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pH and cation-responsive supramolecular gels formed by cyclodextrin amines in DMSO†

Wei Deng, David H. Thompson

Purdue University, Department of Chemistry, 560 Oval Drive, West Lafayette, IN, USA 47907.

Abstract

Amine-modified cyclodextrins are capable of forming pH and cation-responsive organogels in DMSO at low molar fractions.

Supramolecular gels of low molecular mass have attracted considerable attention recently as smart materials.¹ These noncovalently bonded materials are typically designed to self-assemble *via* hydrogen bonding, van der Waals and/or π – π interactions. Some of these gels display responsiveness to external stimuli, such as temperature, pH, redox potential or light changes,² leading to a host of diverse applications in sensors, drug delivery, catalysis and templated synthesis.³ Moreover, reversible multi-stimuli responsive supramolecular gels have been reported to exhibit the four basic logic gate functions of AND, OR, NAND, and NOR.⁴

Cyclodextrins (CDs) have been widely applied in supramolecular architectures due to their well-known host–guest interactions in aqueous media and their rich hydrogen bonding capabilities. Previously, a series of supramolecular hydrogels produced by modified β -CDs that utilized host–guest and hydrogen bonding interactions, showed excellent chemical and thermal responsiveness.⁵ The gelation of CDs in organic solvents, however, still poses a challenge due to the weak host–guest interactions that occur in these solvents. To our knowledge, there is only one report of such a system that describes a β -CD/pyridine gel system from rigorously anhydrous solutions of native β -CD in pyridine.⁶ Herein, we report hepta-6-amino- β -CD (**1**, Scheme 1) as an efficient supramolecular gelator in DMSO, which displays reversible pH and cation responsiveness.

While intermolecular hydrogen bonding exists between native CDs, solutions of unmodified CDs do not form gels in DMSO, due to the weak interactions between CDs in this solvent that prevent the formation of a network structure. We converted the 6-hydroxymethyl positions of β -CD to 6-aminomethyl groups using standard methods⁸ to form **1**. We expected that amine substituents would contribute to more extensive hydrogen bonding, thereby enabling fibril formation as well as enhanced coordination capabilities with transition metal ions. Initially, we prepared gels of **1** in DMSO by heating dilute solutions to 120 °C, followed by cooling to room temperature to enable slow gel development over a few

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davethom@purdue.edu; Tel: +1 765-494-0386.

days (Table 1). In order to accelerate the gelation process, ultrasonic dispersion was performed using a 1/8" microtip probe. When DMSO solutions of compound **1** were sonicated at 50 watts intensity for 5 min at 40 °C, a turbid gel was obtained after cooling to room temperature. The critical gel concentration (CGC) was 1.0 wt% in DMSO. A ternary phase gel was also produced when water was used as cosolvent at low volume ratios in the isotropic phase. When the percentage of water increased to more than 30%, however, the gel phase was lost, producing a white precipitate.

Atomic force microscopy (AFM) was used to evaluate the supramolecular gel formation process. Samples of different concentrations were prepared on mica substrates by slow evaporation of DMSO at 20 °C under vacuum overnight. At low concentrations, the AFM images display a fibril-type morphology (Fig. 1a). The height of single fibrils is similar to the 1.5 nm diameter of β -CD, while the height at fibril cross-links is approximately double that of the individual fibrils. This suggests that the fibrils are composed of single chains of self-assembled **1** molecules and that the gel is produced by physical entanglement of these fibrils. At higher concentrations, AFM images reveal a more highly cross-linked structure, with a network distributed across the mica surface (Fig. 1b). Solvent molecules are presumed to reside within the pores of the intact gel. At millimolar concentrations, the organogel exhibits numerous thick fibrils with extensive cross-linking (Fig. 1c). The fibril height was much larger than that of the β -CD diameter, suggesting that fibril alignment and cohesion produces thicker fibrils and more extensive fibrillar entanglements under these conditions. Intermolecular hydrogen bonding and van der Waals contact between neighboring amino CDs and proximal fibrils are proposed as the fiber-forming and physical cross-linking forces, respectively, owing to the abundance of NH_2 and OH groups in the CD rims and hydrophobic toroidal surface of **1**. This assumption is supported by experiments wherein urea was added to the gel; under these conditions, the sample was transformed into a sol due to weakening of both hydrogen bonds between cross-linked fibrils of **1** and neighboring amino CDs.

