Macromolecules
ARTICLE

Macromolecules **2010**, *43*, 4113–4119 **4113**
DOI: 10.1021/ma1002968

Reaction Rates and Mechanisms for Radical, Photoinitated Addition of Thiols to Alkynes, and Implications for Thiol−Yne Photopolymerizations and Click Reactions

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Received February 5, 2010; Revised Manuscript Received March 23, 2010

ABSTRACT: Because of its utility in network polymerization, dendrimer synthesis, and monomer development, the photoinitiated addition of thiols to alkynes has rapidly become an important tool for polymer scientists. Yet, because this chemistry has only recently been applied to cross-linked polymer development, understanding of the nature of how the yne structure affects the reactions and information on the relative reactivities of alkynes bearing various substituents is unavailable as is the relative addition rate of the thiol to the yne as compared to the vinyl sulfide. Herein, the photoinitiated addition of octanethiol to various alkynes is explored. The most rapid addition of thiols to alkynes is that to cyclooctyne, although the resulting vinyl sulfide does not permit subsequent thiol addition. Furthermore, in the absence of radical initiators and light, thiols add spontaneously to cyclooctynes, suggesting limitations to the orthogonality of the strain-promoted copper-less azide, alkyne cycloadditions. In order of decreasing reaction rates, the consecutive addition of two thiols occurs with the aliphatic 1-octyne > propargyl acetate > methyl propargyl ether > 2-octyne. Ethyl propiolate and methyl propargylamine exhibit very small reaction rates with thiols, and no consecutive addition is observed.

Introduction

The thiol−ene photopolymerization has received significant attention in recent years. Though the reaction is radically mediated, the unique mechanism (alternating propagation across the ene and chain transfer to the thiol) results in a regular step-growth network.[1−3] Accordingly, thiol−ene network polymerizations may benefit from the spatial and temporal control that radical photoinitiation affords it while the resulting materials possess the intrinsic benefits of step-growth polymers[4] (e.g., regular network architecture resulting in toughness, delayed gel point resulting in high conversion of glassy polymers and low extractables). Additionally, thiol−ene polymerizations are insensitive to oxygen inhibition and generally exhibit very rapid polymerization rates.[5] For the radical thiol−ene photopolymerizations various functional groups have been evaluated in regards to their reaction rates and analysis of which steps are rate limiting, including aliphatic alkenes, allyl ethers, vinyl ethers, acrylates, vinyl silanes, and norbornenes.[6] One general trend that has been identified is that increasing electron density of the vinyl moiety also increases the reaction rate.[1,6] A notable exception to this trend is the norbornene group, which, presumably because of the ring strain alleviated by the dissolution of the π bonds upon thiol addition, also exhibits a very high reaction rate.

While the radical addition of thiols to alkynes was described as early as the 1930s,[7−9] the use of this reaction in photoinitiated network polymerizations has only recently been explored.[10−12] While much of the previous research examined the monoaddition of thiols to phenylacetylene,[13−15] much of the research of the past year has focused on the consecutive diaddition of thiols to akynes, which reaction has been utilized for the synthesis of polyfunctional materials,[16] dendrimers,[17] and polymer brushes[18] in addition to cross-linked polymers. The general radical-mediated mechanism is presented in Figure 1. Briefly, a thiyl radical adds across the alkyne triple bond to form a vinyl sulfide radical. This radical abstracts a hydrogen from a thiol, regenerating the thiyl radical and forming a vinyl sulfide. Subsequently, a thiyl radical adds across the double bond of the vinyl sulfide generating a dithioether radical which abstracts a hydrogen atom from a thiol, thereby regenerating the thiyl radical and forming a dithioether. This polymerization mechanism is analogous to that of the thiol−ene photopolymerization, in which alternating propagation and chain transfer reactions lead to a radical-mediated step-growth polymerization. Because thiols add consecutively to the alkyne, the thiol−yne polymerization is also analogous to the epoxy−amine polymerization, in which two epoxies add to a single primary amine.[19]

Because of the bireactive nature of the alkyne functionality, the thiol−yne photopolymerization addresses one of the fundamental and intrinsic limitations of the thiol−ene reaction. Because each alkene in a step-growth thiol−ene polymerization is monofunctional while each alkene in a chain growth radical polymerization is difunctional as it forms two new bonds,[20] thiol−ene polymerizations typically result in materials with relatively low cross-link density, which contributes to low glass transition temperatures and low moduli.[11] Thus, thiol−yne reactions have the potential to improve these properties while still retaining other advantageous characteristics of thiol−ene polymerized materials. However, since the photopolymerization of thiol−yne networks has only recently been explored, the relative reactivities of various ynes, which in part determines monomer utility, have not been adequately addressed.

In thiol−yne photopolymerizations previous reports have utilized aliphatic alkynes, propargyl ethers, and propargyl esters as monomers due to their availability and ease of

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Published on Web 04/06/2010

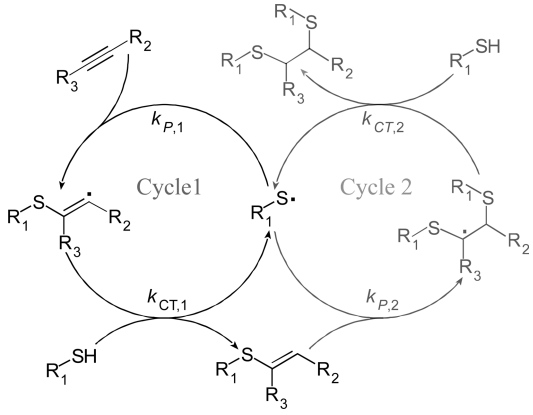

Figure 1. Generalized radical thiol−yne polymerization scheme. Cycle 1 represents the initial addition of a thiol to an alkyne while cycle 2 represents the subsequent addition to the vinyl sulfide product from the first addition. Because the participation of the vinyl sulfide is dependent on the identity of the initial alkyne as demonstrated herein, this cycle is presented in gray to indicate that this reaction may or may not occur, depending on the initial yne structure. For terminal alkynes, R_3 = H.

