

Selective Fabrication of α - and γ -Polymorphs of Glycine by Intense Polarized Continuous Wave Laser Beams

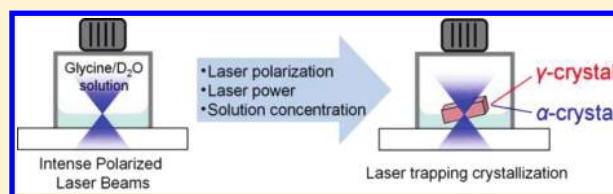
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ABSTRACT: The polymorph control of glycine in D₂O solution is successfully demonstrated by a laser trapping technique using a linearly or circularly polarized CW near-infrared laser beam. Focusing each laser beam into an air/solution interface of the solution always generates the stable crystal polymorph of either α - or γ -form at the focal spot. The formation probability of each polymorph strongly depends on various experimental conditions of laser polarization, power, and solution concentration. For the supersaturated and saturated solutions, circularly polarized laser irradiation enhances γ -crystal formation, while for the unsaturated solution the laser polarization effect becomes prominent and linearly polarized laser light at a specific power provides the maximum γ -crystal probability of 90%. The present polymorphism is achieved by laser-induced effects such as concentration increase, temperature elevation, and molecular rearrangement, whose mechanism is discussed in view of laser polarization dependence of these effects.



1. INTRODUCTION

Polymorphism is known as the phenomenon involving a molecule crystallizing into more than one crystal forms, and has received significant interest in many fields of molecular, material, pharmaceutical, biological, and chemical sciences for the past several decades.^{1–3} Despite each crystal polymorph consisting of the same molecule, the respective crystals exhibit distinct chemical, physical, and optical properties such as solubility, melting point, compressibility, bioavailability, refractive index, absorption, and so on.^{3–5} Therefore, for obtaining a crystal with specific functions, it is important and indispensable to accurately control polymorphism in crystallization processes.

Glycine has been widely employed as a model compound in polymorphism research.^{6–18} Under ambient conditions, its crystal has three polymorphs (α , β , and γ) with the order of relative thermodynamic stability $\gamma > \alpha > \beta$.^{6–11} The kinetically most accessible α -form is prepared by conventional crystallization methods from the neutral aqueous solution.¹¹ The thermodynamically least stable β -crystal is prepared from water–ethanol solution and rapidly transforms into α -form in air or water.^{12,13} The thermodynamically most stable crystal of γ -form is generated in solutions under high pressure and under considerable slow evaporation, or at the extremes of pH and at high ionic strength.^{11,14–18} X-ray crystallography revealed that the α -form crystal has double layers of cyclic glycine dimers linked by a hydrogen bond network,⁶ while the γ -form has helical chains packed hexagonally through lateral hydrogen bonds.⁷ Spontaneous crystallization of glycine from the neutral aqueous solution is controlled kinetically rather than thermodynamically, resulting in α -crystal formation.

Garetz and Myerson have demonstrated pioneering research on crystallization and polymorph control by means of nanosecond pulsed laser irradiation, and named this phenomenon nonphotochemical laser-induced nucleation (NPLIN).^{19–25} So far they have succeeded in the crystallization of various organic compounds of urea, amino acids, and proteins by irradiating the laser into their aqueous solutions. Their interpretation for the crystallization mechanism is based on reorientation of the molecules under an intense electromagnetic field; namely, their molecular alignment favorable to crystallization is triggered by optical Kerr effect. The polymorphism of glycine was absolutely controlled by switching the laser polarization in a specific range (1.46–1.55) of supersaturation values, and linearly polarized (LP) and circularly polarized (CP) lasers provided γ - and α -forms, respectively.²³ Recently, this NPLIN technique was also applied to an inorganic chemical of potassium chloride, and the pulse width effects on the crystallization were discussed.^{26–28}

Laser trapping due to radiation pressure of a focused laser beam has attracted much attention as a method with great potential for crystallization, crystal growth, and crystal polymorph control.^{29–32} Over the past few decades, this technique itself has been widely employed as optical tweezers for trapping and manipulating micrometer-sized materials in many research fields such as physics, optics, and biology.^{33–36} In 2007, the authors for the first time succeeded in demonstrating crystallization by applying this technique to a glycine D₂O supersaturated solution.²⁹ The crystallization is

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induced by focusing a continuous wave (CW) near-infrared (NIR) laser beam into a solution surface, and we call this phenomenon “laser trapping crystallization”. Most recently, the present authors also reported crystal polymorph control of glycine in the supersaturated and unsaturated solutions, which depended on laser power of a LP laser.^{31,32} The control mechanism was explained in terms of local variation of a supersaturation value (SS) induced by laser trapping of the liquid-like clusters and the subsequent temperature elevation.

In this paper, we have studied how to control more selectively the crystal polymorph of glycine in D₂O solution by radiation pressure of a 1064-nm laser beam. Crystallization probability, crystallization time, and γ -form preparation probability were examined by changing solution concentration, laser power, and laser polarization. The laser irradiation always provides only one single crystal, and it can be ascribed to be either α - or γ -form. The preparation rate of the two polymorphs strongly depends on laser polarization, and in particular, almost absolute polymorph control is achieved in the unsaturated solution. There the precursor liquid-like clusters are not much prepared in advance, so that the assembled structure itself can be determined by the laser polarization. The entire mechanism is discussed in view of concentration increase, temperature elevation, and molecular rearrangement depending on laser polarization.

