Chemical Modifications to Structurally-Simple Low Molecular Mass Organogels

by

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ABSTRACT

CHEMICAL MODIFICATIONS TO STRUCTURALLY-SIMPLE LOW MOLECULAR MASS ORGANOGELS

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1,3:2,4 Dibenzylidene-D-sorbitol (DBS) is the gold-standard for low-molecular-weight organogelators (LMOG). Derivatives of DBS and dimethyl urea, the smallest known LMOGs, have been developed to isolate and determine which molecular features are essential for organogelators to form self-assembled fibrillary networks (SAFiNs). For this study, π-π stacking and hydrogen-bonding are the primary non-covalent interactions that are examined. It is expected that π-π stacking is a strong contributing factor towards gelation. The synthesis and testing of 1,3:2,4 dicyclohexanecarboxylidene-D-sorbitol (DCHS), removed π-π stacking potential, but conserved all other aspects of DBS, giving an excellent basis for comparison. DCHS was found to form a gel in 1 of 23 solvents as compared to DBS which managed to form gels in 17 of 23 solvents.
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Chapter 1 – Introduction

Objective & Hypothesis

1. To alter the ability sorbitol and urea-based derivatives to form gels in a wide array of solvents through modification of structure resulting in the loss of ability to form hydrogen bonds.

2. To alter the ability sorbitol and urea-based derivatives to form gels in a wide array of solvents through modification of structure resulting in the loss of ability to \(\pi-\pi\) stack.

The global gelation ability of 1,3:2,4-dibenzylidene-D-sorbitol or N,N’-dimethylurea will be impeded by eliminating the ability to hydrogen bond and/or to \(\pi-\pi\) stack depending on the gelator.
Introduction

Over the past decade, interest towards research and development of organogelators has been rapidly increasing[1]. The rising interest is attributed, in part, to the fact that gels are common everyday materials that are used in shampoo, soap, cosmetics, as well as being investigated in applications including: controlled drug release, structuring edible oils, and remedying oil spills[1,2]. LMOGs have potential to replace hardstock fats including saturated and trans fats as they are perceived negatively; however, they provide desirable functionality, texture, and palatability[3-8]. LMOGs may be used to structure liquid oils, high in unsaturated fats, whilst imparting similar functionality, texture, and palatability as compared to hardstock fats.

An all-encompassing definition for gels has yet to be defined but a common definition “if it looks like Jello, it is a gel” is commonly employed [9]. Polymer gels are widely used in most fields. However, molecular gels despite their growing application in the field were serendipitously discovered[10]. Predicting the chemical structure of potential gelators a priori continues to elude scientists as the challenge is confounded by the influence solvent has on the gelators ability to gel a given solvent. To date, Hansen Solubility Parameters (HSP) are the best method for predicting compatibility between gelator and solvent[11-13].

LMOGs, when placed in compatible solvents, self-assemble, forming aggregates with various morphologies, depending on the LMOG and solvent[2,14]. Solvent chemistry affects the ability of a LMOG to self-assemble as it influences the non-covalent interactions, including hydrogen bonding, π-π stacking, van der Waal forces, and London dispersion forces, which are necessary for gelator-gelator interactions[14]. These non-covalent interactions drive one-dimensional (1D) crystallization of fibers that entangle and form junction zones resulting in a 3 dimensional (3D) network[15]. The 3D network then entraps the solvent, resulting in a gel with
solid-like rheological properties[14]. By establishing a basis of factors contributing to a compound being a good gelator, a greater understanding for future applications and the possibility of new discoveries of LMOGs may be achieved. Self-assembly in molecular gels is extremely sensitive to types and locations of functional groups present on the gelator[16,17]. Changing these functional motifs can reduce or completely impede the capacity of a gelator to form a gel in a specific solvent[16,17]. The majority of gelators are restricted to a select group of solvents, giving less credence to the existence of an undiscovered universal gelator.

Currently one of the most widely studied LMOGs is DBS for its ability to gel a wide array of solvents[2,18]. DBS exhibits the majority of the traits that are believed to make an ideal gelator, and has been the subject of many experiments altering DBS[2]. Testing these DBS derivatives against DBS gives us a great deal of information on which molecular features and non-covalent interactions drive LMOGs to self-assemble.
Chapter 2 – Literature Review

What is a Gel?

From the first attempt to introduce the concept of a gel theory in 1861 by Thomas Graham, the definition has constantly been evolving[19]. The difficulty in defining gels led Dr. Dorothy Jordan Lloyd to broadly define gels as being a bi-phasic system that must be composed of a solid and liquid at room temperature[20]. This definition was useful, but was based on a false premise since not all colloids are gels and not all gels are colloids[21]. Definitions that followed in the subsequent decades were too specific or not inclusive enough. For example, Hermans defined gels as “coherent colloid disperse system of at least two components that exhibit mechanical properties characteristic of the solid state” and “both the dispersed component and dispersing medium extend themselves continuously throughout the whole system”[22]. A more inclusive definition was created by Ferry, “A gel is a substantially diluted system which exhibits no steady state flow[23]”. In order to account for both the microscopic and macroscopic properties two requirements need to be fulfilled for a substance to be classified as a gel: 1) has a continuous microscopic structure with macroscopic dimensions that is permanent on the time scale of an analytical experiment and 2) is solid-like in its rheological behavior despite being mostly liquid[14].

Organogels

Organogels are gels with the liquid phase being composed of an organic solvent. This comes as opposed to a hydrogel in which the liquid phase is water. LMOGs are different from polymeric gels in which they are arbitrarily limited to $\leq$3000 Daltons and assemble via highly specific non-covalent interactions [24-26]. These interactions lead to formation of fibrillar structures which combine into what is called a self-assembled fibrillar network (SAFIN)[15]. Molecular gels tend to be thermally activated in a two-step process. LMOGs are heated in a solvent
to obtain a solution and then left to cool. Cooling drives the aggregation and formation of the gel. The interactions that form SAFINs are hydrogen bonding, π-π stacking, van der Waals forces, and electrostatic interactions[15].

![Diagram of gel classification]

Figure 2-1 – Classification of gels (Taken from Sangeetha and Maitra) [27]

More recent studies have taken a much more time-appropriate approach to assessing whether a compound is indeed a gel. A solid-liquid mixture (gelator and solvent) is heated in a vial until a solution is formed and allowed to cool to room temperature. The compound is sealed and allowed to sit for 24 hours. At this point the vial is inverted to detect flow. If there is no flow then the study will classify the mixture as a gel.

**Molecular Gels**

Molecular gels are LMOGs that have undergone supramolecular aggregation and SAFIN formation [14]. Molecular gels can form at very low concentrations (<2 % wt)[14]. Through multiple steps. First the gelator is dispersed throughout the solvent and heated until a solution is formed. Following the formation of a solution, cooling the solution results in super-saturation, the driving force in aggregation of LMOGs via stochastic nucleation[28]. This nucleation occurs through highly specific interactions including hydrogen-bonding, π-π stacking, van der Waal
forces, and London dispersion forces, all which promote the preferred 1D growth of fibers[9,29-32]. The fibers vary in morphology, but common morphologies are tubules, strands, tapes, and chiral ribbons[28]. This step is often where regular crystallization processes undergo macroscopic phase separation, however molecular gels also undergo a microscopic phase separation. The 1D fibers branch off at junction zones which function to connect the 1D fibers forming a 3D network[28]. This 3D network entraps the liquid component on both a microscopic level via non-covalent interactions and a macroscopic level, via capillary forces and surface tension[28]. The ability to entrap the liquid component gives molecular gels their characteristic solid-like rheological properties[28].

![Hierarchical organization of self-assembled supramolecular gels](Taken from Okesola et al. 2015) [2]

**Sorbitol-Based Gelators**

The use of sugar-based gelators has been extensively investigated for use in both organogels and hydrogels[33,34]. Sugar-based gelators tend be biocompatible and thus are excellent candidates for edible and biocompatible applications[1]. D-sorbitol (Figure 2-3) is a sugar alcohol that can be synthesized from D-glucose and D-fructose. D-sorbitol has been employed as a thickener as well as a zero calorie sweetener in the food industry in various other
consumer products such as cosmetics[1]. LMOG derivatives of D-sorbitol have been employed for fundamental research in the field of molecular, in part because it is readily available. One of the most prominent derivatives of D-sorbitol is 1,3:2,4-dibenzylidene-D-sorbitol (DBS).

![D-Sorbitol](image)

*Figure 2-3 - Structure of D-Sorbitol*

DBS was first synthesized by Meunier in 1891 through an acid-catalyzed condensation reaction (Figure 2-4) and upon its formation it was noted that it formed ‘transparent gels’[35]. It was initially thought that multiple isomers of DBS were formed, however it was later discovered that both the mono and tri-substituted products were formed as byproducts[36]. Wolfe and co-workers, in addition to proving that a single species was being produced, managed to further deduce the structure of DBS by treatment with lead tetra-acetate, demonstrating that the structure was composed of either a 1,2,3,4 or 3,4,5,6 acetal functional groups. Differentiating between these two possibilities was done through acid hydrolysis yielding the protected sugar L-xylose confirming the 1,2,3,4 configuration (as opposed to D-arabinose which would indicate the 3,4,5,6 configuration). Furthermore through mild and controlled hydrolysis of DBS, 2,4-monobenzylidene-D-sorbitol was produced.
DBS is an amphiphilic chiral molecule that is said to have a ‘butterfly-shape conformation’[2] with the sorbitol back bone being deemed the ‘body’ and the benzylidene rings the ‘wings’[2]. The hydrophobic benzylidene wings allow for DBS to dissolve in a wide array of organic solvents[2]. DBS has the potential to gel an unusually large selection of organic solvents[2]. However, due to the serendipitous discovery of DBS, the mechanism of DBS gelation is not fully understood, but it is believed that hydrogen-bonding and π-π stacking are the main driving forces behind gelation. Selective addition of methoxy groups to either the 5-OH position or 6-OH position was tested. It was discovered that no gelation occurred when the 6-OH position was protected however, if the 5-OH position was protected then gelation still occurred. This suggests that the 6-OH group is a vital part of DBS self-assembly, likely acting as a hydrogen bond donor.
Polymer composites have been often increased tensile strength through the addition of various fibers into polymer matrices such as glass fibers, carbon fibers, aramid fibers, and boron fibers. This increase in tensile strength gives a more desirable mechanical properties profile. Modifying the brittleness of polymer composites remains a challenge; the issue is attributed to the incompatibility of the fibers and polymer matrices. DBS can be integrated into many polymer matrices, some examples including isotactic polypropylene, poly(propyleneglycol), poly(ethyleneglycol), and polyurethane (PU). When DBS is integrated into a liquid precursor of PU, a gel is formed. Polymerization initiated through UV-radiation formed in situ nanofiber reinforced polymer composites. A 12 wt% DBS nanofiber reinforced PU (12% DBS/PU) displayed less brittleness than a glass fiber reinforced polyurethane polymer (12% GF/PU), but the 12% DBS/PU had a much lower specific gravity of 1.108 compared to 12% GF/PU which had a specific gravity of 1.182. DBS supramolecular nanofibers were shown to be effective reinforcing and toughening agents as well as an effective lightweight alternative to reinforcing polymers while maintain polymer transparency (Figure 2-6).
Figure 2-6 - Stress/strain curve of fiber reinforce PU composites (Taken from Jin et al.)[38]

Derivatives of DBS have been prepared in order to see how the introduction of different functional groups to the benzylidene rings would affect gelation properties such as gel-to-sol transition time, microstructure, and the thermal storage performance. DBS derivatives have also been formulated to act as a hydrogel rather than its typical use as an organogels. The DBS derivative, DBS–CONHNH2, has been used to formulate active pharmaceutical ingredients (APIs), so far these include ibuprofen, naproxen, and mesalazine. Sonication followed by heating and cooling of the APIs and gelator within water, formed a stable two-component gel, with the APIs interacting through their carboxylic acid groups with the amine-like groups found on DBS–CONHNH2. Gelation of APIs in this fashion have advantages over conventional methods of delivery, mainly that drugs can be released in gradual doses. Additionally, this method of delivery can help assist with stomach transition, which can avoid side-effects such as stomach ulceration caused by drugs such as naproxen. This is managed through the release rate being tied to the pH;
a pH of 8 (intestinal pH) 100% of the drug is released (Figure 2-7), whereas at lower pH, a diminished release rate occurs.

![Figure 2-7 – Representative illustration of the release of APIs in a DBS–CONHNH2 hydrogel when the pH is increased (Taken from Okesola et al. 2015)[2]](image)

**Urea-Based Gelators**

The ability of urea to aggregate has been thoroughly investigated. Urea and thiourea have the ability to self-assemble through intermolecular hydrogen bonding and create inclusion complexes with \( n \)-alkanes and other long-chain molecules[39-43]. These complexes form linear or parallel tunnel hydrogen-bonding arrangements that allow for these inclusion complexes to incorporate long alkane chains[39]. In contrast, N-alkyl and N,N’-di-alkyl ureas do not form such inclusion complexes, but some have been shown to form both organogels and hydrogels, with hydrogels being formed more often from gelators with multiple urea moieties[44-48].

Alkyl-substituted urea derivatives have been found to form gels in numerous types of organic solvents despite relatively simple structures. N,N’-Dimethylurea (DMU) has the lowest molecular weight of any known organogelator to date[49,50]. The gelation of N,N’-dialkyl ureas as well as morphology of aggregates is highly dependent on alkyl chain length[49]. Shorter chain length seem to give a greater capacity to form gels[49]. Typical morphologies of aggregates
include helices and lamellae, with this being dependent on the type of solvent[51]. Urea-derivatives contain amide functional groups, giving them the ability to form hydrogen bonds. This ability to hydrogen bond is believed to be the driving force behind gelation in urea-derivatives (Figure 2-8)[39,52-55].

