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Chemically triggered rapid degradation of tetraPEG gels cross-linked with a diacylhydrazine-containing cross-linker

Satsuki Sekiguchi, Takamasa Sakai, Kousuke Tsuchiya*

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Controlling the degradability of cross-linked polymer materials is essential for designing soft materials that combine structural stability during use with on-demand disassembly at the desired time. Herein, we report a chemically degradable tetra-armed poly(ethylene glycol) (tetraPEG) hydrogel cross-linked with a newly designed diacylhydrazine-containing cross-linker. The cross-linker incorporates cysteine residues as reactive sites and a diacylhydrazine moiety as a chemically cleavable unit that undergoes rapid scission in response to sodium hypochlorite (NaClO). The cross-linker exhibited efficient reactivity toward maleimide compounds through thiol-maleimide click chemistry, enabling the formation of a stable tetraPEG network from tetraPEG bearing maleimide end groups. Upon treatment with NaClO, the tetraPEG gel underwent rapid degradation in a concentration-dependent manner. Microscopic analysis further revealed that the squared diameter decreased nearly linearly with time, consistent with a diffusion-limited surface erosion process. The degraded polymer component was almost identical to the original tetraPEG precursor, indicating that network cleavage occurred selectively at the diacylhydrazine units to release soluble tetraPEG chains. These results demonstrate that diacylhydrazine-based cross-linking provides an effective strategy for constructing robust yet chemically degradable hydrogel networks with controllable degradation behavior.

Introduction

Cross-linked polymers such as thermosets and hydrogels are widely used as structurally robust materials in a broad range of applications. Their covalently cross-linked network structures endow them with high mechanical integrity and environmental stability. However, the stable structures hamper the degradation of the materials at a desired time point. Therefore, modulating the degradability of polymeric materials is crucial for regulating material lifetime and end-of-life behavior, particularly in applications where transient or removable soft materials are required.

Dynamic covalent chemistries, including vitrimer-type bond exchange systems, have been extensively utilized for the construction of reconfigurable network platforms, enabling the development of recyclable and self-healing materials.[1-5] Dynamic network structures can facilitate degradation or reprocessing, but may simultaneously compromise long-term material stability because the progressive bond exchange allows continual network reorganization.[6-8] From this perspective, an alternative and complementary strategy is to construct networks with stable covalent bonds that maintain structural integrity during use but undergo rapid and selective scission only when exposed to an external chemical trigger. Recently, we developed cross-linked rubber materials based on polybutadiene with a peptide cross-linker.[9] These materials showed selective degradation at the peptide cross-linking sites. However, the insoluble fraction partially remained after the degradation process, indicating that the more rapid and efficient bond-cleaving reaction is necessary to achieve complete degradation.

Certain reversible bond-forming reactions, such as Diels–Alder cycloaddition, can impart stimuli-responsive rearrangement to otherwise robust polymer networks.[5, 10] However, the reverse reactions often require harsh conditions. For example, the retro Diels-Alder reaction typically demands high temperatures to cleave the covalent bonds. Other cross-linked polymer systems have employed chemically reactive cross-linkers that allow on-demand cleavage of network structures.[11] In this context, we utilized the diacylhydrazine moiety as a chemically-triggered degradable cross-linker for stable covalent bond formation within network structures. The diacylhydrazine moiety has been reported to undergo rapid cleavage under mild conditions with the evolution of gaseous nitrogen in the presence of sodium hypochlorite (NaClO). Kihara et al. have demonstrated that various types of polyamides incorporating the diacylhydrazine backbones exhibited dual characteristics: high material stability (both thermal and chemical) and rapid degradation when exposed to NaClO.[12-14] The diacylhydrazine moiety was also applied to cross-linked polymer systems.[15, 16]

In this study, we developed a novel cross-linker incorporating both diacylhydrazine and cysteine units, where diacylhydrazine functions as a NaClO-triggered degradable unit while the cysteine residues provide reactive sites for cross-linking. The amino-acid-derived amide linkages are expected to contribute to the structural stability of the cross-linked network,[9, 17] while the diacylhydrazine unit is readily cleaved in response to chemical stimuli mediated by NaClO. As a cross-linked polymer system, we selected hydrogel materials based on tetra-armed poly(ethylene glycol) (tetraPEG) bearing maleimide termini because tetraPEG hydrogels provide a well-defined uniform platform for evaluating network formation and degradation behavior.[18-20] Controlling the degradation behaviour of the tetraPEG-based hydrogels is important for applications

[a] Department of Chemistry and Biotechnology, Graduate School of Engineering, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8656, Japan.
† Footnotes relating to the title and/or authors should appear here.
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including biomedical materials.[21-24] In particular, soft materials that can maintain their function during use and then degrade or be removed at an appropriate time are of considerable interest for bioadaptive and temporary biomedical applications, such as tissue sealants, wound dressings, drug-delivery matrices, and scaffolds. Using this system, we successfully demonstrated efficient tetraPEG gel formation via thiol-maleimide click chemistry and the rapid degradation of the resulting hydrogel in response to NaClO even at extremely low concentrations. This work establishes a chemically triggerable tetraPEG hydrogel platform in which stable covalent cross-links are rapidly and selectively cleaved by NaClO, leading to diffusion-limited surface erosion and near-quantitative release of intact tetraPEG chains.