synthesis.[11,16−18,21] In addition to these functional groups, we herein examine the relative reactivities toward thiols of two other terminal alkynes (methyl propargylamine and ethyl propiolate) as well as two internal akynes (2-octyne and the ring-strained cyclooctyne). Exploring the reaction between thiols and various alkynes, including cyclooctyne, allows for more informed monomer design for the thiol−yne photopolymerization. Additionally, this study holds implications for the use of azide−alkyne click reactions as it both demonstrates limitations to the orthogonality of such reactions and portends the development of hybrid copolymerization schemes.

Catalyzed by copper(I), terminal alkynes add to azides to form 1,2,3-triazole rings.[22] Terminal as well as internal alkynes were recently shown to react to form similar triazole rings when catalyzed by ruthenium(II),[23] whereas cyclooctynes have been demonstrated to add to azides spontaneously.[24] This spontaneous reaction has been used for in vivo imaging of biological processes as well as star polymer and hydrogel network synthesis.[25−27] Additionally, a phototriggered click reaction has been demonstrated by photochemical conversion of a cyclopropanone to dibenzocyclooctyne for subsequent copper-less click addition to an azide.[28] The click and copper-less click azide−alkyne reactions have received particular attention in biological applications as both azides and alkynes are considered generally unreactive toward functional groups typically displayed on biomolecules.[29] However, results presented herein demonstrate the spontaneous addition of thiols to cyclooctyne in a nonpurged environment, suggesting that the orthogonality of the strain-promoted copper-less click reactions may be compromised in biological media where cysteine and other thiol-containing biomolecules are often present.

Experimental Section

Purchased Materials. Structures of materials used in this study are shown in Figure 2. Reactants octanethiol, butyl 3-mercaptopropionate, 1-octyne, propargyl acetate, methyl propargyl ether, ethyl propiolate, and methyl propargylamine were purchased from Sigma-Aldrich. The internal alkyne, 2-octyne, was purchased from TCI America. The ultraviolet-active photoinitiator 1-hydroxycyclohexylphenyl ketone (I184) was obtained from Ciba Specialty Chemicals. All purchased chemicals were used as received.

Synthesis of Cyclooctyne. Cyclooctyne was synthesized by a modified method of Brandsma and Verkruijsse[30] as detailed below. All reactions were run in flame- or oven-dried glassware

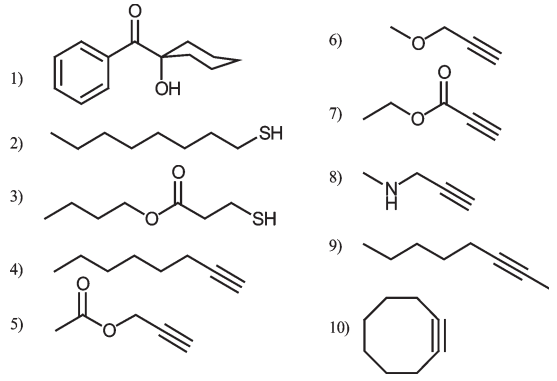

Figure 2. Materials used: (1) I184, (2) octanethiol, (3) butyl 3-mercaptopropionate (4) 1-octyne, (5) propargyl acetate, (6) methyl propargyl ether, (7) ethyl propiolate, (8) methyl propargylamine, (9) 2-octyne, and (10) cyclooctyne.

under an argon atmosphere. NMR spectra where recorded on a Varian INOVA 500 MHz instrument, and chemical shifts are reported in parts per million (δ) from TMS using the residual $CHCl_3$ peak as an internal reference (7.26 ppm); coupling constants (J values) are reported in hertz. Gas chromatography−mass spectrometry was performed on a Thermo Finnigan Polaris Q instrument (electron impact, 70 eV).

1-Bromocyclooctene. *cis*-Cyclooctene (25 mL, 182 mmol) was added to a round bottom flask containing dry dichloromethane (96 mL) and cooled to −15 °C. Bromine (9.35 mL, 182 mmol) was added in a slow stream over about 20 min, at which point a characteristic brown color persisted. Excess bromine was evaporated under a rapid stream of air, and then the solution was further concentrated by rotary evaporation. The crude 1,2-dibromocyclooctane was redissolved in pyridine (72.8 mL) and brought to reflux with rapid stirring. After refluxing overnight, a thick slurry had formed, and the reaction was cooled to ambient, diluted with toluene, and filtered, rinsing with three portions of toluene. The solution was concentrated and purified by flash chromatography (100% hexanes) to yield a clear oil (18.85 g, 99.7 mmol, 55% over two steps). R_f = 0.70 (100% hexanes, stained with ceric ammonium molybdate). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.03 (t, J = 8.5, 1H), 2.63−2.59 (m, 2H), 2.13−2.07 (m, 2H), 1.66−1.60 (m, 2H), 1.58−1.47 (m, 6H). GC-MS: m/z 191, 190 (M^+), 189, 188 (M^+), 162, 161, 160, 110, 109, 81, 79, 77, 67 (base), 65, 53, 51, 41.

