

Structural reorganization and crack-healing properties of hydrogels based on dynamic diselenide linkages

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ABSTRACT

We report the dynamic behavior of diselenide-containing hydrophilic polyurethanes and hydrogels based on diselenide exchange reactions in an aqueous media. Diselenide-containing linear and cross-linked polyurethanes were synthesized via polyaddition reactions using diselenide-containing diol in combination with pyridinium diol that enhances the hydrophilicity of the polymer chains. The obtained linear polyurethanes underwent photo-induced diselenide exchange reactions with small diselenide compounds and degraded to smaller fragments, confirming the dynamicity of the obtained hydrophilic polyurethanes. The prepared hydrogels displayed characteristic large swelling behavior based on the structural reorganization through diselenide exchange either under photo-irradiation at 365 nm or even in the dark at room temperature. The diselenide-containing hydrogels also showed crack-healing behavior under the same exchanging conditions, presenting the utility of diselenide linkages as simple and useful units to offer high dynamicity to hydrogels.

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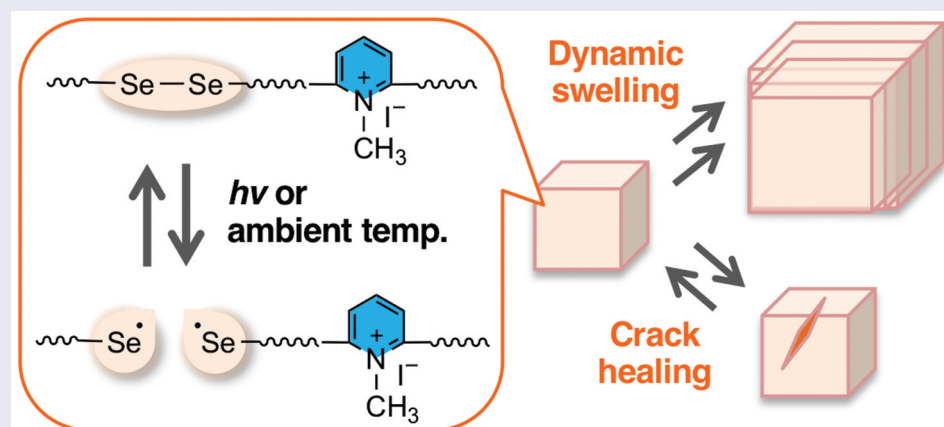
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Introduction

Hydrogel is a versatile platform of biocompatible materials with its water-rich composition and softness, and the ones with stimuli-responsive functions have particularly attracted an increasing attention for the application in such as drug delivery [1,2], gene transfection [3–5], tissue engineering [6,7], and artificial muscles [8–10]. One of the powerful tools for the functionalization of hydrogels is dynamic covalent bonds (DCBs) [11–15], which can reversibly exchange under certain environmental conditions while they act as covalent bonds without those stimuli and thus more robust than common non-covalent supramolecular interactions. To date, a variety of DCBs have been

demonstrated such as esters [16], olefins [17,18], Diels–Alder adducts [19,20], alkoxyamines [21–23], disulfides [24–27], imines [28,29], boronic esters [30–32], and others [33,34], and they can afford hydrogels with intelligent functions such as stimuli-induced degradation [26] and self-healing ability [27,30,35].

One of the attractive DCB candidates for the hydrogels is diselenide bonds, because of the biocompatibility of selenium analogues of various sulfur-containing biomaterials [36–40], and the intrinsic and highly dynamic properties, unlike the other common DCBs that necessitate high temperatures and/or external additives [16–23]. In contrast to the analogous disulfide bonds that

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generally require strong UV irradiation or high temperatures above 150°C for their exchange reactions [24,27], diselenide bonds can exchange under much milder photo and thermal treatment as pioneered by Xu and co-workers [41–44], owing to the lower dissociation energy of diselenide bonds (172 kJ mol⁻¹) than that of disulfide bonds (240 kJ mol⁻¹) [45]. Several studies on diselenide-containing functional polymers have subsequently been reported such as reprocessable thermosets [46,47], degradable micelles/vesicles [48,49], shape-memory polymers [50], and photo-patternable elastomers [51]. Our group has also previously investigated the damage-healing properties and photostability of aromatic diselenide-containing polymers [52]. However, there still have been a few reports on diselenide-containing hydrogels, and those reports are mostly limited to the ones on drug delivery and degradable materials [41,53–56]. We herein report the structural reorganization properties and crack-healing behaviors of diselenide-containing hydrogels based on diselenide exchange reactions.

