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Role of Thiol Oxidation by Air in the Mechanism of the Self-Initiated Thermal Thiol-ene Polymerization

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Cuong Minh Quoc Le,^{a,b} Fabrice Morlet-Savary^{a,b} and Abraham Chemtob^{*a,b}

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A spontaneous thiol-ene polymerization has been reported in the literature for a broad range of monomers, generally under conditions avoiding solvent, heating and the intentional formation of radicals. In the search for a mechanism accountable to self-initiated thiol-ene polymerization, this study demonstrates the significant role played by thiyl radicals produced by thiol oxidation through dissolved atmospheric oxygen in the thiol-ene mixture. To determine the factors underlying the reactivity, self-initiated polymerization kinetics, thiol solvation and the nature of initiating radicals are studied by means of various techniques including real-time FTIR, ¹H NMR spectroscopy and spin-trapping experiments. Our data support that the driving force for thiol air oxidation is the polarization of the S-H bond. Thiol substituents with electron-withdrawing properties and/or hydrogen-bonded thiol-solvent (or thiol-alkene) complexes favor self-initiation by increasing S-H bond polarization, thereby easing an electron transfer to molecular oxygen.

Introduction

The radical-initiated addition of thiols to alkenes to yield thioether products has been known for more than a century.^{1,2} However, it is only since the 2000s that this reaction has been the subject of a renewed interest as part of efforts to find chemical reactions meeting the “click” chemistry criteria.³ As small molecule reactions, thiol-ene reactions have mostly been used for anchoring a catalyst on a polymer support,⁴ patterning surfaces,⁵ or functionalizing biological molecules⁶ (e.g., peptide⁷ or carbohydrate⁸). However, the major use for thiol-ene reaction is in polymerization.⁹ Generally, a thiol-ene step polymerization involves a radical photoinitiator and neat monomers with two or more SH/C=C groups per molecule in order to generate a crosslinked structure. As is often the case in photopolymerization, the applications focus on film curing used as coatings or photoresists.¹⁰ When a solvent is present, other polymer products may be formed including hydrogels,¹¹ latexes,¹² and dendrimers.¹³ The resulting step-growth poly(thioether)s have been proposed as an alternative to conventional chain-growth polymers (e.g., acrylic polymers) since they circumvent some limitations including oxygen inhibition, stress relaxation and heterogeneous network formation.¹⁴ Despite these advantages and a growing number of publications, research on thiol-ene step-growth (photo)polymerization crucially never succeeded in getting

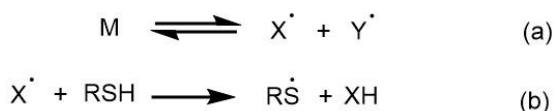
established as a solid alternative to conventional chain-growth photopolymerization.

The inherent limitations of thiol-ene chemistry and poly(thioether)s have contributed to this situation. The very low odor detection level of low-molecular-weight thiols is often advanced as a handicap.¹⁵ However, thiols are used today in many chemical manufacturing processes (e.g., chain-transfer agent in radical polymerization¹⁶) or as components of commercial products (e.g., cleaners or hair care products¹⁷). A second problem is the sub-ambient glass transition temperature (T_g) of poly(thioether)s leading to poor mechanical properties.¹⁰ Significant efforts have contributed to overcome this limitation including the increase of crosslinking density,¹⁸ the mixing with high T_g resins,¹⁹ and the introduction of stiffer polymer backbones²⁰ or crystalline domains.²¹ A last significant and unresolved problem of thiol-ene systems is spontaneous polymerization.²² Lack of chemical stability has been reported in the literature for a broad range of thiol-ene monomers, generally in the absence of solvents, at ambient temperature and under conditions avoiding the formation of radicals.^{23–25} Premature polymerization prevents storage and shipment of thiol-ene formulations, or at best, reduce shelf life.²⁶ Additionally, the lack of photolabile systems adds complexity and cost to the polymerization process. The inability to precisely control the onset of polymerization (temporal control) also precludes modern photopolymerization technologies like photolithography or 3D printing.

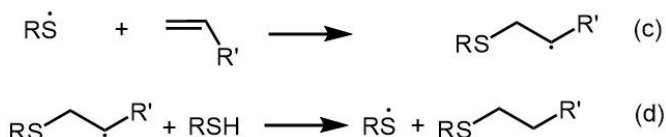
^a Université de Haute-Alsace, CNRS, IS2M UMR7361, F-68100 Mulhouse, France.
E-mail : abraham.chemtob@uha.fr

^b Université de Strasbourg, France

Initiation



Propagation



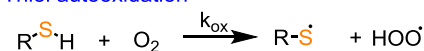
Scheme 1. Radical chain reaction scheme of a self-initiated thiol-ene polymerization. M can be an alkene or a thiol. Termination reactions are not detailed but include a number of recombinations of carbo-centered and thiyl radicals.

The mechanism of spontaneous thiol-ene polymerization is not well established.^{27,28} It is considered to involve a self-initiated polymerization process since the thermal homolysis of impurities present in the monomers (e.g., peroxides or hydroperoxides) is assumed to be negligible.²⁹ Other monomers susceptible to self-initiated polymerization are reported in the literature, including styrene,³⁰ methyl methacrylate³¹ and some donor/acceptor monomer pairs.³² Unlike thiol-ene systems, their self-polymerization proceeds at very slow rates at ambient temperature and can be effectively stopped with inhibitors. The difference between thiol-ene monomers and other self-initiating monomers can be understood by considering the self-initiated thiol-ene polymerization as a conventional *radical chain reaction* consisting of the usual initiation, propagation, and termination reactions (**Scheme 1**). The initiation involves the thermal generation of primary radicals (X^\bullet and Y^\bullet) from the monomer itself (Scheme 1, (a), self-initiation step). The mechanism of this reaction for thiol-ene monomers is unclear although several hypotheses (discussed in the next section) were put forward. In most self-initiated polymerizations, this first step is a chemical equilibrium strongly displaced backward, that is, strongly favorable to reactant (monomer), therefore the formation of X^\bullet is slow and very limited. Thiols can rapidly transfer a hydrogen atom to most types of radicals.³ Therefore, the second part of the initiation involves the reaction of X^\bullet to a thiol molecule (RSH) to produce the chain-initiating radical RS^\bullet (Scheme 1, (b), self-initiation step). Propagation consists of a group of two reaction steps: *addition* and *H-abstraction*. The initiating radical RS^\bullet can add to the C=C bond to form a carbon-centered radical via a reversible process (Scheme 1, (c), propagation step). This latter subsequently abstracts a hydrogen atom from another thiol molecule to yield the desired thioether product and a new thiyl radical needed to begin a new cycle (Scheme 1, (d), propagation step). The propagation cycle is repeated a number of times and allows the growth of polymer chains. Compared to other monomers, the self-initiated polymerization of some thiol-ene systems is more difficult to control because of two characteristics. Firstly, the probability of self-initiation at ambient temperature may be assumed to be higher due to a lower activation energy. Secondly, the two propagation steps

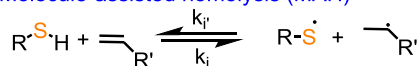
Comonomer complex



Thiol autooxidation



Molecule-assisted homolysis (MAH)



Scheme 2. Putative mechanisms of the self-initiation of a thermal thiol-ene polymerization.

