Supporting Information for:

Does the γ Polymorph of Glycine Nucleate Faster? A Quantitative Study of Nucleation from Aqueous Solution

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Function Fitting

The datasets in the main article were fit with exponential and Weibull functions. Here we explain how we did this. For an exponential $P(t)$ with rate k, plotting $\ln P(t)$ against t gives a straight line of slope $-k$. So our exponential fits are fits of a straight line to $\ln P(t)$ as a function of t. However, we expect the final few points to be noisy as there we have few samples remaining uncrystallised ($P(t)$ is then small), and so the statistics are poor there. So we use a weighted least squares fitting,[1] with point i weighted by $P_i = P(t_i)$, which is optimal assuming that the variance in $\ln P_i$ scales approximately as $1/P_i$.[1] The function minimised is then

$$\sum_{i=1}^{n} P_i \left(\ln P_i - k t_i\right)^2 \tag{S1}$$

For a Weibull distribution, $P(t)$ can be written as

$$\ln\left[-\ln[P(t)]\right] = \beta \ln(t) - \beta \ln(\tau) \tag{S2}$$

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This equation gives a simple linear relationship between the two variables. For our data we then use the standard least squares method on a plot of $\ln[-\ln[P(t)]]$ against $\ln(t)$ to determine values of β and τ.

Microplate cooling

The plate and samples cool to room temperature within the first hour of the experiment. The temperature of a well in the centre of the plate and a well in one of the corners of the plate are plotted in Figure S1. The corner well took 20 minutes to cool to within 1 $^{\circ}C$ of room temperature. The centre well took 30 minutes to cool to within 1 $^{\circ}C$ of room temperature. Both wells were within 0.1 $^{\circ}C$ of room temperature after 1 hour.

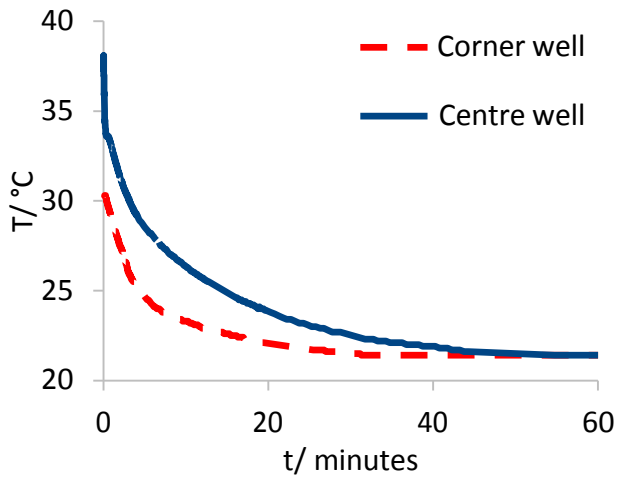

Figure S1: A plot of the temperature of the glycine solution in the wells as a function of time for the hour after injecting the solution into the wells.

Growth rate calculation

We estimated growth rates for all the nucleation events occurring between 1 and 48 hours for one of the runs from dataset G. After each nucleation event, the largest distance across the crystal was measured on each image for an hour after nucleation. We give an example of how we measured crystal size as a function of time in Figure S2.

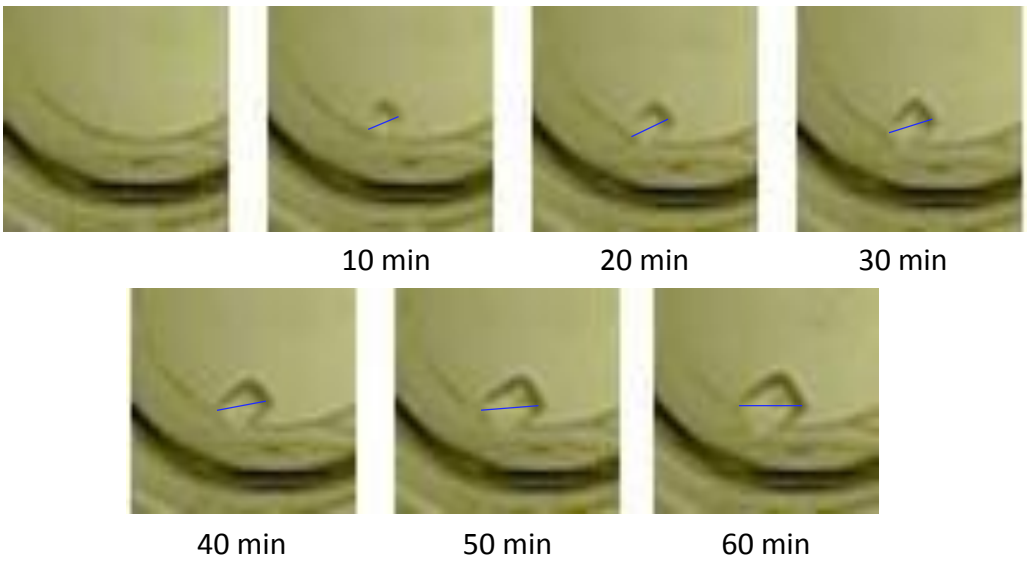

Figure S2: A crystal nucleating and growing over an hour long period. We show a zoomed-in image of part of a single well in 7 successive images. Each image is labelled by time since the time of the last image in which no crystal was visible. For the crystals the size is measured by the greatest distance across the crystal. This is indicated by a blue line marked on the crystal.