Experimental

Materials

Four-armed PEG (weight-averaged molecular weight M_w = 20,000 g mol^{-1}) with maleimide-functionalized termini (tetraPEG-MA) was purchased from SINOPEG Biotech Co., Ltd. (Fujian, China). Adipic dihydrazide was purchased from Tokyo Chemical Industry Co., Ltd. (Tokyo, Japan). (*R*)-3-(*tert*-Butoxycarbonyl)thiazolidine-4-carboxylic acid (Boc-Thz-OH) was purchased from Combi-Blocks Inc. (San Diego, CA, USA). 1-[3-(Dimethylamino)propyl]-3-ethylcarbodiimide (EDC) hydrochloride salt was purchased from Watanabe Chemical Industries Ltd. (Hiroshima, Japan) and used as received. Methoxyamine hydrochloride salt was purchased from Sigma-Aldrich (St. Louis, MO, USA). The other chemicals were purchased from FUJIFILM Wako Pure Chemical Co. (Osaka, Japan) and used as received without purification unless otherwise noted.

Analysis

The ^{1}H and ^{13}C NMR spectra of the synthesized compounds were recorded on a JNM-ECX400 (JEOL Ltd., Tokyo, Japan) at 25 °C at 400 MHz and 100 MHz, respectively. The samples were dissolved in deuterated dimethyl sulfoxide (DMSO-d_6) or deuterium oxide (D_2O) and tetramethylsilane (TMS) was used as an internal standard. UV-visible absorption spectra were recorded on a V-670 spectrophotometer (JASCO, Tokyo, Japan) at 25 °C. The sample solutions were poured into a plastic cell with an optical length of 10 mm. Optical microscopic observation was performed using Leica M165 C (Leica Microsystems GmbH, Wetzlar, Germany) at 25 °C. Gel permeation chromatography (GPC) was performed on a Nexera series with a system controller SCL-40 (Shimadzu Corporation, Kyoto, Japan). The samples were eluted with 0.1 M $NaNO_3$ aqueous solution and a flow rate of 1.0 mL min^{-1} using a Shodex column SB-803HQ (Resonac, Tokyo, Japan). The chromatogram of each sample was detected by a RI detector RID-20A and a photo diode array detector SPD-M40 (Shimadzu Corporation), and the number- (M_n) and weight-average molecular weight (M_w) were calculated by LabSolution software using poly(ethylene glycol) standards. Matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometric analysis was conducted using an ultrafleXtreme MALDI-TOF spectrophotometer (Bruker Daltonics, Billerica, MA) operating in a linear positive mode at an accelerating voltage of 15 kV. The sample was dissolved in water/acetonitrile (0.8 mg mL^{-1}) containing 0.1% TFA mixed with a solution of α-cyano-4-hydroxycinnamic acid (CHCA) in water/acetonitrile (10 mg mL^{-1}) and deposited on a target plate.

Synthesis of diacylhydrazine cross-linker (DCH)

A solution of EDC HCl salt (0.7076 g, 0.37 mmol) in chloroform (15 mL) was added to a solution of Boc-Thz-OH (0.8610 g, 0.37 mmol), adipic dihydrazide (ADH, 0.3215 g, 0.19 mmol), and triethylamine (0.5120 mL, 0.37 mmol) in chloroform (25 mL) in a round-bottom flask equipped with an addition funnel at −10 °C under argon. The resulting solution was stirred at 25 °C for 12 h. The precipitate was then separated by suction filtration. The filtered solid was washed with chloroform and water, and dried under vacuum to give Boc-Thz-modified ADH (**1**) as a white solid. The yield was 0.1734 g (15.5%).

The crude product of **1** was then dissolved in trifluoroacetic acid (TFA, 2 mL). After stirring at 25 °C for 3 h, the solvent was removed by vacuum distillation. The resulting solid was poured into diethyl ether, and the precipitate was filtered and dried to give Thz-modified ADH (**2**) as a white solid. The yield was 0.1128 g (97%).

The product **2** (0.1100 g, 0.027 mmol) was then dissolved in methanol/water (2/1, 30 mL) and methoxyamine HCl salt (0.2290 g, 0.27 mmol) was added to this solution. After stirring at 25 °C for 12 h, the precipitate was removed by suction filtration. The filtrate was then concentrated by a rotary evaporator. The crude product was dispersed in acetone (30 mL), and stirred at 25 °C for 12 h. The precipitate was filtered and dried under vacuum to give a cross-linker DCH as a white solid. The yield was 0.048 g (46%). ^{1}H NMR (400 MHz, D_2O, 25 °C, ppm): δ 4.31 (t, *J* = 8 Hz, 2H), 3.11 (d, *J* = 8 Hz, 4H), 2.37 (m, 4H), 1.66 (m, 4H). ^{13}C NMR (100 MHz, D_2O, 25 °C, ppm): δ 175.52, 167.51, 53.45, 32.97, 24.87, 24.18. MS (MALDI-TOF): *m/z* calcd for $C_{12}H_{25}N_6O_4S_2$ $[M+H]^+$: 381.137, found 381.139.

