A User's Guide to the Thiol-Thioester Exchange in Organic Media: Scope, Limitations, and Applications in Material Science

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The exchange of thiolates and thiols has long been held as a nearly ideal reaction in dynamic covalent chemistry. The ability for the reaction to proceed smoothly in neutral aqueous media has propelled its widespread use in biochemistry, however, far fewer applications and studies have been directed towards its use in material science which primarily is performed in organic media. Herein, we present the exploration of this dynamic exchange in both small molecule and polymer settings with a wide sampling of thiols, thioesters, organic bases, and nucleophilic catalysts in various organic solvents. Effects of the character of the thiol and thioester, pKa or nucleophilicity of the catalyst, and heat on the reaction were investigated. The mechanism regarding the previously unexplored effectiveness of nucelophilic catalysts, such as quinuclidine or DABCO, to affect the thiol-thioester exchange was also explored. Finally, the use of the thiol-thioester exchange in a network polymer to reduce applied stresses or change shape of the material following polymerization was shown and the ability of basic and nucleophilic catalysts to promote these effects were benchmarked. The influence of polarity in these networks was also explored, with the rate of exchange shown to be easily tuned by the addition of diluents with varying polarities. Presented here is a so-called "user's guide" to the thiol-thioester exchange; we hope that this guide is instructive to practitioners in the field of material science which seek to utilize the thiol-thioester exchange in both linear and network polymers.

Introduction

Dynamic bonds are covalent linkages which, if placed under the correct conditions, can form an equilibrium between the exchanging reactants and their products.[1] As the field of chemistry has matured, reactions which display this dynamic behaviour while having sufficiently rapid kinetics,[2] excellent chemoselectivity, and occur under operationally simple, ambient reaction conditions have been discovered and developed.[3] One such reaction, which exemplifies the "gold standard" of this subset of covalent bonds is the thiol-thioester exchange (**Fig. 1A**). This reaction allows for the efficient, often stoichiometric (1:1 thiol:thioester) interchange of functionality at low concentrations, in the presence of multiple functional groups, at room temperature, and in aqueous media. The latter point makes this dynamic linkage ideally suited for use with biomolecules, which are predominately water soluble. Accordingly, the thiol-thioester exchange has been utilized in the presence of or attached to biomolecules to reversibly, yet productively, induce proximity between two units (see: Kent's Native Chemical Ligation, NCL, **Fig. 1B**),[4] sample various macromolecular conformations (see: Gellman's backbone thioester exchange, **Fig. 1C**),[5] or to form a large library of different compounds *in situ* for selection of tightly binding ligands (see: Larson's self-screening dynamic combinatorial thioester library, **Fig. 1D**);[6] each of these demonstrations employs water as the primary reaction solvent. Moreover, past kinetic studies regarding this exchange by Castro,[7] Hupe and Jencks,[8] Bruice,[9] and Whitesides[10] were performed solely in aqueous media.

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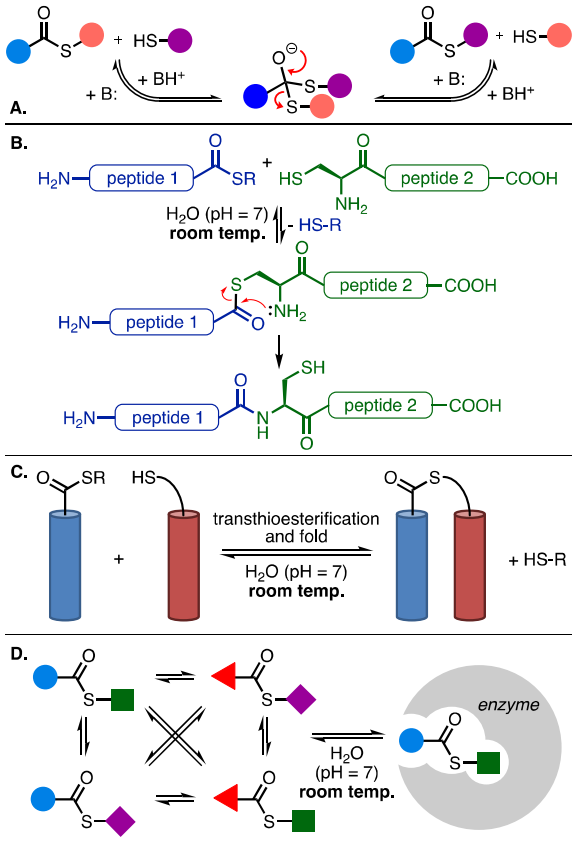


Fig. 1 **A.** The mechanism of the base-promoted thiol-thioester exchange; **B.** The productive exchange of an N-terminal cysteine and a C-terminal thioester to induce intramolecularity between two peptide units, subsequent intramolecular S→N acyl transfer yields the native peptide bond; **C.** exchange of a thiol with a C-terminal thioester to evaluate higher order structural stability in small, foldable peptides in the presence of a competing small molecule thiol incapable of forming a folded ensemble; **D.** dynamic exchange of multiple thiols and thioesters to produce a large library of compounds in the presence of an enzyme to rapidly discover the tightest binding ligand *in situ*.

Whereas evident application of the thiol-thioester exchange has been made in biochemistry, few, if any, uses in material and polymer sciences can been noted. In light of our lab's recent efforts towards the development of thiol-x chemistries to produce both network and linear polymers,[11] it is our belief that a thioester linkage which utilizes free thiols to undergo dynamic exchange could be seamlessly and conveniently integrated. The incorporation of this dynamic bond into a polymer would allow for rapid, post-polymerization reorganization of the ensemble in response to an external stimulus if accessible thiolate is present. However, one caveat must be considered: due to issues of solubility in water mixtures, the formation and subsequent processing of many polymers are normally performed in organic media or in bulk. This stands in stark contrast to previous reports which studied structure/activity relationships and kinetics of the thiol-thioester exchange in aqueous media. As multiple applications of a post-polymerization exchange in thiol-x based polymers could be envisioned,[12] understanding the scope, limitations, and capabilities of the exchange of thiols with thioesters in organic solvents and how factors such as the character of the thiol, thioester, and catalyst affect the exchange will first need to be more deeply explored.

In this report we probe the exchange of a panel of thiols and thioesters in a broad sampling of organic solvents with diverse polarities to ascertain the capabilities and limitations of this reaction utilizing alternative media and catalysts. The members of these panels were purposefully selected to give both a comprehensive overview of the reactivity of commercial thiol-containing building blocks and for their ability to be easily attached to various cores to form multifunctional monomers. Further investigation regarding the effect of pKa of both the thiol and organic base, as well as the character of the solvent were also undertaken. The effect of heating on the thiol-thioester exchange was also explored. The peculiar efficiency of highly nucleophilic catalysts to promote the thiol-thioester exchange was discovered and the mechanism of this process was explored. Proof-of-concept demonstrations of the thiol-thioester exchange to productively relax stress and effect shape change in a network polymer, utilizing the conditions developed here, is presented. It is our devout hope that this report represents a comprehensive and detailed overview of the triumphs and pitfalls of the transthioesterification reaction in organic media.

Practitioners attempting to utilize this dynamic reaction in material pursuits will hopefully find this so-called "user's guide" instructive towards monomer design, catalyst selection, and formulation of their polymers. Moreover, we anticipate that due to the robust and modular nature of this exchange, as described below, that use in both linear and networks polymers to modulate molecular weight, rearrange backbone sequence, or reduce/remove applied stresses will be evidenced. This paper constitutes an initial stepping stone to practitioners working in material science to broadly incorporate the thioester functional group into polymers, especially those derived from thiol-x chemistries.

