Published in final edited form as:

Chem Phys Lett. 2013 August 6; 580: 135–140. doi:10.1016/j.cplett.2013.06.055.

Amide I Band and Photoinduced Disassembly of a Peptide Hydrogel

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Abstract

Peptide hydrogels are promising candidates for a wide range of medical and biotechnological applications. To further expand the potential utility of peptide hydrogels, herein we demonstrate a simple yet effective strategy to render peptide hydrogels photodegradable, making controlled disassembly of the gel structure of interest feasible. In addition, we find that the high-frequency amide I' component (i.e., the peak at $\sim 1685\text{ cm}^{-1}$) of the photodegradable peptide hydrogel studied shows an unusually large enhancement, in comparison to that of other peptide fibrils consisting of antiparallel β -sheets, making it a good model system for further study of the coupling-structure relationship.

Introduction

Peptide self-assembly offers a unique opportunity for the engineering of soft materials that are both biologically functional and compatible [1–3]. In particular, the self-assembly process has been exploited to create fibrillar peptide networks, or hydrogels, that are able to swell in the presence of water [4] and, as a result, have been targeted for various biological and biomedical applications, for example as drug delivery systems [5], tissue engineering scaffolds [6], and for uses in the acceleration of hemostasis [7]. Many previous studies have shown that peptide sequences that contain alternating hydrophobic and hydrophilic residues with complementary charge distributions prompt hydrogel formation [8,9]; examples include, but are not limited to, KLD-12 (AcN-(KLDL)₃-CNH₂) [10], RADA-16 (AcN-(RADA)₄-CNH₂) [5], EAK-16 ((AEAEAKAK)₂) [6], EMK16-II ((MEMEMKMK)₂) [11], and (FKFE)_{n=2,3} [12–15]. Moreover, macroscopic hydrogels formed from such peptides typically consist of extensive β -sheet-rich fibrillar networks that are stabilized by both favorable hydrophobic and electrostatic interactions [8,16].

For many applications, it is desirable to possess the ability to control the structural integrity of the hydrogel of interest via one or multiple external stimuli. For example, in controlled drug release applications one would benefit greatly from the ability to precisely control the hydrogel degradation process [17,18]. As such, much effort has been devoted to the generation of 'smart' hydrogels that are responsive to an external factor such as a change in pH [19], temperature [20], salt concentration [21], or other chemical and physical stimuli

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[15,22]. To take advantage of the unique properties of light, several attempts have been made to create photoresponsive hydrogels [18,23–26]. For polymer-based hydrogels, several studies have demonstrated the feasibility of using the photoinduced structural transition of a cross-linker [27], such as an azobenzene group, or the cleavage of a photolabile moiety [28], such as an *o*-nitrobenzyl group, to manipulate the gel-sol transition. To date, only a few studies have explored the utility of photons to trigger formation of peptide hydrogels [24,29,30]. To further extend the potential utility of peptide hydrogels, we herein introduce a new method that employs a photolabile lysine derivative, namely lys(Nvoc) (Nvoc = 4,5-dimethoxy-2-nitrobenzyloxycarbonyl), and light to irreversibly disassemble a hydrogel matrix formed via a peptide whose sequence contains the photocaged amino acid. It has been shown that upon irradiation with near-UV light lys(Nvoc) dissociates to recover the amino acid lysine [31] and *o*-nitrosobenzaldehyde [32], as indicated in Figure 1. Thus, our method is based on the hypothesis that introduction of a charged group into an otherwise hydrophobic region of the peptide matrix is sufficient to perturb the highly ordered balance between intra- and inter-sheet interactions that maintain the structural integrity of the hydrogel matrix, and ultimately facilitate the disassembly of the hydrogel's underlying β -sheet-rich nanofibrillar network. What is more, lys(Nvoc) has previously been tested in live cellular systems, confirming that its photocleavage products do not effect biological activity, furthering its potential utility in biological environments [33,34].