Model reaction with *N*-ethylmaleimide

To an NMR tube were added DCH (8.2 mg, 21.6 μmol) and D_2O (0.6 mL) and the mixture was vortexed until DCH was completely dissolved. *N*-Ethylmaleimide (6.7 mg, 54.0 μmol) was added to this solution in the NMR tube and the mixture was agitated using ThermoMixer C (Eppendorf, Hamburg, Germany) at 25 °C and 800 rpm. The reaction progress was monitored via ^{1}H NMR spectroscopy at 5, 10, 20, and 30 min intervals. The chemical structure of the reaction product was elucidated using ^{1}H–^{1}H COSY and ^{13}C NMR spectroscopy.

Preparation of tetraPEG gel using DCH

TetraPEG-MA and DCH were separately dissolved in citrate-phosphate buffer (0.1 M, pH 3.4). The concentration of

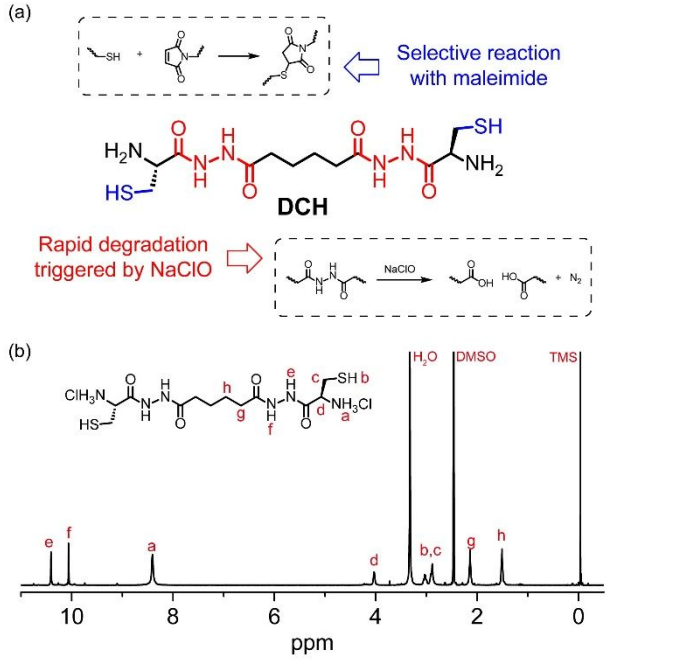
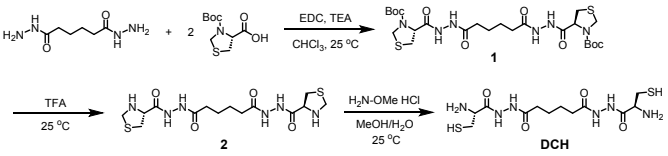


Figure 1. (a) The chemical structure of degradable cross-linker DCH containing thiol and hydrazide moieties and (b) ^{1}H NMR spectra of DCH hydrochloride salt in DMSO-d_6.



Scheme 1. Synthetic route of degradable cross-linker **DCH**.

tetraPEG-MA was 40 g L^{-1}, and the amount of DCH was adjusted so that thiol groups were equimolar to the maleimide groups (1.0 equiv.). The DCH solution was mixed with the tetraPEG-MA solution and the resulting mixture was stirred for 30 s and defoamed for 10 s by a Rotation and Revolution Method Mixer (Awatori Rentaro, THINKY Corporation, Tokyo, Japan). A PTFE tube (diameter: 1.0 mm) was filled with the solution using a syringe and left overnight (12 h) until the gelation was completed. The gel was pushed out from the PTFE tube by syringe. The resulting cylindrical tetraPEG gels were 1.0 mm in diameter and 10 mm in length (initial state), and directly used for the degradation test without further treatment.

Degradation test in the presence of NaClO

The NaClO solution (initial concentration: 5 wt%) was used for the degradation test of the tetraPEG gels. The concentrations of NaClO solution used in this experiment were 5, 1, 0.5, 0.25, 0.1, 0.05, 0.025, and 0.00625 wt%. The freshly prepared cylindrical tetraPEG gel was placed in the center of a petri dish and NaClO solution (2 mL) was poured on the tetraPEG gel. The time course of degradation behavior of the tetraPEG gel was then monitored by stereomicroscopic observation. In the case of time course experiment, the size (diameter d of the cylindrical gel) of the cylindrical tetraPEG gel was measured at each time point to evaluate the squared diameter d^2 at time t, which is proportional to the cross-sectional area of the cylindrical gel.

