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Optically Transparent Hydrogels from an Auxin–Amino-Acid Conjugate Super Hydrogelator and its Interactions with an Entrapped Dye

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Dedicated to Professor Santanu Bhattacharya

Abstract: Low-molecular-weight organic hydrogelators (LMHGs) that can rigidify water into soft materials are desirable in various applications. Herein, we report the excellent hydrogelating properties of a simple synthetic auxin–amino-acid conjugate, naphthalene-1-acetamide of L-phenylalanine (**1-NapF**, $M_w = 333.38$ Da), which gelated water even at 0.025 wt%, thereby making it the most-efficient LMHG known. Optically transparent gels that exhibited negligible scattering in the range 350–900 nm were obtained. A large shift from the theoretical pK_a value of the gelator was observed. The dependence of the minimum gelator concentration (MGC) and the gel-melting temperatures on the pH value indicated the importance of H-bonding between the carboxylate groups on adjacent phenylalanine molecules in the gelator assembly. FTIR spectroscopy of the xerogels showed a β-sheet-like assembly of the gelator. Variable-temperature ^{1}H NMR spectroscopy demonstrated that π stacking of the aromatic residues was also partly involved in the gelator assembly. TEM of the xerogel showed the presence of a dense network of thin, high-aspect-ratio fibrillar assemblies with diameters of about 5 nm and lengths that exceeded a few microns. Rheology studies showed the formation of stable gels. The entrapment of water-soluble dyes afforded extremely fluorescent gels that involved the formation of J-aggregates by the dye within gel. A strong induced-CD band established that the RhoB molecules were interacting closely with the chiral gelator aggregates. H-bonding and electrostatic interactions, rather than intercalation, seemed to be involved in RhoB binding. The addition of chaotropic reagents, as well as increasing the pH value, disassembled the gel and promoted the release of the entrapped dye with zero-order kinetics.

Keywords: amino acids · dyes · gels · hormones · hydrogen bonds

Introduction

Gels contain 3D, continuous- and interpenetrated solid- and liquid phases. Even though the gelation of water is challenging for low-molecular-weight organogelators (LMOGs), a wide variety of hydrogelators have been reported, often based on biomolecules, such as peptides, sugars, and nucleobases.[1–3] These gelators utilize various supramolecular interactions to self-assemble into fibrous aggregates that can entrap and immobilize water.[4,5] Gels that are obtained from low-molecular-weight amino acid derivatives may have important applications in drug delivery because of their controlled-release characteristics and because the peptide building blocks can be degraded enzymatically.[6] The simplified molecular architectures of these gelators allow for their straightforward synthesis and scale-up. There is also a constant impetus to convert drugs and other bioactive molecules into hydrogels.[7–9] The direct application of these hydrogels in biology and materials science provides the necessary fillip for this exploration.[10] A stimulus-responsive gelation process (in which the gel could be unraveled under an external stimulus, such as pH value, enzymes, etc.) offers an added advantage in drug entrapment and controlled release.[11–13]

The assembly of dipeptide and tripeptide-based gels has been extensively studied.[14] Miravet and co-workers performed NMR investigations to highlight the exchange dynamics between discrete gelator molecules and the gel-network in valine-based gelators.[15] They also showed that various additives interacted differently with the gel network. By varying the protecting groups on lysines, Hirst et al. correlated the thermal stability of the gels with the solubility and cooperative assembly of the gelator molecules.[16] A proline-based supramolecular hydrogel exhibited efficient, highly stereoselective, and heterogeneous organocatalysis for the direct aldol reaction.[17] Lysine-based gelators of both organic and aqueous media have been explored in detail by Suzuki and Hanabusa.[18] The release of small (model) drug

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molecules from the gels of *N,N′*-dibenzoyl-L-cystine (DBC) was studied by Friggeri et al.[19] Gels that were derived from *N*-acetyl-L-cysteine were shown to be responsive to redox reactions in addition to changes in pH value and temperature.[20] Simple fluorenylmethoxycarbonyl (Fmoc) derivatives of many amino acids and peptides have also resulted in hydrogelation.[6,21]