To validate our method, we chose the well characterized, *de novo* designed hydrogel-forming oligopeptide (FKFEFKFE) as our model system. This peptide (hereafter referred to as the KFE8 peptide) has been shown to self-assemble into hydrogels that consist of fibrillar networks of extensive β -sheet structures that are stabilized by both aromatic-aromatic side chain interactions on one face of the β -sheet and favorable electrostatic side chain interactions on the other face [13,16]. Herein, we demonstrate that replacement of two phenylalanine residues in the KFE8 peptide sequence with lys(Nvoc) does not alter the ability of the peptide to self-assemble into a macroscopic hydrogel; however, these mutations render the thus-formed hydrogel photoresponsive. The latter may prove to be exceedingly useful in applications wherein precise spatiotemporal control of hydrogel degradation is required, for example, in the encapsulation and release of therapeutics and other bioactive macromolecules [18].

Experimental

2.1. Materials

D₂O (D, 99.96 %) and deuterium chloride (D, 99.5 %) were purchased from Cambridge Isotope Laboratories (Andover, MA). Fmoc-Lys(4,5-dimethoxy-2-nitrobenzyloxycarbonyl)-OH (Fmoc-Lys(Nvoc)-OH) was purchased from Anaspec, Inc. (Fremont, CA), and used without further purification. Fmoc-protected amino acids were purchased from Advanced Chem Tech (Louisville, KY). Rink amide resin (Subs. = 0.28) was purchased from Novabiochem (San Diego, CA). KFE8 and KFE8-C peptides were synthesized using standard fluoren-9-ylmethoxycarbonyl (Fmoc) chemistry protocol on a PS3 peptide synthesizer (Protein Technologies, Tuscon, AZ), and purified by reverse-phase HPLC (1100 Series; Agilent Technologies, Santa Clara, CA). The identity of the peptides was verified using MALDI-TOF mass spectrometry (Voyager-DE RP, Applied Biosystems, Foster City, CA).

2.2. Sample preparation

Peptides were first dissolved in a 50/50 mixture of 0.1 M deuterium chloride (DCl) in D₂O/ acetonitrile, and the resulting solution was lyophilized overnight, allowing the removal of residual trifluoroacetic acid (TFA) from the HPLC purification, which absorbs in the amide

I' region of the peptide IR spectra. Peptide samples used in the subsequent experiments were prepared by directly dissolving the lyophilized peptide in a D₂O solution with the targeted NaCl concentration (100 mM) and sonicated (20 – 60 minutes) to obtain a homogeneous solution. Samples were left to rest overnight to ensure complete hydrogelation. The pH of all samples was between 2 and 3, measured with an Orion 410A pH meter (Thermo Scientific, Pittsburgh, PA) before gelation. Similarly, the peptide concentration of each sample was measured before NaCl salt was added and gelation was induced. Specifically, the concentration of the photocaged peptide was determined via the absorbance of the cage moiety at 350 nm, using an extinction coefficient of 10,970 M⁻¹ cm⁻¹ [35], while the concentration of the wild-type peptide was determined via the absorbance of phenylalanine residues at 257.5 nm [36,37].

2.3. FTIR measurements

FTIR spectra were collected at 25 °C on a Nicolet Magna-IR 860 spectrometer at a resolution of 4 cm⁻¹. The sample was injected into an assembled CaF₂ cell that was divided into two compartments (one for the reference, and one for the sample), using a homemade Teflon spacer. The reference side contains the NaCl solution (in D₂O) used to prepare the hydrogel sample. This enabled the collection of the sample and reference spectra under identical conditions. An automated translational stage was used to cycle the sample and reference sides into and out of the IR beam, to correct for the slow instrument drift. For each cycle, 8 single-beam spectra were collected on each side, and the final spectra correspond to the average of 32 such cycles. The pathlength of the assembled cell was 52 μm determined via the interference fringes of the empty cell. The spectra were baseline-corrected using instrumental software (OMNIC 6.1a).

2.4. AFM measurements

All AFM experiments were performed in air at room temperature, using a multimode atomic force microscope (Nanoscope IIIa; Digital Instruments, Santa Barbara, CA), equipped with an E-type piezoscanner. 5 μL of sample solution was applied to a freshly-cleaved mica surface for ~5 seconds, rinsed with 300 μL MPW, and subsequently dried with a slow stream of N₂ gas. Tapping-mode imaging was carried out with a silicon probe (TESP) from Veeco (Camarillo, CA). Height and deflection images were obtained with a scan rate of 1 Hz, integral gain of 0.4, and a proportional gain of 0.6. Multiple images were obtained for each sample at different locations on the mica substrate, to confirm either the presence or absence of fibrils.