(c) and (d) of a thiol-ene polymerization may be very fast, even at ambient temperature, due to high addition and H-abstraction rate constants, k_{add} and k_{H} , respectively. Thus, polymerization can start even when the concentration of initiating radicals is low. As predicted by Le Chatelier's principle, the consumption of initiating radicals drives forward the self-initiation equilibrium (Scheme 1, (a)) leading to an enhancement of the phenomenon. The efficiency of radical inhibitors in producing stable thiol-ene mixtures is generally limited because the rapid propagation steps compete with the inhibition reaction.^{23,27,28,33,34}

Three main mechanisms of self-initiated thiol-ene polymerization have been suggested in the literature (**Scheme 2**). The first mechanism involves the participation of a *comonomer complex*. For example, Klemm et al. provided spectroscopic evidence (UV-vis, NMR) that supports the formation of a ground-state charge-transfer complex between a thiol and an alkene.^{35,36} This latter is postulated to undergo a redox reaction yielding primary radicals. A second mechanistic hypothesis suggests that thiyl radicals are produced by *oxidation of thiols by molecular oxygen* (air).³⁷ The reaction of thiols and thiyl radicals with molecular oxygen has been the subject of intensive investigations³⁸ since the pioneering work of Kharasch on thiol-olefin cooxidation (TOCO) process. A third mechanism would imply the *molecule-assisted homolysis* (MAH) where the homolytic cleavage of the S-H bond could be assisted by hydrogen transfer to alkene to form a C-H bond.³⁹ A large body of evidences points out that styrene self-initiated polymerization proceeds by MAH between a Diels-Alder dimer and a monomer molecule.⁴⁰ Currently, there is no consensus as to the correct (or at least dominant) mechanism because there is a lack of experimental data. Understanding spontaneous initiation of radical chain reactions is generally challenging because it is based on slow and equilibrium reactions, but the elucidation of a dominant self-initiation mechanism would be a major contribution to the development of the thiol-ene polymerization field. By this way, more efficient mitigation strategies could be found to prevent premature polymerization. The present research aims to elucidate the main mechanism(s) of self-initiation of thiol-ene monomers, and to determine the factors that underlie the reactivity of a self-initiated thiol-ene polymerization, in

particular as regards to experimental conditions (solvent,

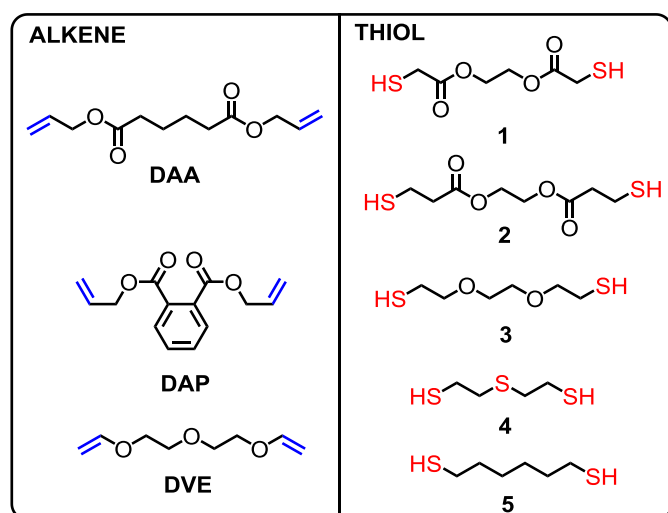


Fig. 1. Chemical structures of bifunctional thiols and alkenes.

atmosphere) and the structure of ene and thiol compounds.

To address these questions, diallyl adipate (**DAA**), diallyl phthalate (**DAP**), di(ethylene glycol) divinyl ether (**DVE**) are used as model alkenes (Fig. 1). The advantage of allyl ethers and vinyl ethers is their inability to homopolymerize or to react by thiol-Michael reaction (nucleophilic addition of thiolate to alkene) due to their electron-donating substituents. Thus, the radical-mediated thiol-ene polymerization is considered to be the predominant process in the presence of thiols. The reactivity of these 3 dienes with a series of 5 dithiols (acetate **1**, propionate **2**, tri(ethylene glycol) **3**, alkylsulfide **4**, hexane **5**, Fig. 1) was investigated under conditions avoiding the intentional formation of radicals. To provide insight into the underlying factors that govern the self-initiation mechanism of neat thiol-ene monomers, three areas are studied thoroughly: *self-initiated polymerization kinetics* in bulk and in solution, *thiol solvation*, and *identification of initiating radicals*.

Experimental section

Chemicals

Diallyl phthalate (**DAP**, TCI, > 98%), diallyl adipate (**DAA**, TCI, 99.8 %), di(ethylene glycol) divinyl ether (**DVE-2**, BASF), ethylene glycol bismercaptoacetate (**1**, TCI, 97.5%), ethylene glycol bis(3-mercaptopropionate) (**2**, TCI, 98.1%), 2,2-(ethylenedioxy)diethanedithiol (**3**, TCI, 99.6%), 2,2'-thioldiethanethiol (**4**, Bruno Bock, 95%), 1,6-hexanedithiol (**5**, TCI, 99.1%) were used as received without further purification to be as near of real conditions of use (with some exceptions noted in the text). Diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide (TPO, TCI, > 98%) and 2-isopropylthioxanthone (ITX, Aldrich, analytical standard) were used as photoinitiators and photosensitizer, respectively. *N-tert-butyl- α -phenylnitron*e (PBN, TCI > 98%) was used as spin trapping agent. All solvents were used with analytical grade without further purification.

Characterization

Self-initiated thiol-ene bulk polymerization - Monitoring of the reaction kinetics by Fourier Transform - Near IR spectroscopy (FT-NIR). For experiments in the presence of air, stoichiometric amounts of dithiol and diene monomers were mixed in a 1 mL centrifuge tube and 0.25 mL of this mixture were immediately transferred to a 2-mm thick quartz cuvette (internal volume: 700 μ L, width: 10 mm). The cuvette without stopper was placed vertically into the closed chamber of a Bruker FTIR (IFS66/s) spectrometer. The FTIR spectra were recorded at room temperature and regular intervals during a total period of 14 h. For experiments in the presence of inert atmosphere, thiol and ene monomers were degassed separately by three successive freeze-thaw cycles and stored under nitrogen. Mixing of the two monomers and transferring the mixture to a 2-mm thick quartz cuvette closed by a rubber-cap were also carried out under nitrogen. The chemical stability of the thiol-ene mixtures was studied in the NIR region of 4000-6500 cm^{-1} with a DTGS detector. Each of the IR spectra obtained from the spectrometer is an average of ten scans, each with a resolution of 4 cm^{-1} . Spectra were taken at intervals varying between 0.5 and 10 min depending on the system reactivity. The second overtone stretch of the CH of the alkene group at 6130 cm^{-1} was used to calculate the conversion. Calibration and method validation were carried out by ^1H NMR (see Fig. S1 of supporting information SI for details). It is useful to note that the kinetic profiles were not significantly changed when the cuvette was exposed to daylight light (Fig. S2 in SI). Additionally, premature polymerization was slowed down but not prevented when thiols were purified by passing through an aluminium oxide column (Fig. S3 in SI). This control experiment adds support to a purely thermal self-initiated polymerization which is sensitive to the presence of small concentrations of impurities (see section I.2 for details).

Photoinitiated thiol-ene bulk polymerization - Monitoring of the reaction kinetics by real-time FT-IR spectroscopy. Stoichiometric amounts of dithiol and diene monomers were mixed in a 5 mL amber vial containing 1 mol% of TPO photoinitiator with respect to the monomers. The thiol-ene mixture was sandwiched between two KBr crystals using a 100 μ m Teflon O-ring spacer. The resulting unit was then compressed in a Presslok demountable cell holder and inserted inside the horizontal sample chamber of a iS50 spectrometer (Thermo Fisher Scientific). Irradiation by a 385 \pm 5 nm LED lamp (LC-L1V3, Hamamatsu, 22.2 mW cm^{-2}) was led into the spectrometer chamber by means of a flexible light guide. The light guide was positioned at a distance of 5 cm from the KBr crystals to ensure complete radiation exposure of the sample. The light guide was also tilted at an angle of 5° so that it did not block the path of the IR beam. The FTIR spectra were acquired in transmission mode using a MCT detector. The spectra were recorded during 120 s in the 2000-7000 cm^{-1} range, with a spectral resolution of 8 cm^{-1} and an interval of 0.14 s. The ene conversion was calculated from the C-H stretch of allylic double bond at 3100 cm^{-1} .

