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Investigation and Demonstration of Catalyst/Initiator-Driven Selectivity in Thiol-Michael Reactions

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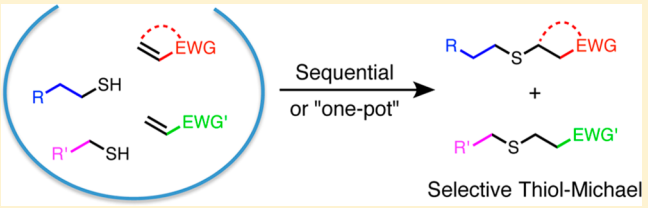
Supporting Information

ABSTRACT: Thiol-Michael "click" reactions are essential synthetic tools in the preparation of various materials including polymers, dendrimers, and other macromolecules. Despite increasing efforts to apply thiol-Michael chemistry in a controlled fashion, the selectivity of base- or nucleophile-promoted thiol-Michael reactions in complex mixtures of multiple thiols and/or acceptors remains largely unknown. Herein, we report a thorough fundamental study of the selectivity of thiol-Michael reactions through a series of 270 ternary reactions using ^{1}H NMR spectroscopy to quantify product selectivity. The varying influences of different catalysts/initiators are explored using ternary reactions between two Michael acceptors and a single thiol or between a single Michael acceptor and two thiols using three different catalysts/initiators (triethylamine, DBU, and dimethylphenylphosphine) in chloroform. The results from the ternary reactions provide a platform from which sequential quaternary, one-pot quaternary, and sequential senary thiol-Michael reactions were designed and their selectivities quantified. These results provide insights into the design of selective thiol-Michael reactions that can be used for the synthesis and functionalization of multicomponent polymers and further informs how catalyst/initiator choice influences the reactivity between a given thiol and Michael acceptor.



INTRODUCTION

Although known for over a century, the thiol-Michael addition reaction,[1] generally classified as a "click" reaction[2] between a thiol and an α,β-unsaturated carbonyl-containing compound, has recently generated high levels of interest and implementation across many areas of materials chemistry.[3] Over the past two decades, this reliable synthetic tool has found multiple applications in many areas of macromolecular materials chemistry including the synthesis of linear polymers,[4] dendrimers and hyperbranched polymers,[5] copolymers[6] and cross-linked networks,[7] and hydrogels.[8] Thiol-Michael reactions have also proven very useful for the postsynthetic modification of polymers through side chain[9] and end group functionalization[10] with particular utility in the functionalization of reversible addition−fragmentation chain transfer (RAFT) polymers.[10b−e] The benefits of thiol-Michael reactions in macromolecular synthesis and materials science is not surprising given their high to quantitative yields, range of available catalysts/initiators, high selectivity and functional group tolerance, and ability to progress in a wide range of solvents as well as under solvent-free conditions. These attributes, coupled with the variety of activated alkene and thiol functionalities available, result in a highly efficient, modular click reaction.

The most common means of carrying out thiol-Michael reactions typically fall into two categories that differ in how they are promoted, i.e., those that are catalyzed by base and those initiated by a nucleophile.[3d−f,11] Bowman and co-workers have recently extended these methodologies by developing photoinitiated reactivity by masked or caged photobases, thus allowing both spacial and temporal control over thiol-Michael reactivity.[12] The fact that a range of conditions can be used to promote thiol-Michael additions between a wide variety of thiol and alkene functionalities underlies the versatility and power of this click reaction as a tool for the design of advanced materials while also allowing fine-tuning of their structures and physical properties. Ueda and co-workers, for example, have made use of thiol additions to divinylsulfones to prepare a range of high refractive index materials.[4a,b,d] Thiol−acrylate reactions have also been used to prepare a variety of biodegradable polymers[4c,7a,c] and dendrimers[5d] with potential use as drug carriers and in the controlled release of therapeutics. Hubbell and co-workers have taken advantage of cysteine-vinyl sulfone additions to link protein polymers with poly(ethylene glycol) to generate hydrogels with applications as tissue support and repair scaffolds.[8b,c] Bowman and co-workers have demonstrated the use of two different thiol-Michael reactions to prepare composite polymer networks that have two glass transition temperatures, resulting in polymer networks possessing shape memory properties.[7d] Bowman has also shown that photoinitiated thiol-Michael reactions can be applied to lithographic photopatterning.[12c] These examples highlight only some of the different materials that have been synthesized utilizing thiol-Michael addition reactions over the past dozen years, and the

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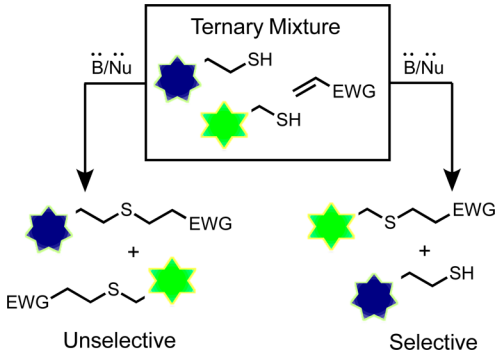
field of thiol-Michael "click" reactions only appears to be expanding[3e] its reach and impact.

As a means of further expanding the utility of thiol-Michael reactions, several researchers have recently begun to explore the selectivity of thiol-Michael reactions within more complex mixtures of multiple thiol and/or Michael acceptor components.[5a,e,7d,11d,e,12c,13] The facile reactivity of thiols with a range of alkene substrates, widely regarded as an advantage within the click paradigm, can often be a disadvantage in this regard. Although the selective addition of a single thiol to a single Michael acceptor is typically very high, selectivity within ternary mixtures of, for example, two thiols with one Michael acceptor (Scheme 1) or two Michael acceptors with one thiol is far from

Scheme 1. General Representation of Unselective versus Selective Thiol-Michael Reactions Originating from a Ternary Mixture of Two Thiols and One Michael Acceptor[a]



[a]B = base, Nu = nucleophile, EWG = electron withdrawing group; similar unselective or selective reactivity may be observed within ternary mixtures of two Michael acceptors and one thiol (not shown).

guaranteed. In fact, the interplay between the choice of thiol, alkene, catalyst/initiator, and solvent may lead to selectivity (or lack thereof) that would not be predicted otherwise by simply evaluating the kinetics of individual thiol-Michael reactions in isolation. Hoyle, Lowe, and Bowman have noted[3d,14] that having the ability to control the reactivity of thiol and Michael acceptor components, and ultimately introduce selectivity, within ternary and more complex mixtures "is both the challenge, and the opportunity, for thiol-click chemistry as it applies to the chemical, biological, physical and engineering fields". Discovering how to target the addition of a specific thiol to a specific Michael acceptor reliably within ternary or quaternary mixtures of thiol-Michael components can both streamline syntheses by eliminating protection/deprotection steps and open new means of controlling the structures and physical properties of multifunctional macromolecules.

