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Tools for Identifying Gelator Scaffolds and Solvents

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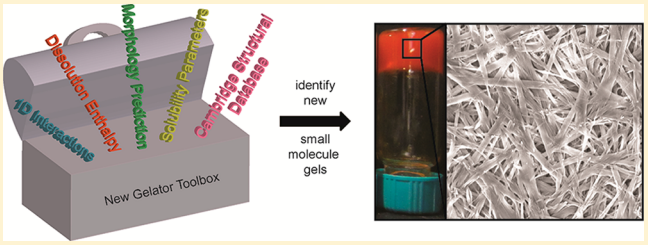
ABSTRACT: Small molecule gelators are serendipitously discovered more often than they are designed. As a consequence, it has been challenging to develop applications based on the limited set of known materials. This synopsis highlights recent strategies to streamline the process of gelator discovery, with a focus on the role of unidirectional intermolecular interactions and solvation. We present these strategies as a series of tools that can be employed to help identify gelator scaffolds and solvents for gel formation. Overall, we suggest that this guided approach is more efficient than random derivatization and screening.



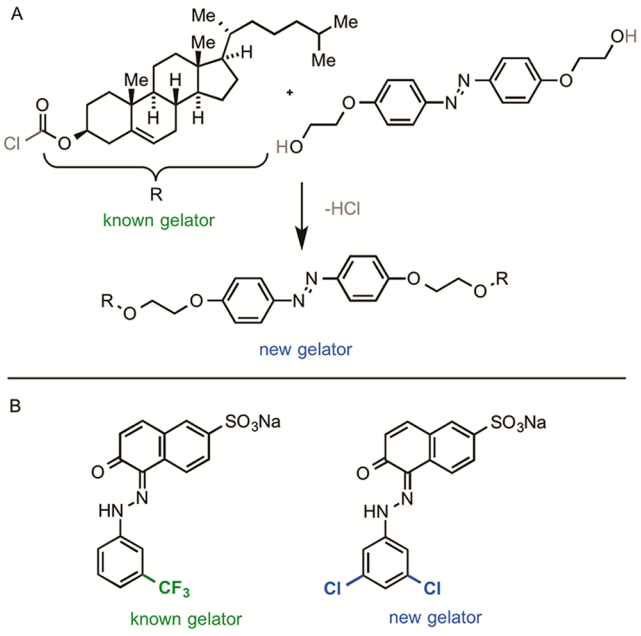
The first small molecule gelator was serendipitously discovered in 1841 during a failed crystallization.[1] There was surprisingly little interest in these materials until the early 1990s.[2] We suspect that the Nobel Prize awarded to Cram, Lehn, and Pedersen for their pioneering work in supramolecular chemistry led to an increased focus on supramolecular materials.[3] Molecular gels are now a widely studied class of soft materials with many applications, including drug delivery,[4] sensing,[5] remediation,[6] and tissue engineering.[7]

Gels form through the self-assembly of small molecules into supramolecular structures that immobilize the solvent via capillary forces and surface tension.[8] This self-aggregation is driven by noncovalent intermolecular interactions such as hydrogen bonding,[9] π-stacking,[10] van der Waals interactions,[11] and halogen bonding.[12] Because noncovalent interactions are involved, gel formation is responsive to changes in the local environment (e.g., temperature and pH). Physical interactions among the large aggregates (e.g., micelles, ribbons, fibers, sheets, and platelets) and with the solvent give rise to the macroscopic gel properties (e.g., resistance to flow).

Overall, gelation is both a complex and poorly understood process; understanding which molecules will form gels and under what conditions (e.g., concentration, solvent) remains a significant challenge.[13] As a consequence, many researchers have identified new gelators simply by modifying gelator scaffolds that were discovered serendipitously.[14] For example, Wu and co-workers[15] created a light-responsive gelator by appending an azobenzene group to cholesterol (a known gelator)[16] (Scheme 1A). This approach can be particularly useful for taking known gelators and tailoring them for a specific application. For example, we modified a known azo-sulfonate gelator[17] to create a new gelator that exhibits improved sensitivity to nitrite anions (Scheme 1B).[5d] Although successful, this approach is limited to existing gelator scaffolds and specific solvents, which may not be suitable for every application.