Amongst the amino acid derivatives that have been considered, diphenylalanine (FF) has emerged as a potent assembly unit and various FF derivatives have provided access to a range of peptide nanomaterials.[22] Hydrogels that were derived from the self-assembly of Fmoc-FF and Fmoc-protected tripeptide arginylglycylaspartic acid (RGD) have been used for culturing cells by Ulijn and co-workers.[23] This result exemplified the biocompatibility of these gels. The entrapment and release of various biomolecules, such as cytochrome C, salicylic acid, and vitamin B12, from F-based hydrogels have been reported.[24,25] Adams and co-workers studied the controlled release of Naphthol Yellow and Direct Red as model drugs from Fmoc-based hydrogels.[6] They also investigated the gelation ability of naphthalene derivatives of FF.[26]

We have previously reported a tetrameric sugar-based hydrogelator and we have also investigated the interactions of nanoparticles with organogels that were derived from alanine derivatives.[2,27] Herein, we report the exceptional hydrogelating ability of amide conjugate of naphthalene-1-acetic acid and L-phenylalanine (**1-NapF**). Naphthalene-1-acetic acid (1-NAA) is a well-known plant hormone; it is a synthetic auxin that promotes shoot-growth in plants by the elongation of cells.[28] This structurally simple synthetic auxin–amino-acid conjugate acts as a "supergelator" and can gel acidic water at concentrations ≤ 0.025 wt% (equivalent to one gelator molecule holding ≥ 74000 water molecules). This hydrogelation was possible in, and influenced by, the presence of common salts and buffers in aqueous media. The molecular contributors to the gelation process were delineated through various variable-temperature and variable-pH studies. The ensuing transparent gel was used to entrap, and subsequently release, Rhodamine B (RhoB) dye upon exposure to a chaotropic agent or by changing the pH value. RhoB was chosen as a model drug because it allowed "visualization" of its interactions with the gel through spectroscopic techniques.

Results and Discussion

Design of the gelator: The F moiety seemed to be important for gelation because it gave access to π stacking or CH–π interactions through the phenyl side-chain. The simple Fmoc-F only achieved hydrogelation within a restricted pH region.[29] Xu and co-workers prepared many other amide derivatives of F, including the 2-naphthalene acetamide derivative of F that showed striking similarity to the **1-NapF** reported herein, except that the linkage at the naphthalene unit was at the 2-position rather than at the 1-position.[30] In all of these gelators (Fmoc-FF, Fmoc-F, etc.), the aromatic groups provided rotational freedom through an intervening methylene residue. These compounds were often better gelators than their conjugated counterparts, which emphasized the importance of rotational freedom of the aromatic moiety for efficient hydrogelation. Although stacking interactions were undoubtedly important for gelation, the rotational freedom of the aromatic moiety seemed to accentuate the gelation process. This accentuation was presumably due to an expansion of the conformational space for the aromatic rings to achieve the most-optimal packing. Considering these key features, we designed **1-NapF** to have large rotational freedom for the π surface (Figure 1). MM2 energy-minimization studies on **1-NapF** indicated that it possesses a bent L-shape in which intramolecular CH–π interactions were dominant (see the Supporting Information, Figure S1).

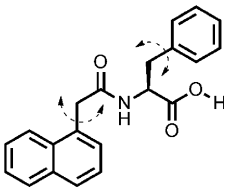

Figure 1. Synthetic auxin–amino-acid conjugate supergelator; rotational freedom (double-sided arrows) of the aromatic residues was possible in **1-NapF**.

Apparent pK_a of the gelator: The titration of a solution of **1-NapF** (10 mM) in dilute NaOH (pH 11) was performed as described earlier by Tang et al.[31] The apparent pK_a of **1-NapF** was about 5.3 (Figure 2), which indicated a significant

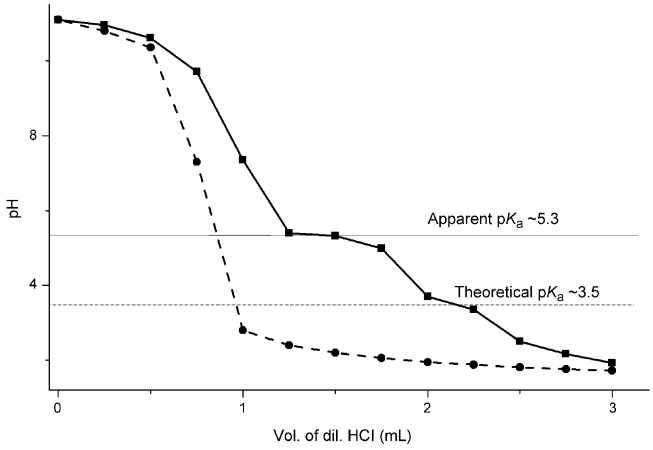

Figure 2. Titration curve for the determination of the pK_a value of **1-NapF**; solid line: 10 mM **1-NapF**, dashed line: H_2O (control). The apparent pK_a value for the gelator was 5.3.

