Dynamic Covalent Bonds Hot Paper

DOI: 10.1002/anie.201403442

Dynamic Diselenide Bonds: Exchange Reaction Induced by Visible Light without Catalysis**

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Abstract: *Dynamic covalent bonds are extensively employed in dynamic combinatorial chemistry. The metathesis reaction of disulfide bonds is widely used, but requires catalysis or irradiation with ultraviolet (UV) light. It was found that diselenide bonds are dynamic covalent bonds and undergo dynamic exchange reactions under mild conditions for diselenide metathesis. This reaction is induced by irradiation with visible light and stops in the dark. The exchange is assumed to proceed through a radical mechanism, and experiments with 2,2,6,6-tetramethylpiperidin-1-yloxyl (TEMPO) support this assumption. Furthermore, the reaction can be conducted in different solvents, including protic solvents. Diselenide metathesis can also be used to synthesize diselenide-containing asymmetric block copolymers. This work thus entails the use of diselenide bonds as dynamic covalent bonds, the development of a dynamic exchange reaction under mild conditions, and an extension of selenium-related dynamic chemistry.*

Dynamic covalent bonds have attracted considerable attention and been extensively used in dynamic combinatorial chemistry (DCC) and supramolecular chemistry.[1] Dynamic covalent bonds are reversibly formed covalent bonds that can undergo formation, cleavage, or metathesis under defined conditions. Examples of dynamic covalent bonds include disulfide bonds, Se–N dynamic bonds, imine bonds, acylhydrazone bonds, and the six-membered ring that is formed during a Diels–Alder cycloaddition. These dynamic covalent bonds can be used in fabricating polymers, self-healing materials, responsive systems, and superamphiphiles.[2] Through DCC, a series of compounds with various dynamic covalent bonds have been discovered,[1] including new macrocycles, protein-specific drugs, ligands for various biomolecules, structures with host or guest affinity, and even new catalysts. Though widely applied, most dynamic covalent bonds require a change in conditions (formation and cleavage of imine bonds), heating (Diels–Alder cycloaddition), or additives (Se–N dynamic bonds) to undergo formation or cleavage. DCC is rarely done under fixed and/or mild conditions. Therefore, it is important to develop further systems with dynamic covalent bonds that are free of additional requirements or harsh conditions, such as heat or irradiation with UV light.

Among these dynamic covalent bonds, disulfide bonds are widely found in natural biomolecules, including proteins. Their dynamic chemistry can be realized under irradiation with UV light or in the presence of catalytic reductants (e.g., thiols). Different compounds containing disulfide bonds can undergo an exchange reaction—disulfide metathesis—to redistribute sulfur-containing residues through different mechanisms,[3] for example, radical mechanisms under irradiation with UV light and anion mechanisms in the presence of a reductant. Disulfide bonds are one of the dynamic linkages in DCC and are widely used as dynamic covalent bonds.[4] Aside from applications in DCC, the dynamic exchange reaction of disulfide bonds can also be used to prepare main-chain or side-chain disulfide-containing polymers and other asymmetric disulfide-containing molecules as well as for modifying proteins.[5] Although disulfide bonds are dynamic and have been widely used, the direct exchange between two disulfide bonds requires irradiation with high-energy UV light or the addition of catalysts, such as thiols or other reductants. These disadvantages may limit the application of disulfide metathesis especially in vivo because both UV light and thiols may damage biomolecules.

In comparison to disulfide bonds, diselenide bonds possess a lower bond energy (diselenide bonds: 172 kJ mol^{-1}; disulfide bonds: 240 kJ mol^{-1}).[6] This suggests that diselenide bonds can be more dynamic, and that metathesis might happen under much milder conditions. Selenium-related organic[7] and polymer[8] chemistry has also been recently developed. We have already utilized the excellent redox properties of selenium to develop sensitive responsive systems that were fabricated with main-chain or side-chain monoselenide- or diselenide-containing polymers for drug delivery or glutathione peroxidase (GPX) mimicry.[8] We have also discovered the dynamic Se–N bond,[9] which sparked our interest in selenium-related dynamic chemistry. Whereas the exchange reaction between selenol and diselenide has been studied,[10] the dynamic formation of diselenide bonds has not yet been described. We have now studied the exchange reaction of diselenide bonds to overcome the disadvantages