Previous investigations of the selectivity of alkenes for different thiols are summarized in Table 1a, whereas the selectivities of thiols for different alkenes are summarized in Table 1b. As noted earlier, Bowman and co-workers have pioneered many of the early studies of selectivity within ternary thiol-Michael reactions under both base-catalyzed and nucleophile-initiated conditions.[5e,7d,11d,12c] For example, they have shown that hexanethiol reacts preferentially with ethyl vinyl sulfone over hexyl acrylate in a ternary mixture when initiated by methyldiphenylphosphine under solvent-free conditions.[11d] The high selectivity for the vinyl sulfone over the acrylate was used to control the gelation behavior of a cross-linked polymer network comprised of a tetrafunctional thiol, bifunctional alkene, and a monofunctional acrylate. In a subsequent work, Bowman and co-workers expanded their study to include the alkenes *N*-propylmaleimide, phenyl vinyl sulfonate, methyl acrylate, and methyl methacrylate as well as the thiols benzenethiol, methyl thioglycolate, and methyl 3-mercaptopropionate.[5e] Ternary mixtures of two thiols with methyl acrylate revealed that the addition of benzenethiol to acrylate is moderately favored over the addition of thioglycolate (66:34, Table 1, entry 1), whereas both benzenethiol and thioglycolate show greater than 90% selectivity over mercaptopropionate and hexanethiol (entries 2−5). It has also been shown that simply changing an initiator or catalyst, while leaving thiol and alkene components the same, can result in a change in selectivity (entries 7 and 8).[11e] All of these factors become important for the design of multistage or one-pot reactions involving multiple thiol and alkene components, where it is desirable for selectivities to be very high, ideally greater than 98%.

For reactions involving two Michael acceptors, the selective addition of methyl-3-mercaptopropionate to highly activated Michael acceptors *N*-propylmaleimide or phenyl vinyl sulfonate was observed within ternary mixtures with either methyl acrylate or methy methacrylate (Table 2, entries 2−5). High selectivity is even observed for the addition of methyl-3-mercaptopropionate to methyl acrylate in the presence of methyl methacrylate (entry 6). Taken together, the selectivities demonstrated in Tables 1 and 2 were used to design A^*A_2 and B^*B_2 monomers for the efficient, sequential, and selective syntheses of dendrimers.[5e] The A^*A_2 monomer contained a highly reactive vinyl sulfonate focal point (A) and two less reactive methacrylate branches (A_2), whereas the B^*B_2 monomer contained a more reactive thiolglycolate focal point (B) and two less reactive alkanethiol branches (B_2). The A^*A_2 and B^*B_2 monomers were used to grow a fifth generation dendrimer rapidly and efficiently, requiring less than 12 h of time. Bowman's research on controlling the gelation of cross-linked polymer networks[7d] and streamlining dendrimer growth[5e] are powerful demonstrations of the utility of selective thiol-Michael addition reactions. That being said, it can be argued that widespread implementation of selective thiol-Michael addition is currently limited by the lack of a thorough study detailing the selectivity within complex mixtures of common thiols and Michael acceptors as promoted by a variety of initiators/catalysts.

Herein, we report the differences in selectivity for a series of 270 ternary reactions involving combinations of six different alkenes (*N*-methyl maleimide, ethyl vinyl sulfone, *n*-butyl isocyanate, methyl acrylate, methyl methacrylate, and ethyl crotonate) and five different thiols (methyl thioglycolate, methyl-3-mercaptopropionate, benzenethiol, *β*-mercaptoethanol, and hexanethiol) as promoted by three different initiators (triethylamine, 1,8-diazabicyclo(5.4.0)undec-7-ene, and dimethylphenylphosphine) (Figure 1). Insights from the results of ternary reactions were then used to design and demonstrate selectivity within sequential quaternary and senary thiol-Michael addition reactions as well as a representative one-pot quaternary reaction. Our results highlight exceptional control of the thiol-Michael addition reaction that may be applied to the design of multifunctional materials. The results also highlight the attention that should be given to subtle variations in reaction conditions and/or components when designing selective thiol-Michael reactions, as what may seem like a trivial change can lead to very different results.

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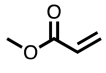
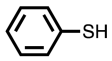
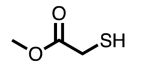
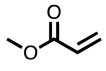
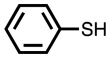
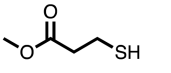
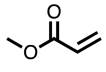
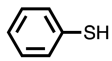
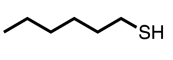
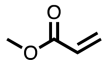
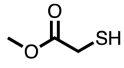
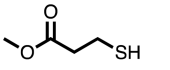
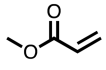
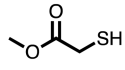
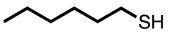
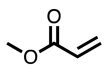
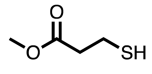
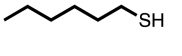
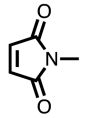
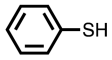
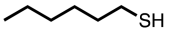
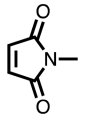
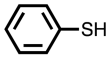
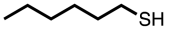
Table 1. Summary of Previous Investigations[5e,11d,e] of Selectivity within Ternary Mixtures of One Michael Acceptor and Two Thiol Components[a]

Entry	Alkene	Thiol A	Thiol B	Cat/Init	A (%)	B (%)	Selectivity
1				TEA	66	34	1.9
2				TEA	97.5	2.5	40
3				TEA	99.5	0.5	200
4				TEA	92.5	7.5	12
5				TEA	99.5	0.5	200
6				TEA	90.8	9.2	10
7				TEA	94	6	16
8				DBU	77	23	3

[a]TEA = triethylamine, DBU = 1,8-diazabicyclo(5.4.0)undec-7-ene.

RESULTS AND DISCUSSION

Selectivity of Ternary Thiol-Michael Reactions. Six different alkene and five different thiol functionalities that are commonly used in thiol-Michael or thiol-isocyanate reactions were chosen to probe the selectivity of the thiol-Michael addition reactions (Figure 1). It should be noted that isocyanates, such as compound **3**, are not Michael acceptors. However, their base or nucleophile-promoted reactivity with thiols to generate thiourethanes follows an anionic mechanism similar to that of thiol-Michael reactions. For simplicity, thiol-isocyanate reactions will be classified alongside thiol-Michael reactions throughout this manuscript. For fully exploring the selectivity of a given thiol for a pair of Michael acceptors, as well as a given Michael acceptor for a pair of thiols, all ternary combinations of thiols and Michael acceptors were investigated. Equimolar combinations of Michael acceptors (**1**–**6**) and thiols (**7**–**11**) in $CDCl_3$ were reacted using either TEA (0.1 equiv) or DBU (0.1 equiv) as a catalyst or DMPP (0.01 equiv) as an initiator. For all Michael acceptors, the reactions were complete within 1 h as determined by the disappearance of vinylic signals by ^{1}H NMR spectroscopy. Thiol-isocyanate reactions involving *n*-butyl isocyanate (**3**) were also complete within 1 h, and completeness was evaluated by the appearance of the amide hydrogen signal and the upfield shift of methylene proton signals adjacent to the isocyanate group. Selectivities of the ternary combinations of thiols and Michael acceptors were assessed by relative integrations of signals diagnostic to each potential thiol-Michael product. Results of each ternary reaction series were then summarized in a selectivity table. Two representative examples of such tables are shown in Figure 2. The remaining selectivity tables are provided in Figures S1–S8. The selectivity table shown in Figure 2a represents ternary mixtures of *N*-methyl maleimide (**1**) and two different thiols (**7**–**11**) as catalyzed by TEA. The table in Figure 2b summarizes selectivity within the same set of ternary mixtures involving maleimide **1**; however, DBU is used to promote the reaction rather than TEA. Table entries represent the ratio of thiol A product formed versus thiol B product formed, expressed as percentages. For aiding visualization, the percentages are color-coded as shown in the figure inset.

