The Thiol-Michael Reaction: From First Principles to Applications in Macromolecular Synthesis

by

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Introduction to Click Chemistry

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Chapter 3

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

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Chapter 4

Evaluating Nucleophile Byproduct Formation During Phosphine- and Amine-Catalyzed Thiol-Methyl Acrylate Reactions

Scheme 4.1: (a) Acid-base equilibrium resulting in the formation of a thiolate anion in the presence of base. (b) General mechanism for the formation of thiolate and nucleophile byproduct resulting from the addition of a nucleophile to the vinyl group of an acrylate followed by deprotonation of thiol by the resulting enolate intermediate. (c) Catalytic cycle for the reaction of thiolate with acrylate to give a thiol-Michael addition product.

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**Figure 4.2:** Compiled ¹H NMR results for the reaction between PEG-diacrylate polymer 6 and methyl 3-mercapropionoate (7) (3.2a) initiated by either DMPP, DEA, or HA (3.2b-d, respectively) in the absence of solvent. Unlike the solvated results highlighted in Figure 1 of the main text, all reactions go to completion as indicated by the lack of any vinylic protons between 5.8-6.5 ppm. Only trace amounts of byproduct are observed in the Figure 3.2c and 3.2d (DEA and HA, respectively), and no byproduct is observed in Figure 3.2b (DMPP).

**Figure 4.3:** (a) Reaction of PEG-diacrylate polymer 6 with 2.0 equiv of PEG-thiol 9 as catalyzed by 2.0 equivs of nucleophiles 3a-c to give target polymer 10 as well as potential formation of nucleophile byproduct polymers 11 and 12. (b) GPC traces of
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**Figure 4.4:** Compiled GPC results for reaction between PEG-diacrylate polymer 6 and PEG-thiol 9 as promoted by 2.0 equivalents of DMPP, DEA, or HA (i.e. 1:1 nucleophile:acrylate) or 10.0 equivalents of DMPP, DEA, or HA (5:1 nucleophile:acrylate).

**Scheme 4.3:** General comparison of the pathways and relative rates for consumption of acrylate by a nucleophile (left cycle) leading to an undesired nucleophile byproduct, or by a thiolate (right cycle), which leads to a desired thiol-Michael product. Relative magnitudes of the rates of nucleophile initiation and catalytic anionic cycle pathways are adapted from reference 3.14.

**Scheme 4.4:** Potential pathways for reactions between a thiolate and phosphonium ester salt. (a) A multi-step elimination-addition pathway wherein thiolate initially deprotonates the phosphonium ester resulting in elimination of DMPP and a subsequent thiol-acrylate reaction. (b) Direct substitution wherein thiolate acts as a nucleophile, displacing DMPP and resulting in the desired thiol-Michael product. (c) Substitution involving nucleophilic attack of a phosphonium methyl group by thiolate to give a methyl thioether and tertiary phosphine byproduct.

**Figure 4.5:** Chemical scheme and $^1$H NMR spectroscopic results of a model for the reaction of a phosphonium ester with a nucleophilic thiolate. Addition of the bromide salt of phosphonium ester 5a (i.e. model compound 13) to the sodium salt of methyl 3-
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**Figure 4.6:** Summary of substitution and elimination-addition pathways studied computationally. At the top are rate-determining steps for substitution at a DMPP methyl group (a), substitution at the β-carbon of the phosphonium ester (b), and for the deprotonation of the phosphonium ester by thiolate (c). Transition state free energies for each rate-determining step are given in kcal/mol and are relative to the starting phosphonium ester/thiolate salt in a solvent model for CHCl₃. At the bottom is the computed profile for each pathway in CHCl₃ with rate-determining steps a–c labeled. Complete computational results in both CHCl₃ and DMSO are in section 3.10.

**Figure 4.7:** ¹H NMR spectrum (500 MHz) obtained upon the addition of 10.0 equivalents of DMPP to a mixture of 1-hexanethiol and methyl acrylate, solvent free (Table 3.1, entry 6). Residual DMPP signals are observable just above the baseline between δ 7.0-7.8 ppm and as a doublet at δ 1.8 ppm.