DMU, as the lowest molecular weight organogelator can form a gel in silicone oil and carbon tetrachloride in concentrations as low as 2 wt%[44,49]. DMU as compared to short chain N,N'-dialkylthioureas has been found to be the more efficient gelator, gelling various solvents at lower concentrations highlighting the significant role played of hydrogen bonding potential [49]. Despite this, longer chain N,N'-dialkylthioureas are much more capable of forming gels than their short chain counterparts[49]. This illustrates that even though intermolecular hydrogen bonding is thought to be an important quality for an effective gelator to have, it is not vital and that other intermolecular interactions as in this case, London dispersion forces, can contribute to the formation of effective 3D networks[49].

![Proposed hydrogen-bonded structure of N,N'-Dimethylurea](Taken from Yamanaka 2013)[55]

LMOGs with multiple ureide have been looked at for the possibility that they are able to alter the strength and morphology of gels as a result of increased hydrogen-bonding sites[55]. Bis-urea gelators have been found to be effective LMOGs, whilst exhibiting desired electro-optical properties. Certain bis-urea LMOGs have developed a switchable fluorescent supramolecular
system, in which the emission is stronger and red-shifted when observed in a gel state as compared to a non-gelled solution\cite{55,56}. Bis-urea derivatives that contain aliphatic or aromatic groups have proven to be efficient gelators as well\cite{48,49,57}. Bis-urea compounds that contain pyridine exhibit unusual self-assembling behavior as opposed to compounds that contain benzene\cite{53}. Pyridyl units are able to act as hydrogen bond acceptor, forming hydrogen bonds with the hydrogen of the urea moiety (Figure 2-9), resulting in self-assembling behavior involving both intramolecular and intermolecular hydrogen bonding\cite{53}.

\begin{center}
\textbf{Figure 2-9} - 
\begin{enumerate}
\item a) Self-assembly via hydrogen-bonding in urea-derivatives containing pyridine
\item b) Self-assembly via hydrogen-bonding in urea-derivatives containing a benzene group (Taken from Yabuuchi \textit{et al.} 2003)\cite{53}
\end{enumerate}
\end{center}
Advances in Edible Oleogel Technologies – A Decade in Review

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Alternative Oil Structuring Strategies:

Numerous approaches to oil structuring exist (Figure 2-10) with the most common alternative structuring method to colloidal fat crystal networks being the direct dispersion of a gelator into liquid oil. Direct dispersal of gelators includes: lipid-based, ethylcellulose (EC) and colloidal silicon dioxide (CSD). Lipid-based gelators are subdivided into waxes, fatty acids and monoglycerides [58]. To achieve gelation, following dispersal of the gelator into the oil phase, the resulting sol is often cooled to induce nucleation and crystal growth, leading to the formation of self-assembled networks [58]. Indirect methods require the formation of structural framework in an aqueous solvent or water continuous emulsion [59-61]. The gel network must be conserved during the careful removal of aqueous solvent. The use of oil sorption involves the enrichment, in this case by oil, of a porous material leading to an increased density [62]. Absorbent fillers have already been employed in foods in order to contain moisture and adjust product parameters such as consistency, flowability, and texture [63].
Monocomponent gels utilize a single gelator to structure liquid oil and mixed gels require synergistic interactions between multiple gelators [64]. Mixed system gelation is influenced by heterogeneous nucleation, increased nucleation rate, and network strengthening [58]. Mixed component gelation is found in wax-based oleogels due to variable components and ratios of natural waxes [58]. Oleogelators often require additional processing or processing aids before gelation is achieved; for example, EC is poorly soluble in oil and must be heated above its glass transition temperature (140°C) in order to achieve uniform dispersion [58]. While for CSD, high shear must be applied to disrupt aggregate formation, allowing uniformed dispersal of small aggregates that form a continuous network [65].
Waxes & Shellac:

Wax gelators are comprised of varying fractions of n-alkanes, fatty alcohols, and fatty acids depending on the origin of the wax and the proportions of these constituents have a critical role on gelation. Wax esters form platelet-like or needle-like crystals in edible oils at low concentrations compared to TAGs and they do not have negative health detriments [66]. Candelilla wax (CDW), carnauba wax (CBW), rice bran wax (RBW) and beeswax (BW) are of great interest as food-grade waxes for use as edible oleogels [67-71]. CDW, sourced from the leaves of Euphorbia cerifera, is composed of n-alkanes, between 29 and 33 carbons and structures safflower and canola oil at concentrations of 1 wt% and 2 wt%, respectively [66,72,73]. BW oleogels, compared to CBW and CDW oleogels formed in canola oil, have superior adhesive and cohesive properties (Table 2-1) [70]. CDW is typically the most elastic (i.e., highest hardness value) and BW is the lowest [70]. Oleogels comprised of BW, CBW, and CDW reduced peroxide value compared to pure canola oil [70].

Table 2-1 - Textural properties of oleogels prepared with natural waxes. Reproduced from Lim, Hwang, & Lee. Oil-structuring characterization of natural waxes in canola oil oleogels: rheological, thermal, and oxidative properties.

<table>
<thead>
<tr>
<th></th>
<th>Candelilla wax</th>
<th>Carnauba wax</th>
<th>Beeswax</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hardness (N)</strong></td>
<td>25.12 ± 2.05a</td>
<td>10.43 ± 0.13b</td>
<td>5.46 ± 0.28c</td>
</tr>
<tr>
<td><strong>Adhesiveness (N-s)</strong></td>
<td>1.97 ± 0.14c</td>
<td>2.95 ± 0.24b</td>
<td>4.74 ± 0.52a</td>
</tr>
<tr>
<td><strong>Cohesiveness</strong></td>
<td>0.14 ± 0.02c</td>
<td>0.20 ± 0.01b</td>
<td>0.33 ± 0.02a</td>
</tr>
<tr>
<td><strong>Gumminess (N)</strong></td>
<td>3.51 ± 0.65a</td>
<td>2.03 ± 0.05b</td>
<td>1.79 ± 0.12b</td>
</tr>
</tbody>
</table>

Plant waxes, such as CDW and CBW, form ‘needle-like’ crystals [72,74]. Previously, it was believed that ‘needle-like’ crystals were required to form the entangled network to bind oil. More recently, the morphology of the wax crystals of sunflower wax (SW), RBW and CDW were
reported as platelets [75]. These findings align with observation made in mineral waxes, which have been reported as ‘platelet-like’ morphologies [76]. Additionally, the dimensionality of ‘needle-like’ structures, observed on optical light micrographs, matched observations of the platelets observed through cryogenic scanning electron microscopy [75]. Further, nanoplatelets are on the same nanoscale order of magnitude as the nanoplatelets observed in fat crystal networks (Hwang, Kim, Evans, Koga & Lee, 2015). Fat crystal networks, prepared by blending tristearin and triolein, found nanoplatelets of approximate sizes $150 \times 60 \times 30$ nm to $370 \times 160 \times 40$ nm (Acevedo & Marangoni, 2010), while for sunflower wax in soya bean oil the nanoplatelets were 100 to 250 nm in thickness (Hwang, Kim, Evans, Koga & Lee, 2015).

Shellac is a resin purified from secretions of the insect Laccifer Lacca and has had a long history of uses in pharmaceuticals, cosmetics and foods applications [77,78]. Shellac has properties congruent to those of an oleogelator in that they are lipophilic, have the ability to self-assemble, and are thermo-reversible [78]. Shellac structures edible oils at concentrations as low as 2 wt.% and may do so in the presence of water. Water-in-oil emulsions were stable for longer than 18 weeks when shellac was added at concentrations as low as 1.6 wt.% [78]. The rate of cooling greatly alters the crystallization kinetics and resulting crystal network formation (Figure 2-11). Slower cooling rates delayed the onset of nucleation and crystal formation, resulting in larger, less dense crystals [78]. The resulting crystal network led to weaker oleogels compared to the same blends cooled at faster rates ($1^\circ$/min vs. $10^\circ$/min) [78]. It is believe the increased surface area of smaller crystals creates increased opportunity for crystal-crystal interactions resulting in a strengthened crystal network [78].
Figure 2-11 – Microscopy images showing changes in crystallization of shellac in liquid oil depending on cooling rates. Images on left were taken prior to crystal formation, center were taken as initial crystals were formed, and right were taken after crystal formation was complete. (Taken from Patel et al. 2013)[78]
**Ethylcellulose:**

![Structure of Ethylcellulose]

EC is derived from cellulose where hydroxyl groups have been ethylated and the degree of substitution (DoS) determines its solubility, (i.e., $1.0 < \text{DoS} < 1.5$ soluble in water; $2.4 < \text{DoS} < 2.5$ soluble in organic solvent). Typically, EC has a DOS of $\sim 2.5$ (Figure 2-12) [79,80]. EC has applications in plastics, ceramics, coatings, pharmaceuticals, cosmetics and as a food additives [79-84]. EC is relatively inexpensive, commercially available and food grade [85]. Until recently, EC has been the only polymer applied as an edible oleogelator; however, hydroxypropyl methylcellulose also has similar oil structuring properties [85,86]. EC, upon addition to the oil, must be heated above its glass transition and subsequently cooled to return the polymer into a rigid state forming intermolecular interactions via hydrogen bonding to produce an entangled network that entraps the oil [87,88]. Gravelle et al., 2014 correlated the mechanical properties of EC oleogels with the mass fraction of EC, mass fraction of surfactant, EC molecular weight, oil type, surfactant type and EC/surfactant ratio [88]. The setting temperature for gelation of EC oleogels was found to influence the gel strength (i.e., higher setting temperatures formed more ordered cross-linked polymer chains) [80]. Conversely, when the setting temperature was at lower temperatures, hydrogen bonds formed more sporadically leading to a less ordered weaker network.
with reduced hardness and fracture force (Figure 2-13). EC oleogels were more elastic when surfactants were incorporated into the gel structure [80].

![Figure 2-13 – Single Compression Cycle Curves of 15% wt. EC oleogel in Canola Oil and Multiple Temperatures (Taken from Davidovich-Pinhas et al. 2015)](image)

The mechanical properties of edible EC oleogels change depending on the type of oil being used. The parameters of the oil which influence the mechanical properites include: molecular weight, TAG composition, polar oxidation products and surface-active molecules [89]. Solvent polarity was correlated to the mechanical behavior of EC oleogels, which was attributed to polar functional groups interfering with EC interactions. The presence of small, surface-active molecules with the ability to hydrogen bond, such as oleic acid and oleic alcohol in small proportions (<0.5%), resulted in a significant increase in gel strength [89]. Gel strength was measured through NMR T₂ relaxation times, shorter pulsed reaction times were indicative of more restricted mobility of solvent and thus a stronger gel [89].

The ability of EC to form an oleogel depends on the ability to hydrogen bond, forming a 3D network from 1D polymer strands. Hydrogen bonding also aids in determining the gelator
solubility. To quantify the importance of hydrogen bonding to solubility, castor/soy oil-based-EC systems were made at various concentrations of EC and Hansen solubility parameters (HSP) were calculated and and correlated to shear rate-dependent viscosity which is an indicator of polymer/solvent interaction [89]. Castor oil was selected as one of the solvents due to its polarity; 85% castor/soy oil-based-EC system was found to form the optimal oleogel [89]. This ratio exceeds the 60% castor/soy oil-based-EC oleogel composition predicted by HSP parameters to be the optimal solubility for the EC oil blend [89]. This reveals not only is hydrogen bonding important in oleogel system solubility, but also reinforces the glaring need for well-developed encompassing formula to predict optimal gel solubility.

**Templating Polymeric Oleogelators:**

Most food polymers are hydrophilic in nature and are not their dispersible in oil making them ineffective gelling systems. However, systems containing water as the continuous phase in emulsions may be used as a templates to gel the dispersed oil [58]. For example, EC polymers are pre-hydrated initiating polymer-solvent interactions as well as forming physical crosslinks between polymers. This gels the aqueous phase, which is then dehydrated carefully to preserve the conformational framework of the polymer network entrapping the dispersed liquid oil. Indirect dispersion utilizes the framework created at oil-water interfaces and following the removal of water, leaves oil entrapped in the ‘dried’ microstructural network [59-61]. Using water continuous emulsions as templates can create oil powders, gels and soft solids that can structure very high concentrations of oil with minimal oil leakage over prolonged storage periods [65].

Porous additives hold some beneficial traits for aiding in structuring oils. Sorption techniques are used in many field such as pollution control and catalysis. The recent usage of newly developed porous materials to help clean up oil spills can be applied to structuring oils [58]. Hydroxyl propyl
methylcellulose was used to stabilize an aqueous foam as a template to adsorb oil (Patel, Schatteman, Lesaffer, & Dewettinck, 2013). The incorporation of hardstock fats, at a 5 wt.%, to this template improved the thixotropic recovery properties (Patel & Dewettinck, 2015). The sorption process results in the increase in the density of a material through physical interactions at an interface. Preliminary studies have shown that porous cellular structures could be quite effective, absorbing 100 times its own weight and containing up to 98 wt.% liquid oil [63].

Ceramides:

![Figure 2-14 - Structure of Spingosine and a Generic Ceramide](image)

Ceramides are a class of polar lipids characterized by the presence of a sphingosine base, which contains an 18-carbon unsaturated aliphatic chain) and a fatty acid (Figure 2-14). Sphingosine-derivatives, such as ceramides and sphingolipids, play an important role in cell signaling and regulate integral aspects of cell development including: differentiation, proliferation, and apoptosis [90]. As an oleogelator, some ceramides can structure oil reducing the need for trans and saturated to structure oil and they have positive health benefits. Ceramides reduce total serum cholesterol by 30% and improve the serum lipoprotein profile [91]. Ceramides induce apoptosis
by promoting production of interleukin 1B and regulate apoptosis regulating tumor cell growth [92]. Ceramides have a role in inhibiting carcinogenesis of colon cancers, attributed to its effects on cell differentiation, growth, and apoptosis [92]. C2 in particular has been show to decrease cell viability of colon prostate, ovarian, and leukemia cell lines, while longer fatty acid chain counterparts are ineffective [93].

