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"Click" Chemistry in a Supramolecular Environment: Stabilization of Organogels by Copper(I)-Catalyzed Azide−Alkyne [3 + 2] Cycloaddition

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Small-molecule organogelators represent remarkable examples of molecular self-assembly.[1] Such compounds make networks of fibers that can immobilize up to 10^5 liquid molecules per gelator and increase the viscosity of organic media by factors up to 10^{10}, with the potential to respond to a variety of stimuli.[2] The aggregation of gelator molecules into fibrous networks is driven by multiple weak interactions, such as dipole−dipole, van der Waals, and hydrogen bonding,[1] thereby distinguishing organogels from polymer gels, which have three-dimensional structures created by cross-linked covalent bonds.[3] Recently, several different methods for in situ enhancement of gel thermostability have been reported, including post-polymerization of gel fibers, the addition of polymers, the use of host−guest interactions, and the use of metal ion coordination.[4]

"Click" chemistry represents a modular approach toward synthesis that uses only the most practical chemical transformations to make molecular connections with excellent fidelity.[5] The 1,3-dipolar cycloaddition of alkynes and azides[6] (AAC) to give substituted 1,2,3-triazoles has emerged as a powerful linking reaction in both uncatalyzed[7] and metal-catalyzed[8] forms. The practical importance of the process derives from the easy introduction of azides and alkynes into organic compounds and the stability of these groups toward other reaction conditions. The copper-catalyzed (CuAAC) version has proven to be popular in applications ranging from drug discovery to surface science where rapid and reliable bond formation is required. We describe here the introduction of azide and alkyne groups into organogelator compounds and the cross-linking of their noncovalent polyvalent networks by the CuAAC reaction (Figure 1).

We used low molecular weight organogelators based on the undecylamide of *trans*-1,2-diaminocyclohexane, **1**, first described by Hanabusa and co-workers (Figure 1).[9] Since azides and alkynes are small and nonprotic, their placement at the end of the hydrophobic chains of the gelator was not expected to severely disrupt the intermolecular interactions that lead to gelation. The "clickable" compounds **2** and **3** were indeed found to make stable organogels, albeit at a higher concentration (5 wt %) than **1** (3 wt %). For this exploratory study, we used the racemic form of the chiral gelators; enantiopure materials usually make more stable gels.

The addition of 5% 2,6-lutidine to acetonitrile assists the CuAAC reaction; in this solvent system, neither **1**, **2**, nor **3** form gels at room temperature at concentrations of 3 wt %. In contrast, stable organogels were obtained when CuI and cross-linkers were incorporated with **2** or **3** at an optimized[10] gelator:cross-linker ratio of 10:1 (Table 1, entries 1−4). The direct triazole cross-linking of azide + alkyne gelators **2** + **3** (entry 5) also made a substantial difference in that a room-temperature gel was obtained, but it was weak relative to those produced by the addition of aliphatic α,ω-cross-linkers. Gels made from **2** or **3** were found to be strengthened by the incorporation of an equimolar amount of **1** into the mixture (entry 6), and introduction of Cu^I and cross-linkers into these samples gave gels with even greater thermostability (entry 6 vs 8, 7 vs 9−11; other examples in Supporting Information).

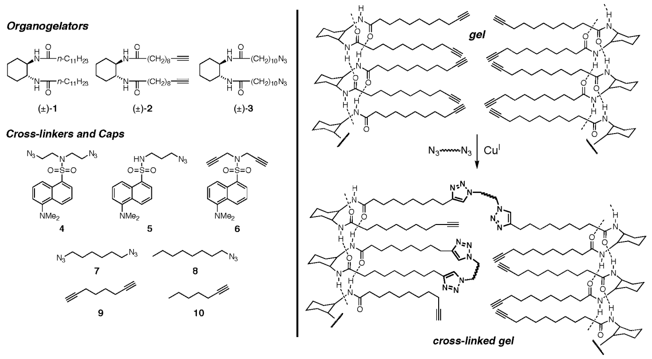

Figure 1. Left: Organogelators (**1**−**3**), cross-linkers (**4**, **6**, **7**, **9**), and caps (**5**, **8**, **10**) used in this work. Right: Proposed hydrogen-bond pattern for gelation by **1**−**3** and cross-linking by the CuAAC reaction.

