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Developments in Dynamic Covalent Chemistries from the Reaction of Thiols with Hexahydrotriazines

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Supporting Information

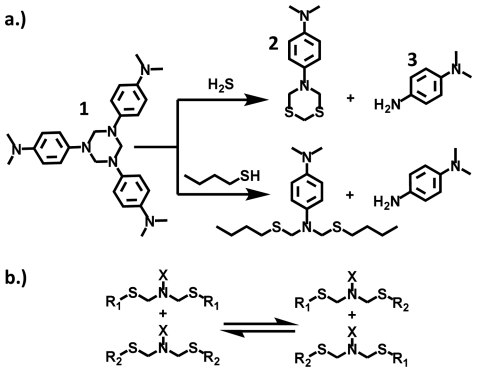
ABSTRACT: Dynamic covalent chemistries have garnered significant attention for their potential to revolutionize technologies in the material fields (engineering, biomedical, and sensors) and synthetic design strategies as they provide access to stimuli responsiveness and adaptive behaviors. However, only a limited number of molecular motifs have been known to display this dynamic behavior under mild conditions. Here, we identified a dynamic covalent motif—thioaminals—that is produced from the reaction of hexahydrotriazines (HTs) with thiols. Furthermore, we report on the synthesis of a new family of step-growth polymers based on this motif. The condensation efficiently proceeds to quantitative yields within a short time frame and offers versatility in functional group tolerance; thus, it can be exploited to synthesize both small molecule thioaminals as well as high molecular weight polymers from the step-growth polymerization of HTs with dithiols. Careful evaluation of substituted HTs and organic thiols supported by DFT calculations led to a chemically diverse library of polymers based on this motif. Finally, dynamic substitution reactions were employed toward the facile preparation of functional oligomers and macromolecules. This dynamic covalent motif is particularly attractive for a range of applications that include material design and drug delivery due to the economic feasibility of synthesis.

Dynamic covalent chemistries, where covalent bonds have the ability to be reversibly broken and reformed under equilibrium control, have attracted significant recent attention.[1] Through the manipulation of this equilibrium one can encourage formation of a desired product, reform starting materials, or exchange with additives to form new products. These reversible motifs have been incorporated into macromolecules enabling them, in response to a stimuli, to reorganize at the molecular-level which can translate to the macroscopic scale in remarkable material properties that include enhanced mechanical performance,[2a,b] self-healing,[2c−g] shape-memory,[2h,i] modulated fluorescence,[2j] and reversible gelation.[2k] Dynamic covalent chemistries are revolutionizing synthetic design strategies and the field of adaptive materials.

There are, however, only a limited number of molecular motifs known to undergo dynamic behavior under mild conditions. For instance, literature reports have extensively detailed the dynamic behaviors of acetals,[3a] alkoxyamines,[3b] borate esters,[3c−e] Diels−Alder cycloadditions,[2d] disulfides,[3g] hydrazones,[3h] imines,[3i] oximes,[3j] and olefins[3k] (metathesis). While these have provided a very wide range of structural variations, the number of these motifs has not grown significantly with the surge in interest of this field, though additional motifs have been reported.[4] In addition, dynamic covalent chemistries generally require a catalyst to trigger dynamic behaviors. For instance, hydrozones require an acid catalyst,[5] disulfides will respond to redox conditions as well as light, and olefins a metathesis catalyst. There are few examples of catalyst free dynamic covalent motifs (Diels−Alder cycloadditions and alkoxyamines but these have very specific structural requirements). The discovery of dynamic covalent motifs that offer catalyst free responses has significant advantages in applications where the addition of a catalyst may not be tolerated such as the biomedical realm.

Described herein is a new family of step-growth polymers from the facile transformation of hexahydrotriazines with dithiols under mild conditions to yield poly(thioaminal)s. Interestingly, the thioaminal repeat unit of these polymers was found to be a dynamic covalent motif that undergoes exchange reactions

Scheme 1. (a) Reaction of Hexahydrotriazine with Hydrogen Sulfide (top) and Butane Thiol (bottom) and (b) Exchange Reaction between Thioaminals



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through a chemical trigger, thiol additives, confirmed by both experiment and computation.