Over the past decade, several research groups have identified key structural features and molecular properties that correlate with gel formation. Additional efforts have focused on elucidating the relationship between solvent structure and gelation. This synopsis will describe the strategies that resulted from these studies. Each tool has been successfully implemented to generate novel gelator scaffolds or identify alternative solvents for gel formation.

Scheme 1. Modifying Known Gelators



1. Importance of Unidirectional Interactions. In a seminal paper, Hanabusa and co-workers hypothesized that gelation is promoted by molecules that exhibit "intermolecular interactions for building up macromolecular-like aggregates".[18]

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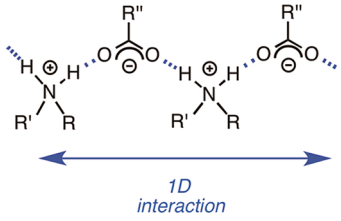
An example of these so-called unidirectional (1D) interactions is depicted in Scheme 2.[19] The secondary amine forms two

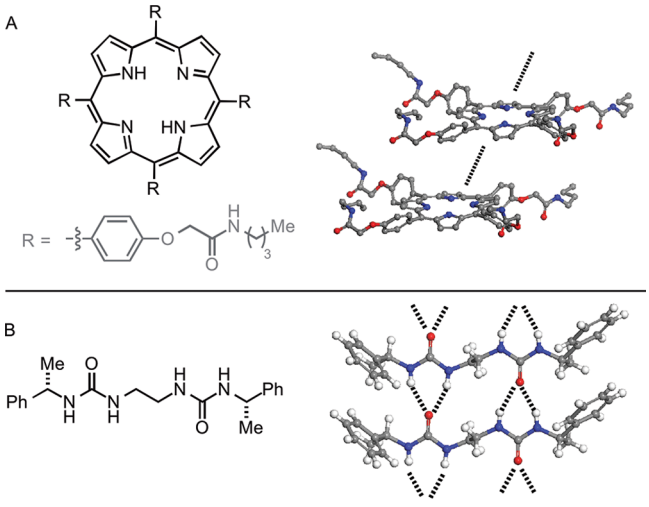
Scheme 2. Representative Unidirectional (1D) Interactions



hydrogen bonds with the carboxylate to form a linear "macromoleular-like aggregate". In contrast, if the amine is primary (R = H) or ammonium (R, R′ = H), then the intermolecular interactions can extend into the 2D and 3D.

Solid-state analyses performed on a number of gelators has revealed the presence of 1D interactions in the gel state.[4a,20] To make this correlation, the authors identified obvious 1D interactions in the single-crystal X-ray structure and then demonstrated that a similar packing mode is observed in the gel (or xerogel) using powder X-ray diffraction (PXRD). Some recent and representative examples include the following: a porphyrin-based gelator that self-assembles into columns via a directional π-interaction (Scheme 3A)[21] and a urea-containing

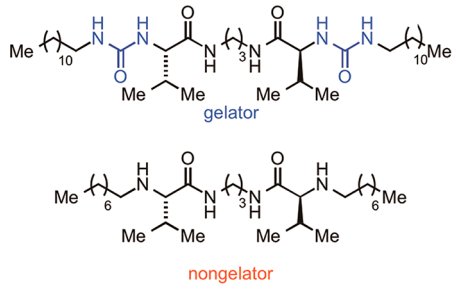
Scheme 3. Unidirectional Interactions Observed in Both Crystal Structures and Gels



scaffold that promotes directional hydrogen bonding (Scheme 3B).[22] Although there appears to be a correlation between gel-forming scaffolds and the presence of 1D intermolecular interactions, many molecules exhibit these interactions but do not form gels.[23] In addition, it can be experimentally challenging to obtain high quality single crystals with a similar solid-state structure as the gel because the gel phase is often a kinetically trapped state[24] and not a thermodynamic minimum that is reached in crystallizations. Thus, few gelators have reported crystal structures and fewer still have crystal structures that match the gel form.[25] Nonetheless, targeting 1D interactions has proven to be one of the most successful strategies for identifying new gelator scaffolds.

