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A Fuel-Driven Chemical Reaction Network Based on Conjugate Addition and Elimination Chemistry

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Fuel-driven chemical reaction networks provide an opportunity to develop chemical systems that operate out-of-equilibrium. There remains a need to design and develop new fuel-driven chemical reaction networks capable of repeated operation using simple and benign chemistry. Herein, we propose a new chemical reaction network for fuel-driven transient formation of covalent bonds, based on redox-controlled conjugate addition and elimination chemistry. By investigating the separate reactions making up the cycle, we find that the bond formation, breaking and regeneration processes can be realized. At present, substantial side reactivity prevents achieving repeated operation of a full cycle in a single system. If such obstacles would be overcome, this chemical reaction network could be a valuable addition to the toolbox for out-of-equilibrium systems chemistry.

Within systems chemistry there is a need for new fuel-driven chemical reaction networks as they will allow powering and out of equilibrium operation of chemical systems. Inspired by the functional behavior seen in living systems, fuel-driven chemical reaction networks have been used in many exciting examples, including oscillators,[1–4] self-replicating systems,[5–7] fuel-driven transient hydrogel formation,[8,9] polymerization,[10] fuel-controlled chemical reactivity,[11] and fuel-driven molecular motion.[12] At the base of many of these discoveries are chemical reaction networks where a fuel can reversibly and thereby temporarily change the properties of a chemical building block. Fuel-driven chemical reaction networks capable of repeated operation are rare and in some cases have problems in terms of biocompatibility, harsh chemistry or irreversible side reactivity.[13] Therefore, there remains a need to design and develop novel fuel-driven chemical reaction networks. Fuel-driven transient material formation is a promising application of chemical reaction networks. Most examples of fuel-driven systems focus on non-covalent assembly of supramolecular materials.[13] It would also be interesting to develop a new fuel-driven reaction cycle that enables formation and breakdown of covalent bonds, for instance as crosslinks in a polymer material. As such, it would allow transient adjustment of the mechanical properties or porosity of soft materials. An essential part in the design of such a fuel-dependent polymeric material is that the reaction network contains both the bond forming and breaking processes. Here, we propose a novel fuel-driven chemical reaction network based on redox-controlled conjugate addition and elimination chemistry. We tested this cycle using several model reactions. Although we were able to demonstrate several individual steps in the cycle and observed some signs of operation of the full cycle, we were not able to demonstrate a full cycle in one pot, most likely due to substantial side reactivity of some of the cycle intermediates.

To realize a chemical reaction network with the desired effects, the reactions of the network have to fulfil a complex set of requirements: 1) run at ambient conditions on acceptable time scales; 2) be selective to the desired bond forming and breaking reactions; 3) form an unstable bond during the cycle; 4) regenerate the original bond formation precursor after a full cycle; 5) have only limited off-cycle reactivity of the fuel. Based on the above requirements, we here propose a new fuel-driven chemical reaction network.

The conjugate addition of a thiol to an electron deficient olefin (an enone) was chosen as the bond forming reaction. First, a thiol will be liberated by reduction of a disulfide using a reducing agent as fuel. This thiol reacts with an enone in a conjugate addition, to form a sulfide adduct, which can be further oxidized to a sulfoxide using an oxidizing agent. Elimination of a sulfoxide is prone to occur using base or under heating, regenerating the enone double bond.[14,15] The sulfenic acid elimination product can then react with a reducing agent to regenerate the thiol and close the cycle (Figure 1). Overall, the reductant acts as the fuel driving this cycle to transiently produce the sulfide addition product, which constitutes bond formation. Oxidation will lead to destabilization and elimination of the sulfide adduct, constituting bond breaking.

Before testing this fuel-driven cycle, some possible pitfalls associated to the chemistry in this cycle should be noted. Firstly, the oxidation of the sulfide to a sulfoxide requires a relatively strong oxidizing agent.[16,17] The presence of such an oxidant may also lead to irreversible epoxidation or dihydroxylation of the enone double bond[18] causing the removal of substrate from the cycle. To avoid this potential side-reaction, maleimide was selected as the first enone in our cycle because it is less prone to oxidation.[19,20] Based on literature procedures,

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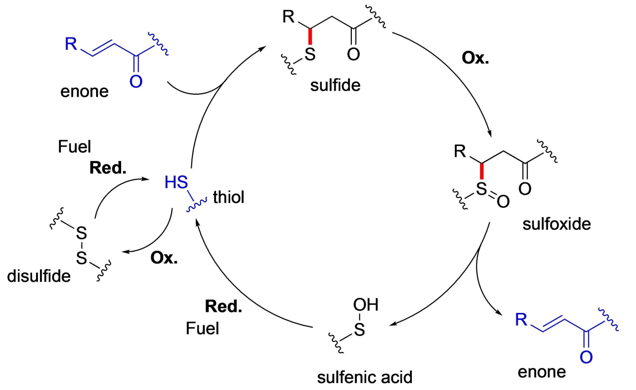

