



# Gelation Landscape Engineering Using a Multi-Reaction Supramolecular Hydrogelator System

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## Supporting Information

**ABSTRACT:** Simultaneous control of the kinetics and thermodynamics of two different types of covalent chemistry allows pathway selectivity in the formation of hydrogelating molecules from a complex reaction network. This can lead to a range of hydrogel materials with vastly different properties, starting from a set of simple starting compounds and reaction conditions. Chemical reaction between a trialdehyde and the tuberculosis drug isoniazid can form one, two, or three hydrazone connectivity products, meaning kinetic gelation pathways can be addressed. Simultaneously, thermodynamics control the formation of either a keto or an enol tautomer of the products, again resulting in vastly different materials. Overall, this shows that careful navigation of a reaction landscape using both kinetic and thermodynamic selectivity can be used to control material selection from a complex reaction network.

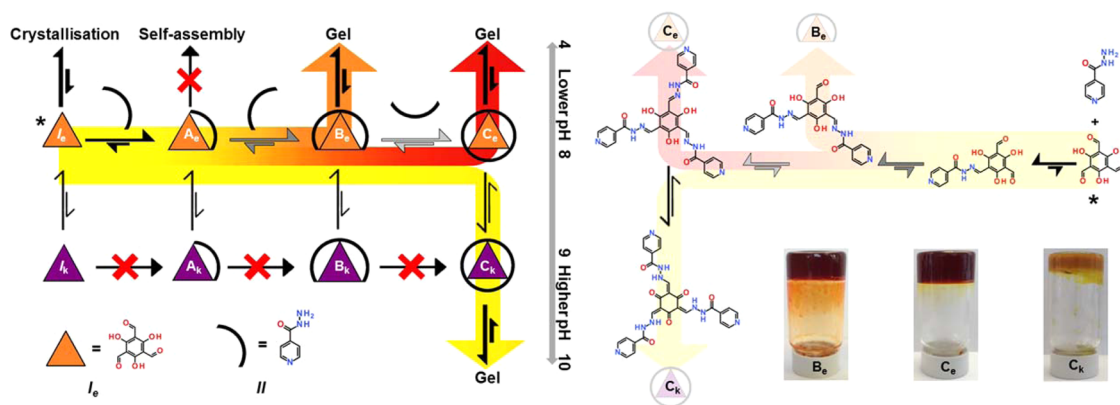
Both thermodynamic and kinetic parameters controlling self-assembly processes can be used to control pathway selection in assembling supramolecular materials. The resultant assemblies or materials can have vastly different properties, depending on the chosen self-assembly path.<sup>1</sup> Thermodynamically, pushing an assembly down a certain pathway to a stable energy well within the assembly landscape can use solvent, temperature, or pH changes. Kinetically, the landscape can be navigated using the activation energies associated with certain assembly processes, to address metastable states over time or to kinetically trap a certain state. Materials generated from these complex pathways include crystal forms (polymorphism), viruses, protein networks, supramolecular polymers, and certain low-molecular-weight gelators (LMWGs).<sup>1</sup> LMWGs represent the main materials of interest in this Communication, but the principles of the research may be applied to any supramolecular assembly process.<sup>2</sup> LMWGs have been used and envisioned to have a number of applications, including drug delivery commercial products and as templates for crystal, particle, or

cell growth, to name but a few.<sup>3</sup> With this in mind, research groups from around the world have studied these materials for a number of years through the use of pre-synthesized LMW compounds which undergo supramolecular polymerization. More recently, exploitation of chemical reactivity to both form and deform the gelatinous materials and to sample the pathway complexity of the self-assembly, but to date have not used the chemical reaction pathways to control selectivity.<sup>4</sup> These reported works have generally focused on single-step reactivity and have not researched multi-step reactivity or two or more types of reactivity in a single gelation system. Further work has begun to appear in which catalytic control over chemical reactivity is used to control the assembly processes of the gel components, the material properties and spatial distribution of the material.<sup>5</sup> This has led to many elegant methodologies to tackle the pathway complexity of supramolecular assembly in which kinetic and thermodynamic materials are isolated. With this in mind we hypothesized that chemical reactivity could play an important role in the production of multiple materials by controlling pathway selection in complex reaction networks (instead of the supramolecular assembly landscape).<sup>4</sup> To do this we introduced multiple-step reactivity (kinetic control) and pH-dependent tautomerization (thermodynamic control) to a reaction network capable of reversibly and irreversibly forming a range of potential hydrogelators from a set of simple starting chemicals (Figure 1). In the present case, this yielded three distinct gel materials from effectively the same chemical starting point (a mixed solution of the reactants).

