1. Experimental Determination of the LLPS Boundary

In addition to determining the solubility boundary, we have also attempted to determine the liquid-liquid phase separation (LLPS) boundary (binodal curve) through rapid cooling of solutions of compound Z dissolved in the process solvent. A temperature-controlled microscope stage (Linkam Scientific DSC600) was used for this purpose. Solutions of known composition were prepared by dissolving Z in the solvent at an appropriate temperature. Due to the poor solubility of Z in the solvent at ambient temperature, the solvent needed to be above 30 °C if it were to dissolve Z at appreciable concentrations. In each experiment, a 20 μL droplet of the (warm/hot) solution was pipetted out into a small aluminum pan (DSC pan – a pan typically used for differential scanning calorimetry) and this pan was then placed on the cold stage mounted to the base of a stereo microscope (Leica MZ16). This stage was pre-heated to a temperature that exceeded the temperature of the droplet by 2 °C before the DSC pan containing the droplet was placed on it. The microscope stage was then cooled rapidly at 2 °C/min using liquid nitrogen flow. This rate of cooling was chosen such that sufficient time for heat transfer from the droplet was available and the temperature of the droplet follows closely that of the stage. The droplet was monitored through the microscope during the cooling, and the temperature at which the solution suddenly turned cloudy (without producing obvious crystalline particles, which would occur later) was recorded as the LLPS temperature at the known composition of the droplet.
Our attempts to experimentally characterize the LLPS boundary, however, were not successful. While the experimental method discussed above appears simple, the needed elevated temperature of the solution posed an unexpected experimental challenge. When the solution temperature was above 40 °C, the solvent would evaporate from the droplet rapidly during the cooling, thus changing the concentration of $Z$ in the droplet. When we attempted to cover the droplets using a suitable glass cover to prevent this solvent evaporation, the cover would fog up quickly during the cooling, thus compromising our ability to watch the droplet through the microscope. In each experiment, we weighed the droplets before and after the experiment, and found that in many cases the mass difference due to solvent evaporation exceeded 40%. These experimental data points were thus deemed unreliable. After several unsuccessful attempts, in the end we could only obtain one data point that could be considered reliable. For this experiment the needed cooling time was short, which helped reduce the error due to solvent evaporation. The possible error in solute concentration due to solvent evaporation for this case was less than 10%. This data point was shown in Figure 4 with a (+) sign.

Given the time constraints of the project, we had to be content with this situation and had to rely on Crystal 16 data and on theoretical models to generate the complete phase diagram.

2. Equation of State for a Square-Well Fluid

Ramakrishnan and Zukoski proposed a semi-empirical equation of state (EOS) expressed in a perturbation form of a modified van der Waals equation of state as

$$\frac{P}{\rho kT} = 1 + \frac{(2\pi/3)\rho \sigma^3}{(1 - \rho/\rho_b)^2} + \frac{\rho \sigma^3 \omega}{(1 - \rho/\rho_b)^3}$$  \hspace{1cm} (S1)

in which $P$ is the pressure, $\rho$ is the particle number density, $k$ is the Boltzmann’s constant, $T$ is the absolute temperature of the system, $\sigma$ is the molecular diameter, and $\rho_o, \rho_b$ are constants. To adapt the EOS given by eq S1 to a square-well fluid, the authors expressed $\omega$, the (van der Waals) parameter that captures the molecular interactions, as a function of square-well parameters $\varepsilon$ and $\lambda$ through $\omega(\varepsilon, \lambda) = (\varepsilon/kT) f(\lambda)$. With this relation, the EOS for a square-well fluid becomes

$$\frac{P}{\rho kT} = 1 + \frac{(2\pi/3)\rho \sigma^3}{(1 - \rho/\rho_b)^2} + \frac{\rho \sigma^3 (\varepsilon/kT) f}{(1 - \rho/\rho_b)^3}$$  \hspace{1cm} (S2)

