S1. Molecular Dynamics (MD) Simulation Details

S1.1 Simulation Scheme

GROMACS code(1) was used for MD simulations. Dodecahedron box of volume 216.48 nm^3 was used to create simulation boxes at different supersaturation ratios. Experimental solubility of the glutamic acid molecule at 300K was used as a basis to decide the number of water (solvent) molecules and glutamic acid (solute) molecules in the simulation box. Optimized Potentials for Liquid Simulations - All atom (OPLS-AA) was used to model the intermolecular and intramolecular interactions. The definitions of intramolecular interactions were obtained from the built-in database of the GROMACS package. Simple Point Charge Extended (SPCE) water model was used to model the water molecules. The functional form of van der Waals, electrostatic, and mixing rules for such interactions are given below.

$$U_{LJ}\left(r_{ij}\right) = 4\varepsilon_{ij}\left[\left(\frac{\sigma_{ij}}{r_{ij}}\right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}}\right)^{6}\right] \tag{1}$$

$$U_{Co}\left(r_{ij}\right) = \frac{1}{4\pi\varepsilon_0}\frac{q_i q_j}{r_{ij}} \tag{2}$$

σ_{ij} , ε_{ij} , and q_i are the atom-specific parameters, as described in the OPLS/AA force field.

Lorentz-Berthelot mixing rules were used to calculate atom-specific parameters and are given below.

$$\sigma_{ij} = \frac{1}{2}\left(\sigma_{ii} + \sigma_{jj}\right) \tag{3}$$

$$\varepsilon_{ij} = \sqrt{\varepsilon_{ii}\varepsilon_{jj}} \tag{4}$$

The potential mesh Ewald (PME) method was used for the summation of intermolecular interaction. The cut-off distance was 1 nm.

The simulations were performed using the GROMACS package for a total of 7 ns, including the 1 ns equilibration at isothermal (NVT) and isobaric (NPT) ensembles. The production run of 5 ns was performed in the isobaric ensemble. Before equilibration, the system's energy was minimized using the steepest descent algorithm with an initial step size of 0.01 nm. Leap-frog stochastic dynamics integrator was used for further simulations. The integrator applied the temperature coupling with a time constant of 0.1 ps. For isothermal equilibration, velocities were generated using Maxwell distribution. The pressure coupling during the NPT equilibration was achieved using the Berendsen coupling algorithm. In the production run, Parrinello-Rahman pressure coupling was used. The output files containing the coordinates, velocities, and energies were obtained at every 1 ps. All of the output files were used to obtain the results averaged over the entire trajectory. The number of glutamic acid molecules and water molecules in a simulation box

were decided on the basis of the experimental solubility of glutamic acid molecules and is given in the literature.(2, 3)

S1.2 Force Field Validation

The choice of OPLS/AA force field was validated by comparing the free energy of solvation calculated using the simulations and the experimental value reported in the literature. The simulations were conducted as follows:

(1) A single GLU was put into the box of 216.48 nm^3. The box was then solvated with the SPCE water molecules.

(2) The box was energy minimized to a threshold of 100 kJ mol^{-1}.

(3) The system was equilibrated for 1 ns each on NVT and NPT ensembles.

(4) Various states of GLU were generated by gradually decoupling the intermolecular interaction (van der Waals and electrostatic). The state at $\lambda = 0$ represents the fully decoupled GLU such that the intermolecular interactions at this state are completely turned off. The state at $\lambda = 1$ represents the fully coupled GLU such that all intermolecular interactions are fully on. Points in-between 0 and 1 represent the fraction of decoupling.

(5) 2 ns simulations at all 13 states (2 end states and 11 in-between states) were carried out.

(6) The free energy change required for GLU to be solvated in water was then calculated using Bennet Acceptance ratio (BAR) using the built-in command of GROMACS (gmx bar). The schematic of this process is given in **Figure S2**.(4)

The box geometry used in the simulations combined with the SPCE water model yields the free energy of solvation value of -293.27 ± 5.136 kJ mol^{-1}. The calculated value matches closely with the value reported in the literature -300 kJ mol^{-1}. The plot of energy change from each subsequent state given by the λ value is shown in **Figure S3**.(5)

After validating the force field with the experimental free energy of solvation, the frequency-dependent dielectric constant was calculated. This frequency-dependent dielectric constant was then compared with the frequency-dependent dielectric constant at the highest supersaturation of 2.5 considered in this study. The stead-state dielectric constant value of 2.33 increases slightly to 2.41 from the undersaturated environment of glutamic to high supersaturation environment. It indicates that, although the glutamic acid molecules are experiencing higher electrostatic interaction at high supersaturation, the overall increase is not significantly different.

S2. Analysis of the MD simulation trajectories

S2.1 Choice of glutamic acid molecules

The trajectory was visually inspected with the help of VMD. Then the glutamic acid molecules which experience the significant force were shortlisted. The high force acting on the glutamic acid molecule is due to interaction with the other glutamic acid molecules in the trajectory. The molecules that do not significantly interact were termed as non-significant. The running average

of the norm of force vs. time of such molecules shows that the norm of force remains around a steady value during the simulation. The molecules that significantly interact were termed as significant. The running average of the norm of force vs. time of such molecules shows that the norm of force keeps increasing during the simulation. The movie of the trajectory of the system, which represents supersaturation $\sigma = 2.5$, is given separately as an MP4 file. The difference between significant and non-significant interactions is shown in **Figure S5**.

S2.2 Obtaining Radial Distribution Functions (RDFs)

The Radial Distribution Functions of glutamic acid molecules in water have shown that the thickness of the solvation shell around glutamic acid molecules is 0.6 nm when the solvent is water.(3) Using the command "gmx distance," pairs of glutamic acid molecules where the distance between the two glutamic acid molecules is less than twice the thickness of the solvation shell was obtained. For all such portions of the trajectory, the Radial Distribution Function (RDF) of water around various functional groups was obtained. For all of the RDFs, oxygen on the water molecule was observed.

S2.3 Obtaining Spatial Distribution Functions (SDFs)

Spatial distribution (SDFs) functions were plotted using the TRAVIS package.(6) For all the SDFs, the entire simulation box was binned in 100 points in each direction. At all the grid points, the number of water molecules was averaged over time and normalized with respect to the bulk density of water molecules, which yields the SDF relative density. The "isolvaue" option in the VMD package was used to visualize simulation box portions at specific density values.

S2.4 Obtaining the Interaction Energy Landscape

The double-well approach described in the previously published article(3) was used to obtain the configuration of glutamic acid molecules at the transition state at low and high supersaturations. Both molecules at the transition state were rotated around the center of geometry at the intervals of 51.42^{o} around the x-, y-, and z- axes. The interaction energy was calculated at each rotation by summing up the van der Waals and electrostatic contributions.