pK_a shift of about 1.8 compared to the theoretical pK_a of N-protected phenylalanine (3.5). As reported by Chen et al., the apparent pK_a value of this class of molecules is strongly dependent on their hydrophobicity, denoted by their logP value.[26] The calculated logP value for this compound was 1.963 and hence the calculated pK_a value was 5.6, which was quite close to the observed value. However, during the titration, the aqueous solution of anionic **1-NapF** started to

become translucent much above the pK_a value (in the pH range 9–7). At a pH value below the pK_a, a white precipitate started to appear and complete phase-separation occurred at pH < 4.5. Based on these observations, we surmised that **1-NapF** molecules started aggregating through the formation of NH–CO H-bonds at higher pH. However, the equilibrium was more towards the solubilized form. As the carboxylate groups became neutralized, aggregation dominated through H-bonding interactions between the NH–CO and the carboxylic acid residues. However, as discussed below, the concentration of **1-NapF** was much higher than the minimum gelator concentrations (MGCs) for **1-NapF**. The high concentration of **1-NapF**, in conjunction with strong stirring, resulted in precipitation.

Gelation properties: Upon addition of **1-NapF** to boiling water, it underwent slow dissolution and the resulting sol cooled to form an optically clear, thermoreversible gel at room temperature with a MGC of $< 0.5\ mg\,mL^{-1}$. However, we observed that, by decreasing the pH value of the aqueous medium to pH ≈ 4 by using dilute HCl, the MGC could be lowered to ≤ 0.025 wt%, which meant that only 1 mg of **1-NapF** could stabilize ≥ 4 mL of dilute HCl solution against inversion. Gelation was only observable at pH values > 3.5, and precipitation of the gelator was observed below this pH value. The MGC values kept increasing with the pH of the medium. The gel-melting temperatures (measured by the tube-inversion method) showed a consequent decrease with an increase in the pH value, thereby indicating a weakening of the aggregation propensity and increased solubility of the gelator as the pH value was increased. These data are summarized in Table 1.

Table 1. MGC and T_m for the hydrogels at different pH values.

pH	MGC[a] [wt%]	T_m [°C][b]
4	0.1	> 80[c]
5	0.1	67
6	0.5	61

[a] Minimum gelator concentration in 0.1 M acetate buffer at a particular pH value; [b] gel-melting temperature at 0.5 wt% in 0.1 M acetate buffer; [c] at pH 4, the gel underwent a lot of sineresis above 80 °C but did not "melt".

A representative UV/Vis spectrum and digital image of the hydrogel is shown in Figure 3. The optical clarity was probably due to the minimal amount of gelator required and to the formation of thin aggregates (as confirmed by TEM, see below). Under these conditions, the scattering grain-boundaries would be very few. Furthermore, there were no chromophores in **1-NapF** that absorbed in the visible region, although the gels absorbed very strongly in the near-UV range (below 325 nm) due to the presence of naphthalene groups in **1-NapF** (for the UV/Vis spectrum of a solution of **1-NapF** in MeOH, see the Supporting Information, Figure S2). Owing to their transparency in the visible-light region, these gels were amenable to spectroscopic investigation, such as UV/Vis and CD spectroscopy, of the entrapped dye (see below).

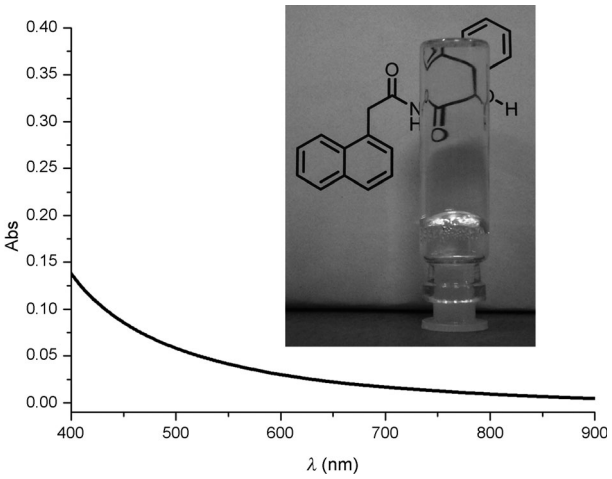

Figure 3. UV/Vis spectrum for the hydrogel in 0.1 M acetate buffer (pH 5); note the low scattering value, even at 400 nm. Inset: image of the resulting transparent gel.