2. EXPERIMENTAL SECTION

2-1. Sample Preparation. Glycine (>99.0%, Wako) and D₂O (99.9%, Cambridge Isotope Laboratories, Inc.) were used as a solute and a solvent without further purification, respectively. We selected D₂O as a solvent in order to suppress the local temperature elevation due to light absorption through overtone vibration bands of solvent molecules. It is reported that the temperature elevation is 22–24 K/W in H₂O and 2 K/W in D₂O under the irradiation of 1064-nm laser.³⁷ Three kinds of glycine/D₂O supersaturated (136%), saturated (100%), and unsaturated (68%) solutions were prepared by dissolving glycine (0.30, 0.22, and 0.15 g, respectively) in 1.0 g of D₂O at 60 °C with vigorous shaking for 3 h, and then they were slowly cooled down to room temperature (23 °C). The molar concentration of each solution is 3.7, 2.7, and 2.0 M. After being aged for half a day, the solutions were used for further experiments. A small amount (15 μ L) of the solutions was poured into a handmade sample glass bottle with a highly hydrophilic surface, and the solution thin film with about 150 μ m thickness was formed. These samples were immediately and completely sealed with a spigot to avoid solvent evaporation. Under the present sample conditions, no spontaneous crystallization took place at least for one month even in the supersaturated solution. Each sample was set on the stage of an inverted microscope with a thermo-plate kept at 23 °C for the following laser trapping crystallization experiment. The local temperature elevation at the focal spot upon trapping by 1064-nm laser in the supersaturated, saturated, and unsaturated solutions were estimated to be 6.8, 6.0, and 5.4 K/W, respectively, by simple comparison of the absorption coefficient of the solutions.

2-2. Optical Setup. Figure 1 shows a schematic illustration of an optical setup in this experiment. A NIR laser beam from a CW Nd³⁺:YVO₄ laser (Spectra Physics, J20-BL-106C, $\lambda = 1064$ nm) was used as a laser trapping light source. A He–Ne laser (Coherent, 6069DU) adjusted coaxially with the trapping laser was introduced to the inverted microscope in order to check the focal position. After confirming that the He–Ne laser was focused at a solution interface of the thin film through an objective lens (60 \times magnification, NA 0.90), the He–Ne laser was switched off, and then the NIR laser was turned on. The power of the NIR laser throughout the objective lens was tuned from 0.8 to 1.4 W by the adjustment of a half-wave plate coupled with a polarizing beam splitter. Under the current condition, the power density and the oscillating optical electric field were

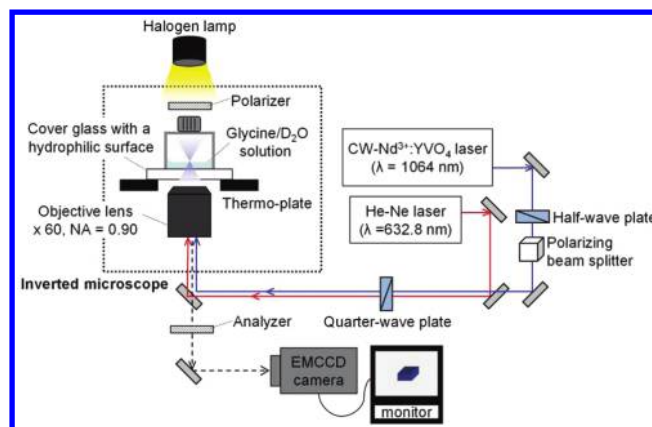


Figure 1. Experimental setup for laser trapping crystallization.

calculated to be 0.28–0.49 GW/cm² and 3.5–4.6 $\times 10^7$ V/m, respectively. The laser power of 1.4 W was the maximum available in the present experimental setup. Since the intensity of less than 0.8 W provided quite low crystallization probabilities within 30 min-irradiation especially in the unsaturated solution, crystal polymorph in this research was examined in the power range from 0.8 to 1.4 W. Incidentally, if the crystallization was achieved at less than the power of 0.8 W, we confirmed that all of the generated crystals were ascribed to be α -form, independent of laser polarization. The solution films prepared from respective glycine/D₂O solutions were exposed for 30 min to either LP or CP laser by switching a quarter-wave plate. The crystallization process was directly monitored by an EMCCD video camera (Flövel, ADT-40C) under halogen lamp illumination and through a pair of orthogonal polarizers.

