Kinetics of 12-Hydroxyoctadecanoic Acid SAFiN Crystallization Rationalized Using Hansen Solubility Parameters

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ABSTRACT: Changes in solvent chemistry influenced kinetics of both nucleation and crystallization of 12-hydroxyoctadecanoic, as determined using differential scanning calorimetry and applying a modified Avrami model to the calorimetric data. Altering solvent properties influenced solvent–gelator compatibility, which in turn altered the chemical potential of the system at the onset of crystallization, the kinetics of gelation, and the resulting 12HOA crystal fiber length. The chemical potential at the onset of crystallization was linearly correlated to both the hydrogen-bonding Hansen solubility parameter and the solvent–gelator vectorial distance in Hansen space, \( R_h \). Our work suggests that solvent properties can be modulated to affect the solubility of 12HOA, which in turn influences the kinetics of crystallization and the self-assembly of this organogelator into supramolecular crystalline structures. Therefore, modulation of solvent properties during organogelation can be used to control fiber length and thus engineer the physical properties of the gel.

INTRODUCTION

Self-assembled fibrillar networks (SAFiNs), comprised of low molecular mass organogelators (LMOGs), have garnered remarkable attention for recovery of spilled oil,\(^1\) controlled drug release,\(^2\)–\(^4\) antibacterials,\(^5\) and use as edible oleogels.\(^6\) Despite the rapidly growing body of literature devoted to molecular gels,\(^7\) new LMOGs are still, more often than not, discovered serendipitously and it remains challenging to predict, \( a \ priori \), the structure of potential gelators or to foresee solvents that may gel by a known gelator.\(^8\)–\(^11\) Design challenges result from the antagonistic parameters that promote crystal growth, while limiting solubility to form hierarchical one-dimensional (1D) architectures. In other words, a gelator must be sufficiently soluble to be compatible with the solvent and at the same time sufficiently insoluble for self-assembly to occur.\(^12\) Okesola et al. illustrate the point further by accurately stating that most LMOGs sit on a knife edge between solubility and precipitation.\(^12\) To impair rational design even further, there is no universal gelator capable of gelling all solvent classes and \( per \ se \) both the gelator and solvent chemistry need to be considered.\(^7,8\)

Molecular gels, unlike polymer gels, are formed by small molecules, typically less than 3000 Da, and require a zero-dimensional (0D) to 1D conversion driven by noncovalent interactions between LMOGs. LMOG assembly develops from a multistep process where a sol is cooled and subsequently supersaturation drives aggregation via stochastic nucleation. The nucleation event requires highly specific interactions (i.e., hydrogen-bonding,\(^13,14\) \( \pi-\pi \) stacking, electrostatic interactions, and van der Waals interactions\(^15\) ) that promote preferential 1D growth. The resulting fibers are described as “crystal-like”, and the extended crystalline aggregates, comprised of monomers held together by noncovalent bonds, act in a manner similar to that of polymer chains in polymeric gels to immobilize the solvent. This 1D growth results in the formation of crystalline nano- or microfibers, which become entangled and form junction zones, thus resulting in a three-dimensional (3D) network. The solvent is trapped within this 3D network of self-assembled fibrils, resulting in the formation of a gel matrix.\(^16\) Solvent plays a key role in this assembly process.\(^17\)–\(^19\) Chemical processes taking place in solution, including aggregation or crystal growth, are affected by solution properties,\(^20\) and since self-assembly is influenced by both specific solvent–solute interactions and bulk solvent properties, such as viscosity, density, and polarity, it is almost impossible to pinpoint which solvent parameters will influence self-assembly.\(^29\)

It is unrealistic to consider a solvent as a macroscopic continuum characterized by a single physical property, and unfortunately not one solvent parameter accounts for all interactions. Katrikzky et al. stated that “...the simple concept of polarity as a universally determinable and applicable solvent characteristic is a gross oversimplification”.\(^30\) An accurate measure of solvation accounts for solvent–solute interactions and separates them quantitatively according to whether the interactions are nonspecific or specific. Self-assembly of molecular gels requires the same solubility considerations as those for polymer gels. Also, there must be consideration for additional factors pertaining to how solvents affect intermo-
lecular, noncovalent interactions between gelator molecules. As an example of the solvent–gelator interplay, two solvents may share a similar bulk physical parameter, but the functional groups of the solvent may alter the nature of gelator–solvent interactions. Thus, LMOGs may not be similarly amenable to gelation by a common gelator, and their gels may exhibit very different mechanical properties. To illustrate, both 3-pentanone and 1-butanol have static relative permittivities of ~17,31 only 3-pentanone is gelled by 12-hydroxyoctadecanoic acid (12HOA); a solution is obtained in 1-butanol under otherwise equivalent conditions.22,32,33 For this reason, detailed evaluations of how different solvent parameters alter or influence gelation are direly needed.