Tool #1: Append Functional Groups with Directional Interactions. One approach to identify new gelators based on Hanabusa's hypothesis is to utilize functional groups that exhibit directional interactions. As an example, both the urea and amide functional groups, which exhibit directional hydrogen bonding, have been successfully utilized to create new gelators.[20a,26] Recently, Rubio and co-workers designed a new family of amphiphilic organogels by incorporating two urea groups into the molecular scaffold (Chart 1).[9] The resulting molecules

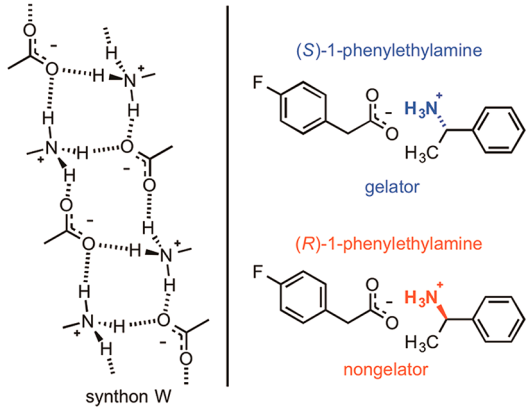
Chart 1



formed gels in a wide range of solvents and exhibited remarkably high thermal stability. Infrared spectroscopic studies confirmed the presence of hydrogen bonding and molecular modeling supported a 1D aggregation mode. Notably, similar compounds without the urea group did not form stable gels, suggesting that the increase in hydrogen-bonding interactions was important for gelation.[27]

Tool #2: Search the Cambridge Structural Database for Scaffolds. Another approach based on Hanabusa's hypothesis is to specifically target molecular scaffolds that exhibit unidirectional interactions in the solid state. For example, Dastidar and co-workers used the Cambridge Structural Database (CSD) to identify 32 primary ammonium monocarboxylate salts that exhibit a 1D hydrogen-bonding network, which they called synthon W (Scheme 4).[23] They synthesized all 32 compounds

Scheme 4. 1D Hydrogen Bonding Networks in Gelators and Nongelators



and found that just nine were gelators. Single-crystal X-ray diffraction (SCXRD) and PXRD were used to confirm that all nine gelators exhibited synthon W packing within the fibers. Although successful, it is important to note that 23 compounds that exhibited the same packing motif did not form gels. A striking example is that one enantiomer of phenylethyl amine is a gelator when paired with 2-(4-fluorophenyl)acetic acid while the other enantiomer is not (Scheme 4).

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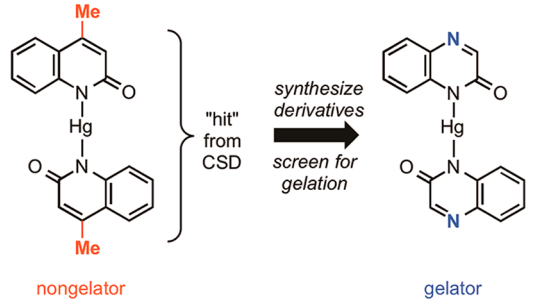
A slightly different approach is to mine the CSD for scaffolds that exhibit 1D interactions in the solid state and make derivatives. For example, we searched the CSD for molecules that contain a 1D Hg-π interaction.[28] We identified a quinoxalinone framework, synthesized several derivatives, and screened them for gelation (Scheme 5). Although the original

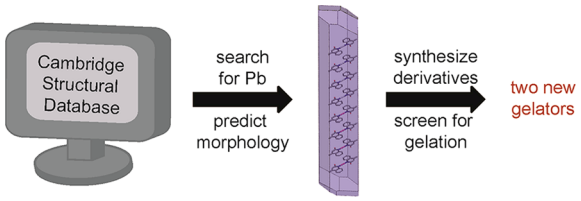
Scheme 5. Gelator Inspired by CSD Search



structure did not form gels, a structurally related derivative was a gelator. Unfortunately, the solid-state packing motif of the gel was not confirmed because crystal structures that matched the gel form were not accessible. Further derivatization created a new library of mercury containing complexes with five new gelators discovered among the 11 synthesized compounds.[6b]

Tool #3: Derivatize Scaffolds with High Aspect-Ratio Crystals. Although both CSD approaches described above led to new gelators, the process of selecting a promising scaffold was both time-consuming and qualitative. A better approach would be to select scaffolds based on the strength of the 1D intermolecular interactions in the solid state. We hypothesized that morphology prediction tools could provide this information because the relative growth rates of each crystal face are proportional to the strength of the intermolecular interactions in that direction (Scheme 6).[29] In other words, molecules

