutions of urea in water were induced to nucleate when exposed to intense, plane-polarized pulses of near-infrared laser light.<sup>5,6</sup> The urea solution did not absorb light at this wavelength, which ruled out a photochemical mechanism for the process. We attributed this phenomenon to the electric-field-induced alignment of urea molecules in pre-existing clusters of randomly oriented urea molecules, helping them to organize to form a crystallite. In that study, the crystalline structure of urea (which has only one known polymorph) induced by light was the same as that formed when urea spontaneously nucleates from aqueous solution.

The nucleation of crystals from liquid solution has great technological importance, as it is the primary method for the preparation and purification of industrially important chemicals such as pharmaceuticals, explosives, dyes, and photographic materials.<sup>7</sup> Unfortunately, little is understood about this process. There is growing evidence that the description of this process by classical nucleation theory is not even qualitatively correct and that crystallization from solution may actually be a two-step process: a first, diffusion-controlled step involving the formation of a liquidlike cluster of solute molecules, and a second, rate-limiting step involving the organization of such a cluster

into an ordered crystalline structure.<sup>8–10</sup> Such a picture is consistent with our experimental observations concerning the laser-induced nucleation of aqueous urea solutions.<sup>5</sup>

In a further complication, chemical compounds often display the ability to crystallize into more than one structure. These different forms, known as polymorphs, may result in solids with great differences in chemical and physical properties such as melting point, dissolution rate, bioavailability, solubility, and hardness.<sup>11,12</sup> The control of crystallization from solution is an area of intense research but little fundamental knowledge. Living organisms are able to control the morphology of crystals through biomineralization.<sup>1</sup> In a different approach, the growth of crystal surfaces can be inhibited or promoted by the adsorption of tailor-made additives—impurity molecules exhibiting stereospecific interactions not unlike enzyme–substrate interactions.<sup>11</sup>

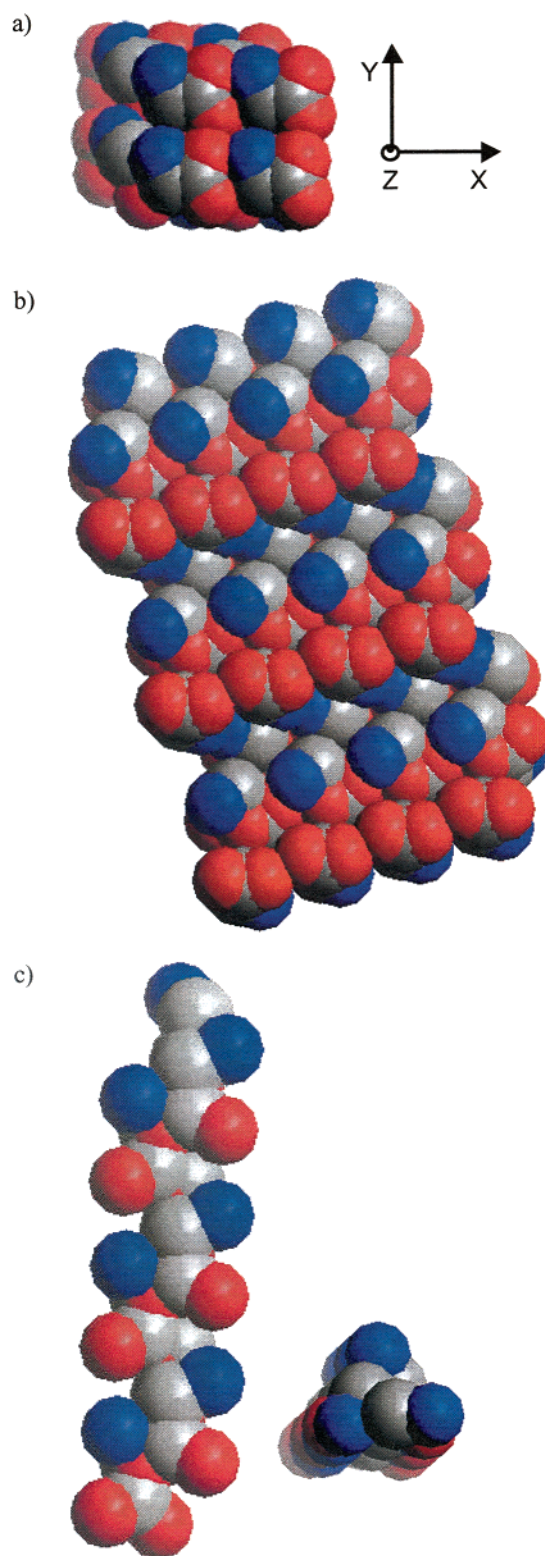
We report here that the nonphotochemical, laser-induced nucleation (NPLIN) of solutions of the amino acid glycine ( $\text{NH}_2\text{CH}_2\text{COOH}$ ) in water produced the unexpected polar  $\gamma$ -polymorph. Glycine is known to form three polymorphs, known as  $\alpha$ -,  $\beta$ -, and  $\gamma$ -glycine.<sup>13,14</sup> (As  $\beta$ - and  $\gamma$ -glycine crystals spontaneously convert to  $\alpha$ -glycine in the presence of  $\alpha$ -crystals in a saturated aqueous solution,  $\alpha$  is known to be the most stable of the three polymorphs.) The structures of  $\alpha$ - and  $\gamma$ -glycine are shown in Figure 1.