Cyclooctyne. A 0.2 M solution of lithium diisopropylamide (LDA) was prepared by adding *n*-BuLi (1.0 equiv) to a 0.22 M solution of diisopropylamine (1.1 equiv) in THF at −15 °C, which was stirred for 30 min and then brought to ambient. To a solution of 1-bromocyclooctene (12.279 g, 61.7 mmol) in THF (62 mL) at −15 °C was added 0.2 M solution of LDA in THF (154.25 mL, 30.85 mmol, 0.5 equiv). Upon completion of LDA addition, the resultant dark brown solution was stirred for 1 h and then poured into water (600 mL), extracted with hexanes (750 mL in three portions), dried with $MgSO_4$, filtered, and concentrated. The crude material was purified by flash chromatography (100% hexanes) to yield a clear, sharp smelling oil (688 mg, 6.4 mmol, 21%). The remaining 1-bromocyclooctene was also recovered. R_f = 0.36 (100% hexanes, stained with permanganate). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.19−2.13 (m, 4H), 1.90−1.81 (m, 4H), 1.65−1.58 (m, 4H). GC-MS: m/z 109, 108 (M^+), 107, 105, 93, 92, 91, 81, 80, 79 (base), 78, 77, 67, 65, 63, 52, 51, 50, 41.

Cyclooctyne Dimer. When 1-bromocyclooctene was treated with 1.0 or more equiv of LDA, all *in situ* formed cyclooctyne was converted to a species whose molecular weight is twice that of cyclooctyne, presumably a dimer. GC-MS: m/z 216 (M^+), 201, 187, 173, 159, 145, 147, 145, 134, 131, 119, 117, 105, 93, 92, 91 (base), 79, 77, 67, 51, 41.

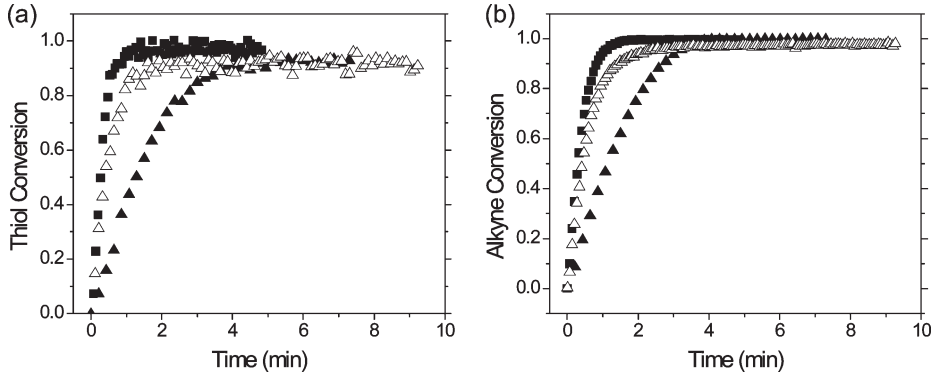

Figure 3. Conversion of thiols (a) and alkynes (b) for reaction mixtures including 2 M octanethiol and 1 M alkyne: 1-octyne (■), propargyl acetate (△), and methyl propargyl ether (▲). Reactions were initiated with 10 mW/cm^2 light filtered at 365 nm. All samples were prepared with 1 wt % photoinitiator I184.

Real-Time Fourier Transform Infrared Spectroscopy (FTIR). FTIR studies were performed on a Nicolet 750 Magna FTIR spectrometer with a KBr beam splitter and an MCT/A detector under dry air. Series scans were recorded at a rate of one scan every 2 s. Thiol conversions were determined by the depletion of the S−H absorption peak at 2670 cm^{-1}. Alkyne conversion was determined for the terminal akynes by depletion of the C−H absorption peak at 3100−3200 cm^{-1} while internal alkyne conversion was determined by depletion of the C≡C absorption peak at 2200 cm^{-1}. Vinyl sulfide peaks (C=C) were identified for reactions involving ethyl propiolate, methyl propargylamine, and cyclooctyne and occupied wavenumbers between 1650 and 1700 cm^{-1}. Samples were placed in a horizontal transmission apparatus, between sodium chloride windows, and reaction was initiated with an EXFO Omnicure light source, 100 W Hg arc lamp, with a 365 nm filter. All reactions were performed with 1 wt % I184 initiator and an intensity of 10 mW/cm^2, measured with an International Light Inc. radiometer, model IL1400A.

Results and Discussion

Thiol Addition to Terminal Alkynes. It was previously demonstrated that the thiol−yne copolymerization of pentaerithrytol tetrakis(mercaptopropionate) (PETMP) and 1,9-decadiyne proceeds as portrayed in Figure 1 with two thiols adding consecutively to a single alkyne.[11] As might be anticipated, the reaction between 1-octyne and 2 equiv of octanethiol occurs similarly (Figure 3) with nearly complete consumption of both thiols and alkynes.[11] (The relative rates of consumption of alkynes and their corresponding vinyl sulfides are addressed explicitly in a subsequent section.) Furthermore, propargyl acetate and methyl propargyl ether exhibited the 2 to 1, thiol-to-alkyne reactivity, although at diminished rates (Figure 3 and Table 1).

Such behavior is not universal to terminal alkynes, however. Methyl propargylamine and ethyl propiolate both react with thiols whereas the consecutive addition is not observed. Figure 4 shows the thiol and alkyne conversions for a 2:1 stoichiometric reaction. It can be seen here that thiols and alkynes are consumed on an approximately equimolar basis. (Since the concentration of thiols is twice that of alkynes, this equimolar consumption is represented with a thiol conversion of approximately half that of alkynes.) No consumption of the intermediate vinyl sulfide species was observed, indicating failure of both the thiol−ene reaction or the homompolymerization of the vinyl sulfide intermediate, which, for the reaction with propiolate, shares a similar structure to acrylates. Moreover, the rates of reaction were comparatively low for photoinitiated addition of thiols to these terminal alkynes.