Results and discussion

Synthesis of degradable cross-linker

The thiol group of cysteine is highly reactive with various electrophiles and serves as a key moiety for bioorthogonal reactions with a maleimide group. To combine the selective reactivity of Cys and rapid degradability, we designed a diacylhydrazine-based cross-linker containing two Cys residues at both ends (Figure 1a). The diacylhydrazine-based cross-linker (DCH) was synthesized by solution phase coupling of adipic dihydrazide with L-thioproline followed by sequential deprotection (Scheme 1). Boc-protected condensate (**1**) of adipic dihydrazide with two Boc-Thz-OH was synthesized using a condensing agent EDC, and the Boc groups were then assignable to α and β-protons of Cys residues appeared at 4.0 and 2.9 ppm, respectively, whereas the signals assignable to hydrazide protons were observed at 10.1 and 10.4 ppm. In addition, the peaks corresponding to the *tert*-butyl group and methylene protons of the thioproline moiety completely disappeared. Therefore, the synthesis of DCH containing thiol and hydrazide groups was clearly confirmed. DCH showed high

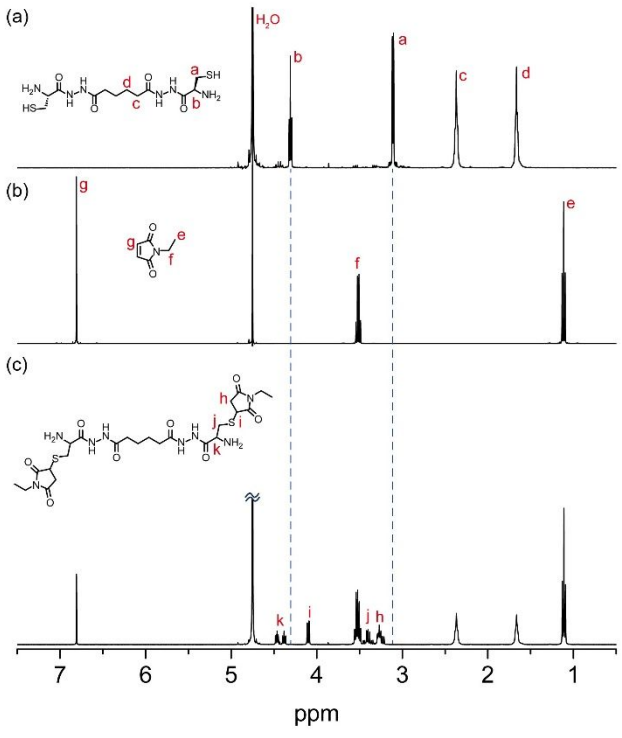


Figure 2. Model reaction of DCH with *N*-ethylmaleimide. ^{1}H NMR spectra of (a) DCH, (b) *N*-ethylmaleimide, and (c) the mixture of DCH and *N*-ethylmaleimide after 5 min reaction in D_2O.

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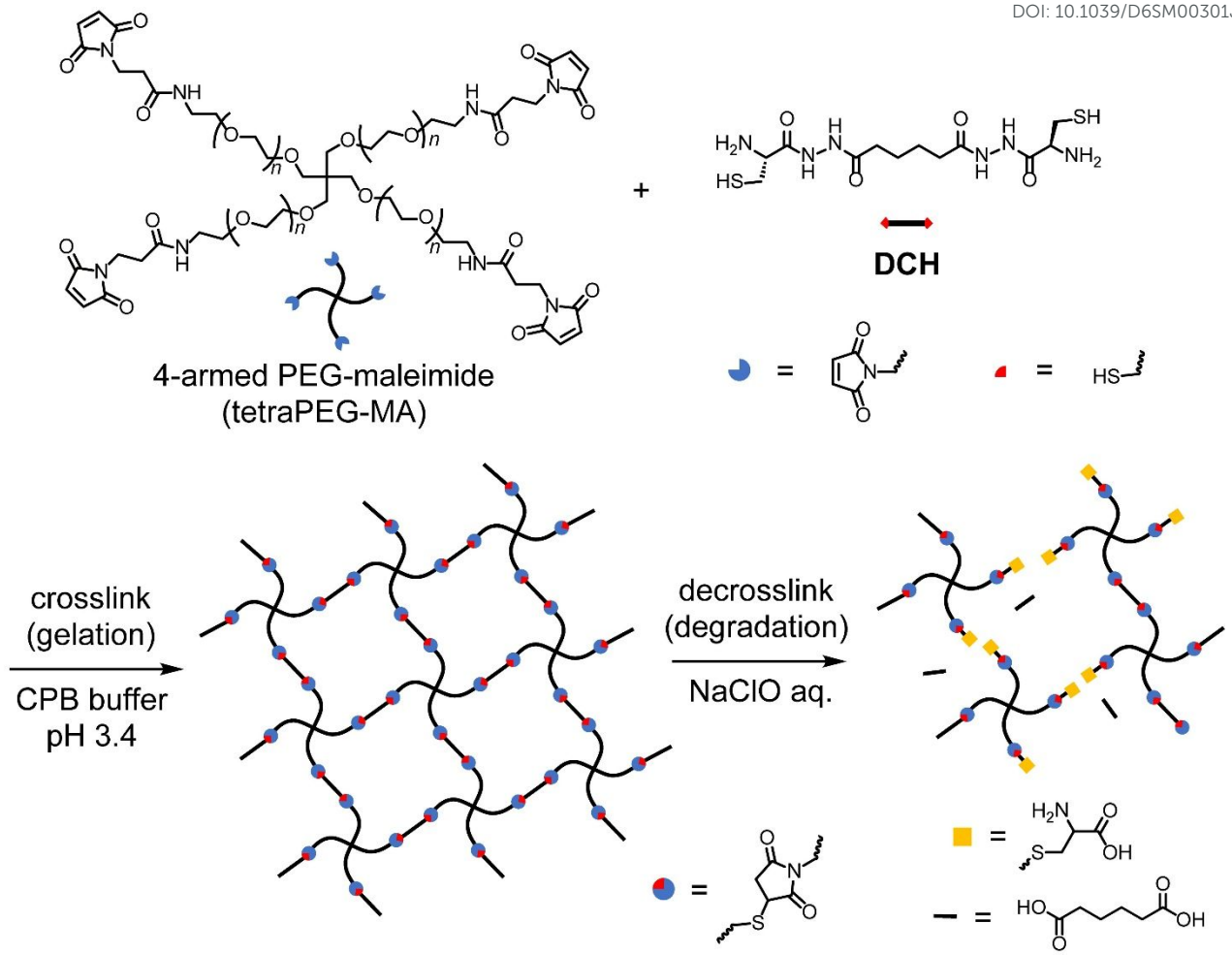