Comparing the results summarized in Figures 2a and 2b reveals how significant the choice of catalyst or initiator can be in the design of selective thiol-Michael reactions. When catalyzed by TEA, two sets of ternary reactions involving *N*-methyl maleimide as the Michael acceptor exhibit selectivity greater than 99%: thioglycolate (**7**) and benzenethiol (**9**) each add preferentially to maleimide (**1**) in the presence of hexanethiol (**11**). In the presence of DBU, however, no ternary reactions show greater than a 60:40 split between thiol-Michael products, not even those that were selective when TEA was used as the catalyst. Selectivity generally improves when the same ternary reactions are initiated by DMPP (Figure S1). For example, the selective addition of 3-mercaptopropionate (**8**) in the presence of hexanethiol (**11**) increases from 72% with TEA to 93% with DMPP. Selectivity tables for all combinations of

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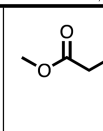
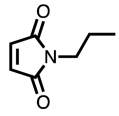
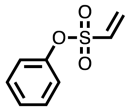
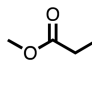
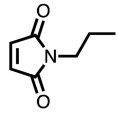
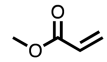
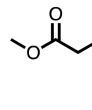
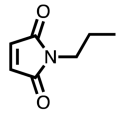
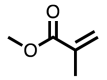
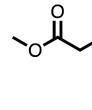
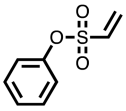
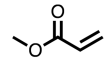
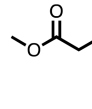
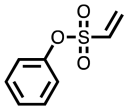
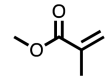
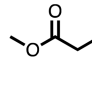
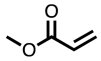
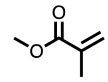
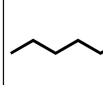
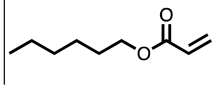
Table 2. Summary of Previous Investigations[5e,12c] of Selectivity within Ternary Mixtures Composed of One Thiol and Two Different Michael Acceptors[a]

Entry	Thiol	Alkene A	Alkene B	Cat/Init	A (%)	B (%)	Selectivity
1				TEA	71.5	28.5	2.5
2				TEA	92.5	7.5	12
3				TEA	100	0	>200
4				TEA	98	2	50
5				TEA	100	0	>200
6				TEA	99.5	0.5	20
7				MDPP	90	10	9

[a]MDPP = methyldiphenylphosphine.

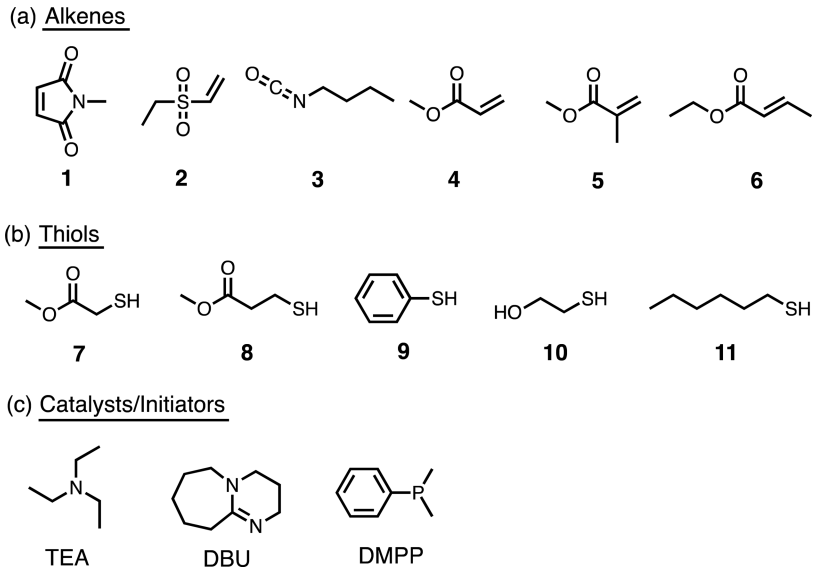


Figure 1. Chemical structures of (a) alkenes **1**–**6**, (b) thiols **7**–**11**, and (c) catalysts/initiators used in the current study.

ternary reactions reveal the underlying reactivity details necessary to make informed choices when designing more complex yet still selective multicomponent thiol-Michael reactions.

Collectively, selectivity tables for ternary thiol-Michael reactions enable some general conclusions to be made. Ternary reactions involving two Michael acceptors and one thiol reveal that *N*-methylmaleimide (**1**), ethyl vinyl sulfone (**2**), *n*-butyl isocyanate (**3**), and to a lesser but still useful extent methyl acrylate (**4**) all exhibit superior selectivities for all thiols as compared to those of methyl methacrylate (**5**) and ethyl crotonate (**6**). This is true independent of the choice of catalyst/initiator. In fact, little to no product formation was observed for thiol-Michael reactions involving methyl meth-

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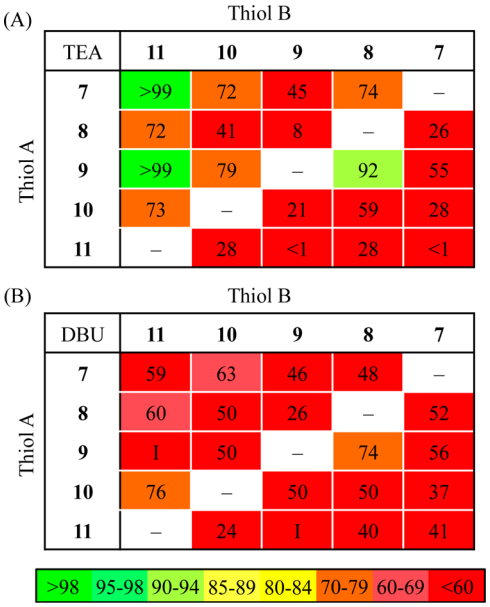

Figure 2. Selectivity charts highlighting the effect of catalyst/initiator on the selectivity of maleimide (**1**) for thiols (**7**–**11**). (a) Selectivities for the TEA-catalyzed reaction between **1** and pairs of thiols **7**–**11**. (b) Selectivities for the DBU-catalyzed reaction between 1 and pairs of thiols **7**–**11**. "I" indicates "inconclusive" as a mixture of products was obtained but selectivity could not be quantified due to significant overlap of signals in the ^{1}H NMR spectrum.

acrylate or ethyl crotonate in chloroform regardless of which thiol or catalyst/initiator was used. In the cases of ternary reactions involving two thiols and one Michael acceptor, the most reactive, and therefore selective, thiols were found to be thioglycolate (**7**), benzenethiol (**9**), and 3-mercaptopropriolate (**8**) in roughly that order, whereas hexanethiol (**11**) was the least reactive in nearly all cases.