2-3. Polymorph Analysis. The polymorph of formed crystals was identified by Fourier transform infrared spectroscopy (FT-IR) measurement, in which the IR spectra were measured in the range 4000–400 cm⁻¹ with the resolution of 4 cm⁻¹ (HORIBA FT-720). The crystals prepared in the supersaturated solution were simply kept in the solution at room temperature for 3 h after the generation, and the resultant large crystals were analyzed by FT-IR. Meanwhile, the crystals formed in the saturated and unsaturated solutions cannot grow up spontaneously in these solutions, since the remaining solution after the crystallization is below the saturation condition. The solvent was evaporated by opening the spigot slightly in order to promote the crystal growth, and then FT-IR measurement was carried out for the large crystals obtained after one day. The solution-mediated phase transformation of glycine in solution was carefully checked in our previous experiment. It is a well-known phenomenon that α -glycine gradually changes into the thermodynamically most stable γ -one in solution for a long period,³⁸ and we also confirmed that it was started at 4 days after the crystallization.³¹ Therefore, no transformation should take place during the crystal growth process since all of the formed crystals were picked up from the sample bottle within one day after their crystallization. As we reported in the previous paper,³¹ α - and γ -forms can be clearly characterized from ND₃ stretching at 3200–2950 cm⁻¹, deformation at 1170–1150 cm⁻¹, and rocking at 830–760 cm⁻¹ in the spectra. The characterization by FT-IR measurement is in good agreement with that by X-ray crystallographic analysis for the single α - and γ -form crystals.³¹

3. RESULTS AND DISCUSSION

3-1. Crystallization Probability Depending on Laser Polarization, Power, and Solution Concentration. In laser trapping crystallization, one single crystal is always generated at the focal spot whenever the crystallization takes place. This characteristic formation process enables us to investigate the crystallization probability systematically through a direct observation using an EMCCD camera. The series of experiments were performed using 10 samples for each condition of

laser polarization, power, and initial solution concentration. A crystallization event which was achieved within 30 min was counted as a successful sample. Figure 2a,b shows the number

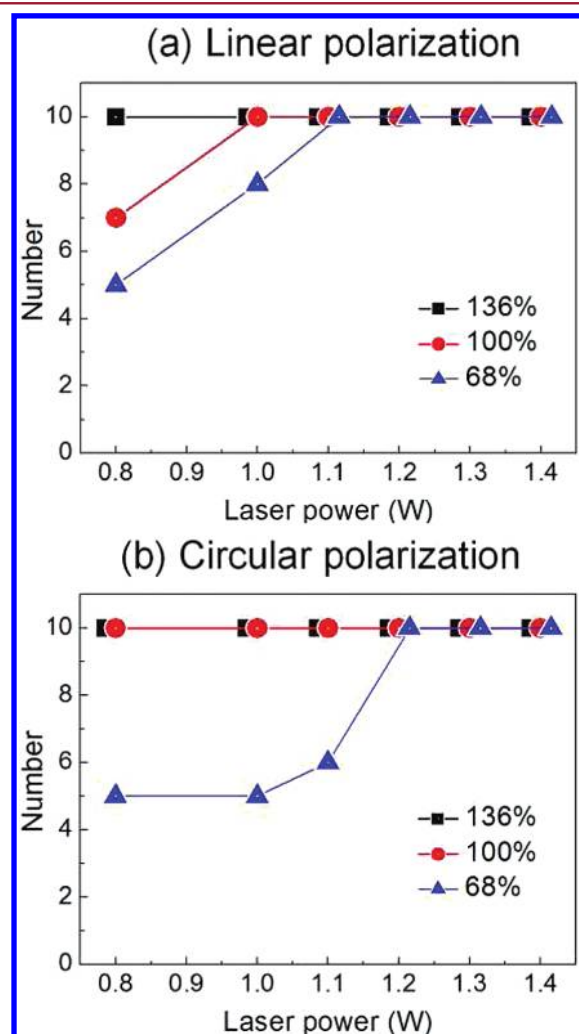


Figure 2. Number of successful samples for crystallization against laser power with LP (a) and CP (b) lasers.

of successful samples as a function of power of LP and CP lasers, respectively. In the case that the supersaturated solution was used as an initial sample, the crystallization was always achieved under all irradiation conditions. Meanwhile, in the case of the saturated solution, the probability depended on the polarization at the low laser power. The CP laser irradiation always achieved the crystallization, while at 0.8 W of the LP laser the probability decreased to 70%. Thus, in the saturated solution the CP laser irradiation can efficiently induce the crystallization compared to the LP one. In the unsaturated solution, the strong polarization dependence of the probability was observed at the lower power range from 0.8 to 1.1 W. The LP laser caused the monotonous increase in the probability during this power range, while the CP laser showed the drastic increase at 1.1–1.2 W. Consequently, the probabilities at both 1.1 and 1.0 W of the LP laser were about 1.6 times higher than those of the CP laser, meaning that the LP laser effectively leads to the crystallization in the unsaturated solution. This polarization dependence in the unsaturated solution is the opposite tendency to that in the supersaturated/saturated ones.

It is summarized that the crystallization probability is clearly dependent on laser polarization especially at the lower laser power.