Effect of the salt on the thermal stability of the gels: The thermal stability of the **1-NapF** hydrogels was also investigated in different salt solutions (Table 2). The chosen salts had a common cation (Na^+) and the anions were chosen according to the Hofmeister series wherein ions are arranged according to their efficiency to precipitate proteins.[32] It is known that anions that have higher charge-density (e.g., sulfate) have stronger interactions with water compared to the anions that have lower charge-density (e.g., perchlorate). Thus, above the isoelectric point of proteins, sulfate ions accelerate protein-aggregation and act as kosmotropes whilst perchlorate ions act oppositely as chaotropes to increase the solubility of proteins. The thermal stability of **1-NapF** hydrogels in salt solutions followed the Hofmeister series: the gels melted at higher temperature in the presence of sulfate ions compared to chloride or nitrate ions. The equilibrium between discrete, solubilized gelator molecules and those that were involved in aggregates was shifted in the presence of these salts. The solubility of the gelator was lowered in the presence of sulfate anions (the salting-out effect) and the gel-assembly remained stable, even at higher temperatures.

Table 2. T_m for the hydrogels in different salt solutions at pH ≈ 6.5.

Salt solution	T_m[a] [°C]
Na_2SO_4	> 94
NaCl	85
$NaNO_3$	80
$NaClO_4$	83
H_2O	80

[a] Gelator concentration: 1 mg mL^{-1}, salt concentration: 0.5 M.

Characterization of the hydrogel: *Variable-temperature ^1H NMR spectroscopy*: This study was performed on a gel

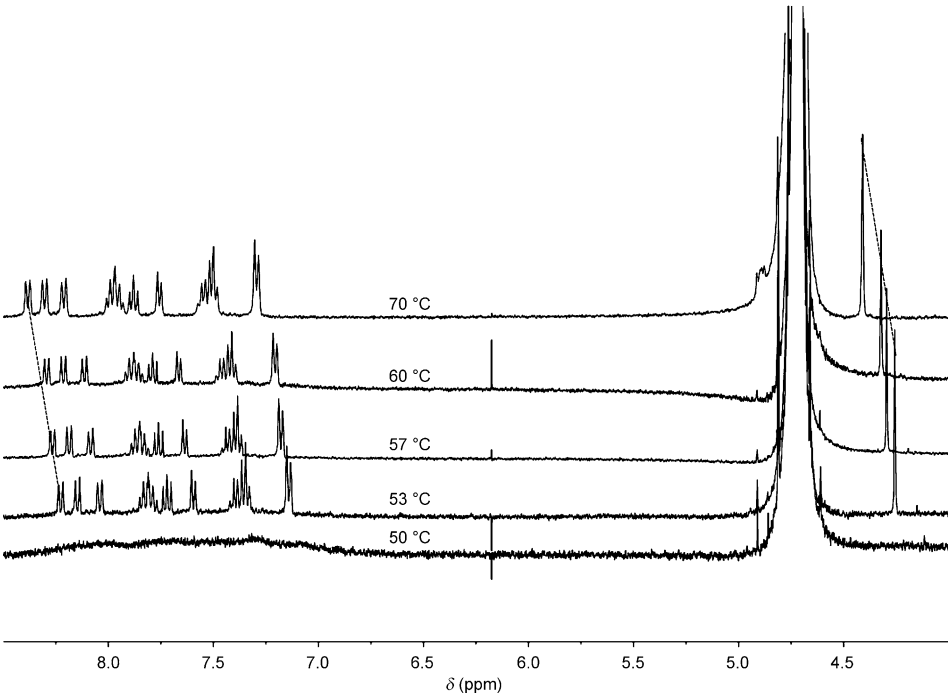

Figure 4. Selected regions in the variable-temperature ^{1}H NMR spectra of the hydrogel; as the temperature increased, a downfield shift was observed for all of the peaks (dashed lines).

