Strong dc Electric Field Applied to Supersaturated Aqueous Glycine Solution Induces Nucleation of the γ Polymorph

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Applying a strong static electric field to supersaturated aqueous glycine solutions resulted in the nucleation of the γ polymorph. This is the first report of a strong dc field inducing the nucleation of a neutral solute in a supersaturated solution. We attribute this effect to the electric-field-induced orientation of the highly polar glycine molecules in large preexisting solute clusters, helping them organize into a crystalline structure. This result also lends further support to our proposed optical-Kerr mechanism for nonphotochemical laser-induced nucleation.

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Crystallization from liquid solution is a ubiquitous phase transition that has great technological importance, but whose mechanism is not well elucidated. It is used to separate and purify industrially important substances such as pharmaceuticals, pigments, dyes, and explosives [1]. Nucleation, the initial step in the process of crystallization involving the formation of a critical nucleus, is still poorly understood [2]. There is growing evidence that nucleation from solution is often a two-step process: the formation of a nanoscale, liquidlike solute cluster, followed by an organizational step in which the cluster takes on a crystalline structure [3].

The process of nucleation is further complicated when the solute under study has the possibility of crystallizing into more than one crystal structure, known as polymorphism. Different polymorphs of a substance may exhibit great differences in chemical and physical properties such as melting point, solubility, dissolution rate, bioavailability, and hardness [4,5]. Living organisms are able to control morphology and polymorphism through biomineralization [6,7]. The addition of certain impurity chemicals can inhibit or promote the growth of particular crystal surfaces. Such tailor-made additives operate through stereospecific interactions not unlike enzyme-substrate interactions [8]. New polymorphs of organic molecules constitute novel materials that may have important industrial applications.

About nine years ago, we accidentally discovered that intense nanosecond near-infrared laser pulses could induce supersaturated aqueous urea solutions to nucleate [9]. We called this phenomenon nonphotochemical laser-induced nucleation (NPLIN) to distinguish it from the better-known, century-old field of ultraviolet and visible light-induced nucleation in supersaturated vapors, the mechanism of which typically involves the photochemical generation of a nonvolatile product that acts as a nucleus for the growth of the condensed phase [10].

Several years ago, we showed that supersaturated aqueous glycine solutions with concentrations of 4.5 to 4.8 molal (3.7 to 3.9 M) could be induced to crystallize into either the α or γ polymorph depending on the polarization state of the laser beam [11]. Spontaneous nucleation at these concentrations always produces α glycine, although γ glycine is the most stable polymorph. We attributed both the urea and glycine observations to the interaction of preexisting large solute clusters with the intense electric field of the light, causing an organization of the cluster through the electric-field-induced alignment of molecules (i.e., the optical-Kerr effect [12]) in the cluster. Linear and circular polarizations induce different types of alignment and thus induce the nucleation of different polymorphs. This "polarization switching" is the strongest evidence to date that the mechanism for NPLIN is not photochemical.

Very recently, we found that the laser intensity threshold for inducing nucleation in aqueous urea (which has only one polymorph) was higher for circularly polarized light than for linearly polarized light, at both 532 and 1064 nm [13]. Since urea is known to form rodlike clusters [14], and the optical-Kerr effect aligns polarizable rods better with linear than circular polarization, these threshold results lend additional support to our proposed electric-field-induced alignment mechanism for NPLIN.

One serious problem with our hypothesis is that the calculated induced-dipole interaction energy in our NPLIN experiments $\frac{1}{2}(\Delta\alpha)E^2 = 10^{-4}$ kT is orders of magnitude too small to account for the observed reduction in nucleation time, where E is the oscillating optical electric field (6×10^7 V/m), $\Delta\alpha$ is the solute molecule polarizability anisotropy, k is the Boltzmann constant, and T is the Kelvin temperature [15]. Cooperative effects among many solute molecules in a large solute cluster might account for this discrepancy [16].

There is theoretical evidence that a strong dc electric field can induce crystallization. Molecular dynamics simulations by Svishchev *et al.* showed that supercooled water can be induced to crystallize by a dc field of magnitude 5×10^9 V/m [17], while simulations of supercooled water in the absence of a field have yielded crystallization only once, after a heroic seven-year effort by Matsumoto *et al.* [18]. dc-electric fields have been used by a number of researchers to affect the crystallization of proteins and ionic compounds from solution, although the mechanism here typically involves the migration of charged protein molecules or ions, thus altering the local supersaturation or causing convection [19–21].