S2.5 Similarity Region of the Interaction Energy Landscape

At each rotation, to calculate the similarity between α and β polymorph, the crystal structures of the two polymorphs were analyzed. Using the atomic coordinates obtained from Cambridge Crystallographic Database (CCDC), the distances between each atom of the unit cell between all the other atoms on other molecules in the unit cell were calculated for both polymorphs. Eight different atom pairs were shortlisted, which fully differentiate between the α and β polymorphs. All these distances were normalized with the pair having the highest distance. The new set of relative distances were used to obtain similarity with α and β polymorphs at each rotation of glutamic acid molecules. Every point was assigned a similarity with either α and β polymorphs based on minimum relative error. Only the points which show greater than 20% match with either of the polymorphs were considered.

S3. Umbrella Sampling

The Umbrella sampling technique was employed at supersaturation ratios 1.2, 2, and 2.5. The glutamic acid molecules were position restrained in two distinct cubic simulation boxes. The glutamic acid molecules were position restrained to configuration obtained from the crystal structure of α polymorph to calculate the activation barrier required to form α polymorph. The glutamic acid molecules were position restrained to the configuration obtained from the crystal structure of β polymorph to obtain the activation barrier required to form β polymorph. Both simulation boxes were equilibrated for 1 ns each on the isothermal and isobaric ensemble while glutamic acid molecules were restrained. Then position restrain on one of the glutamic acid molecules was removed, and that glutamic acid molecule was allowed to move away from the other glutamic acid molecule. The pull force constant was set to 1000 kJ mol^{-1} nm^{-1}. The pull spring constant was set to 2 nm ns^{-1}. The production run was stopped when the distance between the center of mass of the two glutamic acid molecules was higher than 1.2 since that is higher than twice the solvation shell thickness. It also prevents the interaction of the free glutamic acid molecule with the periodic image of position restrained glutamic acid molecule. The force profiles were obtained during the production run are shown in figure S9. Based on the distances between the two glutamic acid molecules in both cases, the configuration of glutamic acid molecules at certain times was shortlisted for an Umbrella sampling production run. For the Umbrella sampling production run, each configuration was equilibrated in NPT ensemble for 100 ps, and the production run was performed for 1 ns. During Umbrella sampling simulations, the pull spring constant was set to zero. The weighted histograms analysis method (WHAM) method was used to analyze the force profiles at each of the sampled distances to calculate the mean energy required to pull the glutamic acid molecule away from the restrained glutamic acid molecule.

Section S4 Kinetic Monte-Carlo Simulations

S4.1 Simple kMC

Probability of glutamic acid molecule in bulk forming either α or β polymorph was calculated using simple kinetic Monte-Carlo simulations. The following equations were used to obtain normalized probabilities. Results were averaged over 10^7 kMC steps.

$$P_\alpha \propto e^{\frac{-\Delta E_\alpha}{RT}} \tag{5}$$

$$P_\beta \propto e^{\frac{-\Delta E_\beta}{RT}} \tag{6}$$

$$P_{\alpha,N} = \frac{P_\alpha}{P_\alpha + P_\beta} \tag{7}$$

$$P_{\beta,N} = \frac{P_\beta}{P_\alpha + P_\beta} \tag{8}$$

Where P denotes probability, ΔE represents activation barrier, subscript α denotes α-polymorph, subscript β denotes β-polymorph, subscript N is to describe normalized values.

S4.2 3D Lattice kMC

A cubic box of volume 21648 nm^3 was constructed. The distance between grid points and the timestep was kept such that a molecule can only jump 1 grid point based on the effective diffusion coefficient obtained from the slope of mean squared displacement (MSD) of the molecules. The molecules were represented by point particles. The probability of formation of either of the polymorph was calculated using equations (5) – (8). When the two molecules were only a grid point away, then molecules were removed from the box if the polymorph is formed based on the random number generated. The system was simulated for 100 ns, and the number of molecules left in the box is shown in **Figure S14**. The number of molecules left is close to the solubility limit, which validates the simple kMC simulation approach. The number of molecules used in the simulation box and the diffusion coefficients obtained MSD vs. time plot are shown in **Table S1**.

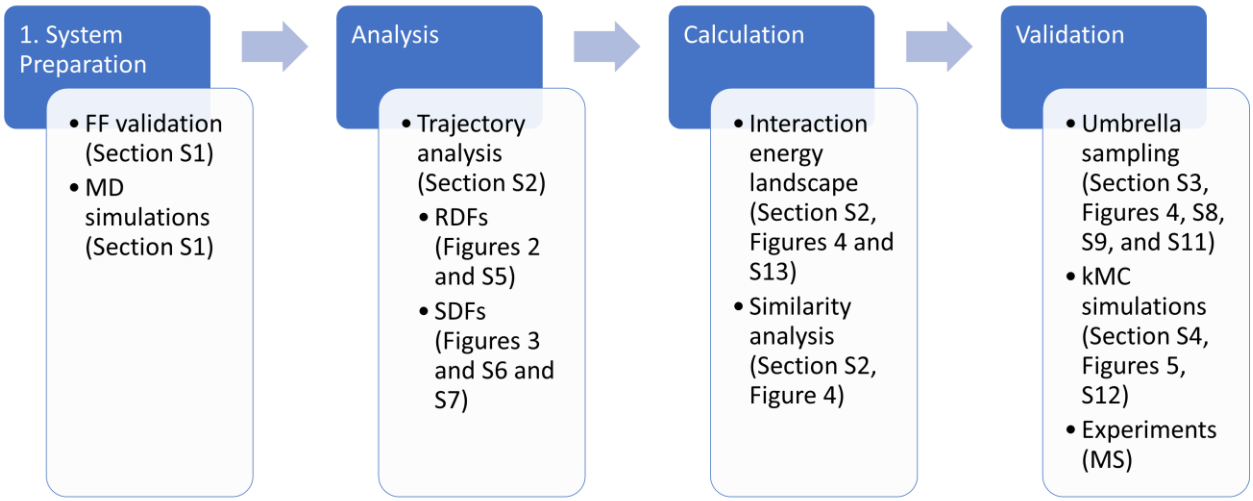

Figure S1: Overview of the protocol followed in this study.

