Polarization Switching of Crystal Structure in the Nonphotochemical Light-Induced Nucleation of Supersaturated Aqueous Glycine Solutions

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By switching between linear and circular polarization in the irradiation of supersaturated solutions of the amino acid glycine in water with intense nanosecond pulses of near-infrared laser light, we have obtained the γ and α phases, respectively, through nonphotochemical light-induced nucleation (NPLIN). This is the first report of light polarization controlling crystal structure. The intensity dependence of NPLIN in aqueous urea is also reported.

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Spontaneous symmetry breaking during phase transitions is a fundamental issue in fields ranging from chemistry [1] to cosmology [2]. Crystallization from solution is such a process that has great technological importance, as it is used to separate and purify industrially significant substances such as pharmaceuticals, dyes, explosives, and photographic materials [3]. A comprehensive theory of nucleation from solution does not exist at present, but there is growing evidence that it is a two-step process: the formation of liquidlike clusters of solute molecules, followed by the rate-limiting organization of such a cluster into a protocrystal [4].

Several years ago we discovered that intense pulses of near-infrared light from a *Q*-switched Nd:YAG laser could induce the nucleation of supersaturated aqueous urea solutions [5]. The crystals that formed tended to be aligned with their needle axes parallel to the electric field direction of the incident linearly polarized laser pulses, leading us to suggest that this phenomenon was probably caused by the optical Kerr effect: the interaction between the electric field of the light and the anisotropic polarizability of the urea molecules, $(NH_2)_2CO$, causing them to align in the direction of the field. In the absence of laser light, spontaneous nucleation in this system can take days or weeks, but in the presence of light, it takes place within the duration of one laser pulse (9 ns). The light is thus reducing the nucleation induction time by a factor of 10^{13}.

We use the term nonphotochemical light-induced nucleation (NPLIN) in order to distinguish this photophysical phenomenon from the more familiar visible or ultraviolet light-induced nucleation, based on a photochemical mechanism [6], that is responsible for laser-induced chemical vapor deposition [7] and the formation of atmospheric aerosols [8]. Several experiments, including diffusion [9] and light scattering [10] measurements, indicate that in supersaturated solutions the average solute cluster size increases with time. These experiments support the proposed two-step mechanism of nucleation from solution and suggest that NPLIN requires the presence of larger solute clusters and, by acting on such clusters, accelerates the rate-limiting organizational step of nucleation.

Since studying aqueous urea, we have observed NPLIN in ethanol solutions of urea, as well as a variety of aqueous solutions of small organic molecules, including glycine, L-alanine, adipic acid, L-glutamic acid, and succinic acid. The amino acid glycine (NH_2CH_2COOH) is a particularly interesting case, as it can exist in three distinct crystalline phases (polymorphs) known as α, β, and γ glycine. Different polymorphs of the same compound can result in solids with great differences in physical and chemical properties, such as melting point, hardness, solubility, dissolution rate, and bioavailability. Therefore the control of a polymorph structure is an important technological objective.

The three polymorphs of glycine can be formed under different solution conditions. α glycine is formed by spontaneous nucleation of pure aqueous glycine, while γ glycine is formed from aqueous acetic acid or ammonia solution [11], or by the addition of compounds that inhibit the growth of α glycine, such as racemic hexafluoravaline [12]. The structures of α and γ glycine are shown in Fig. 1. The α glycine structure consists of hydrogen-bonded double layers, whose basic unit is a cyclic hydrogen-bonded dimer (two antiparallel glycine molecules). The γ glycine structure consists of helical chains of roughly parallel head-to-tail glycine molecules. These chains are hexagonally packed via lateral hydrogen bonds. In aqueous solution, as well as in α, β, and γ glycine, each glycine molecule exists in the form of a zwitterion, in which a proton is transferred from the carboxyl to the amine group ($^+NH_3CH_2COO^-$). The growth mechanism of α glycine is probably based on the addition of cyclic dimers. In acidic or basic solution, the zwitterions gain or lose protons, respectively, reducing the magnitude of the