sample that was prepared at the MGC in sodium phosphate buffer (pD = 4.5); this gel exhibited a macroscopic "melting" at 52 °C. As a result, the spectra in the gel phase between 25 and 50 °C were too broad to be of use (not shown). Above 52 °C, a sudden sharpness in the peaks was observed (Figure 4). As discussed earlier, there was an equilibrium between the solubilized and aggregated gelator molecules, and the solubility of the gelator increased on increasing the temperature. For the peaks that are highlighted by dashed lines in Figure 4, a uniform downfield shift of $\Delta\delta = 0.009$ ppm °C^{-1} was observed (from $\delta = 8.24$ to 8.40ppm and from $\delta = 4.25$ to 4.40 ppm). This downfield shift was due to de-stacking of the aromatic groups on heating. In the gel state, CH–π interactions between the aromatic groups provided a somewhat-shielded environment around these protons, which unraveled slowly and non-cooperatively upon heating. However, the shifts in the δ values were not as large as those previously observed in other systems.[33] Thus, it was likely that the gelation process involved greater contributions from H-bonding interactions between the carboxylic acid residues, and was assisted by the CH–π interactions of the aromatic groups. Moreover, the two parameters that could disrupt the gel, an increase in the pH value and the use of chaotropic agents, such as urea, indicated a greater role for hydrogen-bonding interactions. Through H-bonding, the **1-NapF** molecules assembled into fibrous assemblies, as observed by TEM.

Transmission electron microscopy: Thin, high-aspect-ratio fibrils were formed by the gelator at pH 5 (Figure 5); the fibrils were about 5 nm in diameter and a few microns long (Figure 5, top). In the bottom image of Figure 5, these fibers formed mesh-like aggregates. However, we were unable to obtain good quality images at high magnification to rule out the possible formation of nanotubes. We believe that the assembly process was similar to the amyloid fibrillation. This premise was supported by FTIR and dye-adsorption studies (see below). However, in our case, the fibrillar assembly was observed at pH values below the pK_a value, in contrast to the work by Tang et al., who observed large flat ribbons with Fmoc-FF under these conditions.[31] The reason for this difference was in the molecular structures of Fmoc-FF and **1-NapF**. Our gelator had a smaller π surface as well as fewer H-bonding elements than Fmoc-

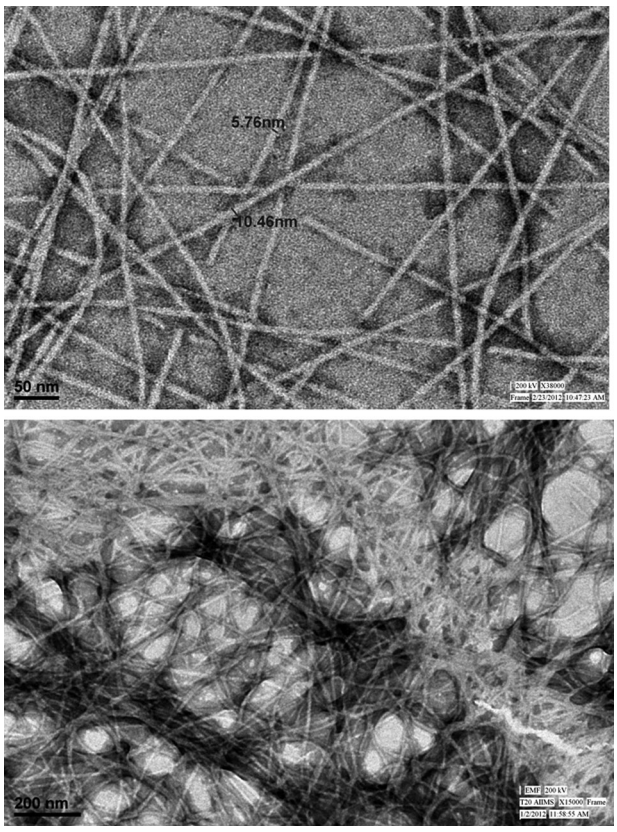

Figure 5. TEM images of gel fibers that were stained with phosphotungstic acid. Top: Thin, high aspect-ratio fibrillar assemblies with diameters of about 5 nm and lengths of a few microns; bottom: a dense mesh of the fibers that entrapped water molecules.