Experimental

Materials

Hexamethylene diisocyanate (HDI), di-*n*-butyltin dilaurate (DBTDL), and tri(ethylene glycol) (TEG) were purchased from Tokyo Chemical Industry Co., Japan. Poly(ethylene glycol) (PEG) ($M_n = 1,000$ g mol⁻¹) was purchased from Kanto Chemical Co., Inc., Japan. Triethylamine and all organic solvents were purchased from Wako Pure Chemical Industries, Ltd., Japan. Triethanolamine (TEA) was purchased from Sigma-Aldrich, USA. HDI was vacuum distilled and stored under N₂ atmosphere at 5°C before use. 1,4-Dioxane was distilled and stored under Ar atmosphere before use. Other chemicals were used as received. Bis(2-hydroxyethyl) diselenide (DSe) [53] and 2,6-bis(hydroxymethyl)-1-methylpyridin-1-ium iodide (iPDM) [57] were prepared according to the literature procedures.

Instruments

Both ¹H and ¹³C nuclear magnetic resonance (NMR) spectra were recorded on a Bruker (USA) DPX300 spectrometer at 300 MHz (75 MHz for ¹³C-NMR) in DMSO-*d*₆. Fourier transform infrared (FT-IR) spectra were recorded on a JASCO (Japan) FT/IR-4100ST spectrophotometer on a NaCl plate for liquid samples or in KBr pellets for solid samples. Gel permeation chromatography (GPC) measurement was performed on a Malvern Panalytical (England) Viscotek GPC-1000 system at 40°C using polystyrene as a standard and DMF with 0.05 M LiBr as the eluent (0.6 mL min⁻¹).

Synthesis of ionic linear polyurethanes (IPU)

PEG ($M_n = 1,000$ g mol⁻¹) (0.623 g, 0.623 mmol) and iPDM (0.0875 g, 0.311 mmol) were added to a 30 mL Schlenk flask, and dried at 100°C under vacuum for 2 h. DSe (0.0773 g, 0.311 mmol) and DBTDL (3.0 μL, 2.50×10^{-3} mmol) were added to another Schlenk flask and freeze-dried over 1,4-dioxane. DSe and DBTDL were dissolved in dehydrated DMF (3.00 mL) under N₂ atmosphere at room temperature, and the solution was transferred via a syringe to the Schlenk flask containing PEG and iPDM. Then, HDI (0.209 g, 1.25 mmol) was added to the solution. After stirring at room temperature for 24 h, the polymerization was quenched by the addition of methanol. The mixture was dropped into diethyl ether. The precipitant was purified by reprecipitation from chloroform to hexane, and dried under vacuum to give a yellow solid (IPU) (0.997 g, quantitative yield). ¹H-NMR (300 MHz, DMSO-*d*₆): δ = 8.66 (pyridinium, 4-H), 8.00 (pyridinium, 3,5-H), 7.70 (pyridinium-CH₂OCONH), 7.17 (CONH), 5.52 (pyridinium-CH₂OCONH), 4.18 (SeCH₂CH₂O), 4.13 (*N*-CH₃), 4.03 (PEG-CH₂OCONH), 3.50 (PEG), 3.11 (SeCH₂), 2.94 (CONHCH₂), 1.36 (CONHCH₂CH₂), 1.22 (CONHCH₂CH₂CH₂) ppm.

Synthesis of non-ionic linear polyurethanes (NIPU)

PEG ($M_n = 1,000$ g mol⁻¹) (3.11 g, 3.11 mmol), DSe (0.386 g, 1.56 mmol), and 2,6-bis(hydroxymethyl)pyridine (PDM, 0.228 g, 1.56 mmol) were added to a 50 mL two-neck flask, followed by freeze-drying over 1,4-dioxane. Dehydrated DMF (13.8 mL) and HDI (1.05 g, 6.23 mmol) were added to the flask under N₂ atmosphere, followed by the addition of 0.75 mL (1.25×10^{-2} mmol) of DBTDL diluted in dehydrated tetrahydrofuran (THF) (10.0 μL DBTDL in 1.00 mL THF). After stirring at room temperature for 24 h, the polymerization was quenched by the addition of methanol. The mixture was dropped into a saturated NaCl aqueous solution. The precipitant was dissolved in chloroform, dried over anhydrous Na₂SO₄, and dropped into hexane. The precipitant in hexane was dried under vacuum to give a light yellow solid (NIPU) (3.54 g, 81% yield). ¹H-NMR (300 MHz, DMSO-*d*₆): δ = 7.70 (pyridine, 4-H), 7.29 (pyridine, 3,5-H), 5.19 (pyridine-CH₂OCONH), 4.96 (CONH), 4.33 (SeCH₂CH₂O), 4.20 (PEG-CH₂OCONH), 3.64 (PEG), 3.16 (CONHCH₂ and SeCH₂), 1.49 (CONHCH₂CH₂), 1.33 (CONHCH₂CH₂CH₂) ppm.

