

# Kinetics of the Formation of Organic Molecular Nanocrystals

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## ABSTRACT

Nanoparticles of the molecular crystal naphthalene were prepared through a solvent exchange process. The gradual replacement of the solvent acetone with water induces aggregation and precipitation of naphthalene. Near the phase boundary in this ternary system we found regions in which nanocrystals with diameters on the order of 100s of nanometers formed. The particle size vs time after mixing was measured using dynamic light scattering, showing the progress of the growth of the crystals.

The preparation and characterization of nanoparticle systems have seen considerable growth recently,<sup>1</sup> although their study and use has been common for decades, especially in the chemical industry. Paints, inks, microemulsions, polymer latex systems, to name just a few, all consist of particles with sizes in the tens to hundreds of nanometers, dispersed in a liquid. Possible quantum size effects in the electronic and optical properties, the large surface-to-volume ratio, and advantages in processing and forming composite materials make the development of these methods of interest for a wide variety of applications. Aggregation and self-assembly of molecules are also a key steps in crystallization and/or precipitation.

Many techniques for the preparation of nanoparticle dispersions rely on solubility changes inducing nucleation and growth of the particles, often with the addition of surfactants to limit particle growth and/or stabilize the particles. One technology relies on a rapid change in solubility of a particular molecule by mixing solvents.<sup>2–7</sup> A solid is dissolved in a good solvent, then rapidly injected into a solvent in which the material has poor solubility but that is miscible with the first solvent. The “good” solvent disperses and the sudden change in the surroundings of the molecules causes aggregation, often in ordered structures and sometimes occurring over periods ranging from seconds to days. Added surfactants can stabilize these nanoparticles, although surfactant-free nanoparticles have also been reported.<sup>4</sup> While a large variety of inorganic nanoparticles such as semiconductors<sup>5</sup> have been prepared using this method, there is also considerable interest in preparing dispersions of organic materials in polar solvents, for example, in pharmaceuticals where aqueous formulations are needed for biocompatibility. Some organic nanocrystals prepared using this method include beta-carotene,<sup>2</sup> perylene,<sup>3</sup> polydiacetylene,<sup>6</sup> and J-aggregates of a merocyanine dye at room temperature.<sup>7</sup>

As a rapid, nonequilibrium process, the particle formation in this injection method it is not always easily accessible to characterization because of the small distance and time scales. The nucleation and growth of nanoparticles as a result of changes in solubility, though, is important to fields such as bulk crystallization, protein folding, and aggregation in disperse systems. In particular, the initial stages of particle nucleation are key aspects of these processes that are not fully understood, as pointed out by recent advances in the understanding of biomineralization<sup>8</sup> and protein crystallization.<sup>9</sup>

Here we report on an alternate method of preparation that both slows down the formation and allows optical characterization of the initial stages of growth of organic molecular nanocrystals. The particles are those that are formed in ternary systems composed of a binary solvent mixture and the molecular precursor solute. By adjusting the ratio of solvents (e.g., adding water to a solution), the solubility of the molecules is changed, inducing aggregation and precipitation. Prior to precipitation, nanoparticle dispersions are formed. These particles are not only interesting as novel materials themselves, but their nucleation and growth may be models for a variety of phenomena such as nanoparticle formation in injection methods, solution crystallization, and association in mixed solutions. The quasi-adiabatic nature of the method we use for the nanoparticle formation allows study of this aggregation in a more fundamental and controlled way. And while considerable research has focused recently on the preparation of inorganic nanoparticles, much less effort has been devoted to organic materials, despite their great potential and natural connection to biological systems.

The solvent exchange preparation method was used for several reasons. One relates to the fact that the initial particle nucleation and subsequent growth in the injection methods described earlier occur very rapidly and are likely to be nonequilibrium processes. In the gradual method described

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here, we observe the particle formation under equilibrium or quasi-equilibrium conditions. In addition, the ratio of the components in the binary solvent gives us some control of a key parameter in the particle growth. The growth described here could shed light on numerous other systems in which molecules and particles aggregate and/or crystallize due to changes in their environment, including the majority of bulk crystal growth. Finally, the method has application in its own right for the preparation of nanocrystals.