The normalizing constant $\rho_b$ was chosen as $1.605 \sigma^{-3}$ as suggested by Heyes and Aston to give a good agreement with hard-sphere compressibility factors obtained through machine calculations. Note that Reference 1 contained a typographical error in the 3rd term on the RHS of eq S2, which has been corrected here.
Ramakrishnan and Zukoski have found that they can adjust $f$ and $\rho_b$ as two constants and match the thermodynamic properties predicted for square-well fluids by eq S2 to those obtained from machine simulations. For this, these authors have used the Monte-Carlo study by Lomakin et al. Lomakin et al. provide a table of critical temperature and critical density for square-well fluids for various values of $\lambda$ obtained through machine calculations. From thermodynamic relationships, at critical temperature both the first and second derivatives of the pressure w.r.t density vanish. Hence one can use the values of $(\rho \sigma^3)_c$ and $(\sigma/kT)_c$ tabulated by Lomakin et al. for a given $\lambda$ and solve the relations $(\partial P/\partial \rho)_T = 0$ and $(\partial^2 P/\partial \rho^2)_T = 0$ simultaneously to obtain the values of $f$ and $\rho_b$ that match $(P/\rho kT)$ from eq S2 to that from machine simulations.

The evaluation of these derivatives is further simplified when one transforms eq S2 by introducing the dimensionless variables $\bar{P} = (P \sigma^3/kT)$ and $\bar{\rho} = (\rho \sigma^3)$. In terms of these alternate variables eq S2 becomes

$$\frac{\bar{P}}{\bar{\rho}} = 1 + \frac{b \bar{P}}{(1 - \bar{P}/\bar{P}_o)^2} + \frac{\bar{\rho}(\sigma/kT)_c}{(1 - \bar{P}/\bar{P}_o)^3}$$

in which $\bar{P}_o = \rho_o \sigma^3$, $\bar{\rho}_o = \rho_o \sigma^3$, and $b = (2\pi/3)$. One may then re-formulate the needed derivatives as $(\partial P/\partial \rho)_T = kT(\partial \bar{P}/\partial \bar{\rho})_T$ and $(\partial^2 P/\partial \rho^2)_T = kT \sigma^3(\partial^2 \bar{P}/\partial \bar{\rho}^2)_T$. The required equations to solve for $f$ and $\rho_b$ are then $(\partial \bar{P}/\partial \bar{\rho})_T = 0$ and $(\partial^2 \bar{P}/\partial \bar{\rho}^2)_T = 0$. Note that eq S3 and its derivatives are generic in nature and do not require the knowledge of the molecular diameter $\sigma$ to use. Ramakrishnan and Zukoski found that this procedure for fitting eq S1 to machine calculations is valid for $\lambda$ in the range 1.005 to 1.8.

Table S1 provides these values of $f$ and $\rho_b$ calculated by us from this procedure as a part of the current work. In calculating these $f$ and $\rho_b$ values, we used appropriate limiting values for $(\rho \sigma^3)_c$ and $(\sigma/kT)_c$ as discussed by Lomakin et al. The values shown in Table S1 may be interpolated through simple piece-wise polynomial functions to facilitate calculations.

The above eq S2 can also be transformed into a form that uses volume fraction $\phi$ as the variable of choice, by using the defining relations $\phi = (\pi/6) \rho \sigma^3$, $\phi_o = (\pi/6) \rho_o \sigma^3$, and $\phi_b = (\pi/6) \rho_b \sigma^3$, as

$$\frac{4\pi P a^3}{3\phi kT} = 1 + \frac{4 \phi}{(1 - \phi/\phi_o)^2} + \frac{6 \phi(\sigma/kT)_c}{\pi (1 - \phi/\phi_b)^3}$$

which is eq 2 of the main text with $2a = \sigma$. It follows that the choice of $\rho_o = 1.605 \sigma^{-3}$ results in $\phi_o = 0.8404$. Note that Reference 23 of the main text contained a typographical error in specifying the value for $b$, which has been corrected here.
3. Phase Diagram Calculations

3.1. Solubility Boundary

At solid-liquid equilibrium, the chemical potential of the solute in the solid and liquid phases is equal. For this case, if $\varepsilon$ and $\lambda$ are known, one can solve $\mu_s = \mu_L$ at a given temperature $T$ to obtain the equilibrium volume fraction (solubility) $\phi$. Assuming the solid to be incompressible, the other condition for equilibrium, the equality of pressures, can be ignored. In our case, we do not know the values for $\varepsilon$ and $\lambda$ that represent the intermolecular interactions of compound Z in the process solvent (98% (w/w) water – 2% (w/w) methanol). However, the experimental solubility data can be used to estimate these parameters by following the reverse procedure for solubility prediction discussed above.