Individually, most ceramides are poor gelators, with the exception of short-chain ceramides, for example N-acetoyl-D-erythro-sphingosine (C2 ceramide) [93]. Increasing the fatty acid chain length adversely affects the ability of ceramide to gel vegetable oil and at 2 wt.%, fatty acid chain length greater than 6 carbons do not gel. At 5 wt.%, organogels are observed beyond 6 carbons [93]. It has been reported that shorter fatty acid chain lengths promote fibril growth, whereas longer chain lengths promote spherulitic or platelet crystal morphologies [92]. Additionally, as fatty acid chain length increases so does melting temperature but it negatively correlates to the elastic modulus of the organogel [93].

At low concentrations, long chain length ceramides (i.e., ceramide III), β-sitosterol and stearic acid are ineffective individual gelators. Stearic acid and ceramide III form platelets and β-sitosterol forms spherulites (Figure 2-15) [92]. A dramatic difference in microstructure is observed when stearic acid and cholesterol are added in a 1:4 ratio to canola oil. Fibers result at the 1:4 ratio, highlighting the complexity and changes in structure that occur when varying the concentrations of multiple-gelators (Figure 2-16) [92]. Despite forming fibers, which have limitations in food applications, both the cosmetics and pharmaceutical industries may find these useful. Oleogels derived from different ratios of stearic acid, ceramide III and β-sitosterol produce very different morphologies with very different physicochemical properties [92]. Further research in these ratios, find ideal combinations that are appropriate for edible applications.
Figure 2-15 – Polarized light micrographs of viscous solutions of 5 wt% stearic acid, β-sitosterol and ceramide III in canola oil (Taken from T.-M. Wang and M. A. Rogers, 2015)

Figure 2-16 – Polarized light micrographs of a 5% wt mixture in canola oil as compared to Fibers (Taken from T.-M. Wang and M. A. Rogers, 2015)
β-Sitosterol and γ-Oryzanol Oleogels:

![Structure of β-Sitosterol and γ-Oryzanol](image)

Figure 2-17 – Structure of β-Sitosterol and γ-Oryzanol

Individually, neither β-sitosterol nor γ-oryzanol (Figure 2-17) self-assemble efficiently enough to entrain oil. When combined at a 60:40 wt.% γ-oryzanol/β-sitosterol ratio (or a 1:1 molar ratios) they form hollow tubules at concentrations as low as 2%, leading to a strong oleogel [6,94]. To form gels several criteria are required for this system listed in decreasing order of importance: synergistic hydrogen bonding, a ring system, and alkyl residue [95]. Although the co-crystallization of β-sitosterol with γ-oryzanol is the most widely studied phytosterol co-crystal, other plant sterols such as ergosterol, stigmasterol, cholesterol, cholestenol form similar structures with varying tubule diameter and wall thickness [94]. Small-angle X-ray scattering (SAXS) determined that tubule diameters were between 67 and 80 Å, wall thickness was between 8 and 12 Å (Figure 2-18) and tubule length exceeding 1000 Å [94]. These multifaceted oleogelators are already deemed food grade [83] and phytosterols lower blood cholesterol levels and contribute satiety making these attractive alternatives to colloidal fat crystal networks [6,82]. In sunflower oil, oleogels are transparent and by varying the sterol type and concentration, the mechanical and rheological properties of the oleogel can mimic saturated fats [96]. β-sitosterol and γ-oryzanol also modify volatile molecule release [97].
The ratio between γ-oryzanol, β-sitosterol and vegetable oil effects the crystalline structures observed and their ability to entrain liquid oil [98]. The ternary phase diagram (TPD) (Figure 1-9) displays a wide array of ratios of γ-oryzanol, β-sitosterol, and canola oil which exhibit numerous polymorphic forms, melting points, and morphological characteristics [98]. A mixed crystalline phase was observed at γ-oryzanol ratios between 30% and 100%, β-sitosterol levels between 0% and 20%, and canola oil between 0% and 70%. This region of the TPD required large supercooling to initiate nucleation, when nucleation occurred it was rapid, leading to numerous small crystals [98]. Lamellar crystals formed having a spherulitic morphology. The large central region consists of 20% – 70% γ-oryzanol, 60% - 10% β-sitosterol and 20% - 60% canola oil and forms a single crystalline phase, which seems ideal as a trans and saturated fat replacer. The TPD
illustrates various polymorphic phases and microstructural elements that may be modified simply by altering the proportions of γ-oryzanol, β-sitosterol and canola oil [98].

*Figure 2-19 – Ternary Phase Diagram (Taken and modified from F. M. AlHasawi and M. A. Rogers, 2013)*
Carbohydrate-Based Oleogelators:

Most carbohydrate-based gelators are considered biocompatible [1] leading to very little research on the safety of these oleogelators. Sugar alcohols, such as sorbitol derivatives aim to be low cost, efficient oil gelators in the presence of water. Dialkanoate derivatives of both D-sorbitol and D-mannitol showed differences in gelation ability between Man-4 and Sor-4 as well as Man-8 and Sor-8 (Table 2-2). This highlights the importance of chirality on gelation, as the only difference in chemical structure between D-mannitol and D-sorbitol are the orientation of the hydroxyl group on C2 [99]. The importance of hydrogen bonding is also stressed as the protected Man-8 was unable to gel oil. In the presence of water, the hydrophobic tails of Man-8 and Sor-8 encouraged the molecules to align in the oil phase resulting in gel formation [99]. Carbohydrate-based oleogelators are thus far an under-researched area, with high potential in providing edible gelators, capable of structuring oil in the presence of water.
Edible Oleogel Applications

Oleogels have been investigated in a wide array of products that are high in either saturated or trans fats. Frankfurters, high in saturated fat, form solid-like, stable emulsions that are capable of retaining water. Organogel-based emulsions with γ-oryzanol/β-sitosterol were first investigated to formulate frankfurters [96]. Sensory analysis showed no significant difference between the 20% backfat control and a 10% backfat combined with 10% sunflower oleogels [96]. Interestingly, the organogel-structured emulsion at a 30:70 ratio (γ-oryzanol: β-sitosterol) was more elastic,
gummy and chewy compared to the 60:40 ratio (γ-oryzanol: β-sitosterol) [96]. Frankfurters made using β-sitosterol, γ-oryzanol and sunflower oil were a suitable replacer for the pork backfat [96]. EC has also been used to reduce the saturated fat content of frankfurters (Zetzl, Marangoni, & Barbut, 2012). Cooked frankfurters with the beef-fat replaced with EC and various vegetable oils showed no significant differences in chewiness or hardness compared to the control products made with beef fat (Zetzl, Marangoni, & Barbut, 2012). The physical attributes of the frankfurter could be tailored by varying the molecular weight of EC, EC concentration and fatty acid distribution of the vegetable oil (Zetzl, Marangoni, & Barbut, 2012). One advantage of EC oleogels in this application arise from the interconnected structure with 0.5 to 6 μm holes where the liquid oil was entrapped (Zetzl, Marangoni, & Barbut).

Beeswax (BW) and SW oleogels made with hazelnut oil (HO) or virgin olive oil (VOO) have been investigated and assessed by a sensory panel with butter and margarine as a point of comparison (Figure 2-20). BW and SW oleogels, made with either HO or VOO, have similar structural and thermal properties compared to commercially-available spreads [100]. The hedonic traits of these edible spreads tested positively and ~ 50 % of consumers ‘would buy or try once and then buy the oleogel products’ illustrating that consumers may accept the oleogel alternatives as a replacement of spreadable fats (Yilmaz & Ögütcü, 2015). The firmness of a 2–6 % sunflower wax in soybean oil oleogel was similar to margarine containing 18–30 % hydrogenated soybean oil in non-hydrogenated soybean oil; however, the melting point was significantly higher than the commercial margarine (Hwang, Singh, Bakota, Winkler-Moser, Kim & Liu, 2013). Replacing conventional shortenings with wax oleogels into baked goods, such as cookies, increases the spread factor and reduces the snapping force (Jang, Bae, Hwang, Lee & Lee, 2015). Therefore,
oleogels provide desirable spreadability and the replacement of shortening with the oleogels may be used to produced cookies with soft eating characteristics (Jang, Bae, Hwang, Lee & Lee, 2015).

![Image of oleogels](image_url)

**Figure 2-20** – **HO and VOO oleogels prepared with BW and SW compared to commercially available butter and margarine (Taken from Yılmaz and Öğütcü 2015)**

Shellac, a food-grade resin and potential oleogelator, has many food applications including use in spreads, chocolate pastes, and cakes [77,78]. Shellac oleogels made with rapeseed oil and water were acceptable substitutes for commercial shortening [77]. Shortenings must provide the desired textural aspects of baked goods and if oleogels are to replace shortening they must not compromise certain attributes such as their ability to shorten gluten networks. Comparative sensorial parameters of the cake prepared with traditional shortening versus the shellac oleogels showed statistically significant differences in the cakes’ volume, cell size, moistness, stickiness, and sponginess and no significant difference was observed for the crumbliness [77]. Shortenings, often used for their foamability, allow air to be incorporated into the batter without separating.
which produces homogenous crumb giving rise to the tenderness of cakes [77]. The crumb structure of a cake produced with a traditional shortening verses a shellac oleogel are similar in appearance (Figure 2-21). Not only has shellac been used as a shortening alternative, but so have SW and BW in HO and these oleogels have been incorporated into cookies [101]. Cookies made from an oleogel or a commercial shortening were comparable and the oleogel outperformed the traditional shortening with regard to the textural, compositional and hedonic traits. This is a prime example of the organogels’ potential to achieve uncompromised taste and texture with no trans and reduced saturated fats.

![Figure 2-21 – (Left) Cake prepared using shellac oleogel emulsions/(Right) Cake prepared using commercial shortening(Taken from Patel et al. 2014)[77]](image)

Ice cream, typically high in saturated fat, is an ideal candidate to have a portion of the milk fat replaced with wax oleogels [71]. Botega et al. combined emulsifiers and wax oleogels and observed no significant differences in the fat globule size when 15% fat was either from the wax oleogel or milk fat (Figure 2-22). The ice cream formula consisted of either 10 or 15 wt.% oleogel (i.e., oleogel consisted of 10 wt.% wax in high-oleic sunflower oil) [71]. Ice cream made with 15 wt.% RBW and glycerol monooleate was melt-resistant but less effective when formulated with dairy fat (Figure 2-22) [71]. RBW and EC soybean oleogels have been incorporated into cream
cheese [102]. EC oleogels with skim milk, whey protein isolate and non-fat dry skim milk were coagulated for 14-16 hours [102]. The oleogel cream cheese (OCC) samples had improved nutritional profiles compared to full-fat control, with a 90% reduction in saturated fat and 120% increase in unsaturated oil. Full-fat controls and OCC samples were found to have similar textural attributes (Figure 2-22) because of the similar lipid globule size between control and OCCs [103].

![Figure 2-22 – (Left) Fat Particle Size in Different Ice Cream Formulations/ (Right) Meltdown Rate of Different Ice Cream Formulations in a continuous freezer (white bars) and batch freezer (black bars) (Taken from Botega et al. 2013) [71]](image-url)
Figure 2-23 – Textural properties of samples using a cone penetrometer test, superscript represents whether statistically significant or not (Taken from Bemer et al. 2016)[102]

Conclusions

The field of oleogel structuring, despite having limited commercially available products, has shown a great deal of promise [58]. Oleogelators have resulted in the development of many edible applications, such as baked goods, frankfurters and ice cream. Many of these structured oleogels are on par and in certain instances are more desirable to consumers and have an enhanced nutritional profile. Therefore, oleogelators seem to be a potential solution for the reduction and possibly elimination of *trans* and saturated fats from processed foods.
There is still the need for new efficient, low-cost gelators compatible with specific processing conditions of respective products. EC has been found to have an excellent capacity to structure oils but in large scale operations is unfeasible to meet the high temperature required to disperse it in oil. Plant waxes provide ideal hedonistic characteristic which are most comparable to traits provided by saturated and trans fats but problems arise in stability over extended periods. There is currently a distinct gap in knowledge in regard to identifying ideal ratios of ceramides, fatty acids, cholesterol, phytosterols in terms of structuring oils, crystal morphology and resulting suitability for edible applications. Carbohydrate-based gelators although extensively studied have had minimal research in the field of edible oleogels. Success over the last few years with edible applications of oleogels will continue increased interest and research in the field. Despite the serendipitous discovery of oleogelators, increased research have discovered numerous applications and provided a more comprehensive view of the field.
Chapter 3 – Molecular Nuances Governing the Self-Assembly of 1,3:2,4-Dibenzylidene-D-Sorbitol -- A Rationalized Approach using Hansen Solubility Parameters

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Abstract

1,3:2,4 Dibenzylidene-D-sorbitol (DBS) is the gold-standard for low-molecular-weight organogelators (LMOGs). DBS gelates a wide array of solvents, as illustrated by the large Hansen sphere representing gels \(2\delta_d = 33.5, \delta_p = 7.5, \text{ and } \delta_h = 8.7 \text{ MPa}^{1/2}; \text{ radius } = 11.2 \text{ MPa}^{1/2}\). Derivatives of DBS have been synthesised to isolate and determine molecular features essential for organogelation. Herein, \(\pi-\pi\) stacking and hydrogen-bonding are the major non-covalent interactions examined. The importance of \(\pi-\pi\) stacking was studied using 1,3:2,4 dicyclohexanecarboxylidene-D-sorbitol (DCHS), which eliminates possible \(\pi-\pi\) stacking, while still conserving the other structural aspects of DBS. DCHS is a poor gelator; only one of the several solvents examined, carbon tetrachloride formed a gel. 1,3:2,4 diethylidene-D-sorbitol (DES), another DBS analogue incapable of \(\pi-\pi\) stacking and with a very different polarity, gelated a large Hansen space \(2\delta_d = 34.0, \delta_p = 10.9, \text{ and } \delta_h = 10.8 \text{ MPa}^{1/2}; \text{ Radius } = 9.2 \text{ MPa}^{1/2}\). DES gels solvents with higher \(\delta_p\) and \(\delta_h\) than DBS. To assess the role of hydrogen bonding, DBS was acetylated (A-DBS). The Hansen space gelated by A-DBS shifted to less polar solvents with higher hydrogen bonding Hansen solubility parameters (HSPs) \(2\delta_d = 33.8, \delta_p = 6.3, \text{ and } \delta_h = 9.6 \text{ MPa}^{1/2}; \text{ Radius } = 11.1 \text{ MPa}^{1/2}\) than DBS. This systematic structural modification is the first step in exploring how specific intermolecular features alter aspects of Hansen space corresponding to positive gelation outcomes.
Introduction

