J|A|C|S
COMMUNICATIONS

Published on Web 11/17/2008

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

Jing Chen and Anne J. McNeil*

Department of Chemistry and Macromolecular Science and Engineering Program, University of Michigan, 930 North University Avenue, Ann Arbor, Michigan 48109

Received September 26, 2008; E-mail: ajmcneil@umich.edu

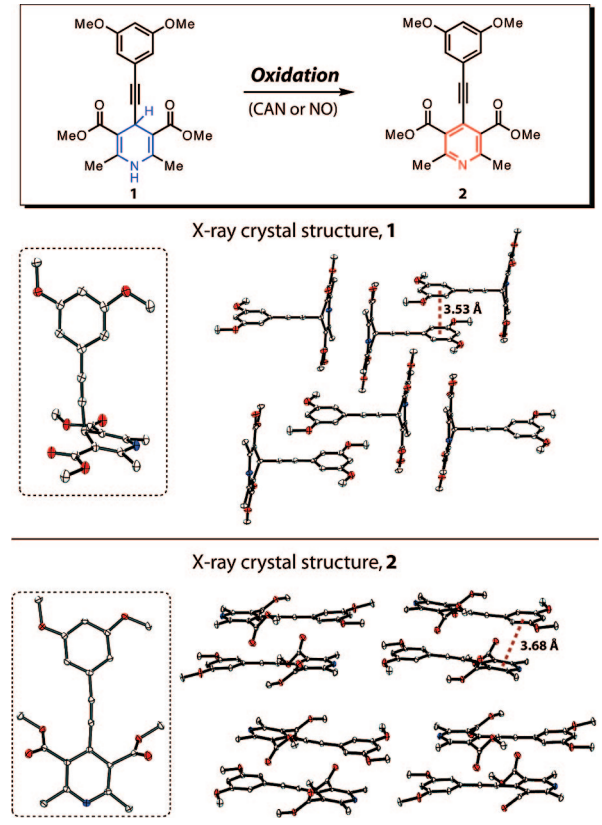
Molecular gels have been studied for over 160 years[1] and are now used in diverse applications such as regenerative medicine,[2] drug delivery,[3] biosensing,[4] and environmental remediation.[5] Despite their utility, many applications rely on a narrow set of gelator structures because there is no 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

10.1021/ja807651a CCC: $40.75

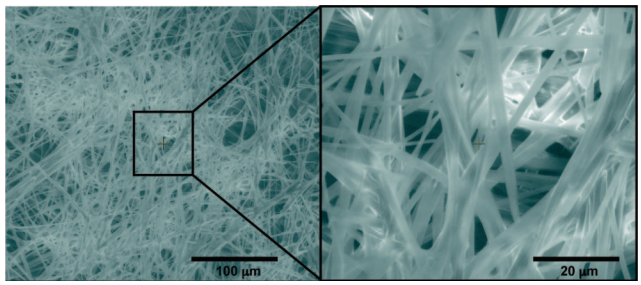


Figure 1. Scanning electron micrograph of the gel formed by **2** (26 mM) in 1/1.25/3.75 of CH_3CN/DMSO/H_2O.

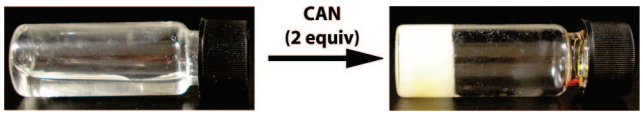


Figure 2. Adding an aqueous solution of CAN to **1** (26 mM, 4/1 DMSO/H_2O, left) produces **2** and gelation (2/1 DMSO/H_2O, right).

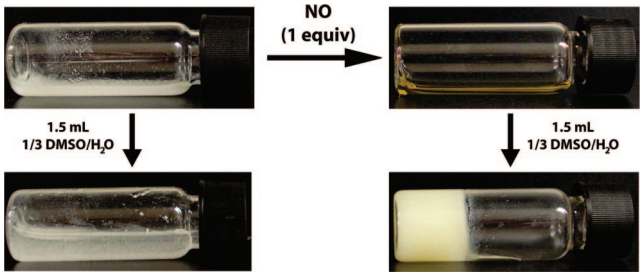


Figure 3. Adding NO to a mixture of **1** in CH_3CN (43 mM, upper left) results in oxidation to **2** (upper right). Adding an aliquot of DMSO/H_2O results in a solution for **1** (lower left) and a gel for **2** (lower right).

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.

Acknowledgment. We thank Dr. Jeff W. Kampf for performing X-ray crystallography, Ms. Anna Merkle for assistance with NO, and the University of Michigan for funding.

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.

