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A reactive nitrone-based organogel that self-assembles from its constituents in chloroform

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The reversible reaction of an aldehyde with a hydroxylamine affords a nitrone which is capable of forming a stiff gel with chloroform at concentrations as low as 0.20 wt% (6 mM). The gelator forms dynamically from its constituents and the gel assembly can be degraded in a controlled manner through a recognition-mediated reaction that targets the nitrone component of the gel network.

Small organic molecules that possess the ability to form a gel with organic solvents (organogels) and with water (hydrogels) have received increasing attention[1] in recent years. In particular, gels that are assembled from more than one organic component offer the prospect[2] of materials with properties that can be controlled very precisely. Multi-component gels are typically constructed from a group of molecules that have complementary recognition or reactive elements. The reversible nature of self-assembly processes invite the application of gel formation to drive selection processes in constitutionally dynamic libraries (CDLs). Previously, we[3] and others[4] have exploited kinetically controlled reaction processes as tools for dynamic systemic resolution (DSR). In DSR, a specific component of a CDL is targeted by a recognition-mediated reaction and is thereby selected and amplified from the library. In many cases, the level of amplification achieved using this strategy is limited. We envisaged that, in order to maximise amplification during DSR, a two-stage selection process could be developed. In this strategy, initial incorporation of the target compound into a structured phase, such as a gel, provides the first level of selection from the CDL. This gel could then be processed using our kinetically-controlled DSR strategies, providing a second level of selection. Previously, several groups have reported[5] gels that have been assembled from two or more components through the formation of dynamic covalent bonds. However, in order to implement our approach, the gelator identified must satisfy three criteria – (i) form from its constituents through dynamic covalent bond formation, (ii) possess recognition elements capable of assembling the three-dimensional network necessary to create the gel and, finally, (iii) be compatible with our recognition-mediated DSR technology. As part of our studies directed at developing DSR strategies, we synthesised compounds **1** to **5**.

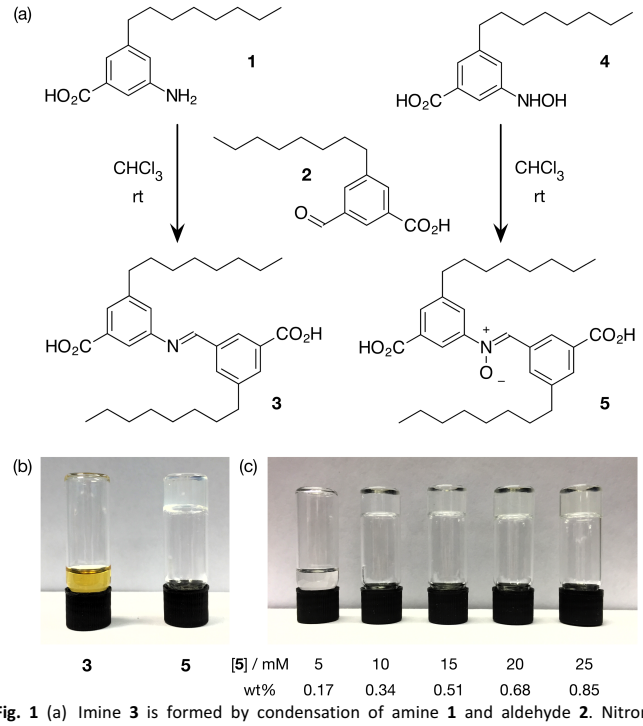

Fig. 1 (a) Imine **3** is formed by condensation of amine **1** and aldehyde **2**. Nitrone gelator **5** is formed by condensation of hydroxylamine **4** and aldehyde **2**. (b) Vial inversion tests of imine **3** and nitrone **5** each prepared at 40 mM in chloroform. (c) Vial inversion tests of nitrone **5**, at a range of concentrations in chloroform, indicate that the critical gelation concentration (CGC) is between 5 and 10 mM.