Experimental

Materials

All reactions were carried out under an argon atmosphere with dry solvents using anhydrous conditions unless otherwise stated. ^{1}H NMR (400 MHz) and ^{13}C NMR (101 MHz) were recorded in C_6D_6 (internal standard: 7.15 ppm, ^{1}H; 128.26 ppm, ^{13}C), in THF-d_4 (internal standard: 3.58 ppm, ^{1}H; 67.57 ppm, ^{13}C), in $CDCl_3$ (internal standard: 7.26 ppm, ^{1}H; 77.00 ppm, ^{13}C), in MeCN-d_3 (internal standard: 1.94 ppm, ^{1}H; 118.3 ppm, ^{13}C), in DMSO-d_6 (internal standard: 2.50 ppm, ^{1}H; 39.52 ppm, ^{13}C), in MeOD-d_3 (internal standard: 3.31 ppm, ^{1}H; 49.15 ppm, ^{13}C), on a Bruker DRX-400MHz spectrometer. Chemical shifts (δ) were reported as parts per million (ppm) and the following abbreviations were used to identify the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, sept. = septet, m = multiplet, b = broad and all combinations

thereof can be explained by their integral parts. Column chromatography was carried out employing EMD (Merck) Geduran Silica Gel 60 (40-63 μm) with the indicated solvent mixtures. The following chemicals: 2-mercaptopyridine (99%), thiophenol (97%), s-phenyl thioacetate (98%), 1-octanethiol (98.5%), methyl 3-mercaptopropionate (98%), cysteamine (~95%), acetyl chloride (98%), pyridine (anhydrous, 98.8%), 1-heptanol (98%), diethylene glycol methyl ether (>99%), and 2-tert-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (>98%) were purchased from Sigma-Aldrich and used as received. The following chemicals: di-tert-butyl dicarbonate, triethylamine, 1,8-diazabicyclo[5.4.0]undec-7-ene were purchased from Chem-Impex and used as received. 2-(boc-amino)ethanethiol was prepared using published procedures.[13] All deuterated solvents utilized in this study (C_6D_6, THF-d_4, $CDCl_3$, MeCN-d_3, DMSO-d_6, and MeOD-d_3) were obtained from Cambridge Isotope Laboratories, Inc. and were used as received.

General procedure for the acylation of thiols (compounds 1b – 1f).

To a 250 mL round-bottomed flask equipped with a magnetic stir bar was added 20.0 mmol (1.00 equiv) of a given thiol, this was diluted with 65.0 mLs (~0.30 M) of reagent grade dichloromethane (DCM), and stirred at room temperature until a homogeneous solution had formed. The flask was equipped with an ice bath and allowed to cool to an internal temperature of ~5°C. After this period, 4.18 mLs (3.04 grams, 30.0 mmol, 1.50 equiv) of triethylamine (TEA) was added via syringe in a single portion and the reaction mixture was allowed to re-equilibrate to an internal temperature of ~5°C (approximately 5 minutes). Then 2.13 mLs (2.36 grams, 20.0 mmol, 1.50 equiv) of acetyl chloride was added dropwise via syringe over the period of 10 minutes; following this addition the reaction flask was capped, the ice bath was removed, the reaction mixture was allowed to warm to room temperature and stir overnight (~16 hours). After this period, ~65.0 mLs of aqueous HCl (1N) was slowly added to the reaction mixture and the biphasic solution was rapidly stirred for ~15 minutes at room temperature. The biphasic mixture was transferred to a 250 mL separatory funnel and after separation from the first aqueous layer was washed additionally with an aqueous solution of 1N HCl (~65 mLs, 1X), an aqueous solution of $NaHCO_3$ (~65 mLs, 2X), brine (~65 mLs, 1X), dried over Na_2SO_4, filtered, and the combined organics were concentrated *in vacuo*. The crude residue was submitted to column chromatography (generally: 0% EtOAc/100% hexanes → 5% EtOAc/95% hexanes → 10% EtOAc/90% hexanes) and concentration of selected fractions gave the desired thioester product which was used directly with no further purifications.

Acylated 2-mercaptopyridine (1b). 1.73 grams; 56% yield; red/brown oil; R_f = 0.29 (TLC conditions: 30% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ= 8.62 (ddd, *J*= 4.9, 1.9, 0.9 Hz, 1H), 7.79 – 7.71 (m, 1H), 7.61 (dt, *J*= 7.9, 1.0 Hz, 1H), 7.30 (ddd, *J*= 7.5, 4.9, 1.2, Hz, 1H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C) 192.99, 151.52, 150.38, 137.45, 130.25, 123.74, 30.87.

Acylated 1-octanethiol (1c). 3.68 grams; 98% yield; clear oil; R_f = 0.53 (TLC conditions: 10% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ= 2.86 (t, *J*= 7.32 Hz, 2H), 2.91 (s, 3H), 1.59 – 1.52 (m, 2H), 1.38 – 1.26 (m, 10H), 0.87 (t, *J*= 6.81 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C) 196.22, 31.93, 30.79, 29.95, 29.32, 29.29, 29.23, 28.98, 22.78, 14.24.

Acylated 2-(boc-amino)ethanethiol (1d). 4.29 grams; 98% yield; clear oil; R_f = 0.32 (TLC conditions: 20% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ= 3.69 (s, 3H), 3.11 (t, *J*= 7.0 Hz, 2H), 2.63 (t, *J*= 6.94 Hz, 2H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C) 195.61, 172.24, 51.99, 34.30, 30.68, 24.33.

Acylated methyl 3-mercaptopropionate (1e). 3.11 grams; 96% yield; clear oil; R_f = 0.33 (TLC conditions: 10% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ= 4.80 (bs, 1H), 3.31 – 3.27 (m, 2H), 3.00 (t, *J*= 6.53 Hz, 2H), 2.34 (s, 3H), 1.43 (bs, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C) 195.86, 155.89, 40.11, 30.77, 29.52, 28.50.

General procedure for the allylation of mono-alcohols (compounds 3a – 3b).

To a flame dried 100 mL round-bottomed flask equipped with a magnetic stir bar under an atmosphere of argon was added 30.0 mLs (1.00 M) of dry THF via cannula. To this flask was added 1.38 grams (36.0 mmol, 1.20 equiv) of sodium hydride (~60% suspension in mineral oil, quickly washed before use with hexanes to remove the mineral oil) and the flask was equipped with an ice bath and allowed to cool to an internal temperature of ~5°C. To this now cooled reaction mixture, 30.0 mmol (1.00 equiv) of the mono-alcohol (either diethylene glycol methyl ether or 1-heptanol) was added dropwise over the course of ~10 minutes using a syringe and the ice bath was removed following this addition. The reaction was allowed to stir for an additional 1 hour at room temperature to ensure the complete deprotonation of the alcohol species. After this period the flask was re-equipped with an ice bath and once again cooled to an internal temperature of ~5°C. To this now cooled reaction mixture, 3.12 mLs (4.36 grams, 36.0 mmol, 1.20 equiv) of allyl bromide was added dropwise via syringe over the course of ~10 minutes, the ice bath was removed following this addition, and the reaction was allowed to stir for an additional 3 hours at room temperature. After this period the septum of the flask was removed, water was slowly dripped into the flask with stirring until no further bubbling occurred (formation of H_2 from the destruction of excess NaH), and the slow addition of water was continued until a clear solution had formed. The volatile components of the now quenched reaction mixture were removed *in vacuo* to give a crude, viscous residue. This viscous residue was dissolved in reagent grade DCM (~100 mLs), transferred to a 250 mL separatory funnel and was washed with water (~100 mLs, 1X), brine (~100 mLs, 1X), dried over Na_2SO_4, filtered, and the combined organics were concentrated *in vacuo*. Utilizing this procedure, allylated **3a** was found to be sufficiently pure after workup and was used directly with no further purifications. In the case of allylated **3b** some starting material remained and the crude residue was submitted to column chromatography (0% EtOAc/100% hexanes → 5% EtOAc/95% hexanes). Concentration of the selected fractions gave the desired allylated product **3b** which was used directly with no further purifications.

Allylated diethylene glycol methyl ether (3a). 2.46 grams; 51% yield; clear liquid; R_f = 0.19 (TLC conditions: 20% EtOAc/hexanes – as visualized by a $KMnO_4$ stain); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ= 5.98 – 5.89 (m, 1H), 5.32 – 5.18 (m, 2H), 4.04 (dt, *J*= 5.7, 1.4 Hz, 2H),

3.70 – 3.57 (m, 8H), 3.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C) 134.88, 117.28, 72.40, 72.07, 70.80, 70.72, 69.54, 59.20.

Allylated 1-heptanol (3b). 2.02 grams; 42% yield; clear liquid; R_f = 0.52 (TLC conditions: 10% EtOAc/hexanes – as visualized by a $KMnO_4$ stain); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ= 5.97 – 5.87 (m, 1H), 5.29 – 5.15 (m, 2H), 3.96 (dt, *J*= 5.6, 1.4 Hz, 2H), 3,42 (t, *J*= 6.7 Hz, 2H), 1.62 – 1.55 (m, 2H), 1.37 – 1.23 (m, 2H), 0.88 (t, *J*= 6.84 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C) 135.24, 116.84, 71.94, 70.67, 31.97, 29.92, 29.33, 26.30, 22.77, 14.25.

NMR studies.

See supporting information for exact details of each NMR experiment.

Formation of crosslinked thioester network polymers via photopolymerization.