2.5. Photocleavage measurements

Irradiation of samples was carried out by placing the sample in the optical path of a FluoroLog fluorometer (HORIBA Jobin Yvon), at room temperature. The excitation wavelength was set to 355 nm with a band width of 30 nm (i.e., the excitation slit width was set to 0.75 cm). The intensity of the excitation light at the sample was estimated to be about 8.8 mW cm⁻². To allow for a direct comparison of FTIR spectra and AFM images of the irradiated sample, both the filled FTIR cell and an aliquot of the stock solution (for AFM) were placed together in the optical path of the 355 nm light, and irradiated for a given amount of time.

2.6. Rheological measurements

Rheological measurements were performed on a TA Instruments RFS II rheometer at 25 °C using an 8 mm parallel plate and a gap size of 250 μm. Approximately 24 μL of the aged hydrogel sample (10 mM peptide in 100 mM NaCl D₂O solution) was placed on the stage.

Three frequency sweeps were performed and averaged for each sample after equilibration on the stage.

2.7. Spatial control experiments

An appropriate quantity of lyophilized KFE8-C peptide solid was first dissolved in 110 μL of 200 mM NaCl solution in D_2O to give a final peptide concentration of 4.5 mM. This peptide sample was then sonicated for 1 hour, vortexed for 1 minute, and centrifuged to obtain a homogeneous solution, which was immediately deposited between two plain microscope cover slides separated by a rubber spacer and allowed to equilibrate for approximately 2 hours to facilitate hydrogel formation. A light-blocking mask, designed to allow irradiation of a specific region of the hydrogel, was applied to the outside of the microscope slide. The subsequent photocleavage experiment was carried out following the method described above.

Results and discussion

In order to construct a photoresponsive peptide hydrogel, a phototrigger needs to first be incorporated into the peptide sequence of interest. In addition, this phototrigger must meet the following requirements to be effective in the current application: (1) it does not alter the peptide's ability to form hydrogels, (2) upon absorbing a photon it induces disassembly of the β -sheet structures underlying the hydrogel's nanofibrillar networks, and (3) it should be biocompatible and non-cytotoxic if biological/biomedical applications are envisaged. Based on our recent work on the light triggered disassembly of fibrillar peptide aggregates [35] and the study of Lauffenburger and coworkers [12,13] on peptide hydrogels, we herein chose lys(Nvoc) as the phototrigger and the KFE8 peptide as a model system. Lauffenburger and coworkers [12] have shown that at peptide concentrations between 1–10 mM and salt concentrations >5 mM, the KFE8 peptide readily self-assembles into a macroscopic hydrogel with an underlying nanoscale β -sheet-rich fibrillar network. More importantly, the amphiphilic nature of the KFE8 peptide promotes formation of β -sheets with two distinct layers, namely a hydrophilic layer where negatively and positively charged side chains of adjacent peptides pack together via ionic interactions, and a hydrophobic layer that is stabilized by non-covalent interactions between adjacent non-polar side chains. This pattern of alternating hydrophobic and electrostatic interactions provides an avenue for us to use light and lys(Nvoc), which results in a charged lysine upon excitation with a near-UV photon, to modulate these stabilizing forces and, hence, disrupt the structural integrity of the target peptide hydrogel. Specifically, we replaced the central phenylalanine residues in the KFE8 peptide with lys(Nvoc) with the resulting peptide exhibiting the following sequence: FKK*EK*KFE (where K* represents lys(Nvoc) and the resulting peptide is hereafter referred to as KFE8-C peptide). As KFE8 is known to adopt *in-register* antiparallel β -sheets, the central phenylalanine residues were chosen as the sites of mutation so as to minimize any potential resulting perturbations.

Similar to the KFE8 peptide, we found that at a peptide concentration of 10 mM, the KFE8-C peptide rapidly self-assembles to form a self-supporting macroscopic hydrogel within a few hours. As shown in Figure 2A, the AFM image of an intact KFE8-C hydrogel depicts a network of nanofibers, similar to those reported for hydrogels formed by the wild-type KFE8 peptide [13,38]. In addition, rheological measurements indicate that hydrogels formed by both peptides exhibit similar viscoelastic properties that are consistent with previously reported values (Figure 2B) [38]. In particular, the elastic moduli (G') of both peptide gels are approximately 10-fold higher than the respective viscous moduli (G''), consistent with the notion that the peptide samples have indeed formed rigid hydrogels [38,39]. Taken together, these results indicate that incorporation of lys(Nvoc) into the amino acid sequence of the KFE8 peptide does not alter the propensity of the peptide to self-assemble and

subsequently transition to a gel state, and also suggest that the lys(Nvoc) cages and the adjacent phenylalanine residues cluster into a single aromatic layer as expected for this type of amphiphilic peptides.