Due to the interplay between solvent and gelator, solvent parameters have been closely linked to gelation ability.31 Raynal and Bouteiller used Hansen solubility parameters (HSPs) when evaluating the gelation behavior of numerous LMOGs.34 Their meta-analysis revealed that the gels all had solvents with similar HSPs with only a few exceptions.34 In a refinement of Hildebrand’s theory on solubility parameters, HSPs are semiempirical decompositions of the original Hildebrand solubility parameters (HiSP) into dispersive (d), polar (p), and hydrogen-bonding (h) solubility parameters; namely,

\[
\delta_{Hi}^2 = \delta_{H,d}^2 + \delta_{H,p}^2 + \delta_{H,h}^2
\]  

(1)

Readers are directed to Hansen’s original contribution in 1967 for a clear explanation of how solvents and polymers were assigned a solubility parameter, whose values can be found in standard reference tables.41 These three parameters can be treated as coordinates for a point in three dimensions also known as the Hansen space. The nearer two molecules, e.g., solvent and gelator, are in this 3D space, the more likely they are to dissolve into each other. To determine if the parameters of two molecules are within range, a value called the interaction radius \(R_h\) is given to the substance being dissolved. This value determines the radius of the sphere in Hansen space, and its center is the three Hansen parameters. To calculate the distance \(R_h\) between Hansen parameters in Hansen space, the Pythagorean theorem in 3D for spherical geometry is used:

\[
R_h^2 = 4(\delta_{12}^2 - \delta_{11}^2)^2 + (\delta_{22}^2 - \delta_{21}^2)^2 + (\delta_{12}^2 - \delta_{11}^2)^2
\]  

(2)

where \(\delta_{12}\) is the dispersive HSP for the gelator and \(\delta_{11}\) is the dispersive HSP for the solvent. The HSPs for HOA were estimated using the group contribution method37 and were found to be \(\delta_d = 16.59 \text{ MPa}^{1/2}\), \(\delta_p = 2.86 \text{ MPa}^{1/2}\), and \(\delta_h = 6.77 \text{ MPa}^{1/2}\).

The objective of this study is to explore the relationship between gelator solubility in different solvents, of differing HSPs, and correlate this solubility to kinetics of gelation and the mechanical properties. To illustrate, both 3-pentanone and 1-butanol were used as models for gelation. Therefore, 12HOA was selected from the plethora of gelators due to its broad gelation ability, and it has been extensively studied in numerous solvents15–49 and in complex fluids such as mixed solvent systems, gelled microemulsions, and lamellar phases.15–36

### METHODS

Solvent selection criteria were maintained as simply as possible with the aliphatic chain being linear and saturated and the functional group located in the middle of the molecule. All solvents (hexane, heptane, octane, decane, dodecane, tetradecane, hetanohil, heptanol, octanohil, decanol, nonanenitrile, decanal, dodecanal, octylamine, decylamine, and 5-nonanone) and 12-hydroxyoctadecanoic acid (12HOA) were obtained from Sigma-Aldrich (Cherry Hill, NJ, USA) with purity greater than 0.95%. 12HOA was dispersed at 2 wt % in 2 mL of Imave (Bethesda, MD, USA) and was reported as a water hardliner (YWR, Randor, PA, USA). After 12HOA was dispersed in each solvent and capped, the vials were placed in a hot water bath set at 90 °C for 20 min. After the sol appeared clear, it was removed and stored for 24 h at 20 °C.

#### Differential Scanning Calorimetry.

Samples of 10 mg each of 2 wt % 12HOA in various organic solvents were transferred into Alod-Al hermetic DSC pans. The DSC chamber (Q2000, TA Instruments) was precooled to 20 °C before the sample was placed into the chamber and continually flushed with nitrogen (0.5 mL min−1). The samples were heated to 90 °C and cooled to 2 °C min−1, under nonisothermal conditions, to determine the peak crystallization temperature and then were heated to 90 °C at 2 °C min−1 to decide the melting temperature. Kinetics of crystallization was monitored using a running integral of the crystallization peak obtained during cooling. Samples were run in triplicate, and the mean and standard deviation were plotted.