To a 10.0 mL speed mixer vial was added 250 mgs (0.87 mmol, 1.00 equiv) of **TEDAE**, 427 mgs (0.87 mmol, 1.00 equiv, "100% excess thiol") of pentaerythritol tetra(3-mercaptopropionate) (**PETMP**), and the basic or nucleophilic catalyst. This clear resin was then manually mixed with a pipette tip for ~2 minutes to make a homogenous mixture. Following this, approximately 8.91 mgs ($3.48x10^{-2}$ mmol, 0.04 equiv, 4.00 mol%) of 2,2-dimethoxy-2-phenylacetophenone (DMPA), which had been crushed with the flat side of a spatula to form a fine powder, was added and the resin was further manually mixed with a pipette tip for an additional ~2 minutes to form a homogeneous mixture. At this time the clear resin was poured between two glass slides treated with Rain-X (ITW Global Brands, Houston, TX) using 250 µm thick spacers (Small Parts Inc., Logansport, IN). The material was irradiated (365 nm, 5.00 µW/cm^2, room temperature) for ~10 minutes to yield the thioester-containing crosslinked network polymer. The conversion was found to be essentially quantitative by FT-IR, revealing complete consumption of the "ene" species. These fully-formed polymers were used directly for all subsequent studies.

Dynamic Mechanical Analysis (DMA).

All stress relaxation experiments were performed in tensile elongation using a Q800 DMA (TA Instruments) or a RSA-G2 (TA Instruments). For stress relaxation, the built-in stress relaxation mode was used, with a 10% strain for ambient temperature tests. For temperature stepping tests, which are performed repeatedly on the same sample, a 4% strain was used to avoid significant sample deformation between scans. Films were cut into rectangular sections and measured with callipers prior to loading into the DMA.

Fourier transform infrared spectroscopy (FT-IR)

Fourier Transform Infrared Spectroscopy was performed using a Nicolet 6700 FT-IR, Thermo Scientific. Samples were prepared by placing the resin in between two NaCl salt plates and sheering the sample without the use of any spacers. The polymerization reaction was initiated using a 365 nm LED (50.0 mW/cm^2). The light was switched on after 60 seconds of data acquisition. Functional group conversion was monitored by measuring a decrease in the thiol functional group at 2560 cm^{-1}. Conversions were calculated by the ratio of peak area to the peak area prior to the reaction.

Results and Discussion

As was stated in the introduction, the thiol-thioester exchange reaction is normally performed in aqueous media where a significant number of pKa values for both thiols and bases have been tabulated. Thus, predicting the ability of a thiol to form a thiolate and undergo this dynamic exchange is trivial. However, far fewer, if any, pKa values have been tabulated for thiols or bases in organic solvents, especially so for solvents of lower polarity. Thus, predicting the ability of a thiol to form a thiolate in organic media *de novo* is far more troublesome. Here we have sought to utilize a wide sampling of thiols that ranged in p*K*a (in regards to the thiol), of which almost no known pKa values in organic solvents are reported, and would be able to be attached to/or part of accessible multifunctional cores. Accordingly, the commercial thiols, as can be seen in Figure 2 (*right*), were chosen. For the sake of simplicity, the selected thioesters were merely the acylated analogues of the thiol panel, as also can be seen in Figure 2 (*left*). With these representative thioesters and thiols in hand, we devised an experiment where their exchange in various organic solvents would be monitored by ^{1}H-NMR and quantified in comparison to an internal standard (1,3,5-trimethoxybenzene). Calibration curves of each of the thioesters at various concentrations in comparison to the internal standard were collected and used to correct for any instrumental error. Organic solvents which are *i*. most commonly used by practitioners in the field, *ii*. have a wide range of polarities (P' = 3.0 to 6.6), and *iii*. are commercially available as their exhaustively deuterated analogues (benzene, THF, chloroform, acetonitrile, DMSO, and methanol) were selected. Triethylamine (TEA-H$^+$, pKa = 10.8 in H_2O), due to its wide availability and mild basicity, was selected as our general catalyst for this exchange experiment. A relatively large amount of TEA was utilized in these experiments (10 mol%) to allow equilibrium to be quickly established (see supporting information) and to aide in handling of the material. Future studies with materials incorporating the thiol-thioester exchange will concentrate on reducing the loading of catalyst. Accordingly, we hope to show, as opposed to merely tabulating various pKa values of thiols and bases in different solvents, the experimental proof of exchange for these varied thioesters and thiols and the extent of that exchange between them (K_{eq}).

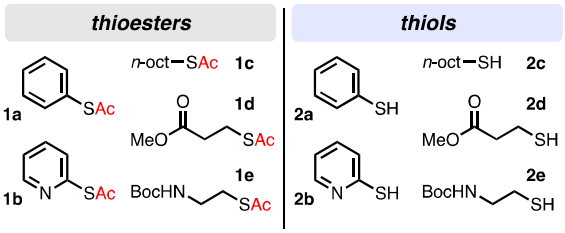
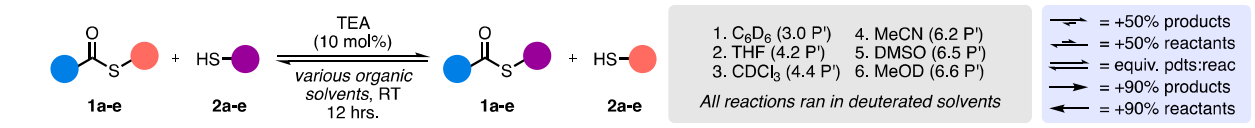


Fig. 2 The selected panels of thioesters (*left*, **1a** – **1e**) and thiols (*right*, **2a** – **2e**) for use in our exchange studies.

Collecting and organizing the results of our screen yielded some striking outcomes (**Fig. 3**). Firstly, the exchange is, as can be

expected, highly dependent on the polarity of the media; non-polar solvents such as benzene, chloroform, and THF generally stifle any exchange. This can likely be attributed to the inability of the base catalyst to form sufficient quantities of thiolate to promote