In situ covalent bond formation between the water-soluble trialdehyde 1,3,5-triformylphoroglucinol (*I<sub>r</sub>*) and isoniazid (isonicotinic acid hydrazide, *II*) gave discotic compounds. This reactivity between hydrazides and aldehydes is well-known for its use in dynamic covalent chemistry.<sup>6</sup> Hydrazone formation can be catalyzed by protons or hydroxyl anions as well as by certain amines, and although this catalysis can occur in our system, it has

Received: July 15, 2015

Published: October 26, 2015



**Figure 1.** Pathway complexity reaction network diagram (left) showing the supramolecular assembly of three hydrogels from a single starting point (\*) of dissolved core and periphery components. The multiple-step reactivity (horizontal arrows) between a core trialdehyde ( $I_e$ , orange triangle) and a peripheral hydrazide ( $II$ , black semicircle) samples kinetically the assembly landscape. Thermodynamically controlled tautomerization (hooked vertical arrows between orange (enol) and purple (keto) triangles) samples a different part of the conjectural gelation landscape. Self-assembly (vertical thick black arrows) from the chemical reactivity products is the result of the process conditions selecting the reaction product, giving three distinct gelatinous materials,  $B_e$  (orange pathway),  $C_e$  (red pathway), and  $C_k$  (yellow pathway).  $A_e$  is the mono-substituted enol intermediate observed experimentally.  $I_e$  crystallizes out at low pH (<7) in water.

no effect on the kinetic or thermodynamic selectivity of the complex reaction pathway.<sup>7</sup> The reaction pathway of  $I_e$  and  $II$  should give three possible enol hydrazone species, products  $A_e$ ,  $B_e$ , and  $C_e$ , and three possible keto hydrazone species,  $A_k$ ,  $B_k$ , and  $C_k$  (Figure 1), referring to singly, doubly, and triply reacted sets of products, respectively. The triply reacted product is found in two tautomeric forms, enol ( $C_e$ ) and keto ( $C_k$ ), while  $A_e$  and  $B_e$  are observed experimentally.

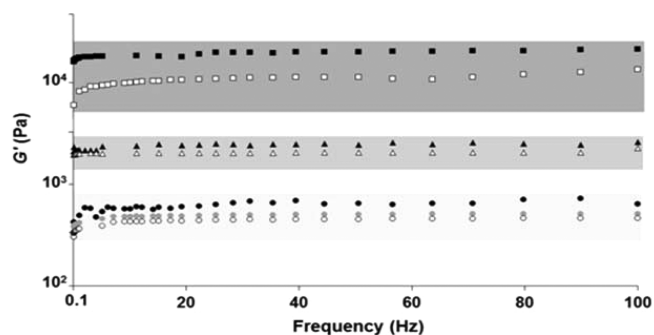
There are a number of ways in which to set gels formed from this reactive molecular system. Reaction conditions lead to three different gels,  $C_e$ ,  $C_k$ , and  $B_e$  gels (Figure 1). Gels are heat and time stable. The methodologies in brief for synthesizing the gels are as follow (see Supporting Information (SI) for details):

(1) Mix the core  $I_e$  with a number of equivalents of  $II$  at pH 8, and raise the pH to 9.5–12. This gives  $C_k$  gel, chemically the thermodynamically stable monomer. Equivalents of reactants, salts, or mode of changing the pH do not change the experimental outcome.

(2) Mix the core  $I_e$  with a number of equivalents of  $II$  at pH 8, and leave in solution for a set period of time (hours) before lowering the pH using glucono- $\delta$ -lactone (GdL).<sup>8</sup> This gives  $C_e$  gel, a kinetically trapped monomer in reference to tautomerization, less stable than  $C_k$ .