Table 1. Rates of Thiol Depletion (M/min) for Reactions Performed with Indicated Alkynes at (a) 2 M Octanethiol and 1 M Alkyne or (b) 2 M Each Octanethiol and Alkyne; Participation of the Vinyl Sufide in Cycle 2 of Figure 1 Is Qualitatively Indicated (c)[a]

alkyne	initial rates 2:1[a] thiols: alkyne	initial rates 2:2[b] thiols: alkyne	subsequent addition of thiol to vinyl sulfide[c]
1-octyne	4.5 ± 0.3	4.4 ± 0.4	> 5
propargyl acetate	2.3 ± 0.2	2.1 ± 0.1	> 5
methyl propargyl ether	0.68 ± 0.04	0.68 ± 0.04	> 5
ethyl propiolate	0.077 ± 0.01		~0
methyl propargylamine	0.026 ± 0.005		~0
2-octyne	0.24 ± 0.03	0.23 ± 0.03	> 5
cyclooctyne	5.4 ± 0.4	6.6 ± 0.4	~0

[a] All reactions performed with 1% I184 at 10 mW/cm^2 intensity light filtered at 365 nm.

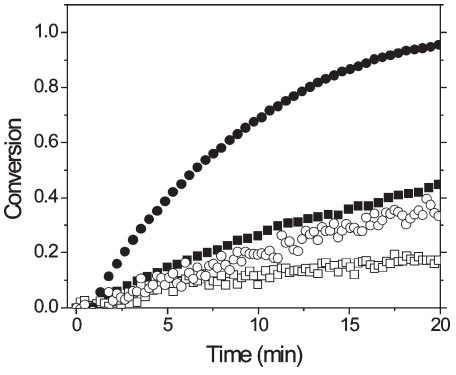

Figure 4. Conversion of thiols (open symbols) and alkynes (closed symbols) for reaction mixtures including 2 M octanethiol and 1 M alkyne: ethyl propiolate (circles) and methyl propargylamine (squares). Reactions were initiated with 10 mW/cm^2 light filtered at 365 nm. All samples were prepared with 1% photoinitiator I184.

Unlike with thiol−ene reactions, explaining the differences in relative reactivities among the various alkynes in terms of electron density is problematic. Thiyl radicals, like oxygen-centered radicals, have an electrophilic character. Thus, in thiol−ene reactions, addition to electron-rich vinyl groups is generally favored. For the thiol−yne photoaddition, such polar effects could explain the slow addition to ethyl propiolate as the electron-withdrawing carbonyl decreases the electron density of the π bonds as has been hypothesized previously.[13] Such reasoning, however, fails to explain why methyl propargylamine, with its electron-rich amine, reacts even more slowly than does the ethyl propiolate. It was considered that the basic secondary amine could

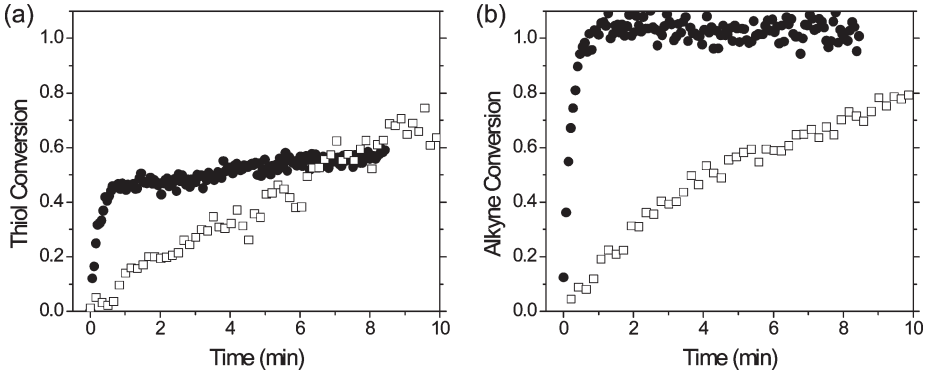

Figure 5. Functional group conversion, (a) thiols and (b) alkynes as a function of time for reaction of octanethiol with 2-octyne (□) and cyclooctyne (●). Reactant concentrations were 2 M octanethiol and 1 M alkyne. Reactions were initiated with 10 mW/cm^2 light filtered at 365 nm. All samples were prepared with 1% photoinitiator I184.

potentially deprotonate a fraction of the thiols present and thus decrease the reaction rate. This hypothesis was discounted by examining IR spectra of defined concentrations of thiols in the presence and absence of methyl propargylamine (thiols and methyl propargylamin at 2 M each). With a uniform pathlength, the thiol peak area, corresponding to the S−H stretch, was not diminished for those samples in the presence of the amine. Unfortunately, an adequate hypothesis of the factors determining the kinetic effects of polar substituents remains elusive.

Regardless of the cause for the relative reactivities of various alkynes toward octanethiol, conclusions can be made regarding the potential for application in polymer synthesis. The utility of the thiol−yne reaction is largely the bireactive character of the alkyne. Since methyl propargylamine and ethyl propiolate lack this feature and the reactions are relatively slow, the utility of these functional groups in monomer design is limited, at least under the experimental conditions examined herein. It is probable that the use of higher light intensities and more effective initiators could produce sufficient radicals to drive these less rapid reactions to forward. However, the respective trends described herein would likely persist.

Thiol Addition to 2-Octyne and Cyclooctyne. The thiol−yne addition also occurs between thiols and internal alkynes. Reactions involving internal alkynes differ from the other terminal alkynes explored herein in terms of both reaction rates and functionality of the alkyne groups. Thiols add to 2-octyne much more slowly than to 1-octyne. Unlike the other less reactive propargylamine and propiolate, however, the 2-octyne does permit the consecutive additions as demonstrated by the consumption of two thiols for every alkyne (Figure 5).