When amine **1** and aldehyde **2** (Fig. 1a) are dissolved in chloroform at a concentration of 40 mM, after 24 hours a clear yellow solution (Fig. 1b) containing imine **3** results. The formation of imine **3** in this solution can be tracked readily – 500 MHz ^{1}H NMR spectroscopy reveals the disappearance of

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[b] Electronic supplementary information (ESI) available: General and synthetic procedures, gelation properties and nitrone reactivity, comparison of gel formation in different solvents, SEM images, and NMR spectra, see DOI:

the aldehyde proton resonance at δ 10.08 and the appearance of a resonance corresponding to the imine proton at δ 8.64. Surprisingly, when aldehyde **2** is reacted with hydroxylamine **4** (Fig. 1a) under identical conditions, the suspension transforms into a stiff, clear gel (Fig. 1b) within 1 hour. The rate of gel formation can be influenced both by concentration – more concentrated reagent mixtures form the gel more rapidly – and by sonication[6] – samples subjected to sonication also form the gel more rapidly. Gels prepared from the reaction of **2** and **4** in chloroform are stiff, clear and persist for up to six months before collapsing as a result of the chemical degradation of nitrone **5** under ambient laboratory conditions. The formation of a stiff clear gel is exclusive to chloroform. In other chlorinated solvents, **5** forms weak, turbid gels (see ESI, Fig. S2 and Table S3) and in all other solvents is either freely soluble or completely insoluble. In order to probe the concentration dependence of gel formation mediated by nitrone **5** in chloroform, we prepared a number of samples (Fig. 1c) at different concentrations. Stiff gels were formed by nitrone **5** down to a concentration of 10 mM. At 5 mM, the sample exists as a viscous solution. A series of experiments in smaller concentration steps (see ESI, Fig. S4) revealed that the critical gelation concentration (CGC) for the gelator **5** in chloroform is 6 mM or 0.20 wt%. The CGC of nitrone **5** in chloroform compares favourably[7] to many organogels reported in the literature, and, to the best of our knowledge, is the first example of a nitrone-based gelator.

In order to probe the structural requirements for the assembly of a gel network from **5**, we examined a number of control compounds. Clearly, the nitrone functional group, present in **5**, is essential for gel formation, as imine **3** forms only clear solutions (Fig. 1b) at all concentrations. Removal of either or both of the *n*-octyl chains severely impacts gel formation, usually resulting in precipitation of the corresponding nitrone. For example, reacting **2** with the hydroxylamine bearing no *n*-octyl group results in a clear solution of the corresponding nitrone at low concentration and formation of a precipitate above 10 mM. Reacting hydroxylamine **4** with 3-carboxybenzaldehyde results in weak, turbid gels above 10 mM. Removal of the carboxylic acid from either or both of **2** and **4** extinguishes the ability of the system to form a gel with chloroform completely. Further evidence for the key role of the carboxylic acid comes from the treatment of the gel formed by **5** with dilute solutions of NEt_3 in chloroform. Layering of a 50 mM solution of NEt_3 in chloroform on top of a gel formed a 25 mM solution of **5** in the same solvent results in dissolution of the gel within an hour and formation of the corresponding dicarboxylate (See ESI, Fig. S5), thus demonstrating the ability of this gel to act as a sensor in response[8] to a chemical trigger.

It is clear from these results that the formation of a gel with chloroform is dependent on the presence of all three functional groups – *n*-octyl chain, carboxylic acid and nitrone – in the correct ratio. The structure of nitrone **5** is somewhat atypical when considered as a potential gelator. Whilst **5** is equipped with carboxylic acids, which allow dimerisation through hydrogen bonding, its method of assembly into a gel is not as obvious as in many other gelators reported[9] previously, especially given that the nitrone functional group is clearly essential for gelation.