**Figure 4.8:** ¹H NMR spectrum (500 MHz) obtained upon the addition of 10.0 equivalents of DEA to a mixture of 1-hexanethiol and methyl acrylate, solvent free (Table 3.1, entry 11). Trace 1,2-dihexyl disulfide peaks are observed just above the baseline at 2.7 and 1.7 ppm.

**Figure 4.9:** ¹H NMR spectrum (500 MHz) obtained upon the addition of 0.25 equivalents of HA to a mixture of 1-hexanethiol and methyl acrylate, solvent free (Table 3.1, entry 13). The methylene protons β to the byproduct ester appear as a triplet
at 2.90 ppm. Poor signal to noise prevents the meaningful integration of the byproduct triplet as can be seen above (0.02).

**Figure 4.10:** $^1$H NMR spectrum (500 MHz) obtained upon the addition of 0.50 equivalents of HA to a mixture of 1-hexanethiol and methyl acrylate, solvent free (Table 3.1, entry 14). The methylene protons β to the ester appear as a well-resolved triplet observed just above the baseline at 2.90 ppm. A comparison of the integrations of the methylene protons β to the ester in both the byproduct (0.04) and product (2.21) affords a byproduct to product ratio of $<2:98$.

**Figure 4.11:** $^1$H NMR spectrum (500 MHz) obtained upon the addition of 1.0 equivalent of HA to a mixture of 1-hexanethiol and methyl acrylate, solvent free (Table 3.1, entry 15). In this case the integrations of the methyl protons of the byproduct and product were compared to determine product ratios. The greater integration of the methyl group (3 protons) as compared to the methylene protons β to the ester (2 protons) provides greater signal to noise and a more reliable integration. The byproduct to product ratio was determined to be approximately 4:96.

**Figure 4.12:** $^1$H NMR spectrum (500 MHz) obtained upon the addition of 10.0 equivalents of PA to a mixture of 1-hexanethiol and methyl acrylate, solvent free (Table 3.1, entry 17). Propylamine was chosen in addition to hexylamine because of its lower boiling point. Again, the integrations of the methyl protons of the byproduct and product were compared to determine product ratios. The inset shows two resolved singlets at 3.71 (byproduct) and 3.72 (product) ppm. The byproduct to product ratio was determined to be 4:96.
Figure 4.13: $^1$H NMR spectrum (500 MHz) obtained upon the addition of 1.0 equivalent of DMPP to a mixture of 1-hexanethiol and methyl acrylate in CDCl$_3$ (1.0 M). Signals corresponding to the phosphonium ester byproduct are not observed. Identical results were obtained when the same reaction was carried out in DMSO and THF. (Table 3.2, entries 1-3)

Figure 4.14: $^1$H NMR spectrum (500 MHz) obtained upon the addition of 1.0 equivalent of DEA to a mixture of 1-hexanethiol and methyl acrylate in CDCl$_3$ (1.0 M). The methylene protons β to the ester are observed slightly above the baseline at 2.90 ppm. Poor signal to noise prevented a more accurate determination of the product to byproduct ratio. Identical results were obtained when the same reaction was carried out in DMSO and THF. (Table 3.2, entries 4-6)

Figure 4.15: $^1$H NMR spectrum (500 MHz) obtained upon the addition of 1.0 equivalent of HA to a mixture of 1-hexanethiol and methyl acrylate in CDCl$_3$ (1.0 M). The methylene protons β to the ester of byproduct 5c are observed at 2.90 ppm and provide a product to byproduct ratio of approximately 5:95. (Table 3.2, entry 7)

Figure 4.16: $^1$H NMR spectrum (500 MHz) obtained upon the addition of 1.0 equivalent of HA to a mixture of 1-hexanethiol and methyl acrylate in THF (1.0 M). After the completion of the reaction the mixture was concentrated under reduced pressure and analyzed by $^1$H NMR in CDCl$_3$. The methylene protons β to the ester of byproduct 5c are observed slightly above the baseline at 2.90 ppm. While byproduct is observed, poor signal to noise complicates an accurate determination of the product to byproduct ratio. Similar results were observed in DMSO. (Table 3.2, entries 8-9)
**Figure 4.17:** $^1$H NMR spectrum (500 MHz) obtained upon the addition of 2.0 equivalents of DMPP to a 2:1 mixture of PEG-diacrylate 6 and PEG-thiol 9. The absence of any vinylic signals from PEG-diacrylate 6 between 5.8-6.5 ppm indicates complete consumption of acrylate moieties.