We report here a study of particle formation and growth of simple organic molecular nanocrystals using dynamic light scattering (DLS). The measured quantity in DLS arises from the fluctuations of the phase shifts due to particle motion (e.g., diffusion).<sup>10</sup> It is a standard technique for particle sizing in the sub micrometer range. In it, the autocorrelation function of the scattered light irradiance, determined here as the photon count correlation function, is computed. DLS has been used only infrequently for crystallization studies because of problems due to multiple scattering.

In DLS experiments, one measures the fluctuations of scattered light caused by the motion of the particles, and the particle motion information is contained in the normalized signal autocorrelation function (ACF).

The temporal ACF is

$$g^{(2)}(\tau) = \langle n_{\text{ph}}(0)n_{\text{ph}}(\tau) \rangle / \langle n_{\text{ph}} \rangle^2 \quad (1)$$

where  $n_{\text{ph}}$  is the scattered photon count rate, measured as a function of correlation delay time  $\tau$ . The field ACF is related to the photon count ACF by the Siegert relation:

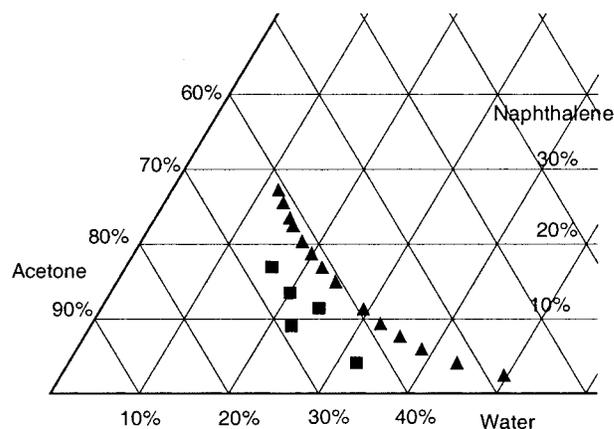
$$g^{(2)}(\tau) = 1 + \beta |\exp(-Dq^2\tau)|^2 \quad (2)$$

where  $\beta$  is an experimental constant between 0 and 1,  $D$  is the free diffusion coefficient of the particles and  $q$  is the magnitude of the scattering vector. From the Stokes–Einstein equation:

$$D = k_{\text{B}}T/6\pi\eta a \quad (3)$$

where  $k_{\text{B}}$  is the Boltzmann constant,  $\eta$  is the viscosity, and  $T$  is the temperature, we calculate  $a$ , the radius of the particles.

Light from a 2 mW HeNe laser (Spectra Physics) was coupled (FiberPort, Optics For Research) into a multimode optical fiber, out through another coupler, and into the sample in a cuvette with a 1 cm path length. The light scattered at 90° to the incident beam was focused by a 5.5 mm focal length lens and passed through a 20  $\mu\text{m}$  pinhole to obtain a small scattering coherence area, as well as through a narrow band interference filter (Edmund Industrial Optics, 632 nm center, 10 nm bandwidth) to reduce stray light. A second fiber coupler and fiber brought the light to an avalanche photodiode (EG&G), whose signal was processed by an ALV5000 (ALV GmbH, Germany) hardware autocorrelator. The data were analyzed using the ALV NonLin routine,<sup>11</sup> a nonlinear constrained regularization of the autocorrelation



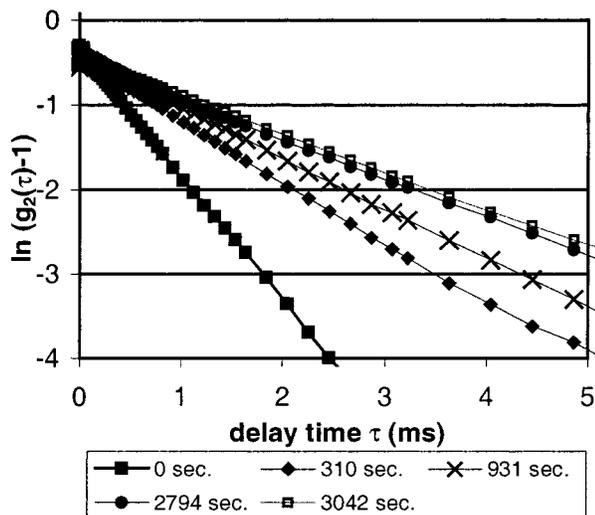
**Figure 1.** Ternary phase diagram of the naphthalene acetone water system; the values are weight percent. Squares correspond to bulk precipitation observed in this work, triangle are from reference 13.

function, between delay times of 2  $\mu\text{s}$  and about 2 ms, and distributions of the scatterer diffusion coefficients were found. To determine the corresponding hydrodynamic radii, the viscosity of the water/acetone solvent mixture, taken from reference 12, and the ambient temperature (25 °C) were used in eq 3.