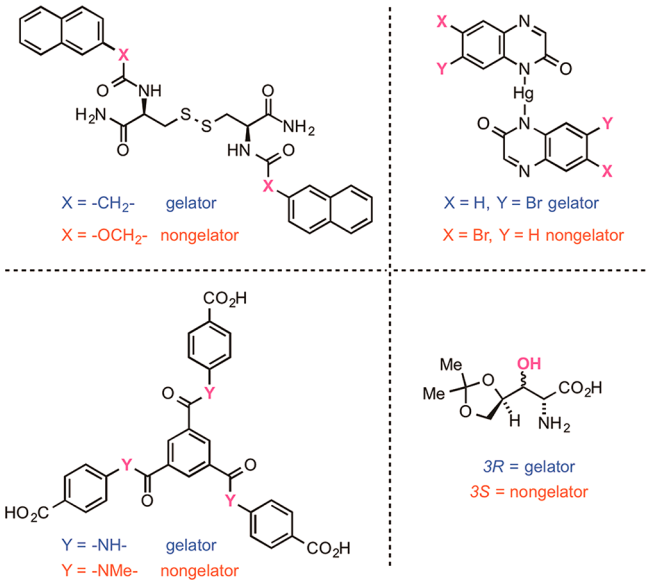
Scheme 6. New Gelators from High Aspect-Ratio Crystals



exhibiting strong unidirectional interactions in a single direction will produce a high aspect-ratio morphology (e.g., a needle). We further hypothesized that these high aspect ratio-forming molecules represent potential gelator scaffolds. To test this hypothesis, we predicted the morphologies of 186 Pb-containing crystal structures. We selected two scaffolds from the highest 5% of predicted aspect ratios, synthesized derivatives, and screened for gelation. Remarkably, two new gelators were identified with minimal derivitization.[30]

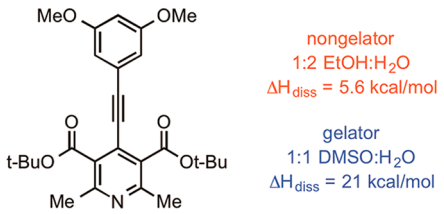
As noted above, the focus has largely been on molecular structure and unidirectional interactions. One significant remaining challenge is addressing the fact that subtle changes to a gelator structure can unpredictably disrupt gel formation; some representative examples can be found in Chart 2.[6b,31] In addition, solvent structure plays an equally important, though often underappreciated, role in gel formation.

Chart 2



2. Importance of Solvent. Though the focus has largely been on gelator/gelator intermolecular interactions, solvent/gelator interactions also play a critical role. The adage has long been that gelators should not be too soluble or too insoluble.[14f,32] Focusing on bulk gelator solubility, however, is an oversimplification, as we found no correlation between solubility and gelation ability among two different sets of gelators and three different solvent systems.[33] Instead, a more nuanced look at the competing gelator/gelator and gelator/solvent interactions is warranted. For example, the enthalpy of dissolution (i.e., solid gelator dissolving in the liquid solvent) captures both the enthalpic cost of disrupting the favorable gelator/gelator interactions and the enthalpic gain from the newly formed solvent/gelator interactions. Chart 3 highlights how a change in

Chart 3



the solvent can lead to substantial changes in both dissolution enthalpy and gelation ability. Importantly, this large difference in enthalpy can only be attributed to changes in solvating the gelator, as the gelator/gelator interactions in both cases are identical. For this particular compound, there are weak solvent/gelator interactions in DMSO/H_2O and strong solvent/gelator interactions in EtOH/H_2O. Overall, these results highlight the important role of solvent in gel formation.

Because solvent plays such an important role, gel screening should be done in a variety of different solvents. Nevertheless, only a handful of solvents are often reported for each gelator, which ultimately limits its potential application. Recognizing the importance of solvent identity, many researchers have recently focused on the relationship between solvent parameters (e.g., dielectric constants,[34] Kamlet–Taft parameters,[35] Flory–Huggins parameter,[36] $E_T(30)$ parameters,[37] Teas parameters,[38]

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Hildebrand solubility parameter,[39] and Hansen solubility parameters[40] (HSPs)) and gel formation. Of these, the HSPs have been particularly successful in modeling gelation behavior for a diverse range of gelators.[41] As a consequence, examining the Hansen space of each gelator has led to a powerful new approach for identifying additional solvents for gel formation.

