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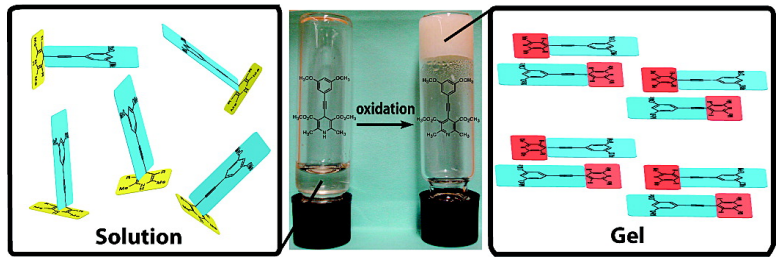

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Analyte-Triggered Gelation: Initiating Self-Assembly via Oxidation-Induced Planarization

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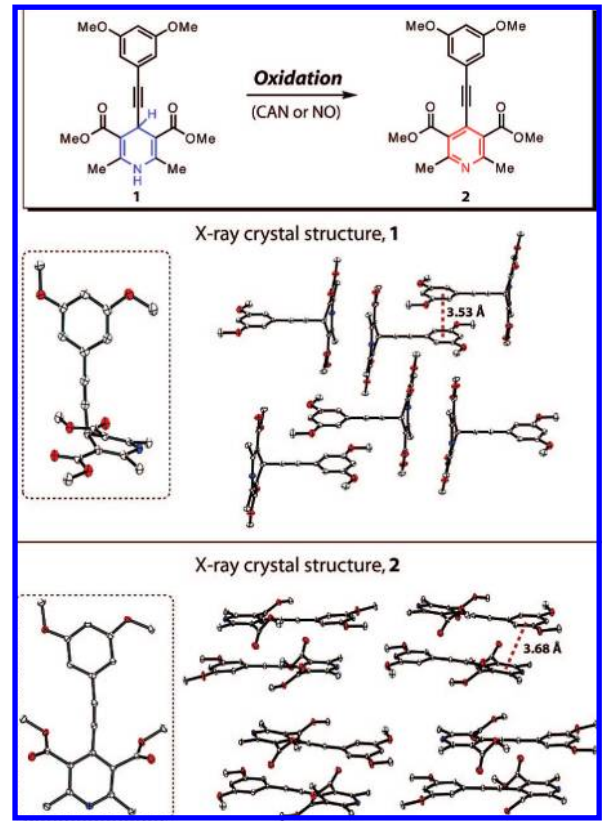
Molecular gels have been studied for over 160 years[1] and are now used in diverse applications such as regenerative medicine,[2] drug delivery,[3] biosensing,[4] and environmental remediation.[5] Despite their utility, many applications rely on a narrow set of gelator structures because there is no 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 identity[6]). 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, Xu[8] and Ulijn[9] 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 isomerizations[11] and employing additives[12] 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/H_2O 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 1[16]); 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 revealed that the π-stacking direction is coincident with the fiber axis (see SI).

Scheme 1



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/H_2O. As anticipated, a gel formed after slow[18] addition of an aqueous solution of CAN to **1** in DMSO/H_2O 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 DMSO[22] and reacts with alcohols and water in the presence of oxygen. Therefore the NO-induced oxidation was performed in CH_3CN. Syringe injection of NO (1 equiv) oxidizes **1** in 75 min. Table 1 depicts the reaction times to

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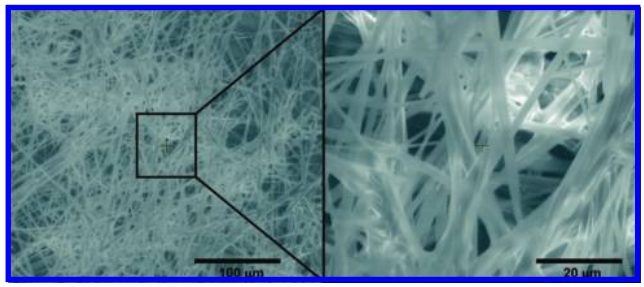

Figure 1. Scanning electron micrograph of the gel formed by **2** (26 mM) in 1/1.25/3.75 of CH_3CN/DMSO/H_2O.

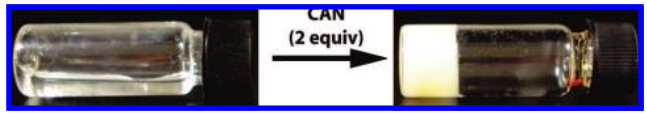

Figure 2. Adding an aqueous solution of CAN to **1** (26 mM, 4/1 DMSO/H_2O, left) produces **2** and gelation (2/1 DMSO/H_2O, right).

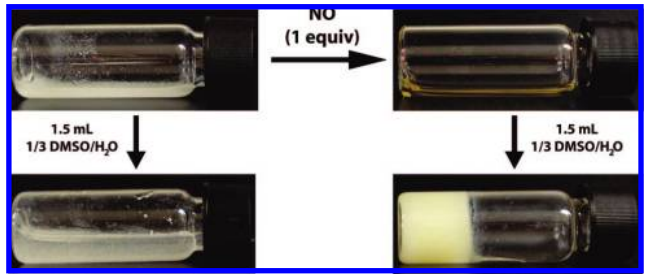

Figure 3. Adding NO to a mixture of **1** in CH_3CN (43 mM, upper left) results in oxidation to **2** (upper right). Adding an aliquot of DMSO/H_2O results in a solution for **1** (lower left) and a gel for **2** (lower right).

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/H_2O 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/H_2O (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 noncovalent interactions such as H-bonding, solvophobic, and electrostatic attraction. We believe that by employing signal amplification these analyte-triggered gelations can be used in chemical sensing. Our current efforts are focused on developing methods for amplification using functionalized polymers.

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 CH_3CN, 1 atm of O_2, rt. [b] Conversion was determined by HPLC analysis using an internal standard.

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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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