Figure 3. Fabrication of tetraPEG gel via cross-linking tetraPEG-MA with DCH and NaClO-triggered degradation.

solubility in water and aqueous buffer solutions and, therefore, can be used as a cross-linker for hydrogel preparation.

Model reaction for cross-linking

Thiol groups can rapidly and selectively react with maleimide groups to form stable thioether linkages.[25] We investigated the availability of DCH as a cross-linking agent by a model reaction using *N*-ethylmaleimide. The aqueous solution of DCH was mixed with the solution of excess *N*-ethylmaleimide (2.5 equiv. to DCH) in D_2O, and the reaction was directly monitored by ^1H NMR spectroscopy (Figure 2). DCH showed two signals corresponding to the a and b protons of Cys at 4.3 and 3.2 ppm in D_2O, respectively (Figure 2a). Upon the addition of *N*-ethylmaleimide to the DCH solution, these signals vanished immediately within 5 min, while new signals emerged at 3.3–3.5 and 4.4 ppm (Figure 2c). The characteristic signal of protons of the maleimide moiety at 6.8 ppm also decreased, indicating that the thiol groups of DCH had reacted with the double bond of *N*-ethylmaleimide. The assignment of the signals in combination with ^1H–^1H COSY and ^{13}C NMR spectroscopy revealed that the thioether compound bearing amino groups was obtained quantitatively (Figure S1 and S2). Given the efficient reactivity of DCH, we employed it as a cross-linking agent for gel preparation.

Gel preparation using 4-arm PEG and DCH

Tetra-armed PEG hydrogels (tetraPEG gel) with precisely controlled branching were synthesized by mixing tetra-armed PEG precursors functionalized with reactive terminal groups such as thiols or maleimides. The distinct homogeneous network structures of the tetraPEG gels have been extensively utilized for mechanistic analyses of the gel network formation/degradation. We fabricated the tetraPEG gel from tetra-armed PEG functionalized with maleimide termini (tetraPEG-MA) with DCH in an aqueous buffer (Figure 3).[26] To control the gelation rate and promote homogeneous network formation, we carried out the reaction under acidic conditions. After mixing the DCH solution with the tetraPEG-MA solution in 100 mM citrate–phosphate buffer at pH 3.4, the solution was solidified within 12 h. The reaction rate between thiol and maleimide groups was determined by monitoring the disappearance of maleimide groups using UV-vis absorption spectroscopy (Figure 4). The absorption peak at 295 nm, characteristic of the maleimide groups in tetraPEG-MA, decreased in intensity after the reaction with DCH. The

absorption peak assignable to the maleimide groups almost disappeared after 12 h at a thiol/maleimide ratio of 1/1, thereby confirming the nearly complete consumption of the maleimide groups. These results indicate that the thiol-maleimide reaction proceeded nearly quantitatively under the gelation conditions, producing a tetraPEG network in which the DCH-derived diacylhydrazine units were incorporated into the cross-linking segments. The resulting tetraPEG gel was stable in water and its equilibrium degree of swelling was 4.5, which is relatively higher than that of authentic tetraPEG gels prepared under similar conditions. This is likely due to the presence of multiple amino groups derived from the cross-linker DCH, which may introduce ionic effects that enhance swelling.