The particles were prepared by first thoroughly dissolving naphthalene (Fisher Scientific, extra pure) in acetone (Acros Organics) and then gradually adding deionized water while stirring. Initially, we investigated a number of points on the ternary phase diagram by qualitatively observing where bulk precipitation occurred. Figure 1 shows a number of points at which we observed this precipitation, along with data from reference 13, which are measurements of supersaturated points of naphthalene in the binary solvent acetone/water at a slightly higher temperature (35 °C). The points are plotted as described in reference 14. Our observations of precipitation match the literature data reasonably well, considering the temperature difference.

On reaching water levels close to the precipitation point, the mixtures became turbid. Increasing the water content led to formation of larger aggregates in the dispersion, which precipitated as macroscopic crystals. This precipitation occurred on a long time scale in the vicinity of this phase transition. Two points on the phase transition were investigated in more detail by light scattering, with ratios 0.040:0.637:0.323 (sample name NAW6) and 0.013:0.523:0.464 (NAW14) weight fractions of naphthalene/acetone/water. In these, larger crystals formed over a period of about one week and precipitated. Nearby regions showed similar qualitative results: the turbidity and precipitation were similar for a range of a few percent of added water around these points. We observed birefringence in the dispersions, suggesting that the particles possess crystalline structure. At regions below these in terms of water content, short-lived particles of naphthalene formed occasionally, which could be redissolved by stirring.

At higher initial concentrations of naphthalene in acetone (0.124:0.699:0.177 naphthalene/acetone/water weight fractions), no turbidity was observed, only bulk precipitation, which occurred abruptly upon reaching a critical point. Weak



**Figure 2.** Autocorrelation functions for the sample NAW6 for various times after mixing.

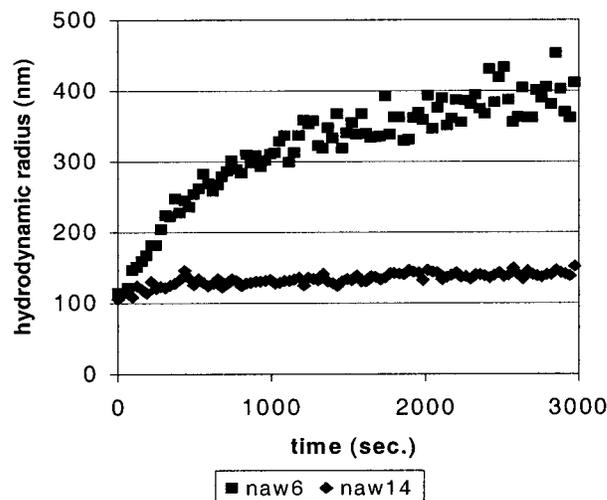
scattering could be observed in the supernatant. This was also the case for mixtures before particle formation was observed.

The initial particle formation was investigated for the mixtures NAW6 and NAW14, those that contained semi-stable particle dispersions. The water was added to the naphthalene/acetone mixture in a cuvette, and the light scattering measurements were begun immediately. Autocorrelation functions of 30-second duration were begun immediately after the initial mixing and repeated for a total of about 50 min. Generally, the first run was discarded as it contained artifacts due to fluid motion in the sample from the addition of water.

Some of the ACFs are presented in Figure 2 for the sample NAW6. The linear slopes of the lin-log plots suggest relatively monodisperse particles. As can be seen, there are large changes in particle radius in the first few minutes after mixing for this sample.