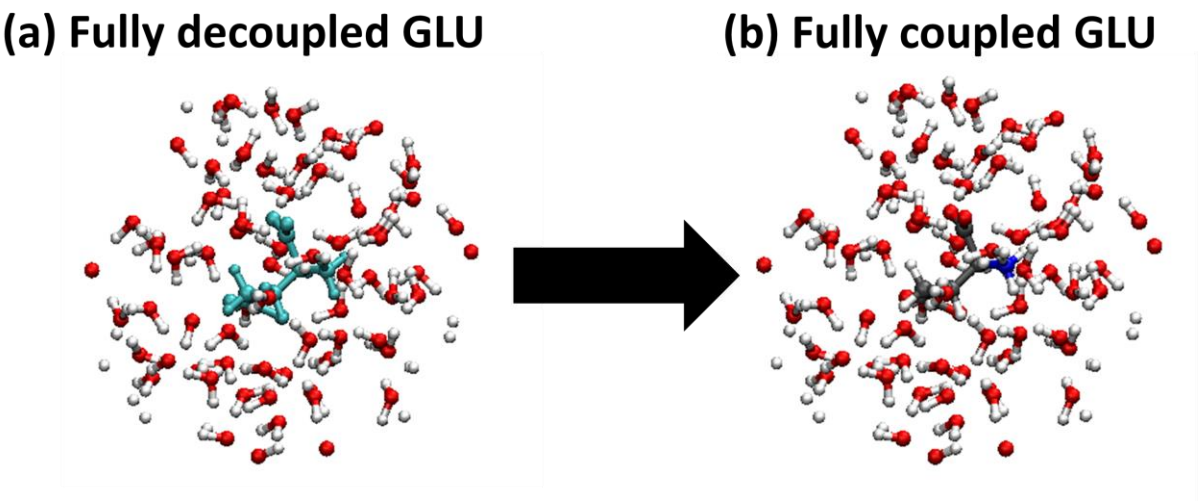

Figure S2: The overview of calculation free energy of solvation simulation protocol. (a) Interaction of fully decoupled glutamic acid molecule (green) with the surrounding water molecule. This state is represented by $\lambda = 0$, where all intermolecular interactions of the glutamic acid molecule are turned off. (b) Interaction of fully coupled glutamic acid molecule with the surrounding water molecule. This state is represented by $\lambda = 1$, where all intermolecular interactions of the glutamic acid molecule are turned off.

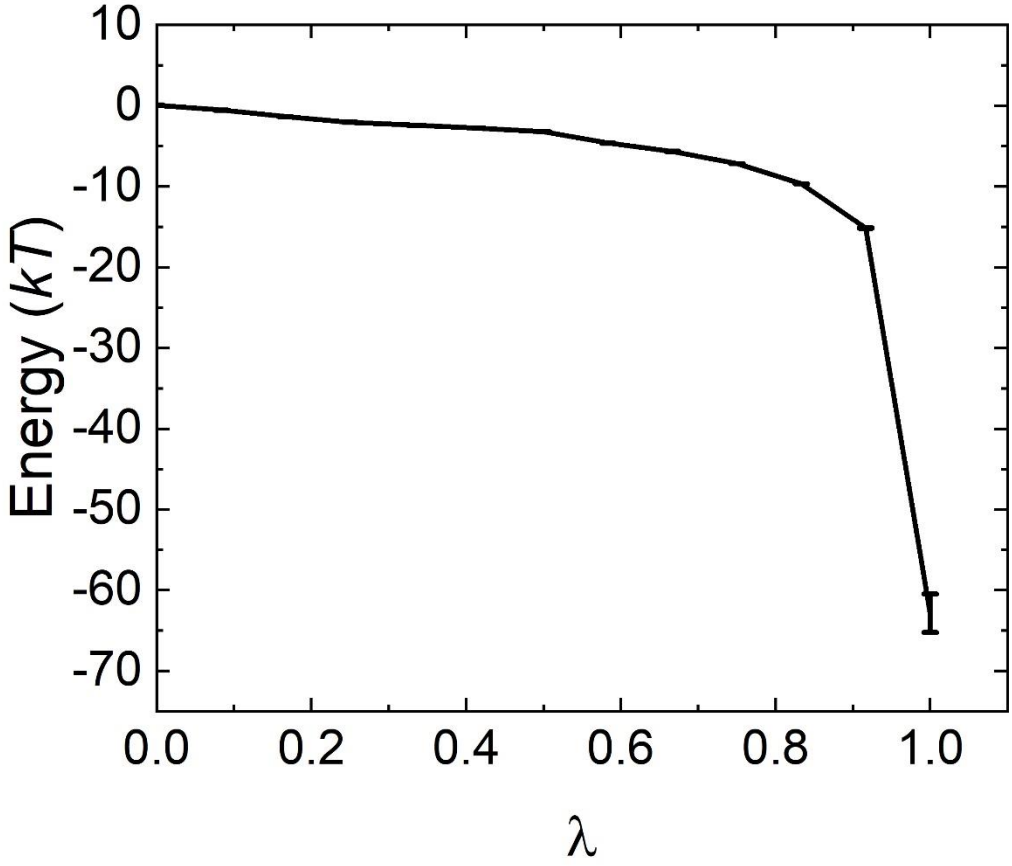

Figure S3: Energy change at subsequent λ point.