Diselenide bond exchange reaction between IPU and DSe

IPU (10 mg) and excess amount of DSe (20 mg, 8.1×10^{-2} mmol) were dissolved in water (10.0 mL)

and stirred under the conditions as follows: i) irradiated by 9 W handy UV lamp at 365 nm from a distance of 8 cm, and ii) stored in a brown glass vial at room temperature. After stirring for 24 h, water was removed by freeze-drying. The products were purified by reprecipitation from methanol to diethyl ether and dried under vacuum.

Synthesis of cross-linked polyurethanes (CLPU)

PEG ($M_n = 1,000 \text{ g mol}^{-1}$) (0.623 g, 0.623 mmol) and iPDM (0.0875 g, 0.311 mmol) were added to a 30 mL Schlenk flask, and dried at 100°C under vacuum for 2 h. DSe (0.0773 g, 0.311 mmol), TEA (0.0619 g, 0.415 mmol), and DBTDL (4.5 μL , 3.75×10^{-3} mmol) were added to another Schlenk flask and freeze-dried over 1,4-dioxane. DSe, TEA, and DBTDL were dissolved in dehydrated DMF (3.70 mL) under N_2 atmosphere at room temperature, and the solution was transferred via a syringe to the Schlenk flask containing PEG and iPDM. Then, HDI (0.314 g, 1.88 mmol) was added to the solution. After vigorous stirring for about 1 minute, the mixture was transferred to a PTFE Petri dish and stored under N_2 atmosphere at room temperature for 5 days to give an orange transparent cross-linked polyurethane gel. The obtained gel was immersed in diethyl ether for 5 h, chloroform for 12 h, and hexane for 5 h, and finally dried under vacuum to give a bulk cross-linked polymer (1.16 g, quantitative yield). The obtained CLPU bulk sample was cut to $5 \times 5 \times 1 \text{ mm}^3$ pieces and stored in a brown glass vial. FT-IR (KBr): 3405, 2925, 2869, 2373, 2339, 1712, 1632, 1536, 1459, 1352, 1252, 1106, 949, 849 cm^{-1} .

A control polymer was synthesized in a similar manner. PEG ($M_n = 1,000 \text{ g mol}^{-1}$) (0.623 g, 0.623 mmol) and iPDM (0.0875 g, 0.311 mmol) were added to a 30 mL Schlenk flask, and dried at 100°C under vacuum for 2 h. TEG (0.0467 g, 0.311 mmol), TEA (0.0619 g, 0.415 mmol), and DBTDL (4.5 μL , 3.75×10^{-3} mmol) were added to another Schlenk flask and freeze-dried over 1,4-dioxane. TEG, TEA, and DBTDL were dissolved in dehydrated DMF (3.70 mL) under N_2 atmosphere at room temperature, and the solution was transferred via a syringe to the Schlenk flask containing PEG and iPDM. Then, HDI (0.314 g, 1.88 mmol) was added to the solution. After vigorous stirring for about 1 minute, the mixture was transferred to a PTFE Petri dish and stored under N_2 atmosphere for 5 days to give an orange transparent cross-linked polyurethane gel. The obtained gel was then immersed in diethyl ether for 5 h, chloroform for 12 h, and hexane for 5 h, and finally dried under vacuum to give a bulk cross-linked polymer (1.16 g, quantitative yield). The obtained CLPUctrl bulk sample was cut to $5 \times 5 \times 1 \text{ mm}^3$ pieces and stored in a brown glass vial. FT-IR (KBr): 3430, 2924, 2869,

2373, 2341, 1707, 1653, 1540, 1463, 1353, 1254, 1104, 950, 846 cm^{-1} .

Water-swelling behavior of bulk CLPUs

The bulk CLPU samples ($5 \times 5 \times 1 \text{ mm}^3$, 50 mg) were immersed in deionized (DI) water (20 mL) and put under the conditions as follows: i) irradiated by 9 W handy UV lamp at 365 nm from a distance of 8 cm at room temperature, ii) stored in a brown glass vial at room temperature, and iii) stored in a brown glass vial and put in a refrigerator at 5°C.