In principle the two parameters $\varepsilon$ and $\lambda$ can be estimated by fitting the solubility data to $\mu_s = \mu_L$. However, we note that $\varepsilon$ and $\lambda$ cannot be determined independently. The direct multiplication of $(\varepsilon/kT)$ and $f$ in the RHS of eq 2 lends to many possible combinations of $\varepsilon$ and $\lambda$ that can fit the data. Moreover, the strength of interaction $\varepsilon$ itself is expected to be a function of temperature which may be expressed through a simple linear relationship $^{4}$ as $\varepsilon/k = \alpha_0 + \alpha_1 T$. With this expression, we have three parameters ($\alpha_0$, $\alpha_1$, and $\lambda$) that need to be fit to describe the solubility data. Rather than fitting all three parameters, which is mathematically discouraged, we pre-assigned a value to $\lambda$ and fit only for $\alpha_0$ and $\alpha_1$ through standard nonlinear regression procedure. We varied the value of $\lambda$ systematically in the range of 1.05 to 1.75 (in which eq 2 is valid $^1$) and found that for $\lambda = 1.315$, with $\alpha_0 = 713.88 \pm 44.67$, and $\alpha_1 = -0.816 \pm 0.137$, we not only can describe the solubility data excellently, but also can obtain an LLPS curve (binodal) that passes through the experimental data points.

3.2. Co-existence and Spinodal Boundaries

The co-existence curve (binodal) may be obtained by solving simultaneously eqs 2 and 3 as $P^I = P^II$ and $\mu^I_L = \mu^II_L$ at a given temperature $T$ to determine the volume fractions $\phi^I$ and $\phi^II$ of the solute in the two liquid phases at equilibrium. This solution procedure can be tricky because of the existence of a trivial solution at $\phi^I = \phi^II$. To tackle this complexity, we follow the procedure below.

| $\lambda$ | $\bar{\rho}_b$ | $-f$ |
|-------|-------|-------|
| 1.005 | 2.574 | 0.588 |
| 1.05  | 2.674 | 1.110 |
| 1.1   | 2.827 | 1.512 |
| 1.2   | 3.163 | 2.346 |
| 1.3   | 3.809 | 3.352 |
| 1.4   | 5.245 | 4.601 |
| 1.5   | 7.048 | 5.898 |
| 1.6   | 10.533| 7.469 |
| 1.7   | 18.963| 9.243 |
| 1.75  | 28.972| 10.146|
| 1.76  | 32.092| 10.322|
| 1.77  | 35.832| 10.498|

Table S1. Values of $\bar{\rho}_b$ and $f$ as functions of $\lambda$. 

1.05 2.674 1.110
1.1 2.827 1.512
1.2 3.163 2.346
1.3 3.809 3.352
1.4 5.245 4.601
1.5 7.048 5.898
1.6 10.533 7.469
1.7 18.963 9.243
1.75 28.972 10.146
1.76 32.092 10.322
1.77 35.832 10.498

1.76 32.092 10.322
1.77 35.832 10.498
First, we determine the critical temperature and critical volume fraction at which the binodal and the spinodal meet. At this upper consolute temperature (UCST) and composition, the derivatives of the chemical potential with respect to the volume fraction must vanish. From this condition, we obtain $T_c$ and $\phi_c$ by solving $(\partial \mu / \partial \phi)_T = 0$ and $(\partial^2 \mu / \partial \phi^2)_T = 0$ simultaneously using $\epsilon$ and $\lambda$ obtained from the solubility data fit. Despite its complex looking form, analytical differentiation of eq 3 with respect to $\phi$ is simple when one substitutes eq 2 in eq 3. The $T_c$ and $\phi_c$ values thus obtained for compound Z are 102.9 °C and 0.1920, respectively. This $\phi_c$ corresponds to a mass concentration of 24.45% (w/w). Once $T_c$ and $\phi_c$ are obtained, we reduce the temperature slightly and calculate $\phi^1$ and $\phi^\Pi$ at that temperature by using $\phi_c + 0.001$ and $\phi_c - 0.001$ as the initial guesses for $\phi^1$ and $\phi^\Pi$ toward solving $P^1 = P^\Pi$ and $\mu^1_L = \mu^\Pi_L$. The freshly obtained $\phi^1$ and $\phi^\Pi$ are then passed on as initial guesses for the next temperature, which will be slightly less than the previous one. This procedure quickly ensures convergence of the iterative numerical computation and will not result in trivial solutions. The spinodal curve also can be calculated using this procedure. In this case we need to solve only $(\partial \mu / \partial \phi)_T = 0$ for the two solutions of $\phi^1$ and $\phi^\Pi$ at a given temperature.