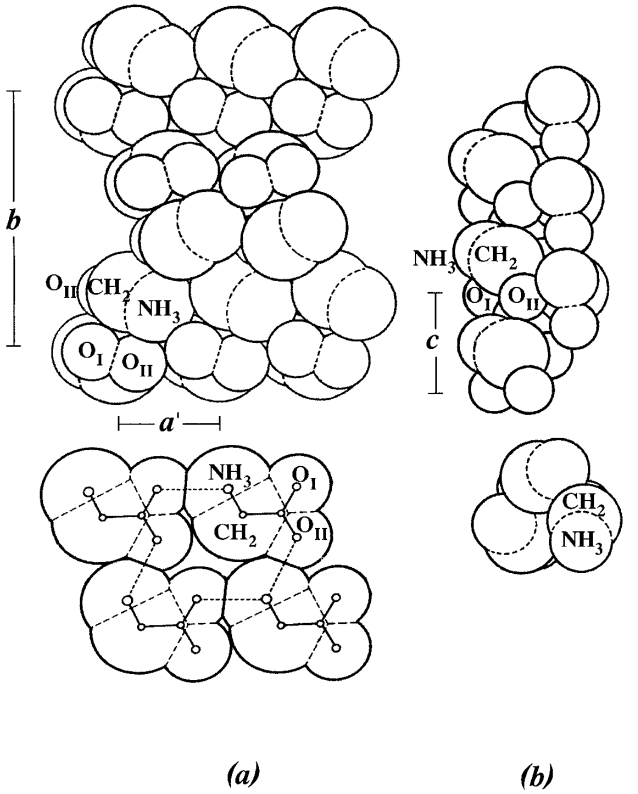

FIG. 1. (a) Two views of the packing of molecules in α glycine [13]. The bottom view shows the packing and hydrogen bonding in one layer of glycine molecules (viewed along the b axis). The top view (along the c axis) shows how cyclic dimers pack together to form hydrogen-bonded double layers. (b) Two views of the packing of molecules in γ glycine [11]. The top view shows a helical chain (viewed perpendicular to the c axis). The bottom view (along the c axis) shows the threefold symmetry of a helical chain. These helical chains pack together hexagonally through lateral hydrogen bonds.

molecule's dipole moment and making cyclic dimer formation less favorable, thus inhibiting the growth of α glycine. β glycine can be formed by precipitation from ethanol-water mixtures [14]. Although α glycine forms spontaneously from aqueous solution, γ glycine is the most stable phase at room temperature [15], indicating that the spontaneous nucleation of glycine is kinetically rather than thermodynamically controlled.

We recently reported that by using linearly polarized near-infrared laser pulses, the light-induced nucleation of glycine unexpectedly produced the γ polymorph, while identical solutions allowed to nucleate spontaneously, always produced the α polymorph [16]. We have since repeated this experiment using circularly polarized light and have found that the α polymorph is always produced.

Supersaturated solutions of glycine in water, with concentrations ranging from 3.7 to 3.9 M, were prepared by combining appropriate amounts of solid glycine with 2 g of water in 1.3-cm diameter Pyrex test tubes with screw-on caps. Supersaturation was achieved by heating the samples in an ultrasonic bath at 69 °C and holding them at that temperature for several hours until the glycine was completely dissolved. The solutions were then slowly cooled overnight to room temperature (21 °C, $c_{\mathrm{sat}} = 2.69$ M, where c_{sat} is the concentration of a saturated solution). Solutions prepared in this way could last for several weeks before spontaneously nucleating.

Solutions aged from 3 to 8 days were exposed for 1 min to the 1064-nm wavelength radiation of a Quanta-ray DCR-1 Q-switched Nd:YAG laser oscillator-amplifier system set at maximum output power. This laser produces a 10-pps train of 9-ns laser pulses. A portion of the annular beam with approximately constant intensity was selected by passing the beam though a 2-mm diameter circular aperture. A Glan-Thompson polarizer was placed in the beam path to ensure linear polarization. The average power through the aperture and polarizer was 0.65 W, corresponding to an energy of 0.065 J/pulse. After accounting for focusing by the curved walls of the test tube, we estimate the peak intensity of the light incident on the sample solution to be 0.7 (± 10%) GW/cm^2. To produce circularly polarized light, a quartz quarter-wave retardation plate at 1064 nm was placed after the polarizer.

Aged supersaturated solutions were exposed to either linearly or circularly polarized laser pulses. In either case, about 30 min after exposure, small macroscopic crystals of glycine could be seen either resting on the bottom of the test tube or floating on the meniscus of some solutions. These crystals were allowed to grow for several hours before vacuum filtration from the solution. Dried crystals were crushed and analyzed using powder x-ray diffraction. Of 18 solutions exposed to 0.7 GW/cm^2 circularly polarized light, 8 nucleated, all forming α glycine. Of 46 solutions exposed to 0.7 GW/cm^2 linearly polarized light, 22 nucleated, all forming γ glycine. Solutions exposed to pulses from the laser oscillator alone set to maximum power (0.2 GW/cm^2) could rarely be induced to nucleate (1 out of 22).