Preparation and self-healing behavior of CLPU hydrogels

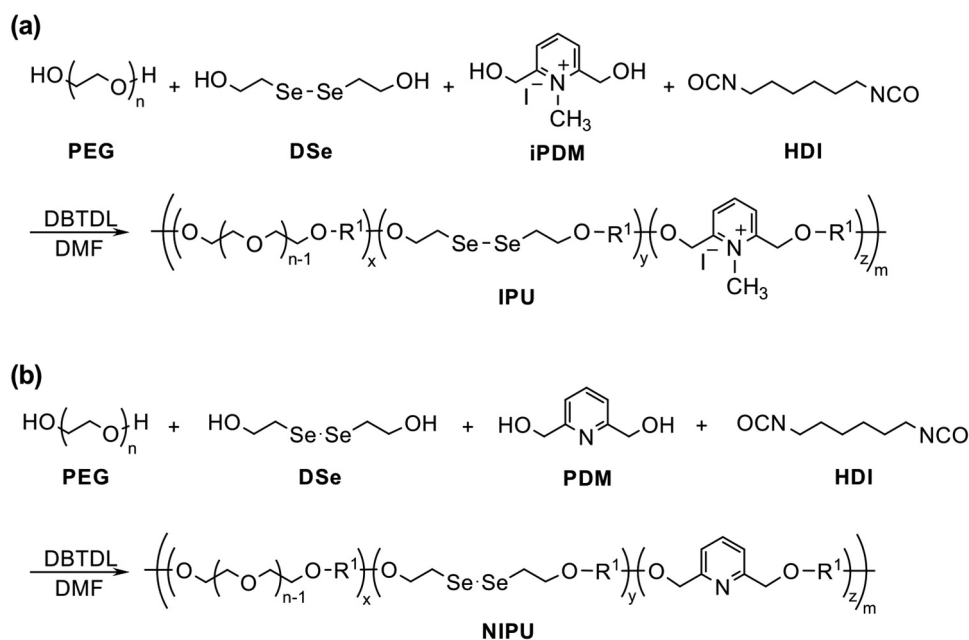
The as-prepared CLPU gels before drying were immersed in DI water for 5 h. Then, the water was changed to fresh DI water. The procedure was repeated 5 times to give CLPU hydrogels. The hydrogels were scratched by a surgical knife, the healing experiment was performed under the conditions as follows: i) irradiated by 9 W handy UV lamp at 365 nm from a distance of 8 cm at room temperature, ii) stored in a brown glass vial at room temperature, and iii) stored in a brown glass vial and put in a refrigerator at 5°C. The healing behavior of the scratched samples was observed by optical microscopy.

Results and discussion

Synthesis and hydrophilicity of ionized linear polyurethanes (IPU)

As a model polymer of diselenide-containing hydrogel, we first prepared a hydrophilic linear polyurethane (IPU) that contains diselenide bonds and pyridinium units in the main chain. The polyaddition reaction was carried out using poly(ethylene glycol) (PEG) ($M_n = 1,000 \text{ g mol}^{-1}$), bis(2-hydroxyethyl) diselenide (DSe), (2,6-bis(hydroxymethyl)-1-methylpyridin-1-ium iodide (iPDM), and hexamethylene diisocyanate (HDI) in the presence of di-*n*-butyltin dilaurate (DBTDL) as the catalyst (Scheme 1(a)). We prepared the three types of IPU with different DSe and iPDM ratios to investigate the proper composition (Table 1) for both sufficient dynamicity and hydrophilicity. We also prepared non-ionized polyurethane (NIPU, Scheme 1(b)) as a control sample following the same manner as IPU using PDM instead of iPDM. The structures of the obtained polyurethanes were characterized by ^1H NMR (Figure 1), and GPC measurement confirmed the formation of polymer products.

We then investigated the hydrophilicity of IPU with different iPDM ratios by adding these polymers into deionized water (1.0 mg mL^{-1}). IPU1 and IPU2



Scheme 1. Synthesis of (a) ionic and (b) non-ionic polyurethanes with diselenide linkages.

Table 1. Results of the synthesis of diselenide-containing linear polyurethanes.

Sample	DSe (mol%) ^a	iPDM (mol%) ^a	PDM (mol%) ^a	Yield (%)	M _n ^b	M _w /M _n ^b
IPU1	6.0	13	–	Quant.	27,600	1.33
IPU2	8.5	9.0	–	Quant.	21,600	1.31
IPU3	14	5.0	–	91	20,300	1.24
NIPU	13	–	12	81	17,500	2.60

^a Calculated from ¹H NMR spectra.

^b Estimated by GPC measurements.

with larger pyridinium ratios completely dissolved in water to afford transparent solutions, while the aqueous solution of IPU3 with the least iPDM ratio

resulted in a slight suspension (Figure 2). These results suggested that at least 9 mol% pyridinium unit ratio endow sufficient hydrophilicity with the herein designed diselenide-containing polyurethanes.

