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Polymer thermoreversible gels from organogelators enabled by 'click' chemistry

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Abstract

[1,2,3]-Triazole-based polymers made by means of the copper(I)-catalyzed azide-alkyne [3+2] cycloaddition (CuAAC) exhibit selective gelling ability for DMSO and organic solvent mixtures containing at least 80% DMSO by volume. The organogels were characterized by FT-IR, DSC, TEM, and rheology.
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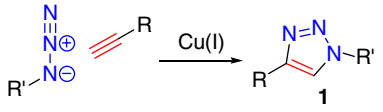
Gels are viscoelastic materials in which fluids have been immobilized by low concentrations (usually < 5 wt %) of solutes (gelators),[1] mainly by surface tension and capillary forces.[2] Their unique supramolecular architectures and applications as functional soft materials has made the search of new gelators and the understanding of their mode of action a very active research area in both academic and industrial contexts.[3] The networks of the gels formed by polymeric gelators arise from the interactions and entanglement of covalently bonded chains, whereas in gels formed by low-molecular-weight gelators (LMWGs), the networks are held together by non-covalent interactions.[4] Compared with LMWGs, the number of standard polymers able to construct a three-dimensional (3D) network in organic solvents is considerably lower,[5] probably due to the lack of appropriate cross-linking points. Among the extensive list of organic gels reported in the literature, gels of dimethyl sulfoxide (DMSO) are of especial interest due to their use in numerous medical applications.[6] In addition to anti-inflammatory, anti-cancer, anti-oxidant, and analgesic activities attributed to this solvent, its membrane-penetrating ability enhances the diffusion of other therapeutic substances through the skin.[7] Hence, this polar solvent is one of the most studied pharmaceutical agents in the last five decades.

Herein, we describe the synthesis of new polymeric organogelators prepared by 'click' chemistry[8] and their selective gelation property in DMSO[9] or DMSO/organic solvent mixtures containing at least 80% DMSO by volume. As far as we are aware this is the first example of a thermoreversible organogel enabled by a 'click' polymer.[10]

Scheme 1 outlines the most representative example of the 'click' reactions: the copper(I)-catalyzed azide-alkyne [3+2] cycloaddition (CuAAC)[11] to generate 1,4-disubstituted-1,2,3-triazoles **1**. This reaction was used for the



Scheme 1. Cu(I)-catalyzed azide-alkyne [3+2] cycloaddition.

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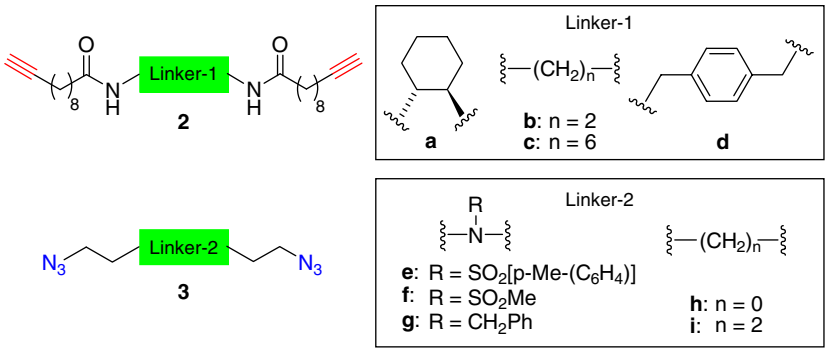

Fig. 1. Bis-acetylenes and bis-azides used in this work.

solution-phase polymerization of bis-alkylamides **2** and bis-azides **3** (Fig. 1). Monomers **2** were synthesized by standard DCC-coupling of 10-undecynoic acid with suitable diamines, whereas monomers **3** were synthesized by nucleophilic substitution of the proper chloride derivatives.[11]