In addition to the crystallization probability, the time required for crystallization (described as crystallization time in this paper) was simultaneously recorded. The crystal formation can be recognized in EMCCD images within milliseconds due to the fast crystal growth following the nucleation. Actually, after the crystallization, the small crystal grew from the size of several micrometers to a few tens of micrometers only in 3 s.²⁹ Table 1 shows average crystallization

Table 1. Average Crystallization Time under Each Concentration: LP and CP Lasers with Various Intensities

	0.8 W	1.0 W	1.1 W	1.2 W	1.3 W	1.4 W
Linear Polarization						
136%	79	64	91	67	47	41
100%	322	409	218	222	197	203
68%	385	446	350	284	364	513
Circular Polarization						
136%	99	75	65	54	57	81
100%	872	600	302	248	355	218
68%	516	404	395	394	413	102

time under each experimental condition. The samples giving no crystallization during the 30 min-irradiation were excluded from the calculation. Since the calculated sample number is different in each experimental condition, these data should be compared with each other in consideration of crystallization probabilities. Here, we attempt to analyze the crystallization time by averaging the whole data in each concentration. The average crystallization time under the LP laser irradiation was 65, 260, and 390 s in the supersaturated, saturated, and unsaturated solutions, respectively, while in the case of the CP laser, the corresponding time was 72, 430, and 330 s. The average time with the CP laser became longer than that with the LP one in the supersaturated/saturated solutions, while the unsaturated solution showed the opposite result. Thus, as in the above crystallization probability, the polarization dependence of the crystallization time in the unsaturated solution was different from that in the supersaturated/saturated ones. These results suggested to us that the crystallization mechanism under radiation pressure of polarized CW laser beams in the unsaturated solution should be discussed separately from the supersaturated/saturated ones.

In order to understand the crystallization process depending on the initial solution concentration, it is essential to discuss a glycine liquid-like cluster and its subsequent concentration increase by laser trapping. The liquid-like cluster has been investigated experimentally and theoretically,³⁹ and it has been shown that the cluster consists of solute and solvent molecules weakly linked by intermolecular interactions. Nowadays, it is suggested that this cluster formation should be included in crystallization processes of various organic molecules.^{40,41} Myerson et al. pointed out the existence of glycine liquid-like clusters on the basis of the experiments on the diffusivity.⁴² They reported that the diffusion of glycine in the aqueous solution gradually becomes slower with the concentration increase and is dramatically suppressed at the saturation point. The rapid decrease of the diffusivity was explained in view of the cluster formation. Also, in 2005, they successfully obtained the direct information on the clusters by means of small-angle

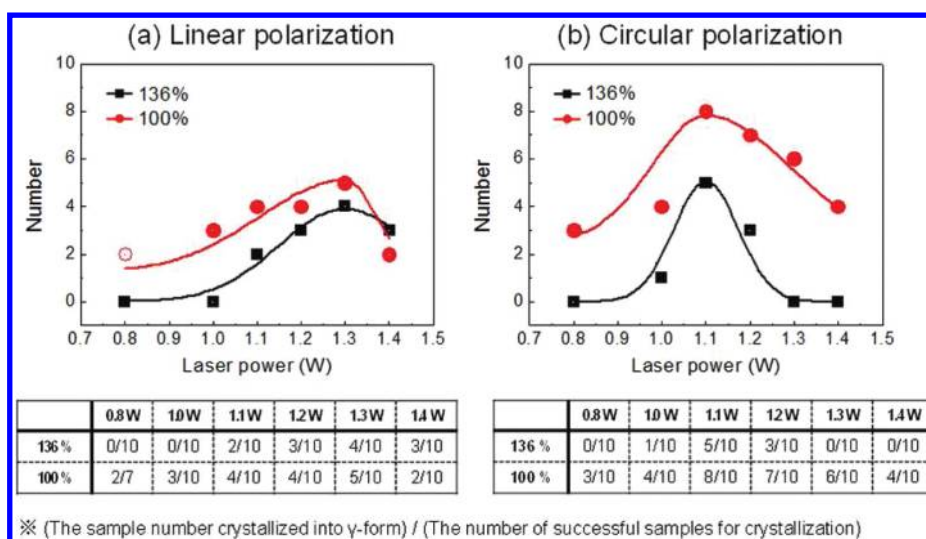


Figure 3. Sample number crystallized into γ -form as a function of laser power with LP (a) and CP (b) lasers in the supersaturated/saturated solutions. Filled symbols show the 100% crystallization probability, while unfilled marks correspond to the lower probability.

X-ray scattering (SAXS) measurement, in which the clusters consisting of the cyclic dimers are formed with the concentration increase.⁴³

On the other hand, a highly focused laser beam can exert trapping force on the liquid-like clusters toward the focal spot. This is ascribed to the dipole gradient force of the nonuniform light field, which is also called radiation pressure.^{44–46} The magnitude of the trapping force is determined by size and polarizability of the cluster under Rayleigh approximation. The gradient force, F_{grad} , is expressed as

$$F_{\text{grad}} = \frac{1}{2} \alpha \nabla E^2$$

$$\alpha = 4\pi\epsilon_2 r^3 \frac{(n_1/n_2)^2 - 1}{(n_1/n_2)^2 + 2}$$

where E is the electric field strength of the incident light, α is the polarizability of the cluster to be trapped, r is the radius of the cluster, and ϵ_2 is the dielectric constant of the surrounding medium. The values of n_1 and n_2 are the refractive indices of the cluster and the surrounding medium, respectively. The equation indicates that the trapping force acts strongly on the cluster with larger size or higher polarizability and is also proportional to laser power.