#### Microscopy.

The supramolecular structure of 2 wt % 12HOA in the solvents was imaged using a Linkham imaging station (Linkham, Surrey, England) equipped with a Q imaging 2560 × 1920 pixel CCD camera (Microsculpture, Surrey, Canada) and a 10× Olympus lens (0.25 N.A.; Olympus, Tokyo, Japan). Samples were placed on a glass slide, and a coverslip was placed on top of the sample. The slide was transferred onto a Peltier temperature control stage (LTS120, Linkham) using a water reservoir as the heat sink. The samples were heated to 90 °C and cooled to 2 °C min−1 to 20 °C to observe fiber formation using nonpolarized light. Light micrographs were calibrated with a 100 μm micrometer. Fiber length was measured using ImageJ (Bethesda, MD, USA) and was reported as a mean ± standard deviation of 10 different crystals on three separate micrographs for a total of 30 crystals per solvent.

#### X-ray Diffraction.

The X-ray diffraction (XRD) or wide-angle X-ray scattering (WAXS) patterns of 12SHA gels in different solvents were obtained by use of a Bruker HiStar area detector and an Enraf-Nonius FRS71 rotating anode X-ray generator equipped with a Rigaku Osinc mirror optic system (−0.06° to 2θ nominal dispersion for Cu Kα; l = 1.5418 Å) operating at 40 kV and 40 mA. All of the data were collected at room temperature over a period of about 300 s. The sample to detector distance was 10.0 cm, and the standard spatial calibration was performed at that distance. Scans were 4° wide in omega (ω) with fixed detector, or Bragg, angle (2θ) of 0°, and fixed platform (f and c) angles of 0° and 45°, respectively. In all cases, the count rate for the area detector did not exceed 100,000 cps.

### RESULTS AND DISCUSSION

Solvents were selected based on their ability to be gelled by 2 wt % 12HOA; all solvent–gelator combinations resulted in gels with the exception of octylamine and decylamine; both formed viscous solutions.37 Depending on the solvent, the melting and crystallization profile (i.e., profile shape and onset and end temperatures) for 12HOA differed. The difference between 12HOA thermograms, in assorted solvents, included the amount of crystalline mass (i.e., solubility), the degree of undercooling \(T_m - T_c\) at the onset of crystallization, or the temperature difference between the onset of melting/fusion \(T_m\) and the onset of crystallization \(T_c\) (Figure 1A, B). A lower degree of undercooling required to initiate crystallization suggests that the gelator is not as soluble in the solvent and it tends to crystallize more readily from solution. This, of course, will be a strong function of the solubility of the gelator in each solvent. HSPs were devised to overcome the limitations of the Hildebrand solubility parameter that do not include the effects...
of specific intermolecular interactions such as polar and hydrogen bonding. HSPs are ordinarily used to select solvents for dissolving polymers. However, the importance of HSPs in new fields has been rapidly emerging and was recently introduced to the field of molecular gels by Raynal and Bouteiller. HSPs for each solvent are easily obtained using the HSPiP software (4th edition version 4.1.07) via the simplified molecular-input line-entry (SMILE) input function. Neither δp nor δd correlate to the degree of undercooling required to initiate crystallization. However, the degree of undercooling is strongly and significantly correlated to both δh and Ra (Figure 2C,D). It has previously been shown that many gelation parameters are correlated to δh and Ra.

When the difference between δh for the solvent and 12HOA (δh = 6.77 MPa1/2) decreases, the degree of undercooling required to initiate gelation increases. Hence, a high degree of undercooling is required when the solvent and gelator are more compatible with one another. Likewise, when Ra decreases, undercooling increases; i.e., as chemical dissimilarity between the solvent and gelator increases (i.e., Ra between two solvents increases), the degree to which the solution needs undercooled to initiate crystallization decreases.

This decrease may be attributed to the difference in chemical potential at the onset of crystallization, \( \Delta \mu_c \),

\[
\Delta \mu_c = \frac{\Delta H_m}{T_m} \Delta T
\]

where \( \Delta T = (T_m - T_c) \) is the effective undercooling experienced by the solution at the onset of crystallization, while \( \Delta H_m \) and \( T_m \) are the melting enthalpy and the onset of melting temperature determined experimentally by DSC. This form of the chemical potential for a solution is only valid if the solution is ideal (see below). The chemical potential, \( \Delta \mu_c \), was plotted as a function of the HSPs (Supporting Information Figure S1), and the correlations to δh and Ra were very strong. This is not surprising since chemical potential is strongly correlated to the degree of undercooling (Figure S2), suggesting ideality in solution behavior. Thus, as the solvent—gelator chemical nature becomes more dissimilar (i.e., a greater Ra), the chemical potential required to initiate self-assembly increases.