If our proposed mechanism for NPLIN is correct, and the induced-dipole interaction energy $\frac{1}{2}(\Delta\alpha)E^2 = 10^{-4}$ kT is sufficient to induce nucleation, then perhaps a comparable permanent-dipole interaction $\mu E_{\mathrm{dc}} = 10^{-4}$ kT ought to be sufficient to induce nucleation with a static electric field E_{dc}, where μ is the permanent-dipole moment. Glycine, which is a zwitterion ($^{+}\mathrm{NH_3CH_2COO^{-}}$) in aqueous solution, has an enormous permanent electric dipole moment, $\mu = 47 \times 10^{-30}$ C m, 8 times larger than μ_{water} [22]. The dc-electric field that must be applied to produce an interaction energy of 10^{-4} kT is $E_{\mathrm{dc}} = 6 \times 10^5$ V/m, after accounting for the dielectric constant of water. To test this hypothesis, we exposed supersaturated aqueous glycine solutions to strong dc-electric fields.

Aqueous glycine solutions were prepared in 1.3-cm diameter Pyrex test tubes (1.0-cm inner diameter) with screw-on caps. The reagents, glycine (Plus One Pharmacia Biotech $\geq 99.7\%$) and water (Fisher W11-1, Environmental Grade, ≥ 18 MΩ cm), were used without further purification. The supersaturated solutions studied had concentrations in the range of 5.5 to 6.0 m. Glycine was dissolved in water by ultrasonication at $64 \pm 4\,^{\circ}$C over several days, and the resulting solutions were cooled slowly overnight to room temperature, 20 °C, where the saturation concentration $c_{\mathrm{sat}} = 3.0$ molal [23]. These solutions had supersaturations (SS) ranging from 1.85 to 2.0; $\mathrm{SS} = c/c_{\mathrm{sat}}$, where c is the solution concentration. Such solutions could last from weeks to months before spontaneously nucleating.

Solutions were aged for 2 to 5 weeks and exposed to a 6×10^5 V/m dc field for 10 min. Semicylindrical electrodes were constructed from a 5 cm × 5 cm × 5.5 cm block of brass, with the center drilled out so that the sample tubes would fit snugly; the block was then split in half, and material was removed to create a 5 mm gap, as shown in Fig. 1. The electrodes are insulated and held firmly in position by Delrin plates, screwed together to make a covered box, with 5-mm thick spacers to hold the cylindrical electrodes at the proper spacing. There are two long narrow gaps in the insulation, matching the electrode gap, so that most of the length of the sample tube is visible from either side, and there is a small hole in the bottom insulating plate, with a mount for an optical fiber. A Glassman EH regulated power supply provided 0–15 kV dc. At voltages higher than 8 kV, breakdown occurred near the rounded edges of the electrodes near the cylinder-gap intersection, so experiments were limited to the range 7–8 kV.

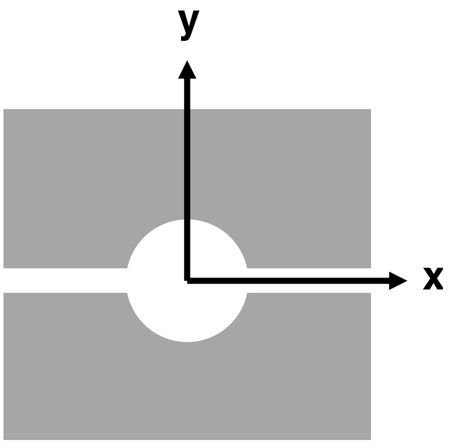

FIG. 1. Cross section of brass electrode assembly. Gap spacing is not to scale in this schematic drawing. All sharp edges were rounded in the actual electrodes.