1,3,5-hexahydro-1,3,5-triazines (HTs) have found recent materials applications in healable gels and thermosetting high-modulus materials as well as use in the detection of heavy metals.[6] One particularly unique reaction of HTs involves the formation of dithioazines from hydrogen sulfide (Scheme 1).[7] From our investigations this transformation was found to be quantitative under mild conditions (25 °C) and inspired us to expand on the range of sulfur containing substrates that would undergo similar reactions (Figures S1, S2).[3k] We extended the scope of this transformation by investigating the reaction between 1-butanethiol and **1** following the reaction with ^{1}H NMR (Figure S3). Gratifyingly, this reaction proceeds to the dithioaminal also in quantitative yields, though the reaction requires longer time for full conversion (reaction is complete after ~80 min vs 30 min for dithiazine) (Scheme 1).

To obtain a more comprehensive understanding of these transformations, computational studies with the dispersion-corrected B3LYP-D3 method were employed to investigate mechanisms involved in dithioazine formation in the reaction of Me-HT with H_2S (Figure 1). It is intriguing that the reaction of between HT and H_2S does not result in the formation of trithioazine, in which all of the amino groups were replaced by sulfur, but instead stops after formation of dithioazine. The mechanism for the reaction between H_2S and Me-HT involves the opening of the HT ring concurrent with the insertion of thiol into the ring-opened heterocycle (see SI).[8] Calculations indicate that dithioazine formation is favored over trithiane formation due to the fact that the free energy barrier for dithiazine formation is 19 kcal/mol, almost 27 kcal/mol lower than that for formation of trithiane (see SI for details). This preference for dithioazine formation may be simply understood considering the relative free energy barrier for insertion of H_2S into the C−N bond adjacent to the sulfur atom in **5** is 39 kcal/mol, which is 29 kcal/mol larger than the barrier for formation of the regioisomeric product by the insertion of H_2S into the C−N bond adjacent to the other nitrogen atom in **8**. This large difference can be simply understood by considering that a partial positive charge develops on the breaking carbon atoms next to the sulfur or nitrogen atoms in the transition states for these reactions (Figure S4). Evidently, the partial positive charge is better stabilized by the neighboring nitrogen atom than by sulfur leading to the lower barrier for insertion of H_2S into the C−N bond adjacent to nitrogen atom. Since insertion of a third molecule of H_2S will always lead to neighboring sulfur atoms interacting with partial positive charge in the transition state, it is unsurprising that the free energy barrier for trithiane formation is large and that the reaction exclusively favors formation of the disubstituted product under mild conditions. Reactions of HTs with alkanethiols will also lead exclusively to the formation of bis-substituted products. However, in contrast to reactions of HTs with H_2S, those involving alkanethiols are more likely to proceed via a different mechanism involving protonation and insertion by a single molecule of the alkanethiol because of steric effects (Figure S5). Despite the different mechanisms, the exclusive formation of a disubstituted product in quantitative yields lends support to the utilization of this transformation as a polymer forming process.

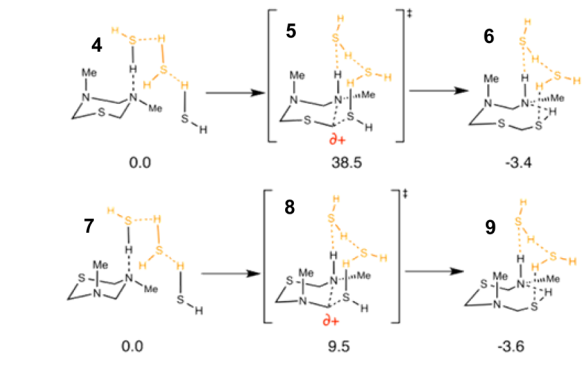

Figure 1. Computed mechanism for insertion of H_2S into the heterocyclic ring of 3,5-dimethyl-1,3,5-thiodiazine (a) adjacent to sulfur (top) adjacent to nitrogen (bottom). Relative free energies are shown below each structure.