The reactions between **2** and **3** (1:1 molar ratio) were carried out under refluxing degassed CH_3CN (0.2 M in each monomer), and in the presence of 2,6-lutidine (20 mol %), sodium ascorbate (10 mol %, from a 2 M aqueous solution), and CuI or $Cu(CH_3CN)_4PF_6$ (5 mol %) as the catalyst.[12] The resulting precipitated 'click' polymers[13] were filtered and subsequently washed with $H_2O/CH_3CN/Et_2O$. ^1H NMR ($CDCl_3$) of the soluble fractions defined the characteristic proton of the triazole rings **1** at 7.2–7.4 ppm. MALDI-TOF MS analyses revealed broad molecular weight distributions with 5–12 units of each monomer. Shorter chains were somehow obtained when the reactions were carried out under typical aqueous conditions.[11]

Some of the polymers obtained by 'click' condensation of **2a–d** and **3e–i** in CH_3CN proved to be selective gelators of DMSO, with minimum gelator concentrations in the range 3–5 wt % (Table 1). Interestingly, only the polymers of the type $\{(\mathbf{2a–b})_x(\mathbf{3e–f})_y\}$ showed some organogelling properties, highlighting the requirement of having at least a sulfonyl group in the polymer backbone for the organogelling property. Any other combination of the monomers showed in Figure 1 failed to form stable gels. Such peculiar influence of the $–SO_2$ group was not observed when similar monomers were used to stabilize organogels by in situ cross-linking.[14] More brittle gels were also obtained for mixtures of DMSO and a variety of cosolvents (e.g., toluene, chlorobenzene, ethyl acetate, *N*,*N*-dimethylformamide) in a ratio 80:20 v/v. Organogelling properties were previously reported for the monomer **2a**.[14] The use of tri- or tetravalent alkyne/azides provided more robust polymers (higher cross-linking) but no gelation ability was observed. Intriguingly, the $\{(\mathbf{2a–b})_x(\mathbf{3e–f})_y\}$ macromonomers did not yield supramolecular aggregates in any solvent upon treatment either with 0.1 M EDTA aqueous solution for 24 h at 65 °C or with coppersorb. Such clean-up process removed all the Cu ions associated to the polymer backbone, especially to the triazole rings,[11] as indicated by inductively coupled plasma mass spectroscopy (ICP-MS). These results might suggest the importance of Cu ions interactions with the polymer backbone (typically with triazole rings) in forming the thermoreversible gels. The Cu ions could probably help the cross-linking between the supramolecular polymers and play a critical role in the formation of a closely packed 3D-network. Curiously, the addition of different concentrations of either Cu salts or other metal ions with reported affinities for triazole rings (e.g., Co(II), Zn(II), Ni(II)) to the polymers $\{(\mathbf{2a–b})_x(\mathbf{3e–f})_y\}$ after EDTA treatment yielded only partial gels, which were easily disrupted upon shaking. At present, we have no clear explanation for this effect and further experiments are necessary to clarify the probable influence of the Cu ions in the mechanism of the gelation. No gelation was either observed by using the materials obtained by thermal[14] polycondensation (absence of copper catalyst) of the appropriate divalent azide/alkyne-containing monomers.

It is worth recalling here the attention of the reader regarding a previous publication on the use of the CuAAC for the stabilization of organogel structures.[15] Some of the monomers used in this work were also used in the cited work albeit for a completely different purpose. Therein, the monomers were only used to induce crosslinking

Table 1
Properties of representative DMSO-based organogels at 25 °C[a]

Polymer components	MGC[b] (wt %)	T_{gel}[c] (°C)		G'[f] ($\times 10^3$ Pa)	G''[g] ($\times 10^3$ Pa)
		DSC[d]	DB[e]		
2a–3e	3	63–74	76	18.7 ± 1.1	11.50 ± 0.12
2b–3e	5	57–64	66	16.3 ± 1.4	9.02 ± 0.17
2b–3f	5	49–58	60	15.3 ± 1.2	10.23 ± 0.19
2a–3f	5	41–53	54	17.2 ± 1.3	10.06 ± 0.11