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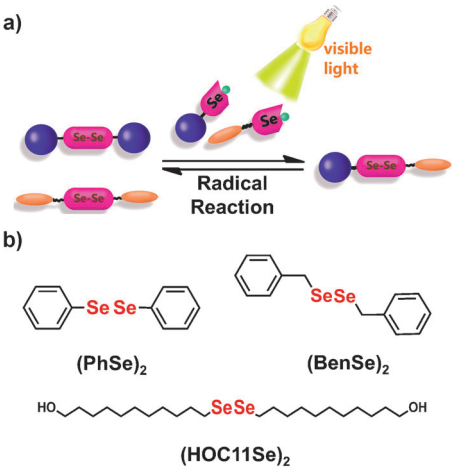
[**] This work was financially supported by the National Basic Research Program of China (2013CB834502), the Foundation for Innovative Research Groups of the National Natural Science Foundation of China (21121004), Tsinghua University Initiative Scientific Research Program (2012Z02131), the NSFC-DFG joint grant (TRR 61), and The Importation and Development of High-Caliber Talents Project of Beijing Municipal Institutions. We acknowledge Prof. Xi Zhang and Prof. Meixiang Wang (Tsinghua University) for their stimulating suggestions, and Prof. Hideyuki Otsuka (Kyushu University), Dr. Lei Tao, and Dr. Haijun Yang (Tsinghua University) for constructive discussions.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201403442.



Scheme 1. a) A visible-light-induced diselenide exchange reaction. b) Three model compounds used in diselenide exchange.

of disulfide metathesis and to promote the development of selenium-related dynamic chemistry.

Herein, we present a diselenide metathesis reaction that is induced simply by visible-light irradiation or heating to 70 °C (Scheme 1 a). Three diselenide-containing compounds were used to study diselenide metathesis: diphenyl diselenide ($(PhSe)_2$), dibenzyl diselenide ($(BenSe)_2$), and di-(1-hydroxy-undecyl) diselenide ($(HOC11Se)_2$; Scheme 1 b). In the last part of this study, we show that diselenide metathesis can also be used to prepare diselenide-containing block copolymers. This study of diselenide metathesis revealed that the dynamic nature of diselenide bonds represents a new form of dynamic chemistry, which requires neither irradiation with UV light nor additives and further enhances selenium-related dynamic chemistry.

We employed ^1H and ^{77}Se NMR spectroscopy to monitor the reaction (Figure 1). The reaction was performed at room temperature (15 °C) in chloroform using different reactants at different concentrations (5 mM or 20 mM) under light irradiation with a common lamp of 26–28 Lux and no catalyst. At equilibrium with reactant ratios of 1:1, half of each reactant has been exchanged to generate a mixture containing the two reactants and the exchange product in a ratio of 1:1:2. At higher concentrations, the exchange reaction reaches equilibrium faster. The exchange between $(PhSe)_2$ and $(HOC11Se)_2$ can reach equilibrium in 90 or 50 minutes at a concentration of 5 mM and 20 mM, respectively (Figure 1 a, b). As shown in Figure 1 a and Figure S2 b, the peak of $SeCH_2$ in $(HOC11Se)_2$ has moved from 2.91 ppm to 3.01 ppm after the reaction. The exchange between $(BenSe)_2$ and $(HOC11Se)_2$ was slower and reached equilibrium in five and three hours at 5 mM and 20 mM, respectively (Figure 1 c; see also Figure S3). The exchange reaction between $(PhSe)_2$ and $(BenSe)_2$ is even slower, and equilibrium had not been reached even after 24 hours (Figure S2 e). To further confirm that such an exchange reaction involves diselenide bonds, ^{77}Se NMR spectroscopy was used (Figure 1 d, e; Figure S2 f). In the ^{77}Se NMR spectra, two new peaks appeared after each reaction, which are attributed to asymmetric diselenide