Figure 1. DSC melting and crystallization profiles for 12HOA in nonane (A) and nonanoanitrile (B).

Figure 2. Degree of undercooling determined by the temperature difference between the onset of crystallization and melting as a function of HSPs and Ra.
and gelator polarity, then the quantifiable activation energy should be a function of the static relative permittivity. With our new understanding of HSPs, the data were re-examined and a strong correlation between the activation energy and $\delta_d$ or $R_a$ was observed (Figure 3). These findings are in line with observations made for the chemical potential (Figure S1) and undercooling (Figure 2). As the solvent and gelator move apart in Hansen space, the dissimilarity of the gelator and solvent increases causing the chemical potential required to initiate self-assembly to increase, which in turn causes an increase in the activation energy.

The effects of gelator solubility characteristics in different solvents on 12HOA crystallization kinetics were also explored. The amount of crystalline mass formed in time was estimated using DSC. The area under the melting endotherm, at different times/temperatures, was assumed to be proportional to the amount of crystalline mass formed. Panels A and B of Figure 4 show a typical crystallization profile determined in this fashion. The profiles were, in turn, fitted to a modified Avrami model, adapted for nonisothermal crystallization, in order to determine an apparent crystallization rate constant ($k_{app}$). The index of crystallization is a function of both the dimensionality of crystalline growth and the type of nucleation (sporadic vs instantaneous).

$$Y = Y_{max} \left(1 - e^{k_{app}(t-z)^n}\right)$$

Figure 3. Activation energy, determined using an effective supercooling parameter and a probability density function, as a function of Hansen solubility parameters. Data were originally presented in Rogers and Marangoni and were reanalyzed as a function of HSPs.

Figure 4. DSC profiles and their corresponding running integrals for nonane (A) and nonoanitrile (B). Rate constants (C, D) for nucleation and crystallization determined from the modified Avrami model as a function of $\delta_h$ and $R_a$.  

Langmuir 2016, 32, 12833−12841
where \( y_{\text{max}} \) is the phase volume upon completion of crystallization, \( z \) in the induction time, and \( n \) is the Avrami exponent. A nonlinear regression of the model to the data was carried out using Graphpad Prism 5.0 (GraphPad Software, La Jolla, CA, USA) where \( y_{\text{max}} \) was confined to 100%, because all data sets were normalized to their maximum value, and \( n \) was confined to 2, since 1D crystals and sporadic nucleation were observed using polarized light microscopy;\(^{35}\) \( k_{\text{app}} \) and \( z \) were not confined. Correlations between \( z \) and the various parameters were not done because the values for \( z \) provided

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Figure 5. Bright-field micrographs of 2 wt % 12HOA in various solvents. Scale bar in bottom right is 100 μm.
the same information as the degree of supercooling (Figure 2). The rate constants were not correlated to $\delta_p$ or $\delta_d$, but a strong function with $\delta_h$ and $R_a$ was observed (Figure 4C,D).

An increase in the rate constant of crystallization, suggests that as the solvent and gelator become further apart in Hansen space, the degree of undercooling and chemical potential required to initiate self-assembly decrease. Numerous studies have tried to link the driving force for crystallization to the microstructure of the corresponding gel network in various solvents.\textsuperscript{13,63,64} The growth dimensionality of a molecular gel network becomes closer to 1 when experiencing low driving forces for crystallization (i.e., very slow cooling rates or high isothermal crystallization temperatures). Conversely, at high cooling rates, under higher driving forces for crystallization, this dimensionality increases, indicating more spherulitic crystal growth patterns. These increases have been attributed to crystallographic mismatch branching (CMB), leading to the formation of shorter fibrils and more highly branched networks.\textsuperscript{65–67} Highly branched networks tend to have a higher elastic modulus and improved solvent holding capacity.\textsuperscript{68} Recent work by Rohner et al. has eloquently shown that the rate of gelation is controlled by the solubility of the gelator, in their case an acid–amine complex, which mediates the initial nucleation step required for gel assembly.\textsuperscript{69} This initial nucleation step is observed in our study by the differing degrees of undercooling.