(3) Mix the core  $I_e$  with a number of equivalents of  $II$  at pH 8, and immediately on mixing lower the pH using GdL at room temperature. The lower pH gives  $B_e$  gel if the correct time variable within the reaction kinetics from reacting  $I$  and  $II$  through  $A_e$  to  $B_e$ . This is the kinetic selectivity of an intermediate monomer in the stepped reaction sequence.

Gelation methodologies 1 and 2 form two different gels,  $C_k$  (high pH) and  $C_e$  (low pH), both triple-hydrazone compounds. The gels are distinctly different in terms of not only their rheological characteristics but also their color (Figures 1 and 2). The  $C_e$  gel is red whereas the  $C_k$  gel is yellow; the color is indicative of the tautomeric form and is thus chemically based. The  $C_e$  gel is more robust, having both higher  $G'$  value and “yield stress” than the  $C_k$  gel (Figure 2 and SI, Figures S2–S7). The critical gelation concentrations (CGCs) for  $C_e$  and  $C_k$  are 0.2% and 0.5% by weight, respectively, also indicating a difference in the materials. Further rheological studies provided evidence on the connectivity between the supramolecular fibers of  $C_e$  and  $C_k$ .



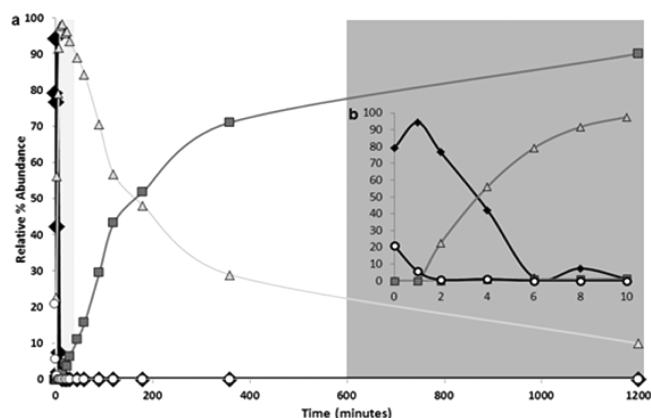
**Figure 2.** Rheological frequency range sweeps of the gels showing the three different gel types,  $C_e$ ,  $C_k$ , and  $B_e$ , having three distinct rheological properties with  $G' \approx 11\,000$ , 800, and 3000 Pa, respectively.  $C_e$  gels: black squares, ex situ gel; open squares, gel method 2.  $C_k$  gels: gray circles, ex situ gel; open circles, gelation and mixing at pH 10; black circles, gel method 1.  $B_e$  gels: black triangles, gel method 3; open triangles, ex situ gel.

The effect on the rheology of increasing concentration of  $C_e$  revealed a good match with the cellular solid/SAFIN models for gels.<sup>4,5</sup> The temporal changes during the kinetics of the gelation process also provide insights into the assembly process. The Avrami constants (also known as fractal dimensions) for  $C_e$  and  $C_k$ , 2.4 and 1.4, respectively, reveal a strong contrast in the assembly processes and connectivity, explaining the rheological differences. The self-assembled materials were found to be not only physically but also chemically different. Isolating  $C_e$  or  $C_k$  from these gels generated two distinct, analytically different tautomers (see SI for details of isolation through simple filtration and washes). Analytical data indicate that the tautomers isolated from the two pH ranges give  $C_e$  at low pH and  $C_k$  at high pH. This pH-dependent thermodynamic control selects the gelation pathway for  $C_e$  and  $C_k$ . The calculated reaction pathways and energy differences between the two tautomers,  $C_e$  and  $C_k$ , were determined to be relatively small. In the  $C_3$  geometry,  $C_k$ , as expected, is more stable.<sup>9</sup>  $C_e$  is kinetically trapped in a metastable state (see SI). Computational calculations indicate that  $C_k$  is 0.6 kcal/mol more stable than  $C_e$  and the reaction pathway has high-energy transition states (7–10 kcal/mol).