Since the relatively large and stable liquid-like clusters are already formed in the supersaturated/saturated solutions, their efficient laser trapping is achieved due to their large volume in these solutions and the subsequent increase in their local concentration leads to the crystallization at the focal spot. Meanwhile, in the unsaturated solution the large and stable clusters are hardly expected. We suggest that, even in such a solution, the clusters are newly and forcibly formed at the focal spot under radiation pressure, and their laser trapping would contribute to the crystallization. In relation to this viewpoint, we remember the papers by Osborne et al. and Chirico et al. reporting that molecular diffusion of organic dye in a focal volume is suppressed under radiation pressure as “biased diffusion”.^{47,48} The suppression of molecular diffusion under radiation pressure surely leads to generation and growth of the liquid-like clusters in the focal volume. The resultant clusters are stably trapped at the focal spot, and then their assembling is

started. Once the clusters begin to assemble, their effective volume and polarizability become larger, and the local concentration nonlinearly increases with time. Actually, Tsuboi et al. recently reported the particle-like assembly at the focal spot under radiation pressure in an unsaturated glycine/D₂O solution (0.1 M), of which concentration is much lower than that in this experiment.⁴⁶ Thus, the formation process of the liquid-like clusters in the unsaturated solution is ascribed to radiation pressure. The process is obviously different from the spontaneous cluster formation in the supersaturated/saturated ones, which should be responsible for the opposite polarization dependence of probability and time of the crystallization.

3-2. Crystal Polymorph Depending on Solution Concentration. The FT-IR measurement revealed that the crystals prepared under radiation pressure were ascribed to be either α - or γ -form. The former is the kinetically most accessible crystal form in the neutral solution, and the latter is the thermodynamically most stable one. The spontaneous crystallization of glycine in the neutral aqueous solution preferentially gives α -form, meaning that the process proceeds under kinetic control. The conditions which can lead to the high SS with avoiding the kinetically controlled crystallization process, for example, the considerable slow evaporation of the solution, enable glycine to crystallize into γ -form.¹⁷ Note that in the present experiment the polymorph of crystals formed by the laser irradiation within 30 min were investigated. During such a short period, the spontaneous crystallization process in conventional experiments should be kinetically controlled, and α -crystal formation is always achieved. Actually, we also confirmed that the rapid evaporation for a few hours always gave α -form in D₂O solutions. For this reason, our attention is paid to the γ -form preparation probability under each experimental condition. Figure 3a,b shows the sample numbers crystallized into γ -form against power of LP and CP lasers, respectively, in the supersaturated/saturated solutions. As seen in the figure, the probability strongly and clearly depended on laser polarization, power, and initial solution concentration. In this section, laser power and initial solution concentration dependence of the probability are discussed from the viewpoint of the local SS variation at a focal spot.

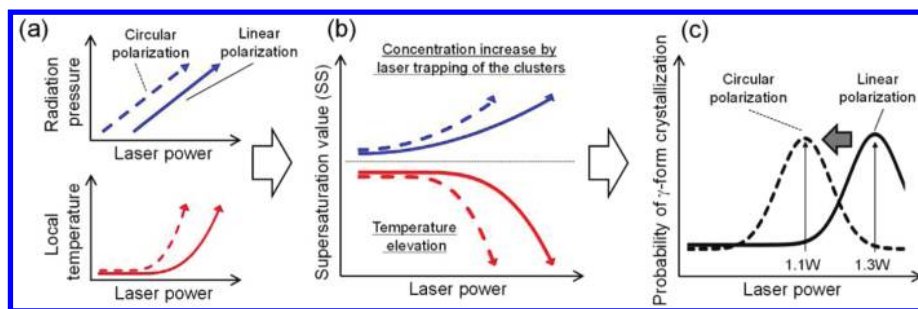


Figure 4. Mechanism of polymorph control by laser trapping crystallization in the supersaturated/saturated solutions. The local SS variation due to the laser power-dependent effects, concentration increase and temperature elevation, are shown in parts a and b, while bell-shaped curves by the multiplication of two effects under the irradiation of LP and CP lasers are depicted in part c.

First, we notice the probability variation under the LP laser irradiation in Figure 3a. In this work, we confirmed that the saturated solution showed the similar tendency to the result in the supersaturated solution which was already reported in our previous paper.³¹ That is, the probability initially increased with the power, the peak value was attained at 1.3 W, and it decreased at 1.4 W. Consequently, the probability curve showed a bell shape, which can be explained in view of laser trapping of the liquid-like clusters due to radiation pressure and local temperature elevation by photon absorption of glycine molecules (solid lines in Figure 4a). The former trapping effect results in the elevation in the local SS at the focal spot, while the latter heating effect compensates its elevation (Figure 4b). The heating effect suddenly becomes prominent above a certain laser power where the thermal dissipation is overcome by input laser power. The probability is represented by the multiplication of these two conflicting factors, and the resultant bell-shaped curve against laser power is given as shown in Figure 4c.

Another notable result is that the saturated solution showed higher probabilities of γ -form preparation compared with the supersaturated one in almost the whole range of laser power. Since the supersaturated solution is metastable in the phase diagram before laser irradiation, the kinetically accessible crystallization, leading to α -form, is easily promoted. Conversely, in the saturated solution no spontaneous crystallization takes place. By irradiating the laser beam into the saturated solution, the local concentration at the focal spot is possibly increased enough to induce γ -form while avoiding the kinetically accessible crystallization.