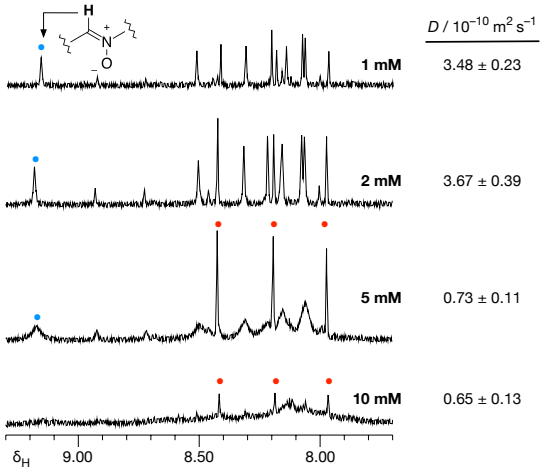

Fig. 2 Partial 700.1 MHz ^{1}H NMR spectra of a series of mixtures of aldehyde **2** and hydroxylamine **4** in $CDCl_3$ at initial concentrations from 1 mM to 10 mM. The spectra were recorded two days after mixing the reagents in $CDCl_3$. The resonances marked with a blue circle correspond to the indicated proton in nitrone **5**. The sharp resonances marked with red circles arise from aldehyde **2**. Apparent diffusion coefficients (*D*), determined by 700.1 MHz ^{1}H DOSY experiments are shown next to each partial spectrum. *D* was determined using the proton resonances arising from the terminal part of the *n*-octyl chains in **5** (See ESI).

In order to examine in more detail the assembly process involved in the creation of a gel from chloroform and nitrone **5**, we examined the behaviour of **5** at concentrations up to 10 mM (above the CGC of 6 mM) in $CDCl_3$ by diffusion-ordered NMR spectroscopy (DOSY)[10]. The 700.1 MHz ^{1}H NMR spectra of these samples (Fig. 2) reveal a significant change in behaviour as the concentration increases from 1 mM (significantly below the CGC) to 10 mM. Even at 1 mM, the condensation of **2** and **4** to form **5** is evidenced by the appearance of a resonance at around δ 9.15 corresponding to the nitrone proton (blue circle, Fig. 2). The line widths of the resonances corresponding to **5** broaden markedly as the concentration increases until, at 10 mM, the ^{1}H NMR spectrum is generally broad and featureless. This NMR data is consistent with the physical data discussed previously – **5** forms a viscous solution at 5 mM and a stiff gel at 10 mM. The resonances in the aromatic region of the ^{1}H NMR spectrum of **5** become much too broad to obtain acceptable DOSY data across this concentration range. However, the resonances arising from the terminal portions of the *n*-octyl chains present in **5**, although broadened (see ESI, page S26), are still suitable for analysis using a DOSY experiment, even at 10 mM. We therefore conducted four DOSY experiments, at the concentrations shown in Fig. 2, and extracted the apparent diffusion coefficients (*D*) using these resonances. Clearly, the system undergoes a major structural transition at around 5 mM, suggesting large scale incorporation of **5** into the growing gel network resulting in a sharp decrease in the apparent diffusion coefficients for the end segments of the *n*-octyl chains.

In order to probe the superstructure formed by nitrone **5** within the gel, we prepared a xerogel by drying a sample at an

initial concentration of 40 mM in $CDCl_3$. Wide angle X-ray scattering, performed on this xerogel (Figure 3a), suggests that the sample possesses little long-range ordering. The most intense broad peak, at 2θ = 25.4°, corresponds to distance of 3.5 Å, suggesting that there may be significant π-π stacking present in the xerogel. The peak at 2θ = 3.8°, corresponds to distance of around 25 Å, suggesting that there may be some longer-range structure present in the sample.

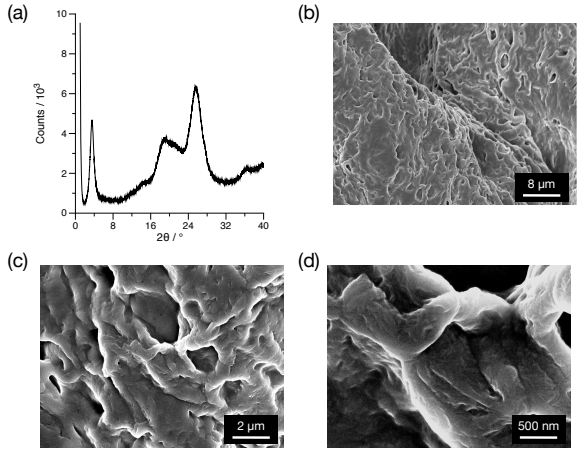

Fig. 3 (a) Wide-angle X-ray scattering data for a xerogel obtained by drying a sample of **5** prepared originally at a concentration of 40 mM in $CDCl_3$. Scanning electron micrographs of a xerogel obtained by drying a sample of **5**, prepared in $CDCl_3$ at 40 mM. Magnification increases from (b) ×2500 through (c) ×10000 to (d) ×40000.