Sorbitol-derived molecules have garnered attention as low molecular-mass organogelators (LMOGs), with prospective applications in the food, cosmetic, and pharmaceutical industries.\[1,2,71,104,105\] Organogels made from LMOGs are thermo-reversible and form gels at low concentrations.\[106\] Further to this, there is a requisite that molecular gelators be non-toxic for the aforementioned applications, making biocompatible carbohydrate-based gelators excellent candidates for medical and edible applications.\[1,27\] Although sorbitol-derivatives are under investigation, DBS has extremely wide-reaching interest because it gels an unusually wide array of organic solvents.\[1,2,18,107\] The gelation capacity of DBS has been attributed to its ability to make intermolecular hydrogen-bonds between free hydroxyl groups, π-π stack between aromatic groups, and its ‘butterfly-like’ shape.\[108-111\] Sorbitol acts as the body and the benzylidene rings as wings. The hydrophobic benzylidene wings are responsible for DBS being slightly soluble in numerous organic solvents.\[112\]

Molecular gelators are driven to self-assemble via non-covalent intermolecular interactions such as hydrogen-bonding, π-π stacking, electrostatic interactions, and van der Waals interactions into 3-dimensional (3D) networks consisting of fibers.\[2,113,114\] These non-covalent interactions promote one-dimensional (1D) fibrillar growth, with the 1D fibers interacting to form temporary and permanent (i.e., formed via crystallographic mismatches giving rise to daughter fibers) junction zones, resulting in a self-assembled fibrillar network (SAFiN).\[115\] The SAFiN entraps solvent molecules on a microscopic level, via non-covalent interactions, and on a macroscopic level, via capillary forces and surface tension giving rise to solid-like rheological properties.\[116\] These interactions can be disrupted by heating the gel above the sol-gel transition temperature, but will reform once the sol is cooled below the transition temperature.
Hansen solubility parameters (HSPs) are used to quantify the potential of gelator-solvent combinations to form SAFiNs due to the interplay between the two components. HSPs, originally developed to identify solvents capable of dissolving polymers, have been adapted to study the assembly of small molecular gelators.[117] Raynal and Bouteiller were the first to recognize that, barring few exceptions, solvents gelled by a specific gelator have similar HSPs.[117] Other approaches, such as the Hildebrand solubility parameters, were unable to account as well for specific intermolecular interactions that drive self-assembly.[117] A gelator must be both sufficiently soluble in a solvent so it does not precipitate out of solution and sufficiently insoluble to facilitate self-assembly/crystallization, producing a gel.[118-120] Since a gelator must balance non-covalent interactions between the solvent and other gelator molecules to produce a gel, then molecular gelators capable of gelling solvents tend to reside within a confined, specific region of HSPs.

HSPs may be used as effective *a priori* tools in predicting the ability of small molecules to self-assemble into SAFiNs for specific solvents.[117,121] HSPs are derived from the total cohesive energy density or the negative energy of vaporization per cm$^3$ of sample, corresponding to the Hildebrand parameter ($\delta_t$) (eq. 1). HSPs contain three components: dispersive ($2\delta_d$), polar ($\delta_p$), and hydrogen bonding ($\delta_h$) forces.[12] A greater affinity between gelator and solvent exists when their Hansen space coordinates (eq. 1) are similar thus leading to the two compounds being miscible:

$$\delta_t^2 = \delta_d^2 + \delta_p^2 + \delta_h^2$$

(eq. 1)

where $\delta_d$ is the dispersive HSP, $\delta_p$ is the polar HSP, and $\delta_h$ is the hydrogen bonding HSP.[13]
Already, HSPs have provided tremendous insights into why gelators are capable of assembling in certain solvents and not others.[117] However, there are only limited studies on using HSPs to explain which gelators will gel a solvent.[117] In part, this is because the number of studies that systematically modify the chemical structures of the gelator to observe the gelation outcome in a wide array of solvents is scarce[122,123]. Although work has been amassed to determine how molecular features of the LMOG influence gel properties of DBS[124], there has yet to be a study examining how these modifications alter the Hansen space that corresponds to gel formation.

Methods

Materials 1,3:2,4-Dibenzylidene-D-sorbitol (98%, BOC Science, New York, USA), m.p. 221.1 °C (Figure 3-6), and 1,3:2,4-Di-O-Ethylidene-D-sorbitol (95%, Sigma Aldrich, Oakville, Canada), m.p. 167.1 °C (Figure 3-6) were used as received. The solvents used for gelation tests included: salicylaldehyde (98%), dimethyl sulfoxide (≥99.9%), o-xylene (97%), isobutyl alcohol (≥99%), triethylene glycol (99%), butylamine (99.5%), hexanoic acid (≥99.5%), α,α-dichlorotoluene (≥95%), tetramethylurea (99%), carbon tetrachloride (≥99.5%), benzyl methacrylate (96%), acetophenone (99%), chloroform (≥99.5%), triethylamine(≥99.5%), hexanes (≥98.5%), and benzene (≥99%) were obtained from Sigma Aldrich, Oakville, Canada. N,N-dimethylformamide (≥99%) was obtained from ACROS (New Jersey, USA. Acetone (HPLC-grade), acetonitrile (HPLC-grade), toluene (≥99.5%), pyridine (≥99%), and methylene chloride (≥99.5%) were obtained from Fisher Scientific (Ottawa, Canada). Ethyl alcohol (95%) was obtained from Commercial Alcohols (Brampton, Canada).
Synthesis of 1,3:2,4-dibenzylidene-5,6-diacetyl-D-sorbitol: DBS (BOC Sciences, New York, USA) was combined with 22 eq of pyridine (≥99 %, Fisher Scientific, Ottawa, Canada) and 22 eq of acetic anhydride (≥97 %, Fisher Scientific, Ottawa, Canada) in a round-bottom flask (RBF) and stirred at room temperature for one hour. The reaction mixture was then concentrated in toluene (≥99.5 %, Fisher Scientific, Ottawa, Canada) (3 x 200 mL) on a rotary evaporator and the dried under vacuum.

1,3:2,4-dibenzylidene-5,6-diacetyl-D-sorbitol (A-DBS): yield 100 %; [α]D +5.6 (c 1.0, CHCl3); m.p. 208.2 °C (Figure 3-6). 1H NMR (CDCl3, 400 MHz, 295 K) (Figure 3-7) δH: 7.31–7.35 and 7.47–7.52 (2 m, 4H and 6H, aromatics), 5.62 (s, 1H, CHPh), 5.57 (s, 1H, CHPh), 5.45 (m, 1H, H-5), 4.60 (dd, 1H, J = 2.4, 12.4 Hz, H-6b), 4.40 (dd, 1H, J = 1.3, 12.6 Hz, H-1b), 4.28 (dd, 1H, J = 5.0, 12.4 Hz, H-6a), 4.18 (dd, 1H, J = 1.9, 8.0 Hz, H-4), 4.15 (dd, 1H, J = 2.0, 12.7 Hz, H-1a), 3.97 (t, 1H, J = 1.6 Hz, H-3), 3.84 (d, 1H, J = 1.6 Hz, H-2), 2.07 and 2.04 (2 s, 2 x 3H, 2 CH3CO). 13C NMR (CDCl3, 100 MHz, 295 K) (Figure 3-8) δC: 170.8, 169.7 (2 C=O), 137.8, 137.5, 129.3, 128.9, 128.4, 128.3, 126.6, 126.2 (Ar), 101.0 (CHPh), 100.6 (CHPh), 76.4 (C-4), 70.4 (C-2), 70.1 (C-1), 69.1, 68.9 (C-3, C-5), 62.4 C-6), 21.1, 21.0 (2 CH3CO). HREIMS m/z calculated for C24H26O8Na [M]+ 442.1628, found 442.1621; purity ~96 % by NMR.

Synthesis of 5,6-diacetyl-D-sorbitol: 1,3:2,4-Dibenzylidene-5,6-diacetyl-D-sorbitol was combined in a RBF with an 80 % acetic acid (99 %, Sigma Aldrich, Oakville, Canada)/20 % deionized water solution and stirred at 80 °C. The reaction was monitored by thin layer chromatography with an eluent of 9:1 (methylene chloride (≥99.5 %, Fisher Scientific, Ottawa, Canada):methanol (99.8 %, Sigma Aldrich, Oakville, Canada)). After one hour, the reaction was stopped and co-concentrated with toluene (≥99.5 %, Fisher Scientific, Ottawa, Canada). The
product was then purified by silica column chromatography with an eluent of 9:1 (methylene chloride (≥99.5 %, Fisher Scientific, Ottawa, Canada):methanol (99.8%, Sigma Aldrich, Oakville, Canada)) and dried under vacuum.

**5,6-diacetyl-D-sorbitol**: yield 83%; [α]D +36.3 (c 1.0, CHCl₃). ¹H NMR (CD₃OD, 400 MHz, 295K) (Figure 3-11) δH: 5.10 (m, 1H, H-5), 4.60 (dd, 1H, J = 2.5, 12.2 Hz, H-6b), 4.18 (dd, 1H, J = 5.6, 12.2 Hz, H-6a), 3.99 (dd, 1H, J = 2.2, 8.2 Hz, H-4), 3.75 (m, 1H, H-2), 3.68 (dd, 1H, J = 4.7, 11.3, H-1b), 3.64–3.56 (m, 2H, H1a, H-3), 2.06 and 2.04 (2 s, 2 × 3H, 2 CH₃CO). ¹³C NMR (CD₃OD, 100 MHz, 295 K) (Figure 3-12) δC: 173.3, 173.1 (2 C=O), 73.1 (C-2), 72.7 (C-5), 70.7(C-3), 70.5 (C-4), 67.6, 67.0 (C-1, C-6), 21.0, 20.9 (2 CH₃CO). HRESIMS m/z calculated for C₁₀H₁₈O₈Na [M+Na]+ 289.0894, found 289.0883.

**Synthesis of 1,3:2,4-dicyclohexanecarboxyldiene-5,6-diacetyl-D-sorbitol (A-DCHS)**: 5,6-Diacetyl-D-sorbitol was combined in a RBF with 6 eq of cyclohexanecarboxaldehyde (97 %, Sigma Aldrich, Oakville, Canada) at 50 °C. HCl (Sigma Aldrich, Oakville, Canada, 37 %) was added dropwise and the stirring rate was increased as the viscosity of the reaction mixture increased, the reaction was stopped after one hour. The product was washed out in methylene chloride and deionized water and the organic layer was collected. The organic layer was then concentrated and purified by silica column chromatography using an eluent of 9:1 hexanes:ethyl acetate.

**1,3:2,4-dicyclohexanecarboxyldiene-5,6-diacetyl-D-sorbitol (A-DCHS)**: yield 67 %; [α]D +2.6 (c 1.0, CHCl₃); m.p. 95.3 °C (Figure 3-6). ¹H NMR (CDCl₃, 400 MHz, 295 K) (Figure 3-15) δH: 5.28 (m, 1H, H-5), 4.48 (dd, 1H, J = 2.0, 12.3 Hz, H-6b), 4.25–4.18 (m, 2H, H-6a, >CHC₆H₁₂), 4.17–4.10 (m, 2H, H-1b, >CHC₆H₁₁), 3.79 (bd, 1H, H-1a, H-4), 3.54 (bs, 1H, H-3), 3.42 (bs, 1H, H-2), 2.01 and 2.00 (2 s, 2 × 3H, 2 CH₃CO), 0.96–1.87 (4 m, 22H, 2 >CHC₆H₁₂).
C NMR (CDCl$_3$, 100 MHz, 295 K) (Figure 3-16) $\delta$C: 170.6, 169.3 (2 C=O), 104.78, 104.71 (2 $>CHC_6H_11$), 75.2 (C-4), 69.9 (C-2), 69.5 (C-1), 68.4, 68.3 (C-3, C-5), 62.2 (C-6), 41.6, 41.4, 27.5, 27.4, 27.1, 26.9, 26.29, 26.26, 25.5, 25.48, 25.46, 25.43, 25.2 (2 $>CHC_6H_{11}$), 20.7 (2 CH$_3$CO). HREIMS m/z calculated for C$_{24}$H$_{38}$O$_8$ [M]$^+$ 454.2567, found 454.2569; purity ~94% by NMR and HREIMS.

**Synthesis of 1,3:2,4-dicyclohexanecarboxyldiene-D-sorbitol (DCHS)**

1,3:2,4-Dicyclohexylidene-5,6-diacetyl-D-sorbitol was placed in a 0.05 M solution of sodium methoxide in methanol (99.8%, Sigma Aldrich, Oakville, Canada) and stirred for one hour. The reaction was monitored by TLC using an eluent of 2:1 hexanes:ethyl acetate. The reaction was quenched with Dowex 50 H$^+$ resin until the pH was 7.0 and then the Dowex 50 H$^+$ resin was filtered out. The filtrate was then concentrated and dried under vacuum. The product was then purified through silica column chromatography using an eluent of 2:1 hexanes:ethyl acetate.