References

(1) (a) *Molecular Gels: Materials with Self-Assembled Fibrillar Networks*; Weiss, R. G., Terech, P., Eds.; Springer: Dordrecht, The Netherlands, 2006. (b) Low Molecular Mass Gelator; *Topics in Current Chemistry*, Vol. 256; Springer: Berlin, Heidelberg, 2005. For recent reviews, see: (c) Sangeetha, N. M.; Maitra, U. *Chem. Soc. Rev.* **2005**, *34*, 821–836. de Loos, M.; Feringa, B. L.; van Esch, J. H. *Eur. J. Org. Chem.* **2005**, 3615–3631. Estroff, L. A.; Hamilton, A. D. *Chem. Rev.* **2004**, *104*, 1201–1218.
(2) For a recent example, see: Tysseling-Mattiace, V. M.; Sahni, V.; Niece, K. L.; Birch, D.; Czeisler, C.; Fehlings, M. G.; Stupp, S. I.; Kessler, J. A. *J. Neurosci.* **2008**, *28*, 3814–3823. Silva, G. A.; Czeisler, C.; Niece, K. L.; Beniash, E.; Harrington, D. A.; Kessler, J. A.; Stupp, S. I. *Science* **2004**, *303*, 1352–1355.
(3) For a recent review: Vintiloiu, A.; Leroux, J.-C. *J. Controlled Release* **2008**, *125*, 179–192.
(4) For recent examples, see: Yang, Z.; Ho, P.-L.; Liang, G.; Chow, K. H.; Wang, Q.; Cao, Y.; Guo, Z.; Xu, B. *J. Am. Chem. Soc.* **2007**, *129*, 266–267. Yang, Z.; Xu, B. *Chem. Commun.* **2004**, 2424–2425.
(5) For a recent example, see: Bardelang, D.; Camerel, F.; Margeson, J. C.; Leek, D. M.; Schmutz, M.; Zaman, M. B.; Yu, K.; Soldatov, D. V.; Ziessel, R.; Ratcliffe, C. I.; Ripmeester, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 3313–3315.
(6) For example, an effect of the solvent chain length was reported to play an unknown but measurable role in molecular self-assembly; Jonkheijm, P.; van der Schoot, P.; Schenning, A. P. H. J.; Meijer, E. W. *Science* **2006**, *313*, 80–83.
(7) Hirst, A. R.; Coates, I. A.; Boucheteau, T. R.; Miravet, J. F.; Escuder, B.; Castelletto, V.; Hamley, I. W.; Smith, D. K. *J. Am. Chem. Soc.* **2008**, *130*, 9113–9121.
(8) For a recent review, see: Yang, Z.; Liang, G.; Xu, B. *Acc. Chem. Res.* **2008**, *41*, 315–326.
(9) For a recent example, see: Das, A. K.; Collins, R.; Ulijn, R. V. *Small* **2008**, *4*, 279–287.
(10) For a recent example, see: Shome, A.; Debnath, S.; Das, P. K. *Langmuir* **2008**, *24*, 4280–4288.
(11) For a recent example, see: Matsumoto, S.; Yamaguchi, S.; Ueno, S.; Komatsu, H.; Ikeda, M.; Ishizuka, K.; Iko, Y.; Tabata, K. V.; Aoki, H.; Ito, S.; Noji, H.; Hamachi, I. *Chem.—Eur. J.* **2008**, *14*, 3977–3986.
(12) For a review of two-component gels, see: Hirst, A. R.; Smith, D. K. *Chem.—Eur. J.* **2005**, *11*, 5496–5508.
(13) For related examples, see: (a) Zang, L.; Che, Y.; Moore, J. S. *Acc. Chem. Res.* **2008**, DOI: 10.1021/ar800030w. (b) Ajayaghosh, A.; Praveen, V. K. *Acc. Chem. Res.* **2007**, *40*, 644–656. (c) Hoeben, F. J. M.; Jonkheijm, P.; Meijer, E. W.; Schenning, A. P. H. J. *Chem. Rev.* **2005**, *105*, 1491–1546.
(14) For rheological measurements on these gels, see Supporting Information.
(15) For the role of the 2,6-dimethyl substituents in a related gelator, see: Baddeley, C.; Yan, Z.; King, G.; Woodward, P. M.; Badjić, J. D. *J. Org. Chem.* **2007**, *72*, 7270–7278.
(16) X-ray crystal structure images were generated using ORTEP-3. H-atoms were omitted for clarity.
(17) Pfister, J. R. *Synthesis* **1990**, 689–690. See also: Nair, V.; Deepthi, A. *Chem. Rev.* **2007**, *107*, 1862−1891.
(18) Note that rapidly adding CAN in one aliquot lead to a precipitate.
(19) The equilibrium solubilities were measured by UV−vis spectroscopy in 2/1 DMSO/H_2O at room temperature: **1** (0.29 ± 0.04 mg/mL) and **2** (0.61 ± 0.07 mg/mL).
(20) Lim, K. G.; Mottram, C. *Chest* **2008**, *133*, 1232–1242.
(21) (a) Zhu, X.-Q.; Zhao, B.-J.; Cheng, J.-P. *J. Org. Chem.* **2000**, *65*, 8158–8163. (b) Itoh, T.; Nagata, K.; Matsuya, Y.; Miyazaki, M.; Ohsawa, A. *J. Org. Chem.* **1997**, *62*, 3582–3585.
(22) (a) Shaw, A. W.; Vosper, A. J. *J. Chem. Soc., Faraday Trans. 1* **1977**, *73*, 1239–1244. (b) *Dimethyl sulfoxide (DMSO) Solubility Data; Bulletin #102B*; Gaylord Chemical Company, L.L.C.: Slidell, LA, 2007.

JA807651A