Owing to slow crystal growth rates, intensity dependence studies in aqueous glycine are very time consuming and subject to substantial uncertainties. Instead, we measured the intensity threshold for NPLIN on a series of 12.0 M aqueous urea solutions that had been aged for 4 days. Aqueous urea has the advantage of fast growth rates, such that macroscopic crystals appear within seconds of NPLIN [5]. Solutions were exposed to 1-min trains of linearly polarized 1064-nm laser pulses of increasing intensity: 1/16, 1/4, 1/2, 3/4, and full laser intensity (0.7 GW/cm^2), with 20-sec pauses between trains, and we noted the intensity at which each solution nucleated. Figure 2 shows the results of those measurements. Of 18 solutions illuminated, 7 nucleated. The intensity dependence is clearly nonlinear, with a threshold above 0.04 GW/cm^2. No additional solutions nucleated when the intensity was increased from 3/4 to full intensity, suggesting that all the solutions capable of

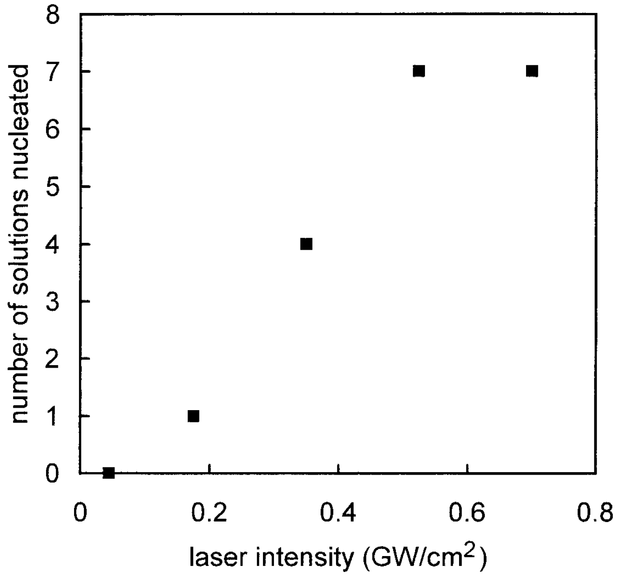

FIG. 2. Intensity dependence of NPLIN in aqueous urea, showing the number of solutions that nucleated at or below a given laser intensity. The total number of solutions illuminated was 18.

undergoing NPLIN (i.e., with large enough clusters in the laser-beam path) had done so at or below 0.53 GW/cm^2.

The extremely strong intermolecular forces (dipole-dipole and hydrogen bonding) that exist between glycine molecules result in the presence of strongly bound groups of molecules (dimers, trimers, ..., n-mers) that could behave as rigid entities in their response to an applied field. Some of these groups would resemble the structural building blocks of α glycine and others the building blocks of γ glycine. For example, a cyclic dimer is the basic unit of the double planes of molecules seen in α glycine, whereas a helical dimer is the basic unit of the hexagonally packed helical chains of γ glycine. A distribution of these n-mers would exist in any liquidlike cluster of glycine molecules. The larger these n-mers, the more they would resemble the double planes and helical chains of α and γ glycine, respectively. The larger n-mers would therefore have exaggerated anisotropic polarizabilities compared to an individual glycine molecule, with the longer helical chains having rodlike polarizabilities and larger double planes having disklike polarizabilities.

For simplicity, we consider the case that the polarizability tensor of a molecule or n-mer can be represented by an ellipsoid of revolution, where a is the rotation axis. In that case, in the molecular reference frame $\{a, b, c\}$ the tensor is diagonal with elements α_a and $\alpha_b = \alpha_c$. An applied optical field partially aligns these ellipsoids, and their resulting uniaxial orientation distribution can be characterized by the order parameter $K_z = \langle\cos^2\theta\rangle$, where θ is the polar angle between the molecular a axis and the laboratory z direction. K_z is equal to 1 for perfect z alignment, 0 for complete x-y alignment, and 1/3 for an isotropic distribution. For linear z-polarized and circular xy-polarized electric-field-induced alignments, K_z is, to order E_0^2, given by

$$\begin{aligned} K_z^{\mathrm{LP}} &= 1/3 + (E_0^2/45kT)(\alpha_a - \alpha_b), \\ K_z^{\mathrm{CP}} &= 1/3 - (E_0^2/90kT)(\alpha_a - \alpha_b), \end{aligned} \tag{1}$$

where E_0 is the amplitude of the electric field, T is the temperature, and k is the Boltzmann constant [17].