**Figure 4.18:** $^1$H NMR spectrum (500 MHz) obtained upon the addition of 2.0 equivalents of DEA to a 2:1 mixture of PEG-diacrylate 6 and PEG-thiol 9. Unreacted PEG-diacrylate 6 is observed as indicated by the vinylic signals between 5.8-6.5 ppm.

**Figure 4.19:** $^1$H NMR spectrum (500 MHz) obtained upon the addition of 2.0 equivalents of HA to a 2:1 mixture of PEG-diacrylate 6 and PEG-thiol 9. Unreacted PEG diacrylate is observed as indicated by the vinylic signals between 5.8-6.5 ppm.

**Table 4.3:** Calculated transition state and reaction enthalpies and free energies for each step of the elementary reactions summarized in Pathways A-D. All values are given in kcal/mol at 298.15 K as calculated at the M06-2X/6-311G(2D,P)//B3LYP/6-31+G(D) level$^{3.29,3.30}$ using the program Gaussian09.$^{3.32}$ Values for each pathway A-D are reported relative to their respective starting materials.

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**Chapter 5**

*Structurally Diverse Dendritic Architectures by Orthogonal Thiol-Maleimide and Furan-Maleimide “Click” Chemistries*

**Figure 5.1:** Common macromolecular architectures: linear polymers comprised AB monomers, branched polymers comprised of AB monomers, and hyperbranched polymers comprised of AB$_n$ monomers.
**Figure 5.2:** Dendrimer and dendron architectures. Key structural motifs are highlighted. Surface groups (multivalency), branching units (de Gennes dense packing), and interior cavities (host-guest chemistry).

**Scheme 5.1:** The divergent growth of dendrimers emanates outward. Blue and red spheres react to afford a new generation (growth step), and pendant green spheres are subsequently converted to blue spheres (activation step). The number of reactive sites on the periphery grows exponentially with each generation. This iterative process is repeated to grow higher generation dendrimers.

**Scheme 5.2:** The convergent growth of dendrimers emanates inward. Blue and red spheres react (growth step), and green spheres are subsequently converted to blue spheres (activation step). This iterative process is repeated to obtain a dendron. Growth is controlled: at most two reactions must occur in parallel. In a final step, the dendron is reacted with a branched core to afford the resulting dendrimer.

**Scheme 5.3:** Dendrimer synthesis using orthogonal Sonogashira and Mitsunobu reactions. Adapted from reference 5.26.

**Scheme 5.4:** Orthogonal thiol-ene (AB$_2$ growth, green) and copper(I)-catalyzed azide alkyne cycloaddition (CD$_2$ growth, blue) click reactions for the preparation of 6$^{th}$ generation dendrimers.

**Scheme 5.5:** Orthogonal, selective thiol-Michael additions between alkyl thiols (teal) and a sulfone (red), and a thioglycolate (blue) and meth acrylates (pink) to afford the rapid and efficient synthesis of a 5$^{th}$ generation dendrimer.

**Scheme 5.6:** Synthesis of A-R-B$_2$ monomer in 9 steps from 3,5-dihydroxybenzoic acid.
Scheme 5.7: Synthesis of A-R’-B₂ monomer in 4 steps from 10.

Scheme 5.8: Synthesis of hydrophobic, 2, and hydrophilic, 5, furan-maleimide linkers.

Scheme 5.9: Synthesis of tri-maleimide functionalized core, 19, in three steps from mesitylene.

Scheme 5.10: A-R-B₂ and A-R’-B₂ monomers can be mixed iteratively to afford any combination of dendritic architectures including homogenous (top) and specifically layered (bottom) structures.