The electric-field distribution in the region between the electrodes can be calculated assuming infinitely long semicylindrical electrodes [24]. The resultant distribution is shown in Fig. 2. If a unit potential of 1 V is applied to these electrodes, the magnitude of the resultant field ranges from 0.62 V/cm near the inner tube wall on the y axis to 2.4 V/cm near the inner tube wall on the x axis. For the main central area of the cross section, the resultant field is roughly constant, ranging from about 0.9 to 1.1 V/cm.

The actual field magnitude at a particular location in the solution is equal to these factors multiplied by the externally applied voltage, divided by the dielectric constant, ε, of the solution, assumed to be equal to that of water ($\varepsilon_{\mathrm{water}} = 80$).

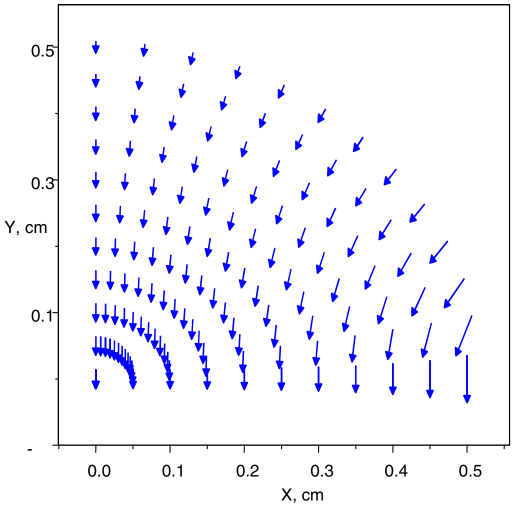

FIG. 2 (color online). Electric-field vector pattern for ideal infinite semicylindrical electrodes with a radius of 0.65 cm. Only one quadrant of the pattern is shown owing to the system symmetry. The electrode gap is along the x axis.

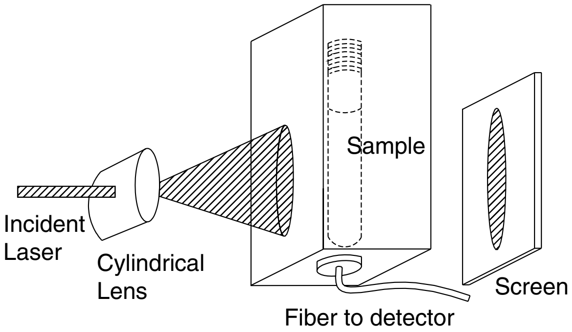

FIG. 3. Schematic of laser illumination and detection optics. For clarity of presentation, the electrodes, which are inside the insulated box that surrounds the sample, are not shown in this diagram.

A low power monitoring continuous-wave laser beam at a wavelength of 532 nm, defocused in one direction with a cylindrical lens to generate a pencil-shaped beam, was directed through the electrode gap and illuminated the length of the sample tube, as shown in Fig. 3. The transmitted light was imaged on a white paper screen. Light scattered perpendicular to the beam was collected with an optical fiber attached at the bottom of the cell and monitored with a power meter. The optical fiber and power meter were useful for monitoring the growth of slowly growing crystals over long time periods (hours), but imaging the transmitted beam on white paper was more useful for detecting the early stages of crystal growth. Small perturbations in the refractive index in the liquid, appearing as shadowy ripples in the imaged light, were often observed, even when crystals were too small to be seen with the naked eye, and before changes in the monitored power through the optical fiber indicated increased scattering due to crystal growth.

Exposure to the dc field successfully induced the nucleation of γ glycine (33% at 1.9–2.0 SS after 14 days; 40% at 1.9–2.0 SS after 36 days; 24% at 1.85 SS after 16 days). These percentages represent the percent of the exposed solutions that nucleated within the 10-min exposure time. Spontaneous nucleation rates at these concentrations for a 10-min time window are 2 to 3 orders of magnitude lower (0.07% to 0.15% at 1.9–2.0 SS; 0.02% at 1.85 SS), so there is no doubt that nucleation was induced by the field. The fact that γ glycine was formed might at first seem like additional proof that the glycine was not spontaneously produced; however, we have found that at supersaturations above 1.8, the spontaneous nucleation of aged glycine solutions tend to produce a mixture of α and γ rather than the pure α polymorph that is produced spontaneously at lower supersaturations, with more γ the higher the concentration, as shown in Table I. Towler *et al.* obtained α glycine up to an SS of 2.4, although their nucleation experiments are performed under agitation, whereas ours are carried out under quiescent conditions [25]. Aging appears to be critical to the polymorph obtained at high supersaturation. High concentration samples nucleated by agitation without aging produced the α polymorph. After even 1 d of aging, the dominant α polymorph showed ‘‘contamination’’ with the γ form.