Conversely, while the addition of a single thiol to a cyclooctyne is relatively rapid, the subsequent addition does not measurably occur (Figure 5). It is noted that even following complete conversion of the cyclooctyne, the thiol consumption continues to increase, though only marginally and over extended times. This outcome may be due, in part, to thiyl radical combination. The vinyl sulfide peak remained static following complete consumption of the cyclooctyne, indicating constant concentration and no participation in additional reactions (Figure 6). The absence of any dithioether was confirmed with ^{1}H NMR spectroscopy. The differences in reactivity between 2-octyne and cyclooctyne are interesting and merit further investigation. Presumably, the slow reaction of thiols with 2-octyne and its corresponding vinyl sulfide is caused by steric interactions. A single thiol, adding to 1-octyne, adds exclusively to the unsubstituted terminal carbon. For the initial addition to the cyclooctyne, steric interactions are overcome by the enthalpic energy released by the π bond dissolution when the ring-strained cycloalkyne is converted to a vinyl sulfide. Because a cyclooctene is not under significant ring strain, such energetic advantages do not aid in the consecutive reaction. Nevertheless, it is interesting that no reaction is observed for the cyclooctene sulfide while it is observed for the vinyl sulfide product of the 2-octyne, thiol addition. The reason for this behavior, again, may be steric interactions. Following the addition of a thiol to the cyclooctyne, the cyclooctene sulfide is conformationally liberated, which may result in hindering of the approach of the potentially attacking thiyl radical by the bulky alkyl cycle.

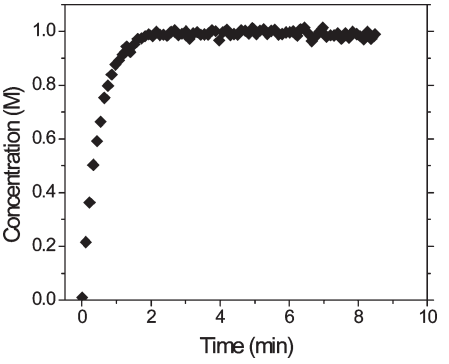

Figure 6. Concentration of cyclooctene sulfide product with respect to time during exposure of reaction mixture at 2 M octanethiol and 1 M cyclooctyne. Reaction initiated with 1% I184 at 10 mW/cm^2 365 nm light.

Reaction Orders with Respect to Thiol and Alkyne Concentrations. At low conversions, the polymerization rate in a thiol−yne polymerization is equivalent to the rate of thiol consumption, which scales to the concentrations of reactants according to

$$R_p = -\frac{d[SH]}{dt} \sim [C \equiv C]^{\alpha}[SH]^{\beta} \quad (1)$$

where α and β represent the reaction orders relative to alkyne and thiol concentrations. Using ethylene glycol diacetate as an inert diluent, concentrations of octanethiol and the corresponding alkynes were varied independently to observe the effect of varying the concentration of a single reactant on thiol consumption. Regressing a linear fit to the log values of both the initial reaction rate and the initial reactant concentrations provided the values presented in Table 2. It was

observed that the reaction was first order with respect to thiols for the reaction with 1-octyne. This result agrees with previous experiments on similar reactants. The same relationship holds for terminal alkynes including propargyl ether and propargyl acetate which may be the result of vinyl radical stabilization by the sulfide substituent which would decrease the rate of chain transfer to another thiol.[31] Such an explanation does not account, however, for the scaling of the reaction rate with respect to concentrations of thiols and cyclooctynes. In this latter case, the reaction rate is 0.4 with respect to the cyclooctyne and 0.6 with respect to thiol.

Determination of Relative Reaction Rates of Thiol−Yne and Thiol−Vinyl Sulfide Additions. At any time point, no observable accumulation of the intermediate vinyl sulfide occurs for stoichiometric reactions (2:1 thiol:alkyne) between 1-octyne and octanethiol, suggesting that the subsequent addition of a thiol to the vinyl sulfide intermediate is significantly faster than the initial addition of a thiol to the alkyne (Figure 3). This result confirms previous studies that quantitatively demonstrated the second addition to occur ~3 times more rapidly than the first.[11] Similarly, no accumulation of vinyl sulfide was observed during the consecutive additions of two thiols to propargyl acetate, methyl propargyl ether (Figure 3), or 2-octyne (Figure 5), demonstrating that the increased rate of the second addition is not unique to radical thiol−yne reactions with terminal, aliphatic alkynes.

For reactions in which the initial concentration of thiol is twice that of alkyne and proceeds according to the mechanism described in Figure 1, the rates of consumption of reactants can be described by the following equations:

$$\frac{d[SH]}{dt} = -k[C\equiv C]^{\alpha}[SH]^{\beta} - rk[C=C]^{\gamma}[SH]^{\delta} \quad (2)$$

$$\frac{d[C\equiv C]}{dt} = -k[C\equiv C]^{\alpha}[SH]^{\beta} \quad (3)$$

$$[C=C] = [SH] - 2[C\equiv C] \quad (4)$$

Table 2. Reaction Rate Orders for the Initial Addition of Thiols to Alkynes As Determined by Initial Rates Where $R_p = [C\equiv C]^{\alpha}[SH]^{\beta}$

alkyne	α (order in [C≡C])	β (order in [SH])
1-octyne	0	1
propargyl acetate	0	1
methyl propargyl ether	0	1
2-octyne	0	1
cyclooctyne	0.4	0.6

Here, k is the reaction rate constant for the addition of a thiol to an alkyne and r is the ratio of the reaction rate constant for the subsequent thiol−vinyl sulfide addition to the initial addition. Parameters α, β, γ, and δ are reaction rate orders for alkynes and thiols participating in the first addition and vinyl sulfides and thiols participating in the subsequent addition. Both the sum of α with β and that of γ with δ must equal one.