**1,3:2,4-dicyclohexanecarboxyldiene-D-sorbitol (DCHS):** yield 95%; $[\alpha]_D$ +13.6 (c 1.0, CHCl$_3$); m.p. 89.3 °C (Figure 3-6). $^1$H NMR (CDCl$_3$, 400 MHz, 295 K) (Figure 3-19) $\delta$H: 4.25 (d, 1H, $J$ = 6.8 Hz, $>CHC_6H_{12}$), 4.22 (d, 1H, $J$ = 6.4 Hz, $>CHC_6H_{12}$), 4.15 (dd, 1H, $J$ = 1.2, 12.8 Hz, H-1b), 3.98 (m, 1H, H-5), 3.84–3.76 (m, 2H, H-1a, H-6b), 3.75–3.67 (m, 2H, H-3, H-6a.), 3.60 (dd, 1H, $J$ = 1.6, 7.6 Hz, H-4), 3.34 (bs, 1H, H-2), 0.90–1.81 (4 m, 22H, 2 $>CHC_6H_{12}$). $^{13}$C NMR (CDCl$_3$, 100 MHz, 295 K) (Figure 3-20) $\delta$C: 104.93, 104.90 (2 $>CHC_6H_{11}$), 78.1 (C-4), 70.4 (C-2), 69.9(C-1), 69.7, 69.4 (C-3, C-5), 63.9 (C-6), 42.0, 41.8, 27.9, 27.7, 27.6, 26.6, 25.79, 25.77 (2 $>CHC_6H_{11}$). HRESIMS m/z calculated for C$_{20}$H$_{34}$O$_6$Na [M+Na]$^+$ 393.2248, found 393.2238; purity ~95% by NMR and HREIMS.

**Nuclear magnetic resonance spectroscopy** $^1$H NMR (400 MHz) and $^{13}$C NMR (100 MHz,) spectra were recorded at 295 K in CDCl$_3$ (calibrated at $\delta$C 77.0 ppm and using residual CHCl$_3$ at
\( \delta_H \) 7.24 ppm), CD\textsubscript{3}OD (calibrated at \( \delta_C \) 49.0 ppm and using residual CH\textsubscript{3}OH at \( \delta_H \) 3.31 ppm). All chemical shifts are reported in parts per million (ppm). All coupling constants (\( J \)) are reported in Hertz (Hz) for \( ^1H \) NMR spectra. Assignments of proton and carbon peaks were made using 2D COSY and HSQC experiments. Multiplicities are abbreviated as singlet (s), broad singlet (bs), doublet (d), doublet of doublets (dd), doublet of a doublet of a doublet (ddd), triplet (t), doublet of a triplet (dt), triplet of a doublet (td), quartet (q), doublet of a quartet (dq), quartet of a doublet (qd), quintet (quin), and multiplet (m).

**Gelation test** Each 5 % wt gelator/solvent combination was combined and the solid was dissolved by heating the sample to 90 °C in 2 ml screw top glass vials (Sigma Aldrich, Oakville, Canada) for 30 min until a transparent sol formed. The vials were cooled to room temperature (20-22 °C) and left there for 24 h. Sample vials were then inverted for 30 min and examined to see if flow occurred. Solvent gelator combinations were categorized as a gel if no flow was observed, a sol if they flowed and were transparent, and a precipitate if flow was observed and they were opaque or if the gelator had precipitated.

**Hansen spheres** A globally constrained optimization procedure in Mathematica 9 (Wolfram Research, Champaign, IL) was used to calculate minimal enclosing spheres that contained all the points pertaining to each category (i.e., sol, gel, or precipitate). The optimization procedure was implemented using the “NMinimize” built-in function in Mathematica to obtain the sphere center in terms of Hansen coordinates while solving for the smallest possible radius. The NMinimize function was used to obtain the global optimization problem numerically and a direct search method, differential evolution, was selected as the numerical algorithm to reach a numerical global optimum solution.[125] The selection of this direct search method was based on its robustness despite being computationally more expensive.[126] Four effective digits of precision were sought
in the final results; these criteria were used to halt the iteration process. 2D and 3D renditions of the resulting spheres were plotted.

**Optical Microscopy** A small portion of the gel was taken from a glass vial after 24 hours of storage at room temperature and placed on a 75 mm x 25 mm glass microscope slide (Fisher Scientific, Ottawa, Canada) and then a 25 mm x 25 mm glass coverslip (Fisher Scientific, Ottawa, Canada) was placed on top of the sample. A Nikon Eclipse Ti-S inverted light microscope (Nikon Instruments, New York, USA) equipped with a QIMAGING Retiga 2000R color camera (QImaging, Surry, Canada) and a Nikon Plan Apo 10X/0.45 DIC N1 lens (Nikon Instruments, New York, USA) and a Nikon Plan Apo 40x/0.95 DIC M/N2 40X lens (Nikon Instruments, New York, USA) were used to acquire polarized light micrographs.

**Scanning electron microscopy** Scanning electron microscopy (SEM) of the xerogels was examined after they were dried from acetonitrile. A small aliquot of the gelator-acetonitrile gel was placed on a SEM stub and placed into an oven (Fisher Scientific, Isotemp®, Fair Lawn, NJ, USA) at 35 °C for 10 min, allowing acetonitrile to evaporate. The sample on the SEM stub was mounted on a sputter coater (Emscope K550 sputter coater, Ashford, Kent, UK) and coated with gold using a 20 mA deposition current, 7 nm min\(^{-1}\) deposition rate for 2 minutes. The sample was transferred to a specimen holder onto the SEM stage (Hitachi S-570, Tokyo, Japan). Images were taken using Quartz PCI Imaging software (Quartz Imaging Corp., Vancouver, Canada).

**Differential Scanning Calorimetry** 10 to 12 mg of each gelator were transferred into Alod-Al hermetically sealed DSC pans. The DSC chamber (Q2000, TA instruments, New Castle, DE) was pre-cooled to 20 °C before the sample was placed into the chamber that was continually flushed with nitrogen (0.5 ml/min). The samples were heated to at 2 °C/min to 250 °C to determine the
peak melting temperatures and then data storage was turned off and the DSC cell was cooled to 20 °C.

**X-ray diffraction** A Rigaku multiflex powder X-ray diffractometer (Rigaku, Tokyo, Japan) with a 1/2 ° divergence slit, 1/2 ° scatter slit, and a 0.3 mm receiving slit, was set at 40 kV and 44 mA to determine the polymorphic form of the network. Scans were performed from 1 to 30° with a 0.02° step at 1° min⁻¹.

**Optical Rotation** Optical rotations were measured at room temperature (20-22 °C) on a Rudolph Research Autopol III polarimeter using a Rudolph Research Analytical type 2 polarimeter sample cell with a length of 10 cm and volume of 1.3 ml. Optical rotations were reported as follows: [α]D (c in g per 100 mL, solvent).

**Computational Modeling** The structures used for the calculations were optimized using Gaussian software g09/g16[127] and the DFT/B3LYP[128] method with 6-31G[129] as a basis set. There were no imaginary frequencies. The distances are between atoms at the extreme ends of the X, Y and Z-axes to which the van der Waals radii of the terminal atoms have been added. The van der Waals radii used for hydrogen and oxygen are 1.2 Å and 1.52 Å, respectively.[130]
Results and Discussion

Scheme 3.1 – The pathway for synthesizing DCHS starting from DBS.

Synthesis of DCHS was initially attempted using D-sorbitol, cyclohexanecarboxaldehyde and an acid catalyst (hydrochloric acid); however, issues that complicated purification were encountered, including the formation of mono-, di-, and tri-substituted products and multiple isomers of each product. Scheme 3.1 was devised for a more directed approach to synthesizing DCHS. In Scheme 3.1, DBS was used as the starting material and was subsequently acetylated to protect the two hydroxyl groups to form acetylated DBS (A-DBS). The advantage of this method was to limit the number of derivatives formed during the synthesis. Benzylidene groups were then hydrolyzed exposing four hydroxyl groups that then are acetalated with cyclohexane carboxaldehyde to form acetylated DCHS (A-DCHS). The final step was a Zemplén deacetylation reaction forming DCHS.
Table 3-1 – Gelation outcomes of 5 wt. % sorbitol-derived gelators in a wide range of solvents

<table>
<thead>
<tr>
<th></th>
<th>DBS</th>
<th>A-DBS</th>
<th>DES</th>
<th>DCHS</th>
<th>A-DCHS</th>
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<tr>
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<td>Gel</td>
<td>Gel</td>
<td>Precipitate</td>
<td>Solution</td>
<td>Solution</td>
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</table>

In assessing the gelation ability of each of the 5 sorbitol derived molecules, the only obvious trend that emerged was substituting the benzyl for cyclohexyl groups. This substitution eliminates π-π stacking and imparts stearic impediments to highly ordered packing, preventing gelation in all solvents except for carbon tetrachloride (Table 3-1). By defining gelator-solvent combinations as solutions, precipitates or gels and by selecting solvents to cover a wide array HSP an adequate representation of Hansen space for each outcome could be sought (Figure 3-1). The
advantage of using this approach is that it provides an encompassing view of how these potential gelators behave globally. To illustrate this point, if carbon tetrachloride had been the only solvent examined, then it would have been concluded that DBS, A-DBS and DCHS were all good gelators, while A-DCHS and DES were not able to act as SAFiNs, which does not adequately represent the global findings for these molecular changes.

Figure 3-1 – 3D Hansen space for solution spheres (blue), precipitate spheres (green), and gelation spheres (red) for sorbitol-derived gelators.
Each gelator was tested in 23 solvents for their gelation outcomes (i.e., solution, precipitate or gel) and plotted in Hansen space (Figure 3-1). The HSPs of solvents were used to create the minimal enclosing spheres for each outcome. This method results in the generation of coordinates for the centre of the sphere and the radius which may be compared between gelators to observe the global effects on gelation. Qualitatively, the process of self-assembly, in molecular gels, is intricate and must balance parameters influencing solubility and those contrasting forces that govern epitaxial growth into axially symmetric elongated aggregates.[114,131,132] Hansen solubility parameters can quantitatively define the balance required for these parameters.[12,13]

For example, if DBS ($2\delta_d = 35.3$, $\delta_p = 8.3$, and $\delta_h = 10.1$ MPa$^{1/2}$) is added to tetramethylurea ($2\delta_d = 33.4$, $\delta_p = 8.2$, and $\delta_h = 11.0$ MPa$^{1/2}$), a solution is obtained. The distance between two molecules ($R_{ij}$) can be calculated using eq. 2:

$$R_{ij} = \sqrt{4(\delta_{di} - \delta_{dj})^2 + (\delta_{pi} - \delta_{pj})^2 + (\delta_{hi} - \delta_{hj})^2}$$

where $i$ represents the HSPs for the gelator and $j$ for the solvent and the 4 before the dispersive component allows for a spherical fit. For DBS in tetramethylurea $R_{ij}$ is 2.01 MPa$^{1/2}$. When the solvent and potential gelator are very close in Hansen space they have similar interactions and the gelator is solvated by the solvent. Conversely, if DBS is added to hexane ($2\delta_d = 29.8$, $\delta_p = 0$, and $\delta_h = 0$ MPa$^{1/2}$) the $R_{ij}$ is 14.1 MPa$^{1/2}$ and DBS precipitates out of solution. Gelation, which requires a meticulous balance between contrasting parameters including solubility and those intermolecular forces that control epitaxial growth into axially symmetric elongated aggregates, occurs at intermediate $R_{ij}$ values.

Of the gelators tested, DBS gelled the most solvents (17 of 23 solvents) and had the largest gelation sphere with a radius of 11.2 MPa$^{1/2}$ (Table 3-2). The distance between the centre of the
solubility sphere and the Hansen coordinates for DBS is 1.72 MPa$^{1/2}$, indicating that when solvent and gelator are in proximity in Hansen space it results in solvation of the gelator. Clearly, for DBS, the solution sphere is confined within the gelation sphere and the only solvent that resulted in a precipitate was located just outside of the gelation sphere (**Figure 3-1** and **Figure 3-23**). Compared to DBS (2$\delta_d = 35.3$, $\delta_p = 8.3$, and $\delta_h = 10.1$ MPa$^{1/2}$), DES (2$\delta_d = 34$, $\delta_p = 9.6$, and $\delta_h = 13.4$ MPa$^{1/2}$) was the most dissimilar of the tested potential gelators. In the case of DES (**Figure 1** and **Figure 3-24**), the center of the solution sphere is located 3.71 MPa$^{1/2}$ away from the coordinates of DES. Unlike DBS where the precipitate was located outside the solution and gel spheres, the solution sphere is enclosed in the gelation sphere but the precipitate sphere and gelation sphere have considerable overlap (**Figure 3-1**). Since there was considerable overlap between the spheres, we examined if the direction of the solvent relative to the gelator had an influence of the gelation outcome (**Figure 3-2**).

In trying to understand why there is considerable overlap between the spheres for DES, the difference (i.e., $\delta_p($gelator$) - \delta_p($solvent$)$) between the Hansen coordinates was plotted (**Figure 3-2**). Unlike $R_{ij}$ calculations, the difference in Hansen coordinates preserves the directionality of the tensor distance. For example, solvents that are below or to the left of the 0,0 point have a greater HSP than the gelator. The difference in Hansen coordinates between the solvents and DBS (**Figure 3-2 A-C**) illustrates the expected result (i.e., solvents that are close to 0,0 on **Figure 3-2**, which represent DBS, result in solutions, at intermediate distances they are gels and the furthest point represents precipitates). DES does not show the same trend (**Figure 3-2 D-F**); specifically, **Figure 3-2 D** illustrates that gels ONLY result when the solvent point is below $\Delta\delta_p = 0$ MPa$^{1/2}$, while precipitate states exist above this line. In comparing the intermolecular interactions that would drive DBS to gel versus DES, DBS can rely on both hydrogen bonding and $\pi-\pi$ stacking, while
DES only relies on hydrogen bonding. It can be concluded that DES will only gel in solvents that are more polar than the gelator; however, the reason for this has not been elucidated.