We see that linear and circular polarization have the opposite effect on the alignment of molecules or n-mers. Changing the sign of $(\alpha_a - \alpha_b)$ also reverses the aligning effect of a given applied polarization. (In the more general case of $\alpha_a \neq \alpha_b \neq \alpha_c$, linear polarization tends to align the *most* polarizable axis along z, while circular polarization tends to align the *least* polarizable axis along z.) Figure 3 summarizes the types of alignment behavior that are obtained in the two limiting cases of rodlike ($\alpha_a \gg \alpha_b = \alpha_c$) and disklike ($\alpha_a \ll \alpha_b = \alpha_c$) polarizabilities and in the limit of complete alignment. For a rodlike polarizability, linearly polarized light induces the molecules to align with their rod axes parallel to the applied field ($K_z = 1$), while circularly polarized light induces molecules to align with their rod axes in the xy plane, but with a random azimuthal angle in that plane ($K_z = 0$). For a disklike polarizability, linearly polarized light induces the molecules to align with their disk axes perpendicular to the applied field, in the xy plane, with random azimuthal angle in that plane ($K_z = 0$). Circularly polarized light induces molecules to align with their disk axes in the z direction, perpendicular to the xy plane in which the applied field is rotating ($K_z = 1$). We thus see that linearly polarized fields are most effective in aligning

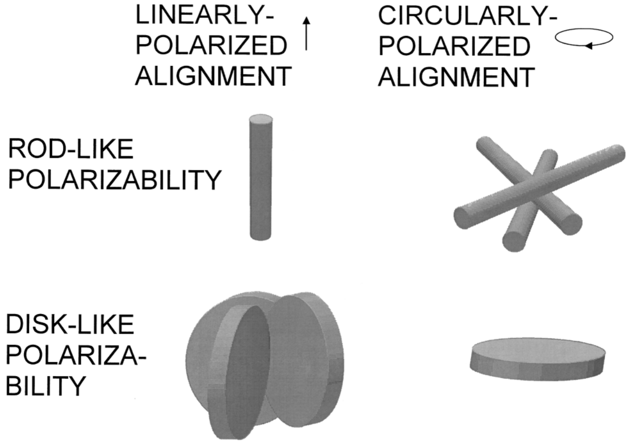

FIG. 3. Different types of alignment for disklike and rodlike polarizabilities in the presence of intense linearly or circularly polarized light. This figure shows the complete alignment achieved in the limit of infinite electric field. The alignments achieved experimentally with the laser field are on the order of 1°, so that the orientation distributions produced are only slightly different from an isotropic distribution.

n-mers with rodlike polarizabilities (e.g., the helical chains that are precursors of γ glycine), while circularly polarized fields are most effective in aligning n-mers with disklike polarizabilities (e.g., the double planes that are precursors of α glycine).

The optical field strengths in the NPLIN experiments exceeded 6×10^7 V/m. Although glycine has an enormous permanent dipole moment of 47×10^{-30} C m [18], its interaction energy with the optical field averages to zero at optical frequencies [16]. The polarizability tensor components of glycine are (7.8, 7.2, and 6.0) $\times$ 10^{-40} C m^2/V in the C-C direction, perpendicular to the C-C direction but in the plane of the molecule and perpendicular to the plane of the molecule, respectively [19]. For an individual glycine molecule, this gives rise to an interaction energy, $-(\Delta\alpha)E_0^2/2$, of 0.2 J/mol, or about 10^{-4} kT at room temperature, where $\Delta\alpha$ is the polarizability anisotropy. Such a weak interaction would result in a very slight alignment of glycine molecules. For larger n-mers, this interaction energy would scale with n and would be further enhanced in the stacking direction [20], but would not produce enough of a lowering of the barrier to nucleation to account for the observed reduction in nucleation induction time.

The applied field is probably affecting the prefactor in the Van't Hoff-Arrhenius law [21]. The complexity of a glycine cluster is substantial and probably not amenable to kinetic models in which a reaction is characterized by a single reaction pathway. Such a cluster is subject not only to extremely strong short-ranged hydrogen bonding interactions between nearest neighbors, but also to strong long-ranged dipole-dipole interactions owing to the zwitterionic character of the glycine molecules. These strong interactions place such a system beyond the capabilities of present computational methods [22].

We had earlier argued that a photochemical or photothermal mechanism based on the absorption of light from the laser was unlikely because the solution absorbs very weakly at the near-infrared wavelength of the laser [5,16]. The observation of polarization switching rules out an absorption mechanism; if an excited electronic or vibrational state were populated through the one-photon or two-photon absorption of light by glycine, this state would be the same whether the excitation were linearly or circularly polarized, resulting in the same outcome independent of the polarization state. Hypothetical mechanisms involving impurity molecules or particles can also be ruled out for similar reasons. The observation of the different effects of linear and circular polarization on the crystallization of glycine represents the strongest evidence to date that the mechanism of NPLIN involves the interaction of solute molecules with the electric field of the light.

Our findings reveal a new approach to controlling crystal structure during nucleation of crystalline materials from solution. The use of polarization is much cleaner than other methods that require additives. In addition, polarization switching might lead to the formation of unknown polymorphs of some substances.

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