Degradation of IPU by diselenide bond exchange reaction with DSe

The dynamic property of the diselenide-containing linear polyurethanes in water was investigated using IPU2. A photo-induced diselenide exchange reaction between IPU2 and an excess amount of DSe (15 folds

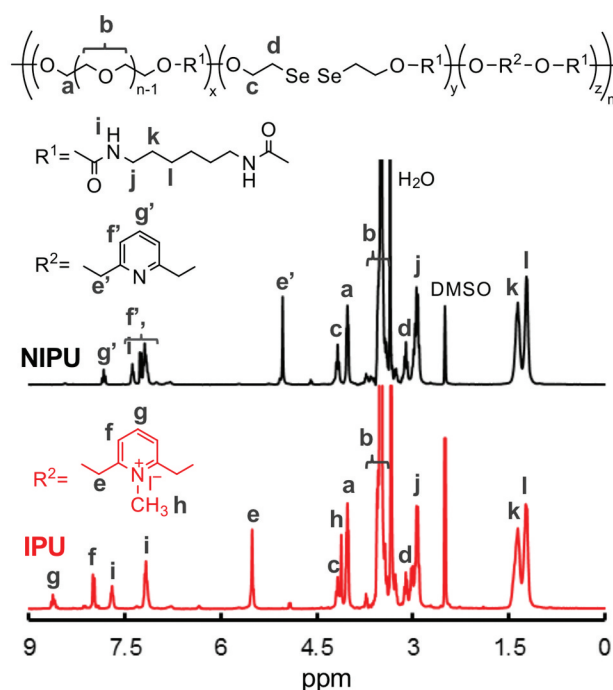


Figure 1. ¹H NMR spectra of NIPU and IPU (300 MHz, DMSO-*d*₆).

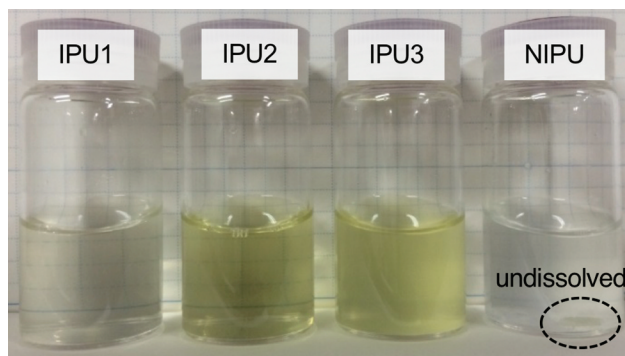


Figure 2. Photographs of the aqueous solutions of IPUs and NIPU (1.0 mg mL^{-1}).

of the Se-Se bond in IPU2) was performed in water under photo-irradiation at 365 nm, and the reaction was monitored by GPC measurement. After 24 hours of the irradiation at room temperature, the GPC curves shifted to lower molecular weight region with a decrease of M_w from 12,200 to 7,200 (Figure 3). Although the molecular weight decrease was not significant due to the smaller composition ratio of diselenide bond (*ca.* 1.2 moieties per chain) as determined by water solubility test, this result indicated that the diselenide linkages in the polymer chain exchanged with the low molecular diselenide (DSe), confirming the photo-induced exchanging ability of diselenide bonds in the designed hydrophilic polyurethanes in water.

Preparation of cross-linked polyurethanes (CLPUs)

The dynamic properties of diselenide bonds in hydrogel networks were then investigated using diselenide-containing hydrophilic cross-linked polyurethanes (CLPUs), which would reflect the dynamic nature of diselenide bonds much clearer than the IPUs with

a few diselenide compositions. CLPUs were prepared in a similar manner as IPUs, where triethanolamine (TEA) was used as a cross-linker in addition to PEG ($M_n = 1,000 \text{ g mol}^{-1}$), DSe, iPDM, and HDI (Scheme 2 (a)). As a control sample, chemically cross-linked hydrophilic polyurethane was concurrently synthesized by using tri(ethylene glycol) (TEG) instead of DSe (Scheme 2(b)). The feed compositions of each CLPU are summarized in Table 2. After 5 days of polymerization, the CLPUs were obtained as transparent gels swollen with DMF. The crude gels were purified by immersion in diethyl ether, chloroform, and hexane in sequence, and then dried under vacuum to obtain bulk samples of CLPUs. FT-IR spectroscopy of the obtained CLPUs showed the disappearance of the peak corresponding to isocyanate groups at around 2270 cm^{-1} and the emergence of the peaks corresponding to urethane groups at around 1712 cm^{-1} and 1661 cm^{-1} (Figure 4), indicating that HDI had completely reacted with the OH groups. All the CLPUs were obtained quantitatively, indicating the quantitative conversion of the fed monomers into the cross-linked networks.