It is important to reiterate that all ternary results discussed above refer to reactions carried out in chloroform. The selectivity tables shown in Figure 2 and the Supporting Information can be expected to change, often dramatically, if a different solvent is used. For example, thiol-Michael reactions that are not productive in chloroform, such as those involving methyl methacrylate and ethyl crotonate, can be promoted quite easily in a more polar solvent such as DMSO or DMF.[11b,15] Combined experimental and theoretical investigations of thiol-Michael reactions have shown that rates of thiol-Michael addition reactions are generally accelerated when carried out in more polar solvents.[11e,f] This is especially true when the reactions are carried out under base-catalysis as higher dielectric solvents are more capable of shifting acid–base equilibria toward the production of reactive thiolate anions. This increase in reaction rate in polar solvents can, however, come at the cost of decreased selectivity as differences in thiol pK_as are less pronounced. Chloroform was picked as the solvent of choice for examining and promoting selective thiol-Michael reactivity in ternary reactions because its low dielectric enables greater, and sometimes unique, selectivity. We should note that, although all of the results presented herein are for the thiol-Michael addition reaction in chloroform, the selectivity of the thiol-Michael addition was also examined in tetrahydrofuan. In general, and as expected, the selectivity decreased in

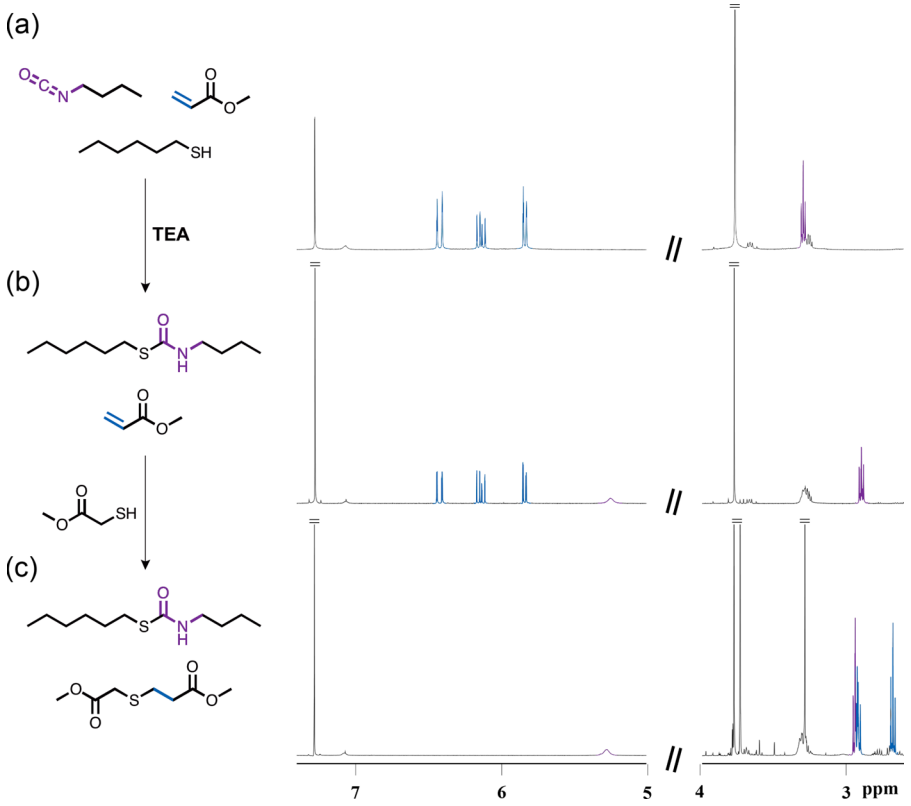

Figure 3. ^{1}H NMR spectra showing (a) the ternary mixture of isocyanate (**3**), methyl acrylate (**4**), and hexanethiol (**11**) prior to the addition of any catalyst, (b) selective addition of **11** to **3** upon addition of TEA, and (c) subsequent addition of thiolglycolate (**7**) to methyl acrylate catalyzed by residual TEA. Trace impurities in *n*-butyl isocyanate can be observed at 7.07, 3.68, and 3.28 ppm.

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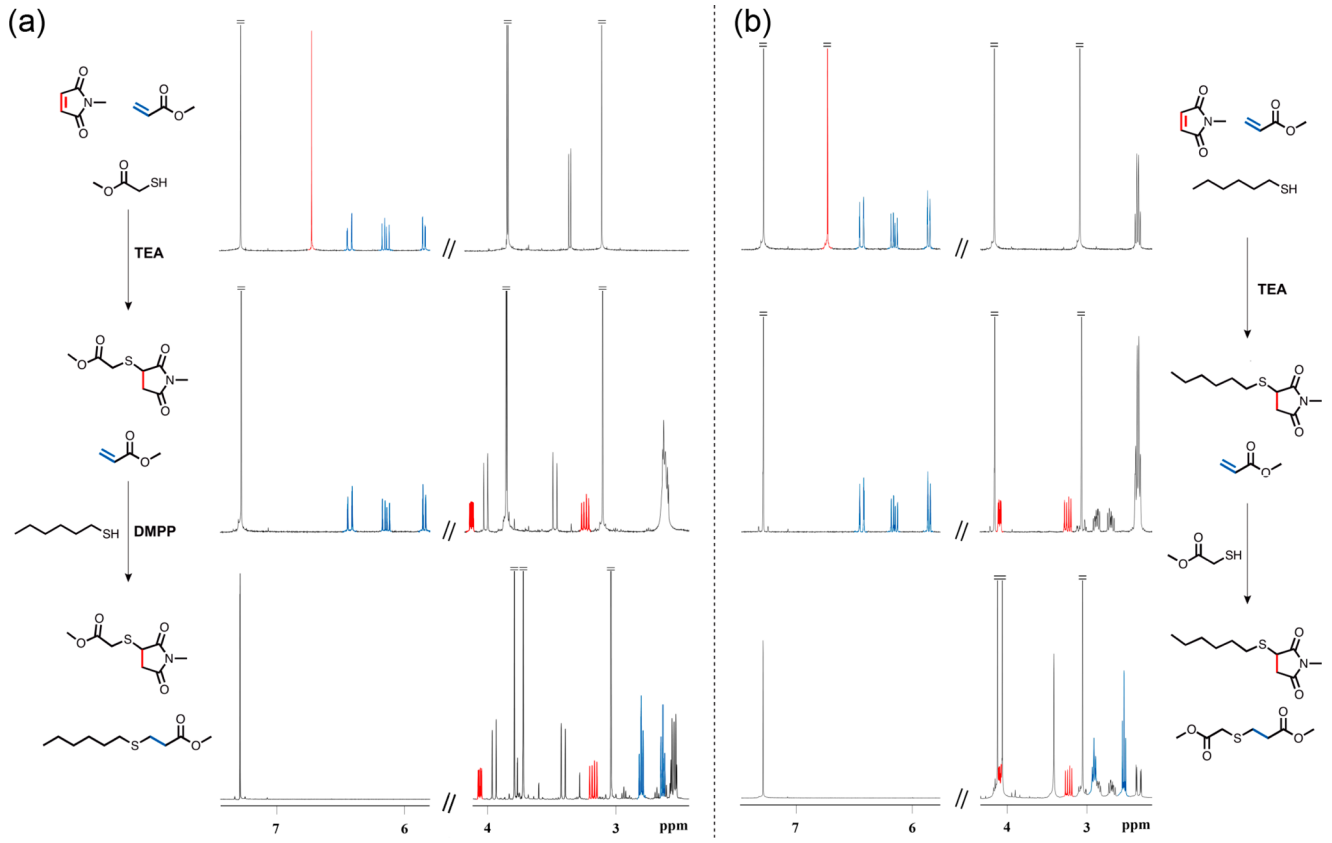