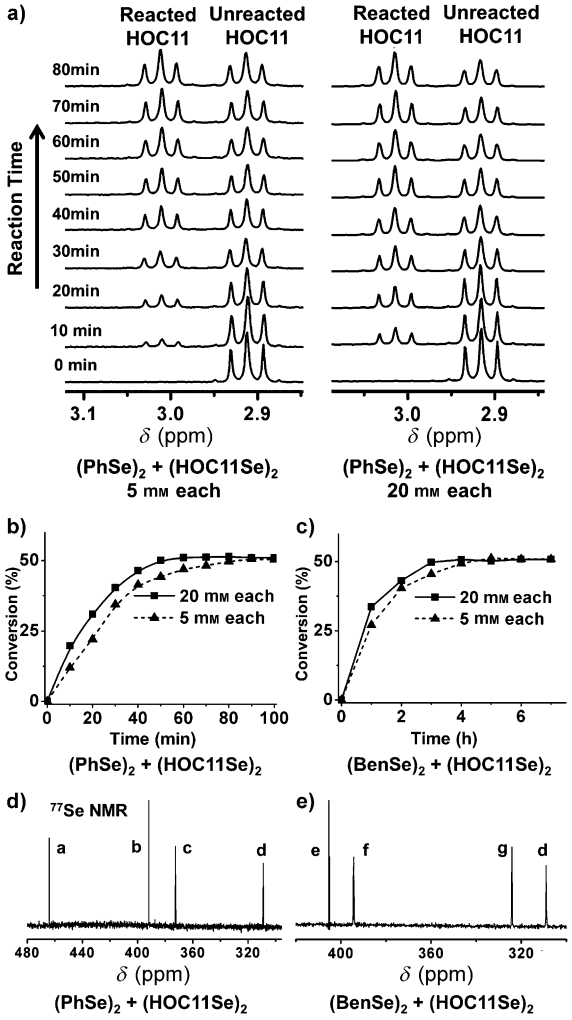


Figure 1. ^1H NMR and ^{77}Se NMR data obtained during diselenide exchange. The conversion of the reaction was determined in terms of the amount of reacted $(HOC11Se)_2$. a) After exchange with $(PhSe)_2$, the peak corresponding to the CH_2Se protons in $(HOC11Se)_2$ shifted from 2.91 ppm to 3.01 ppm. b) Dependence of the conversion of the exchange reaction between $(PhSe)_2$ and $(HOC11Se)_2$ on the concentration. c) Dependence of the conversion of the exchange reaction between $(BenSe)_2$ and $(HOC11Se)_2$ on the concentration. The reaction proceeds faster at a higher concentration. d, e) The ^{77}Se NMR spectra after the reaction. Peaks a (464.1 ppm) and d (309.0 ppm) belong to $(PhSe)_2$ and $(HOC11Se)_2$; peak e (405.3 ppm) belongs to $(BenSe)_2$; peaks b (391.9 ppm) and c (372.6 ppm) belong to the exchange product (HOC11Se)(SePh); peaks f (394.4 ppm) and g (324.2 ppm) belong to the exchange product (HOC11Se)(SeBen). See the Supporting Information for full ^1H NMR spectra.

products that contain two different selenium atoms. These ^1H NMR and ^{77}Se NMR spectra confirm that diselenide metathesis has occurred, and that the reaction rate differs for different reactants.

The exchange reaction is dependent on light irradiation, which indicates that a radical mechanism is operating. This dependence was observed in two different ways. First, the exchange rate could be significantly accelerated when a photoreactor was used to increase the light intensity. In a photo-