$\alpha$ -Glycine, the most stable polymorph, is formed when aqueous glycine solutions, in which glycine molecules exist as zwitterions ( $^+\text{NH}_3\text{CH}_2\text{COO}^-$ ), spontaneously nucleate. The preferential crystallization of the  $\gamma$ -form can be induced in aqueous solution, using additives such as racemic hexafluorovaline, which binds to the four fast-growing  $\{011\}$  faces of  $\alpha$ -glycine, inhibiting the growth of that form.<sup>15</sup> The  $\gamma$ -form can also be crystallized from acetic acid or ammonia solutions.<sup>14</sup> The growth mechanism of  $\alpha$ -glycine may be based on the addition of cyclic hydrogen-bonded dimers.<sup>11</sup> The protonation of  $\text{CO}_2^-$  groups under acidic conditions or the deprotonation of  $\text{NH}_3^+$  groups

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**Figure 1.** (a) Structure of a glycine molecule (including the molecular coordinate system referred to in the text) and packing of molecules in  $\alpha$ -glycine. (b) Another view of the packing of molecules in  $\alpha$ -glycine.<sup>13</sup> (c) Two views of the packing of molecules in  $\gamma$ -glycine.<sup>14</sup> In  $\alpha$ -glycine, cyclic dimers pack together to form hydrogen-bonded double layers (viewed along the  $c$  axis) in part b. The packing and hydrogen bonding in one layer (viewed along the  $b$  axis) of  $\alpha$ -glycine are shown in part a. In  $\gamma$ -glycine, helical chains, viewed perpendicularly to the  $c$  axis (left) and along the  $c$  axis showing the 3-fold symmetry (right), pack together hexagonally through lateral hydrogen bonds. Structures were generated using Materials Studio; in all parts, carbon atoms are shown in gray, nitrogen atoms in blue, and oxygen atoms in red.

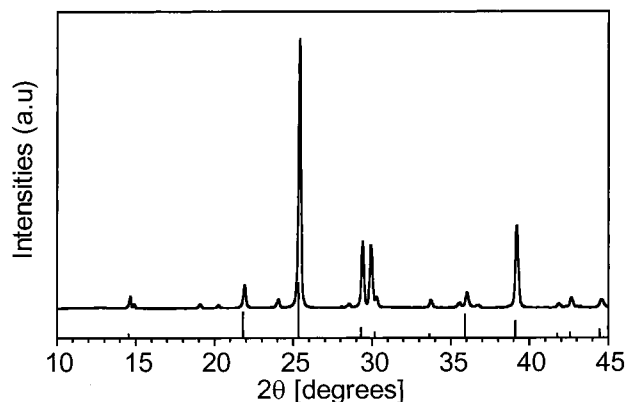
under basic conditions would make dimer formation less favorable, thus inhibiting the growth of  $\alpha$ -glycine under these conditions.