Moreover, we employed Fourier transform infrared (FTIR) spectroscopy to help assess the structural characteristics of these peptide hydrogels, as well as the light-induced structural transitions. As shown (Figure 3A), the amide I' band of the KFE8 peptide hydrogel is characteristic of a predominant population of antiparallel β -sheet structures, as evidenced by the two sharp peaks centered at 1620 and 1685 cm^{-1} , which arise from the out-of-phase and in-phase vibrational coupling of the C=O oscillators within the antiparallel β -sheet unit cell, respectively [40,41]. As expected, exposing this sample to 355 nm light for 90 minutes did not change the amide I' profile, indicating that light has no effect on the structural integrity of the KFE8 hydrogel. As indicated (Figure 3B), while the amide I' band of the KFE8-C peptide also shows that it forms antiparallel β -sheets, the high-frequency amide I' component (i.e., the peak at $\sim 1685 \text{ cm}^{-1}$) shows an unusually large enhancement, in comparison to that of the wild-type KFE8 peptide and other peptide fibrils consisting of antiparallel β -sheets. As this band corresponds to the totally symmetric representation of the antiparallel β -sheet unit cell, it is typically only weakly IR active [40,42–46]. While the strongly enhanced absorptivity of the 1685 cm^{-1} component is certainly very interesting, we cannot offer a definitive mechanistic interpretation of this intensity enhancement. One possibility is that it manifests an unusual geometric alignment of the backbone carbonyl oscillators of the constituent β -sheets in the KFE8-C hydrogel, as transition dipole couplings depend on various geometric factors [47,48]. Another possibility is that it arises from exciton couplings involving both the carbonyl group of lys(Nvoc) and the peptide amide groups. To differentiate between these two possibilities, further structural determination and computational simulations are required, which is beyond the scope of the current study. As expected (Figure 3B), irradiation of the KFE8-C hydrogel sample with low-intensity light ($\sim 8.8 \text{ mW cm}^{-2}$) centered at 355 nm, which is derived from the excitation source of a FluoroLog-3 fluorimeter (HORIBA Jobin Yvon), results in the complete disassembly of the underlying β -sheet-rich fibrils, as evidenced by the formation of a broad amide I' band centered at approximately 1650 cm^{-1} , an IR feature typically associated with disordered and monomeric peptide species [49].

To confirm that irradiation with 355 nm light can indeed cause the KFE8-C hydrogel to degrade at a macroscopic level, we carried out additional experiments. As shown (Figure 4A and 4B), after an hour of irradiation (using the aforementioned light source), the KFE8-C hydrogel transforms into a non-viscous solution, further validating the effectiveness of the method. Consistently, the AFM image of this non-viscous solution confirms the absence of any remaining fibrillar structures (Figure 5). Taken together, these results suggest the complete degradation of the peptide hydrogel, stemming from the photoinduced disassembly of the underlying β -sheet-rich fibrillar networks. Further supporting evidence comes from control experiments (Figure 6), which shows that light is ineffective at altering the structural integrity of hydrogels formed by the wild-type KFE8 peptide.

A distinctive advantage of using photons to trigger hydrogel disassembly is that it potentially offers both temporal and spatial control over the degradation process. Such controllability is expected to be useful in many applications, for example, in the targeted delivery of therapeutic drugs or agents and tissue engineering [50]. To demonstrate that the disassembly of the KFE8-C hydrogel can be manipulated with spatial selectivity, we carried out a crude controlled degradation experiment wherein a simple mask was used to allow a designated region of the hydrogel to be illuminated. As shown (Figure 7), the results confirm our expectation that the current photocleavage method indeed provides a convenient means to control hydrogel degradation in a site-specific manner.