Thiol solvation by ^1H NMR spectroscopy. A CDCl_3 solution of thiol **1** at a concentration of 63 mM was placed into a 5-mm o.d. NMR tube. The tube was fitted with a rubber septum and 5 μL of tetramethylsilane were injected. NMR spectra were recorded by means of a Varian 300 spectrometer (300 MHz). A known volume of the solvent (or alkene) of interest was added to the NMR tubes to obtain a 24 molar excess relative to the thiol and the spectrum was recorded after injection. The chemical shifts were measured relative to the signal of tetramethylsilane.

Electron paramagnetic resonance (EPR). A *tert*-butylbenzene solution of 100 mM thiol **1** and 30 mM PBN was placed into a 6-mm o.d. EPR tube. The tube was fitted with a rubber septum, and the EPR spectrum was recorded by means of a Bruker EMX-plus EPR spectrometer. The EPR spectrum was recorded after 15 scans (modulation amplitude: 1G, receiver gain: 1.10^5 , power: 6.325 mW, time constant: 20.48 ms) and simulated using WINSIM software. For control experiments, ITX (10 mM) was added to the thiol-PBN solution and the EPR tube was irradiated in a circular photochemical reactor equipped with 25 LEDs (385 nm, 2.7 mW cm^{-2}) for 5 min. In experiments involving the addition of solvent (or alkene), the solutions were placed in a 1-mm o.d. capillary tube before measurement.

Results and discussion

I. Self-initiated polymerization kinetics

I.1 Bulk polymerization

Preliminary experiments show that spontaneous thiol-ene polymerization rates can vary significantly with the solvent used, the reaction vessel or the number of samples taken for analysis. To avoid repeatability problems and obtain reproducible kinetic data, the polymerization was thus carried out with neat reactants (without solvent and initiator). Its progress was also monitored online by Fourier transform near-infrared spectroscopy (FT-NIR) without periodic sample removal for analysis.⁴¹ Bulk polymerization involving stoichiometric amounts of thiol and ene functional groups was performed at ambient temperature in a closed 2-mm thick spectroscopic cuvette placed in the dark chamber of a spectrometer.

Fig. 2 displays plots of **DAA** conversion as function of time (up to 14 h) in presence of 5 different thiols (**1-5**) in the presence of air (**A**) or in inert atmosphere (**B**). In the presence of air, only **DAA-1** and **DAA-2** monomer mixtures readily undergo a premature polymerization. However, the polymerization rates are significantly lower under inert atmosphere. This behavior indicates that one of the self-initiation mechanisms may be oxygen-assisted or/and moisture-assisted (propagation reactions are insensitive to oxygen and water).⁴² The other thiols stand in marked contrast, since their polymerizations proceed at very slow rates (**3, 4**) or does not take place (**5**) both in the presence of

air and under nitrogen. It seems therefore that the reactivity of thiols depends on the inductive characteristics of their substituent since thiols bearing an ester substituent (**1, 2**) having a marked electron-withdrawing character readily undergo a self-initiated polymerization with **DAA**. However, it remains to differentiate the respective contributions of self-initiation and propagation on the overall polymerization rate. As shown by modelling and experimental kinetic measurements,^{43,44} the rate-limiting step for the thiol-ene polymerization involving allyl ethers like **DAA** is H-abstraction

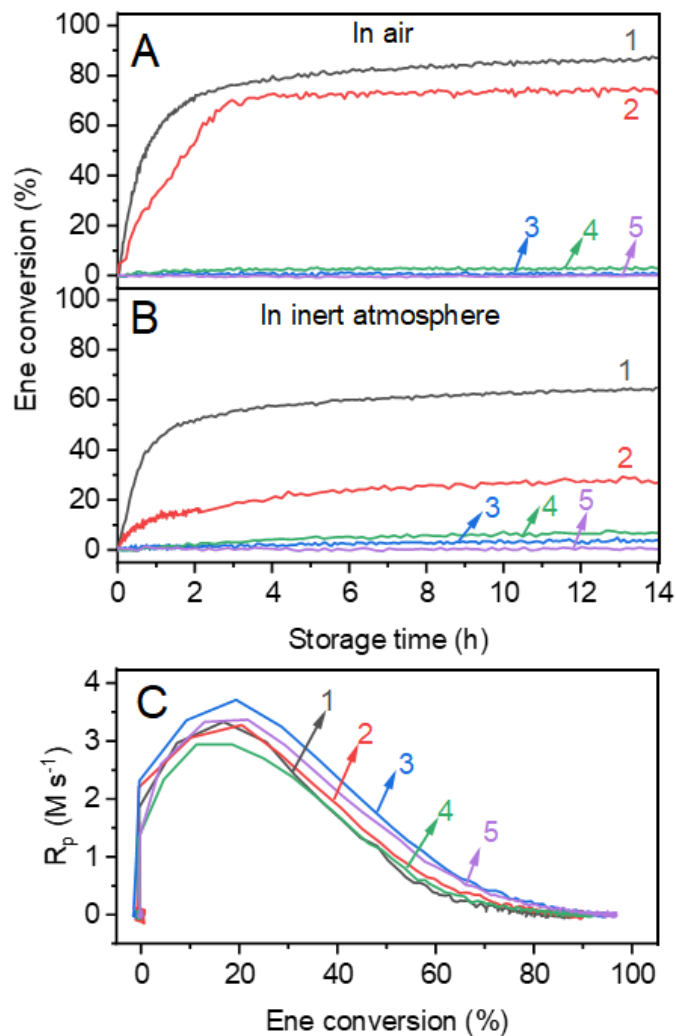


Fig. 2. Dependence of storage time on monomer (alkene) conversion for stoichiometric polymerization of bulk **DAA**-thiol (**1, 2, 3, 4** and **5**) mixtures performed either in the presence of air (**A**) or under inert atmosphere (**B**). Polymerization was carried out at ambient temperature in the dark and under nonradical-inducing conditions. The disappearance of the second overtone stretch of the CH of the alkene group at 6130 cm^{-1} allows to evaluate ene conversion as a function of storage time.⁴² Photopolymerization rate versus ene conversion plot for a photoinitiated polymerization involving the same thiol-ene mixtures is shown in **C** (irradiance = 22.2 mW cm^{-2} , [TPO] = 1 mol%).

($k_{\text{add}}/k_H \gg 1$). Under these conditions, the polymerization rate (R_p) expression simplifies as detailed in SI. R_p depends on thiol concentration and on a combination of rate and rate constants: R_i (self-initiation rate), k_t (rate constant for termination) and k_H (rate constant for H-abstraction).

$$R_p = \sqrt{\frac{R_i}{2k_t}} k_H [\text{Dithiol}] \quad (1)$$

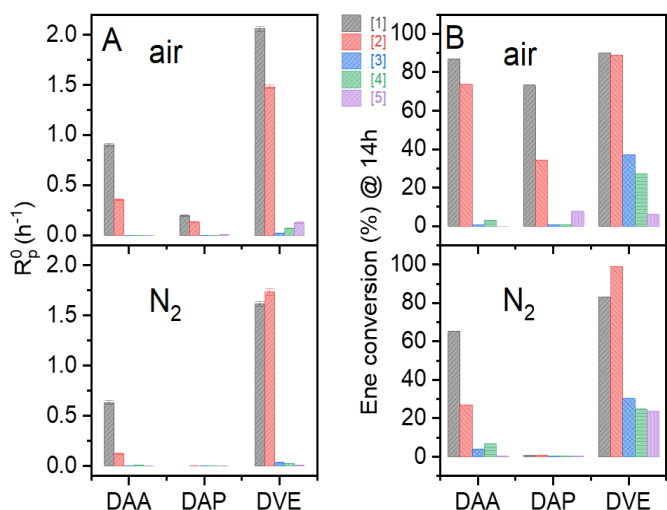


Fig. 3. Initial polymerization rates (R_p^0) (A) and ene conversion after 14 h (B) in the presence of air and under nitrogen for **DAA**, **DAP** and **DVE** depending on the thiol used (1-5).