Supersaturated solutions of glycine in water, with concentrations ranging from 3.7 to 3.9 M, were prepared by combining solid glycine and water in 1.3 cm diameter Pyrex test tubes with screw-on caps. Great care was taken to exclude dust from samples. Supersaturation was achieved by sonicating and heating the test tubes to 50 °C and holding them at that temperature for several days. Once the glycine was completely dissolved, the solutions were slowly cooled to room temperature (21 °C;  $c_{\text{sat}} = 2.69$  M, where  $c_{\text{sat}}$  is the concentration of a saturated solution). Solutions prepared in this way lasted for several weeks before spontaneously nucleating. By aging these supersaturated solutions, we could increase the average glycine cluster size and thus increase the probability of nucleation.<sup>16</sup>

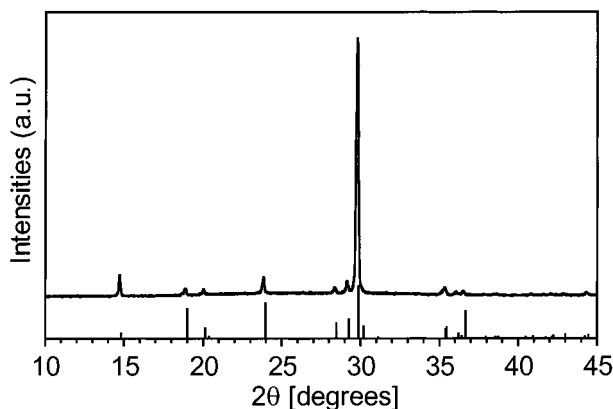
After they were aged for 4 days, the solutions were illuminated with the 1.06  $\mu\text{m}$  wavelength, plane-polarized output of a Quanta-Ray DCR-1 Q-switched Nd:YAG laser oscillator–amplifier system. This laser produced a 10 pps train of 9 ns laser pulses. (Such high-energy laser pulses are invisible, and to avoid exposure of the eye to direct or reflected light, shielding and protective goggles must be used.) A portion of the annular beam with approximately constant intensity was selected by passing the beam through a 2 mm diameter circular aperture, finally passing through a test tube containing the aged solution. A video camera was set up to record any changes in the state of the sample during and after laser illumination. Most experiments were performed with the laser oscillator and amplifier set at maximum power. After accounting for beam focusing due to the curved walls of the test tube, using a ray-tracing computer program, we estimated the peak intensities incident on the solutions to be  $0.7(\pm 10\%)$  GW/cm<sup>2</sup>. With the oscillator alone, peak intensities were about one-third this value. During all experiments, a control sample with the same concentration and age as the illuminated sample was mounted nearby.

When glycine solutions were exposed to amplified laser pulses for several minutes, no changes were immediately apparent, in contrast to our earlier studies of supersaturated aqueous urea solutions, in which macroscopic crystals were visible within seconds of the laser illumination. However, 30 min after exposure, a small, irregular bundle of crystals was observed to be growing at the bottom of the test tube. After several hours, these crystals had grown to a size of about 10 mm<sup>3</sup>. These crystals were removed from the solution and dried. Their structure was determined by grinding all the crystals of a sample into a powder and recording an X-ray diffraction pattern. The pattern obtained (Figure 2) matched that of  $\gamma$ -glycine but also showed the presence of a small percentage of the  $\alpha$ -polymorph. (Such a sample left in solution for longer periods of time contained larger fractions of  $\alpha$ -glycine, suggesting that the  $\gamma$ -glycine initially produced was slowly converting to the  $\alpha$ -form.) The X-ray analysis of crystals formed when control samples nucleated spontaneously indicated the presence only of the  $\alpha$ -polymorph (Figure 3). Unamplified laser pulses ( $\sim 0.2$  GW/cm<sup>2</sup>) did not induce nucleation. Also, exposure of unaged solutions to amplified laser pulses did not induce nucleation.