Figure 1. Proposed reductant-driven covalent bond formation in a conjugate addition chemical reaction network. The cycle starts when a disulfide is reduced by a reductant to a thiol. Then the thiol reacts with an enone to a sulfide adduct, which is subsequently oxidized to a sulfoxide by the oxidant. The elimination of the sulfoxide will release the enone and sulfenic acid, which can be reduced back to the thiol, closing the cycle. The substrates of the conjugate addition (the thiol and enone) are depicted in blue. The transiently formed covalent S–C bond is depicted in red. Ox. indicates oxidant, Red. indicates reductant.

we selected dichloromethane as solvent for the reaction network.[14,15] Secondly, the reductants and oxidants should be chosen carefully as they might react with each other in non-productive side reactions. If these side reactions outcompete the reaction cycle, the desired covalent bond will not be generated during operation of the cycle.

To gain insights in the operation of the cycle, the reaction network was split to four individual parts that were investigated separately. At each step the final products were isolated and applied as the reactant in the next reaction. Only after ensuring that every reaction step can take place under the same conditions, with high selectivity and high yield of the desired product, a sustainable cycle can be achieved. Then afterward, all reactions can be put in one pot to test the feasibility of this fuel driven cycle.

The conjugate addition reaction, as the mainstay of the network, was tested first. Catalyzed by triethylamine (10 mol %), thiophenol **2** reacts with *N*-phenylmaleimide **1** to give the sulfide product **3** at a nearly quantitative yield at room temperature within a few minutes (Figure 2). The isolated product **3** (Figure S1, Figure S2) was used as the starting material in the following oxidation step.

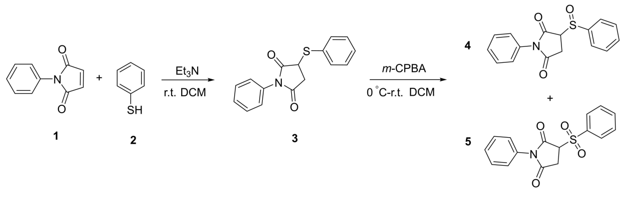

Figure 2. The conjugate addition of thiophenol **2** with *N*-phenylmaleimide **1** and the subsequent oxidation of **3** by *m*-CPBA.

The selective oxidation of sulfide **3** to sulfoxide **4** turned out to be a challenge (Figure 2).[21,22] Meta-chloroperoxybenzoic acid (*m*-CPBA), as one of the most common and efficient oxidants for the oxidation of sulfides in DCM, was first selected for this reaction step.[19,20] The ^{1}H NMR, ^{1}H-^{1}H COSY and ^{1}H-^{13}C HSQC and LC–MS spectra (Figure S3, Figure S5, Figure S6, Figure S14) show that the resulting mixture contains the desired sulfoxide **4** (~41 mol %), the over-oxidized sulfone **5** (~27 mol %), unreacted sulfide **3** (~25 mol %) and maleimide **1** (~7 mol %). The presence of maleimide **1** may be caused by the spontaneous elimination of sulfoxide or sulfone during workup after oxidation. The poor selectivity and low conversion in this oxidation indicate that *m*-CPBA is not an ideal oxidant in this cycle. Alternatively, hydrogen peroxide was also tested as an oxidant. H_2O_2 is a less strong oxidant compared to *m*-CPBA. The rate of oxidation by hydrogen peroxide may be enhanced using a vanadium catalyst that consists of VO(acac)$_2$ and a β-amino alcohol-derived Schiff base ligand.[23,24] Unfortunately, the ^{1}H NMR yields of **4** were ~7 % after 6 days without catalyst and ~13 % after 16 h when catalyzed by the vanadium-Schiff base complex catalyst. Sulfone **5** was also observed in both oxidation by only H_2O_2 and by H_2O_2 with the catalyst (Figure S8, Figure S10).

The next step in the cycle was the elimination of the sulfoxide to regenerate the enone. We tested this reaction on an inseparable mixture of sulfoxide **4** (~70 mol %), sulfone **5** (~29 mol %) and maleimide **1** (~1 mol %) (Figure S11), generated in the previous oxidation step.