One may reasonably assume that k_t and thiol concentration are in the same order of magnitude for the various **DAA**-thiol systems. Hence, k_H and R_i seem to be the most important factors in determining the value of R_p . To compare the value of k_H between the different thiols, the same series of **DAA**-dithiol mixtures is subjected to a photoinitiated polymerization using diphenyl 2,4,6 trimethyl-benzoyl phosphine oxide (TPO) as radical photoinitiator. Under these conditions, a reasonable assumption is to consider R_i constant irrespective of the monomer. **Fig. 2C** shows the plots of photopolymerization rate versus ene conversion for the five **DAA**-thiol systems in presence of TPO. There is little or no difference in reactivity, suggesting that k_H is of the same order of magnitude irrespective of the thiol involved. This result is consistent with literature data that the rate of H transfer depends mainly on the stability of the carbon-centered radical intermediate (unchanged in the series),⁴⁵ and to a lesser extent on thiol substituent.⁴⁶ Consequently, $R_p \propto \sqrt{R_i}$ in the different self-initiated **DAA**-thiol systems and the faster self-initiated polymerization rates observed for **DAA-1** and **DAA-2** (**Fig. 2A and 2B**) may be reasonably ascribed to a greater self-initiation rate.

To know whether these results obtained with **DAA** can be generalized, the same self-initiated bulk polymerization was carried out with **DAP** and **DVE** (**Fig. 1**) using the same set of thiols (1-5) as co-monomer. A number of interesting observations can be made from **Fig. 3** showing the initial polymerization rates (R_p^0) (**A**) and ene conversions after 14 h (**B**) in the presence of air and under nitrogen. The order of reactivity for the series of thiols (1 > 2 > 3-4-5) remains essentially the same irrespective of the alkene used. This confirms that the inductive characteristics of the thiol substituent have a significant effect on the initiation rate, and therefore, on the self-initiated polymerization rate. For a given alkene, the highest polymerization rates and conversions are achieved again with thiols 1 and 2 having an electron-withdrawing ester carbonyl substituent. For a given thiol, the

reactivity is enhanced when vinyl ethers (**DVE**) are involved compared to allyl ethers (**DAA**, **DAP**). A possible explanation may imply increase propagation rates due to the higher electron density of the C=C bonds of **DVE**. The polymerization rate is also slower with **DAP** compared to **DAA**, presumably because of steric effects decreasing propagation rates. However, these two explanations do not take into account the possible effect of alkene structure on self-initiation rate. Finally, the case of **DAP** is particularly interesting because, unlike **DAA** and **DVE**, the polymerization is completely halted in an inert atmosphere irrespective of the thiol used. The addition of water does not change the kinetic profile (**Fig. S4** in SI), indicating that molecular oxygen plays a larger role than atmospheric moisture in the self-initiation mechanism.

1.2 Effect of impurities

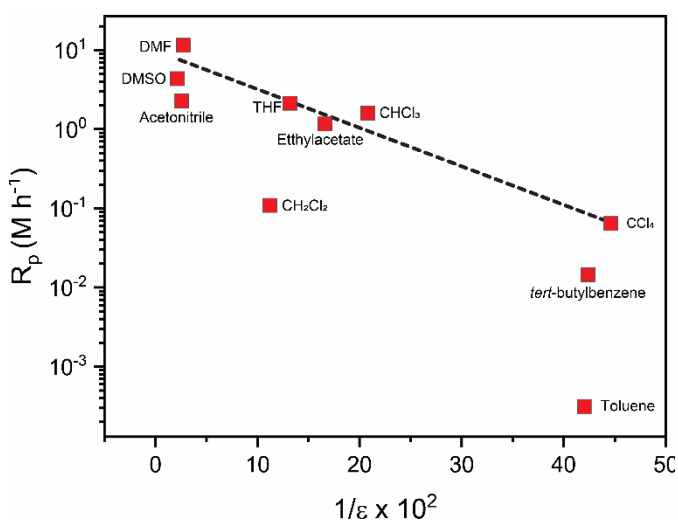


Fig. 4. Relationship between the polymerization rate of **DAA:1** in various solvents and the reciprocal dielectric constant of the solvent at ambient temperature. The polymerizations involve a mixture **DAA:1**:solvent = 1:1:2 equiv.

DAA-1 (1:1 equiv) is used as a model thiol-ene couple to gain insight into the effect of impurities on the course of a self-initiated bulk polymerization. **Table S1** in SI compares the relative initial polymerization rates in presence of four likely contaminants of thiol monomers: water, disulfide (dibutyl disulfide), hydroperoxide (cumyl hydroperoxide) and copper(II) salt (CuSO₄). Only Cu²⁺ and water accelerate the self-initiated polymerization relative to the reaction with neat monomers. Thus, only a minor part of the initiation is assumed to occur by homolysis of disulfide or hydroperoxide. Acceleration of reactivity observed in presence of copper ions suggests that one of the self-initiation reactions may be catalyzed by a transition metal compound. Similarly, the increased polymerization rates in presence of water demonstrate that specific solvation and polarization effects may be important in thiol-ene self-initiation mechanism. However, the effect of water is not systematic as previously mentioned since the polymerization rates of **DAP**-thiol systems are much less sensitive to water.

1.3 Solution polymerization

DAA-1 was then used as model thiol-ene couple to determine the importance of solvent effects on self-initiated polymerization rates. Using a solution of **DAA:1** in different solvents (2 equiv), **Fig. 4** shows the polymerization rates as a function of the inverse of the solvent dielectric constants (ϵ). The order of reactivity is DMF > DMSO > acetonitrile > THF > CHCl₃ > ethyl acetate > CH₂Cl₂ > CCl₄ > *tert*-butylbenzene > toluene. There is a general trend toward an increase of the overall reaction rate with increasing solvent polarity. The few exceptions to this generalization (below the straight line) involve CH₂Cl₂ and the aromatic solvents (toluene, *tert*-butylbenzene). The polymerization rate is increased by about 2 orders of magnitude when polymerization is carried out in DMF ($\epsilon = 36.71$) compared to CCl₄ ($\epsilon = 2.24$). In *tert*-butylbenzene ($\epsilon = 2.36$) and toluene ($\epsilon = 2.38$), the polymerization can be even suppressed.