Initial attempts at the polymerization of **1** and **11** (1,6-hexanedithiol) at 25 °C in *N*-methyl-2-pyrrolidone (NMP) only resulted in oligomer formation; no high molecular weight polymer was formed. The reaction mechanism suggests that small molecule amine byproducts are generated during the thioaminal formation which could in turn affect the reaction equilibrium and thereby prevent the formation of high molecular weight polymer. In the case of **1** the amine generated (**3**) is a high boiling point material (BP = 262 °C) that would be difficult to remove from the reaction by conventional means, such as vacuum. Therefore, a methyl-HT (**10**) was selected for it is ability to form a low boiling point amine (BP = 22 °C) that could be removed by vacuum. The change in substituents also affected the reactivity of this monomer toward thiols. Model studies of **10** showed little conversion with 1-butanethiol at room temperature; higher temperatures (85 °C) were found necessary to facilitate a reaction with thiols. For the polymerization reaction the components **10** and **11** were miscible liquids with boiling points higher than these reaction conditions (162 and 242 °C, respectively). Therefore, subsequent reactions were simply carried out in bulk without the need for solvent. However, it was found that application of vacuum to the reactions involving **10** can lead to changes in the ratio of monomers. Therefore, the polymerization was carried out in two steps to reduce the degree to which the stoichiometry changes during this reaction. The first involved the reaction of **10** and **11** in a sealed vessel over the course of 18 h at 85 °C; this was intended as a means to oligomerize components and was followed by the application of a continuous vacuum to remove the volatile side-product. After the first step of this procedure (18 h) as

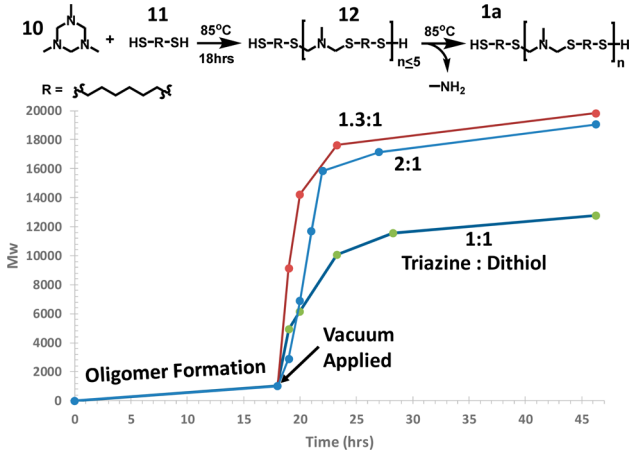

Figure 2. Polymerization method and graph of molecular weight as a function of time for varying ratios of hexahydrotriazines to 1,6-hexane dithiol. Data points are connected for clarity.

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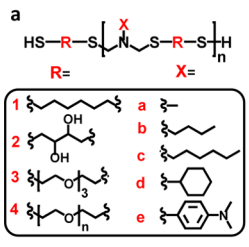
anticipated, low molecular weight oligomers were observed by GPC (Figure 2). When a vacuum was then applied the molecular weight dramatically increased from oligomers (M_n < 1000 g mol^{-1}) to 9000 g mol^{-1} (Figure 2). The molecular weight was observed to continually increase and plateau after ~7 h at a M_n of 17,600 g mol^{-1} and further increased to 19,800 g mol^{-1} with an additional 23 h of applied vacuum at 85 °C. Beyond 28 h, however, the molecular weight was observed to decrease after 46 h. Even with an oligomerization step changes in stoichiometry were still observed. Cold trapping of the species removed by vacuum confirmed the removal of monomer as well as the presence of a small molecule amine (Figure S9).