Taken together, the results presented above demonstrate the validity of using light to modulate the structural integrity of a model peptide hydrogel. This strategy uses a well-documented photocleavage reaction to produce a charged lysine side chain to disrupt the key hydrophobic interactions underlying gel formation. Since hydrogels formed by other peptides also consist of β -sheet networks that are stabilized by alternating hydrophobic and hydrophilic regions, we expect that the current method can be easily applied to other peptide systems for real-time structural manipulation of the corresponding gel structure. In addition, the major advantage of this method is its controllability, as photons can be delivered with both high spatial and temporal resolutions.

Conclusion

In summary, we demonstrate a novel phototriggering method to control the irreversible degradation of a model hydrogel system, formed by a *de novo* designed oligopeptide, KFE8 [12]. Our working hypothesis is that generation of a charge, via a photochemical reaction, in a strategically important site in the peptide sequence is sufficient to destabilize the peptide hydrogel's underlying nanofibrillar scaffold. Specifically, we chose a well studied, non-toxic, and biocompatible nonnatural amino acid, lys(Nvoc), as the phototrigger, which, upon photocleavage, is converted to a charged lysine. Using secondary structure analysis, microscopic imaging, and rheometric analysis, we confirm that the incorporation of lys(Nvoc) into the KFE8 sequence does not alter the hydrogel-forming propensity of the peptide and also the mechanical properties of the hydrogel thus formed; however, it provides a convenient mechanism of using light to trigger the degradation of peptide hydrogels. More important, the current phototriggering method offers easy control over the spatial and temporal selectivity, an attribute that is invaluable to many applications, as in controlled drug and/or protein release systems, injectable scaffolds for tissue engineering and regenerative medicine, and 3D cell culture [4,18]. Furthermore, we find that the high frequency component of the amide I' band of this photodegradable peptide hydrogel shows a significant intensity enhancement, an attribute worthy of further study.

Acknowledgments

We gratefully acknowledge financial support from the National Institutes of Health (GM-065978) and the National Science Foundation-supported Nano/Bio Interface Center (NBIC) at the University of Pennsylvania. We also thank Anne van Oosten, Prof. Paul Janmey, and the Laboratory for Research on the Structure of Matter (LRSM) at the University of Pennsylvania for assistance with rheological measurements, and Dr. Timothy Wade and the Drexel University Department of Chemistry for assistance with the AFM measurements.

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Highlights

We demonstrate a simple strategy to render peptide hydrogels photodegradable.

This strategy may prove to be especially useful in applications wherein high spatiotemporal selectivity is required.

This photodegradable peptide hydrogel exhibits an unusual amide I band.

Figure 1.
Photochemical reaction scheme of lys(Nvoc), showing the photoproducts.

Figure 2.

(A) AFM image of the KFE8-C hydrogel sample, showing the underlying filamentous peptide network. (B) Comparison of the elastic moduli (G') and viscous moduli (G'') of the KFE8 (filled symbols) and KFE8-C (open symbols) hydrogels, showing that incorporation of lys(Nvoc) does not result in any significant change in the rheological property of the peptide hydrogel.

Figure 3.

(A) FTIR spectra of the KFE8 hydrogel in the amide I' region before and after irradiation with 355 nm light for 90 minutes, showing that light is ineffective in this case to change the peptide and hence the hydrogel structure. (B) FTIR spectra of the KFE8-C hydrogel in the amide I' region before and after irradiation with 355 nm light for 90 minutes, showing that the underlying peptide secondary structure undergoes a β -sheet to disordered conformational transition.

Figure 4.

(A) Picture of a 10 mM KFE8-C peptide sample (in D₂O with 100 mM NaCl), showing that the solution does not flow. (B) Picture showing that after irradiation with 355 nm light for 90 minutes the peptide sample in (A) becomes fluidic.

Figure 5. AFM image of the KFE8-C peptide sample in Figure 3, showing the effectiveness in disassembling the underlying β -sheet network.

Figure 6.
Picture of a 10 mM KFE8 peptide sample (in D₂O with 100 mM NaCl) taken after irradiation with 355 nm light for 90 minutes.

Figure 7.

(A) Picture showing a thin layer of KFE8-C hydrogel (formed with 4.5 mM peptide in 200 mM NaCl D₂O solution) in a home-made sample holder, prior to light irradiation. (B) Picture showing a light-blocking mask placed on (A). (C) Picture showing that after irradiation of (B) with 355 nm light for 30 minutes only the uncovered portion of the hydrogel is degraded.