[a] Gels (1 mL) were prepared upon cooling the hot isotropic solutions to 25 °C. Gelation was considered if the solvent was immobilized upon turning the vial upside down after 48 h.
[b] Minimum gel concentration.
[c] Sol-to-gel transition temperature (±1 °C).
[d] The first value corresponds to the onset of the peak and the second value to the maximum.
[e] Temperatures determined by the dropping ball method.
[f] G' = average storage modulus.
[g] G'' = average loss modulus.

between the organogels fibers formed by a LMWG, but the MALDI-TOF MS data demonstrated that polymers from the combination of the alkyne/azide-containing monomers were not obtained in the gel phase. In our case, we report the gelation property of some well-defined [1,2,3]-triazole-based polymers which were not neither obtained nor claimed during the stabilization of organogels via 'click' chemistry.[14] Therefore, the present work is not a simple extension of the previous report since the chemical structures of the organogelator agents in each case are different, making the polymers of the type $\{(\mathbf{2a–b})_x(\mathbf{3c–f})_y\}$ the first examples in the literature of organogelator polymers enabled by 'click' chemistry.

The obtained 'metallogels' can be disrupted by agitation or heating, but the gel state is restored upon cooling. Gels are stable for several months when stored in sealed vials. The thermal stability and gel strength of the organogels were determined to consider the effect of the polymer backbone on the organogelling property (Table 1).

The sol-to-gel transition temperatures (T_{gel}) were first calculated by the dropping ball method[16] and further confirmed by modulated differential scanning calorimetry (DSC).[17] All organogels showed broad endotherms with onset temperatures ascertained in the range 41–63 °C. As expected, T_{gel} rises in an approximately linear manner as the concentration of the polymers increase, indicating that the polymer organogelators form the more closely packed 3D-networks at high concentrations (Fig. 2). Oscillatory rheological measurements confirmed the viscoelastic, rigid and brittle nature of the obtained gels (Table 1). G' was uniformly found to be of greater magnitude than G''. The gels were stable over a wide frequency range (0.1–100 rad/s), and dynamic strain sweep measurements showed that they break at less than 0.5% strain.

The morphology of the supramolecular self-aggregated was visualized by transmission electron microscopy (TEM). All organogels showed similar dense networks formed by fibers of ca. 150–200 nm diameters and lengths in the micron scale, intertwined through numerous junction zones (Fig. 3).

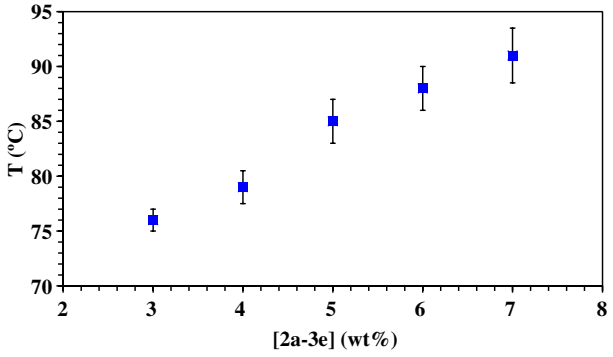

Fig. 2. T_{gel} as a function of the polymer $\{(\mathbf{2a})_x(\mathbf{3e})_y\}$ concentration in DMSO, as measured by the dropping ball method.