Tool #4. Using Hansen Solubility Parameters To Identify Alternative Solvents for Gelation. Hansen solubility parameters describe the cohesive energy density of the solvent using three contributions, hydrogen bonding interactions (δ_h), van der Waals or dispersive interactions (δ_d), and dipole−dipole or polar interactions (δ_p). One can identify alternative solvents for gelation by fitting a large data set containing solvents that both promote and disrupt gelation. Such solvent clusters (i.e., spheres) become readily apparent in the 3D Hansen plots (cf., Figure 1).[42] Solvents that are located within the gelation

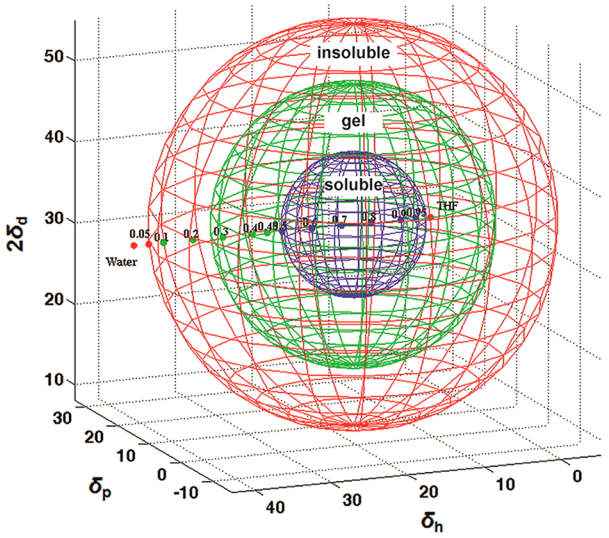

Figure 1. Plot of Hansen solubility data for a sugar-based gelator in THF/H_2O mixtures where δ_d is the dispersive interaction parameter, δ_p is the polar interaction parameter, and δ_h is the hydrogen-bonding interaction parameter (blue/soluble; green/gel; red/insoluble). Reprinted from ref 42. Copyright 2011 American Chemical Society.

"spheres" are likely to be gelled by the particular molecule. Depending on solvent/gelator interactions two (or more) gelation spheres may be observed. Notably, gelators that gel mixed solvent systems can also be modeled (Figure 1).[42] The size of the observed spheres is dependent on the concentration of gelator since gel formation itself depends on this variable.[43] A comprehensive study by Rogers and co-workers examined a variety of solubility parameters to rationalize the gelation behavior of 1,3:3,4-dibenzylidene sorbitol and found that the 3D Hansen model was among the most effective.[44]

The HSP model also provides some insight into the most important gelator/gelator and solvent/gelator interactions in the system. For example, Gao and co-workers fit the data for (*R*)-12-hydroxystearic acid and found that solvents with strong hydrogen-bonding capacity (larger δ_h) correlated with an increase in the critical gelation concentration.[45] This result suggests that the gelation relies on gelator/gelator hydrogen-bonding interactions, which are disrupted by hydrogen-bonding interactions with some solvents. Overall, the HSP approach can be a powerful tool to expand the scope of solvents that form gels, which should ultimately increase the utility of each gelator.

3. Future Outlook and Conclusions. Considerable advances have been made over the past decade to make gelator discovery less serendipitous and more streamlined. Despite these advances, truly predictive methods are still lacking. To achieve this goal, computational efforts to model gel formation (including both self-assembly and solvent) need to be further developed.[46] Importantly, these methods must be able to discriminate between gelators and nongelators, or gelling conditions versus nongelling conditions. Such models will benefit from recent efforts to elucidate the solid-state interactions involved in gelation using minimally invasive techniques, such as atomic force microscopy, cross-polarization magic angle spinning nuclear magnetic resonance spectroscopy, and Raman spectroscopy.[47] We look forward with great excitement to the next decade of research on molecular gels.

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Notes

The authors declare no competing financial interest.

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