![Figure 3-2](image)

*Figure 3-2 – Two-dimensional projections of the distance between the solvent and DBS (A-C), DES (D-F) and A-DBS (G-I) polar (Δδ_p) (B), dispersive (Δδ_d) (C), and hydrogen-bonding (Δδ_h) (D) Hansen solubility parameters.*

Modifying DBS by acetylating the primary and secondary hydroxyl groups did not have a major effect on the gel Hansen sphere (*Figure 3-1, Figure 3-25*). The radius of the gelation sphere was 11.1 MPa^{1/2} compared to a radius of 11.2 MPa^{1/2} for DBS. Although acetylating DBS did not have a major effect on the size of the Hansen space, it did shift the gelation sphere to a lower δ_p and a greater δ_h (*Table 3-2*). Upon acetylation, A-DBS could no longer gel benzene, toluene,
acetonitrile or acetone. Gels are thought to form at intermediate $R_{ij}$ values where they are slightly soluble, but still able to crystallize into SAFiNs entrapping solvent. It is peculiar that A-DBS in toluene and benzene forms precipitates while DBS forms gels (SI Table 1). It was expected that A-DBS should be soluble in these solvents since it has a smaller $R_{ij}$ than DBS, which forms gels, and the solvent should easily be able to interact with the phenol groups of A-DBS. It is clear that DBS forms much finer fibers in benzene than A-DBS (Figure 3-3 E and I). The broadening of the fibers may indicate that solvent is being incorporated between A-DBS molecular in the fibers of the network resulting in fewer, broader crystals that are unable to form a coherent network capable of entrapping the solvent. This would result in the A-DBS fibers precipitating out of solution. It is common thought that to be an effective SAFiN, the functional group driving self-assembly must be connected to a chiral carbon which then imparts supramolecular chirality, limiting growth to one-direction. If solvent molecules are located between gelators molecules the molecular chirality will not be conferred on a supramolecular level and growth will occur more readily in more than one dimension (i.e., fibers broaden or transition to platelets). Since there are fewer, thicker fibers, there will be less fiber-fiber interactions and the crystals will not form a sufficient 3D network and will collapse or precipitate. Unlike A-DBS, DBS has the potential to self-assemble via hydrogen bonding which could still confer the supramolecular chirality, in addition to $\pi-\pi$ stacking, and this could drive the formations of thin fiber and hence gels in benzene and toluene. It can be seen that the magnitude of the $R_{ij}$ is not always sufficient to predict gelation outcome. For example, when comparing DBS and DES in isobutyl alcohol, DBS forms a gel with an $R_{ij} = 8.09$ MPa$^{1/2}$ but DES forms a precipitate with a lower $R_{ij}$ value (5.99 MPa$^{1/2}$). Further, DBS in dimethyl-formamide forms a solution with a $R_{ij} = 5.54$ MPa$^{1/2}$ but DES forms a gel at lower $R_{ij}$ values (4.67MPa$^{1/2}$). This reinforces that not only is the magnitude of $R_{ij}$ important in
determining whether a gel will form but so is the directionality of the distance between the solvent and gelator (i.e., if two solvents are equal distance from the gelator but one has lower HSPs while the other has higher HSPs than the gelator, this may result in different gelation outcomes (see figure 2)).

Neither DCHS (Figure 3-1 and Figure 3-23) nor A-DCHS (Figure 3-1 and Figure 3-25) were efficient gelators in the solvents tested, with each forming a single gel. DCHS and A-DCHS both lack the ability to π-π stack and have bulkier configurations compared to DBS and A-DBS where aromatic phenol groups are planar. It is obvious that π-π stacking plays a more predominant role in gel formation compared to hydrogen-bonding. However, removing π-π stacking potential from DBS had a much more pronounced effect than expected. DBS could gel 17 of 23 solvents, but the DBS analogue, DCHS which does not result π-π stacking only gelled carbon tetrachloride. It is also possible that the planar nature of the benzylidene groups on DBS allowed for superior self-assembly in comparison to the cyclohexyl groups of DCHS, which would adopt a bulkier chair conformation. The idea of the bulkier cyclohexane group affecting the ability to self-assemble is reinforced by the comparison of DES to DCHS. Neither DES nor DCHS can π-π stack but both can form hydrogen bonds, however DES is a much more efficient gelator. Therefore, it is possible that the less bulky ethylidene acetal group featured on DES does not physically constrain gelation.

Polarized light microscopy (Figure 3-3) was used to examine the effect of the gelator and solvent structure on the morphology of the SAfiNs that constitutes the supramolecular network of gels. It is evident that DBS, A-DBS and DES all form SAfiNs within the gelation sphere. As the distance in Hansen space, $R_{ij}$, increases, the aspect ratio of the fibers decrease resulting wider, more dense fibers, an indication they are becoming less soluble. Except for DBS, an $R_{ij}$ above 10 MPa$^{1/2}$ leads the fibrillar morphology to transition to a platelet morphology. One reason for the
remarkable ability of DBS to form SAFiNs in a broad array of solvents is that self-assembly can be driven by either hydrogen-bonding of the primary and/or secondary hydroxyl groups and/or by \(\pi-\pi\) stacking of the benzylidene groups.[2] In the case of DBS, irrespective of the non-covalent interaction that drives gelation both functional groups are attached to a chiral carbon, which is a well-established requisite for SAFiNs with high aspect ratios.[17,133-135] In the case of A-DBS (Figure 3-3 F-J) the fibers are much thicker than for DBS and this morphology does not appear to be simply a product of solubility (i.e., \(R_{ij}\)). Clearly, A-DBS in acetophenone (Figure 3-3 G) has the lowest aspect ratio below an \(R_{ij}\) of 10 MPa\(^{1/2}\). A-DBS gels in aromatic solvents (Figure 3-3 F, G & J) are much less fibrillar and have platelet-like morphologies, a potential molecular mechanism may be that the gelator-gelator \(\pi-\pi\) stacking is impeded since the solvent is capable of \(\pi-\pi\) stacking with itself. This is likely why \(R_{ij}\), albeit important, does not explain certain aspects of SAFiN networks, and it would be very useful if HSPs could be further broken down to account for each non-covalent interaction. In the case of DES, as \(R_{ij}\) increases so does fiber thickness.
Figure 3-3 – Polarized light micrographs of gels containing 5 wt% gelator. DBS (A-E) in acetone (A), chloroform (B), isobutyl alcohol (C), o-xylene (D) and benzene (E); A-DBS (F-J) in benzyl methacrylate (F), acetophenone (G), hexanoic acid (H), benzene (I), and salicaldehyde (J); and, DES (K-O) in dimethyl formamide (K), triethylene glycol (L), hexanoic acid (M), pyridine (N), and acetophenone (O). Scale bars are 10 μm.
The morphologies of sorbitol-derived organogels were also examined by SEM for DBS, DES and A-DBS (Figure 3-4). The morphology of the DBS sample shows a very fine fibrillar network. DES also exhibits a fibrillar morphology when solvent is removed. However, the fibers are much wider than those of DBS. A-DBS in acetonitrile forms a transparent solution with a very slight haze that is caused by very fine aggregates (~ 10 μm crystals (Figure 3-4)) that are suspended; this gelator-solvent combination could be equally well described as a precipitate, however irrespective of the classification, it does not impact our Hansen spheres. The morphology of A-DBS xerogels shows what appear to be micellar structures or spherulitic crystals.
Figure 3-4 – Scanning electron micrographs of DBS, A-DBS and DES xerogels obtained upon drying 5 wt.% gelator in acetonitrile gels.
Powder XRD shows drastic differences between the crystalline structures of the various gelators (Figure 3-5). DBS gels in isobutyl alcohol have higher order reflections and a diffraction peak which corresponds to a Bragg distance of 45.94 Å, a value that is much greater than the largest dimension of a single molecule (11.74 Å) based on computational modeling (Figure 3-5). The unit cell must be comprised of an arrangement of DBS molecules; a tetramer is a reasonable suggestion for the unit cell which facilitates its unusual gelation behaviour. The higher order reflections for DBS dried organogels have previously been reported using DBS in silicone-poly(ethylene glycol)-PPG terpolymer[111]; however, in their spectra the peaks are much broader than observed in this study likely due to the complexity of their solvent system. Irrespective of the molecular feature modified (i.e., the alcohol groups being converted to an acetyl group or benzyl moieties being substituted for cyclohexyl moieties), important features of the nano-assembly (most notably, higher order reflections) are lost. For A-DBS, DES and A-DCHS, the first peak of the diffraction profile corresponds to a Bragg distance that is slightly larger than the shortest dimension of the molecule and there is a lack of detectable higher order peaks. These observations are indicative of lower degrees of crystallinity for the DBS derivatives/analogues.
Figure 3-5 Long spacing for neat gelators in isobutyl alcohol obtained using powder X-ray diffraction with the d-spacings, full-width at half-maximum, and domain size calculated using the Scherrer equation. Molecular dimensions were calculated using Gaussian software g09/g16\cite{127} and the DFT/B3LYP\cite{128} method with 6-31G\cite{129} as the basis set.
Conclusions

The sorbitol-derivatives, DCHS and DES, were synthesized to evaluate the importance of \( \pi-\pi \) stacking in SAFiN formation, while A-DBS was used to assess the importance of hydrogen bonding. The results indicate that \( \pi-\pi \) stacking plays a significant role in the formation of DBS SAFiNs. The cyclohexyl rings featured in DCHS hinder self-assembly due to their lack of planarity and inability to support \( \pi-\pi \) stacking. From plots of HSPs in Hansen space, gelation, solubility, and precipitate spheres have been constructed. They visualize and quantify differences in the intermolecular non-covalent interactions that are significant in these solvent-gelator systems. Overall, this study helps to identify the importance that different intermolecular interactions have on SAFiN formation in this very important gelator system.

Additional Information:

An interactive demonstration of the method to solve for the Hansen sphere for all the gelators and the corresponding code are available online at the Wolfram Demonstration Project (www.XXXX.)

Acknowledgements:

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Supplementary Information – Molecular Nuances Governing the Self-Assembly of 1,3:2,4-Dibenzylidene-D-Sorbitol--A Rationalized Approach using Hansen Solubility Parameters

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Figure 3.6 - DSC melting profiles for the pure D-sorbitol based gelators when heated at 2 °C/min.
Figure 3-7 - $^1$H-NMR of 5,6-di-acetyl-1,3:2,4-di-benzylidene-D-sorbitol; 400MHz, 296 K, CDCl$_3$. 
Figure 3-8 - $^{13}$C-NMR of 5,6-di-acetyl-1,3:2,4-di-benzylidene-D-sorbitol; 100MHz, 296 K, CDCl$_3$. 
Figure 3-9 - COSY of 5,6-di-acetyl-1,3:2,4-di-benzylidene-D-sorbitol; 400MHz, 296 K, CDCl₃.
Figure 3-10 - HSQC of 5,6-di-acetyl-1,3:2,4-di-benzylidene-D-sorbitol; 400MHz, 100MHz, 296 K, CDCl₃.
Figure 3-11 - $^1$H-NMR of 5,6-di-acetyl-D-sorbitol; 400MHz, 296 K, CD$_3$OD.
Figure 3-12 - $^{13}$C-NMR of 5,6-di-acetyl-D-sorbitol; 100MHz, 296 K, CD$_3$OD.
Figure 3-13 - COSY of 5,6-di-acetyl-D-sorbitol; 100MHz, 296 K, CD$_3$OD.
Figure 3-14 - HSQC of 5,6-di-acetyl-D-sorbitol; 100MHz, 296 K, CD$_3$OD.
Figure 3-15 - $^1$H-NMR of 5,6-di-acetyl-1,3:2,4-di-cyclohexanecarboxylidene-D-sorbitol; 400MHz, 296 K, CDCl$_3$. 
Figure 3-16 - $^{13}$C-NMR of 5,6-di-acetyl-1,3:2,4-di-cyclohexanecarboxylidene-D-sorbitol; 100MHz, 296 K, CDCl$_3$. 
Figure 3-17 - COSY of 5,6-di-acetyl-1,3:2,4-di-cyclohexanecarboxylidene-D-sorbitol; 400MHz, 296 K, CDCl₃.
Figure 3-18 - HSQC of 5,6-di-acetyl-1,3:2,4-di-cyclohexanecarboxylidene-D-sorbitol; 400MHz, 100MHz, 296 K, CDCl₃.
Figure 3-19 - $^1$H-NMR of 1,3:2,4-di-cyclohexanecarboxyldiene-D-sorbitol; 400MHz, 296 K, CDCl$_3$. 
Figure 3-20 - $^{13}$C-NMR of 1,3:2,4-di-cyclohexanecarboxylidene-D-sorbitol; 100MHz, 296 K, CDCl$_3$
Figure 3-21 - COSY of 1,3:2,4-di-cyclohexanecarboxylidene-D-sorbitol; 400MHz, 296 K, CDCl₃
Figure 3-22 - HSQC of 1,3:2,4-di-cyclohexanecarboxylidene-D-sorbitol; 400MHz, 296 K, CDCl₃
Figure 3-23 - 2D Projections of 1,3:2,4-di-cyclohexanecarboxylidene-D-sorbitol (Left) & 1,3:2,4 dibenzylidene-D-Sorbitol (Right).
Figure 3-24 - 2D Projections of 1,3;2,4 diethylidene-D-sorbitol
Figure 3-25 - 2D Projections of 5,6-di-acetyl-1,3:2,4-di-cyclohexanecarboxylidene-D-sorbitol (Left) & 5,6-di-acetyl-1,3:2,4-di-benzylidene-D-sorbitol (Right)
Table 3-2 Calculated $R_{ij}$ values between the gelator and solvent.