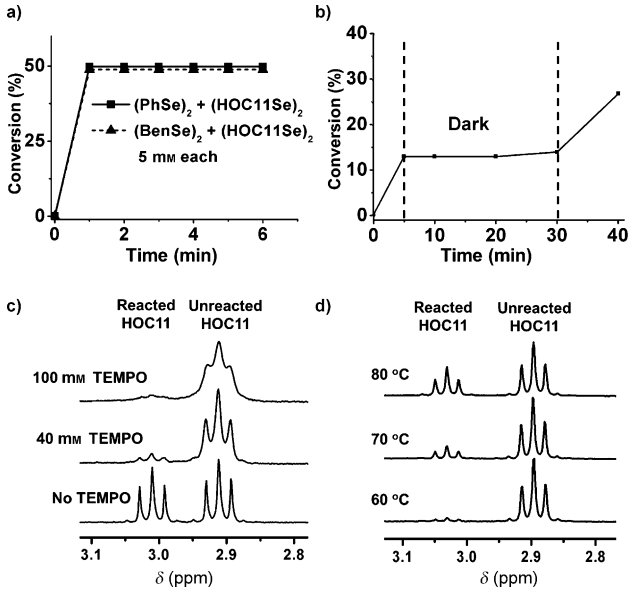


Figure 2. Evidence for a radical mechanism. a) In the photoreactor, diselenide exchange can reach equilibrium in one minute. The concentration of each compound was 5 mM. b) Dependence of the reaction on light. When light irradiation is ceased after five minutes, the exchange stops immediately. c) When TEMPO (40 mM or 100 mM) was added, the reaction between $(PhSe)_2$ and $(HOC11Se)_2$ (5 mM each) was suppressed. d) Dependence of the heat-induced exchange reaction between $(PhSe)_2$ and $(HOC11Se)_2$ (5 mM each, DMSO, 2 h) on temperature.

reactor (365 nm, 100 W, 25 °C), the reactions between $(PhSe)_2$ and $(HOC11Se)_2$ and between $(BenSe)_2$ and $(HOC11Se)_2$ reached equilibrium in one minute (Figure 2a), which is quite fast. Second, when light irradiation was stopped, the reaction also stopped immediately. At room temperature, $(PhSe)_2$ and $(HOC11Se)_2$ (5 mM each) reacted under light irradiation. However, when the solution was placed in the dark, the reaction stopped immediately. When the mixture was irradiated with light again, the exchange reaction continued (Figure 2B). Furthermore, no exchange reaction had occurred even after 24 hours when the mixture had been placed in the dark.

The role of light implies that the exchange reaction proceeds through a radical mechanism. Under irradiation with UV light or when heated, disulfide bonds can generate thiol radicals and undergo metathesis through a radical mechanism.[3a] In some synthetic reactions, $(PhSe)_2$ has been reported to generate radicals as intermediates under light irradiation.[11] Considering these facts, diselenide metathesis likely proceeds through a radical mechanism. To confirm this hypothesis, it was tested whether the addition of TEMPO would suppress the reaction. As shown in Figure 2c, $(PhSe)_2$ and $(HOC11Se)_2$ (5 mM each) were allowed to react under light irradiation for two hours. When two equivalents of TEMPO were added to this "selenol radical" mixture, the reaction was significantly suppressed. By adding three more equivalents of TEMPO, the exchange reaction was further suppressed. The suppression of the exchange reaction by the addition of TEMPO suggests that diselenide metathesis proceeds through a radical mechanism.

Further experiments reveal that merely visible light is sufficient to induce the reaction. Light filters were used to limit the wavelength of the light used. As a result, the exchange reaction still occurs when UV light is filtered out, but proceeds much more slowly (Figure S4). The reaction between $(PhSe)_2$ and $(HOC11Se)_2$ (5 mM each) reaches equilibrium in 18 hours when light below 515 nm is filtered out. Surprisingly, even when all light below 600 nm is filtered out, the reaction still proceeded, but equilibrium was not reached even after 30 hours. This is also due to the fact that the light intensity above 600 nm is low. As diselenide bonds are much weaker than disulfide bonds, it is reasonable that selenol radicals are generated under visible-light irradiation. Visible light is very mild and thus more suitable for biosystems and biomolecules.

Heating can also generate radicals during diselenide metathesis. Without light irradiation, the exchange reaction could be realized in dimethyl sulfoxide (DMSO) at 70 °C, which is not too harsh. As shown in Figure 2d, the reaction rate of $(PhSe)_2$ and $(HOC11Se)_2$ (5 mM each) in the dark varies with temperature. After two hours, the reaction had barely proceeded at 60 °C. With an increase in temperature, the conversion also increased. Even though heat-induced exchange is slower than light-induced exchange, the exchange reaction can successfully proceed at 70 °C. Therefore, the heat-induced exchange reaction also indirectly supports the radical mechanism.