Figure 4. ^{1}H NMR spectra showing the different selectivities for the sequential quaternary thiol-Michael reactions between maleimide (**1**), methyl acrylate (**4**), thioglycolate (**7**), and hexanethiol (**11**) catalyzed/initiated by (a) TEA/DMPP or (b) TEA.

tetrahydrofuran likely due to the higher dielectric constant enabling alternative reaction pathways that are less accessible in chloroform.

Sequential Thiol-Michael Reactions: Quaternary Systems. The evaluation of selectivity within ternary mixtures enables their application to more complex reactions. For example, any selective ternary reaction, i.e., those with greater than 98% formation of a single thiol-Michael product, will give one thiol-Michael product along with either an unreacted Michael acceptor or unreacted thiol. These residual alkenes and thiols provide the ability to carry out sequential quaternary thiol-Michael reactions. An example is shown in Figure 3, wherein the addition of TEA to a ternary mixture of isocyanate (**3**), acrylate (**4**), and thiol (**11**) afforded the **3**-**11** thiol-isocyanate adduct exclusively as indicated by ^{1}H NMR spectroscopy. Figure 3a shows a partial spectrum of the initial mixture of **3**, **4**, and **11** in the absence of any catalyst or initiator. The addition of TEA (Figure 3b) catalyzes the addition of hexanethiol (**11**) to isocyanate (**3**) to give the thiol-isocyanate product as indicated by the presence of the amide hydrogen at 5.27 ppm and the upfield shift of the methylene hydrogens from 3.32 to 2.92 ppm. Acrylate signals are unchanged in Figure 3b, and no thiol−acrylate is observed. After the formation of the thiol-isocyanate adduct, the addition of a second thiol, in this example thioglycolate (**7**), results in the formation of the **4**-**7** thiol−acrylate adduct (Figure 3c). This second thiol-Michael addition is catalyzed by residual TEA in the reaction mixture and is confirmed by the disappearance of the vinylic protons at 6.46, 6.18, and 5.87 ppm concomitant with the appearance of product peaks at 2.92 and 2.68 ppm.

It is also possible to take advantage of variations in reactivity to change the order in which, for example, two different thiols are added to the same set of Michael acceptors. To exhibit such control, however, requires careful consideration of the specific combinations of Michael acceptor, thiol, and catalyst/initiator. An example is shown in Figure 4a and b. In Figure 4a, *N*-methyl maleimide (**1**), methyl acrylate (**4**), and thioglycolate (**7**) are combined in a ternary mixture. Addition of TEA results in the exclusive addition of thiol **7** to maleimide **1**, leaving only unreacted acrylate **4** and residual TEA. Subsequent addition of hexanethiol (**11**) does not, however, result in its addition to acrylate (**4**). This lack of reactivity is consistent with previous observations of Haddleton and Lowe.[11a,b] More specifically, TEA is not an efficient catalyst for promoting thiol-Michael reactions between acrylates and weakly acidic thiols in nonpolar solvents. This highlights a key difference between the reaction sequence shown in Figure 3 and the sequence shown in Figure 4a. In Figure 3, TEA is sufficiently basic to catalyze the addition of relatively acidic thioglycolate **7** to acrylate **4**. TEA is not sufficient, however, to catalyze thiol-Michael reactions between acrylate **4** and less acidic alkylthiols such as **11** (Figure 4a). The nucleophilic initiator DMPP is known to afford quantitative conversion of acrylates with various thiols in less than an hour.[11,15] Therefore, DMPP was chosen to promote the second thiol-Michael reaction between hexanethiol **11** and acrylate **4**, cleanly and quantitatively completing the two-step quaternary sequence.

The same set of four components is used in Figure 4b to carry out an alternative two-step quaternary thiol-Michael reaction sequence using the same four components; however, the order of thiol addition is reversed. Hexanethiol (**11**) reacts

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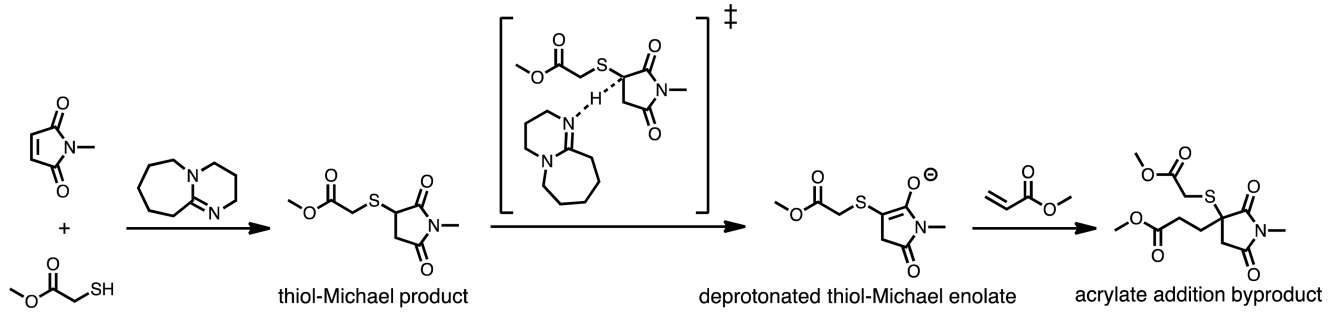
Scheme 2. Proposed Pathway for the Formation of Thiol-Maleimide-Acrylate Byproduct Formation Observed During DBU-Catalyzed Thiol-Michael Reactions within Mixtures Containing Maleimide as Well as an Additional Michael Acceptor, in this Case Methyl Acrylate