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<th>A-DBS (MPa$^{1/2}$)</th>
<th>DES (MPa$^{1/2}$)</th>
<th>DCHS (MPa$^{1/2}$)</th>
<th>A-DCHS (MPa$^{1/2}$)</th>
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Chapter 4 – Structurally Simple Urea-Derived Low Molecular Weight Gelators

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Abstract

N,N'-Dimethylurea (DMU) is the smallest known low-molecular-weight organogelator (LMOG). DMU is limited in the number of solvents it gels, therefore, simple derivatives of urea were studied to identify molecular features that enhance the ability to form self-assembled fibrillar networks (SAFiNs). The addition of π-π stacking, via the addition of benzene groups to form N,N'-dibenzylurea (DBU), is the primary non-covalent interaction being examined, since both π-π stacking and hydrogen-bonding are believed to be significant contributing factors towards gelation. The ability of DMU to form gels was tested alongside N,N'-dicyclohexylurea (DCHU) and DBU, the former two interact only via hydrogen bonding while DBU is capable of hydrogen bonding and π-π stacking. DBU was the most efficient of the three gelators in terms of number of solvents gelled and produced a large Hansen sphere representing solvents which result in gelation (2δd = 37.8, δp = 5.35, and δh = 8.35 MPa1/2; Radius = 8.36 MPa1/2) as compared to the smaller gelation sphere produced by DMU (2δd = 34.6, δp = 2.05, and δh = 2.35 MPa1/2; Radius = 2.88 MPa1/2) and DCHU (2δd = 34.65 δp = 9.4, and δh = 10.85 MPa1/2; Radius = 8.66 MPa1/2). This systematic comparison of LMOGs is essential in understanding the role of different intermolecular features governing gelation of LMOGs.
Introduction

Gelators have been implemented in a vast array of products including cosmetics, food, pharmaceuticals, cleansing products, etc [2,27,114]. LMOGs are a class of self-assembling molecules that form supramolecular gels. These organogels are advantageous in their potential to assemble and form gels in concentrations as low as 2 wt. % [136]. Additionally, LMOGs are thermoreversible, forming gels upon cooling below a specific temperature and return to the sol state by heating above the melting transition temperature, however they are reformed upon cooling again [1]. These properties are highly sought after in industry, resulting in a huge rise in interest into the development of gelators [27].

The self-assembly of LMOGs occurs via highly specific non-covalent interactions such as hydrogen-bonding, π-π stacking, electrostatic interactions, London dispersion forces and van der Waals interactions [2,113,114]. These interactions drive the formation of one-dimensional (1D) fibers, which entangle to form a three-dimensional (3D) networks [15,114]. The 3D network entraps solvent on both a macroscopic level through non-covalent interactions, and microscopically through capillary forces and surface tensions resulting in solid-like rheological properties and loss of fluidity [114,116]. A gelator must be sufficiently soluble in a given solvent in order to avoid precipitation, but insoluble enough in order to form a gel system [118].

Alkyl-substituted urea derivatives, despite their simple structure, have been found to form gels in various types of organic solvents, with DMU being the smallest known organogelator to date [49,50]. Urea-derivatives contain amide functional groups that allow the formation of hydrogen bonds, with hydrogen bonds being thought as the predominant force driving gel formation [113,114]. This work aims to investigate three urea-derivatives DMU, DCHU, DBU, and test their gelation potential by creating 5 wt. % solutions/gels/precipitates in a wide array of
solvents. Comparing these gelators that all contain a urea backbone allows us to investigate the effects of different non-covalent interactions in conjunction with hydrogen bonding, specifically $\pi-\pi$ stacking.

Hansen solubility parameters (HSPs) were developed to identify solvents that were able to dissolve polymers [137]. Raynal and Bouteiller found solvents gelled, by a specific gelator, clustered in Hansen Space, and HSPs have since been adapted to act as an *a priori* method for predicting the ability of gelators to form SAFiNs in given solvents [137,138]. Previous parameters, for example the Hildebrand solubility parameters, neglected to account for intermolecular interactions that drive the formation of SAFiNs [137]. Gelators tend to reside at the edge of the solubility sphere, necessitating that they be sufficiently soluble that they do not precipitate out of solution, but also insoluble enough that self-assembly/crystallization occurs to produce the SAFIN. It is this strict balance of opposing parameters that drives gelators to self-assemble and each solvent gelled will reside in a specific region in Hansen space. HSPs are derived from the total cohesive energy density or the negative energy of vaporization per cm$^3$ of sample, corresponding to the Hildebrand parameter ($\delta_t$) (eq. 1). HSPs decompose the single Hildebrand parameter into three components: a dispersive ($2\delta_d$), polar ($\delta_p$), and hydrogen bonding ($\delta_h$) HSP [12]. A greater affinity between gelator and solvent exists when their Hansen space coordinates (eq. 1) are similar, thus leading the compounds to be soluble:

$$\delta_c^2 = \delta_d^2 + \delta_p^2 + \delta_h^2$$

(eq. 1)

where $\delta_d$ is the dispersive HSP, $\delta_p$ is the polar HSP, and $\delta_h$ is the hydrogen bonding HSP[13]. HSPs have already proven to be a useful tool in determining why gelators are capable of gelling certain solvents but not others[117]. This study aims to compare gelators by retaining specific
structural features, while systematically adding others to allow certain types of intermolecular interactions to be probed independently, in hopes of better understanding their roles in gelation.

**Methods**

**Materials:** The gelators $N,N'$-dibenzylurea, $N,N'$-Dicyclohexylurea (98%), $N,N'$-dibenzylurea and the solvents used for the gelation tests are: salicylaldehyde (98%), dimethyl sulfoxide (≥99.9%), o-xylene (97%), isobutyl alcohol (≥99%), triethylene glycol (99%), butylamine (99.5%), hexanoic acid (≥99.5%), α,α-dichlorotoluene (≥95%), tetramethylurea (99%), carbon tetrachloride (≥99.5%), benzyl methacrylate (96%), acetophenone (99%), chloroform (≥99%), triethylamine (≥99.5%), hexane (≥98.5%), and benzene (≥99%) were obtained from Sigma Aldrich (Oakville, Canada). $N,N$-dimethylformamide (≥99%) were obtained from ACROS (New Jersey, USA). Acetone (HPLC-grade), acetonitrile (HPLC-grade), toluene (≥99.5%), pyridine (≥99%), and methylene chloride (≥99.5%), were obtained from Fisher Scientific (Ottawa, Canada). Ethyl alcohol (95%) was obtained from Commercial Alcohols (Brampton, Canada).

**Gelation Tests:** Each gelator/solvent combination were combined at 5 wt. % and heated to 90°C until a solution formed in 2 ml screw top glass vials (Sigma Aldrich, Oakville, Canada). The vials were then cooled and stored for 24 hours at room temperature (20-22°C). Sample vials were then inverted for 30 minutes and observed to see if flow occurred. Solvent/gelator combinations were categorized as a gel, if no flow was observed, a sol, if they flowed and were transparent, and a precipitate, if flow was observed and they were opaque or if the gelator had precipitated out of the sol.

**Hansen Spheres:** A global constrained optimization procedure in Mathematica 9 (Wolfram Research, Champaign, IL) calculated the minimal enclosing spheres encompassing all points pertaining to each category (i.e. sol, gel, or precipitate). The optimization procedure used the
“NMinimize” built-in function in Mathematica to obtain the vertex of the sphere in terms of Hansen coordinates while solving for the smallest possible radius. The global optimization problem was solved numerically using the NMinimize function and a direct search method, differential evolution, was selected as the numerical algorithm, to reach a numerical global optimum solution[125]. This direct search method was selected based on its robustness despite being computational more expensive [126]. Four digits of precision were sought in the final results; these criteria were used to halt the iteration process.

**Microscopy:** After 24 hours of storage at room temperature, an aliquot of the gel was removed from the glass vial and placed on a 75 mm x 25 mm glass microscope slide (Fisher Scientific, Ottawa, Canada) and a 25 mm x 25 mm glass coverslip (Fisher Scientific, Ottawa, Canada) was placed on top of the sample. A Nikon Eclipse Ti-S inverted light microscope (Nikon Instruments, New York, USA) equipped with a QIMAGING Retiga 2000R color camera (QImaging, Surry, Canada), a Nikon Plan Apo 10X/0.45 DIC N1 lens (Nikon Instruments, New York, USA) and a Nikon Plan Apo 40x/0.95 DIC M/N2 40X lens (Nikon Instruments, New York, USA) were used to acquire polarized light micrographs.

**Scanning electron microscopy:** Scanning electron microscopy (SEM) was used to examine xerogels after removal of the solvent—acetonitrile. A small aliquot of each gelator and acetonitrile mixture was placed on a SEM stub and placed into an oven (Fisher Scientific, Isotemp®, Fair Lawn, NJ, USA) at 35 °C for 10 min allowing for evaporation of solvent. The sample on the SEM stub was mounted on a sputter coater (Emscope K550 sputter coater, Ashford, Kent, UK) and coated with gold using a 20 mA deposition current, 7 nm min-1 deposition rate for of 2 min. The sample was transferred to a specimen holder onto the SEM stage (Hitachi S-570, Tokyo, Japan).
Images were taken using Quartz PCI Imaging software (Quartz Imaging Corp., Vancouver, Canada).

**X-ray diffraction (XRD):** A Rigaku multiflex powder X-ray diffractometer (Rigaku, Tokyo, Japan) with a 1/2 ° divergence slit, 1/2 ° scatter slit, and a 0.3 mm receiving slit, was set at 40 kV and 44 mA to determine the polymorphic form of the networks. Scans were performed from 1 to 30° at 1° min⁻¹.

**Results and Discussion**

In terms of number of solvents gelled, DBU is the most efficient gelator, followed by DCHU, and lastly DMU (Table 4.1). DMU and DCHU form hydrogen bonds through their amide functional groups facilitating their self-assembly in organic solvents. DBU has hydrogen bonding in addition to benzyl functional groups that allow for π-π stacking. Non-covalent interactions facilitate the self-assembly of molecular gelators and π-π stacking and hydrogen bonding are the most common intermolecular interactions in prospective gelators. Oddly, as seen in Table 4.1 DBU gels seven of the eight solvents that contain one or more aromatic rings. It is possible that π-π stacking between gelator and solvent contributes to the formation of SAFiNs, although typically gels have minimal interactions between the solvent-phase and the gelator-phase.
Table 4-1 – Gelation outcomes of urea-derived gelators in 23 solvents at a 5 wt. %.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>DMU</th>
<th>DCHU</th>
<th>DBU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetonitrile</td>
<td>Solution</td>
<td>Precipitate</td>
<td>Precipitate</td>
</tr>
<tr>
<td>Acetone</td>
<td>Solution</td>
<td>Precipitate</td>
<td>Precipitate</td>
</tr>
<tr>
<td>Hexane</td>
<td>Precipitate</td>
<td>Precipitate</td>
<td>Precipitate</td>
</tr>
<tr>
<td>Pyridine</td>
<td>Solution</td>
<td>Gel</td>
<td>Solution</td>
</tr>
<tr>
<td>Dimethyl Sulfoxide</td>
<td>Solution</td>
<td>Precipitate</td>
<td>Solution</td>
</tr>
<tr>
<td>Dimethyl-Formamide</td>
<td>Solution</td>
<td>Precipitate</td>
<td>Solution</td>
</tr>
<tr>
<td>Benzene</td>
<td>Precipitate</td>
<td>Precipitate</td>
<td>Gel</td>
</tr>
<tr>
<td>Toluene</td>
<td>Precipitate</td>
<td>Precipitate</td>
<td>Gel</td>
</tr>
<tr>
<td>O-Xylene</td>
<td>Gel</td>
<td>Precipitate</td>
<td>Gel</td>
</tr>
<tr>
<td>Triethylamine</td>
<td>Precipitate</td>
<td>Precipitate</td>
<td>Precipitate</td>
</tr>
<tr>
<td>Ethanol</td>
<td>Solution</td>
<td>Precipitate</td>
<td>Precipitate</td>
</tr>
<tr>
<td>Dichlorotoluene</td>
<td>Solution</td>
<td>Precipitate</td>
<td>Precipitate</td>
</tr>
<tr>
<td>Hexanoic Acid</td>
<td>Solution</td>
<td>Precipitate</td>
<td>Precipitate</td>
</tr>
<tr>
<td>Dichloromethane</td>
<td>Solution</td>
<td>Precipitate</td>
<td>Gel</td>
</tr>
<tr>
<td>Chloroform</td>
<td>Solution</td>
<td>Precipitate</td>
<td>Precipitate</td>
</tr>
<tr>
<td>Carbon Tetrachloride</td>
<td>Gel</td>
<td>Precipitate</td>
<td>Precipitate</td>
</tr>
<tr>
<td>Tetramethylurea</td>
<td>Solution</td>
<td>Precipitate</td>
<td>Solution</td>
</tr>
<tr>
<td>Butylamine</td>
<td>Solution</td>
<td>Precipitate</td>
<td>Precipitate</td>
</tr>
<tr>
<td>Acetophenone</td>
<td>Solution</td>
<td>Gel</td>
<td>Gel</td>
</tr>
<tr>
<td>Salicaldehyde</td>
<td>Solution</td>
<td>Gel</td>
<td>Gel</td>
</tr>
<tr>
<td>Triethylene Glycol</td>
<td>Solution</td>
<td>Gel</td>
<td>Precipitate</td>
</tr>
<tr>
<td>Isobutyl Alcohol</td>
<td>Solution</td>
<td>Precipitate</td>
<td>Precipitate</td>
</tr>
<tr>
<td>Benzyl Methacrylate</td>
<td>Gel</td>
<td>Gel</td>
<td>Gel</td>
</tr>
</tbody>
</table>

Classifying gelator-solvent combinations as either solutions, precipitates, or gels, in a wide array of solvents, allows for the calculation of Hansen spheres representing each classification. Each gelator was tested in 23 solvents for their ability to self-assemble in various solvents and were plotted in Hansen space. The HSPs of each solvents were used to calculate minimal enclosing spheres for the three outcomes (i.e., gels, precipitates and sols) (Figure 4-1), and the center of the sphere and radius allow for global comparisons between gelators (Table 4-2). This is an ideal approach because self-assembly in molecular gels must balance parameters influencing solubility.
and contrasting forces that govern epitaxial growth into axially symmetric elongated aggregates [114,131,132]. As such, HSPs are an ideal tool to quantitatively define of how molecular modifications to LMOGs effect gelation in a broad range of solvents [12,13].

Table 4-2 – Coordinates for the center of gelation, solution, and precipitate spheres in Hansen space and their radii.