The reaction can be conducted in various solvents. Aside from chloroform and DMSO, the reaction also occurred in acetone, acetonitrile, and methanol (Figure S5). Therefore, diselenide metathesis can be realized in low polar, highly polar, or even protic solvents, such as methanol, and therefore does not seem to depend on specific solvents.

Finally we used diselenide-linked polystyrene ($(PSSe)_2$) as a model polymer to test whether diselenide metathesis can occur in a polymer. An exchange reaction between $(PSSe)_2$ of 90 kDa and 8 kDa (both M_w; structure shown in Figure 3a) can reach equilibrium in 18 hours when the mixture is irradiated with a common lamp. Gel-permeation chromatography (GPC) was used to monitor the reaction (Figure 3b; see also Figure S6). The peak that corresponds to the polymer of 90 kDa $(PSSe)_2$ was observed to decrease in intensity, while a new peak between those for the two reactants appeared. These results indicate that diselenide metathesis can occur in polymer systems, even though the exchange is much slower because of the entanglement of long polymer chains. This exchange reaction provides a new method for the synthesis of diselenide-linked asymmetric or/and amphiphilic block copolymers.

In summary, diselenide bonds have been utilized as dynamic covalent bonds, and diselenide metathesis has been realized. Under irradiation with common-lamp light, the exchange reaction between two different diselenides can reach equilibrium in one to several hours. In a photoreactor, the reaction is faster and reaches equilibrium in only one minute. The dependence of the reaction on light irradiation supports a radical mechanism, and the suppression of the

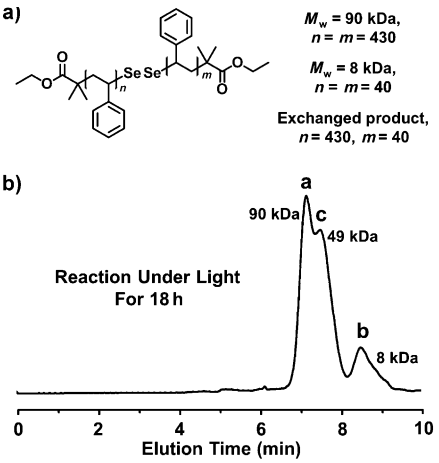


Figure 3. Exchange reaction between two different $(PSSe)_2$. a) Structure of $(PSSe)_2$. b) Gel-permeation chromatogram after diselenide exchange between two $(PSSe)_2$ with different molecular weights. Peaks a and b belong to the reactants $(PSSe)_2$ of 90 kDa and 8 kDa, respectively. Peak c appeared after the exchange reaction under light irradiation and should correspond to a polymer of 49 kDa. See the Supporting Information for more GPC results.

reaction by the addition of TEMPO corroborated this assumption. At 70 °C in the dark, diselenide metathesis also occurred, which further supports the radical mechanism. Using filtered light, we discovered that light with wavelengths above 600 nm is sufficient to induce the exchange reaction. Furthermore, diselenide metathesis can be conducted in different solvents, including protic solvents, and is independent of the solvent used. Finally, diselenide-containing polystyrene was used to demonstrate that diselenide exchange can also occur in polymers. The successful exchange reaction between the two polystyrenes with different molecular weight revealed possible applications of diselenide metathesis in synthesizing block copolymers.

For diselenide metathesis, the reaction requires neither catalysts nor irradiation UV light and therefore proceeds under milder conditions than disulfide metathesis. These mild conditions allow the exchange reaction to be used in biosystems with no damage to biomolecules. The dynamic diselenide bonds and their metathesis have potential use in the modification of biomolecules, such as certain proteins that contain a diselenide bond. Furthermore, diselenide metathesis should enable the synthesis of different diselenide-linked amphiphilic polymers and the fabrication of visible-light-induced self-healing materials containing diselenide bonds. In conclusion, we have studied diselenide metathesis, which further enriches the realm of selenium-related dynamic chemistry. We have shown the potential use of diselenide bonds as dynamic covalent bonds. With the development of selenium-related chemistry, more applications of diselenide metathesis may be discovered.

Received: March 18, 2014
Revised: April 18, 2014
Published online: May 19, 2014

Keywords: dynamic covalent bonds · selenium · supramolecular chemistry

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