Figure 5.3: ^1H NMR highlighting the growth of a homogeneous 2nd generation Dendron using the A-R-B₂ monomer. Growth (a to b) and activation (b to c) steps are easily visualized by ^1H NMR. Disappearance of N-methyl maleimide vinylic protons (blue, a to b) represents a complete growth step. Disappearance of furan allylic and vinylic protons (purple, b to c) concomitant with the appearance of maleimide vinylic protons (blue, b to c) marks a complete activation step.

Figure 5.4: A subset of the various dendrimer architectures accessible with only four monomers (A, B, C, and D) using orthogonal thiol-maleimide and furan-maleimide chemistry.

Figure 5.5: Gel permeation chromatography traces for G1_F through G3_M homogeneous dendrons built from A-R-B₂.

Table 5.1: The predicted masses, observed masses by ESI mass spectroscopy, and PDI’s for G1_F through G3_M homogeneous dendrons built from A-R-B₂.
ABSTRACT OF DISSERTATION

The Thiol-Michael Reaction: From First Principles to Applications in Macromolecular Synthesis

by

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Doctor of Philosophy in Chemistry
Wesleyan University, Middletown, Connecticut, 2018
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Over in a flash…
An offensive smell lingers
Click! It starts anew.
Click chemistry has emerged as a powerful approach to mimic nature’s unparalleled ability to perform combinatorial chemistry with remarkable modularity and diversity. The rapid reaction kinetics and high efficiency of the thiol-Michael click reaction fit well within the click paradigm, however, this reactivity has hindered the orthogonal application of these reactions in some cases. The research presented herein was undertaken to i) develop a deeper mechanistic understanding of the thiol-maleimide reaction to provide insight into the design of selective thiol-maleimide reactions (Chapter 2), ii) develop comprehensive selectivity charts to explore the design of selective, quaternary and greater mixtures (Chapter 3), iii) address concerns surrounding the formation of byproducts along the nucleophile initiated thiol-Michael reaction (Chapter 4), and iv) explore the application of orthogonal click chemistries to the synthesis of previously inaccessible dendritic architectures. With the goal of learning to control, or in essence hide, the high potential reactivity of thiols in a given environment in order to design selective, orthogonal thiol-Michael reactions, we discovered mechanistic insights that led to the design of selective ternary thiol-maleimide reactions (Chapter 2), developed selectivity charts that enabled the selective sequential and one-pot reactions of quaternary and greater mixtures of thiol-Michael reactions (Chapter 3), learned byproduct formation along the amine and phosphine initiated pathways is not as large of a concern as previously thought, and proposed a mechanistic explanation for difference in byproduct formation observed along the amine and phosphine paths (Chapter 4), and applied our newfound understanding of the thiol-Michael reaction to synthesis of novel dendritic architectures (Chapter 5).
Chapter 1

Introduction to “Click” Chemistry
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1.0 Introduction

In 2001, Barry Sharpless conceptualized click chemistry,\textsuperscript{1,1} realizing that in order for chemical reactions to be adaptable to a wide range of processes and demands across fields, reactions first and foremost should be simple. As such, click reactions are defined as those that meet the following stringent criteria: (1) Afford a single product in high yield, (2) Proceed under atmospheric conditions in benign solvent or neat, (3) Are regio- and stereoselective where applicable, (4) Require little to no purification, and (5) Are orthogonal. In their original manuscript, Sharpless and co-workers focused on ‘spring-loaded’ reactions — reactions having a high thermodynamic driving force — such as nucleophilic epoxy-aziridine ring-opening reactions and [3+2] alkyne-azide cycloadditions (Scheme 1.1).\textsuperscript{1,1} It is worth noting that many chemical reactions have high thermodynamic driving forces, but are not considered click. For example, acid-base reactions involving protonation/deprotonation reactions are energetically favored and proceed in high yields, but are not considered click reactions. Why? They are, most typically, not selective. While there are many chemical reactions that exhibit some click characteristics, there are far fewer that exhibit all the click characteristics outlined above, and this is an important distinction. Since Sharpless’ original article, the scope of the click paradigm has expanded, and more recently, considerable attention has been focused on thiol-click reactions, as many satisfy the stringent criteria of click chemistry.\textsuperscript{1,2}
Scheme 1.1: In Sharpless’ seminal review introducing click chemistry he originally introduced the concept of click chemistry in reference to $S_N^2$-type ring opening and Huisgen 1,3-dipolar cycloaddition reactions.