thioesters / thiols	1a	1b	1c	1d	1e
2a		1. **1b** → **1a** (K_{eq} = 56.9) 2. **1b** ⇌ **1a** (K_{eq} = 1.06) 3. **1b** → **1a** (K_{eq} = 18.6) 4. **1b** ⇀↽ **1a** (K_{eq} = 3.94) 5. **1b** ⇀↽ **1a** (K_{eq} = 1.68) 6. **1b** → **1a** (n/d)	1. **1c** ← **1a** 2. **1c** ← **1a** 3. **1c** ← **1a** 4. **1c** ← **1a** 5. **1c** ← **1a** 6. **1c** ← **1a**	1. **1d** ← **1a** 2. **1d** ← **1a** 3. **1d** ← **1a** 4. **1d** ← **1a** 5. **1d** ← **1a** 6. **1d** ← **1a**	1. **1e** ← **1a** 2. **1e** ← **1a** 3. **1e** ← **1a** 4. **1e** ⇀↽ **1a** (K_{eq} = 0.16) 5. **1e** ⇀↽ **1a** (K_{eq} = 0.14) 6. **1e** ⇀↽ **1a** (K_{eq} = 0.15)
2b	1. **2b** *insoluble in media* 2. **1a** ← **1b** 3. **1a** ← **1b** 4. **2b** *insoluble in media* 5. **1a** ← **1b** 6. **1a** ← **1b**		1. **2b** *insoluble in media* 2. **1c** ← **1b** 3. **1c** ← **1b** 4. **2b** *insoluble in media* 5. **1c** ← **1b** 6. **1c** ← **1b**	1. **2b** *insoluble in media* 2. **1d** ← **1b** 3. **1d** ← **1b** 4. **2b** *insoluble in media* 5. **1d** ← **1b** 6. **1d** ← **1b**	1. **2b** *insoluble in media* 2. **1e** ← **1b** 3. **1e** ← **1b** 4. **2b** *insoluble in media* 5. **1e** ← **1b** 6. **1e** ← **1b**
2c *n*-oct–SH	1. **1a** ← **1c** 2. **1a** ← **1c** 3. **1a** ← **1c** 4. **1a** ⇀↽ **1c** (K_{eq} = 0.26) 5. **1a** ⇀↽ **1c** (K_{eq} = 2.91) 6. **1a** ⇀↽ **1c** (K_{eq} = 1.64)	1. **1b** ⇀↽ **1c** (K_{eq} = 5.85) 2. **1b** ⇀↽ **1c** (K_{eq} = 0.40) 3. **1b** ⇀↽ **1c** (K_{eq} = 0.16) 4. **1b** ⇀↽ **1c** (K_{eq} = 2.19) 5. **1b** → **1c** (K_{eq} = 72.3) 6. **1b** → **1c** (n/d)		1. **1d** ← **1c** 2. **1d** ← **1c** 3. **1d** ← **1c** 4. **1d** ← **1c** 5. **1d** ⇌ **1c** (K_{eq} = 1.18) 6. **1d** ⇀↽ **1c** (K_{eq} = 1.37)	1. **1e** ← **1c** 2. **1e** ← **1c** 3. **1e** ← **1c** 4. **1e** ← **1c** 5. **1e** ⇀↽ **1c** (K_{eq} = 1.23) 6. **1e** ⇀↽ **1c** (K_{eq} = 1.49)
2d MeO–C(=O)–SH	1. **1a** ← **1d** 2. **1a** ← **1d** 3. **1a** ← **1d** 4. **1a** ⇀↽ **1d** (K_{eq} = 2.34) 5. **1a** ⇀↽ **1d** (K_{eq} = 3.67) 6. **1a** ⇀↽ **1d** (K_{eq} = 5.64)	1. **1b** ⇀↽ **1d** (K_{eq} = 0.50) 2. **1b** ⇀↽ **1d** (K_{eq} = 0.55) 3. **1b** ⇀↽ **1d** (K_{eq} = 0.60) 4. **1b** → **1d** (K_{eq} = 19.4) 5. **1b** ⇀↽ **1d** (K_{eq} = 12.6) 6. **1b** → **1d** (n/d)	1. **1c** ← **1d** 2. **1c** ← **1d** 3. **1c** ← **1d** 4. **1c** ← **1d** 5. **1c** ⇀↽ **1d** (K_{eq} = 0.66) 6. **1c** ⇀↽ **1d** (K_{eq} = 0.70)		1. **1e** ← **1d** 2. **1e** ← **1d** 3. **1e** ← **1d** 4. **1e** ⇀↽ **1d** (K_{eq} = 0.61) 5. **1e** ⇀↽ **1d** (K_{eq} = 0.82) 6. **1e** ⇌ **1d** (K_{eq} = 1.03)
2e BocHN–SH	1. **1a** ← **1e** 2. **1a** ← **1e** 3. **1a** ← **1e** 4. **1a** ⇀↽ **1e** (K_{eq} = 2.92) 5. **1a** ⇀↽ **1e** (K_{eq} = 4.35) 6. **1a** ⇀↽ **1e** (K_{eq} = 3.93)	1. **1b** ⇀↽ **1e** (K_{eq} = 0.56) 2. **1b** ⇀↽ **1e** (K_{eq} = 0.70) 3. **1b** ⇀↽ **1e** (K_{eq} = 0.73) 4. **1b** ⇀↽ **1e** (K_{eq} = 5.90) 5. **1b** ⇀↽ **1e** (K_{eq} = 10.4) 6. **1b** → **1e** (n/d)	1. **1c** ← **1e** 2. **1c** ← **1e** 3. **1c** ← **1e** 4. **1c** ← **1e** 5. **1c** ⇀↽ **1e** (K_{eq} = 0.69) 6. **1c** ⇀↽ **1e** (K_{eq} = 0.64)	1. **1d** ← **1e** 2. **1d** ← **1e** 3. **1d** ← **1e** 4. **1d** ⇀↽ **1e** (K_{eq} = 0.52) 5. **1d** ⇌ **1e** (K_{eq} = 0.99) 6. **1d** ⇀↽ **1e** (K_{eq} = 0.77)	

Fig. 3 A reactivity grid detailing the exchange of thioesters (**1a** – **1e**, 0.20 mmol, 1.00 equiv) and thiols (**2a** – **2e**, 0.20 mmol, 1.00 equiv) monitored by ^{1}H-NMR in various solvents (all reactions ran at 0.20 M). Triethylamine (TEA, 0.01 mmol, 0.10 equiv, 10 mol%) was utilized as the base catalyst in all cases and the ^{1}H-NMR spectra was acquisitioned after equilibration for 12 hours at room temperature; any degenerate exchange experiments were not performed. All reactions were compared to an internal standard (1,3,5-trimethoxybenzene, 0.04 mmol, 0.20 equiv, 20 mol%) and the extent of exchange, or lack thereof, was quantified utilizing values obtained from their respective calibration curves. If no K_{eq} is reported, either an exchange reaction did not occur or the extent of the exchange could not be determined (no detectable starting material peak).

the dynamic reaction and the inability of these solvents to stabilize charged intermediates formed during the reaction. Alternatively, polar solvents such as acetonitrile, DMSO, and methanol strongly promote the thiol-thioester exchange. It is important to note that one thiol (2-mercaptopyridine, **2b**) and one thioester (the acylated analogue of 2-mercaptopyridine, **1b**) stand in contrast to these generalizations, as is readily apparent in **Fig. 3**. Specifically, thiol **2b** shows no quantifiable exchange under any conditions,[14] whereas, thioester **1b** shows some exchange with all thiols in all solvents. Although thiol **2b** is extremely acidic (pKa = -1.38)[15] and should be fully deprotonated by triethylamine in more polar solvents (MeCN, DMSO, MeOD), no detectable exchange was noted. Likely the lack of reactivity of this thiol can be explained by its equilibrium with the thione tautomer, as has been well studied.[16] This non-productive tautomeric form of thiol **2b** is known to be favoured at lower temperatures and lower concentrations, similar to those utilized here. Moreover, as the thiol is in resonance with the pyridine ring, its nucleophilicity should be significantly reduced, disallowing its initial attack onto the thioester partner. Alternatively, as stated previously, thioester **1b** underwent exchange with all thiols, in all of the solvents attempted. As can be seen with other thiol-thioester pairs, where detectable exchange did not occur until sufficiently polar solvents were utilized (e.g. **1c/2d**, **1c/2e**, **1e/2a**, **1e/2d**, etc), thioester **1b** gave significant and sometimes nearly quantitative yields of the

exchanged products (e.g. **1b/2a**, **1b/2a**, **1b/1c**, etc.) even in solvents of low polarity. Poor solubility of the resultant thiol **2b** in certain media (C_6D_6 and MeCN), as can be seen with the reverse reactions (e.g. **2b**/**1c-e**), could be the factor which pushed the equilibria further towards product. Evidently, thiolate formation is not a required step with these exchange reactions and indicates that the exchange of thioester **1b** is likely proceeding through a different mechanism.

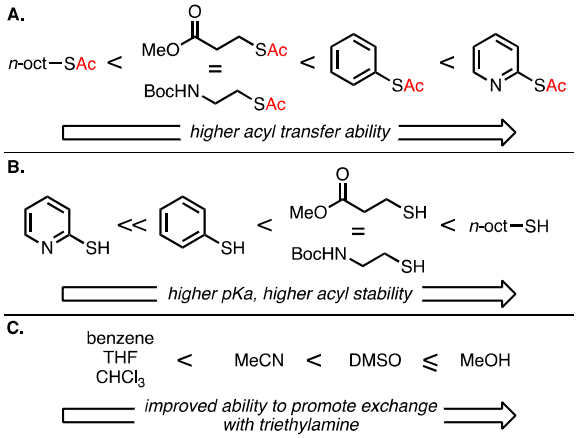
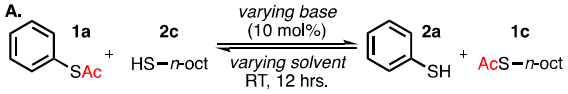


Fig. 4 Benchmarking of the relative exchange activity of thioesters (**A**), thiols (**B**), and solvents (**C**) utilized in our study.

For the most part, the results of this large exchange screen yielded the anticipated results. Thioesters derived from thiols with a *lower* pKa (more acidic) were found to undergo exchange with thiols of a *higher* pKa (less acidic), favouring the acyl group to rest on the thiol with a *higher* pKa and disfavouring the acyl group to rest on the thiol with a *lower* pKa (**Fig. 3**). As an example, thioester **1a**, derived from thiophenol (pKa = 6.62), underwent smooth exchange with the more basic/less acidic thiols **2c**, **2d**, and **2e** in polar solvents (MeCN, DMSO, and MeOH). Alternatively, thioester **1c**, derived from *n*-octanethiol (pKa = 10.6), showed no discernable exchange product with thiol **2a** even in the aforementioned higher polarity solvent. Where comparable acidities of the thiols were noted, especially in the case of thiols **2d** and **2e**, effectively equivalent concentrations of the exchanging reactants were noted (see the exchange of **1d**/**2e** and **1e**/**2d**). From this data, although only qualitative, the relative abilities of the thioesters, thiols, and solvents to promote exchange can reliably be benchmarked (**Fig. 4A**, **B**, and **C**). Accordingly, we have placed the thioesters in ascending ability to transfer their acyl group (*left* to *right*) and the thiols in order of ascending ability to accept an acyl group (*left* to *right*). Although somewhat limited by our use of a mild organic base, triethylamine, we can note that this specific exchange only occurs in more polar solvents, such as methanol (6.6 P'), DMSO (6.5 P'), and MeCN (6.2 P'), where less polar solvents do not promote the exchange ($CHCl_3$, THF, and benzene). Again, we have placed the solvents utilized in this study in their ascending ability to promote the exchange (*left* to *right*).