FF. Hence, the propensity to assemble was weaker. As evident from the bottom image in Figure 5, the fibrillar assemblies formed porous mesh-like structures that could entrap water through H-bonding and surface-tension effects. This network-formation by **1-NapF** was further confirmed by the rheology discussed below.

Rheology: The rheological properties of a gel system provide the portfolio for determining its practical utility.[34] With **1-NapF**, the rheology was performed at pH 5 (just below the apparent pK_a). This gel system showed a G′ value that was approximately 10 times larger than G″; this difference remained almost constant up to about 16% strain (Figure 6, top). As the strain was increased beyond this point, both the storage modulus (G′) and the loss modulus (G″) started to fall because intermolecular forces that held the gel together started being overcome by the applied strain and the fibrils were unable to withstand large deformations. The frequency-sweep experiments showed that both the G′ and G″ values were weakly dependent on the frequency (Figure 6, bottom), which was indicative of an entangled network-like system, as corroborated by TEM analysis. The G′ value for the hydrogel from **1-NapF** was about 300 Pa. Also, it was noted in the work by Tang et al. that gels that were formed through the cooling of hot sols were homogeneous but weak; this observation was mirrored in our system too.[31] It has been noted recently that, for Fmoc-FF, the strength of the gel was intimately pH-dependent.[35]

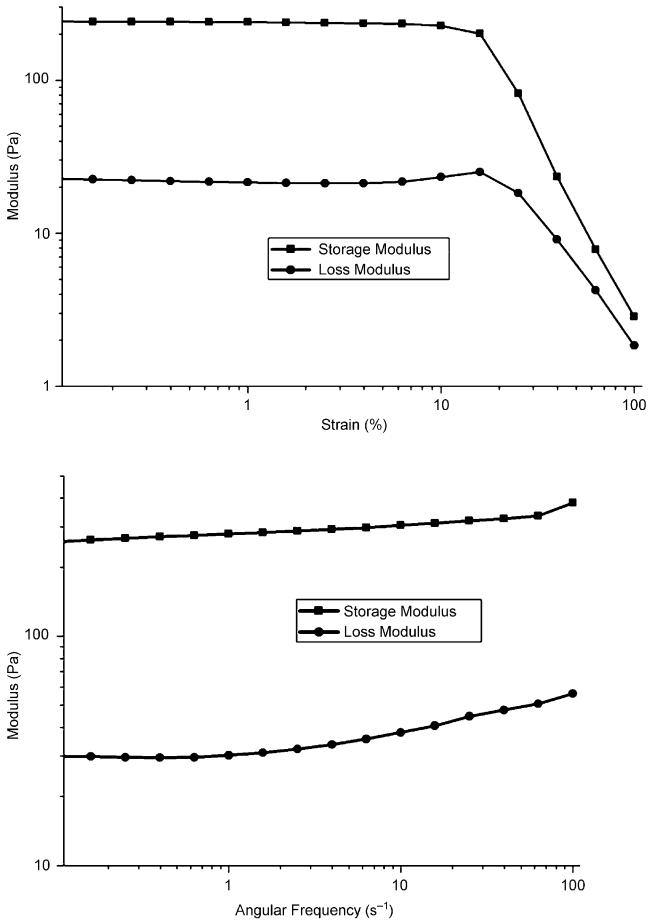

Figure 6. Rheological study of the hydrogel. Top: the amplitude-sweep study shows that the storage modulus ($G' \approx 300$ Pa) was higher than the loss modulus ($G'' \approx 37$ Pa), as expected for gels; bottom: the frequency-sweep study shows the characteristic features of a gel that was formed by an entangled network of fibers.