For cases in which the initial thiol−alkyne addition is thiol controlled and the coefficient r is sufficiently greater than one, the consumption rates of thiols and alkynes can be expressed as in eqs 5 and 6. Here, at all times, vinyl sulfide concentration is sufficiently low relative to thiols that the reaction order γ in eq 2 can be assumed to be one.

$$\frac{d[SH]}{dt} = -k[SH] - rk[C=C] \quad (5)$$

$$\frac{d[C\equiv C]}{dt} = -k[SH] \quad (6)$$

As demonstrated in Figure 8a,b, such a model fits the data obtained for reactions involving 1-octyne, propargyl acetate, methyl propargyl ether, and 2-octyne. In each of these cases, the ratio "r" was determined to be greater than 5 by fitting the model to the experimental data. No improvement of fit was observed between $r = 5$ and $r \gg 5$, establishing a lower limit for the ratio of reactivities and necessitating that for each of these ynes the vinyl sulfide consumption is at least 5 times faster than the yne consumption. Previous experiments in the polymerization of decadiyne and PETMP found the value for the ratio r to be slightly greater than three.[11] The higher values for r determined here may be explained by the fact that reaction products here do not form high molecular weight polymers or networks, perhaps increasing the reactivity of the vinyl sulfide species relative to reactions in which cross-linked polymers are generated.

While it may seem counterintuitive that the addition of a thiol to the more sterically hindered vinyl sulfide is faster than the addition of a thiol to a terminal alkyne, this reaction behavior is consistent with the trends observed for thiol−ene reactions in which increasing electron density of the alkene also increases the reaction rate.[5,6] The sulfide substituent serves to increase the electron density of the vinyl group. This characteristic may also be attributable to the higher barrier

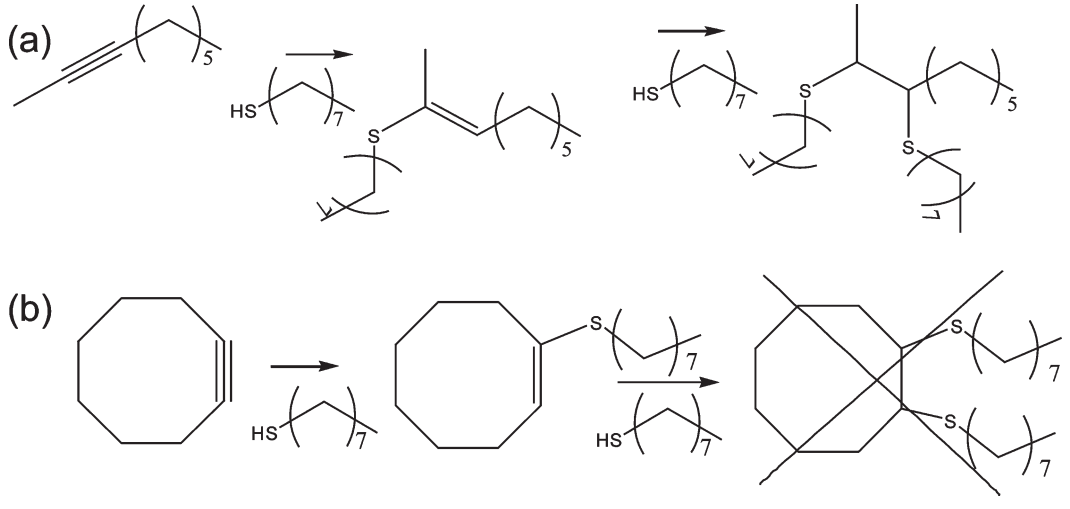

Figure 7. Diaddition of thiol to 2-octyne (a) with vinyl sulfide intermediate and failure of second addition to cyclooctene sulfide (b).