In calculating the volume fractions, we used a solid density of 1.30 g/mL and the solvent (98% Water − 2% MeOH) density as a function of temperature was estimated using the physical property data available for these solvents in the literature.

4. Reaction Kinetics Model

In the reaction kinetics calculations, the density of the reaction mixture $\rho$ was estimated as the mass average value of the known densities of the reactant streams. The specific heat capacity of the product Z was obtained through differential scanning calorimetric (DSC) measurements, and that of the solvents (methanol and water) and the aldehyde A were obtained from the literature. The specific heat capacity for reactant M was available in the existing product literature. We assumed the specific heat capacity of the reaction mixture to remain constant in the range of reaction kinetic experiments, and used a mass average value of $C_p$ for the reaction mixture toward the solution procedure. Also, to avoid parameter interactions in the nonlinear regression procedure, the input data were centralized by introducing transformation of variables suggested by Himmelblau. The simultaneous numerical solution of the differential equations and the parameter estimation calculations were performed using Mathematica (v 11.3, Wolfram Research).

Figure S1 shows the fit of the kinetic model to the experimental data. Note that while the three adjustable parameters that constitute the kinetic model, $k_0$, $E_a$, and $-\Delta H_r$, can in principle be estimated
by simultaneously solving equations 6–8 in a non-linear parameter estimation procedure, such an attempt is not recommended from mathematical considerations. In fact, when we have attempted to fit the three parameters to $T$ vs $t$ data, that exercise has either led to serious convergence problems or yielded unrealistic values for the parameters when converged. This complication is expected, because exponential models such as eq 8 are highly susceptible to interaction between the parameters $k_0$ and $E_a$. Typically a regression procedure that attempts to fit these two parameters simultaneously yields parameter estimates with a high degree of uncertainty. Moreover, we do not have direct experimental measures for the concentrations of the species. In light of these concerns, we have decided to assign a reasonable value (13000 cal/mol) to the activation energy $E_a$ and estimate only $k_0$ and $-\Delta H_r$ by fitting $T$ vs $t$ data. This choice of the $E_a$ value was motivated by the expectation that the reaction rate typically doubles for a 10 degrees rise in temperature in the temperature range of interest.

5. References

1. Ramakrishnan, S.; Zukoski, C. F., Characterizing Nanoparticle Interactions: Linking Models to Experiments, *J. Chem. Phys.* **2000**, *113*, 1237-1248.

2. Heyes, D. M.; Aston, P. J., Square-well and Square-Shoulder Fluids: Simulation and Equations of State, *J. Chem. Phys.* **1992**, *97*, 5738-5748.

3. Lomakin, A.; Asherie, N.; Benedek, G. B., Monte Carlo Study of Phase Separation in Aqueous Protein Solutions, *J. Chem. Phys.* **1996**, *104*, 1646-1656.

4. He, G.; Tan, R. B. H.; Kenis, P. J. A.; Zukoski, C. F., Metastable States of Small-Molecule Solutions, *J. Phys. Chem. B* **2007**, *111*, 14121-14129.

5. Himmelblau, D. M., *Process Analysis by Statistical Methods*, 1st ed., John Wiley & Sons: New York, U.S.A., 1970.

6. Bhamidi, V.; Varanasi, S.; Schall, C. A., Measurement and Modeling of Protein Crystal Nucleation Kinetics, *Cryst. Growth Des.* **2002**, *2*, 395-400.

![Figure S1. Fits of the reaction kinetic model to the $T$ vs. $t$ data obtained during the first 1 min of the experiment. The circles represent the data from the 25% (w/w) experiment and the squares are the data from the 15% (w/w) experiment. The lines are model fits to the data with the rate parameters shown in Table 4.](image)