

Analyte-Triggered Gelation: Initiating Self-Assembly via Oxidation-Induced Planarization

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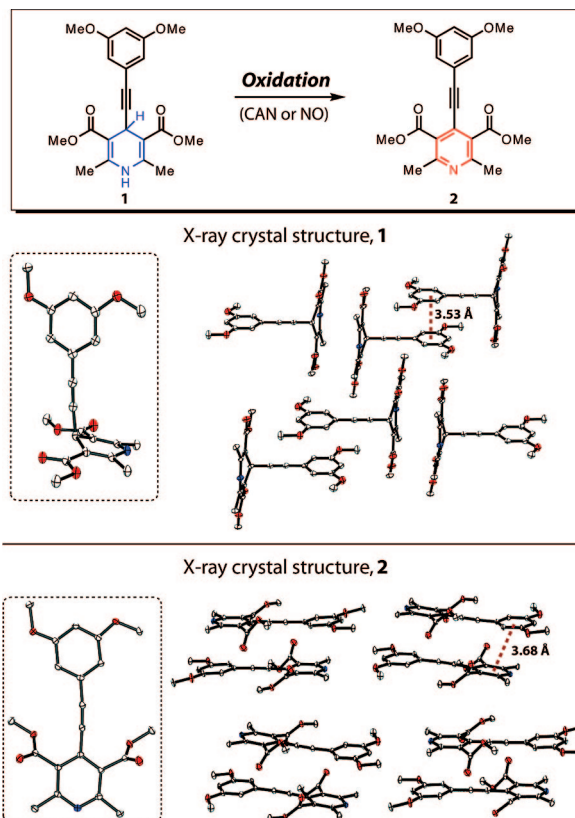
Molecular gels have been studied for over 160 years¹ and are now used in diverse applications such as regenerative medicine,² drug delivery,³ biosensing,⁴ and environmental remediation.⁵ Despite their utility, many applications rely on a narrow set of gelator structures because there is no adequate model to guide their invention. The challenge in designing new gelators is that many factors can influence their self-assembly, including molecular structure and medium effects (e.g., pH, ionic strength, temperature, and solvent identity⁶). Creating a stimulus-induced gelation is even more challenging because of the additional need to design a precursor molecule that does not form a gel.

Because gelation occurs when molecules self-assemble, design strategies have traditionally focused on promoting this process by changing the solubility or solvent–molecule interactions;⁷ for example, Xu⁸ and Ulijn⁹ have used enzymes to cleave a solubilizing group or add an insoluble moiety, and others have used pH to protonate or deprotonate a precursor.¹⁰ Although successful, this approach has been limited. An alternative and underutilized approach is to promote self-assembly by triggering changes in the intermolecular or molecule–molecule interactions; for example, light-induced isomerizations¹¹ and employing additives¹² have been used to influence molecular packing. Although it may be difficult to *predict* whether the molecular change will more strongly effect the solubility or intermolecular interactions, we believe the second approach will prove more useful for *designing* new triggered gelations. As evidence, we describe the successful design of a new analyte-induced gelation using this strategy. Specifically, an oxidation-induced planarization is used to trigger self-assembly and gelation through donor–acceptor π -stacking interactions.

Dihydropyridine **1** was designed as the precursor for the following reasons: (1) Nonplanar **1** should not form a gel due to an absence of obvious 1-D intermolecular interactions. (2) The molecular framework becomes planar upon oxidation to **2** (due to a change in hybridization) which should promote π -stacking.¹³ (3) The electron-rich aryl ethynylene should interact with the electron-poor pyridine in **2** through intermolecular donor–acceptor interactions. As a result, it was predicted that **2** would form a gel under conditions where **1** either precipitated or remained in solution.

Indeed, pyridine **2** forms a gel in mixtures of water with DMSO, alcohols, acetone, and DMF, whereas **1** either precipitates or remains in solution at the same concentrations.^{14,15} The critical gel concentration of **2** is 16 mM (0.6 wt %) at 2/1 DMSO/H₂O and 25 °C. Scanning electron microscopy revealed that the gel consists of high-aspect-ratio fibers under all conditions examined (Figure 1 and Supporting Information, SI). Single crystal X-ray diffraction confirmed that the solid-state packing for **1** and **2** are remarkably different, with oxidized **2** showing predominantly 1-D π -stacking with donor–acceptor interactions (Scheme 1¹⁶); powder X-ray diffraction on the cryo-dried gel confirms that the packing motif in the gel fibers is similar. Raman spectroscopy on single fibers

Scheme 1



revealed that the π -stacking direction is coincident with the fiber axis (see SI).