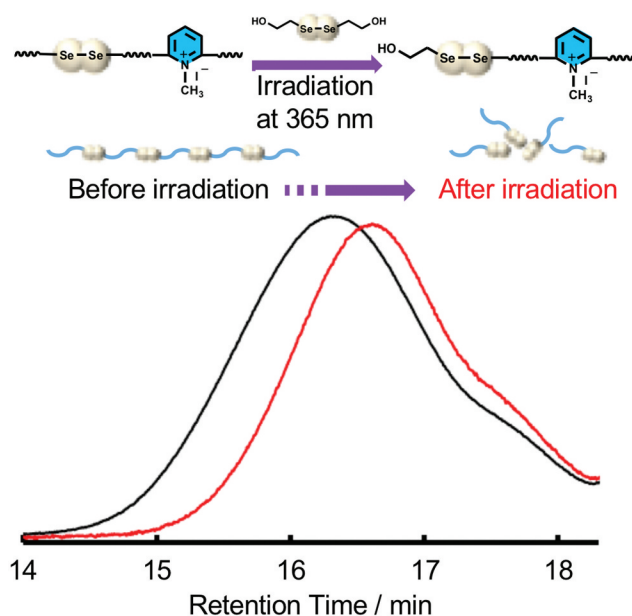
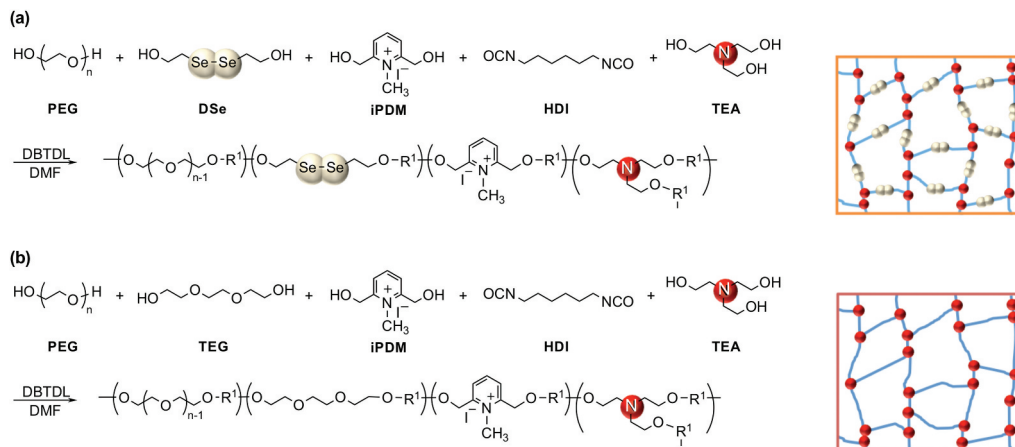


Figure 3. GPC curves of IPU2 before (black) and after (red) the exchange reaction with DSe.



Scheme 2. Synthesis of hydrophilic cross-linked polyurethanes (CLPUs) (a) with diselenide bonds and (b) without diselenide bonds.

Table 2. Compositions of the CLPUs.

Sample	Feed molar ratio ^a				
	PEG	DSe	TEG	iPDM	TEA
CLPU1	0.50	0.16	–	0.34	0.34
CLPU2	0.50	0.25	–	0.25	0.34
CLPU-ctrl	0.50	–	0.25	0.25	0.34

^aAll the products were obtained quantitatively.

Water-swelling behavior of bulk CLPUs

The dynamic property of the obtained CLPUs was first evaluated by water-swelling tests under the photo-irradiation at 365 nm, in the dark at 25°C, and in the dark at 5°C, each of which should offer different dynamic nature to the diselenide bonds and thus different swelling behaviors. In general, chemically cross-linked polymers swell in their good or θ solvents and reach swelling equilibrium states, where the solvation-induced stretching of the polymer chains and elastic force of the stretched chains are equaled [58,59]. On the other hand, the dynamic networks can relax the stretched polymer chains via structural reorganization

induced by bond exchange reactions, which lead to a decrease of the crosslink density and higher swelling degree [60]. The swelling tests were performed with immersing a square-cut specimen of each CLPU in deionized water. The swelling degree (Q) was defined as the following equation:

$$Q = \frac{W_t - W_0}{W_0} \tag{1}$$

where W_0 and W_t are the weight of the bulk sample at the initial and swollen state, respectively. When subjected to swelling under photo-irradiation at 365 nm (Figure 5(a), diamond plots), CLPU1 once reached a maximum swelling degree up to $Q \approx 63$ after 2 days (point B), and then the swelling degree gradually got smaller and finally resulted in complete dissolution of the gel to afford a yellow transparent solution after 5 days (point C) (Figure 5(b)). In contrast, the swelling degree of CLPU1 was drastically suppressed up to $Q \approx 5.4$ in the dark at 5°C (Figure 5(a), filled circle plots), and this is similar to that of CLPU-ctrl without diselenide bond, which