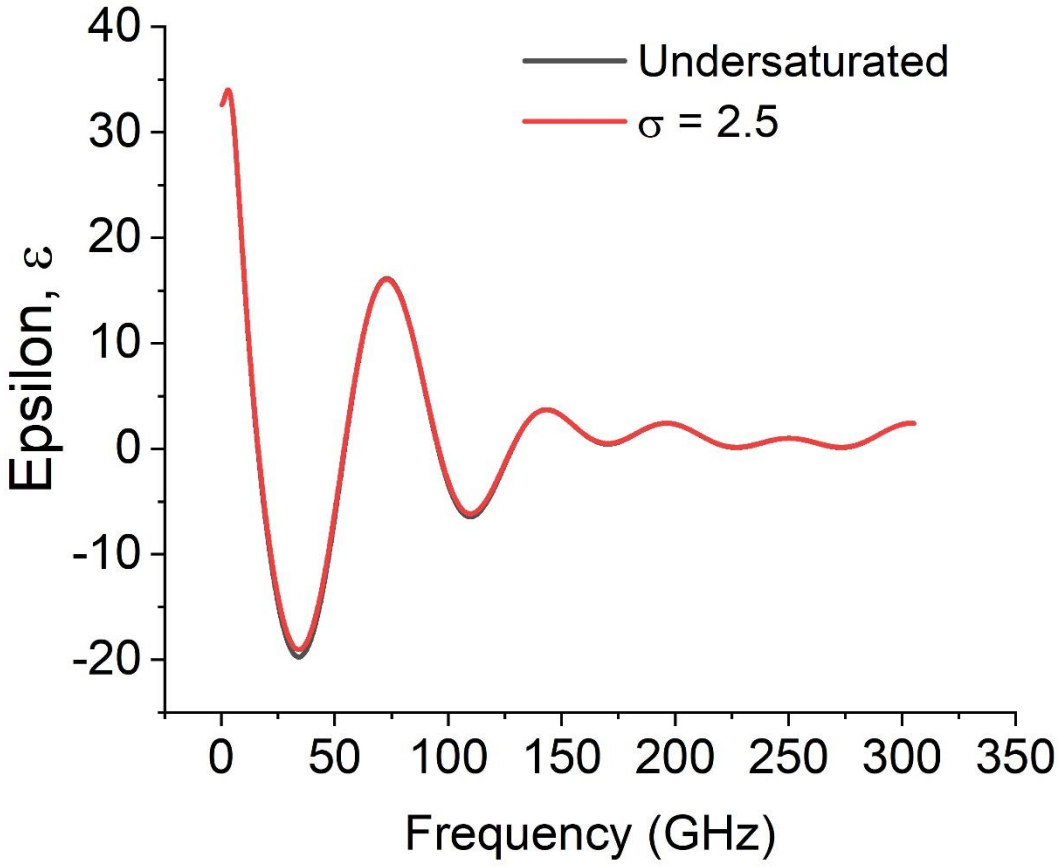

Figure S4: Frequency dependent dielectric constant (permittivity) of GLU in undersaturated environment and in high supersaturation environment.

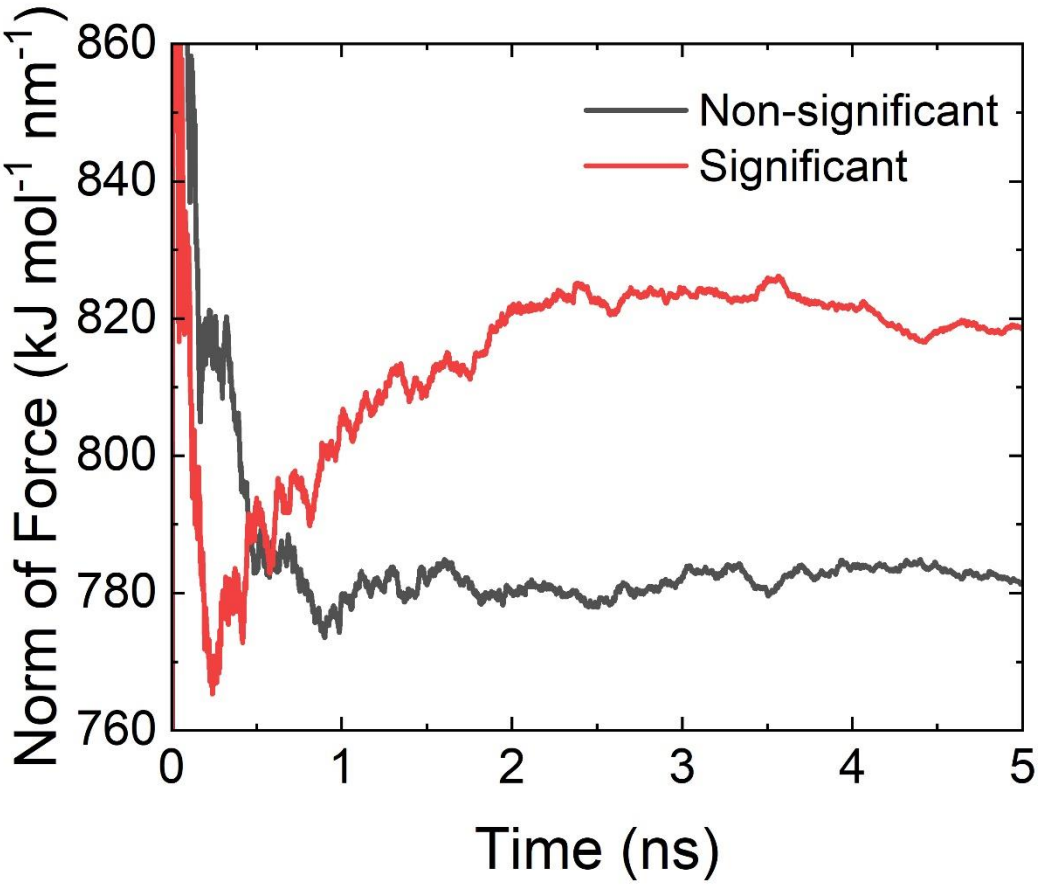

Figure S5: The norm of force on the center of mass (COM) of two glutamic acid molecules. The black curve represents a non-significant glutamic acid molecule that does not interact with the other molecules in the simulation box. The red curve represents the a significant glutamic acid molecules which is chosen for further analysis as it interacts significantly with the other glutamic acid molecules in the simulation box.

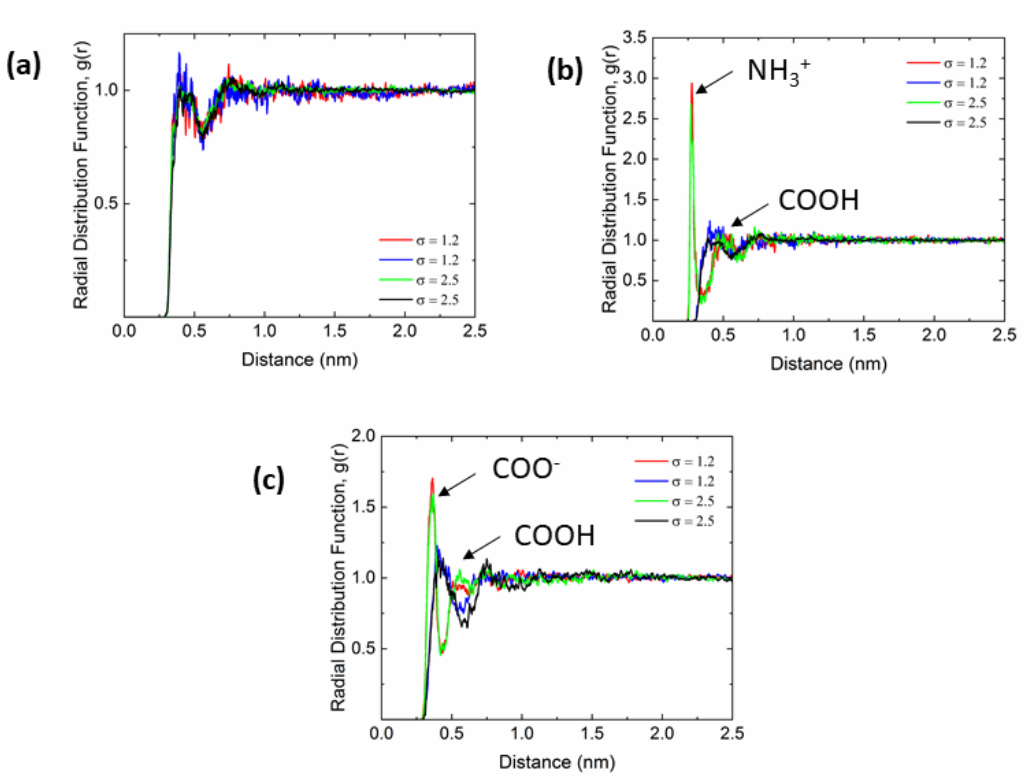

Figure S6: Radial Distribution Functions involving COOH functional group.