FTIR spectroscopy: Solid **1-NapF** and the xerogel of **1-NapF** in water and D_2O were also analyzed by FTIR spectroscopy to investigate the H-bonding interactions between the gelator molecules. Figure 7 shows the amide I and amide II bands in the FTIR spectra. It is well-known that the location of the amide I absorption is primarily determined by the conformation of the backbone and is independent of the amino acid sequence.[36] It was observed that, in solid **1-NapF**, the amide I bond resonated at 1661 cm^{-1}, thereby indicating the presence of β-turn-like conformations. However, the xerogel from water showed a bifurcated amide I band with resonances at 1642 and 1618 cm^{-1}. This result indicated that the β-sheet-like conformations were dominating in the xerogel. Furthermore, the amide II band in the xerogel was broadened, which pointed to the presence of both parallel- and antiparallel β-sheet conformations. The xerogel from D_2O also showed a rather broad amide I resonance that was centered at about 1620 cm^{-1}, which also indicated the presence of β-sheet conformations. The rotational freedom of aromatic groups would allow the adoption of a variety of conformations, which was also indicated in the broadness of the amide frequencies of the xerogel. In this regard, the aggregation of **1-NapF** was analogous to the aggregation of tau protein fragments wherein β-sheet-like conformations were observed.

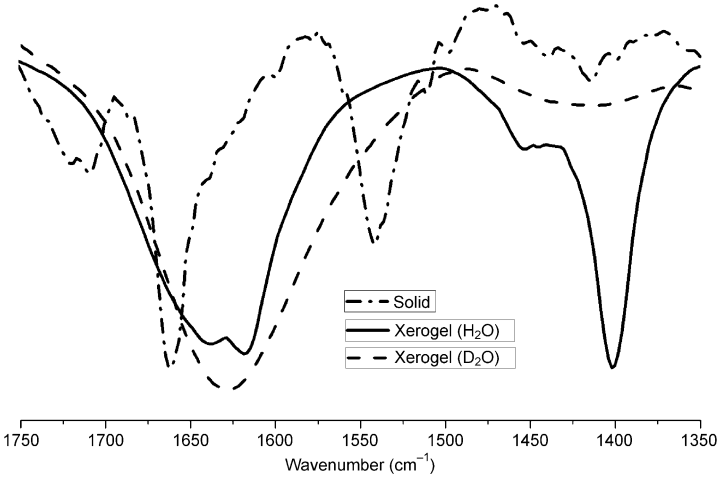

Figure 7. FTIR spectra (amide I and amide II regions) of solid **1-NapF** (dash–dot), the xerogel from H_2O (solid line), and the xerogel from D_2O (dashed line); the spectra were recorded as KBr pellets, which indicated a β-sheet-like structure in the xerogels.

Entrapment of RhoB: When a hot sol of **1-NapF** in acetate buffer was mixed with a solution of RhoB or fluorescein in the same buffer, the resulting sol cooled to form a uniformly-colored, optically clear, highly-fluorescent gel (see the Supporting Information, Figure S5a). The optical clarity of these gels allowed us to probe the interactions between the dye and the gelator molecules through spectroscopic investigations in the visible-light region. We examined whether the entrapment of RhoB was purely physical or whether the dye molecules were interacting chemically with the gelator aggregates. As noted in the NMR study by Miravet and coworkers, entrapped molecules showed interactions with gel fibers.[15]

UV/Vis spectroscopy indicated that the λ_{max} of RhoB in the gel state was red-shifted by about 6 nm compared to the solution state (553 nm in a buffer solution versus 559 nm in the gel, Figure 8). This result was indicative of the formation of J-aggregates. The adsorption of RhoB on solid inorganic

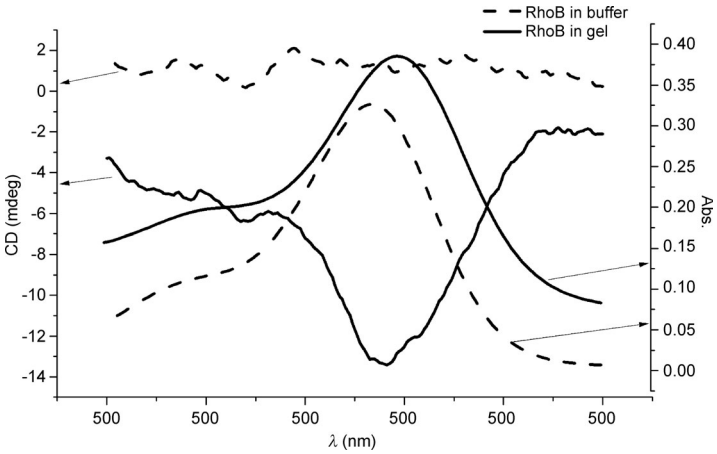

Figure 8. UV/Vis and CD spectra of rhodamine B in the solution state (dashed line) and upon entrapment in a gel (solid line); note the red-shift in the λ_{max} value and the induced-CD band that was formed upon entrapment in the gel.