Table 1. Properties of Organogels Incorporating Azides and Alkynes[a]

entry	components	T_{gel}[b]	G' ($\times 10^4$ Pa)[c]	G'' ($\times 10^4$ Pa)[c]
1	**2** + **4** + Cu^I	86	1.9 ± 0.1	0.22 ± 0.01
2	**2** + **7** + Cu^I	83	14.0 ± 1.3	1.22 ± 0.07
3	**3** + **6** + Cu^I	84	17.9 ± 1.0	1.40 ± 0.05
4	**3** + **9** + Cu^I	91	9.3 ± 1.2	0.86 ± 0.02
5	**2** + **3** + Cu^I	47	nd	nd
6	**1** + **2** + **3**	63	30.2 ± 3.5	2.63 ± 0.07
7	**1** + **2** + **7**	65	5.95 ± 0.05	0.36 ± 0.03
8	**1** + **2** + **3** + Cu^I	69	14.9 ± 0.2	0.65 ± 0.04
9	**1** + **2** + **7** + Cu^I	94	12.5 ± 0.5	0.65 ± 0.08
10	1 + 2 + 7 + Cu^I [d]	93	13.9 ± 0.4	0.74 ± 0.08
11	**1** + **2** + **7** + Cu^I [e]	108[f]	33.8 ± 1.9	2.30 ± 0.15

[a] Each reaction was performed in degassed CH_3CN (1.9 mL) and 2,6-lutidine (0.1 mL), with a gelator concentration of 3 wt % and a gelator:cross-linker ratio of 10:1. CuI was introduced from a 0.1 M stock solution in CH_3CN; the mixture was heated briefly to dissolve and then was allowed to cool to room temperature. The state of each sample was determined by visual inspection after allowing the sample to stand overnight at room temperature, although gelation in each case occurred within 5 min. [b] Gel−sol transition temperature (°C) determined by the inverse flow method (see Supporting Information). [c] G' = average storage modulus; G'' = average loss modulus, both measured by oscillatory rheology as described in the Supporting Information; "nd" = not determined. [d] CuI solution was introduced by layering on top of the pre-set gel and allowed to diffuse into the material for 1 week. The resulting material was then quenched, heated, and cooled to re-form the gel. [e] Reaction components heated at 50−60 °C for 8 h prior to analysis. [f] Heterogeneous stable gel, giving rise to a greater error in T_{gel} measurement (±3 °C).

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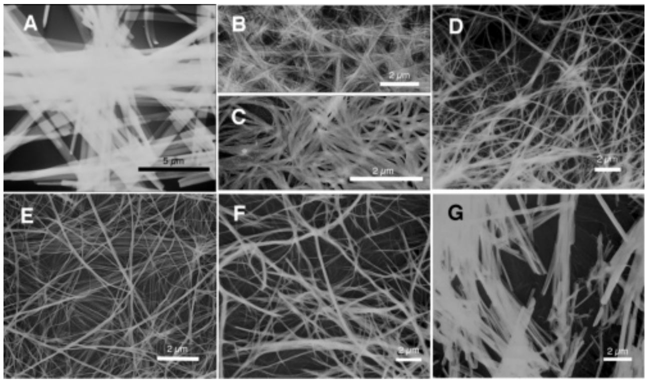

Figure 2. TEM images of gels made with 3 wt % gelator (A) **1** in MeCN; (B) **2** in MeCN; (C) **3** in MeCN; (D) **2** + **4** + Cu^I (Table 1, entry 1); (E) **2** + **7** + Cu^I (entry 2); (F) **1** + **2** + **7** + Cu^I, heated for 20−30 s (entry 9); (G) **1** + **2** + **7** + Cu^I, heated for 8 h (entry 11).