The setting of these gels is also reversible, indicating that the tautomerization is fully reversible (gelation reversibility is via the dissolved pH 8 species). To the best of our knowledge, this is the first example of reversibility of keto–enol tautomerization in this class of compounds in water.<sup>9</sup> At pH 8 the fully soluble  $C_e$  species appears to be an anion in the form of either the mono-deprotonated or doubly deprotonated species as evidenced by MS and UV/vis spectroscopy (see SI). This indicates that the low-pH gelation trigger for  $C_e$  is the protonation of the anion, giving a very low-solubility neutral compound. The apparent  $pK_a$  determined for  $C_e$  was  $\sim 6.8(\pm 0.1)$ . The results also indicate that as the pH is increased the tautomer equilibrium between  $C_e$  and  $C_k$  is shifted ( $\text{OH}^-$  induced, Figure S50). The pH change gives a compound which should have a very high  $pK_a$ ,  $C_k$  which is neutral and once again has a low solubility and self-assembles into the gelatinous material.<sup>9,10</sup> Chemical synthesis of  $C_e$  and gel setting of the dissolved  $C_e$  species at pH 8 yield the same gel as the in situ gelation method (i.e., an ex situ gelation method; see SI for details). This indicates that the gelation pathway is only dependent on the tautomerization covalent chemistry and not the hydrazone reactivity.

The importance of the pyridyl groups in the cross-linking of the supramolecular polymers is highlighted by the fact that the phenyl versions of  $C_e$  and  $C_k$ ,  $D_e$  and  $D_k$ , form supramolecular polymers but do not cross-link to form a gel network (see SI). Crystallization of  $C_e$  and  $D_e$  and determination of the crystal structures reveal that both molecules are indeed the enol tautomer (the first such crystallographic determinations of enol forms of this class of molecules)<sup>9</sup> and both show the propensity to stack one of top of the other due to their discotic shape (see SI for details of structures). The  $D_e$  tape motif is built from a discrete  $R2_8^8$  hydrogen-bonding pattern which involves the methanol solvent interrupting the well-known 1,3,5-benzotriamide H-bonding patterns.<sup>9c,d,f,11,12</sup> The  $C_e$  structure does not show this H-bonding as it crystallizes with DMSO, which acts as a strong H-bonding acceptor, again following the Etter rules.<sup>12</sup> However, this does not prevent the molecule from forming a stacking assembly, showing that the dispersion forces and shape are sufficient to induce supramolecular polymerization. The pyridyl groups are not interacting directly with each other to cross-link the columns of  $C_e$ , but well-known H-bonding patterns with water may play an important role in cross-linking the hydrogel networks.<sup>13</sup>

Varying the ratios of  $I_e$  and  $II$  in the initial solution using methods 1 and 2 always gave  $C_k$  and  $C_e$  gels, respectively. Thus,  $C_k$  and  $C_e$  gel production is essentially independent of stoichiometry (see SI for details). When gelation method 3 was used, a different gel was formed, made up of the twice-reacted gelator  $B_e$  rather than the thrice-reacted  $C_e$  materials, illustrating the kinetic selectivity within the reaction gelation landscape. The majority of cases using gelation method 3 resulted in the gels being orange in color and gave materials rheologically weaker than the  $C_e$  gels but stronger than the  $C_k$  gels (Figures 2 and S18–S20). Isolating the chemical component of these orange gels (see SI for details) revealed that the materials were exclusively made from  $B_e$ . Rheological concentration studies and the Avrami constant (2.2) for  $B_e$  gels show that the gels also follow the cellular solid theory of gels and are highly inter-connected gelatinous materials. All three gels are fibrous in nature, as seen in the SEM morphologies. PXRD stacking distances are 3.32–3.39 Å for all three types of gels, indicating recognizable molecular packing motifs, as confirmed by computational work and crystal structures.<sup>9c,d,f,11</sup> We inves-



**Figure 3.** Reaction pathway kinetics in solution for the formation of anion versions of  $A_e$ ,  $B_e$ , and  $C_e$ . Conversion of  $I_e$  (○) and  $II$  (at a ratio of 1:6, respectively) to  $C_e$  (■) via intermediates  $A_e$  (◆) and  $B_e$  (△) at a constant pH 8 in water. Potential “gelling zones” based on the occurrence for  $B_e$  and  $C_e$  are shown as light gray (first 10 min) and dark gray zones (after several hours), respectively. Solid lines are used as a guide for the eye.  $II$  is not shown for clarity. (a) Analysis of the entire reaction; (b) inset showing the first 10 min of the reaction.