**Figure 6.** Fiber length, determined using polarized light microscopy, as a function of HSPs and $R_a$.  

**Figure 7.** X-ray diffractograms of the WAXS region for a typical orthorhombic and triclinic polymorphic subcell (A). Domain size, calculated using the full width at half-maximum from the X-ray diffraction spectra and the Williamson Hull equation, as a function of the chemical potential (B). SAXS (C) and WAXS (D) peak positions versus chemical potential.
It is clear from this work that the morphology of the SAFiN network is strongly affected by the nature of the solvent used, varying from very fine thin fibers to coarse short fibers (Figure 5). In an attempt to quantify the length, a total of 30 fibers (10 fibers on three different micrographs (Figure S3) were measured using ImageJ.64,65 For 12HOA in different solvents, SAFiN length was linearly correlated with $R_h$ (Figure 6). As stated before, as $R_h$ increases, the degree of undercooling required to initiate crystallization decreases (Figure 2D), and as a result, the driving force for crystallization diminishes. CMB theory states that at low degrees of undercooling, the fibers grow one-dimensionally with little branching.63,64 At low degrees of undercooling (i.e., elevated crystallization temperatures), the crystallographic mismatch nucleation barrier is very high, favoring 1D fiber growth with a corresponding large correlation length or fiber length. When the crystallization temperature decreases (i.e., increased undercooling), there is an increase in supersaturation causing the crystallographic mismatch barrier to be significantly reduced increasing the fiber tip branching.71 The highly branched fibers (i.e., short fiber length) create gels with smaller pore sizes and of higher elasticity.65

By understanding the inter-relationship between HSP, undercooling, chemical potential, and fiber length, the physical properties (i.e., elasticity and solvent binding) of molecular gels may be precisely controlled. What is remarkable about these findings is that using the more simplified measure of solubility, the Hildebrand solubility parameter, there are poor correlations with the undercooling, chemical potential, rate constant, and fiber length (Figure S4). This suggests that the interaction leading to these changes is not simply a difference in the solubility of the gelator in a particular solvent. Instead, it is the magnitude of the hydrogen-bonding solubility parameter and the distance in Hansen space that govern these changes in structure and gelation capacity.

It has been previously reported that, in the polymorphic forms of the 12HOA/solvent gels, at low $\delta_h$ the wide-angle spacing was at 4.3 Å, corresponding to a hexagonal subcell spacing. As $\delta_h$ increases, a transition from a hexagonal to a triclinic parallel subcell (strong peak at 4.6 Å, and two weak peaks at 3.9 and 3.8 Å) was observed.55 Herein, it is clear that the polymorphic form is correlated to changes arising in the chemical potential difference (Figure 7). It is clear that there is an increase in the long space (Figure 7C) with increasing chemical potential difference and at low chemical potentials an orthorhombic polymorphic form results (Figure 7D). The full widths at half-maximum from the X-ray diffraction spectra were used to calculate the domain size using the Williamson–Hull equation:52

$$\text{FW}(S) \times \cos(\theta) = \frac{K \lambda}{\text{size}} + (4 \times \text{strain} \times \sin(\theta))$$

(5)

where FW is the full width at half-maximum, $\theta$ is the diffraction angle, $K$ is the Scherrer constant, and $\lambda$ is the X-ray wavelength. Since few diffraction peaks were observed, we had to assume that the strain was zero. Since the strain was zero, the domain size is calculated from the y-intercept when plotting $\text{FW}(S) \times \cos(\theta)$ vs $\sin(\theta)$. In this case, the domain size could be calculated from

$$\text{size} = (k \times \lambda)/(y\text{-intercept})$$

(6)

This allows the calculated domain size, from the Williamson–Hull equation, to be plotted against chemical potential. It is apparent that as the chemical potential increases, there is a reduction in the domain size of the lamellar spacing.

**CONCLUSIONS**

It is clear that changes in solvent chemistry affect nucleation and crystal growth events that define the physical properties of a SAFiN network, which are highly dependent on LMOG fiber length. The nature of a solvent will change solvent–gelator compatibility, affecting the degree of undercooling, chemical potential, kinetics of gelation, and fiber morphology. These parameters are all inter-related and linearly correlated to both the hydrogen-bonding Hansen solubility parameter as well as $R_h$ the difference in the chemical nature between the solvent and gelator. This work provides evidence that the properties of SAFiN networks are not solely altered by the incorporation of solvent molecules into the SAFiN fibers, causing crystallographic mismatches but also by the kinetics of self-assembly driven by changes in chemical potential and undercooling.

**ASSOCIATED CONTENT**

* Supporting Information
  The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.langmuir.6b03476.

Chemical potential as a function of HSPs (Figure S1), undercooling, as determined using differential scanning calorimetry versus the chemical potential difference at nucleation (Figure S2), a bright-field micrograph of 2 wt % 12SHA in octylamine to demonstrate how fiber length was measured (Figure S3), and undercooling, chemical potential, rate constant of crystalline growth and fiber length as a function of Hildebrand solubility parameters (Figure S4) (PDF)

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* Notes
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