The results of click-mediated gel stabilization were very similar when the reactions were allowed to proceed for only a short time in solution at higher temperature (followed by incubation in the gelled state at room temperature) or exclusively in the gelled state at room temperature by layering on Cu^I after gel formation and diffusion of the catalyst into the matrix.[11] Control experiments showed that enhancement of gel thermostability upon cross-linking was dependent upon the simultaneous presence of the metal in the active Cu^I oxidation state and the appropriate bivalent additive (as opposed to monovalent capping reagents **5**, **8**, and **10**).[11] Similarly, heating in the absence of Cu^I does not induce azide−alkyne cycloaddition. The presence of triazole moieties in cross-linked and capped materials was confirmed by NMR. The removal of Cu ions from the gels did not change T_{gel} significantly, showing that Cu−triazole interactions are not likely to be important to the stabilization of these gels.[12]

Several of the cross-linked gels were found to be stable toward heating through the boiling point of acetonitrile, despite losing some solvent between 60 and 90 °C. In appearance, they were significantly more turbid than the gels made from **1**, **2**, or **3** alone, but did exhibit fully reversible gel-to-sol phase transitions upon repeated heating and cooling. FTIR spectroscopy showed the same characteristic evidence for amide H-bond participation in the gelled state of both non-cross-linked and cross-linked materials.[11]

Rheological measurements confirmed the viscoelastic nature of the gels prepared in this study. The storage moduli were uniformly found to be an order of magnitude greater than respective loss moduli, indicating that these gels are quite rigid. All the gels were stable over a wide frequency range (0.1 to 100 rad/s), and dynamic strain sweep (DSS) measurements showed that they break at less than 1% strain, confirming their brittle nature.[11] The material rigidity as indicated by G' followed no uniform trend with respect to T_{gel}.

Gel morphologies were investigated by transmission electron microscopy (TEM). Gels made from the individual gelators in MeCN (without lutidine) showed differences consistent with the more efficient gelation properties of **1**. Thus, the structure of gelled **1** was characterized by large, rod-like filaments, whereas **2** and **3** both showed smaller, more flexible fibers (Figure 2A−C). Gels made with combinations of agents (Table 1, entries 1−5) in MeCN displayed morphologies very similar to **2** and **3** alone (not shown). TEM images of cross-linked gels made with **2** or **3** in MeCN/2,6-lutidine (Figure 2D,E) were very similar to those of non-cross-linked analogues, suggesting that their significantly greater stabilities are not the result of gross changes in structure. The incorporation of **1** into CuAAC cross-linked samples gave thicker fibers (Figure 2F), but no other dramatic change. Most interestingly, a transition to rod-like structures was observed after heating the cross-linking reaction for 8 h (Figure 2G), obtaining a material of the greatest T_{gel} and rigidity (G') observed in these studies. In all other cases, such prolonged heating gave rise to phase separation rather than gelation. This suggests that such heating drives the CuAAC reaction to greater completion, and that the formation of too high a concentration of triazoles gives rise to self-aggregation phenomena.

We describe here a method to change the properties of thermoreversible gels by the introduction of a chemically innocuous group (azide or alkyne), with subsequent attachment of cross-linkers by a versatile catalytic process. Much of the previous work on polymerizable organogelators uses the gelation process to set a template for a subsequent polymerization, turning noncovalent supramolecular assemblies into covalent polymers. These materials are no longer thermoreversible and tend to lose their well-ordered arrangements of hydrogen bonds. In the method described here, a judicious level of click connectivity is used to modify the properties of organogels while retaining their overall structure and thermoreversibility. We plan to continue our exploration of organo- and hydrogels in this context, incorporating a variety of functional groups into these versatile materials.

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Supporting Information Available: Synthetic procedures, complete experimental details and results of control experiments, rheology, and spectroscopic characterizations. This material is available free of charge via the Internet at http://pubs.acs.org.

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