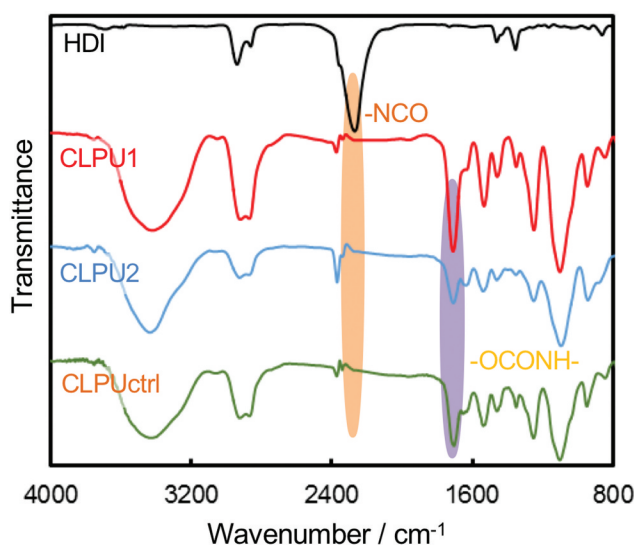


Figure 4. FT-IR spectra of CLPUs in comparison with HDI.

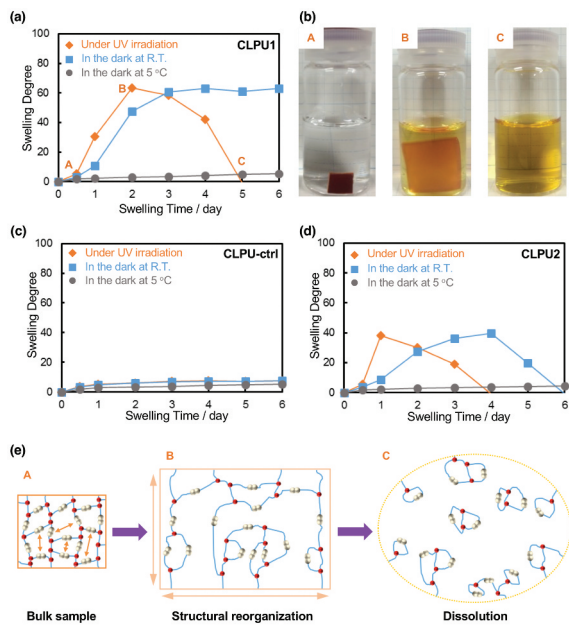


Figure 5. (a) Swelling behavior of CLPU1. (b) Photographs of the specimen of CLPU1 at different swelling states. (c) Swelling behavior of CLPU-ctrl and (d) CLPU2. (e) Illustration of the structural reorganization and entropy-driven cyclization depolymerization of diselenide-containing hydrogels.

showed almost the same swelling behavior with $Q = 5.1 \sim 7.6$ after 6 days in the employed conditions (Figure 5(b)). These results indicate that the large swelling of CLPU1 under photo-irradiation was based on the structural reorganization of the network induced by diselenide exchange reactions. Since the swelling test was carried out in the presence of a large amount of water, depolymerization of the network became favorable under bond-exchanging conditions in an entropy-driven manner, leading to the dissolution of the hydrogels in water (Figure 5(e)) [60]. One can think of the possibility of force-induced diselenide dissociation by the stretching force during the swelling, but it is very unlikely considering the other dynamic networks with weaker dynamic covalent bonds that showed the large swelling

only under the bond-exchanging conditions [60,61]. The suppressed swelling of CLPU1 in the dark at 5°C should derive from the fixed diselenide bonds without photo- and thermal stimuli. Interestingly, CLPU1 in the dark at room temperature also showed large swelling up to $Q = 63$ after 4 days and maintained nearly constant swelling degree (Figure 5(a), square plots), suggesting that the thermal diselenide exchange reaction occurred. This is supported by the result of CLPU2, which dissolved in water even in the dark at room temperature after 6 days (Figure 5(d), square plots). These results well demonstrate that the diselenide bonds in the hydrogel networks possess highly dynamic properties and can autonomously exchange even in an ambient environment.