The chemical diversity of this polymerization was explored using a variety of HT monomers prepared and purified according to previously reported literature procedures.[9,10] The size of the HT substituent **X** was systematically varied, and its effect on the generation of polymer explored (Figure 3a). From the variety of



b

	Mw (g mol^{-1})	Mn (g mol^{-1})	PDI	T_g(°C)	η (Pa · S)‡
1a	19,800	8,100	2.4	-59.1	107.1
1b	17,100	9,000	1.9	-64.3	297.0
1c	8,700	4,900	1.8	-64.5	7.8
1d	5,200	2,900	1.8	-25.8	115.9
1e*	≤2,000	≤1,500	--	--	--
2a	3,800	2,500	1.5	50.8	--
3a	15,000	7,500	2.0	-44.4	46.8
4a	35,600	20,700	1.7	-50.5†	--

‡ measured at 20°C
† MDSC also indicates T_c at 46.4°C
* High retention times, approximation

Figure 3. (a) Chemical compositions of poly(thioether)s prepared. M_w of PEG dithiol (4) 3400 g mol^{-1}. (b) Molecular weight values and thermal and physical properties of associated poly(thioether)s.

HT monomers employed it was observed that the size of the HT substituent influenced the maximum molecular weight of the resulting polymer, where larger substituents resulted in lower molecular weights (Figure 3b). The smallest methyl-substituted HT produced a polymer with M_w of 19.8 kDa, while the cyclohexyl-substituted HT only produced a polymer with an M_w of 5.2 kDa. The use of **1** did not result in polymer formation. This effect is related to the volatility of the byproduct amine generated during reaction. As the mass of substituent **X** increases, the volatility of the small-molecule byproduct of the reaction is reduced, thereby making the polymerization increasingly difficult to drive to high molecular weights. It was also observed that as the size of the substituent **X** increased, the glass transition temperature of the resulting polymer to decreased from −59.1 °C in polymer **1a** to −64.3 °C in polymer **1b**. No obvious trend in thermal stability was observed with the variety of monomers utilized; most of the polymers experienced weight loss at ca. 150 °C and proceeded to 5 wt % at ca. 220 °C. The majority of weight loss (95−20 wt %) occurred between 220 and 300 °C (Figure S10).

Polymers were also prepared using a range of dithiol monomers. As this component does not generate a byproduct that is subsequently removed, the volatility of the monomer is not a consideration. Therefore, monomers of varying lengths (up to low molecular weight polymer dithiols) and bearing different chemical functionalities were employed (Figure 3a). It was observed, through the dithiol monomers utilized, that what appeared to limit the final polymer molecular weight was the glass transition temperature (T_g) of the resulting polymer. As T_g increases, the molecular weight of the polymer generated decreased. As one may anticipate a kinetically controlled process under these conditions.

DSC measurements of these polymers revealed no obvious trend when varying the HT monomer, though a significant difference in the thermal transitions of linear aliphatics (HT R = a,b,c) compared with the cyclohexyl HT substituent ca. −30 vs −47 °C, respectively. The series of dithiol monomers used lead to large variations in these thermal transitions (all DSC data available, see SI).

The structural similarity between thioaminals and known chemically responsive dynamic covalent moieties (e.g., hemiaminals and imines) motivated investigations as to whether this motif is also dynamic covalent. It was surmised that if the material is a chemically responsive structurally dynamic polymer, the presence of a monofunctional thiol should completely depolymerize the polymer and result only in oligomer. Furthermore, because the equilibrium of a dynamic process can be readily manipulated if the monofunctionalized thiol is sufficiently volatile, the polymer should, in principle, be able to be regenerated by its removal. The depolymerization was carried out with polymer **1a** (M_w 17,985 g mol^{-1}) in the presence of a large excess of a monofunctional 1-butanethiol. After heating this mixture for 1 h at 40 °C a GPC trace revealed complete depolymerization. Only low molecular weight oligomers were observed (Figure 4); a result consistent with a polymer that