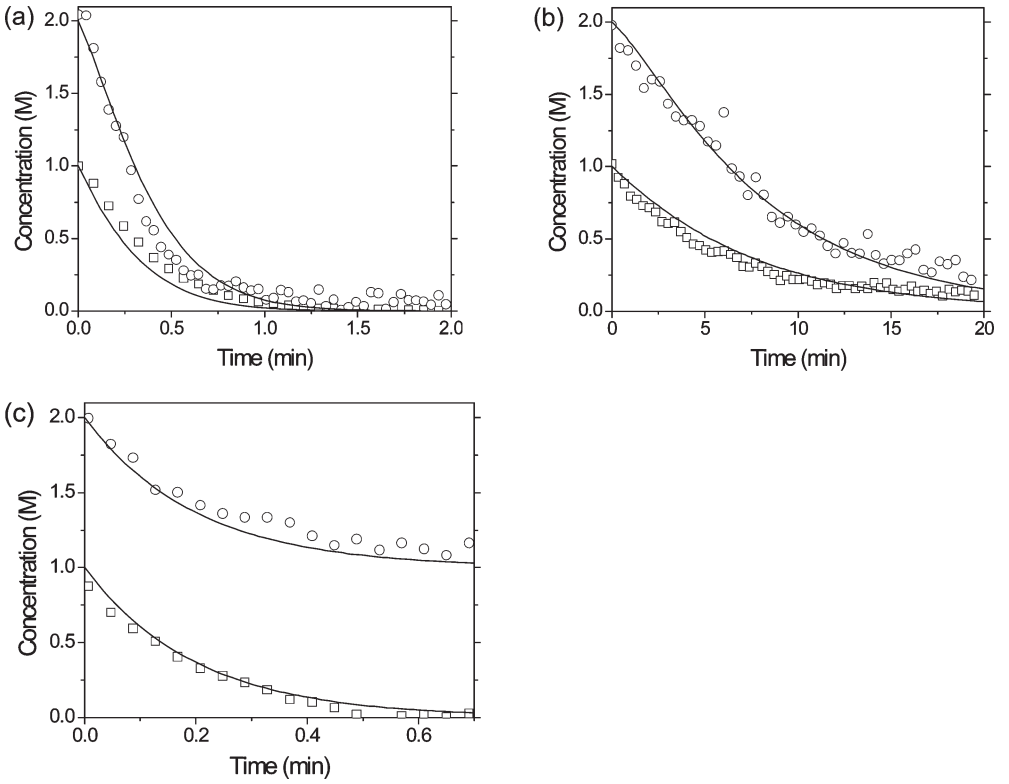

Figure 8. Concentrations of thiol (○) and alkyne (□) for reactions with 1-octyne (a), 2-octyne (b), and cyclooctyne (c). Solid lines represent the fit of eqs 2−4 with $r = 5$ for reactions with 1-octyne and 2-octyne and $r = 0$ for cyclooctyne.

Table 3. Initial Rates of Thiol Consumption with Octanethiol and Butyl 3-Mercaptopropionate under Similar Exposure Conditions (1 wt % I184, 10 mW/cm^2, 365 nm)

alkyne	initial rate with 1-octyne	initial rate with butyl 3-mercapto-propionate
1-octyne	4.5 ± 0.3	4.6 ± 0.3
propargyl acetate	2.3 ± 0.2	2.3 ± 0.1
methyl propargyl ether	0.68 ± 0.04	0.66 ± 0.05
methyl propargylamine	0.026 ± 0.005	0.029 ± 0.003

energy for isomerization of the vinyl radical relative to the alkyl radical.[32]

In contrast to the above situation in which the vinyl sulfide is more reactive, for cases in which the yne is much more reactive than the vinyl sulfide (r is much less than one), the final term of eq 2 becomes zero. Such a model fits the data obtained for reactions involving cyclooctyne (Figure 8c), methyl propargylamine, and ethyl propiolate, suggesting that r, for reactions involving these alkynes, is near zero. Each of these alkynes support the addition of only a single thiol (Figures 4 and 5).

Influence of Thiol on Reaction Rate. For these model studies, a simple aliphatic thiol was chosen for the sake of simplicity. However, it is noted that increased polymerization rates have been observed for thiol−ene photopolymerizations performed with mercaptopropionates relative to mercaptoacetates and simple aliphatic thiols.[5,6]

To examine whether rates could be improved by thiol selection, experiments were repeated for reactions of 1-octyne, propargyl acetate, methyl propargyl ether, and propargylamine with butyl 3-mercaptopropionate replacing the octanethiol. As shown in Table 3, no statistical difference in initial reaction rates was observed.

Spontaneous Reaction of Cyclooctyne with Octanethiol. It was also observed that cyclooctyne and octanethiol reacted spontaneously in the absence of light or a photoinitiator in an unpurged atmosphere (Figure 9). Similar instabilities have been observed in thiol−ene monomer mixtures, and while the precise mechanism of dark initiation is unknown, presumably, it is the result of reactive oxygen species, introduced by the diffusion of molecular oxygen into the reaction mixture. This result suggests that copperless click reactions performed in biological environments where thiols may be present are not likely to be completely orthogonal, but may experience at least some degree of nonspecific reaction.

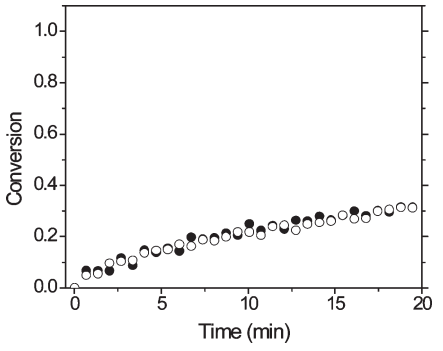

Figure 9. Spontaneous addition of thiols to cyclooctyne in an unpurged environment. Initial concentrations of both octanethiol and cyclooctyne were 2 M. No initiator was present. No light exposure was performed.

Conclusions

The relatively rapid reaction rates coupled with the bireactivity of aliphatic terminal alkynes and terminal propargyl esters make these moieties more advantageous generally for thiol−yne photopolymerizations than the other alkynes explored herein. The reactions of methyl propargyl ether with octanethiol suggest that

propargyl ethers share the difunctional characteristics of terminal aliphatic alkynes, but the utility of such alkyne monomers may be limited by the slow initial addition of a thiol to the alkyne. Additionally, the internal alkyne, 2-octyne, is radically reactive toward thiols, but the rate is substantially slower than that to terminal aliphatic alkynes, propargyl acetate, and propargyl ether. While the initial reaction between cyclooctyne and octanethiol is relatively fast, the failure of the consecutive addition suggests that cyclooctyne by itself is not suitable as a thiol−yne monomer. Should cyclooctyne monomers prove desirable, however, cyclooctynes with reactive handles, cyclooctynols, and cyclooctyne acids have been synthesized and would allow dicyclooctyne monomer synthesis.[24,33] Of potential interest, the cyclooctyne thiol reaction leaves a cyclooctene sulfide that may be polymerizable via ring-opening metathesis polymerizations or cationic reactions.[34−36] Furthermore, the spontaneous reaction of cyclooctyne with thiols in an unpurged environment suggests that in copper-less click reactions in media where thiols are present some degree of nonspecific reaction may occur.

Acknowledgment. This work was supported by NSF Grant CTS 0626023.