The sols were imaged by AFM as shown in Fig. 2. The low pH images exhibited a dendritic morphology instead of fibrils, due to the formation of ammonium salt crystals. After addition of NaOH, a smooth surface was observed without the appearance of any fibrils or crystals. We attribute this to CD deprotonation and loss of hydrogen bonding due to electrostatic repulsion at high pH. These results further support the conclusion that hydrogen bonding contributes to fibril formation and cross-linking.

In order to further understand the role of the amine groups in gel formation, several related amino-CDs compounds were synthesized. The 6-hydroxy groups were converted with hydrazine, ethanolamine, ethylene diamine and iodide to give compounds **2**, **3**, **4** and **5**, respectively. Native β -CD, compounds **2**, **3** and **4**, but not compound **5**, produced gel-like phases in organic solvents such as toluene, but failed to gelate in DMSO due to the structure and flexibility of these substituents, which weakens their hydrogen bonding interactions. It should be noted that hexa-6-amino- α -CD (**6**) also formed a gel in DMSO, albeit at higher concentrations than the beta congener. Compounds **1** and **6** failed to gelate in toluene, in part due to their low solubility in this solvent. These results indicate that the presence of multiple amine groups, presented on the rim of a rigid CD scaffold, plays a key role in the formation

of strong hydrogen bonds within a fibril chain, which then entangles to form a gel, even in highly polar solvents like DMSO.

Our attention then focused on the stimuli responsiveness of these gels. Initially, the pH response of **1** in DMSO was investigated (Fig. 3). Gels of **1** at 2 wt% in DMSO with 10% H₂O were light yellow and opaque. The gel transformed to the sol state after addition of acid or base (Fig. 3a). The pH effect on the gel-to-sol transformations also were investigated by light transmittance as shown in Fig. 3b, using mixtures of **1** at 5 mM in 9 : 1 DMSO : H₂O. The transmittance increased sharply when the pH changed from 9.3 to 8.0, presumably due to electrostatic repulsion between cationic amino groups, causing breakage of intermolecular hydrogen bonding and physical cross-linking. On the other hand, there is a slight increase in the transmittance across the 9.3 to 12.0 pH range, followed by a sudden increase in transmittance between pH 12.0 and 13.0. These pH-dependent gel-sol transformations stem from the reversible protonation reactions of the **1** 1° amine and 2° hydroxyl groups. A reversible sol-gel transition occurred when stoichiometric additions of base or acid were made, respectively, as shown by data from pH cycling experiments (Fig. 3c).

The property of metal ion responsiveness of the gel also was investigated. The organogel showed a quick response to Co³⁺, Ni²⁺, Cu²⁺ and Ag⁺, producing rapid gel-sol transitions upon addition of these metal ions. As shown in Fig. 4a, when 1 wt% AgBF₄ was added to 2 wt% **1** in DMSO, the gel was dissolved to give a clear solution. In this case, Ag⁺ ions presumably coordinate with the amine groups of **1**, leading to disruption of the aggregate structure *via* electrostatic repulsion and disruption of intermolecular hydrogen bonding to produce a gel-sol transformation. This transition was reversible since the gel formed again when the Ag⁺ ions were precipitated by addition of a KI solution. This transition was reversible since alternate addition of Ag⁺ and I⁻ was shown to cycle between the gel and sol states repeatedly (data not shown). Addition of Co³⁺, Ni²⁺ and Cu²⁺, also induced gel-to-sol transformations, whereas, Na⁺, K⁺ and Ca²⁺ had no effect on the organogel. The transmittance of 5 mM **1** organogel in 9 : 1 DMSO : H₂O increased sharply with the addition of Ni²⁺, while the metal ion response to Co³⁺ shows a slower increase, due to the differences in amine binding constants for Ni²⁺ and Co³⁺.⁷ Transmittances increased with the addition of Co³⁺ and Ni²⁺, reaching maxima at 2 : 1 and 0.4 : 1 Mⁿ⁺ : CD stoichiometry, respectively (10 and 2 mM concentrations in 5 mM **1**).