As aging is a necessary prerequisite for NPLIN, we assume that the applied laser pulses are acting on pre-existing clusters and therefore affecting the second, rate-limiting organizational step. Unlike additives, which can act on the solution throughout the nucleation and growth process, a pulse of laser light can act for only the duration



**Figure 2.** Powder diffraction pattern of crystals obtained from the laser-induced nucleation of a supersaturated aqueous glycine solution. Sticks represent a simulated  $\gamma$ -glycine diffraction pattern based on literature parameters.<sup>14</sup>



**Figure 3.** Powder diffraction pattern obtained from the spontaneous nucleation of a supersaturated aqueous glycine solution. Sticks represent a simulated  $\alpha$ -glycine diffraction pattern based on literature parameters.<sup>13</sup>

of a pulse, about 9 ns. Given the known slow rate of glycine crystal growth, the laser can only affect the very earliest stages of this second step, and the mechanism of its action cannot be of the inhibition type discussed above.<sup>11,15</sup>

As was the case with urea solutions, glycine solutions are transparent at the wavelength of the incident near-infrared laser pulses, so that a photochemical mechanism for the observed laser-induced nucleation is unlikely. We postulated in ref 5 that the actual mechanism involves an interaction of solute molecules with the oscillating electric field associated with the laser pulses. The electric fields associated with the most intense beams used in our experiments exceed  $6 \times 10^7$  V/m. Such a field can induce the partial alignment of glycine molecules through the optical Kerr effect, in which anisotropically polarizable molecules experience a torque tending to align them so that their most polarizable axis is parallel to the direction of polarization of the incident light.<sup>17</sup> Glycine is a zwitterion in neutral aqueous solution, with a very large permanent dipole moment,  $\mu = 47 \times 10^{-30}$  C m, about 8 times greater than that of water.<sup>18</sup> Nevertheless, the interaction energy of this permanent dipole with the electric field vector ( $E$ ) of the light, given by  $-\mu \cdot E$ , averages to zero, because the field is changing direction at the optical frequency of  $\sim 3 \times 10^{14}$  Hz, much faster than can be followed by the rotational motion of a glycine molecule. Although there exist nonlinear optical phenomena, such as optical rectification, that can generate a static electric field through the nonlinear mixing of fields at optical frequencies, they are forbidden

in centrosymmetric media such as supersaturated solutions.<sup>17</sup> On the basis of the reported polarizabilities of glycine,<sup>19</sup> the most polarizable ( $y$ ) axis is in the  $C^\alpha-C'O_2$  plane and perpendicular to the  $C^\alpha-C'$  direction ( $\alpha_{yy} = 7.0 \times 10^{-30}$  m<sup>3</sup>), while the least polarizable ( $z$ ) axis is perpendicular to the  $C^\alpha-C'O_2$  plane ( $\alpha_{zz} = 5.4 \times 10^{-30}$  m<sup>3</sup>,  $\alpha_{xx} = 6.5 \times 10^{-30}$  m<sup>3</sup>). The actual energy lowering induced by the optical Kerr effect in this system, given by the expression  $-(\Delta\alpha)E^2/2$ , where  $\Delta\alpha$  is the polarizability anisotropy (i.e. the difference between the largest and smallest components of the molecular polarizability tensor), is on the order of 0.25 J/mol, or  $0.0001kT$ , where  $k$  is the Boltzmann constant and  $T$  is room temperature. This represents a very slight realignment of glycine molecules of, on average, about  $1^\circ$ .