The elimination tests were aimed at establishing whether the sulfoxide product could be converted into the enone and thiol or disulfide, so that the cycle can continue. This experiment was monitored using ^{1}H NMR. The reaction was performed in DCM at room temperature with a 0.1 molar equivalent of the same base is in the conjugate addition (triethylamine). However, no conversion of the oxidized mixture, or generation of maleimide **1** or sulfide **3** was observed. We then switched to 0.1 equivalent of the strong base 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU). Figure 4a shows the ^{1}H NMR spectrum for the starting materials of elimination. The spectrum shows peaks of sulfoxide **4** (2.60 and 3.99 ppm) and sulfone **5** (3.01 and 4.71 ppm), as well as a minor contribution (~1 mol %) from maleimide **1** at 6.86 ppm. Addition of DBU resulted in the disappearance of sulfoxide **4** and sulfone **5**. Surprisingly, after elimination no characteristic protons of maleimide **1** were present in the ^{1}H NMR spectrum but protons of addition product sulfide **3** (2.92 ppm and 4.16 ppm) were observed with a conversion of 17 % (Figure 4b). Also, several protons from unidentified by-products can be seen in the spectrum. (Figure S11). A possible explanation for the presence of sulfide **3** here is that a conjugate addition occurred between elimination product maleimide **1** and thiophenol **2**. The latter may have formed from the disproportionation of sulfenic acid **6** as the another product of elimination (Figure 3a and 3b). Sulfenic acids are inherently unstable and are prone to disproportionate to thiols and sulfinic acids (Figure 3b).[25–27] Although the final reaction did not yield the starting point maleimide and thiol, it does afford the adduct of maleimide

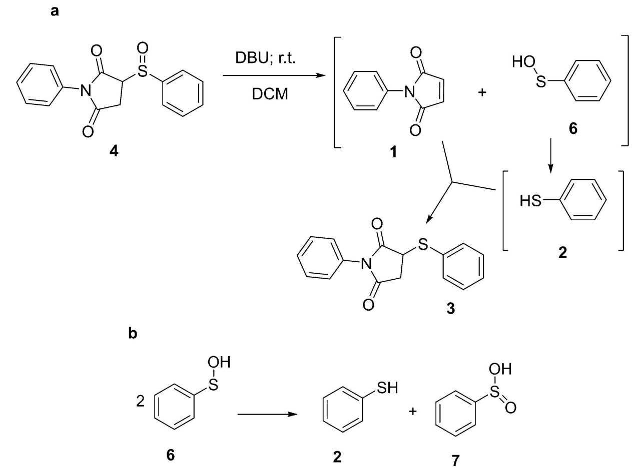

Figure 3. (a) Proposed elimination of sulfoxide **4**. (b) Proposed disproportionation of sulfenic acid **6** to give thiophenol **2** and sulfinic acid **7**. The compounds in brackets (maleimide **1**, sulfenic acid **6** and thiol **2**) indicate that they could be the intermediates which were not detected during characterization).

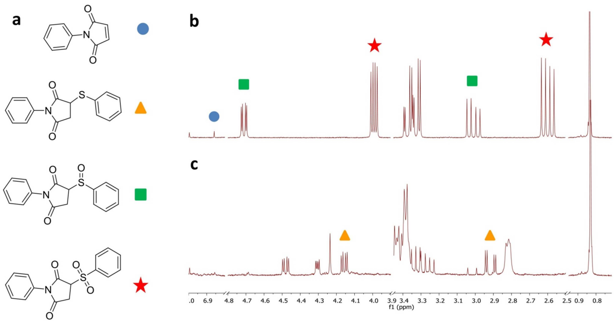

Figure 4. (a) The compounds during the elimination and their schematic representation. ^1H NMR spectra showing the characteristic protons of (b) the starting mixture for elimination: maleimide **1** (blue circle), sulfoxide **4** (green square) and sulfone **5** (red star); (c) sulfide **3** (yellow triangle) after the elimination.

and thiol. This result suggests that in principle it is possible to achieve the proposed chemical reaction network. In the original network, we proposed using a reductant to reduce the sulfenic acid to a thiol. Currently, this reaction is achieved by disproportionation instead of using an external reductant.