Scanning electron microscopy was performed on the same xerogel prepared from nitrone **5** and $CDCl_3$. At all magnifications (Fig. 3b to 3d), there are indications that large voids may be present in the gel, however, there is no clear evidence of the type of structure, for example, fibre formation, that gives rise to the longer range order within the gel network.

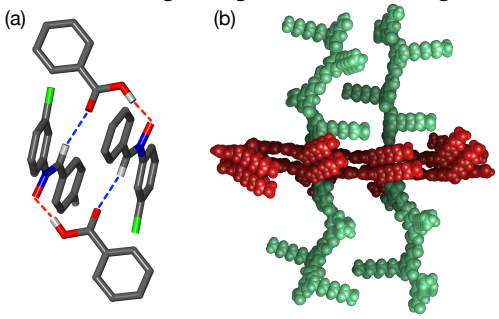

Fig. 4 (a) Stick representation of repeating unit from the solid state structure of *N*-(3-chlorophenyl)-α-phenylnitrone (XEGHEW). Carbon atoms are grey, nitrogen atoms are blue, oxygen atoms are red and chlorine atoms are green. Most hydrogen atoms (white) have been omitted for clarity. Hydrogen bonds between flanking benzoic acid molecules and π-π stacked nitrones are marked in red. Additional C–H•••O contacts between the carboxylic acids and the central nitrones are marked in blue. (b) Proposed assembly of nitrone **5** into a network based on the crystal structure of *N*-(3-chlorophenyl)-α-phenylnitrone. Chains (red) of π-π stacked nitrone **5**, connected by carboxylic acid dimers, are crosslinked (green) by hydrogen bonds between acids on **5** and the nitrone oxygen atoms in the of π-π stacked domain.

A potential gel network assembly model can be constructed by considering the co-crystal formed[11] between benzoic acid and *N*-(3-chloro phenyl)-α-phenylnitrone. In this structure (Fig. 4a), two nitrones form an antiparallel π-π stacked dimer. Additionally, there is a hydrogen bond between the carboxylic acid proton of a flanking benzoic acid molecule and the oxygen atom of one of the π-π stacked nitrones. Extending this assembly motif to nitrone **5** (Fig. 4b), we envision tapes of π-π stacked nitrones connected by carboxylic acid dimers (red, Fig. 4b). These tapes would then be cross-linked by additional strands of carboxylic acid dimer-linked nitrones (green, Fig. 4b) anchored to the π-π stacked strand by hydrogen bonds between nitrone oxygen atoms and carboxylic acid protons.

So far, we have demonstrated that nitrone **5** satisfies two of the three criteria that we identified originally as being essential for use in DSR – (i) formation through condensation of its constituents, **2** and **4**, and (ii) the assembly to afford a stiff clear gel in chloroform. It is therefore necessary to explore whether **5** can satisfy our final requirement, *i.e.* participate in recognition-mediated reactive processes.

Firstly, we examined the environment within the gel by probing the behaviour of a molecule that had been incorporated into the gel. A mixture of aldehyde **2**, hydroxylamine **4** and dye **6** was dissolved in $CDCl_3$ – each compound at a concentration of 20 mM – and placed in an NMR tube and sonicated for 10 minutes. After 2 hours, a stiff, yellow gel had formed in the NMR tube (Fig. 5a, right). For comparison purposes, a 20 mM solution of dye **6** was prepared in $CDCl_3$ (Fig. 5a, left). The ^{19}F NMR spectra of dye **6** obtained in solution and in the gel are essentially indistinguishable (Fig. 5). Indeed, the diffusion coefficient, *D*, for **6** present in each sample, measured using 470.4 MHz ^{19}F DOSY experiments, shows (Fig. 5a) essentially no difference in the environment experienced by **6** in solution and in the gel.