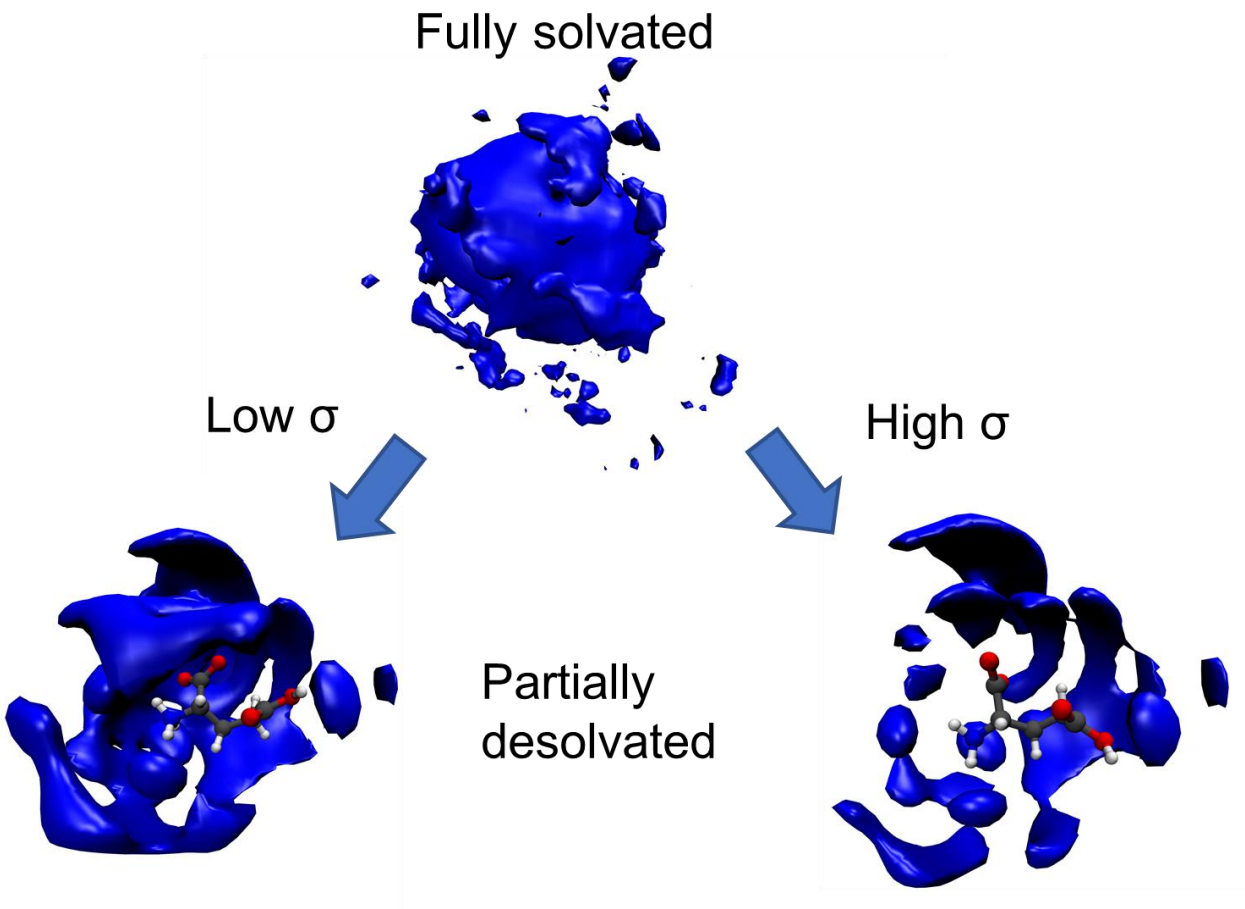

Figure S7: The transition of glutamic acid molecule from fully solvated to partially desolvated configuration and the average solvation shell as a function of supersaturation.

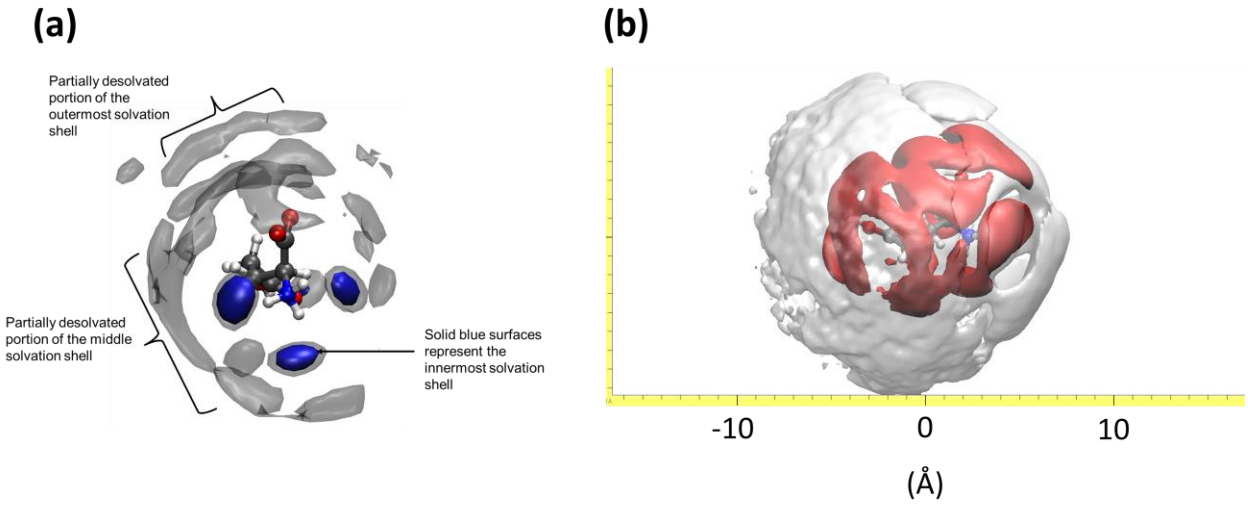

Figure S8: The layers of solvation shell. (a) Visualization of primary, secondary, and tertiary solvation shell. (b) The change in the solvation shell at a distance given by the x-axis. The value of 0 Å in (b) is aligned with the center of mass of glutamic acid molecule