Examination of Table I shows that dc-field-induced nucleation shifts the polymorph distribution toward the γ polymorph and away from the α polymorph, compared to the distribution obtained by spontaneous nucleation. Given that γ glycine has a polar crystal structure, with all glycine dipoles pointing the same direction, whereas α glycine has a centrosymmetric structure, one would expect a dc field to preferentially induce the nucleation of the γ polymorph if electric-field-induced orientation were occurring.

The γ glycine crystals produced at high SS also exhibit a different morphology; it forms needle-shaped crystals as shown in Fig. 4, and these needles grow faster than the pyramidal γ crystals formed at lower concentrations. The transparent needles coming off the main horizontal mass at an angle are the result of secondary nucleation. The fact that the initially formed needle was oriented horizontally is consistent with its induction by the applied dc field, although the location of the initially observed crystal is independent of the position in the sample tube relative to the electrodes. The needle morphology is also observed in spontaneously nucleating solutions at these high concentrations.

The aqueous glycine solutions that were exposed to dc fields have a pH of 6.4–6.5, which is close to, but not exactly at, the isoelectric point of glycine (where the average charge on a glycine molecule is zero), which occurs at a pH of 6.0 [25]. At pH far from this value, there can be a substantial concentration of charged glycine species such as $^{+}NH_3CH_2COOH$ or $NH_2CH_2COO^{-}$. Such species, when subjected to a dc-electric field, will tend to migrate toward the electrode with the opposite charge, effectively increasing the supersaturation near the electrode, which in itself can be responsible for inducing nucleation. Our calculations, based on the multiple equilibria among $^{+}NH_3CH_2COOH$, $NH_2CH_2COO^{-}$, $^{+}NH_3CH_2COO^{-}$, and NH_2CH_2COOH [26], indicate that

TABLE I. Polymorphs obtained from aged aqueous glycine solutions under different nucleation conditions.

SS	Nucleation conditions	Sample size	Percent samples pure α	Percent samples pure γ	Percent samples mixed $\alpha + \gamma$
1.85	Spontaneous	22	86	14	0
1.85	dc field	4	50	50	0
1.9–2.0	Spontaneous	15	13	60	27
1.9–2.0	dc field	5	0	100	0

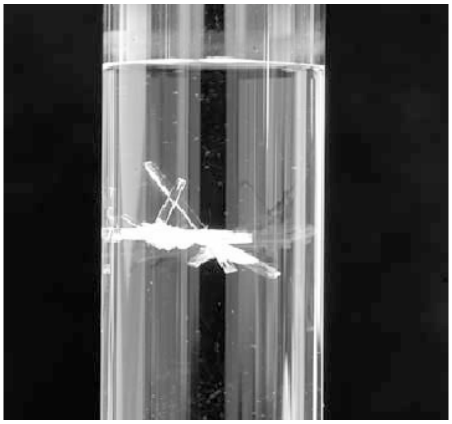

FIG. 4. γ-glycine crystals formed by dc-electric-field-induced nucleation.

for 5.7 molal glycine in pure water, $\geq 99.93\%$ of the species present in solution are neutral zwitterions (compared with 99.96% at the isoelectric point), and thus the ion migration mechanism described above can be ruled out. Moreover, the pH of solutions made from neutral glycine are predicted to be largely insensitive to concentration [26].

Another potential cause of solute migration is electrostriction, in which polarizable molecules can minimize their energy by moving to regions of highest electric field. Because the electric-field distribution in our sample tubes is not uniform, there are electrostrictive energy differences [27] at different locations given by $\frac{1}{2}\langle\alpha\rangle\Delta(E^2)$, where $\langle\alpha\rangle$ is the average polarizability of glycine $(7\times10^{-40}\,\mathrm{C\,m^2/V})$ and $\Delta(E^2) = E_{\max}{}^2 - E_{\min}{}^2 = 2\times10^{12}\,\mathrm{V^2/m^2}$. This gives a maximum energy difference of 10^{-7} kT, which is totally negligible.