In order to establish that the gel could be compatible with our recognition-mediated DSR technology, it was necessary to investigate the reactive properties of the gel, we designed the experiment shown in Fig. 5b. We prepared 0.5 mL samples of the gel at 20 mM in NMR tubes and introduced 0.5 mL of a 20 mM $CDCl_3$ solution of either a recognition-enabled maleimide **7** or a control maleimide **8** in a separate layer above the gel (Fig. 5b, left). The results shown in Fig. 5a demonstrate clearly that molecules can diffuse freely in the gel and therefore we anticipated that **7** or **8** would be able to access the gel network readily. Maleimide **7** is capable[3,12] of reacting with nitrones of the general structure of **5** through a rapid, recognition-mediated autocatalytic cycloaddition driven by the association between the amidopyridine present in **7** and a carboxylic acid on the nitrone partner. By contrast, maleimide **8** bears no recognition site and must react with **5** solely through a bimolecular process. We anticipated that, since nitrone **5** incorporated within the gel would react much more slowly than that present in solution, in the absence of any recognition-mediated acceleration, the cycloaddition between **5** and **8** would be very slow. The results of this experiment (Fig. 5b) are unambiguous. After 24 hours, inversion of the NMR tubes reveals that the recognition-mediated reaction between **5** and **7** has degraded the gel significantly. This degradation continues until, after 48 hours, almost none of the gel remains and nitrone **5** has been processed through the recognition-mediated reaction into the corresponding cycloadduct.

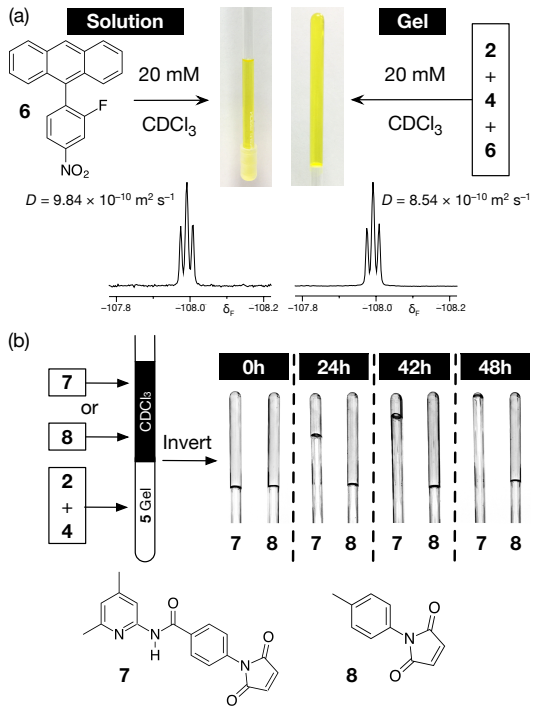

Fig. 5 (a) Inverted NMR tubes containing either **6** in $CDCl_3$ (left) or a mixture of **2**, **4**, and **6** in $CDCl_3$ (right). All components are present at a concentration of 20 mM. The corresponding partial ^{19}F NMR spectra (470.4 MHz, rt, $CDCl_3$) and diffusion coefficients derived from ^{19}F DOSY NMR experiments performed on each sample. (b) Samples of the gel were prepared in NMR tubes and a $CDCl_3$ solution containing either recognition-enabled maleimide **7** or control maleimide **8** or layered above the gel (left). Inversion of these tubes shows the gradual degradation of the gel in the samples containing maleimide **7** (right).

By contrast, there is almost no degradation in the control experiment with maleimide **8**, despite the fact that, as expected, the maleimide is detectable within the gel by ^1H NMR spectroscopy. Other controls (see ESI, Fig. S6) demonstrated that only maleimide **7**, with its combination of recognition *and* reactivity, was capable of destroying the gel network. These results also suggest that incorporation of nitrone **5** within the gel network protects it from reaction with compounds that are not capable of engaging it in a recognition-mediated reaction.

In conclusion, we have described a new class of nitrone-based gelator that satisfies the three requirements we identified initially for operating as a selection tool in dynamic systemic resolution. Firstly, the gelator is created from its constituents through dynamic covalent bond formation. Secondly, the recognition elements present assemble a three-dimensional network creating the gel, thereby offering a first level of selection within the system. Finally, the gelator can undergo irreversible transformation through reaction of its nitrone functional group through a recognition-mediated reaction that targets the gelator specifically and these properties open the possibility of a DSR strategy that targets compounds incorporated[13] in the network and those in the matrix separately with different recognition-mediated reactions. Studies towards the coupling of gel formation with other replication processes are currently ongoing in our laboratory.

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