To test the proposed oxidation-induced gelation a strong oxidant was first used: cerium(IV) ammonium nitrate (CAN).¹⁷ In situ IR spectroscopy indicated that the oxidation is quantitative within 15 s in DMSO/H₂O. As anticipated, a gel formed after slow¹⁸ addition of an aqueous solution of CAN to **1** in DMSO/H₂O at room temperature (Figure 2). Note that this gelation is not due to a change in solvent–molecule interactions because **1** and **2** exhibit similar solubilities under the final reaction conditions.¹⁹

Given this successful result an oxidation-induced gelation was attempted with a weaker oxidant, nitric oxide (NO). NO is an appealing analyte because elevated concentrations in exhaled breath is a biomarker for many diseases.²⁰ NO has been shown to catalytically oxidize related dihydropyridines under an aerobic atmosphere.²¹ Using NO as an oxidant presented a challenge because it is insoluble in DMSO²² and reacts with alcohols and water in the presence of oxygen. Therefore the NO-induced oxidation was performed in CH₃CN. Syringe injection of NO (1 equiv) oxidizes **1** in 75 min. Table 1 depicts the reaction times to

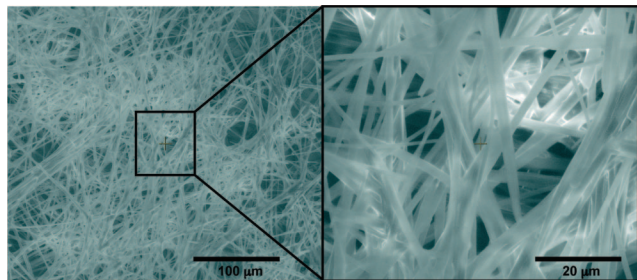


Figure 1. Scanning electron micrograph of the gel formed by **2** (26 mM) in 1/1.25/3.75 of CH₃CN/DMSO/H₂O.

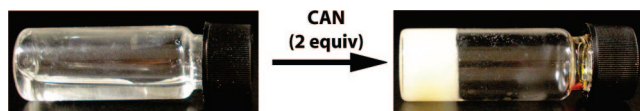


Figure 2. Adding an aqueous solution of CAN to **1** (26 mM, 4/1 DMSO/H₂O, left) produces **2** and gelation (2/1 DMSO/H₂O, right).

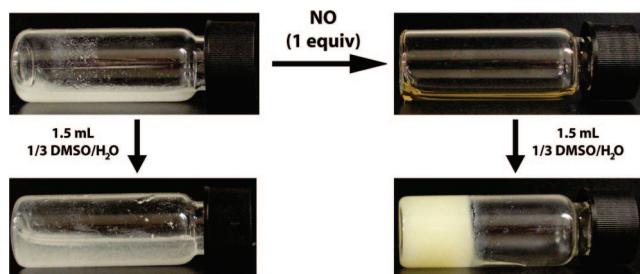


Figure 3. Adding NO to a mixture of **1** in CH₃CN (43 mM, upper left) results in oxidation to **2** (upper right). Adding an aliquot of DMSO/H₂O results in a solution for **1** (lower left) and a gel for **2** (lower right).

90% conversion for various equivalents of NO. Comparing entries 1 and 4 reveal that although the reaction is catalytic in NO, the reaction time is substantially slower at lower NO concentrations. After oxidation a gel formed at room temperature when DMSO/H₂O was added. Control studies showed that the NO-induced oxidation is essential to gel formation since an unexposed solution of **1** does not form a gel upon identical treatment of DMSO/H₂O (Figure 3).

In summary, we invented a new analyte-triggered gelation by employing a molecular design strategy based on a change in intermolecular interactions. Specifically, an oxidation-induced planarization with concomitant donor–acceptor interactions was shown to trigger gel formation. Though the present case exploits π -stacking, the general strategy of using an analyte to introduce gel-promoting intermolecular interactions can be applied using other

Table 1. Time to 90% Conversion in the NO-Induced Oxidation of **1**^a

entry	equiv of NO	time ^b (min)
1	0.25	2900
2	0.50	140
3	1.0	75
4	10	<1

^a Reaction conditions: 13 mmol of **1** in 0.3 mL of CH₃CN, 1 atm of O₂, rt. ^b Conversion was determined by HPLC analysis using an internal standard.

noncovalent interactions such as H-bonding, solvophobic, and electrostatic attraction. We believe that by employing signal amplification these analyte-triggered gels can be used in chemical sensing. Our current efforts are focused on developing methods for amplification using functionalized polymers.

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Supporting Information Available: Experimental details, spectroscopic data; X-ray crystallographic data in CIF format. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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