surfaces is also known to yield J-aggregates.[37] A circular dichroism (CD) study of the gel-entrapped RhoB showed a strong induced-CD band in the region 500–600 nm, in which RhoB is known to absorb (Figure 8). This result further indicated the formation of close chemical interaction between RhoB and the gelator aggregate; as a result, the dye molecules experienced the chiral environment of the aggregate. This observation was reminiscent of the helical assembly of cyanine dye along the polynucleotide template.[38] CD studies were not possible in the UV regions in which the naphthalene and amide groups absorbed owing to extremely high absorptions in these regions.

Confocal microscopy of the gel-entrapped RhoB showed the formation of highly fluorescent assemblies, as expected for J-aggregates. A cottony, fibrous morphology of the aggregate was observed (see the Supporting Information, Figure S5b). However, the melting temperature of the gels did not increase, even with increasing concentration of RhoB. This observation negated the intercalative mode of binding of RhoB in the gel, and was similar to the observation by Rodríguez-Llansola et al. on the thermal stability of gels in the presence of methylene blue.[39] Thus, dye-assembly along the gel aggregate was more likely, owing to H-bonding and electrostatic interactions, as corroborated by the dye-release studies (see below).

The release of the dye from the gel aggregates was investigated by repeated exposure to acetate buffer at pH 5, as well as to a buffer that contained different concentrations of urea (see the Supporting Information, Figure S6). The dye was released from the gel aggregates with a zero-order rate. However, the gel itself dissolved within 24 h when exposed repeatedly to fresh buffer. Degradation of the gel and the consequent release of entrapped dye were accelerated by the presence of urea (a chaotropic agent) in the buffer; it also allowed a faster—but controlled—release of the entrapped dye. The rate of release increased with the concentration of urea, but it still followed zero-order kinetics. Changing the pH value to about 9 also prompted the release of the entrapped material by dissolution of the gel, albeit without any control of the release kinetics. In addition, the presence of salt (0.1 M NaCl) in the buffer also accelerated the release of the dye. Taking all of these observations into consideration, it was clear that H-bonding and electrostatic interactions were involved between RhoB and the gel. Based on these data, a model that indicated the molecular-level interactions between the gelator and the dye molecules was proposed (see the Supporting Information, Figure S7).

Conclusion

We synthesized a structurally simple and extremely efficient hydrogelator, **1-NapF**. This 1-naphthaleneacetyl derivative was about 20 times more-efficient in hydrogelation (MGC $\leq$ 0.025 wt% under optimal conditions) compared to the previously reported 2-naphthaleneacetyl derivative. Optically transparent gels were obtained from **1-NapF**. Gelation was effected at pH $>$ 3.5, and the MGC value increased with the pH value of the medium. A Hofmeister-series-type influence of the added salts was observed on the gel-melting temperatures. H-bonding seemed to be the dominant interaction compared to the aromatic stacking interactions between the gelator molecules, as elucidated by variable-pH and -temperature NMR studies. Gelation involved the assembly of the gelator into high-aspect-ratio fibers, as confirmed by TEM and rheological studies. Entrapment of water-soluble dyes afforded highly fluorescent gels. RhoB formed J-aggregates upon entrapment in the hydrogel and exhibited a strong induced-CD signature. The aggregates of **1-NapF** were easily disrupted by either changing the pH value of medium or by the addition of chaotropic agents, with the latter allowing for a more-controlled disruption. Based on these observations, a model was proposed for the chemical

interactions between the dye and gelator molecules. Because **1-NapF** was prepared from the synthetic auxin 1-naphthalene acetic acid (1-NAA), it may have biological significance that needs further exploration.

Acknowledgements

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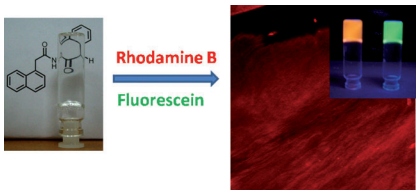
Gels



Flexible gels better: Amide conjugate of 1-naphthaleneacetic acid and L-phenylalanine ($M_w = 333$ Da) was as an exceptional hydrogelator owing to the flexibility of the aromatic residues. The entrapment of fluorescent dyes yielded highly fluorescent gels (see figure).