Table 1 The effect of pKa of the basic catalyst and the polarity of solvent on the thiol-thioester exchange. **A.** *General reaction conditions*: thioester **1a** (0.20 mmol, 1.00 equiv), thiol **2c** (0.20 mmol, 1.00 equiv), varying base (0.02 mmol, 0.10 equiv, 10 mol%), and varying solvent (0.20 M). ^{1}H-NMR spectra were acquisitioned after equilibration for 12 hours at room temperature. All reactions were compared to an internal standard (1,3,5-trimethoxybenzene, 0.04 mmol, 0.20 equiv, 20 mol%) and the extent of exchange, or lack thereof, was quantified utilizing values obtained from respective calibration curves. [a]The reported pKa value in MeCN; all other pKa values shown are those reported in water; **B.** benchmarking of the relative activity of the base catalysts utilized in our study.



entry	*solvent*	*base*	*pka*	*result*
1	$CDCl_3$	pyridine	5.25	**1a** ← **1c**
2	"	TEA	10.8	**1a** ← **1c**
3	"	DBU	13.5	**1a** ⇌ **1c** (K_{eq} = 0.67)
4	"	BEMP	27.6[b]	**1a** ⇌ **1c** (K_{eq} = 0.45)
5	THF	pyridine	5.25	**1a** ← **1c**
6	"	TEA	10.8	**1a** ← **1c**
7	"	DBU	13.5	**1a** ⇌ **1c** (K_{eq} = 3.53)
8	"	BEMP	27.6[b]	**1a** ⇌ **1c** (K_{eq} = 2.63)
9	MeCN	pyridine	5.25	**1a** ← **1c**
10	"	TEA	10.8	**1a** ⇌ **1c** (K_{eq} = 0.26)
11	"	DBU	13.5	**1a** ⇌ **1c** (K_{eq} = 2.11)
12	"	BEMP	27.6[b]	**1a** ⇌ **1c** (K_{eq} = 2.71)

B.

pyridine < TEA < DBU < BEMP

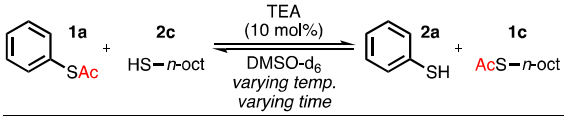
improved basic catalyst for thiol-thioester exchange

One factor previously held constant in our screen was the amine base, triethylamine (pKa = 10.8). Building on the results of our larger screen, we wondered if the less effective/less polar solvents, such as chloroform, THF, and MeCN, could promote exchange if more basic amine bases were employed. Therefore, the strong organic bases 1,8-diazabicycloundec-7-ene (DBU, pKa = 13.5) and 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP, pKa = 27.6 in MeCN)[17] were used in conjunction with thioester **1a** and thiol **2c**. This pair of reactants was chosen because the acyl group has a much higher affinity for the less acidic thiol **2c** in more polar solvents (DMSO and MeOH) but shows no exchange in $CDCl_3$ or THF and borderline activity in MeCN (K_{eq} = 0.26). In the interest of thoroughness and to further establish a trend, the weak base pyridine (pKa = 5.25) was also screened. Stronger organic bases DBU and BEMP were found to be effective in each of the less polar solvents where pyridine showed no discernable exchange product under any circumstances (**Table 1**). As is plain from these experiments, even less polar and certainly more convenient solvents can be utilized in this exchange if sufficiently strong bases (DBU or BEMP) are employed. With these results in mind, we recommend the use of weak bases,

such as pyridine, if operations which evolve protons required to be captured (acylation, sulfonylation, etc.) are carried out in the presence of a thiol and thioester, thus, stifling any possible exchange which could occur with stronger proton acceptors (TEA, DBU, or BEMP) and preserving the initial connectivity and structure of the molecule.

Heat is a common parameter to consider and optimize in any chemical reaction. Generally speaking, the more energy available in a given system (higher applied heat) the correspondingly higher the kinetic constant of that reaction will be; this relationship is the basis of the Arrhenius equation. The thiol-thioester exchange is an interesting case where only very small kinetic barriers separate starting materials from their exchanged products (~4.30 kcal/mol, *see supporting information*). Moreover, the formation of exchanged materials normally only results in mildly more thermodynamically favourable products. As the thermodynamic differences between starting materials and their exchanged products and the kinetic barriers incurred fluxing between these two are significantly lower than the energy available at room temperature (approximately ~22 kcal/mol) we anticipate that higher temperatures would not greatly effect the final equilibrium ratio but would effect the rate at which the exchange reaches equilibrium. Thus, we sought to experimentally probe the effect of heat on the thiol-thioester exchange under our standard "exchange" conditions in organic solvent (1:1, thiol:thioester, TEA [10 mol%], DMSO).

Table 2 The effect of temperature (room temperature and above) on the thiol-thioester exchange. *General reaction conditions*: thioester **1a** (0.20 mmol, 1.00 equiv), thiol **2c** (0.20 mmol, 1.00 equiv), TEA (0.02 mmol, 0.10 equiv, 10 mol%), and DMSO-d_6 (0.20 M). ^{1}H-NMR spectra were acquisitioned after equilibration at the specified temperature for the given time. All reactions were compared to an internal standard (1,3,5-trimethoxybenzene, 0.04 mmol, 0.20 equiv, 20 mol%) and the extent of exchange, or lack thereof, was quantified utilizing values obtained from respective calibration curves.

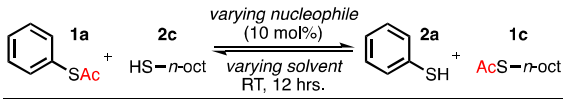


entry	*temperature*	*t*	*conv. to* **1c**	*result*
1	25°C	12 hrs.	79%	**1a** ⇌ **1c** (K_{eq} = 3.76)
2	50°C	"	82%	**1a** ⇌ **1c** (K_{eq} = 4.56)
3	75°C	"	82%	**1a** ⇌ **1c** (K_{eq} = 4.52)
4	25°C	5 min.	24%	**1a** ⇌ **1c** (K_{eq} = 0.36)
5	50°C	"	32%	**1a** ⇌ **1c** (K_{eq} = 0.47)
6	75°C	"	45%	**1a** ⇌ **1c** (K_{eq} = 0.82)

As above, we selected the use of thioester **1a** and thiol **2c** as our reactants and probed their exchange under our standard conditions at various temperatures (room temperature (25°C), 50°C, and 75°C). As anticipated, it was discovered that after allowing these reactions to equilibrate for 12 hours and quenching them with acid (TFA), essentially the same ratio between starting materials and exchanged products were noted for all of the temperatures attempted (**Table 2**). Alternatively, quenching the exchange after only 5 minutes at a given temperature showed much higher kinetics of the exchange with the highest temperature, 75°C, giving largest conversion (45%) to the thermodynamically favourable product **1c** (**Table 2**).

Although strong amine bases capable of forming high concentrations of thiolate were shown to be sufficient catalysts for the thiol-thioester exchange, the activity of nucleophilic catalysts in solvents of low polarity peaked our interest.[18] As our previous screens concentrated on the use of base catalysts with increasingly higher pKa to form a thiolate, nucleophilic catalysts would, hypothetically, depending on their pKa, operate through a different mechanism. We judiciously selected the three different nucleophilic amine catalysts 4-dimethylaminopyridine (DMAP, pKa = 9.60), 1,4-diazabicyclo[2.2.2]octane (DABCO, pKa = 8.80), and quinuclidine (pKa = 11.0) to screen under our standard conditions. Such catalysts were selected because of their mild basicity[19] and increasingly nucleophilic behaviour (quinuclidine > DABCO > DMAP, in MeCN) as observed by Mayr and co-workers.[20] We anticipated that due to the relatively high electrophilicity of thioesters, nucleophilic catalysts could potentially attack the carbonyl of the thioester, forming a zwitterionic intermediate and discharging a thiolate *in situ* which activates the incoming nucleophile via deprotonation in the rate determining step.[21] However, to the best of our knowledge, such a mechanism has not been observed in the thiol-thioester exchange.