The adaptation of the click nomenclature to refer to various thiol-click reactions is due in large part to the highly reactive nature of thiols.\textsuperscript{1,2} The high reactivity of thiols enables their interaction with a wide breadth of substrates. However, it is important to note that the advantage afforded by high reactivity can also be uniquely disadvantageous, because it can sometimes compromise the orthogonality of thiol-click reactions.\textsuperscript{1,2d} In other words, the fact that thiol-click reactions may proceed by radical or base/nucleophile catalyzed processes under mild conditions with a multitude of substrates (see Figure 1.1), means thiol-click reactions are intrinsically susceptible to reacting simultaneously with multiple substrates of the same type (e.g. alkenes, alkynes, alkyl halides). A further consequence of their high reactivity is that, in general, thiol-click reactions proceed more rapidly than most other click chemistries,\textsuperscript{1,2} with high conversions from starting materials to products often achieved in
seconds. In an attempt to develop enhanced control and specificity of thiol-click reactions, considerable work has been dedicated to elucidating the factors that influence thiol reactivity with numerous substrate and catalyst combinations.  \(^1,3\)

**Figure 1.1:** The structural diversity combined with the high reactivity allows thiols to react with a myriad of substrates under radical (alkyne, alkene), base (Michael, isocyanate), and nucleophile (epoxide, halide) regimes. Adapted from reference 1.2d.

Figure 1.1 shows the four general classes of thiol structures (alkyl, thiol propionate, thiol glycolate, and aromatic thiols), and their reactivity towards bases, electrophiles, and nucleophiles. It is important to mention that each thiol type shown in Figure 1.1 is different with respect to participation in radical and Michael addition reactions. The structural variance seen amongst thiols and their corresponding thiy1 and thiolate species, means that thiol-click reactions occur with a range of organic substrates including alkenes (radical), alkynes (radical), electron deficient alkenes (Michael addition), isocyanates (carbonyl addition), epoxides (\(S_N2\) ring opening), and halogens (\(S_N2\) nucleophilic substitution), as
shown in Figure 1.1. While previous work has highlighted the range of thiol-based materials with bespoke physical, mechanical, and chemical properties, the discussion henceforth will be limited to the versatility of the thiol-Michael click reaction.

The Michael addition reaction is broadly defined as the reaction between an enolate-type nucleophile and an α,β-unsaturated carbonyl in a 1,4-conjugate addition fashion. Specifically, when the Michael addition involves a thiol species as a nucleophile then the reaction is classified as a thiol-Michael reaction (Scheme 1.2). While the ability of the Michael addition reaction to readily form C-X bonds has made it a workhorse in small molecule organic synthesis, the broader application of Michael additions — in particular thiol-Michael additions in materials synthesis (e.g. surface modification, polymer functionalization, and polymer synthesis) — has been concomitant with the rise of click chemistry.

**Scheme 1.2:** The thiol-Michael reaction occurs between a thiol (blue) and an α,β-unsaturated carbonyl (red) in a 1,4-conjugate addition fashion to afford the corresponding thiol-Michael adduct.

The thiol-Michael reaction is an attractive means of ensuring spatially and temporally modifiable materials. Bowman et al. demonstrated the ability of photocaged amines to spatiotemporally control the kinetically driven two-stage thiol-acrylate and thiol-methacrylate reactions (Figure 1.2). In general, thiol-Michael reactions are either promoted with substoichiometric amounts of a base or nucleophile catalyst, although Lewis
acids,\textsuperscript{1,8} ionic liquids,\textsuperscript{1,9} and molecular iodine\textsuperscript{1,10} have been shown capable of catalyzing thiol-Michael reactions. Under neither the base nor nucleophile catalyzed paradigms do thiol-Michael addition mechanisms lead to the formation of significant side products, as can be the case with radical-radical termination products formed during radical-mediated thiol-ene reactions. Thus, the ability to afford quantitative conversion absent the formation of side products, even under dilute conditions, renders the thiol-Michael reaction as an attractive candidate for many materials chemistry applications.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Spatial and temporal control is achieved through a “photo-click” reaction - photocaged amine catalysts are released in response to light - that can be used in surface patterning and controlled polymer network formation. Adapted from reference 1.7.}
\end{figure}