To confirm the presence of metal-amine ligation in these samples, FT-IR spectra of **1** with and without Cu²⁺ were performed. Peaks at 3369 and 1658 cm⁻¹ were attributed to the N-H stretching and bending modes in metal-free **1** (Fig. 5a). When Cu²⁺ was added, the N-H absorptions shifted to 3412 and 1639 cm⁻¹ (Fig. 5b). Additionally, the C-H stretching band of CH₂NH at 2927 cm⁻¹, was split into two peaks (2996 and 2912 cm⁻¹) upon Cu²⁺ coordination. These changes suggest that electrostatic repulsion increases between neighboring **1** molecules upon Cu²⁺ ligation to NH, thus weakening the hydrogen bonding within the CD fibrils and promoting the gel-to-sol transition (Fig. 6).

Conclusions

We prepared toluene- and DMSO-based organogels from modified β -CDs containing amine groups at the 1° rim of the macrocycle. Compound **1**, hepta-6-amine- β -CD, displays efficient supramolecular gelation of DMSO at concentrations greater than 1 wt%. The organogels formed by **1** arise from the production of linear fibrils that physically crosslink and entangle to produce higher order supramolecular structures as the concentration of **1** increases. Hydrogen bonding is proposed as the primary fiber-forming and physical cross-linking forces, with the latter also involving van der Waals interactions between the outer walls of the CD toroidal surface. These gels show good stimuli responsiveness toward changes in pH and transition metal cations. The gel state rapidly shifts to the sol state upon addition of acid, base, Co^{3+} , Ni^{2+} , Cu^{2+} or Ag^+ ions. This transition is reversible and can be cycled several times back and forth between the gel state (formed by adjustment of the pH to 9.3 or cation precipitation) and sol state (by pH shift or M^{n+} addition).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1. AFM images of compound **1** initially at (a) 10^{-7} M; (b) 10^{-5} or (c) 10^{-1} M in DMSO. Samples were deposited on mica and imaged after solvent evaporation under vacuum at 20 °C overnight.

Fig. 2. AFM images of compound **1** at 10^{-1} M in DMSO. DMSO solutions after treatment with (a) HCl or (b) NaOH. Samples were deposited on mica and imaged after solvent evaporation under vacuum at 20 °C overnight.

Fig. 3.

pH-responsive behavior of gel **1** at 20 °C. (a) Photograph of the sol-gel-sol transition upon addition of 1 M HCl or NaOH to a dispersion of 2 wt% **1**. (b) Transmittance changes at 800 nm with HCl or NaOH titration, the concentration of **1** was fixed at 5 mM. (c) Gel-sol transition cycles with alternate addition of HCl and NaOH, the concentration of **1** is fixed at 5 mM. All experiments were performed using a 9 : 1 DMSO : H₂O solvent mixture.

Fig. 4.

Responsiveness of **1** gels in DMSO with different metal ions. Gel-sol-gel transition upon sequential Ag^+ and I^- additions (a); formation of sols upon addition of Co^{3+} , Ni^{2+} , Cu^{2+} and Ag^+ in DMSO (b). Transmittance changes at 800 nm with Co^{3+} or Ni^{2+} titration, the concentration of **1** was fixed at 5 mM (c). All experiments were performed using a 9 : 1 DMSO : H_2O solvent mixture.

Fig. 5. FT-IR spectra of (a) gel **1** and (b) gel **1** + CuSO₄ in KBr as the dispersant. Samples were prepared by drying the samples under vacuum overnight to produce powders for KBr pellet formation.

Fig. 6.
Conceptual illustration and photographs for sols and gels of **1** in DMSO/H₂O.

Scheme 1.
Structures of amino-cyclodextrins.

Table 1 Gelation of cyclodextrin derivatives in different organic solvents^a

	1	2	3	4	5	6	β -CD
Toluene	– ^b	+	+	+	– ^b	– ^b	+
DMSO	+	–	–	–	–	+	–

^a+: gelation; –: no gelation.^bPrecipitate.