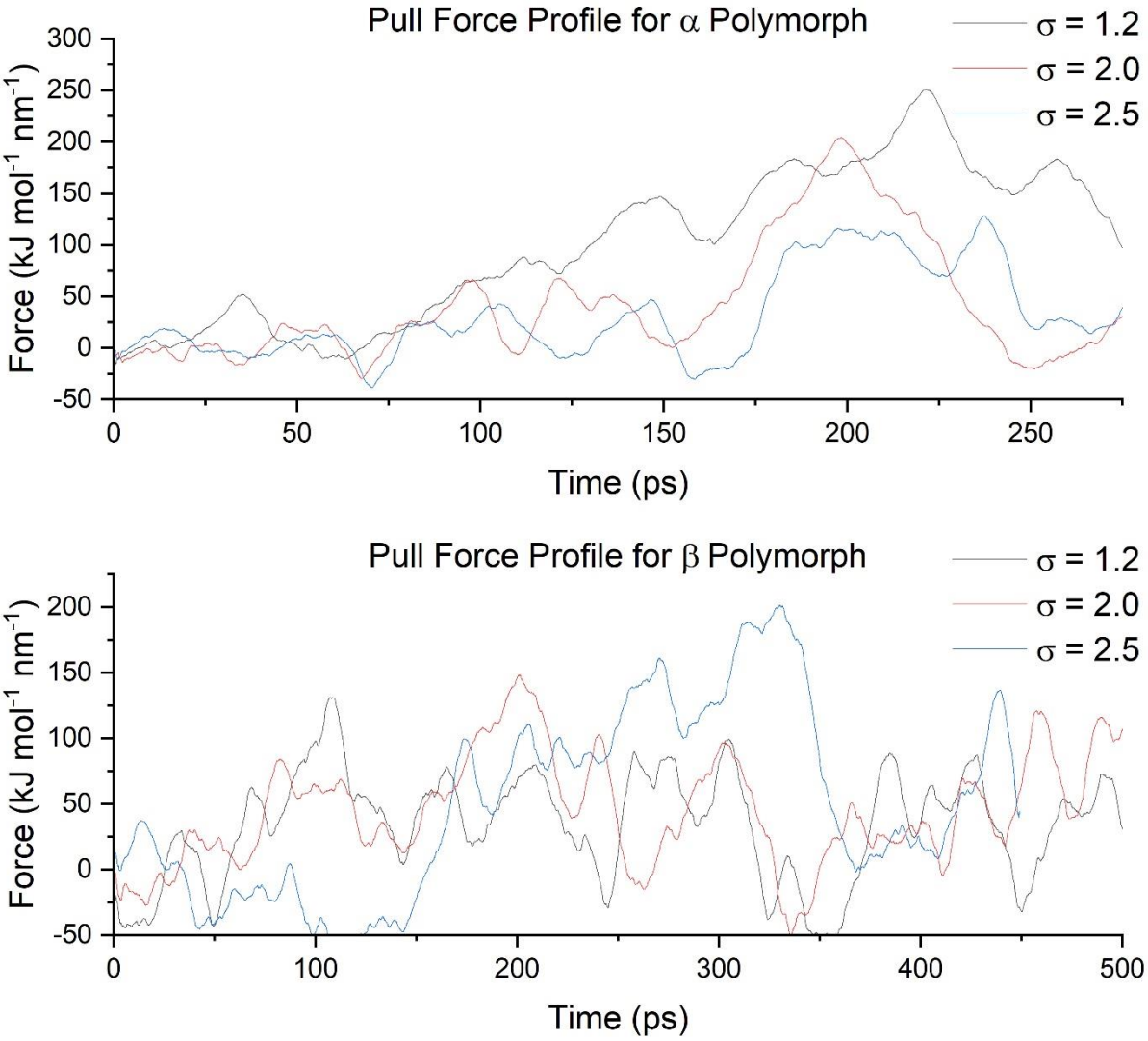

Figure S9: Pull force profiles required to move a glutamic acid molecule away from a restrained glutamic acid molecule as a function of supersaturation with initial configuration resembling to (a) α polymorph, and (b) β polymorphs.