The Northrop lab is broadly interested in thiol-Michael click chemistry, and in particular thiol-maleimide chemistry, for the preparation of novel organic materials such as mechanically interlocked molecules (e.g. psedurorotaxanes and rotaxanes) and dendritic macromolecules. The activating effects of two electron withdrawing carbonyls coupled with
the release of ring strain make the thiol-maleimide reaction an especially efficient thiol-click reaction. Previously, the Northrop lab has demonstrated the synthesis of neutral donor-acceptor [2]rotaxanes wherein thiol-maleimide click chemistry was used to attach bulky substituted tetraphenylmethane stoppers to the pseudorotaxane precursor. More recently, efforts have been focused on applying thiol-maleimide reactions to the synthesis of dendritic macromolecules. Over the past few decades, dendrimers have continued to garner attention due to numerous advantageous properties such as monodispersity, multivalency, globular architecture, and well-defined molecular weight. Despite these promising properties, dendrimers suffer from arduous multi-step syntheses that culminate with difficult purifications and high waste from side products and inefficient conversions, making them attractive candidates for synthesis via thiol-Michael click reactions.

As such the focus of this dissertation is fourfold: (1) evaluate the influence of initiator, thiol, and solvent on a particular thiol-Michael reaction of interest, namely, the thiol-maleimide reaction; (2) investigate the ternary selectivity of common thiol and alkenes to more effectively predict and design selectivity in greater than ternary mixtures; (3) study the formation and subsequent reactivity of nucleophile-Michael byproducts; and (4) apply our findings from (1)-(3) to the design of structurally diverse dendrimers.
1.1. References and Notes


Chapter 2

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2.0. Abstract

The mechanism and kinetics of thiol-maleimide “click” reactions carried out under a variety of conditions have been investigated computationally and using experimental competition reactions. The influence of three different solvents (chloroform, ethane thiol, and $N,N$-dimethylformamide), five different initiators (ethylamine, diethylamine, triethylamine, 1,8-diazabicyclo[5.4.0]undec-7-ene, and dimethylphenylphosphine), and seven different thiols (methyl mercaptan, $\beta$-mercaptoethanol, thioacetic acid, methyl thioglycolate, methyl 3-mercaptopropionate, cysteine methyl ester, and thiophenol) on the energetics and kinetics of thiol-maleimide reactions have been examined using density functional methods. Computational and kinetic modeling indicate that the choice of solvent, initiator, and thiol directly influences whether product formation follows a base-, nucleophile-, or ion pair-initiated mechanism (or some combination thereof). The type of mechanism followed determines the overall thiol-maleimide reaction kinetics. Insights from computational studies are then used to understand the selectivity of ternary thiol-maleimide reactions between $N$-methyl maleimide, thiophenol, and 1-hexanethiol in different combinations of solvents and initiators. The results provide considerable insight into the interplay between reaction conditions, kinetics, and selectivity in thiol-maleimide reactions in particular and thiol-Michael reactions in general, with implications ranging from small molecule synthesis to bioconjugation chemistry and multifunctional materials.
2.1. The Thiol-Maleimide Reaction

2.1.1. Introduction

Reactions between thiols and maleimides have long been recognized as some of the most efficient Michael-type additions.\textsuperscript{2,1-2,3} The withdrawing effects of two activating carbonyls coupled with the release of ring strain upon product formation provide a significant driving force for thiol-maleimide reactions. Given their reliability, efficiency, and selectivity, thiol-maleimide reactions have been a primary means of bioconjugation\textsuperscript{2,4} for several decades. More recently there has been increasing interest in utilizing thiol-maleimide reactions in polymer and materials synthesis.\textsuperscript{2,3,2,5} Much of this interest has grown with the emergence of click chemistry,\textsuperscript{2,6,2,7} especially as applied to the synthesis of macromolecules and new materials.\textsuperscript{2,7-2,9}