Next, our attention is paid to the results under the CP laser irradiation in Figure 3b. The probability variation against laser power and concentration is qualitatively similar to that with the LP laser, which is summarized as follows: (1) higher probabilities in the saturated solution compared to the supersaturated one and (2) probability curves with a bell shape against laser power. We consider that the two results can be explained in the same mechanisms as described above. Namely, the first result is possibly related to the preference of the kinetically accessible crystallization process leading to α -form under supersaturation. The second result is ascribed to SS variation induced by the laser power-dependent effects of laser trapping of the clusters and temperature elevation. These effects are schematically illustrated in Figure 4 and discussed in detail later. The peak position of the bell-shaped curve was observed at 1.1 W, which is 0.2 W lower compared with the LP laser irradiation. That is, strong polarization dependence of the probability of γ -form preparation was confirmed. The result suggests high potential of laser trapping crystallization in

polymorph control, for which the mechanism is discussed in the next section.

3-3. Crystal Polymorph Depending on Laser Polarization in Supersaturated and Saturated Solutions. It is of great significance to discuss the polarization dependence of the probability of γ -form preparation from the viewpoint of radiation pressure acting on the liquid-like clusters in the supersaturated/saturated solutions. In order to explain the mechanism of laser trapping-controlled polymorphism in such solutions, we refer to the results of NPLIN reported by Garetz et al.²³ They successfully controlled the polymorph of glycine by irradiating LP or CP nanosecond pulsed laser into the supersaturated solutions with a specific SS (1.46–1.55), and proposed the mechanism from the viewpoint of the molecular rearrangement in the cluster reflecting on laser polarization. The CP pulsed laser preferentially arranges glycine molecules into a cyclic structure with a disk-like polarizability, which leads to crystallization of α -form having double layers of the cyclic dimers. On the other hand, the LP pulsed laser provides a helical structure with a rod-like polarizability, which triggers crystallization of γ -form with building blocks of the helical chains. In addition, they demonstrated that both LP and CP pulsed lasers induce α -form crystallization at SS below 1.46, while both polarizations produce γ -crystal at SS above 1.55. Thus, these results suggested that polarized laser irradiation at a specific SS range or high/low SS condition is important for the polymorph control of glycine.

In our laser trapping crystallization, glycine crystal was formed by applying radiation pressure of a focused CW laser beam to the solutions at SS below 1.37. The SS in the focal spot is varied by the competition between the concentration increase due to laser trapping and the subsequent temperature elevation, through which the crystallization is induced with a specific probability. When the local SS is just 1.46–1.55 through the fluctuation, the CP and LP CW lasers should induce molecular rearrangement to α - and γ -forms, respectively, as with the above polarized laser pulses. However, the effect may be tentatively induced, since the local SS is always fluctuant. We consider that the polymorph control by polarization in laser trapping crystallization should develop through a few different processes including similar molecular rearrangement to NPLIN, and try to explain the control mechanism in the supersaturated/saturated solutions in terms of the variation of the local SS depending on the polarization.

Figure 4 shows a schematic illustration of the polymorphism depending on laser polarization in these solutions. Myerson et al. successfully obtained the direct information on the conformation of glycine liquid-like clusters in the super-

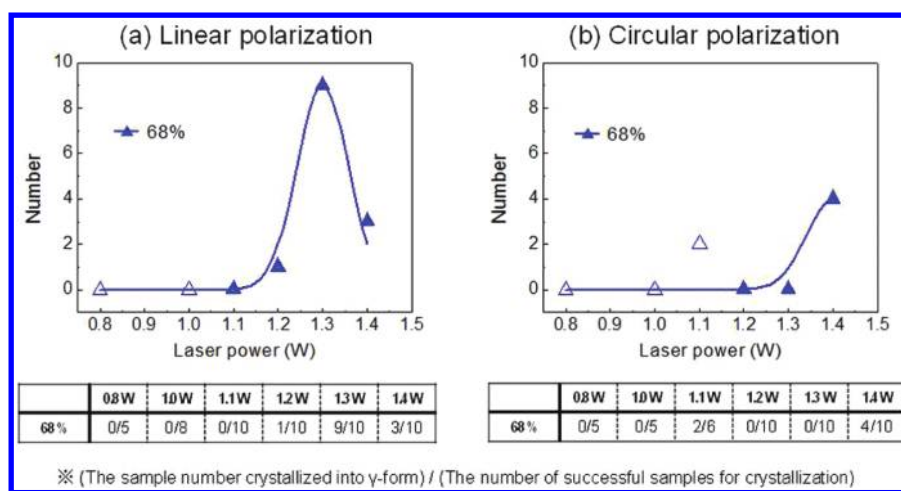


Figure 5. Sample number crystallized into γ -form as a function of laser power with LP (a) and CP (b) lasers in the unsaturated solution. Filled symbols show the 100% crystallization probability, while unfilled marks correspond to the lower probability.