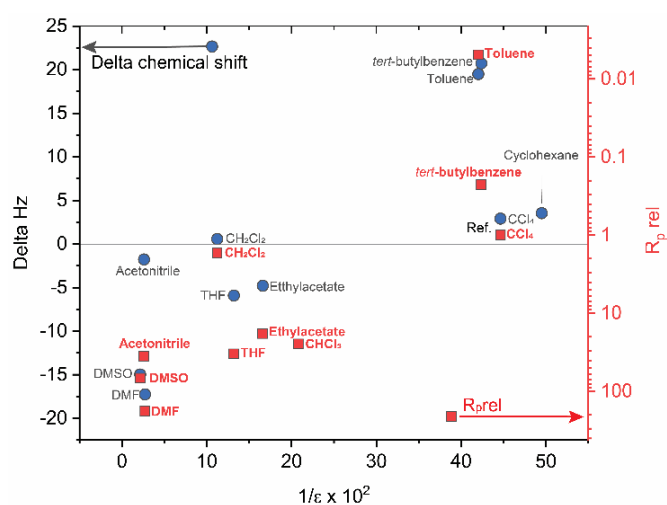


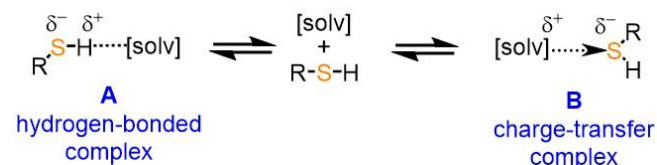
Fig. 5. Change in the chemical shift (circle) of the SH group of thiol acetate **1** in a variety of solvents of different dielectric constant (ϵ) (1:solvent = 1:24). The ¹H NMR experiments were carried out in CDCl₃ in which specific solute-solvent interactions are considered to be minimal. In CDCl₃, the sulfhydryl proton appears as a triplet peak at 2.03 ppm. Solvent effect on the relative polymerization rate (R_p) of **DAA:1** in the same series of solvents (square) taking as reference CCl₄. Polymerizations involve a mixture **DAA:1:solvent** = 1:1:2 equiv.

Even if the nature of the solvent can affect the rate of polymerization by changing the propagation rate constant, it is generally not as strong as observed in our investigation. An additional bias can be attributed to the dependence of polymerization rates on the solubility of molecular oxygen that varies with the solvents mentioned and used. However, this argument can be minimized by the fact that the solvent accounts for less than 40% of total volume in most experiments. In addition, oxygen solubility is lowest in the solvents (DMF or DMSO) where the reactivity is the highest. Therefore, it seems more reasonable to assume a much larger effect of solvent polarity on the self-initiation reaction rate than oxygen solubility. More polar solvents could drive the self-initiation equilibrium toward the production of more radical species X^{*}, and therefore RS^{*} (Scheme 1, (a) and (b)), resulting in faster polymerization rates. This points out the importance of solute-solvent interactions. The solvation of

thiol by solvents and alkene molecules is discussed further in section II.

II. Thiol solvation

Thiols can be involved in two major types of intermolecular interactions (**Scheme 3**).⁴⁷ First, weak H bonds can form between thiols (proton donor) and polar solvents (proton acceptor): RSH...[solv] (**Scheme 3, A**). Second, the site of high



Scheme 3. Equilibrium occurs between “free” and associated thiol and solvent molecules. Two preferential association modes involving thiols are expected to form, a hydrogen-bonded complex (**A**, left) and a charge-transfer complex (**B**, right).

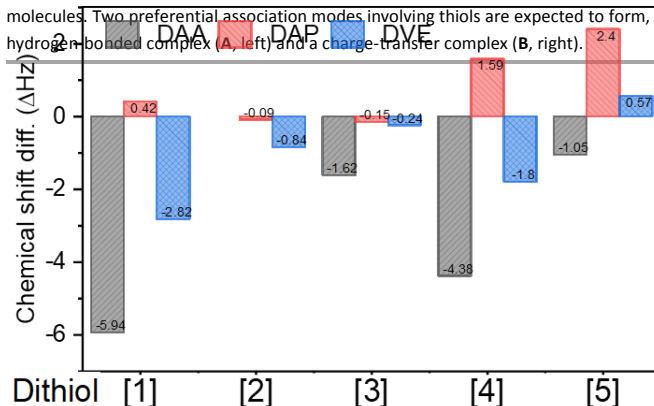


Fig. 6. Change in the chemical shift of the SH group of thiols **1-5** after addition of an excess of alkene **DAA**, **DAP** or **DVE** (thiol:alkene = 1:24). The ¹H NMR experiments were carried out in CDCl₃ with a thiol concentration of 0.06 M. For **DAA:2** pair, the chemical shift was not accessible because of overlapping signals.

electron density of a polar solvent (e.g., free electron pairs) can interact with the sulfur atom of the thiol (electron acceptor) resulting in a charge-transfer complex: solv→S(H)R (**Scheme 3, B**). It is expected that the equilibrium between free and associated thiol and solvent (olefin) molecules may affect the self-initiation rate on the basis of the experimentally observed effect of the solvent on polymerization kinetics.

II.1 Thiol-solvent interactions

¹H NMR is the most direct method to study the nature of thiol solvation in presence of a variety of solvents.⁴⁸ **Fig. 5** displays the change of chemical shift (Δ Hz) of the sulfhydryl proton (SH) for thiol acetate **1** in CDCl₃ after adding an excess of solvent (24 equiv). The chemical shifts are plotted against the inverse of the dielectric constant ($1/\epsilon$) to elucidate the effect of solvent polarity. As reported in the literature, a downfield shift (negative Δ Hz) indicates that H-bonding becomes the dominant mode of interactions, while an upfield shift (positive Δ Hz) evidences a major contribution from charge-transfer interactions (see the ¹H spectra in Fig. S5 in SI).⁴⁸ For polar solvents of high dielectric constants (DMF, DMSO), the pronounced downfield chemical shift indicates strong H-bonding. With poorly polar solvents (THF, ethyl

acetate), the downfield chemical shift is more limited reflecting weaker thiol-solvent interactions. For inert solvents (cyclohexane or CCl_4) and also CH_2Cl_2 , the chemical shift is hardly affected. Thus, the magnitude of the chemical shift varies significantly depending on the solvent polarity and the strength of the hydrogen-bonded complex (solvation). **Fig. 5.** reproduces on the same plot the kinetic data of solution polymerization (**Fig. 4**) to show the relationship between the change of ΔHz and R_p of **DAA:1** induced by the presence of various solvents. With the group of non-aromatic solvents, the correlation of chemical shift (ΔHz) with $1/\epsilon$ is analogous to the correlation with R_p . Reactivity is increased in presence of highly hydrogen bonding solvents. The second group of

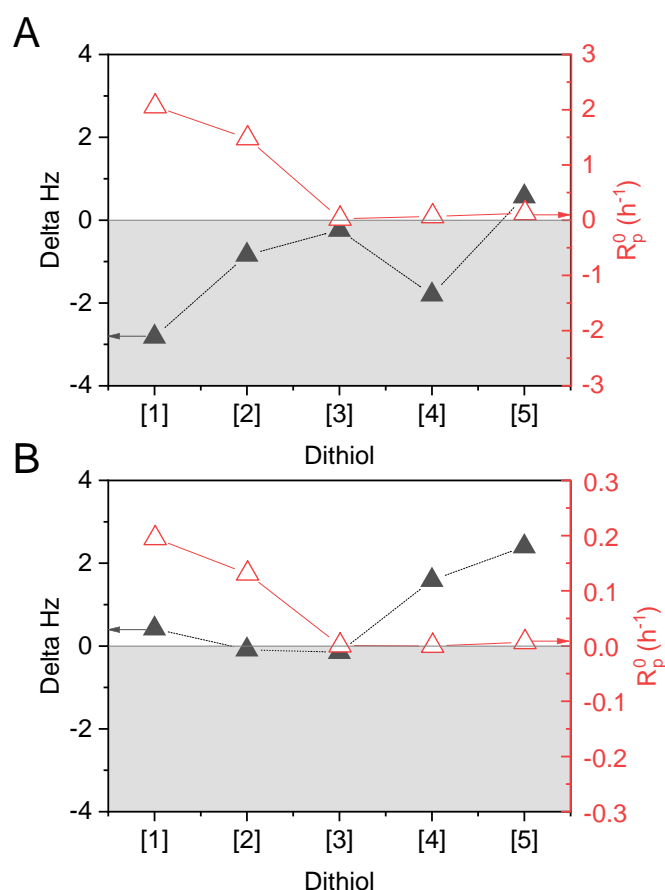


Fig. 7. Self-initiated polymerization rate (R_p^0 , open triangle) of stoichiometric bulk mixtures of **DVE**-thiol (**A**) and **DAP**-thiol (**B**) depending on the thiol used (**1-5**). Change in the chemical shift (ΔHz , solid triangle) of the SH group in CDCl_3 in the thiol-ene mixture ([thiol] = 63 mM).

aromatic solvents (*tert*-butylbenzene, toluene) is an exception to the previously observed trend since a marked upfield chemical shift is observed in this case. It is likely that the predominant solvation proceeds by charge-transfer complex between the thiol and the aromatic π system of the solvent. Despite absolute values of ΔHz comparable to those of highly polar solvents, the polymerization in presence of aromatic solvents shows negligible reactivity.