The sizes of each of the 57 crystals from the run used can be seen in Figure S3(a). For each crystal $t = 0$ was defined as the time of the last image in which there was no visible crystal. We do not know exactly when each nucleation event occurs, just to the nearest 10 minute interval. For this run we analyse images taken every 10 minutes. The minimum size at which we could detect a crystal is about 0.11 mm. We assume the crystal is at the minimum detectable size in the image at $t = 0$, hence we assume the crystal size is 0.11 mm at $t = 0$, and so we estimate a lower bound for the growth rate of each crystal.

Initially growth rates were obtained by applying a linear fit to each size as a function of time for the full hour, the resulting growth rates can be seen in Figure S3(b). The problem with this approach is some of the fastest growing crystals stop growing within the hour; their size plateaus once they are around 1.7 mm across, see for example the pale blue or pale green curves in Figure S3(a). Thus for the fast growing crystals that plateau well before 60 mins, this method of fitting to data for the whole 60 mins, underestimates growth rates. Hence for each series all the data points up to the first point past 1.7 mm only, were used to fit growth rates for the histogram in Figure 3 of the main paper. This is more accurate for the faster growing crystals.

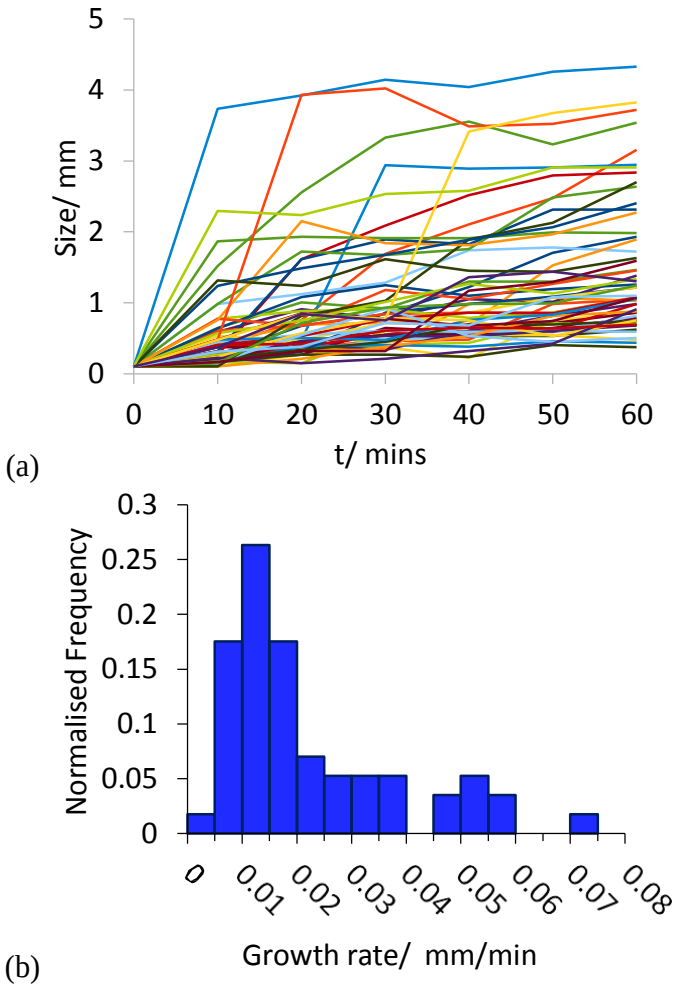

Figure S3: (a) The size of each of the 57 crystals (each plotted as a different colour curve), as a function of time *t*, for an hour after each nucleation event. The *t* is measured as the current time, minus the time of the last image in which a crystal was not visible. (b) A histogram of the growth rates, where the rates are found by applying a linear fit to the size as a function of time from 0 to 60 minutes.

Temperature variation

Here we show the temperature variation in the lab in a 1-week time period. This is the data used to derive the average temperature profile Figure 4 of the main article. The temperature varies from a maximum of $21.4^\circ C$ to a minimum of $20.5^\circ C$ at around 4:00am.