tigated trimers of structures  $B_e$ ,  $C_e$ , and  $C_k$  using B97D with a 6-311g(d) basis.  $C_e$ ,  $C_k$ , and  $B_e$  revealed their propensity to form supramolecular polymers but also the key difference in  $B_e$  forming structurally different aggregates. These are all indicative of fiber formation through supramolecular polymerization resulting in gelation.<sup>2</sup>

The relation between the formation of the  $B_e$  gel material and the kinetics of the reactions in different solution conditions was followed using MS and UV/vis spectroscopy to better understand the relationship between the chemical reactivity and the self-assembly of the gels (see SI for varied experimental settings). Figure 3 shows the reaction of  $I_e$  and  $II$  at pH 8 and indicates the immediate (seconds time scale) formation of  $A_e$  upon mixing  $I_e$  and  $II$ . Within seconds/minutes of mixing,  $B_e$  is formed, almost completely depleting  $I_e$  and  $A_e$ . However,  $C_e$  is not observed in most cases until at least 5–10 min into the reaction. The rate of formation of  $C_e$  is dependent on the amount and type of catalyst present, i.e., pH. For example,  $C_e$  is formed completely within minutes at pH 10 ( $\text{OH}^-$  catalyst) as noted by the quick gelation of  $C_k$  using gel method 2, compared to hours at pH 8.  $C_e$  always forms at high pH ( $>7$ ) as  $B_e$  is fully soluble at these pH values and does not undergo tautomerization. At lower pH values ( $<7$ ), a competition between formation of  $C_e$  from  $B_e$  and the self-assembly of  $B_e$  is established.

The reaction kinetics give clear evidence on why the methodology for gelation (method 3 compared to 2) yields two distinct materials. Adding **GdL** to the gelation mixture via method 3 results in a pH drop to  $<6.6$  (apparent  $pK_a$  for  $B_e$  is  $6.6(\pm 0.1)$ ), indicating that the metastable  $B_e$  is kinetically trapped through self-assembly. The explanation for this kinetic trapping is the mass-transfer limitation of  $B_e$  from the solid-state network of the gel, resulting in limited concentration and low reactivity in solution (see SI for details). Indeed, increasing the pH of a gel via method 3 to  $<6.6$  to resolubilize the compounds causes  $B_e$  to react further to generate  $C_e$  in solution (without adding further  $II$ ). Again lowering the pH below the apparent  $pK_a$  of  $C_e$  results in a  $C_e$  gel. This gel cannot be converted back to a  $B_e$  gel without extensive chemical isolation (i.e., theoretical breaking of covalent bonds between  $I_e$  and  $II$  and isolation of individual species). Isolated  $B_e$  is indeed capable of forming gels



through the pH-triggered mechanism as indicated by the rheology, morphology, and appearance of the gels made from dissolving isolated pure  $B_e$  at pH 8 and lowering the pH. The CGCs of  $B_e$  from both methodologies were identical at 0.3% by weight. Unlike  $C_e$ , when  $B_e$  is added to a high-pH water solution, no gelation occurs and a clear, colorless solution results, indicative of a soluble deprotonated species.

In conclusion, by coupling two chemical reactivities (hydrazone bond formation and tautomerization) to the self-assembly of supramolecular gels, we have shown that engineered reaction pathways within a gelation landscape can be created. We have described the intended production of a number of gel materials starting from one initial solution mixture, depending on kinetic and thermodynamic control over reactions. We hope this connectivity hypothesis between chemical reactivity and self-assembly will lead to new pathway complexity studies in a variety of research fields where multi-step reactivity can be introduced.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b06988.

Chemical synthesis and analysis, rheology, electron microscopy, chemical kinetics analysis, crystallography ( $C_e$  and  $D_e$  (CIF), SuperFlip and CRYSTALS),<sup>14</sup> and computational work (PDF)

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

Heriot-Watt University (G.O.L. and J.S.F.), the Royal Society of Edinburgh/Scottish Government Fellowship (G.O.L.), and the Scottish Funding Council Exchange Scheme (G.O.L.) are thanked for funding. G.O.L. and H.M. thank the Scottish Crucible for the project award "Custom Bubbles". M.J.P. and N.A. thank the European Research Council (ERC FP7/2007-2013/ERC Grant No. 258990). J.M.Z. acknowledges the support of the Leverhulme Trust (RPG-165) and EPSRC U.K. (EP/J006602/1).

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