<table>
<thead>
<tr>
<th>Gelator</th>
<th>Outcome</th>
<th>2δd</th>
<th>δp</th>
<th>δh</th>
<th>Radius</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMU</td>
<td>Precipitate</td>
<td>33.3</td>
<td>0.001</td>
<td>1</td>
<td>3.64</td>
</tr>
<tr>
<td></td>
<td>Gel</td>
<td>34.6</td>
<td>2.05</td>
<td>2.35</td>
<td>2.88</td>
</tr>
<tr>
<td></td>
<td>Sol</td>
<td>34.6</td>
<td>10.64</td>
<td>10.6</td>
<td>9.51</td>
</tr>
<tr>
<td>DCHU</td>
<td>Precipitate</td>
<td>31.87</td>
<td>7.13</td>
<td>8.35</td>
<td>11.17</td>
</tr>
<tr>
<td></td>
<td>Gel</td>
<td>34.45</td>
<td>9.4</td>
<td>10.85</td>
<td>8.66</td>
</tr>
<tr>
<td></td>
<td>Sol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DBU</td>
<td>Precipitate</td>
<td>31.8</td>
<td>7.02</td>
<td>8.67</td>
<td>11.34</td>
</tr>
<tr>
<td></td>
<td>Gel</td>
<td>37.8</td>
<td>5.35</td>
<td>8.35</td>
<td>8.36</td>
</tr>
<tr>
<td></td>
<td>Sol</td>
<td>36.1</td>
<td>11.74</td>
<td>9.21</td>
<td>4.81</td>
</tr>
</tbody>
</table>

In Hansen Space, when the solvent and potential gelator are have a small vector distance (Rij value (eq. 2)) between them they have similar non-covalent interactions and the gelator is solvated by the solvent.

\[
R_{ij} = \sqrt{4(\delta_{d1} - \delta_{d2})^2 + (\delta_{p1} - \delta_{p2})^2 + (\delta_{h1} - \delta_{h2})^2}
\]  

(ij represents the HSPs for the gelator and j for the solvent. Conversely, if the solvent and gelator are far apart in Hansen space, or they have a large Rij value, the gelator precipitates out of solution because the solvent and gelator are incompatible or insoluble in one and other. Molecular gels form in solvents that are at intermediate Rij values because gelation requires a meticulous balance between contrasting parameters including solubility and intermolecular forces.)
DMU produced the smallest radius (2.88 MPa$^{1/2}$) gelation sphere and the largest solution sphere (9.51 MPa$^{1/2}$) of the urea gelators. DMU forms solutions in more solvents than DCHU and DBU, which may be due to the HSP coordinates for the gelators. This is likely due to the different position that DMU occupies in Hansen space compared to both DCHU and DBU, with significantly higher $\delta_p$ and $\delta_h$ values (Table 4-2). The gelation sphere of DMU is located at low values of $\delta_h$ and $\delta_p$. The predominant mechanism of self-assembly of DMU is hydrogen bonding, and the low solvent $\delta_h$ values likely make it easier for the formation of SAFiNs. This is because solvents with low $\delta_p$ values have less potential to form hydrogen bonds and interfere SAFiN formation via hydrogen-bonding. Finally, the lowest values of $\delta_h$ and $\delta_p$ caused DMU to precipitate. This gradient of $\delta_h$ and $\delta_p$ values illustrates the thin line gelators fall upon in terms of solubility.
Figure 4.1 – 2D Projections of DMU in Hansen Space
Figure 4.2 – 2D Projections of DCHU in Hansen Space
Of the tested gelators, DCHU produced the largest gelation sphere with a radius of 8.66 MPa$^{1/2}$ (Table 4-2, Figure 4-2). DCHU was the only gelator insoluble in all tested solvents and the gelation and precipitate spheres overlapped. DBU produced similarly sized and positioned precipitate and gel spheres to DCHU yet distinct differences in both the number of solvents each gelator could gel exist. These differences are attributed to the different HSP coordinates that DCHU and DBU occupy in Hansen space (Figure 4-2, Figure 4-3). However, because these differences are small, it is more likely that DCHU lacks the specific intermolecular interactions.
required for gelation. In this particular case, \( \pi- \pi \) stacking would be responsible for DBU’s ability to form gels except for in dichlorotoluene, whose structure contains a non-heterocyclic aromatic ring which is able to interact with the benzylidene groups. Since the Hansen space coordinates were higher for DCHU and DBU as compared to DMU, the type and number of solvents selection may be responsible, in part, for the limited ability of DCHU to form gels. However, solvent selection based on HSP coordinates is difficult because compounds with large HSPs tend to be solid and as such there are limited solvents that may be selected in this region of Hansen space.

![Figure 4-4 – Polarized Light Micrographs of 5 wt. % DMU, DCHU, and DBU in carbon tetrachloride, toluene, and xylene.](image)

Polarized light microscopy (PLM) was used to observe the crystalline morphology of DMU, DCHU, and DBU and how the crystal structures changes in various solvents. DMU in carbon tetrachloride forms an effective gel and its crystalline morphology was unlike anything else
we observed in any of the other gelator/solvent combination (**Figure 4-4**). The SAFiNs were comprised of ‘feather-like’, highly branched fibrillar crystals. In these ‘feather-like’ networks solvent may reside between the small fibrillar crystals. Perhaps even more interesting is the fact that DMU in toluene and xylene form very similar microstructures yet DMU only forms a gel in xylene. The only obvious difference between these two morphologies is how the crystals form junction zones; in toluene, the crystals are lying almost parallel on each other and in xylene the junction zones are randomly orientated. Although DCHU formed precipitates in the three solvents, the morphology is starkly different when DCHU is in CCl$_4$ compared to toluene and xylene. In CCl$_4$, it is hard to discern if the crystals are short fibers or fine platelets; while in the aromatic solvents the crystals are clearly ‘platelet-like’. DBU forms gels in toluene and xylene but in carbon tetrachloride it precipitates. In CCl$_4$, two distinct morphologies are observed in the same micrograph, there are short, well dispersed fibers mixed with very large aggregates of the small fibers. These subtle differences in morphology highlight the intricate balance required to form SAFiNs. Even though DBU gels both toluene and xylene, the fibers that comprise the network are wider in xylene. In xylene, there were more crystals also present compared to toluene. It is important to note that a small bubble is present in the xylene micrograph, between the aggregates of crystals.

Linear hydrogen-bonding is the current proposed mechanism for DMU gels (**Figure 4-5**) and a similar hydrogen-bonding structure is likely to form in DCHU. The mechanism of assembly for most urea-derived gelators results from their ability to form hydrogen bonds between amide groups. The bulky cyclohexyl groups on DCHU likely encourage stacking of these hydrogen-bonded structures (**Figure 4-5**), explaining the platelet-like morphology of DCHU. DBU, however, forms hydrogen-bonds and exhibits potential for forming π-π stacking interactions. The
additional interactions found in DBU could encourage the formation of thick layered longitudinal fibers; whereas, there is a single direction for SAFiN growth in DCHU. Figures 4-6 and 4-7 illustrate two proposed mechanisms of DBU self-assembly, accounting for two geometric configurations of π-π stacking. Figure 4-6 displays the same linear hydrogen-bonding pattern as Figure 4-5, but shows the possibility for layering permitted by the π-π stacking. Figure 4-7 shows an alternate stepladder type configuration, where hydrogen-bonding occurs in an orientation allowing for offset parallel π-π stacking interactions.

Figure 4-5 – Proposed structures of DMU (Left) and DCHU (Centre) showing hydrogen bonding and of DBU (Right) showing proposed hydrogen bonding and π-π stacking conformation
Figure 4-6 – Proposed stacking 3D structure of DBU self-assembly via hydrogen-bonding (red) and parallel π-π stacking arrangement

Figure 4-7 – Proposed stacking 3D structure of DBU self-assembly via hydrogen-bonding (red) and offset parallel π-π stacking arrangement
Figure 4-8 – XRD results for 5 wt. % gels in toluene

Powder XRD has been used to determine the packing mechanism of self-assembling gels [139,140]. DMU gels in toluene display a diffraction peak corresponding to a Bragg distance much greater than any of the dimensions of the tested single molecules. Such an occurrence is characteristic of a larger repeating structure being formed at the nanoscale and is likely responsible a SAFiN. Certain diffraction peaks are present in all of the XRD results, indicating that similar distances are present between molecules. Furthermore, there is variation in structures formed from solvent to solvent, despite the same gelator being used indicating different polymorphs. This variation demonstrates that solvents play a significant role in the SAFiNs structure.
Table 4-3: The d-spacings (Å), full-width at half maximum (FWHM), and domain size (Å) values for the XRD results featured in Figure 7

<table>
<thead>
<tr>
<th>Gelator</th>
<th>d-spacing (Å)</th>
<th>FWHM</th>
<th>Domain Size (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMU</td>
<td>5.06 ± 0.007</td>
<td>0.125 ± 0.011</td>
<td>&gt;1000</td>
</tr>
<tr>
<td></td>
<td>5.00 ± 0.001</td>
<td>0.149 ± 0.042</td>
<td>&gt;1000</td>
</tr>
<tr>
<td></td>
<td>3.78 ± 0.006</td>
<td>0.092 ± 0.044</td>
<td>&gt;1000</td>
</tr>
<tr>
<td></td>
<td>11.56 ± 0.13</td>
<td>0.135 ± 0.011</td>
<td>&gt;1000</td>
</tr>
<tr>
<td></td>
<td>5.76 ± 0.015</td>
<td>0.150 ± 0.021</td>
<td>&gt;1000</td>
</tr>
<tr>
<td></td>
<td>5.12 ± 0.017</td>
<td>0.153 ± 0.037</td>
<td>&gt;1000</td>
</tr>
<tr>
<td></td>
<td>4.36 ± 0.030</td>
<td>0.193 ± 0.071</td>
<td>631 ± 238</td>
</tr>
<tr>
<td></td>
<td>3.97 ± 0.028</td>
<td>0.146 ± 0.098</td>
<td>&gt;1000</td>
</tr>
<tr>
<td></td>
<td>3.83 ± 0.015</td>
<td>0.155 ± 0.047</td>
<td>992 ± 304</td>
</tr>
<tr>
<td>DCHU</td>
<td>3.01 ± 0.015</td>
<td>0.159 ± 0.113</td>
<td>951 ± 608</td>
</tr>
<tr>
<td></td>
<td>11.66 ± 0.006</td>
<td>0.065 ± 0.040</td>
<td>&gt;1000</td>
</tr>
<tr>
<td></td>
<td>9.20 ± 0.27</td>
<td>0.207 ± 0.017</td>
<td>&gt;1000</td>
</tr>
<tr>
<td></td>
<td>5.78 ± 0.034</td>
<td>0.171 ± 0.012</td>
<td>&gt;1000</td>
</tr>
<tr>
<td></td>
<td>5.59 ± 0.012</td>
<td>0.177 ± 0.043</td>
<td>&gt;1000</td>
</tr>
<tr>
<td></td>
<td>5.03 ± 0.004</td>
<td>0.184 ± 0.015</td>
<td>&gt;1000</td>
</tr>
<tr>
<td></td>
<td>4.91 ± 0.017</td>
<td>0.123 ± 0.120</td>
<td>&gt;1000</td>
</tr>
<tr>
<td></td>
<td>4.56 ± 0.024</td>
<td>0.162 ± 0.012</td>
<td>&gt;1000</td>
</tr>
<tr>
<td></td>
<td>4.00 ± 0.028</td>
<td>0.159 ± 0.098</td>
<td>&gt;1000</td>
</tr>
<tr>
<td></td>
<td>3.85 ± 0.002</td>
<td>0.170 ± 0.015</td>
<td>&gt;1000</td>
</tr>
<tr>
<td></td>
<td>3.61 ± 0.025</td>
<td>0.118 ± 0.012</td>
<td>&gt;1000</td>
</tr>
<tr>
<td></td>
<td>3.50 ± 0.009</td>
<td>0.143 ± 0.106</td>
<td>&gt;1000</td>
</tr>
<tr>
<td>DBU</td>
<td>3.85 ± 0.002</td>
<td>0.170 ± 0.015</td>
<td>&gt;1000</td>
</tr>
</tbody>
</table>
Conclusions

Urea-derivatives were compared to determine their effectiveness as gelators and whether π-π stacking potential was a vital component of an efficient gelator. The results show DBU gels the greatest number of solvents; indicating π-π stacking plays a important role in the formation of SAFiNs, which are pivotal to gelation. The cyclohexyl rings on DCHU likely hinder its ability to self-assemble, likely due to steric hindrance or limiting solubility in the selected solvents. By plotting HSPs in Hansen space and generating gelation, solubility, and precipitate spheres, calculation of R_H values allowed for visualization and quantification of the differences in the intermolecular forces that are essential in solvent-gelator systems.

Acknowledgements:

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Chapter 5 – Conclusions

Potential for organogels and their budding applications in food systems is rapidly emerging as a viable option to structure edible oils. Oleogelators in particular are becoming one of the most prominent categories of organogels, due to their ability to structure liquid oils and replace hardstock fats. A replacement to hardstock fats would have a tremendous positive impact on one of the most pressing health issues, obesity. Edible oleogel applications have been flourishing and are continuing to be incorporated in many commonplace foods.

DBS when compared to DBS-derivatives lacking potential for hydrogen-bonding and/or π-π stacking resulted in a reduced capacity to form gels. A similar trend occurred when comparing DBU, to DCHU and DMU. It is likely the cyclohexyl rings featured in both DCHS and DCHU hinder self-assembly due to their bulkiness, lack of planarity, and inability to support π-π stacking interactions. Furthermore, DBU, was found to have an affinity to forming gels in solvents featuring aromatic functional groups. Hydrogen-bonding interactions have previously been thought to be the predominant intermolecular interaction driving the formation of SAFiNs, however this study has produced results indicative of π-π stacking being at least as important, if not more important to the formation of SAFiNs.

These organogel studies displayed the versatility of HSPs as a tool that could visually represent a large data set of gelation outcomes. Such a representation is much more meaningful when compared to a simple list of the gelation outcomes. For a large data set with a comprehensive array of solvents, HSPs plotted in Hansen Space provided an accurate representation of how certain gelators behave globally. Understanding the mechanisms of SAFiN formation and how solvent properties influence the formation of molecular gels are key to developing an a priori method for tailoring novel gelators to specialized applications. The importance of intermolecular interactions,
specifically, π-π stacking and hydrogen bonding, have been investigated. Our finding suggest that these factors are predominant factors to epitaxial growth, thus future models should weigh these factors appropriately.
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