Table 3 The effect of nucelophilicity of the nucleophilic catalyst and the polarity of solvent on the thiol-thioester exchange. *General reaction conditions*: thioester **1a** (0.20 mmol, 1.00 equiv), thiol **2c** (0.20 mmol, 1.00 equiv), varying nucleophile (0.02 mmol, 0.10 equiv, 10 mol%), and varying solvent (0.20 M). ^{1}H-NMR spectra were acquisitioned after equilibration for 12 hours at room temperature. All reactions were compared to an internal standard (1,3,5-trimethoxybenzene, 0.04 mmol, 0.20 equiv, 20 mol%) and the extent of exchange, or lack thereof, was quantified utilizing values obtained from respective calibration curves.



entry	solvent	nucleophile	t (hrs)	N [b]	result
1	$CDCl_3$	DMAP	12	15.8	**1a** ← **1c**
2	"	DABCO	"	-	**1a** ← **1c**
3	"	quinuclidine	"	-	**1a** ⇌ **1c** (K_{eq} = 0.07)
4	THF	DMAP	12	15.9	**1a** ← **1c**
5	"	DABCO	"	-	**1a** ← **1c**
6	"	quinuclidine	"	-	**1a** ⇌ **1c** (K_{eq} = 0.05)
7	MeCN	DMAP	12	15.5	**1a** ⇌ **1c** (K_{eq} = 0.11)
8	"	DABCO	"	18.8	**1a** ⇌ **1c** (K_{eq} = 0.29)
9	"	quinuclidine	"	20.5	**1a** ⇌ **1c** (K_{eq} = 1.01)
10	DMSO	DMAP	12	14.8	**1a** ⇌ **1c** (K_{eq} = 1.53)
11	"	DABCO	"	-	**1a** ⇌ **1c** (K_{eq} = 2.81)
12	"	quinuclidine	"	-	**1a** ⇌ **1c** (K_{eq} = 3.25)

Screening the effectiveness of nucleophiles was accomplished, again, by reacting stoichiometric quantities of thioester **1a**, thiol **2c**, and catalytic quantities of various nucleophiles (10 mol%) in fully deuterated solvents ($CDCl_3$, THF-d_8, MeCN-d_3, and DMSO-d_6) at room temperature for 12 hours (**Table 3**). Nucleophiles were found to be competent catalysts in the thiol-thioester exchange, with quinuclidine in particular being the most potent catalyst of those surveyed (**Table 3**). Again, as with the use of weak bases (e.g. TEA), more polar solvents were required to promote this exchange with less polar solvents showing only small amounts of exchange (entries 3 and 6). However, the mechanism of this novel class of catalysts was required to be more deeply explored.

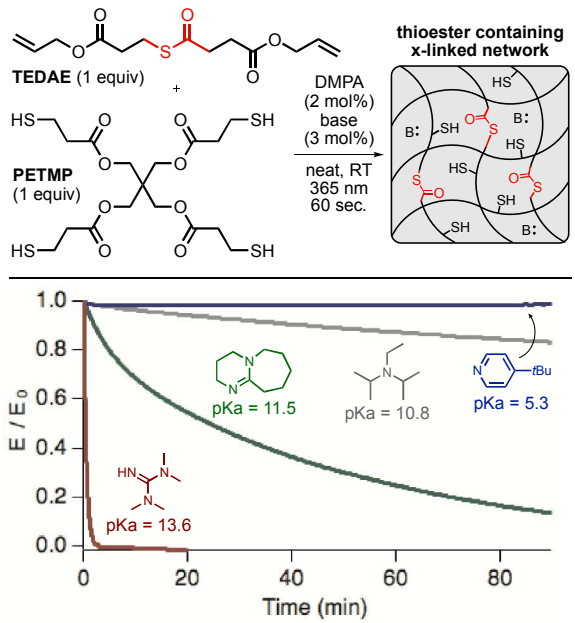


Fig. 5 Increasing the pKa of the organic base in thioester crosslinked network accordingly increases the rate of stress relaxation (constant applied strain of 10%). *General formulations*: **TEDAE** (1.00 equiv), **PETMP** (1.00 equiv), organic base (3.00 mol%), and DMPA (2.00 mol%).

In a small molecule setting it was found that increasing the basicity of the catalyst resulted in an improved robustness of the thiol-thioester exchange even in non-polar media. We decided to test this trend for consistency in network polymers. To do so we mixed the thioester containing diene (**TEDAE**), a tetrafunctional thiol (**PETMP**), a UV photoinitiator (DMPA), and bases which vary in basicity (**Fig. 5**).[22] These non-viscous resins were cast into thin films and cured with UV light at room temperature. Submitting these materials to a stress relaxation test at a constant strain (10%) showed that the aforementioned trend was consistent in a network polymer. Stronger bases such as TMG (pKa = 13.6) and DBU (pKa = 11.5) relaxed stress quickly reflecting a higher rate of thiol-thioester exchange, whereas weaker bases such as DIPEA (pKa = 10.8) and 4-*t*-butylpyridine (pKa = 5.3) yielded slow or no discernable stress relaxation. Although all of these base catalysts were in equal proportions, evidently these networks are only of moderate polarity, thus, smaller amounts of thiolate are generated with increasingly weaker bases. Increasing the polarity of these networks may well be a manner in which to improve the rate and fidelity of this exchange.

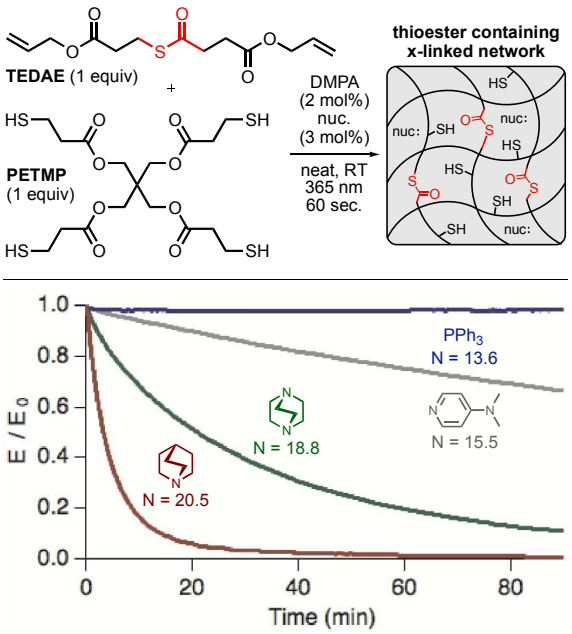


Fig. 6 Increasing the nucleophilicity of the catalyst in thioester crosslinked network accordingly increases the rate of stress relaxation (constant applied strain of 10%). *General formulations*: **TEDAE** (1.00 equiv), **PETMP** (1.00 equiv), nucleophile (3.00 mol%), and DMPA (2.00 mol%). All nucleophilicity values taken from ref. *24* and are values obtained in MeCN.

Although basic catalysts, especially those of higher basicity, were potent catalysts in network polymers for the thiol-thioester exchange, we sought to explore the ability of nucleophilic catalysts to promote this exchange in a similar setting. Again, placing a static amount of various nucleophilic catalysts (3 mol%), polymerizing these resins into thin films, and submitting these materials to a stress relaxation test at constant strain (10%) resulted in a similar trend to that established with small molecules (**Fig. 6**). Catalysts with high nucleophilicties such as quinuclidine (N = 20.5) and DABCO (N = 18.8) yielded correspondingly higher rates of stress relaxation (**Fig. 6**), whereas, those with lower nucleophilicites such as DMAP (N = 15.5) and triphenylphosphine (PPh_3, N = 13.6) gave slower or no stress relaxation. Although these nucleophilic catalysts performed commendably in the thiol-thioester exchange in network polymers, none were as rapid as the so-called super base TMG (**Fig. 5**).