NaClO-triggered degradation of tetraPEG gel

The tetraPEG gel prepared using DCH contains diacylhydrazine linkages between the branching points, which are labile to NaClO-mediated cleavage. We treated the tetraPEG gel with NaClO aqueous solutions of various concentrations to investigate the degradation behavior (Figure 5a). To visualize the degradation process, we fabricated a cylindrical tetraPEG gel (diameter: 1 mm, length: 10 mm) and the degradation was monitored by microscopic observation. Commercially available NaClO solution is typically ca. 5 wt%, and the tetraPEG gel was immediately dissolved at this concentration, indicating that degradation proceeded from the surface (Movie S1). The rapid surface degradation was observed in diluted NaClO solutions, and the cylindrical gel gradually decreased in its diameter, as shown in the snapshots in Figure 5b (Movie S2). The tetraPEG gel was completely dissolved within 2 min when treated with 1 wt% NaClO. Notably, bubble formation was observed during degradation of the tetraPEG gel (Movie S2), indicating that the cleavage of diacylhydrazine units proceeded in the reported NaClO-mediated manner with concomitant evolution of gaseous N_2.

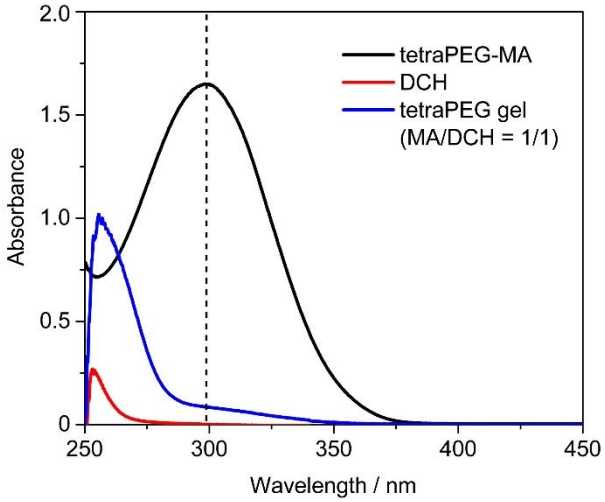

Figure 4. UV-vis absorption spectra of tetraPEG gel obtained via cross-linking tetraPEG-MA with DCH at MA/DCH = 1/1.