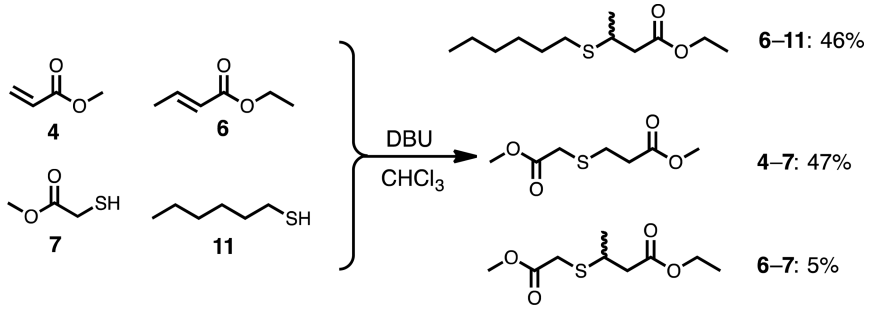


Figure 5. Addition of DBU to a mixture of methyl acrylate (**4**), ethyl crotonate (**6**), thioglycolate (**7**), and hexanethiol (**11**) results in the predominant formation of the **4**-**7** and **6**-**11** thiol-Michael products in 47 and 46% isolated yields, respectively, from the one-pot quaternary reaction. The formation of the undesired **6**-**7** thiol-Michael product is also isolated in 5% isolated yield.[17]

quantitatively with maleimide **1** in the presence of TEA, again leaving unreacted acrylate **4** in the ternary mixture. Addition of thioglycolate (**7**) results in its quantitative addition to **4** as catalyzed by residual TEA. These results serve to again highlight how differences in the reactivity of thiol and Michael acceptor components are taken into consideration when selecting an appropriate catalyst or initiator. TEA is not capable of promoting the addition of a less reactive thiol like **11** to a less reactive Michael acceptor such as **4**. However, TEA is capable of promoting thiol-Michael reactions between a less reactive alkyl thiol (**11**) and a sufficiently reactive Michael acceptor (**1**) as shown in Figure 4b or between a sufficiently reactive thiol (**7**) and a less reactive Michael acceptor (**4**) as shown in Figure 4a.

It may seem that a compound capable of behaving as a strong base and a strong nucleophile, such as DBU, would be sufficient to carry out either of the reaction sequences shown in Figure 4. This turns out not to be the case. For example, DBU is able to catalyze the addition of thioglycolate (**7**) to maleimide (**1**) rapidly and cleanly when no other Michael acceptors are present. If, however, DBU is used to promote the first step of the sequence shown in Figure 4a, then a mixture of products is obtained. Analysis of this mixture by ^{1}H NMR spectroscopy reveals full consumption of maleimide **1** and partial consumption of acrylate **4**. Interestingly, although maleimide is fully consumed, its thiol-Michael product with thioglycolate (**7**) is not cleanly observed as noted by the disappearance of α and β methine and methylene protons of thiol-maleimide product (see Figure S9). We hypothesize that DBU does catalyze the rapid addition of thiol **7** to maleimide **1**, as is well-known, but DBU is also sufficiently basic to deprotonate the resulting thiol-maleimide adduct as shown in Scheme 2. McCormick has recently shown[16] that TEA is capable of deprotonating thiol-maleimide adducts, which can lead to poly(maleimide) side products during the "one-pot" synthesis of maleimide-functionalized RAFT polymers. Given that DBU is a stronger base than TEA, it can be expected that DBU is also able to deprotonate the thioglycolate-maleimide adduct, and the resulting enolate can react with acrylate **4** present in the mixture. Such side reactions are not commonly observed in simple binary thiol-Michael reactions catalyzed by DBU because no other electrophiles, e.g., methyl acrylate, are present once the initial thiol-Michael reaction is complete. These results again highlight the importance of selecting an appropriate combination of thiols, Michael acceptors, and catalyst/initiator when targeting selective ternary or quaternary thiol-Michael reactions.

One-Pot Quaternary Thiol-Michael Reactions. The evaluation of selectivity within ternary reactions also enables their application to one-pot quaternary reactions, wherein all four components (two thiols and two Michael acceptors) are present at the start of the reaction and, ideally, only two products are formed. An example is shown in Figure 5 wherein the addition of DBU to a quaternary mixture of methyl acrylate (**4**), ethyl crotonate (**6**), thioglycolate (**7**), and hexanethiol (**11**) afforded the **4**-**7** acrylate-thioglycolate adduct and the **6**-**11** crotonate-hexanethiol adduct in a nearly 50:50 ratio. Overlap of several spectroscopic signals in the ^{1}H NMR sprectrum (Figure S10) of the products prevented the direct spectroscopic assessment of selectivity by ^{1}H NMR as in the sequential quaternary reactions. For evaluating and quantifying the relative amounts of the four potential thiol-Michael products, the reaction mixture was purified by silica gel chromatophraphy, and all species that eluted from the column were collected and analyzed. The **4**-**7** and **6**-**11** adducts were found to be the major products, accounting for 47 and 46% of

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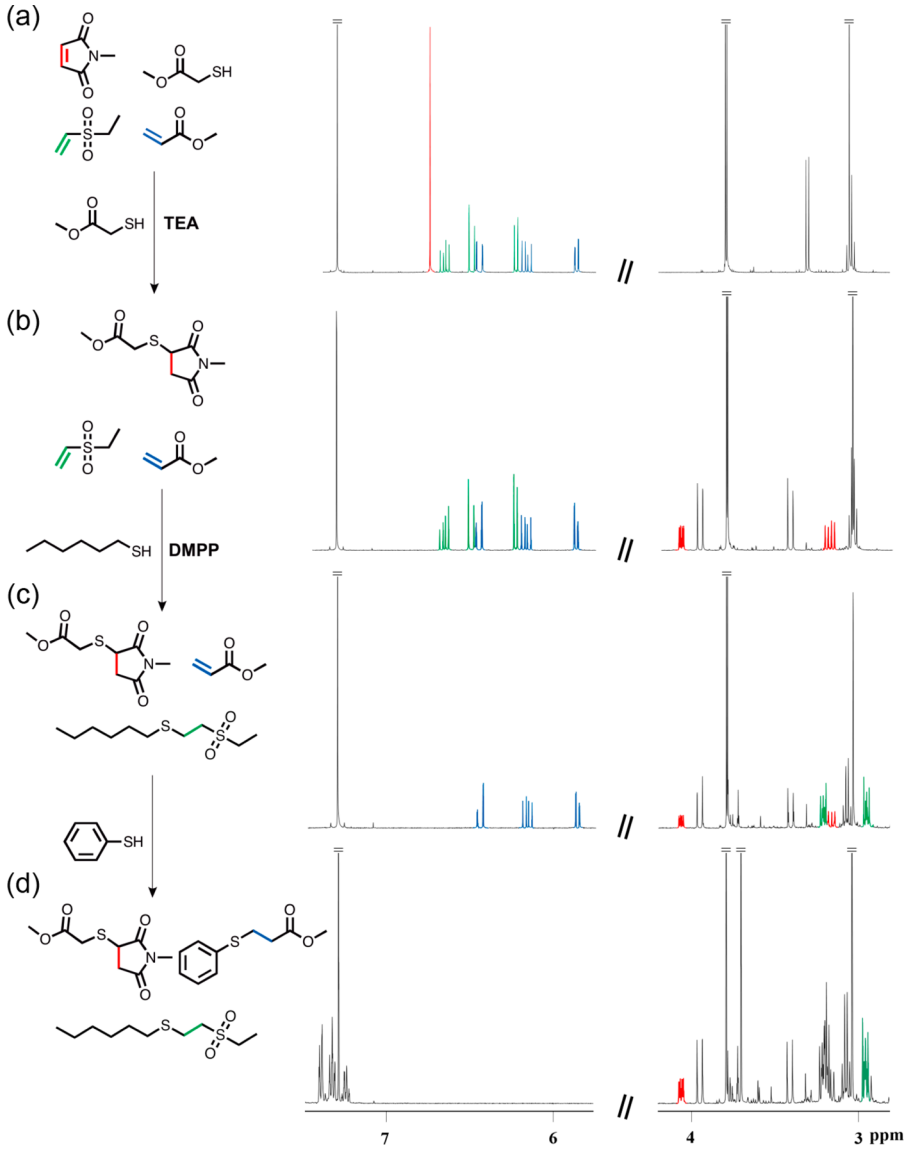