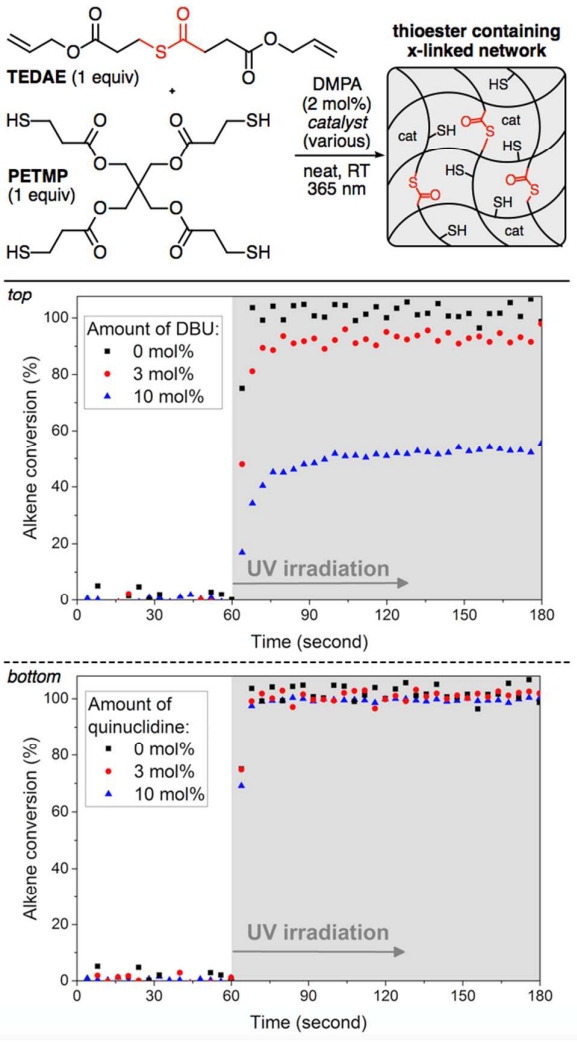


Fig. 7 The kinetics of the thiol-ene reaction between a thioester diene and a tetrafunctional thiol in the presence of varying amounts of DBU (0.00 mol%, 3.00 mol%, and 10.0 mol%); significant inhibition of the thiol-ene polymerization was noted with higher loadings of the basic catalyst. *General reaction conditions*: **TEDAE** (1.00 equiv), **PETMP** (1.00 equiv), DBU (0.00 mol%, 3.00 mol%, or 10.0 mol%), and DMPA (2.00 mol%) monitored by *in situ* IR. Light on at 60.0 seconds and continuously irradiated; 365 nm LED (50.0 mW/cm^2).

While exploring the use of different catalysts for the thiol-thioester exchange in network polymers, we were surprised to discover that the use of increasingly strong amine bases, such as TMG or DBU, could significantly retard the rate of the thiol-ene polymerizaiton reaction. Indeed, when higher concentrations of DBU was used (3.00 or 10.0 mol%) often sluggish or incomplete polymerizations were evidenced (**Fig. 7**, *top*). However, when nucleophilic catalysts were employed, such as quinuclidine, this retardation effect was not noted by FT-IR (**Fig. 7**, *bottom*). As we have discovered and reported elsewhere, amines capable of forming sufficient quantities of thiolate can indirectly retard the thiol-ene polymerization by sequestering the catalytic radical population via the formation of a metastable disulphide radical anion.[23] Evidently, quinuclidine (pKa = 11.0) cannot form sufficient quantities of the thiolate anion to retard the free radical thiol-ene polymerization. This is further evidence that nucleophilic catalysts are operating through a different mechanism then basic catalysts for the thiol-thioester exchange. We would recommend the use of weakly basic yet strongly nucleophilic catalysts, such as quinuclidine or DABCO, to practitioners seeking to make similar materials due to these catalyst's orthogonality to the thiol-ene reaction and potency in the thiol-thioester exchange.

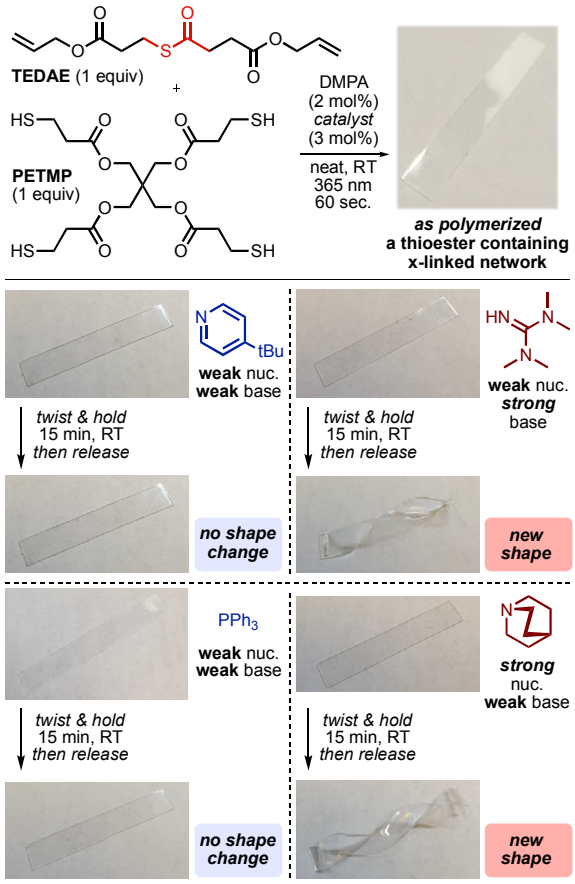


Fig. 8 Shape change in thioester crosslinked network polymers is promoted only with sufficiently strong basic and nucleophilic catalysts (such as TMG and quinuclidine). *General formulations*: **TEDAE** (1.00 equiv), **PETMP** (1.00 equiv), various catalyst (3.00 mol%), and DMPA (2.00 mol%).

As was previously shown, catalysts of greater basicity or nucleophilicity more rapidly promoted the exchange of free thiols and thioesters in crosslinked network polymers (**Figs. 5** & **6**). Obviously, the ability of the network to respond to external forces, such as strain, can productively result in permanent shape change following polymerization by viscous flow. As a visual demonstration of this effect, as well as to show that importance of catalyst selection in these systems, we polymerized several thin films of thioester crosslinked polymers impregnated with different catalysts. These samples were then twisted them into a fusilli-like shape, held for 15 minutes at room temperature, released, and pictured (**Fig. 8**). In agreement with our previous results, weaker bases and nucleophiles, such as 4-*tert*-butyl pyridine and triphenylphosphine, respectively, showed no obvious change in shape over this time period. Whereas stronger bases and nucleophiles, such as TMG and quinuclidine, respectively, completely adopted the shape of the fusilli.

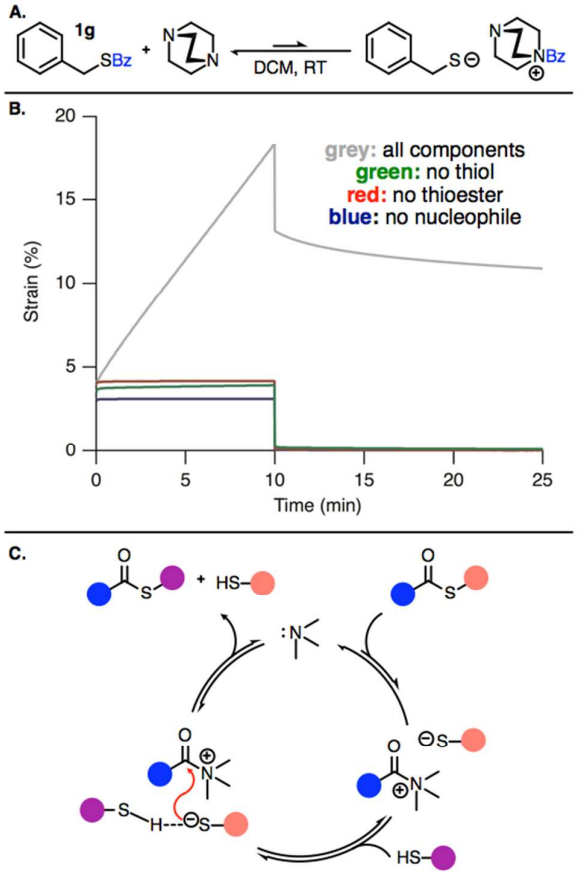


Fig. 9 **A.** The previously reported example of the dynamic transfer of the acyl group of a thioester to DABCO. The reactants (*left*) are highly favoured over the zwitterionic products (*right*) in this system; **B.** creep compliance showing the requirement for free thiol, thioester, and nucleophile (quinuclidine) in the network for rearrangement/relaxation/remolding to occur (a constant stress of 42 kPa was held for 10 minutes and then released), *general formulations*: *all components* (grey line) – **TEDAE** (1.00 equiv), PETMP (1.00 equiv), quinuclidine (5.00 mol%), and DMPA (2.00 mol%); *w/o thiol* (green line) – **TEDAE** (1.00 equiv), PETMP (0.25 equiv), quinuclidine (5.00 mol%), and DMPA (2.00 mol%); *w/o thioester* (red line) – **DAEC** (1.00 equiv), PETMP (1.00 equiv), quinulicidine (5.00 mol%), and DMPA (2.00 mol%); *w/o base* (blue line) – **TEDAE** (1.00 equiv), PETMP (1.00 equiv), and DMPA (2.00 mol%). **C.** a mechanistic proposal for the thiol-thioester exchange promoted by nucleophilic amine catalysts.