II.2 Thiol-alkene interactions

The ^1H NMR spectra of the thiols **1-5** were also examined in the presence of an excess of alkene (**DAP**, **DAA** or **DVE**) under the same conditions as chosen for the solvents (ene:thiol molar ratio = 24). As can be seen in **Fig. 6**, a downfield shift of SH protons is mostly encountered for **DAA** and **DVE** while an upfield shift is generally found with the aromatic derivative **DAP**. Thus, the general behavior of thiol-alkene solvation is qualitatively analogous to that of thiol-solvent systems with a distinct behavior depending on the presence of an aromatic group. With the non-aromatic alkenes (**DAA**, **DVE**), H-bonding is the major mode of interactions with thiols, presumably through the electron-rich C=C bond behaving as H acceptor. In this case, one would expect to find a more pronounced downfield chemical shift when the thiol is more acid, that is, when the S-H bond is polarized by electron withdrawing groups. In support of this assumption, the order of downfield deviation of **1**, **2** and **3** in presence of **DAA** or **DVE** is consistent with the order of acidity $1 > 2 > 3$, and points to stronger H-bonded complexes. However, the trend is not universal and can be circumvented by alterations, in particular for thiols **4** and **5**. Deviations from this order indicate in this case specific interactions. The benzenoid alkene (**DAP**) behaves similarly to the aromatic solvents with the predominance of donor-acceptor complex interactions. With poorly polarized thiols **4** and **5** for example, the marked upfield deviation reflects the predominance of electron-donor complex as expected. But the change of chemical shift is close to zero or even slightly negative with more polarized thiols (**1-3**), suggesting that the effect of charge-transfer complexation on ΔHz is compensated by H-bonded complexation having an opposite effect on the chemical shift. This trend can be rationalized in terms of equilibrium between two types of complexes (Scheme 3).⁴⁹

The relationship between bulk self-initiated polymerization rate (R_p) and thiol-alkene solvation (ΔHz) is shown in **Fig. 7** for two representative cases, **DVE** (**A**) and **DAP** (**B**), depending on whether the alkene is aromatic or not. With the exception of thiol **4**, there is a trend toward a higher reactivity of thiol-**DVE** bulk systems when the thiol favors strong H-bonding (negative ΔHz). Therefore, **DVE** behaves in a manner generally similar to non-aromatic solvents. On the other hand, **DAP** stands in marked contrast with the other alkenes. The charge-transfer complex observed in this case is globally detrimental to the reactivity. With poorly polarized thiols (**4**, **5**), this latter charge-transfer complexation is the dominant interaction, and the polymerization is strongly inhibited. With polarized thiols (**1**, **2**), the polymerization is only slowed down presumably because of an equilibrium with the H-bonded complex. Similar conclusions about the solvation of thiol can be obtained by FTIR spectroscopy by the examination of the effects of increasing amount of solvent (or alkene) on its FTIR spectrum (see **Fig. S6** and **S7** in SI).

III. Nature of the initiating radicals

Most of the evidence to support and elucidate the self-initiation mechanism in thiol-ene polymerization has been so

far indirect, consisting of kinetic and spectroscopic data. The major problem in ascertaining whether self-initiation occurs is to identify the primary or/and initiating radicals (Scheme 1, (a) and (b)). Radical-trapping using *N-tert-butyl- α -phenylnitrone* (PBN) is especially useful for this purpose since it allows the detection by EPR of various short-lived radicals as their nitroxyl radical adducts.^{3,50} To study the type and concentration of primary/initiating radicals, a mixture of thiol and PBN acting as radical scavenger was prepared, and the EPR spectra of the possible radical adducts were then analyzed.

polymerization rates increasing in the order **1** > **2** > **3-4-5** (Fig. 3).

III.2 Effect of solvent

Fig. 8B shows the effect applied by DMF, a strong hydrogen-bonding solvent, on the EPR spectrum of neat **1**. An increasing DMF/thiol ratio (from 0.4 to 4) causes a significant increase of the EPR spectrum intensity indicating the production of more thiyl radicals. As shown in Fig 8C, a similar effect of DMF (2 equiv) has been observed for thiol **2**, but also for the less polarized thiols **3-5**. DMF is expected to give rise to hydrogen

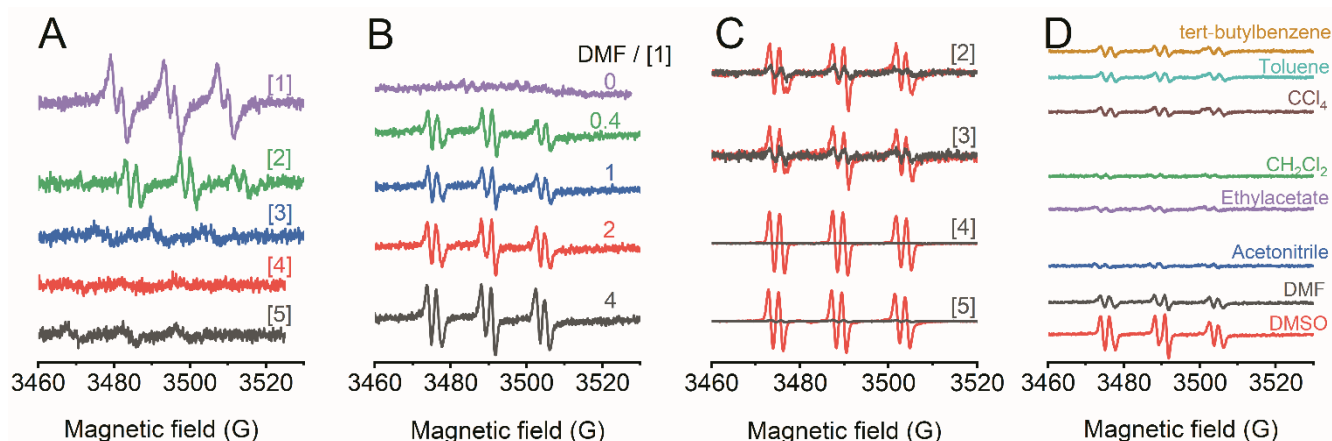


Fig. 8. A. EPR spectra of thiols **1-5** in *tert*-butylbenzene. B. EPR spectra of thiol **1** with increasing amounts of DMF (0.4 – 4 equiv). C. EPR spectra of thiols **2-5** before and after addition of DMF (2 equiv). D. Effect of solvents on the EPR spectrum of **1** (solvent:thiol = 2:1 equiv).

