Less is More When Forming Gels by Dilution

Molecular self-assembly yields soft materials arising from the liquid state when diluted
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Soft materials that change form or function in response to environmental or user-applied stimuli have a wide range of biomedical or other industrial applications.(1) Gel states can form in water from weakly interacting molecules, but can return to the state of a flowing liquid suspension known as a sol upon changes in the concentration of the molecules or the applied temperature. This behavior is known as a reentrant phase transition. A gel-to-sol phase transition typically arises from a reduction in con-centration, meaning a gel becomes a sol upon dilution and a sol becomes a gel with increased concentration. On page XXX of this issue, Su et al. (ref) demonstrate a new paradigm of materials that exhibit a sol-to-gel transition when diluted, thus inverting the common behavior of gels. Their observations offer further insights into systems that undergo reentrant phase transitions in bi-ology.

Self-assembly is a process whereby molecules form specific structures either as a consequence of their proper-ties, or as a result of conditions to which they are exposed. Several self-assembly motifs have been used to prepare soft materials. One such motif leverages molecules with certain supramolecular interactions, such as directional hydro-gen bonding units, to form supramolecular polymers. This type of filamentous assembly is reminiscent of high persistence-length polymers.(2) Another common motif is that of simple surfactants, which assemble into spherical objects known as micelles by hydrophobic association. Surfactants have broad applications as detergents and interface stabilizers (3) and as ingredients in lipid nanoparticle vaccines.

When molecules prepared from different motifs are mixed, self-assembly typically obeys a thermodynamic preference for self-sorting, meaning each species forms its own segregated structures. However, realizing pure self-sorting in practice can be a challenge because of common driving forces by which different molecular motifs associate.(4) Indeed, interesting phenomena emerge from multicomponent co-assembly when underlying driving forces, such as hydrophobic association, are conserved between different self-assembling motifs. In this case, minor adjustments in the strength of the interactions between molecules can dictate the emergence of dramatically different self-assembled structures.(5) As these same interactions are governed by parameters such as concentration, temperature, and salt or pH levels of the solution, the resulting assemblies can be tuned by controlling these parameters to create responsive material plat-forms.

The concentration-dependent inter-action of two orthogonal self-assembly motifs, here being those that assemble by disparate mechanisms of supramolecular polymerization or surfactant micelle formation, is key to the phenomena reported by Su et al. (see the figure). The primary supramolecular polymer motif is a disk-like molecule known as BTA-EG4(6), which on its own is prone to stack in water into elongated nanoscale filaments that can entangle to form a gel. When this supramolecular motif is combined with a surfactant, the formation of supramolecular filaments is initially inhibited as the surfactant disrupts the stacking and ordering of BTA-EG4. Upon dilution, however, the unexpected sol-to-gel transition is observed as interactions between the surfactant and BTA-EG4 are weakened, allowing BTA-EG4 to resume its preferred filamentous assembly. Importantly, the sol and the gel phases both exist at the same relative composition of these two orthogonal motifs, and require only a change in the total overall concentration for the system to oscillate between its sol and gel states. This sol-to-gel transition proved to be a robust phenomenon, arising when combining a suite of different common surfactants with BTA-EG4. The gel phase that forms upon dilution is a transient state. Further dilution crosses the critical gelation threshold of the BTA-EG4 supramolecular filaments and restores the sol.

In demonstrating even more complex gel-sol-gel-sol dilution cascades, Su et al. prepared two different protocols based on multicomponent and orthogonal self-assemblies. The system prepared from BTA-EG4 and surfactant can begin from the state of a robust gel at a very high starting concentration at a molar ratio of 2-to-3 for supramolecular motif to surfactant. At this high initial concentration, spherical assemblies consisting of both motifs become fused to form a network. Upon dilution, a sol emerges that is composed of similar spherical assemblies, but at a concentration below that necessary to form the fused network. Continued dilution from this point re-stores the gel state by formation of the supramolecular filaments preferred by the BTA-EG4 motif. Yet, additional dilution reduces entanglement of these fil-aments below the threshold for gel formation, restoring the sol once again.

An alternate protocol enabling a different gel-sol-gel-sol cascade was also demonstrated by Su et al. when including a third molecule capable of forming yet another orthogonal supramolecular network. This component comprised a ureidopyrimidinone (UPy) supramolecular motif that forms micrometer-long fiber bundles.(7) Although the UPy motif also interacts with the surfactant, the assembled UPy fiber bundles are not evidently disturbed by the presence of surfactant. By this approach, the system of BTA-EG4 and surfactant, at concentrations that previously formed a sol consisting of spherical assemblies, can in-stead form a gel by adding a high con-centration of UPy fibrillar structures. Dilution from this initial point surpasses the gelation capacity of the UPy net-work, while not yet reaching the point of inducing BTA-EG4 filament formation, yielding a sol. Continued dilution activates BTA-EG4 filament formation, which in combination with the remaining UPy fiber bundles, restores a gel state comprising two orthogonal networks of supramolecular polymers -- the BTA-EG4 and UPy networks. Upon further dilution, the system transitions back to a sol once again.

The tunable nature of molecular-scale self-assembly in these materials offers simple synthetic analogues of more complex phenomena observed in nature. For instance, membraneless organelles—distinct compartments within a cell that are not enclosed by a traditional lipid membrane—are thought to arise from liquid-liquid phase separation due to concentration gradients of associating multicomponent systems forming these assemblies in a water environment.(8) The roles of membraneless organelles in biological signaling during both normal and diseased states are increasingly appreciated.(9) The behavior of the simple systems described by Su et al. are therefore reminiscent of more complex self-assembly phenomena in biology, illuminating the importance of subtle thermodynamic driving forces that give rise to concentration-dependent phase separation. This new paradigm in self-assembled materials consisting of highly adaptive and dilution-triggered hydrogels may further-more lead to the design of stimuli-responsive material platforms for in situ modulation of function in therapeutic biomedicine.

REFERENCES AND NOTES

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