We believe these dc-field-induced experiments lend further support to our proposed optical-Kerr mechanism for NPLIN. Furthermore, it represents a new method for controlling nucleation in supersaturated solutions and may provide another technique for controlling polymorph formation, and possibly forming new polymorphs.

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[1] A. S. Myerson and R. Ginde, in *Handbook of Industrial Crystallization*, edited by A. S. Myerson (Butterworths, Montvale, MA, 1992).

[2] D. W. Oxtoby, Acc. Chem. Res. **31**, 91 (1998); Nature (London) **406**, 464 (2000).

[3] P. G. Vekilov, Cryst. Growth Design **4**, 671 (2004).

[4] I. Weissbuch, R. Popovitz-Biro, M. Lahav, and L. Leiserowitz, Acta Crystallogr. Sect. B **51**, 115 (1995).

[5] F. J. J. Leusen, J. Cryst. Growth **166**, 900 (1996).

[6] S. M. D'Souza, C. Alexander, S. W. Carr, A. M. Waller, M. J. Whitcombe, and E. N. Vulfson, Nature (London) **398**, 312 (1999).

[7] J. Aizenberg., D. A. Muller, J. L. Grazul, and D. R. Hamann, Science **299**, 1205 (2003).

[8] I. Weissbuch, L. Leiserowitz, and M. Lahav, Adv. Mater. **6**, 952 (1994).

[9] B. A. Garetz, J. E. Aber, N. L. Goddard, R. G. Young, and A. S. Myerson, Phys. Rev. Lett. **77**, 3475 (1996).

[10] F. C. Wen, T. McLaughlin, and J. L. Katz, Phys. Rev. A **26**, 2235 (1982).

[11] B. A. Garetz, J. Matic, and A. S. Myerson, Phys. Rev. Lett. **89**, 175501 (2002)

[12] J. F. Reintjes, *Nonlinear Optical Parametric Processes in Liquids and Gases* (Academic Press, New York, 1984).

[13] J. Matic, X. Sun, B. A. Garetz, and A.S. Myerson, "Intensity, Wavelength and Polarization Dependence of Non-photochemical Laser-Induced Nucleation in Supersaturated Aqueous Urea" (to be published)

[14] L. Jensen, P.-O. Astrand, A. Osted, J. Kongsted, and K. V. Mikkelsen, J. Chem. Phys. **116**, 4001 (2002).

[15] J. Zaccaro, J. Matic, A. S. Myerson, and B. A. Garetz, Crystal Growth and Design **1**, 5 (2001).

[16] D. W. Oxtoby, Nature (London) **420**, 277 (2002).

[17] I. M. Svishchev and P. G. Kusalik, Phys. Rev. Lett. **73**, 975 (1994).

[18] M. Matsumoto, S. Saito, and I. Ohmine, Nature (London) **416**, 409 (2002).

[19] C. N. Nanev and A. Penkova, J. Cryst. Growth **232**, 285 (2001).

[20] M. Taleb, C. Didierjean, C. Jelsch, J. P. Mangeot, B. Capelle, and A. Aubry, J. Cryst. Growth **200**, 575 (1999).

[21] A. Penkova, O. Gliko, I. L. Dimitrov, F. V. Hodjaoglu, J. Cryst. Growth 275, e1527 (2005).

[22] W. H. Orttung and J. A. Meyers, J. Phys. Chem. **67**, 1911 (1963).

[23] J. W. Mullin, *Crystallization* (Butterworth-Heinemann Ltd., Oxford, 1993), 3rd ed.

[24] E. Butkov, *Mathematical Physics* (Addison-Wesley, Reading, MA, 1968).

[25] C. S. Towler, R. J. Davey, R. W. Lancaster, and C. J. Price, J. Am. Chem. Soc. **126**, 13347 (2004).

[26] E. J Cohn and J. T. Edsall, *Proteins, Amino Acids and Peptides as Ions and Dipolar Ions, 96* (ACS Monograph, Reinhold, NY, 1943).

[27] R. W. Boyd, *Nonlinear Optics* (Academic Press, Boston, 1992).