References and Notes

(1) Cramer, N. B.; Reddy, S. K.; O'Brien, A. K.; Bowman, C. N. *Macromolecules* **2003**, *36*, 7964–7969.
(2) Hoyle, C.; Lowe, A.; Bowman, C. *Chem. Soc. Rev.* **2010**, in press (DOI: 10.1039/B901979K).
(3) Hoyle, C.; Bowman, C. *Angew. Chem., Int. Ed.* **2010**, *49*, 1540–1573.
(4) Bowman, C. N.; Kloxin, C. J. *AIChE J.* **2008**, *54*, 2775–2795.
(5) Jacobine, A. F. In *Radiation Curing in Polymer Science and Technology*; Fouassier, J. P., Rabek, J. F., Eds.; Elsevier Applied Science: London, 1993; Vol. *III*, pp 219−268.
(6) Hoyle, C. E.; Lee, T. Y.; Roper, T. *J. Polym. Sci., Part A: Polym. Chem.* **2004**, *42*, 5301–5338.
(7) Finzi, C. *Gazz. Chim. Ital.* **1930**, *60*, 798–811.
(8) Bader, H. *J. Chem. Soc.* **1956**, 116–121.
(9) Bader, H.; Cross, L. C.; Heilbron, I.; Jones, E. R. H. *J. Chem. Soc.* **1949**, 619–623.
(10) Chan, J. W.; Zhou, H.; Hoyle, C. E.; Lowe, A. B. *Chem. Mater.* **2009**, *21*, 1579–1585.
(11) Fairbanks, B. D.; Scott, T. F.; Kloxin, C. J.; Anseth, K. S.; Bowman, C. N. *Macromolecules* **2009**, *42*, 211–217.
(12) Lowe, A. B.; Hoyle, C. E.; Bowman, C. N. *J. Mater. Chem.* **2010**, in press (DOI: 10.1039/jmb917102a).
(13) Melandri, D.; Montevecchi, P. C.; Navacchia, M. L. *Tetahedron* **1999**, *55*, 12227–12236.
(14) Waters, M. S.; Cowen, J. A.; McWilliams, J. C.; Maligres, P. E.; Askin, D. *Tetrahedron Lett.* **2000**, *41*, 141–144.
(15) Benati, L.; Montevecchi, P. C.; Spagnolo, P. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2103–2109.
(16) Chan, J. W.; Hoyle, C. E.; Lowe, A. B. *J. Am. Chem. Soc.* **2009**, *131*, 5751–+.
(17) Chen, G. J.; Kumar, J.; Gregory, A.; Stenzel, M. H. *Chem. Commun.* **2009**, 6291–6293.
(18) Hensarling, R. M.; Doughty, V. A.; Chan, J. W.; Patton, D. L. *J. Am. Chem. Soc.* **2009**, *131*, 14673–14675.
(19) Dusek, K.; Ilavsky, M.; Lunak, S. *J. Polym. Sci., Part C: Polym. Symp.* **1975**, *53*, 29–44.
(20) Odian, G. *Principles of Polymerization*; Wiley: New York, 1991.
(21) Yu, B.; Chan, J. W.; Hoyle, C. E.; Lowe, A. B. *J. Polym. Sci., Part A: Polym. Chem.* **2009**, *47*, 3544–3557.
(22) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596–+.
(23) Zhang, L.; Chen, X. G.; Xue, P.; Sun, H. H. Y.; Williams, I. D.; Sharpless, K. B.; Fokin, V. V.; Jia, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 15998–15999.
(24) Agard, N. J.; Prescher, J. A.; Bertozzi, C. R. *J. Am. Chem. Soc.* **2004**, *126*, 15046–15047.
(25) DeForest, C. A.; Polizzotti, B. D.; Anseth, K. S. *Nat. Mater.* **2009**, *8*, 659–664.
(26) Laughlin, S. T.; Baskin, J. M.; Amacher, S. L.; Bertozzi, C. R. *Science* **2008**, *320*, 664–667.
(27) Johnson, J. A.; Baskin, J. M.; Bertozzi, C. R.; Koberstein, J. T.; Turro, N. J. *Chem. Commun.* **2008**, 3064–3066.
(28) Poloukhtine, A. A.; Mbua, N. E.; Wolfert, M. A.; Boons, G.; Popik, V. V. *J. Am. Chem. Soc.* **2009**, *131*, 15769–15776.
(29) Sletten, E. M.; Bertozzi, C. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 6974–6998.
(30) Brandsma, L.; Verkruijsse, H. D. *Synthesis* **1978**, 290–290.
(31) Viehe, H. G.; Janousek, Z.; Merenyi, R. *Substituent Effects in Radical Chemistry: Proceedings of the NATO Advanced Research Workshop on Substituent Effects in Radical Chemistry*; Reidel: Louvain-la-Neuve, Belgium, 1986.
(32) Moad, G.; Solomon, D. H. *The Chemistry of Radical Polymerization*; Elsevier B.V.: Amsterdam, 2006.
(33) Heber, D.; Rosner, P.; Tochtermann, W. *Eur. J. Org. Chem.* **2005**, 4231–4247.
(34) Bandari, R.; Prager-Duschke, A.; Kuhnel, C.; Decker, U.; Schlemmer, B.; Buchmeiser, M. R. *Macromolecules* **2006**, *39*, 5222–5229.
(35) Winkler, B.; Rehab, A.; Ungerank, M.; Stelzer, F. *Macromol. Chem. Phys.* **1997**, *198*, 1417–1425.
(36) Inoue, H.; Otsu, T. *J. Polym. Sci., Part A: Polym. Chem.* **1976**, *14*, 845–861.