The changes in particle radius with time after mixing are displayed in Figure 3. For the sample NAW6, the initial measured particle radius was 120 nm, with a relative width of the size distribution of about  $\pm 13\%$ . The increase in size is rapid in the first few minutes, with the particle radius doubling in about 5 min and then increasing more gradually to about 400 nm after 40–50 min. The relative width of the particle size distribution also increases significantly in both relative and absolute terms, to about  $\pm 60\%$  after 50 min.

The sample with the lower naphthalene concentration in acetone, NAW14, did not show this rapid change in particle radius. It started at roughly the same size as NAW6, but increased only slightly to 140 nm in the 50 min. The size distribution also did not change appreciably, with a relative width of approximately 30%. However, this sample also precipitated after about one week, indicating that eventually the particles aggregated. Thus, in both cases primary particles are formed at rapid times ( $< 30$  s). Their growth in intermediate time scales (minutes to hours) depends on the concentration of the solute, and at long times they form a bulk phase in the precipitate.



**Figure 3.** Particle radius vs time after mixing for two samples described in the text.

These results also indicate the need to characterize the growth at long and short times. The particle growth over longer time scales is accessible with dynamic light scattering up to a certain particle diameter; after this, Fraunhofer diffraction might be more suitable, although once they begin precipitating, size characterization will be difficult. Shorter time scales can be measured with either higher intensity incident light, allowing shorter accumulations of the autocorrelation function, or by other techniques such as fluorescence correlation spectroscopy.<sup>15</sup> Both of these are avenues currently being explored in our lab.

The lack of long-term stability of the nanoparticles provokes the question of whether a kinetically stable particle dispersion can exist in such a mixture; i.e., are there two-phase regions of the ternary phase diagram in which the solid phase is a mesoscopic nanophase rather than a bulk crystal? The particles in this case could be stabilized against adding more molecules by the fact that there is a reduced amount of naphthalene in solution; this part of the mixture has now moved back into a single-phase region of the ternary phase diagram. The stability of the nanoparticles themselves to aggregation with each other is more difficult to understand. It may simply be entropy driven, or there may be some Coulomb/double layer repulsion as in aqueous systems, although the naphthalene solubility in water is very low, and so it is hard to imagine the nanoparticles being charged. We did observe a stable nanoparticle dispersion in a mixture with high water content (0.033:0.311:0.656 weight fraction ratio), in which most of the naphthalene quickly precipitated while a fraction remained in suspension. This dispersion was stable only in equilibrium with the precipitated bulk phase; when decanted and left standing, it precipitated leaving a clear supernatant. In this case, the bulk phase precipitate seems to be a reservoir of naphthalene necessary for the stability of the particles. The particle radius in this upper phase was found to be 165 nm.

While little quantitative experimental work has been done on similar systems, with the possible exception of model proteins such as lysozyme,<sup>16</sup> there is a large body of

theoretical work concerning the aggregation and growth of particles.<sup>17</sup> Our experiments are geared toward analysis using classical nucleation theory, e.g., a kinetic theory considering the Gibb's free energy change during the aggregation process. In the microscopic modeling of this growth, we will need to also consider local changes in the concentration of the naphthalene, along the lines of diffusion-limited aggregation theories, as well as changes in the structure of the solvent itself; as aggregation proceeds, less of the acetone will be present in the solvent cage solubilizing the naphthalene and more in the bulk binary solvent, changing its free energy as well.

The preparation of organic nanocrystals described here is a way to access the underlying physics and chemistry of the nucleation and growth processes under quasi-equilibrium conditions and in relatively slow times scales. This, coupled with the use of dynamic light scattering, allow us to investigate the initial particle formation on lengths scales on the order of 100 nanometers. The results raise a number of issues, such as whether there can be a stable nanoparticle phase before precipitation. Another unresolved question concerns the behavior of the primary particles, at very short times. Ongoing improvements in the experimental sensitivity are geared toward allowing us to determine if the nucleation process is a gradual process where particles form at a specific solvent ratio, grow larger as a function of this ratio, and then reach a critical nucleation size, or if the molecules remain in solution until a critical ratio, where the entire nucleation and growth to large particles occurs. Finally, the connection to the other particle formation processes mentioned earlier is only very qualitative; the study of the particle nucleation and growth under quasi-equilibrium conditions will lay the groundwork for a stronger theoretical foundation for the physics of the particle nucleation.

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