saturated solution by SAXS measurement.⁴³ The measurement revealed that the cluster consists of primary building blocks of the cyclic dimers with a disk-like polarizability, called α -form clusters. For the crystallization at lower SS, the α -form clusters are simply packed with each other as concentration increases, resulting in α -form crystallization. Meanwhile, at quite high SS, the thermodynamically most stable γ -form is produced. Under such high SS, the α -form clusters are more tightly packed, and the spontaneous conversion from α -form to the thermodynamically most stable γ -form can be induced. Coming back to our supersaturated/saturated solutions, the α -form clusters should be originally prepared without laser irradiation since the SS of the initial solution is relatively low. Actually, spontaneous crystallization under this condition always provided α -crystal. Therefore, radiation pressure of the CP laser efficiently works on these α -form clusters due to a disk-like polarizability compared to the LP laser as shown in Figure 4a (dashed line). The efficient laser trapping with the CP laser easily increases the SS at the focal spot, and the resultant high SS induces the spontaneous conversion from α - to γ -form clusters. As a result, γ -form probability is increased by the CP laser at lower laser power. However, the concentration increase simultaneously accelerates temperature elevation by photon absorption of the highly concentrated solutes, so that the local SS is decreased (Figure 4b). Consequently, the peak position of the maximum preparation probability on the CP laser is low-shifted by 0.2 W while the bell shaped curve is kept compared to that with the LP laser, which is depicted in Figure 4c. Thus, the polymorphism in the supersaturated/saturated solutions can be explained in view of laser trapping of the liquid-like clusters consisting of building blocks of the dimers under each laser polarization.

3-4. Crystal Polymorph Control by Laser Polarization in Unsaturated Solution. Figure 5 shows the sample numbers crystallized into γ -form against laser power in the unsaturated solution. As is clear from the figure, the γ -form crystallization probability strongly depended on laser polarization in the solution. Notably, the LP and CP laser irradiation at 1.3 W provided the probabilities of 90% and 0%, respectively, and the polymorph control was almost completely achieved at the power. However, the polarization dependence in the unsaturated solution was far different from that in the supersaturated/saturated solutions shown in Figure 3. The

large and stable liquid-like clusters of glycine are hardly expected in the unsaturated solution, so that the polarization dependence cannot be explained only in terms of SS variation by laser trapping of the originally existing clusters and the subsequent temperature elevation, as in the supersaturated/saturated solutions. Therefore, it is necessary to consider in the unsaturated solution that the cluster generation and growth are made possible by radiation pressure itself, so that the polarization strongly affects molecular alignment in the cluster during its generation process. That is, we suggest in laser trapping experiments that LP and CP lasers preferentially produce the γ -form cluster with a rod-like polarizability and the α -form one with a disk-like polarizability, respectively. We consider that the cluster structure during their laser trapping is maintained, although the spontaneous conversion should be taken into account in the case of high SS and high temperature. Through these effects, the polymorphic outcome should be achieved as schematically represented in Figure 6a.

The LP laser irradiation showed no γ -form crystallization in the low power range from 0.8 to 1.1 W in Figure 5a. The crystallization probability suddenly increased at 1.2 W, and achieved the highest value of 90% at 1.3 W in the present work. These results indicate that the laser polarization is strongly effective to the γ -form crystallization at higher laser power, the dynamics of which is shown in the upper part of Figure 6a. Before laser irradiation, the initial unsaturated solution mainly includes glycine monomers, not the liquid-like clusters (Figure 6a1). Some glycine molecules exist as dimers in the solution, which is supported by the report that the radius of gyration is between the monomer and the dimer size in an unsaturated condition.⁴³ As the LP laser is irradiated into the solution, the diffusion of the monomers and the dimers is suppressed under radiation pressure, and the mixture of the α - and γ -form clusters is possibly formed during the concentration increase. The LP laser efficiently traps the γ -form clusters due to the rod-like polarizability (Figure 6a2), leading to the concentration increase of the clusters at the focal spot (Figure 6a3). Once the increased concentration reaches the crystallizable region, γ -form crystallization should be instantaneously induced as a dominant process (Figure 6a4). Here it is notable that the crystallization is achieved just by the γ -form structure directly constructed by the LP laser irradiation. However, the probability decreased to 30% at 1.4 W, which is ascribed to

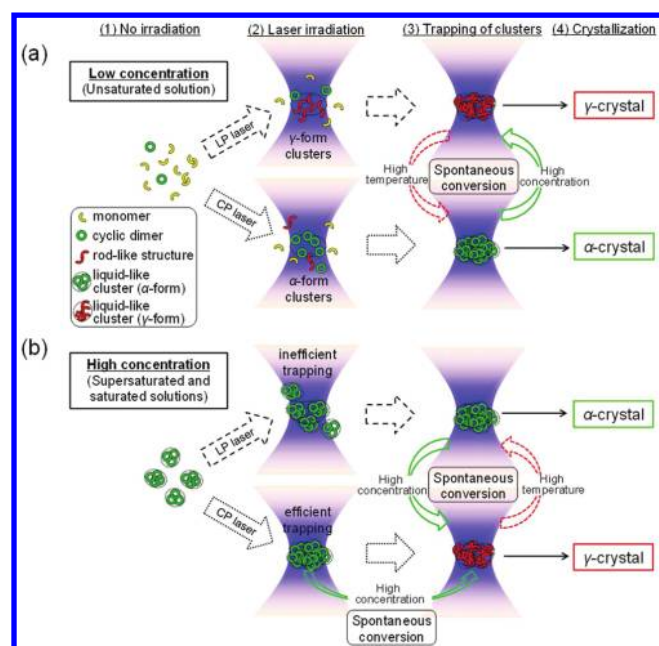


Figure 6. Mechanism of polymorph control by laser trapping crystallization in the unsaturated solution (a) and in the supersaturated/saturated solutions (b).