Polymorphism

To confirm the reproducibility of the XRD pattern shown in the main article, we recorded a second pair of XRD pattern of the crystals formed in the first hour, and of the crystals formed in the following 47 hours of an experiment. The results, shown in Figure S5, are very similar to those

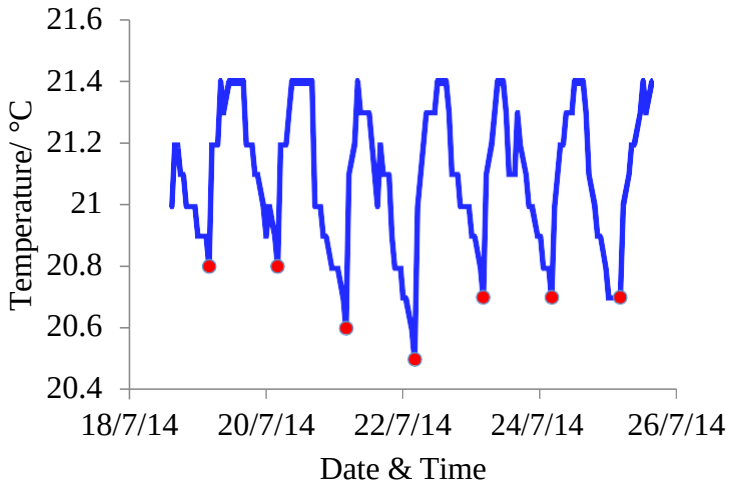

Figure S4: The room temperature recorded over a 1 week time period. The red dots indicate 4:00am of each day which is consistently when the temperature is observed to reach a minimum.

observed in Figure 11 of the main article. In the XRD pattern of the crystals formed in the first hour, no gamma glycine is detectable. The main γ peak (25.1°) to α peak (29.8°) ratio is $1:0.24$ for the $1 < t_N < 48h$.

We also performed XRD on the as-purchased solid glycine (≥ 99% HPLC from Sigma, cat. no. G7126). The XRD pattern is in Figure S6. It is mainly the γ polymorph but there appear to be traces of the α polymorph present. We note that we carefully dissolve the glycine so the polymorphs present before dissolution should be irrelevant.

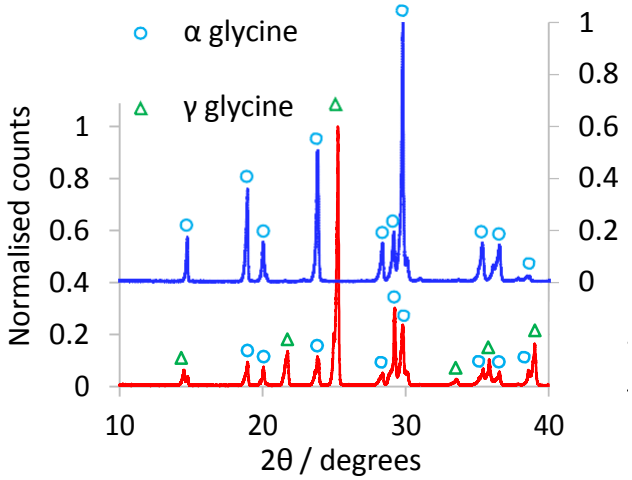

Figure S5: X-ray diffraction pattern of the crystals generated from one microplate. The blue line is the pattern for the crystals that nucleated in the first hour and the red line is the pattern for the samples that nucleated in the following 47 hours.

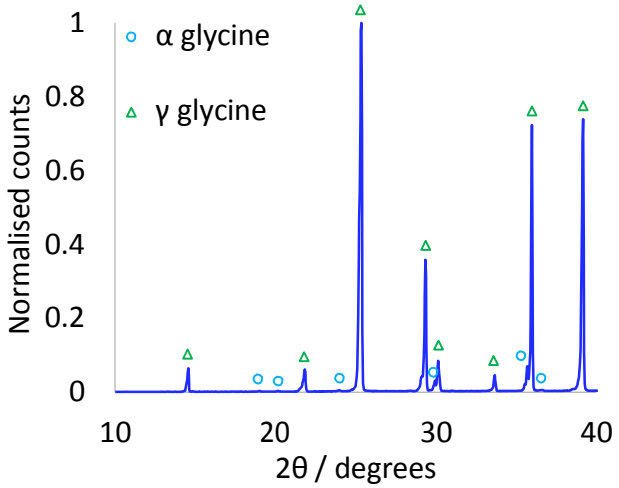

Figure S6: X-ray diffraction pattern of the solid glycine (≥ 99% HPLC from Sigma, cat. no. G7126) we dissolved to make our solutions.

References

(1) Press, W. H.; Flannery, B. P.; Teukolsky, S. A.; Vettering, W. T. *Numerical Recipes in FORTRAN 77*; Cambridge University Press: Cambridge, 1992.