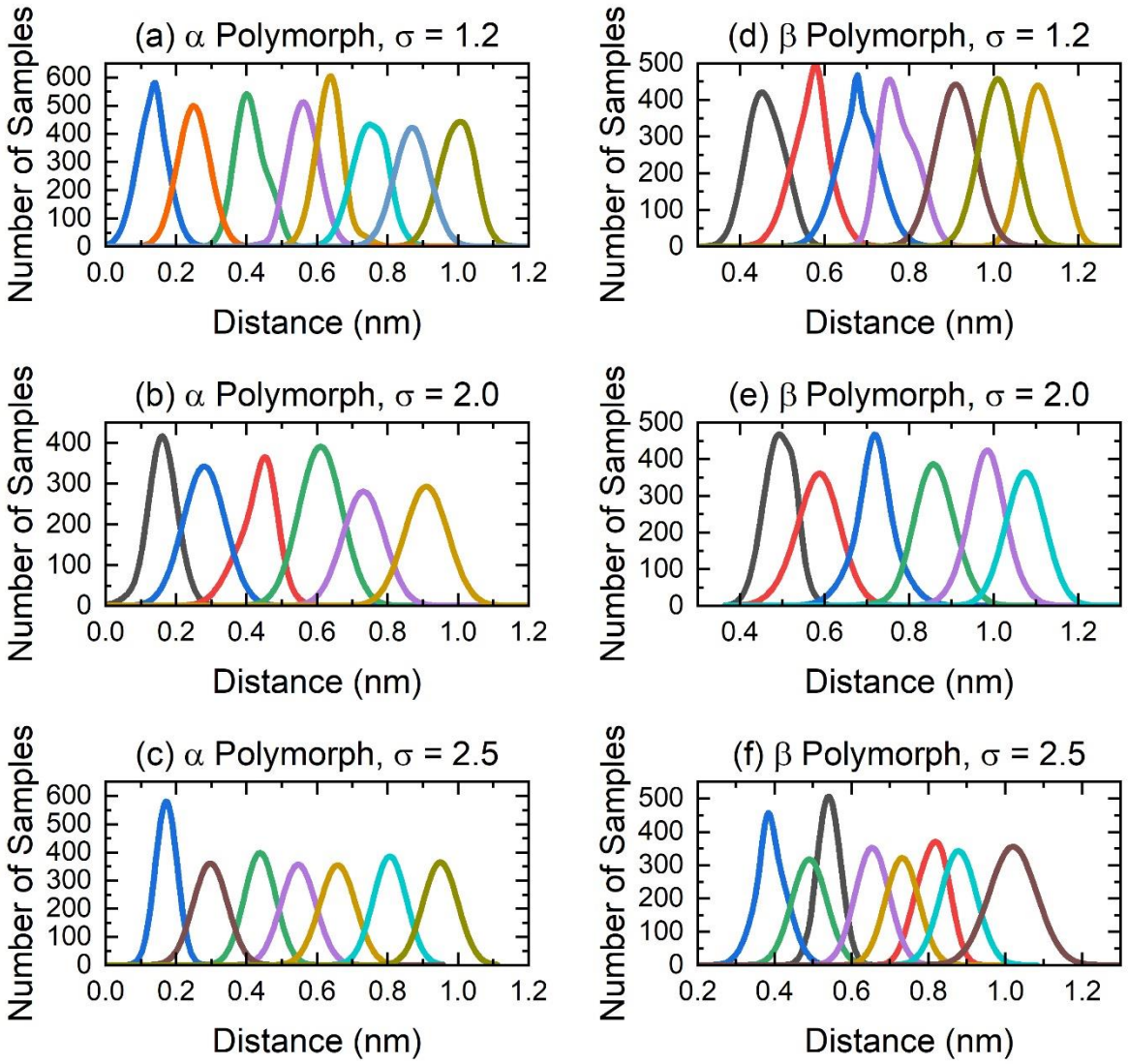

Figure S10: Number of samples at each distance used in Umbrella sampling technique. Different colors are used only to guide the eye. The title describes initial configuration of the two glutamic acid molecules as well as the supersaturation ratio.

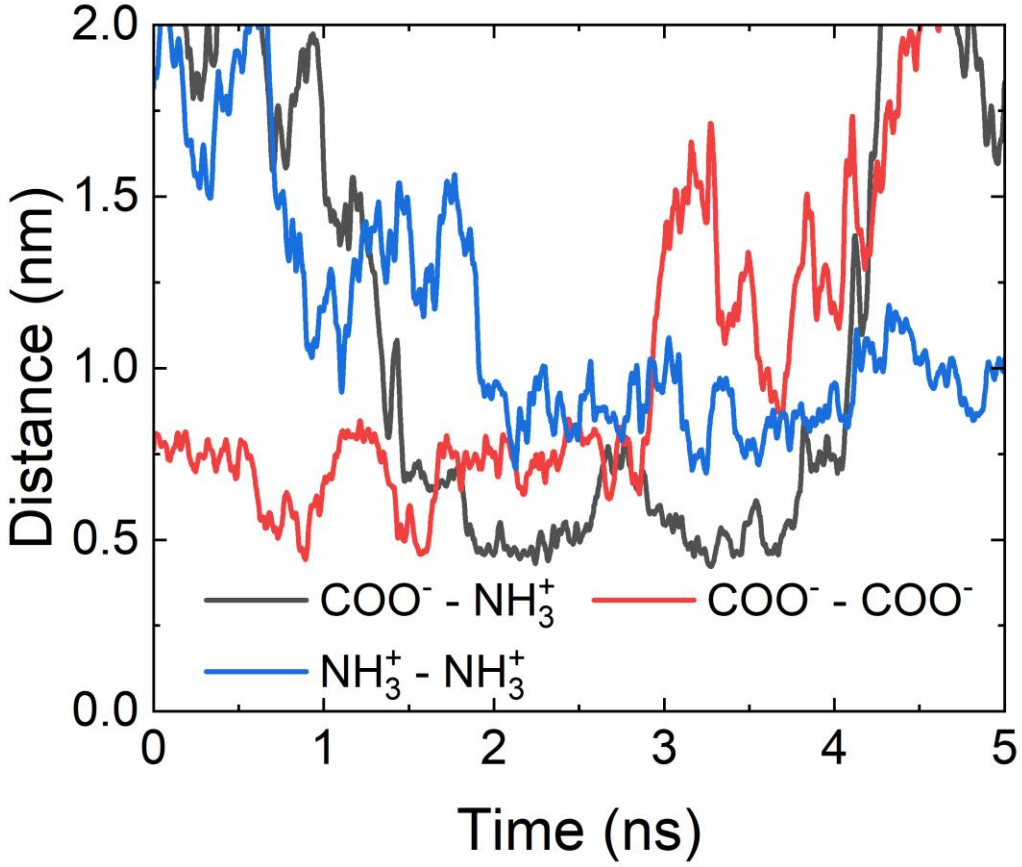

Figure S11: The distance between the two interacting molecules in different orientations given by the interacting functional groups in the legend

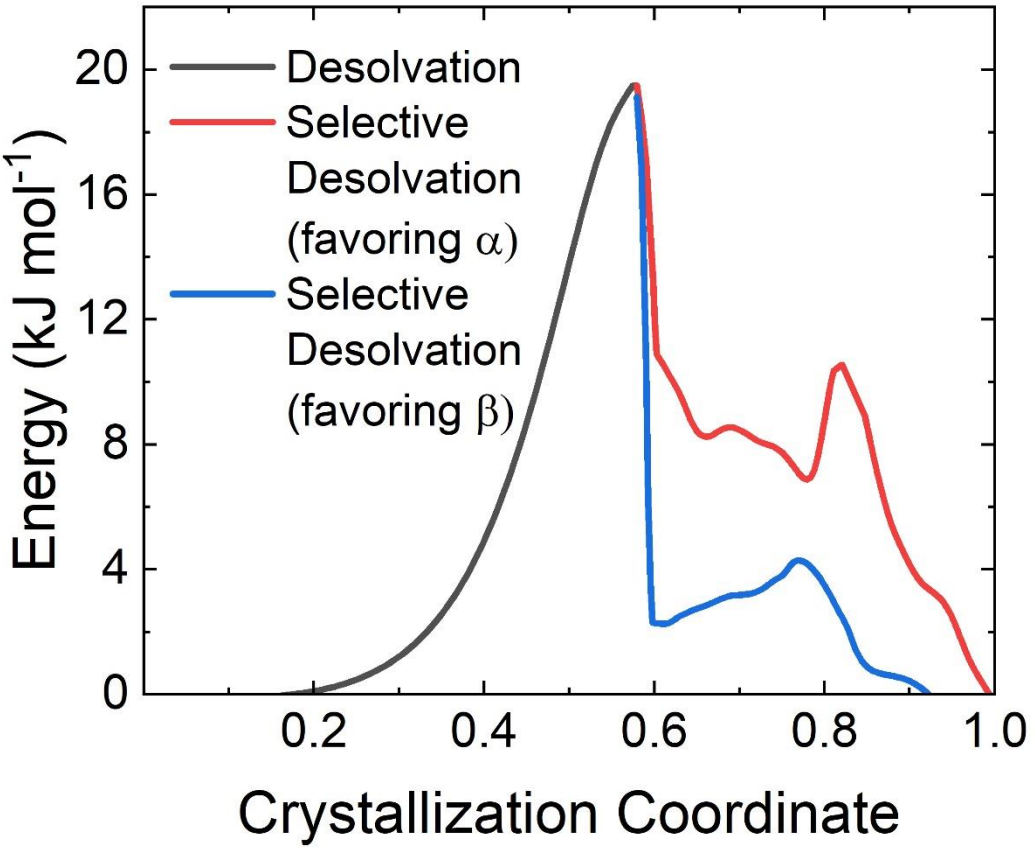

Figure S12: Activation barrier energy profile for σ = 2.