temperature elevation. Laser trapping of the clusters increases the molecular concentration, so that absorption of NIR photons by the molecules becomes larger at higher power. The subsequent temperature elevation perturbs the cluster structure through vigorous molecular vibration and rotation in the clusters. Since the α -form clusters consisting of the cyclic dimers are preferentially generated under supersaturation condition, spontaneous structural conversion from the γ -form to the α -form clusters takes place at the focal spot, resulting in the probability decrease at 1.4 W.

In the case of the CP laser, the probability variation of γ -form crystallization was much more complicated as shown in Figure 5b. Two peak points were observed at 1.1 and 1.4 W, although only $6/10$ samples successfully achieved laser trapping crystallization at 1.1 W. Notably, the probability increased under the high power laser irradiation of 1.4 W, which is only exceptional under all conditions. Since the crystallized sample number at 1.1 W is relatively low, here we note the larger probability at 1.4 W and provide a crucial perspective for the polymorph control by laser polarization in the unsaturated solution. Under the CP laser irradiation, the molecules are aggregated at the focal spot, evolving to the α -form clusters. The resultant clusters preferentially lead to an α -form crystal as shown in the lower part of Figure 6a. Indeed, it was found that the α -form crystallization probability was higher in the entire range of laser power compared to the other solutions. We presume that the γ -form crystallization at 1.4 W is achieved through spontaneous structural conversion from the α -form to the γ -form clusters owing to concentration increase at the focal spot, not owing to direct molecular rearrangement by the polarized laser beam. The structural change should occur through the following processes: the cluster formation from the monomers/dimers, the efficient laser trapping of the formed clusters, and the subsequent concentration increase. The multiple processes imply that much higher laser power is required for the γ -form crystallization. Consequently, the peak position in the unsaturated solution is highly shifted by 0.3 W

compared to that of the supersaturated/saturated solutions. Thus, laser polarization directly affects the association structure of the monomers/dimers in the unsaturated solution, which leads to the more precise polymorph control.

Finally, we attempt to explain the peak at 1.1 W of Figure 5b in relation to the polymorph control in the supersaturated/saturated solutions of Figure 6b. These solutions originally include the large and stable liquid-like clusters, that is, the α -form clusters. Their laser trapping generates the high concentration area, in which α -form crystallization probably takes place under kinetic control. Meanwhile, a very high concentration of the α -form clusters prepared by radiation pressure can undergo spontaneous structural conversion into the γ -form structure, resulting in γ -form crystallization. We presume that the unsaturated solution also includes this crystallization process based on trapping of the clusters transiently formed through concentration fluctuation. Indeed, the peak position was the same as those in the supersaturated/saturated solutions, which supports the contribution of this crystallization process.

4. CONCLUSION

Selective fabrication of α - and γ -polymorphs of glycine was successfully demonstrated by using an LP or CP CW near-infrared laser beam. For the supersaturated/saturated solutions, the probability of γ -crystal preparation on the CP laser irradiation became higher at lower power compared to the LP one. For these solutions, the liquid-like clusters originally existing in the initial solution are gathered by radiation pressure, resulting in the crystallization. During this gathering process, the CP laser irradiation efficiently works on the clusters due to a disk-like polarizability, so that the local concentration increase leading to γ -form crystallization is easily achieved. Conversely, in the unsaturated solution, the LP laser irradiation provided the higher preparation probability of γ -form crystal compared to the CP one. In such a solution, the large and stable clusters are hardly expected, and the clusters are generated and/or grown under radiation pressure in the focal spot. Hence, laser polarization directly affects the molecular alignment in the clusters, and the LP laser preferentially provides the γ -form cluster with a rod-like polarizability. Consequently, the polymorph control was almost completely achieved at 1.3 W. The entire polymorphism was determined by the balance among the polarization-dependent and the laser-power-dependent effects of local concentration increase, temperature elevation, and molecular rearrangement, and their appropriate combination led to the considerably high probability of γ -form crystallization.

In general, it is impossible to accurately predict when and where crystallization takes place in traditional crystallization methods. We believe that our laser trapping crystallization technique should overcome these difficulties, and it will enable us to investigate and elucidate crystallization process and polymorph control by a spectroscopic technique. Indeed this crystallization method is spatio-temporally controllable, so that we can explore systematically molecular crystallization behavior of various amino acids and proteins. It is useful to investigate the effects of wavelength of trapping laser, salt, pH, and so on in order to reveal the entire process and mechanism of laser trapping crystallization. Furthermore, the present results indicate that the investigation of characteristic molecular association at a solution surface is necessary and indispensable for understanding the nature of crystal nucleation. In the near

future, more precise control of a crystal polymorph will be available upon laser trapping crystallization.

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Notes

The authors declare no competing financial interest.

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