Figure 6. ^{1}H NMR spectra showing the selective sequential senary thiol-Michael reaction between maleimide (**1**), vinyl sulfone (**2**), acrylate (**4**), thioglycolate (**7**), hexanethiol (**11**), and benzenethiol (**9**) catalyzed/initiated by TEA and DMPP. (a) Quaternary mixture of **1**, **2**, **3**, and **7** in the absence of TEA. (b) Selective formation of the **1**-**7** product upon addition of TEA. (c) Subsequent, selective formation of the **2**-**11** product as catalyzed by DMPP. (d) Subsequent, selective formation of the **4**-**9** product within the reaction mixture.

the total isolated mass, respectively.[17] The undesired **6**-**7** adduct was isolated in 5% as well as trace amounts of 1-hexanethiol. The elution of excess hexanethiol is consistent with the observation of a small amount of the **6**-**7** adduct given that the formation of the **6**-**7** adduct results in some quantity of unreacted hexanethiol and methyl acrylate. Only unreacted hexanethiol was collected and observed, however, because methyl acrylate is sufficiently volatile that all excess acrylate was lost when concentrating the reaction mixture under reduced pressure. Figure 5 shows one representative example of a highly, though not exclusively, selective one-pot quaternary thiol-Michael reaction. The observation of some undesired **6**-**7** thiol-Michael product may indicate that further optimization of the reaction conditions is necessary. Alternatively, it may be possible for the strongly basic DBU to promote retro-Michael reactivity and allow thermodynamic control of the one-pot quaternary reaction, which could potentially explain the formation of the undesired **6**-**7** product. Additional one-pot quaternary reactions are currently being explored in different solvents and with different initiators with the aim of developing examples of one-pot quaternary reactions that show 100% selectivity.

Sequential Senary Thiol-Michael Reactions. The selectivities of the ternary thiol-Michael reactions were further demonstrated in a selective, sequential senary thiol-Michael addition reaction involving three Michael acceptors and three thiols. Components **1**, **2**, **4**, and **7** were mixed in equimolar amounts and allowed to react in the presence of TEA, resulting in the exclusive formation of the **1**-**7** adduct between *N*-methyl maleimide and thioglycolate (Figure 6). The formation of the **1**-**7** thiol-Michael adduct is easily observed by ^{1}H NMR spectroscopy by the disappearance of the maleimide singlet at 6.73 ppm shown in red (Figure 6a) along with the appearance of two sets of doublet of doublets (4.06 and 3.17 ppm) indicative of thiol-maleimide product formation. Following the formation of the **1**-**7** adduct, hexanethiol **11** and DMPP were

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added to the mixture of vinyl sulfone **2**, acrylate **4**, and the **1-7** glycolate-maleimide product. Nucleophilic DMPP rapidly and efficiently catalyzed the formation of the **2-11** thiol-Michael adduct between hexanethiol and ethyl vinyl sulfone. Panels b and c in Figure 6 show complete consumption of vinylic signals of **2** (6.64, 6.47, and 6.21 ppm) along with the appearance of methylene triplets of the **2-11** product at 3.22 and 2.69 ppm highlighted in green. No side products or evidence of acrylate consumption were observed. Upon the formation of the **2-11** thiol-Michael adduct, benzenethiol was added to the mixture, and the thiol-Michael adduct of benzenethiol and methyl acrylate was formed. Many overlapping peaks in the ^{1}H NMR spectrum of the mixture of all three adducts, **1-7**, **2-11**, and **4-9** (Figure 6d), complicated the precise assignment of the methylene triplets resulting from the formation of the **4-9** thiol-Michael adduct; however, the disappearance of the vinylic hydrogens at 6.42, 6.15, and 5.85 ppm and appearance of signals corresponding to product methylene peaks between 3.15 and 3.25 ppm strongly supported the formation of the **4-9** thiol-Michael adduct. Other reaction orders and combinations of thiols and Michael acceptors can be envisioned based on earlier ternary and quaternary results. Such sequentially selective multicomponent thiol-Michael reactions can be of significant utility to the targeted functionalization of multifunctional polymers.

These examples of selective thiol-Michael addition reactions are a representative fraction of the potential sequential and one-pot selective thiol-Michael reactions that can be designed based upon the ternary selectivity charts contained within the Supporting Information. Even in the context of more routine thiol-Michael reactions, the ternary selectivity charts can be used to troubleshoot common concerns that may arise for a specific thiol-Michael reaction, e.g., they can be used to determine whether a particular thiol will react with a particular Michael acceptor and which catalyst or initiator, of the three investigated herein, is most efficient.

CONCLUSIONS

The results presented herein provide a deeper understanding of the selectivies of common Michael acceptors (**1**−**6**) for thiols (**7**−**11**) and vice versa. Experimental results suggest that the order of reactivity for Michael acceptors studied herein, from most to least reactive, is **1** > **2** > **3** > **4** > **5** ≈ **6**, and the order of reactivity of the thiols studied, from most to least reactive, is **7** > **9** > **8** > **10** > **11**. These trends are generalizations, and the full selectivity charts (Figures S1−S8) highlight the fact that some combinations of thiol, Michael acceptor, and catalyst/initiator may deviate from the above trends in reactivity. The utility of a more detailed understanding of thiol-Michael reactivity is demonstrated through a series of selective sequential and one-pot quaternary reactions as well as a representative example of a sequential senary reaction.

A primary conclusion of the current study is that the design of selective thiol-Michael reactions requires more than simply considering the reactivity of a given thiol or Michael acceptor on its own. Rather, the details of what catalyst/initiator is used, the solvent, and the order of reactions (if sequential) can significantly influence selectivity and must be taken into account. We therefore aim to expand this initial study to include a wider variety of bases and nucleophiles beyond TEA, DBU, and DMPP. Similarly, investigating selectivity in solvents other than chloroform is expected to provide further insight into the design of selective thiol-Michael addition reactions. Discovering and designing thiol-Michael reactions whose selectivity can be tuned to the specific needs (e.g., solvent, pH, functionality, etc.) of a desired application will greatly expand the reach and impact of selective thiol-Michael chemistry. These investigations are currently underway.