As evidenced above, nucleophilic catalysts were discovered to be competent catalysts for the thiol-thioester exchange in both polar solvents and in network polymers (**Table 4**). However, the mechanism of this exchange has not been heretofore reported or probed. As some of these catalysts, such as the weakly basic DMAP (pKa = 9.60) or DABCO (pKa = 8.80), cannot form sufficient quantities of thiolate but do effectively

promote the exchange of thioester **1a** and thiol **2c**, they must be operating through a different mechanism then base promoted exchange. Our first step towards elucidating this mechanism came from Connon and co-workers discovery that nucleophilic catalysts, such as DABCO, can, to a small extent, transfer an acyl group from the thiol of a thioester (such as **1g**) to it's tertiary amine (**Fig. 9A**).[24] Although this results shows that such zwitterionic species can be formed, it does not rule out the ability of the ejected thiolate to directly participate in exchange. To assess if thiol-thioester exchange could occur without the presence of free thiol, a simple control experiment using various network polymers was performed (**Fig. 9B**). Taking network polymers of similar crosslinking density and modulus, while selectively excluding either free thiol, thioester, or nucleophilic catalyst (quinculidine), it was unequivocally shown that only networks containing all three components could effectively undergo creep; exclusion of any of these components resulted in elastic networks that resembled typical cross-linked elastomers (**Fig. 9B**). Based on this evidence we propose the following catalytic cycle for the nucleophile promoted thiol-thioester exchange (**Fig. 9C**): first, the acyl group of the thioester transfers from the thiol to the nucleophile, forming a zwitterionic intermediate by the ejection of a thiolate anion. Secondly, the ejected thiolate will hydrogen bond to the incoming free thiol, which is delivered to the previously activated acyl group, regenerating the nucleophilic catalyst and exchanging the thiol and thioester. As is evident, this proposed mechanism shares many similarities to the well-studied DMAP-catalysed esterification of acid chlorides and alcohols. As this exchange utilizes markedly less electrophilic acyl species (thioesters vs acid chlorides), more polar solvents and potent catalysts are required to evidence exchange.

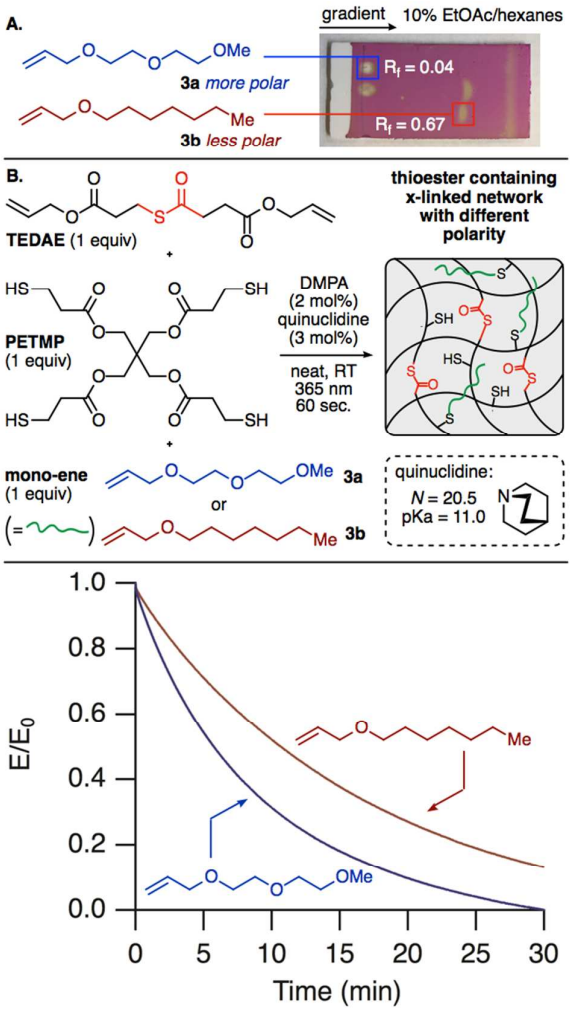


Fig. 10 A. The short PEG-ene **3a** is shown to be significantly more polar than the related alkyl-ene **3b** by thin layer chromatography (TLC); **B.** increasing the polarity of thioester crosslinked network polymers accordingly increases the rate of stress relaxation (constant applied strain of 10%). *General formulations*: **TEDAE** (1.00 equiv), **PETMP** (1.00 equiv), **mono-ene** (1.00 equiv), quinuclidine (3.00 mol%), and DMPA (2.00 mol%).

As polar organic media was found to more readily promote the thiol-thioester exchange with small molecules, we were interested in exploiting this effect in a network polymer. Accordingly, two monomeric olefins (**3a** and **3b**) of similar length but dissimilar polarity were prepared (**Fig. 10A**). Our standard formulation for making thioester crosslinked network polymers was employed, however, a fraction of the thiol which traditionally has remained unreacted was utilized to tether either the polar (PEG-ene **3a**) or non-polar (alkyl-ene **3b**) molecules to the network. These samples were photopolymerized and directly subjected to a stress relaxation test at constant strain (10%). As evidenced, the system

containing the non-polar diluent (**3b**) relaxed applied stress slower than the system containing the polar diluent (**3a**) (**Fig. 10B**). Although this simple control gave only small changes to the performance of the network (stress relaxed ~1.5x faster), organo- or hydrogels, where larger quantities of a polar diluent can be utilized, will likely have much more significant enhancements in their ability to relax stress or be remolded.

Conclusions

At the outset of this manuscript we sought to create a user's guide to the thiol-thioester exchange in organic media for application in material sciences. The following parameters were first explored, weighed, and benchmarked in a small molecule setting: *i*. pKa of the thiol employed, *ii*. electronic character of the thioester, *iii*. polarity of the solvent, *iv*. pKa of the organic base, *v*. the effect of temperature, and *vi*. nucleophilicity of the catalyst. Judicious choice of thiol, thioester, solvent, and catalyst utilizing the guide we have developed here to promote, supress, or tune the thiol-thioester exchange should be straightforward to any practitioner working in this field. The findings gained from utilizing small molecules were then telescoped to network polymers and were shown to be broadly consistent.

As thiol-X chemistries become increasingly popular and ubiquitous in material science, the thiol-thioester exchange presents those working in the field an additional element of control. This exchange can enable not only enable stress relaxation and remolding in crosslinked network polymers, but could also enable sequence shifting, depolymerisation, or recycling in non-crosslinked polymers. This exchange can easily be incorporated into the growing field of "vitrimers" where rearrangement of the network occurs at or near the glass transition, which will be explored in due course. We earnestly hope that the results presented here enable practitioners to easily develop new smart materials using this extremely robust, tuneable, and responsive exchange reaction.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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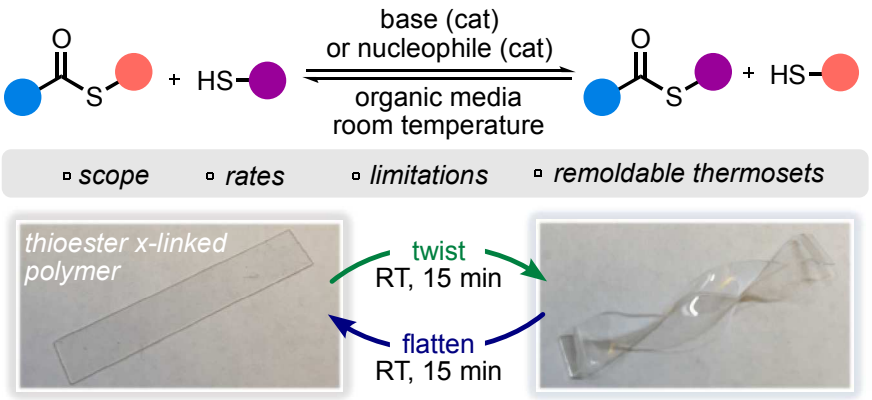

TOC: The dynamic exchange of thiols and thioesters in organic media was explored, leading to room temperature plasticity in crosslinked polymers