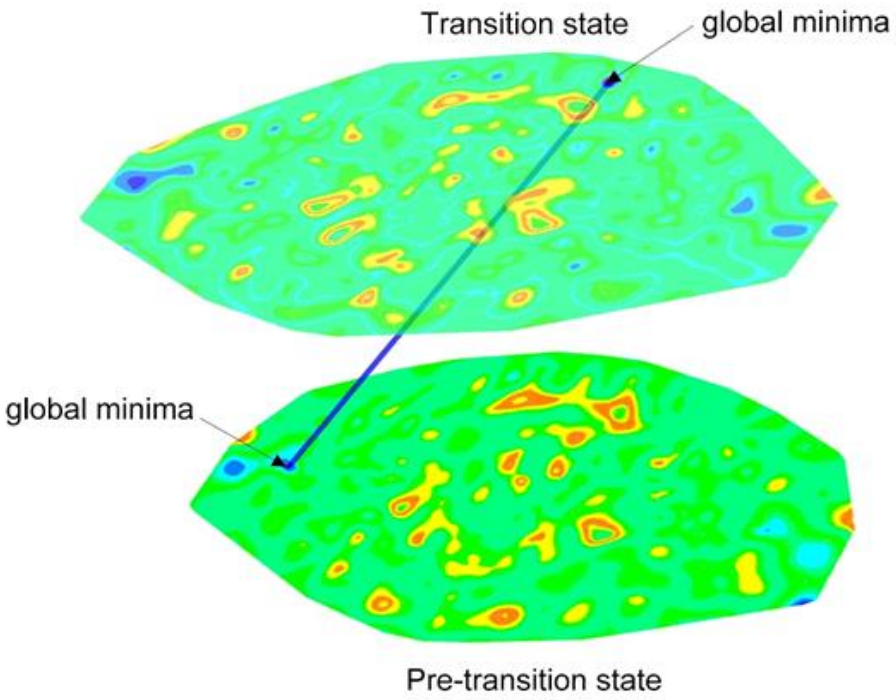

Figure S13: Change of location of global minima from before transition state and at the transition state.

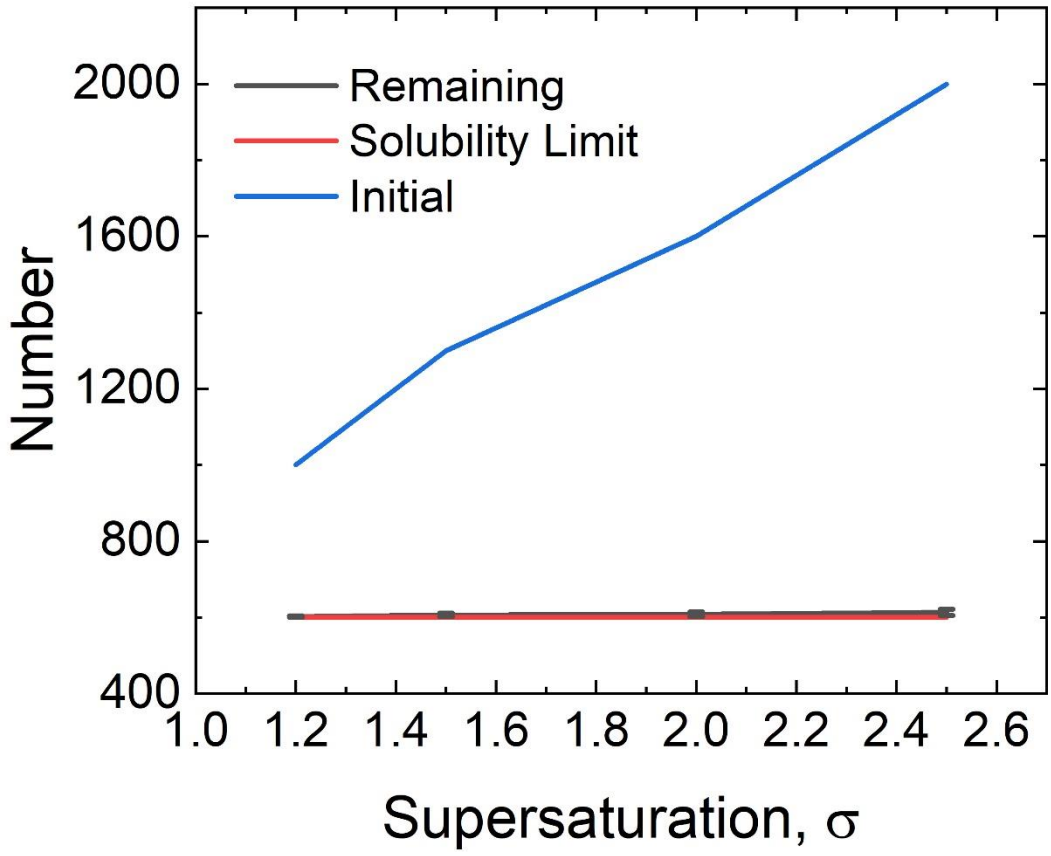

Figure S14: The number of molecules remaining on the lattice after kMC simulation of 100 ns.

Table S1: Number of molecules and the diffusion constant at each supersaturation

Supersaturation	**Number of molecules**	**Diffusion coefficient (nm^2/ns)**
1.2	1000	0.2462
1.5	1300	0.2209
2	1600	0.1685
2.5	2000	0.1593

Table S2: Lattice parameters of glutamic acid polymorphs

Parameter	**Value**
β-polymorph (CCDC refcode: LGLUAC01)	
$\alpha = \beta = \gamma$	90^o
a	5.154 Å
b	6.942 Å
c	17.274 Å
α-polymorph (CCDC refcode: LGLUAC02)	
$\alpha = \beta = \gamma$	90^o
a	7.068 Å
b	10.277 Å
c	8.755 Å

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