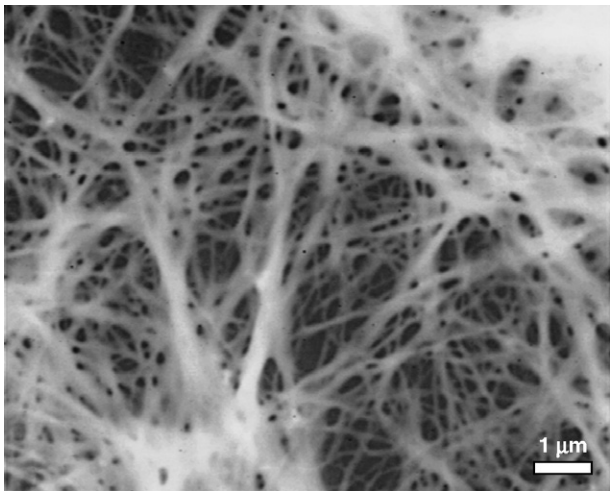

Fig. 3. Representative TEM image of the xerogel made of $\{(\mathbf{2a})_x(\mathbf{3e})_y\}$ in DMSO (3 wt %).

Finally, temperature controlled FT-IR studies demonstrated the participation of hydrogen-bonded amides and van der Waals interactions during the gelation phenomenon. Thus, hydrogen bonding in the gels uniformly shifted both carbonyl and NH resonances to lower energy with respect to the spectra recorded in the solid state, from 1637–1660 to 1630–1637 cm^{-1} for amide I bands; from 1543–1557 to 1538–1542 cm^{-1} for amide II bands; and from 3298–3335 to 3275–3295 cm^{-1} for NH stretching bands, respectively. The gel-to-sol phase transition occurred on increasing the temperature and the IR bands arising from hydrogen amide groups sharply decreased, whereas those from the free groups increased (amide ca. 1660 cm^{-1}). No appreciable differences were observed by the IR stretching bands of the $–SO_2$ groups (ca. 1250 and 1150 cm^{-1}) at different temperatures. Bands in the region of the antisymmetric and symmetric stretching vibrations of C–H (ca. 2850–2930) were also observed for the gel states, thus indicating electrostatic interactions between the alkyl segments.

In conclusion, we have shown the selective organogelation properties of a series of 'click' polymers organogelators for DMSO and organic solvent mixtures containing at least 80% DMSO by volume. Interestingly, the partial permanence of the Cu ions from the catalyst in the polymer matrix was found to be crucial for the thermoreversible organogelling property. Efforts directed towards understanding the gelation mechanism and pharmaceutical evaluation of these DMSO-based organogels are currently underway and the results will be reported in due curse.

Acknowledgments

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17. *Gelation test*: A weighted amount of the polymer organogelator and DMSO (1 mL) were placed in a screw-capped glass vial and heated with a heat-gun until the solid was completely dissolved. The isotropic solution was cooled to room temperature and the material classified as gel if it did not exhibit gravitational flow upon turning upside down the test vial.
Estimation of sol-to-gel phase transition temperature (T_{gel}): Gelation temperatures were determined by the dropping ball method. A glass ball (230 mg, 3 mm diameter) was suspended on top of the sample and the vial sealed. The vial was heated in a thermostated oil batch at the rate of 2 °C min^{-1}. T_{gel} was defined as the temperature at which the ball dropped to the bottom of the gel.
Modulated differential scanning calorimetry (DSC): Measurements were made with a TA Instruments Q1000 calorimeter, with a heating/cooling rate of 2 °C/min from −30 to 120 °C.
Transmission electron microscopy (TEM): Samples were observed with a Jeol JEM 1010 transmission electron microscope operating at a voltage of 90 kV. A piece of the gel was placed onto copper grids (300 mesh) coated with both formvar and silicon monoxide. A Teflon sheet was used to remove the excess solvent by slight contact with the sample, which allowed the formation of a thinner film on the grid. The relatively large size of the polymer pieces made negative staining unnecessary for visualization.
Rheology: Oscillatory rheology experiments (DTS, DFS, and DSS) were performed with an AR 2000 rheometer (TA Instruments).
FTIR spectroscopy: IR spectra of gels were obtained in a Bruker Vector 22 spectrophotometer equipped with a variable temperature cell controller (SPECAC) with the samples sandwiched between KBr pellets (4 cm^{-1} resolution, 16 scans).