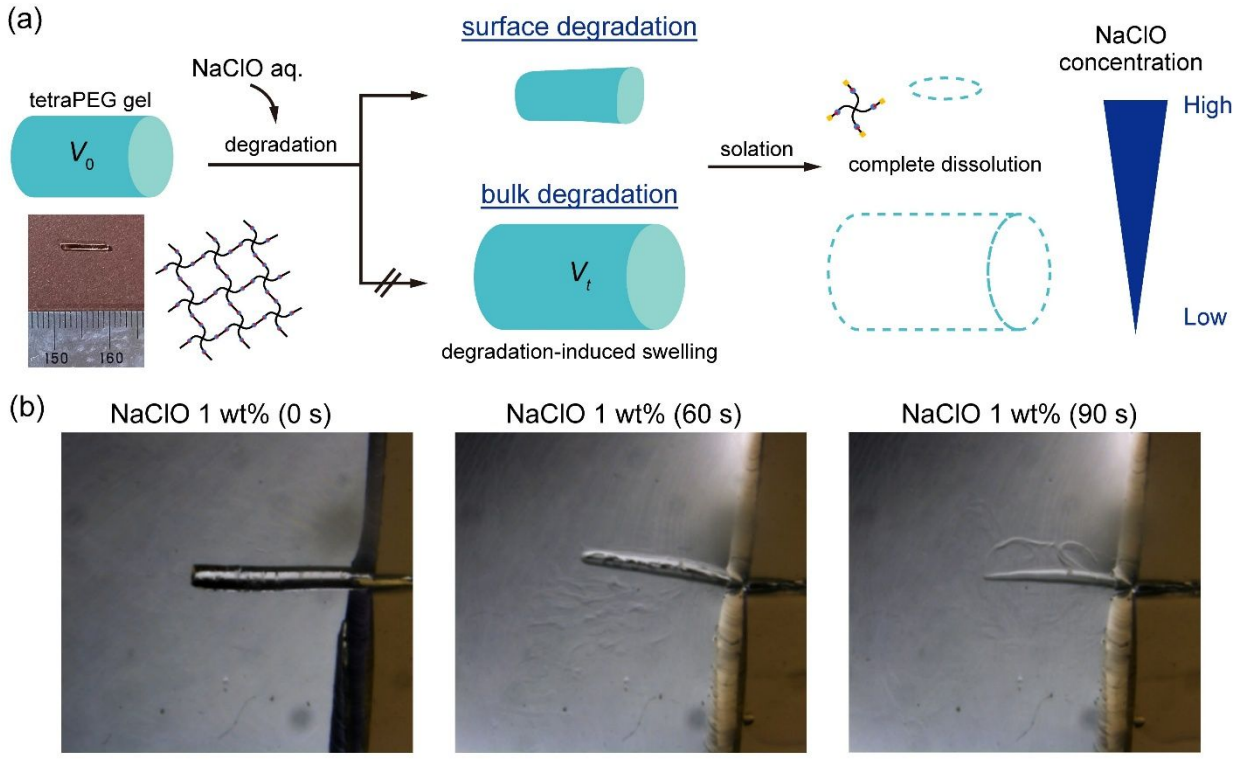

Figure 5. (a) NaClO-mediated degradation of cylindrical tetraPEG gel prepared from tetraPEG-MA and DCH. The tetraPEG gel was degraded via rapid surface degradation at high concentrations of NaClO. (b) Microscopic snapshot images of cylindrical tetraPEG gel in the 1wt% NaClO solution.

Bulk degradation is generally expected when the penetration of the degrading agent into the gel is faster than the cleavage of network junctions. In that case, bond scission proceeds throughout the sample, leading to a gradual decrease in the elastic modulus and the concomitant swelling that is commonly observed for bulk-degrading hydrogels.[27] In contrast, when cleavage of the degradable units is much faster than the inward transport of the reagent, degradation is confined to a thin region near the gel/solution interface, and the sample erodes predominantly from the surface.

To distinguish between these two regimes, we examined the degradation of cylindrical tetraPEG gels in NaClO solutions of various concentrations (Figure 6a). The complete dissolution time increased monotonically with decreasing NaClO concentration, but notably, no appreciable swelling characteristic of bulk degradation was observed even at the lowest concentrations that still caused dissolution. Surface degradation was detectable down to 0.00625 wt% NaClO, whereas neither dissolution nor swelling was observed below 0.003 wt% (Table S1). At extremely low NaClO concentrations, the adipic acid liberated during degradation may affect the reaction, although its concentration remains very low (up to 2 μM). These results suggest that, in the present system, cleavage of the diacylhydrazine units remains sufficiently rapid even under highly dilute conditions, so that the overall degradation behavior is controlled primarily by the transport of NaClO into the gel rather than by the intrinsic bond-cleavage kinetics. Notably, an authentic tetraPEG gel without diacylhydrazine linkers, prepared by tetra-armed PEGs bearing maleimide and thiol terminal groups, showed no degradation in the presence of NaClO except at the highest concentration tested (5 wt%). The authentic tetraPEG gel gradually dissolved in 5 wt% NaClO solution after prolonged incubation (> 24 h), likely because the strong basicity of the NaClO solution caused hydrolysis of the maleimide-derived linkages.

We analyzed the time course of degradation in 0.25 wt% NaClO by monitoring the diameter, d, of the cylindrical gel. For a cylindrical specimen, d^2 is proportional to the cross-sectional area and therefore serves as a convenient measure of the amount of remaining gel. If degradation proceeds predominantly from the outer surface under diffusion-limited conditions, the loss of gel should be reflected in an approximately linear decrease in d^2 with time. Indeed, the measured d^2 value decreased nearly linearly during the degradation process. (Figure 6b). This result supports a surface-erosion mechanism in which NaClO is consumed rapidly at or near the gel surface, while its transport from the surrounding solution determines the overall degradation rate. Collectively, these results indicate that the NaClO-mediated reaction of diacylhydrazine units is sufficiently rapid to drive the surface degradation even under highly dilute conditions.

The degradation products of the tetraPEG gel containing DCH moieties were further analyzed by gel permeation chromatography (GPC) measurement after NaClO treatment (Figure 7). The pristine tetraPEG-MA used for gel formation exhibited a sharp, unimodal peak at 7.8 min with the M_n and the dispersity (M_w/M_n) estimated to be 17,800 and 1.05,