The interaction energies from the optical Kerr effect are far too small to account for a change in the relative stability of  $\alpha$ - vs  $\gamma$ -glycine, which differ in energy by  $\sim 2.5$  kJ/mol.<sup>14</sup> Any explanation must involve a kinetic rather than thermodynamic basis. Given that we have reduced the induction time for nucleation from days to nanoseconds, classical kinetics requires a reduction in activation barrier of about  $30kT$ . If a critical cluster contains several hundred molecules, then the cumulative effect of the laser on a cluster is about  $0.03kT$ , a factor of 1000 too small. The applied electric field is, therefore, probably affecting the prefactor in the van't Hoff–Arrhenius law.<sup>4</sup> A prenucleating cluster is a complex system consisting of several hundred solute molecules, and possibly some additional solvent molecules; hundreds of coordinates are required to describe the instantaneous state of such a system. The crystalline state represents a very small volume in this configuration space. In the case of glycine, with its enormous permanent dipole moment, there are extremely strong and long-range dipole–dipole interactions among all of the molecules in a cluster, as well as strong but shorter range hydrogen-bonding interactions between nearest neighbors. The state of the system can be considered as a particle moving around on a vast, rugged, multidimensional potential energy surface, with three basins of attraction: a liquidlike domain, an  $\alpha$ -crystalline domain, and a  $\gamma$ -crystalline domain. In the absence of light, the system, initially in the liquidlike basin, randomly samples this region, rarely making an attempt to leave this basin, but eventually escaping to the  $\alpha$ -basin more easily than the  $\gamma$ -basin via thermal fluctuations. The presence of light acts to bias the potential surface, tending to funnel the system into regions of the liquidlike basin that are less accessible via thermal fluctuations, where it is more likely to escape to the  $\gamma$ -basin and where the escape time is greatly reduced.

The complexities of this multidimensional system are beyond the capabilities of existing theories and computational methods.<sup>4,20,21</sup> We can nevertheless suggest reasons why  $\gamma$ -glycine is the preferred product of NPLIN. In a prenucleating cluster, glycine molecules are randomly oriented on average, but locally they will take on some level of organization based on strong nearest-neighbor interactions due to dipole–dipole and hydrogen-bonding forces. Local structures likely consist of two basic units: cyclic dimers, consisting of two glycine molecules with antiparallel  $x$  axes stacked along the  $z$  axis (see Figure 1a for definition of axes), and helical chains, with molecules with parallel  $x$  axes, stacked along the  $x$  direction. Cyclic dimers are the building blocks of  $\alpha$ -glycine, while helical chains are the building blocks of  $\gamma$ -glycine (see Figure 1c). We can also imagine helical dimers, subsets of a helical chain. Both types of dimers are strongly bound together by a combination of dipole–dipole and hydrogen-bonding forces and, thus, can behave as rigid entities that could respond to an external force. The polarizabilities of these dimers can be



estimated using the theory of Jones et al.<sup>22</sup> They determine that the polarizability component in the stacking direction is enhanced by a factor of  $[1 - K/4]^{-1}$ , where  $K = (\epsilon - 1)/(\epsilon + 2)$  and where  $\epsilon$  is the dielectric constant of the molecule. For glycine, this factor is about 1.08. The net result is that a helical dimer has a polarizability anisotropy of  $3.2 \times 10^{-30}$  m<sup>3</sup> compared to a cyclic dimer, which has an anisotropy of  $2.3 \times 10^{-30}$  m<sup>3</sup>. Thus, the applied field is able to align the helical dimers more effectively than the cyclic dimers. This could help to explain why the formation of  $\gamma$ -glycine is favored over  $\alpha$ -glycine in NPLIN.

These findings reveal a new approach to controlling polymorph formation; they also suggest a means for creating new polymorphs of some substances. New polymorphs of organic compounds constitute novel materials that may have important industrial applications. We are continuing to study NPLIN in other systems, as well as the effect of strong dc fields on nucleation. Our results should also provide stringent tests of future computational modeling of nucleation from solution.

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