III.1 Effect of thiol substituent

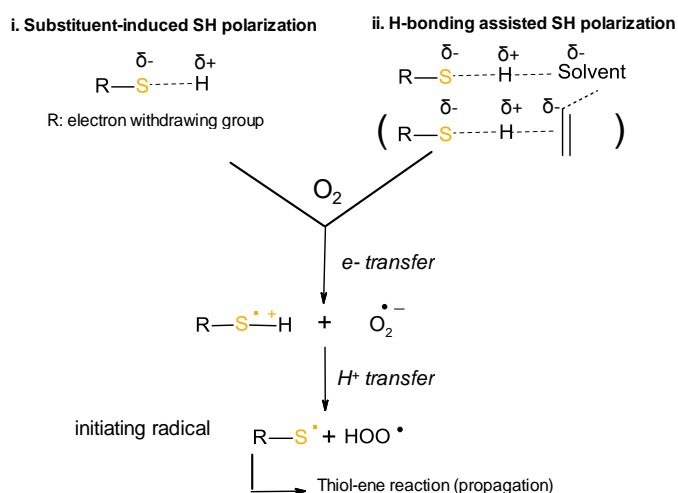
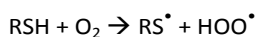
The EPR spectra of mixtures of 30 mM PBN, 100 mM thiol (**1-5**) in *tert*-butylbenzene under air are displayed in Fig. 8A. After 15 scans, only thiols **1** and **2** bearing an ester substituent show an intense six-line spectrum with a well resolved hyperfine structure indicative of a single type of radical that we assume to be a thiyl radical. However, to support our assignment there are no adequate literature data of PBN/ RS^{\bullet} spin adducts^{51,52} (except for the glutathiy radical⁵³). To ascertain the presence of RS^{\bullet} for thiols **1**, **2** and **3**, the expected thiyl radicals can be generated photochemically upon irradiating (385 nm) the same thiol/PBN mixture in the presence of isopropyl thioxanthone (ITX, 10 mM). Upon electronic excitation, ITX is known to induce an intermolecular abstraction of a hydrogen atom from RSH. For thiols **1-3**, we find that the EPR spectra (Fig. S8 in SI) of the irradiated samples are analogous to those of neat thiols. Therefore, the control experiments validate PBN as a spin-trapping probe and support the chemical nature of the trapped radicals. The most probable mechanism is that self-initiation occurs in a single step (without intermediate primary radicals) and involves the formation of thiyl radicals from the thiol, then capable of initiating a thiol-ene polymerization. Contrary to thiols **1** and **2** with an ester substituent, the thiyl radical concentration is very small for **3**, and below the limits of detection for **4**, **5**. Clearly, the yield of thiyl radicals is dependent on the electronegativity of the thiol substituents. This trend is also in line with the thiol-ene

bonding interactions with thiols even in the absence of a strong electron-withdrawing substituent. Additional support for the role of thiol-solvent hydrogen bonded complex in the formation of thiyl radicals comes from the effect of solvent polarity on the concentration of thiyl radicals. Fig. 8D shows the EPR spectra of a system consisting of a mixture of thiol **1** (1 equiv) and various solvents (2 equiv). As expected, the abstraction of the sulfhydryl hydrogen is favored in highly polar solvents (DMF, DMSO) in which thiol-solvent H-bonded complex are present. In contrast, weakly polar (ethyl acetate, CH_2Cl_2) or apolar (aromatic) solvents (CCl_4 , toluene, *tert*-butylbenzene) limit significantly or suppress the production of thiyl radicals. Clearly, there is a relationship between the formation of H-bonded complex, a higher yield of thiyl radicals, and greater polymerization rates in solution (Fig. 4).

IV. Discussion

IV.1 Role of thiol air oxidation in the self-initiation of thiol-ene polymerization

In our search for a consistent mechanism accounting for the self-initiation of thiol-ene polymerization, we have highlighted that atmospheric oxygen, thiol substituent and solvation have a significant effect on the rates of self-initiation and polymerization. These coherent and convergent elements provide a basis for stating that (initiating) thiyl radicals may be formed by air oxidation of thiols through dissolved molecular oxygen in the thiol-ene mixture.

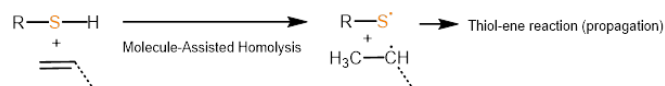


Scheme 4. Polarization of S-H bond induced by thiol substituent or H-bonding with solvent or alkene.

The reaction may involve a proton-coupled electron transfer from thiol to molecular oxygen (**Scheme 4**), probably occurring inside the solvent cage. The process is initiated by an electron transfer from the thiol to molecular oxygen (O_2) yielding superoxide anion ($\text{O}_2^{\bullet -}$) and the thiyl radical cation ($\text{RSH}^{\bullet +}$). The latter species efficiently deprotonates to the corresponding thiyl radical (RS^\bullet) capable to initiate a polymerization. Hence, the self-initiation mechanism could proceed without prior formation of thiolate or the need for a metal catalyst. In this respect, it bears resemblance to the initiation of a thiol-olefin cooxidation (TOCO) reaction,⁴⁹ thiol oxidation into disulfides⁴⁷ or thiol-disulfide exchange.⁵⁴ Recently, this mechanism was also postulated to explain the atmospheric oxygen-promoted addition of thiol to alkene.⁵⁵ In agreement with our study, H-bonding influenced the extent and efficiency of coupling. More generally, our data support that the driving force for thiol oxidation is the polarization of the S-H bond. A polarized S-H bond causes the activation energy of oxidation to decrease, thereby making the transfer of electron to an oxygen molecule more facile. As depicted in **Scheme 4**, an electron-withdrawing substituent (i) and hydrogen-bonded complexes (ii) seem to function in a similar way, activating the thiol by means of its polarization.

i. A thiol substituent effect on the self-initiation rates is evident when the thiol-ene polymerization is carried out in bulk media. Irrespective of the alkene used, the self-initiated polymerization proceeds systematically at an accelerated rate when the thiol bears an electron withdrawing substituent (1, 2). In the case of allyl ethers, the difference of polymerization rates is attributed to a more efficient initiation step promoted by thiol polarization and, to a much lesser extent, to higher propagation rates. The self-initiation rate seems to be a function of the relative substituent-induced polarization of thiol, i.e., the relative acidity of the thiol. Spin-trapping experiments further support this rationale. Thiyl radicals are readily formed provided that the thiol substituents have sufficient electron-withdrawing character (1 or 2). The

influence of H-bonding on S-H polarization is minimized in this



Scheme 5. General mechanism of MAH of thiol by alkene

case by the use of low concentration of thiols (0.1 M) and an apolar solvent (*tert*-butylbenzene).

ii. Solvent-thiol and alkene-thiol H-bonded complexes have been evidenced by ¹H NMR. The formation of solvent-thiol H-bonded complex is generally favored by the electron-donating property of the solvent and an electron withdrawing character of the thiol substituent, although deviations from this behavior are found under certain conditions, in particular with aromatic solvents as discussed in the next section. As demonstrated for the DAA:1 pair, adding a H-bonding solvent (water, DMF, DMSO, etc.) or increasing its amount results in a higher concentration of thiyl radicals and faster self-initiated polymerizations. Alkenes behave somewhat similarly to the solvents, although relatively little data are available because of the limited number of alkenes tested. With allyl ethers (DAA, DAP), the polymerization rate is not negligible when acid thiols (1 or 2) promote H-bonding. When the electron-withdrawing ability of the thiol substituent is insufficient, only weak dispersion forces or dipole-dipole forces arise. S-H polarization is not strong enough in this case to drive the self-initiation towards the production of thiyl radicals, explaining the much lower reactivity observed with thiols 3-5. The situation is very different for vinyl ether (DVE) since the higher electron-donating character of the olefin drives both high initiation and propagation rates, allowing self-initiated polymerization to proceed even when the thiol has a poor acidity.