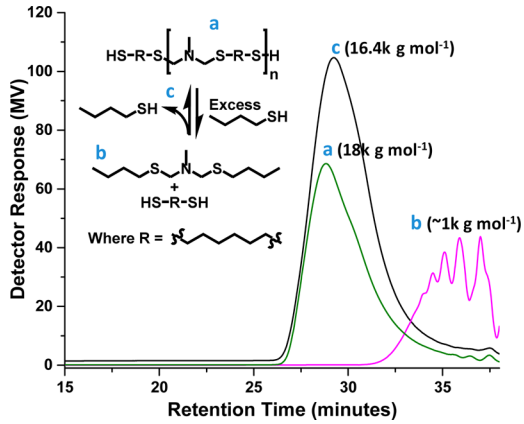


Figure 4. Polymer **1a** (18k, GPC trace a) can be depolymerized with excess of 1-butanethiol (GPC trace b). Removal of 1-butanethiol with vacuum repolymerizes the small molecules to produce a molecular weight similar to the starting polymer **1a** (GPC trace c).

becomes dynamic under the appropriate chemical trigger. The mixture was then heated at 80 °C under vacuum over a period of 18 h to remove the small molecule 1-butanethiol. Gratifyingly, high molecular weight polymer could be regenerated, and GPC of this material displays an M_w of 16,382 g mol^{-1}. In comparison to the original polymer regeneration recovered 91% of the original molecular weight. This result indicates the thioaminal linkage is a chemically responsive dynamic covalent bond; this is useful, which provides access to the facile incorporation of thiol-containing molecules such as therapeutics.

The dynamic covalent character of these poly(thioaminals) was further explored in the preparation of functional oligomers using thiol containing end-capping agents. This was carried out using a mixture of polymer **1a** (M_w = 8768 g mol^{-1}) in a $CHCl_3$ solution together with 2 mol % 4-mercaptophenol. The combination of

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these two followed by 1 h reaction time at 40 °C resulted in a decrease in the total molecular weight of the polymer (Figure S35). The end-capping reaction was further confirmed by ^{1}H NMR by the diagnostic peak *j*, which corresponds with the formation of a thioaminal bond between the aromatic thiophenol and polymer **1a** (Figure S36). GPC traces of polymer **1a** before and after functionalization are consistent with end group functionalization where the molecular weight of the starting polymer (M_n = 8.8k g mol^{-1}) is significantly reduced to M_n = 1.9k g mol^{-1} after reaction with thiophenol (Figure S36). This method of preparing functional oligomers was tolerant to $-NH_2$, $-OH$, and $-$ COOH functional groups, which can be used as handles for further chemical transformations (Figure S37).

The dynamic behavior of the thioaminal bond was triggered by a chemical stimulus and a thiol additive and accelerated by increases in temperature. The stability of a water-soluble poly(thioaminal) was studied in water. Stirring polymer **4a** at 25 °C in water and found to degrade over the course of 90 h (Figure S38), indicating the thioaminal linkeage is susceptible to hydrolysis (Figure S36).

One application for poly(thioamimnal) may include the preparation of therapeutic polymer conjugates. In principle, this would simply require mixture of a thiol-containing therapeutic with the desired poly(thioaminal) and mild heating. This was explored with water-soluble PEG based **4a** and a doxorubicin (DOX) derivative bearing a thiol group that was prepared by a literature procedure.[10] After addition of the two components in a water/acetonitrile mixture at elevated temperatures (80 °C) a sawtooth-like pattern was observed by GPC believed to relate to DOX attachement to integer numbers of the PEG repeat unit (M_n 3400 g mol^{-1}) (see SI for full characterization).

We presented a new polymer forming reaction between hexahydrotriazines and dithiols carried out in solvent free reaction conditions to produce poly(thioaminals). A broad range of chemically diverse polymers can be produced by this strategy that is limited primarily by the volatility of the amine generated during polymer formation. Furthermore, the thioaminal linkage is dynamic covalent triggered by thiols. This provided access to polymers that can be depolymerized and repolymerized and to the facile preparation of functional oligomers. The ability to undergo exchange reactions is particularly suited for applications in the facile preparation of drug conjugates and as a loading strategy.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b08815.

Experimental details and data (PDF)

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Notes

The authors declare no competing financial interest.

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