Nevertheless, several problems still exist regarding the elimination step. The first problem is inefficient elimination concluded by quantitatively analyzing the elimination conversion. We used ^1H NMR to follow the reaction and used methyltriphenylsilane as internal standard. The results show that all maleimide **1**, sulfoxide **4** and sulfone **5** were consumed completely after elimination, but to yield only 17 mol% sulfide **3**. The unidentified by-product peaks in NMR indicate that several side-reactions have happened during this experiment (Figure S12). Such by-product formation results in a substantial reduction of substrate incapable of participating in the cycle. Another reason of the low conversion to sulfide **3** might be that a substantial part of the starting compound thiol is converted to sulfinic acid **7** either by over-oxidation to sulfone and subsequent elimination, or by disproportionation of sulfenic acid **6** (Scheme S1; Figure 3b). The reduction of sulfinic acid back to thiol is nearly impossible so that it irreversibly removes a large portion of the starting substance thiol from the cycle.[28,29] A second problem is that it is difficult to investigate the reduction of sulfenic acid **6** to thiol **2.** As laid out in the original cycle, the reduction of sulfenic acid also needs to be tested as an essential path back to the thiol (Figure 1). Sulfenic acids are highly reactive molecules that are very difficult to isolate or even detect.[30] Therefore, we used the elimination of sulfoxide **4** and sulfone **5** by DBU to generate sulfenic acid in situ, followed by reduction using added triphenylphosphine (PPh_3) without intermediate purification. The mixture was stirred overnight at room temperature, after which it was analyzed by ^1H NMR (Figure S13). However, the ^1H NMR spectrum after reaction with PPh_3 indicated that the yield of sulfide **3** does not show a significant change (decreased ~1% within measurement error) and several more unidentified by-products appeared. At this point, it is difficult to say whether PPh_3 can reduce sulfenic acid, but PPh_3 does not promote formation of more sulfide **3**.

In summary, we have designed a new chemical reaction network for transient formation of covalent bonds, based on redox-controlled conjugate addition and elimination chemistry. We investigated the separate reactions making up the cycle starting at conjugate addition of thiophenol to *N*-phenylmaleimide. The conjugate addition product was used in subsequent oxidation and elimination steps, affording the conjugate addition product without observing the enone product (Figure 5). The bond formation, breakage and regeneration processes were successfully realized in separate reaction tests. Still, there are many obstacles to be overcome before this fuel-driven bond formation chemical reaction network can be applied as a continuous cycle. First of all, no external reductant was applied in this cycle. Under the current conditions, the

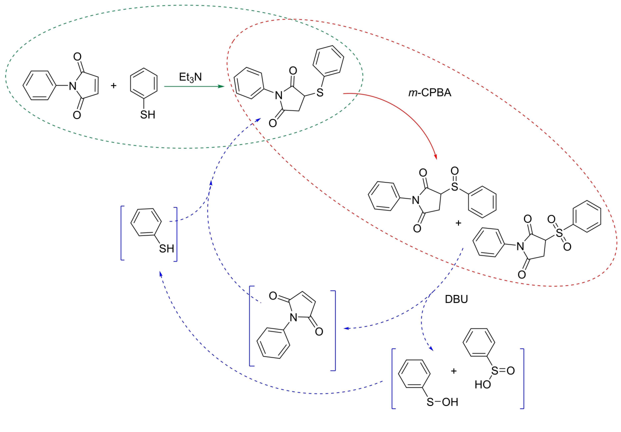

Figure 5. The conjugate addition chemical reaction network tested as separate reactions. The green arrow and dashed frame indicate the addition; the red arrow and dashed frame indicate the oxidation; the blue arrows indicate the elimination and subsequent sulfide formation. The brackets indicate that those compounds were not detected directly but their transient formation is implied by the formation of sulfide **3**.

observed sulfide formation may have originated from disproportionation of sulfenic acid leading to thiol formation and subsequent conjugate addition. Here, disproportionation also leads to removal of some of the thiol starting material from the cycle, in the form of sulfinic acid. Second, too many side reactions lead to a low yield of the desired products. Overoxidation of sulfide **3** by *m*-CPBA, side reactions of sulfenic acid and the possible disproportionation of sulfenic acid result in the irreversible formation of many undesired substances, limiting the efficiency and continuous operation of the cycle. Next, although *m*-CPBA was able to oxidize the sulfide to a sulfoxide, its strong oxidizing ability may cause problems when in the same system as a reducing agent. There, a mild oxidant is desired to achieve selective oxidation to the sulfoxide and to run the full cycle with all components in the system at the same time. Finally, we proposed a coupled cycle of thiol oxidation and disulfide reduction as part of the initial chemical reaction network (Figure 1). We did not test this coupled network as part of the presented results, but it is worthwhile to discuss it here. The thiol-disulfide redox pair reactions have to operate at similar timescales as the conjugate addition-elimination reaction cycle. If the thiol-disulfide cycle is much faster than major cycle, the majority of oxidant and reductant will be consumed unproductively. If the thiol-disulfide cycle is much slower, it will not supply enough thiol to the conjugate addition-elimination cycle. This part should be taken into account in future investigations.

On the whole, this fuel driven chemical reaction network provides an opportunity to achieve transient bond and material formation far from equilibrium. Experiments on separate parts of the cycle indicate that this cycle may work but at present several problems prevent running a full cycle continuously in a single system.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: chemical reaction networks · chemical fuels · conjugate addition · elimination · thiols

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