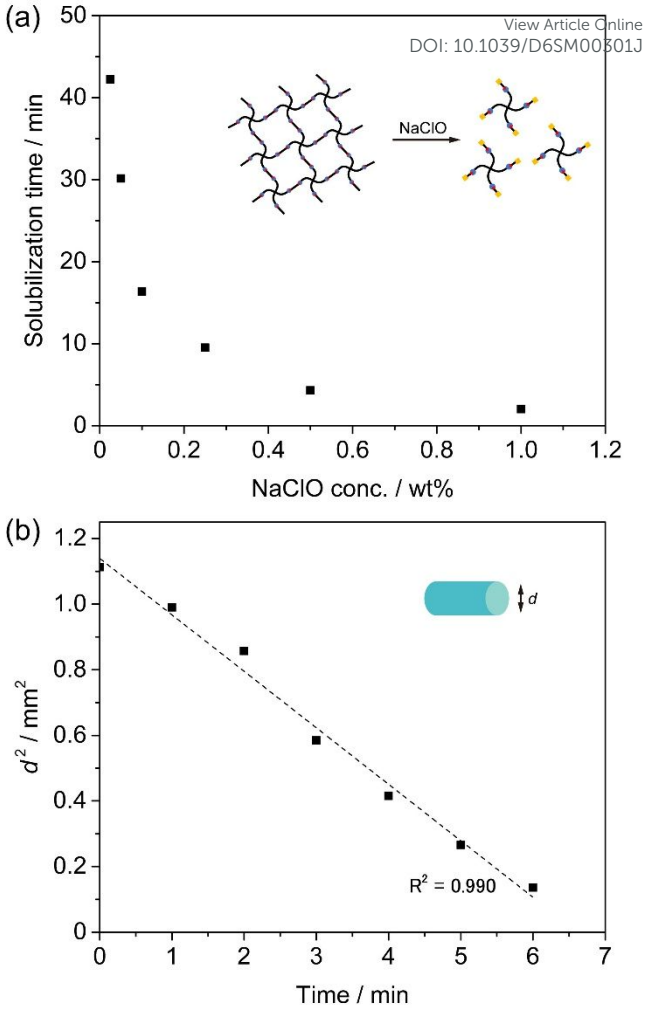

Figure 6. (a) Effect of NaClO concentration on the solubilization time of the cylindrical tetraPEG gel, and (b) time course of the surface area (d^2) of the cylindrical tetraPEG gel in NaClO (0.25 wt%) solution at 25 °C.

respectively. After degradation of the tetraPEG gel with 1.0 wt% NaClO, the solubilized product was directly subjected to the GPC measurement. The resulting degradation product showed a unimodal peak profile comparable to that of tetraPEG-MA. The M_n and M_w/M_n of the degradation product were 16,200 and 1.07, respectively. Minor peaks were also observed in the low-molecular weight region at around 9.5 min, which were mainly attributed to adipic acid derived from DCH units. The GPC profile of the polymeric component in the degradation product were almost identical to that of the original tetraPEG-MA, indicating that the NaClO-mediated cleavage of diacylhydrazine units efficiently liberated the tetraPEG-derived soluble chains with minimal alteration of the polymer backbone and without any obvious high-molecular-weight residual networked fraction.

Conclusions

In summary, we synthesized a new diacylhydrazine-based cross-linker, DCH, as a cross-linking agent for hydrogel formation. The

cysteine moieties of DCH could be utilized as efficient reactive sites via thiol-maleimide click chemistry. The tetraPEG-based

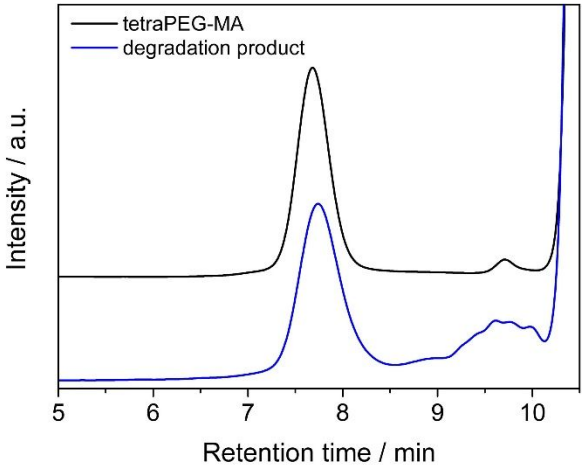

Figure 7. GPC chromatograms of pristine tetraPEG-MA (black) and the degradation product of tetraPEG gel by 1 wt% NaClO treatment (blue).

hydrogel was successfully prepared by reacting a tetra-armed PEG derivative bearing maleimide termini with DCH in aqueous media. The resulting tetraPEG gel underwent rapid degradation when exposed to NaClO, with the decomposition time directly correlating with the NaClO concentration. Notably, degradation was observed even under dilute NaClO conditions, and microscopic time-course analysis of cylindrical gels indicated that degradation proceeded via a diffusion-limited surface erosion mechanism, consistent with rapid cleavage of the DCH units. Thus, the present system achieves both network stability before triggering and efficient de-cross-linking after chemical stimulation. Given that sodium hypochlorite is used at relatively low concentrations as a disinfectant, the present NaClO-responsive degradation system may provide a useful basis for designing soft materials and biomaterials that integrate antibacterial treatment with triggered disassembly. These findings demonstrate that diacylhydrazine-based cross-linking is a promising molecular design strategy for robust polymer networks requiring on-demand dissolution, and they provide a useful framework for the development of chemically triggered transient soft materials.

Author contributions

Conceptualization, K.T.; methodology, K.T.; formal analysis, S.S.; investigation, S.S.; writing—original draft preparation, K.T. and S.S.; writing—review and editing, K.T., S.S. and T.S.; supervision, K.T. and T.S.; project administration, K.T. and T.S.; funding acquisition, K.T. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

Data availability

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All data generated or analysed during this study are included in this published article and its supplementary information files, and are available from the corresponding author on reasonable request.

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Data availability

All data generated or analysed during this study are included in this published article and its supplementary information files, and are available from the corresponding author on reasonable request.