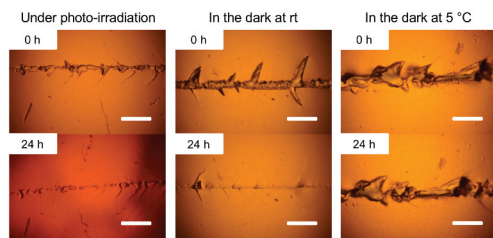


Figure 6. Photographs of the scratches on CLPU1 before and after placed under photo-irradiation at 365 nm in the dark at room temperature, and in the dark at 5°C (scale bar: 0.2 mm).

Crack-healing behavior of CLPU hydrogels

The dynamic properties of the diselenide-containing hydrogels were also investigated by crack-healing tests. Each specimen of the CLPU hydrogels was scratched by a surgical knife and subjected to certain conditions for 24 h, and the crack part was observed by optical microscopy. The results of the healing tests of CLPU1 hydrogels are shown in Figure 6. It can be seen that the scratched area became almost homogeneous with a tiny remnant of the original crack both under photo-irradiation at 365 nm and in the dark at room temperature after 24 h, while no healing was observed with the sample kept in the dark at 5°C. These results indicate that the diselenide exchange reaction occurred and reconstruct the gel network at the crack surface under photo-irradiation and in the dark at room temperature. Since the diselenide exchange reaction dramatically suppressed in the dark at 5°C, the specimen in that condition showed little change with the crack. These results are well consistent with the ones of the previously conducted swelling tests. The test using CLPU2 with a higher diselenide ratio than CLPU1 resulted in more homogeneous surface after photo-

irradiation for 24 h (Figure 7(a), left), plausibly due to the diselenide-rich composition that induces the more diselenide exchange reactions and thus crack-healing properties. On the other hand, CLPU2 in the dark at room temperature showed a bit poorer or comparable healing behavior to CLPU1 (Figure 7(a), right). Considering the crack-healing mechanism that first requires the contact of each damaged surface followed by homogenization of the network by structural reorganization [62], the chain mobility is another important factor. The effect of chain mobility besides the bond exchangeability to the healing performances had actually been observed in our previous study on the diselenide-containing bulk networks [52]. Taking into account the preceding reports on the photo-induced plasticization of the photo-exchangeable polymer networks [63], the particularly better healing of CLPU2 under photo-irradiation presumably derived from the photo-induced increase of the inner chain mobility that derives from the diselenide-rich composition. As a control experiment, we also carried out the same test using CLPU-ctrl without diselenide bonds, which resulted in little change with their crack after subjected

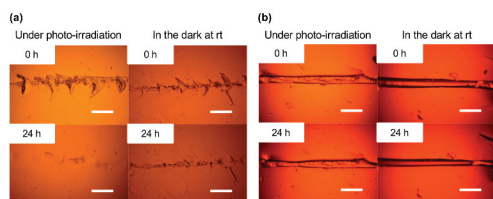


Figure 7. Photographs of the scratches on (a) CLPU2 and (b) CLPU-ctrl before and after placed under photo-irradiation at 365 nm and in the dark at room temperature (scale bar: 0.2 mm).

to either photo-irradiation or placed in the dark at room temperature (Figure 7(b)). These results demonstrate the availability of diselenide bonds as an effective functional unit to endow hydrogels with various dynamic properties that can be triggered by mild conditions.

Conclusions

In this work, we investigated the dynamic properties of diselenide-containing hydrogels with dynamic diselenide linkages and hydrophilic pyridinium units. The model study using linear polyurethanes incorporated with these units confirmed the photo-induced exchangeability of the herein designed polymers. Diselenide-containing crosslinked polyurethane was then synthesized, and the dynamic properties in the hydrogel state were evaluated by water-swelling and crack-healing tests. The water-swelling test revealed the characteristic large swelling and dissolution behavior of the diselenide-containing hydrogels under photo-irradiation at 365 nm and also even in the dark at ambient temperature, presenting the highly dynamic properties of diselenide bonds in the hydrogel networks. Such dynamic properties were also confirmed in the crack-healing test, in which CLPU2 with diselenide-rich composition showed the most efficient healing based on the network reorganization by photo-induced diselenide exchange reaction. The herein obtained knowledge would contribute to the further development of dynamic diselenide chemistry particularly in the field of the soft matters such as biocompatible materials as the appropriate area of the mild stimuli-inducible dynamic nature of diselenide bonds.

Disclosure statement

No potential conflict of interest was reported by the authors.

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