We envision that the subtleties reported herein will be broadly applicable to the synthesis and/or postsynthetic functionalization of multicomponent polymers. The demonstrated ability to (i) introduce thiols or Michael acceptors along sequential, stepwise synthetic routes or (ii) to achieve selectivity when all thiols and Michael acceptors are present in one-pot reaction mixtures can be expected to enable more efficient and facile routes to the synthesis and functionalization of multicomponent materials. Furthermore, ternary selectivity charts detailing the selectivity between Michael acceptors **1**−**6** and thiols **7**−**11** provide valuable insight into the design and troubleshooting of selective thiol-Michael reactions.

EXPERIMENTAL METHODS

General Information. Unless otherwise stated, all chemicals were purchased from commercial suppliers and used as received. Thiol-Michael products except thiol-maleimide adducts **1-7** and **1-11** have been prepared previously.[5e,11d,e,18−22] Thin layer chromatography (TLC) was performed on alumina-backed sheets coated with silica gel 60 F254. TLC plates were visualized using a UV/vis lamp and/or by staining with iodine or *p*-anisaldehyde solution. All ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury (300 and 75 MHz, respectively) or Varian Unity Inova (500 and 125 MHz, respectively) spectrometer using residual solvent as the internal standard. All chemical shifts are quoted using the δ scale, and all coupling constants are expressed in Hertz (Hz).

Adduct **1-7**: An equimolar mixture of *N*-methyl maleimide (50 mg, 0.45 mmol) and methyl thioglycolate (48.8 mg, 0.04 mL, 0.45 mmol) was taken up in 5 mL of chloroform in a small round-bottom flask. One drop of TEA (excess) was added, and the reaction mixture was allowed to stir for 30 min. The mixture was then concentrated under reduced pressure and placed under high vacuum to remove residual TEA, resulting in the formation of analytically pure thiol-maleimide product **1-7** as a light yellow oil. Yield: 97 mg (99%). TOF MS ESI (*m*/*z*) $[M + H]^+$ calcd for $C_8H_{12}NO_4S$, 218.0487; found, 218.0482. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.08 (dd, 1H, *J* = 9.0, 4.0 Hz), 3.97 (d, 1H, *J* = 15.8 Hz), 3.80 (s, 3H), 3.43 (d, 1H, *J* = 15.8 Hz), 3.20 (dd, 1H, *J* = 19.0, 9.0 Hz), 3.04 (s, 3H), 2.57 (dd, 1H, *J* = 19.0, 4.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.3, 174.4, 170.0, 52.6, 38.4, 35.4, 32.8, 25.1 ppm.

Adduct **1-11**: An equimolar mixture of *N*-methyl maleimide (50 mg, 0.45 mmol) and 1-hexanethiol (53 mg, 0.64 mL, 0.45 mmol) was added to a small round-bottom flask and taken up in 5 mL of chloroform. One drop of TEA (excess) was added, and the mixture was allowed to stir for 30 min. After 30 min, the reaction mixture was concentrated under reduced pressure and placed under high vacuum to remove any residual TEA, resulting in analytically pure thiol-maleimide product **1-11** as a light yellow oil. Yield: 102 mg (99%). TOF MS ESI (*m*/*z*) $[M + H]^+$ calcd for $C_{11}H_{20}NO_2S$, 230.1215; found, 230.1224. The product was isolated as a light yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.76 (dd, 1H, *J* = 9.0, 3.5 Hz), 3.19 (dd, 1H, *J* = 18.5, 9.0 Hz), 3.04 (s, 3H), 2.94−2.88 (m, 1H), 2.81−2.76 (m, 1H), 2.58 (dd, 1H, *J* = 18.5, 3.5 Hz), 1.73−1.58 (m, 2H), 1.45−1.39 (m, 2H), 1.37−1.27 (m, 2H), 0.93 (t, 3H, *J* = 6.8 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 176.7, 174.8, 39.1, 36.2, 31.7, 31.3, 28.9, 28.4, 25.0, 22.4, 14.0 ppm.

General Procedures for Multicomponent Thiol-Michael Reactions. Ternary reactions: Equimolar quantities of either two Michael acceptors and one thiol or two thiols and one Michael acceptor were added to a three-dram vial and taken up in chloroform. A catalytic amount of triethylamine (TEA, 0.1 equiv), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 0.1 equiv), or dimethylphenylphosphine (DMPP, 0.01 equiv) was added, and the mixtures were

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allowed to stir at ambient temperature for 1 h. The ternary reaction mixtures were evaporated to dryness overnight before further drying under high vacuum for 1 min. The ternary reaction mixtures were then diluted with $CDCl_3$ and analyzed by ^1H NMR spectroscopy. Relative ratios of thiol-Michael products were determined by integrating signals that are distinctive for each thiol-Michael product. In this manner, all ternary thiol-Michael combinations involving Michael acceptors **1**−**6** and thiols **7**−**11** as promoted by TEA, DBU, and DMPP were evaluated (Figures S1−S8). The results of ternary reactions were used to design and test more complex multicomponent thiol-Michael reaction sequences.

Quaternary reactions: Four component, quaternary reactions involving two Michael acceptors and two thiols were carried out via two different procedures: a sequential procedure A and a one-pot procedure B. Procedure A followed the same initial procedure as described above for ternary reactions with the requirement that only selective (>98% yield of one product) thiol-Michael reactions were chosen. One exception being that increased amounts of catalyst/initiator (1.0 equiv of TEA and DBU and 0.1 equiv of DMPP) were used to ensure complete consumption of the desired Michael acceptor before the addition of any subsequent thiols. Upon completion of the first selective thiol-Michael reaction (as judged by ^1H NMR spectroscopy), an additional thiol or Michael acceptor component was added to the reaction mixture. In some cases, an additional quantity of TEA, DBU, or DMPP was also added. Upon completion of the second thiol-Michael reaction, the mixtures were concentrated under reduced pressure and dried under high vacuum. Procedure B involved the addition of equimolar amounts of two Michael acceptors and two thiols in one three-dram vial followed by the addition of $CDCl_3$ and either substoichiometric TEA, DBU, or DMPP. The one-pot quaternary mixture was allowed to stir under ambient conditions until no changes were observed by ^1H NMR spectroscopy. Upon completion, the mixture was concentrated under reduced pressure and dried under high vacuum.

Senary reactions: Sequential senary reactions involving three Michael acceptors and three thiols designed to yield only three target thiol-Michael products followed a modified version of procedure A. The primary modification was that equimolar amounts of three Michael acceptors and one thiol were included for the first selective thiol-Michael step followed by two subsequent steps each involving the addition of another equivalent of thiol and possibly an additional initiator. As before, the completion of each step was evaluated by ^1H NMR spectroscopy before starting a subsequent step. At the end of the three-step reaction sequence, the mixture was concentrated under reduced pressure and dried under high vacuum.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b01200.

Complete selectivity charts for all ternary combinations of thiols and Michael acceptors and full experimental details for all sequential and one-pot quaternary and sequential senary reactions including all relevant ^1H and ^{13}C NMR spectra (PDF)

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The authors declare no competing financial interest.

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