In summary, estimating the extent of thiol polarization is a reasonable approach to evaluate the effect of monomers' structure or solvent on the rate of self-initiation. It may be used to give a general idea of the behavior to be expected from a thiol-ene monomer pair that has not been studied from the point of view of its storage stability. In spite of this success, there are two deficiencies of the S-H polarization scheme that need clarifications: the effects of aromatic solvents (alkenes) and of an inert atmosphere on the self-initiated polymerization rate.

IV.2 Effect of aromatic compounds

In the presence of polar solvents and alkenes, thiol solvation is generally dominated by H-bonded complexes. An exception to this behavior is found with aromatic solvents (alkenes). In this case, electron acceptor-donor interactions also arise, and two types of complexes may competitively form with consequences on reactivity. Two different situations are encountered depending on the position of the equilibrium. In the first case, there is a dominant contribution of the charge-transfer complex which is reflected by a strong upfield deviation of the S-H protons in ¹H NMR. A prime example is the self-initiated polymerization of DAA-1 in presence of *tert*-butylbenzene or toluene. In this case, the polymerization is

strongly inhibited. Consistent with these results, Szmant and coworkers found a decreased rate of oxidation of various thiols into disulfide when an aromatic solvent is added.⁴⁷ In bulk conditions, the charge-transfer interactions are prominent for **DAP** with thiols **4** and **5**, and the polymerization rates are similarly negligible. In the second case, the charge-transfer complex is in equilibrium with the H-bonded complex. The mix of contributions is not easily determined experimentally, but the opposite effects of the two complexes on the chemical shift result in values close to zero. This special situation is encountered when **DAP** is polymerized with thiols **1-2**. The electron withdrawing character of the substituents of the two thiols drives the equilibrium toward more H-bonded complexes allowing thiol oxidation to proceed, and as a consequence, self-initiated polymerization takes place.

IV.3 Effect of inert atmosphere

Only the polymerization of **DAP**-thiols is halted in nitrogen atmosphere. In contrast, **DAA** and **DVE** can undergo self-initiated polymerization with most thiols in inert atmosphere, but the polymerization rates are appreciably slower than the corresponding polymerizations under air. The finding that atmospheric oxygen is not necessarily required for the self-initiated polymerization to proceed is not without ambiguity about the role of thiol oxidation by air as sole mechanism responsible for self-initiation. Firstly, our experimental data can be reconciled with the thiol oxidation mechanism by considering the difficulty to remove completely atmospheric oxygen. In addition, thiyl radicals may already be present in the neat thiol before mixing with the alkene. EPR spectra of thiols supports the presence of thiyl radicals in thiols **1-3** without the assistance of H-bonding solvents and even when the samples are prepared under nitrogen. Their presence may be ascribed to thiol oxidation promoted by the substituent-induced polarization of the S-H bond as discussed above. This assumption is backed by the observation that polymerization rates are enhanced with the aging of the thiol (**Fig. S9** in SI). This result can be explained with a slow oxidation of thiols by air during storage increasing the concentration of thiyl radicals.

However, the most plausible explanation would be to consider a contribution of a second concurrent self-initiation reaction proceeding without the assistance of molecular oxygen. *Hydrogen atom abstraction from the thiol* (homolysis) is another route yielding thiyl radicals. In presence of alkene, the homolysis of S-H σ -bond is coupled to the addition of the resulting H \cdot to the π -bond of the alkene (**Scheme 5**).²⁴ The driving force is thus the formation of C-H bond at the olefin that reduces the endothermicity of S-H homolysis.⁵⁶ For this reason, it is referred to as “alkene-assisted homolysis”,⁵⁷ or in a more general way as a MAH. The occurrence of a MAH of S-H as initiation mechanism was originally reported by the groups of Pryor⁴⁰ and Nuyken,²⁵ then more recently by Metzger et al.⁵⁸

This bimolecular reaction has no transition state (kinetic barrier) because the combination of two radicals proceeds

without energy of activation. Therefore, the activation energy equals the reaction enthalpy $\Delta_r H$ estimated by DFT calculations. It is found that the reaction enthalpy of a H transfer from thiol **1** to **DAA** amounts to $\Delta_r H_{298} \approx 160$ kJ/mol and does not vary significantly with the nature of the alkene (**Fig. S10** in SI). This value is significantly higher than found in many MAH reactions.⁵⁶ In comparison, the activation energy for thermal initiator decomposition is in the range 120–150 kJ/mol.²⁹ The high endothermicity of MAH thiol hemolysis predicts that polymerization proceeds only at very low rates at ambient temperature which may appear at first glance in contradiction with the experimental results. Elucidation of that point would require a complete kinetic study, but there are arguments in favor of the MAH mechanism. The rate of producing primary radicals (R_i) by MAH is certainly very weak. However, equation 1 describes that for the representative case of allyl ether-thiol, the polymerization rate depends only on the square root of the initiator concentration. In contrast, R_p shows a first-order dependence on [Thiol] and k_H , showing their higher importance in a chain radical process. In our case, bulk conditions ([thiol] = 5.2 M) and the use of the most reactive alkenes⁴⁴ (allyl ethers display the highest k_H : $10^6 - 10^7$ M $^{-1}$ s $^{-1}$) may increase R_p to a level allowing the polymerization to proceed. In addition, the formation of olefin-thiol complex that is reminiscent of the MAH may modify the activation energy for initiation. Further work is required to substantiate the role of MAH in the thiol-ene self-initiated polymerization.

Conclusion

A number of thiol-ene monomer pairs have been shown to undergo self-initiated polymerization under air or nitrogen atmosphere. The self-initiated thiol-ene polymerization is a complex reaction system that may consist of competitive parallel reactions. This study focuses on the role of one-electron transfer reactions from thiol to molecular oxygen in the self-initiation process. There is some evidence that thiol oxidation by air plays a major role in the self-initiation of a spontaneous thiol-ene polymerization, in particular when the reaction is carried out under air. The self-initiated thiol-ene polymerization is depicted as a radical chain reaction involving the initial formation of thiyl radicals by the reaction of atmospheric oxygen with preferentially polarized thiols. H-bonding with electron-donating alkenes or solvents molecules (proton acceptor) or/and electron-withdrawing substituents of the thiol activates the S-H bond, making thiol oxidation easier, and polymerization faster due to a higher production of thiyl radicals. Additional support for an increased formation of thiyl radicals originates from radical-trapping experiments. In reaction systems under exclusion of molecular oxygen, only a minor part of the initiation may occur by this oxidation manifold. It is likely that an additional contribution from molecule-assisted homolysis (MAH) of thiols occurs. Despite these new results, some mechanistic aspects of thiol-ene self-initiated polymerization require further investigation, in particular the contribution of MAH relative to thiol oxidation by air.

Nevertheless, our findings give useful practical information for preventing (or at least limiting) self-initiated thermal thiol-ene polymerization. For this purpose, three levers affecting the rate of thiol oxidation by air are available: S-H bond polarization, reaction atmosphere and thiol purity.

i. Any factor contributing to decrease thiol polarization may reduce self-initiation rate. Thiols substituents with electron-donating ability or negligible inductive properties are most appropriate. Alkenes or solvents (if the system is in solution) with less electron donating ability can also reduce the extent of hydrogen bonding-induced polarization. Interestingly, aromatic monomers or solvents seems to decrease the intrinsic polarity of the thiols due to charge-transfer interactions.

ii. The self-initiation rates are generally slower when the thiol-ene mixture is stored under a nitrogen atmosphere. However, except for a few cases (including the aromatic alkene DAP), the absence of air does not ensure a complete latency.

iii. The use of sufficiently pure reactants, in particular thiols, is apparently an important feature. The presence of disulfides and adventitious peroxides may not be as much of a problem. Self-initiation more likely involves catalytic metal traces, or water as hydrogen-bonding solvent, but not systematically.

Conflicts of interest

There are no conflicts to declare.

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