2.1.2. Thiol-Catalyzed Addition

The mechanism of thiol-maleimide reactions is most often written as a typical Michael-type addition. Entrance into the catalytic cycle (Scheme 2.1a) requires the initial formation of some quantity of nucleophilic thiolate anion. There are two prominent means of forming these initial quantities of thiolate anions: one that utilizes base and another that utilizes nucleophiles.\textsuperscript{2,10} Along the base-initiated mechanism, a catalytic amount of weak base (e.g. triethylamine, Et\textsubscript{3}N) is used to deprotonate some quantity of available thiol (Scheme 2.1b). The resulting thiolate anion, a strong nucleophile, attacks the \(\pi\)-bond of maleimide, resulting in a strongly
basic enolate intermediate. This intermediate deprotonates an additional equivalent of thiol, giving the desired addition product as well as another equivalent of thiolate that can perpetuate the catalytic cycle.

**Scheme 2.1:** (a) Mechanism for the thiolate-catalyzed addition of a thiol to an N-substituted maleimide. (b) Formation of a thiolate anion from an acid-base equilibrium reaction. (c) Formation of a thiolate anion following a nucleophile-initiated mechanistic pathway.

Various nucleophiles can also be used to initiate thiol-Michael reactions. The nucleophile-initiated mechanism (Scheme 2.1c) differs from the base-initiated mechanism in the manner in which a thiolate anion is formed. Along the nucleophile-initiated mechanism the nucleophile (typically a nitrogen or phosphorus-centered nucleophile) first attacks the π-bond of maleimide to give a zwitterionic enolate intermediate. This enolate deprotonates a thiol to give a thiolate anion, which then progresses along the same catalytic pathway as when initiated by a base. It is important to note that the nucleophilic pathway results in the formation of some amount of nucleophile addition byproduct. This byproduct formation is
typically inconsequential, however, as most nucleophile-initiated thiol-Michael reactions proceed rapidly even in the presence of trace amounts (<1%) of initiator.

Thiol-maleimide reactions can also be carried out using radical initiators. In comparison to base-initiated thiol-maleimide reactions, however, radical-initiated thiol-maleimide reactions proceed less rapidly given that the radical-initiated pathway typically favors more electron rich alkenes. Base-initiated thiol-maleimide reactions are also advantageous as they avoid the formation of radical-radical termination products and are not sensitive to \( \text{O}_2 \).

### 2.1.2. Thiol-Maleimide Mechanism

Interestingly, recent studies by Lowe, Haddleton, and Bowman have found that the kinetics and mechanism (base-initiated or nucleophile-initiated) that a given thiol-Michael reaction follows depends on the specific combination of base/nucleophile, Michael acceptor, and thiol. This discovery is very useful for the design of selective thiol-Michael reactions wherein several different thiols or Michael acceptors are present in a single reaction mixture (e.g. ternary or quaternary systems). While research in the area of selective thiol-Michael reactions has increased significantly over the past few years, several mechanistic questions remain. More generally, a comprehensive understanding of the structural, energetic, and kinetic factors that influence whether a given combination of thiol, Michael acceptor, and base/nucleophile follows a base-initiated pathway, nucleophile-initiated pathway, or some combination of both has yet to be developed. There have also been few
investigations\textsuperscript{2,20} aimed at elucidating the influence that experimental conditions (solvent, equivalents of initiator, etc.) have on thiol-Michael energetics and kinetics. Mechanistic details are particularly lacking in the case of thiol-maleimide reactions as a result of their very rapid kinetics.

Herein we present a thorough, fundamental investigation of the mechanism of thiol additions to maleimide derivatives. The energetics of both base-initiated and nucleophile-initiated mechanisms have been studied computationally at the M06-2X/6-311G(2D,P)//B3LYP/6-31+G(D) level of theory.\textsuperscript{2,21,2,22} Initial computational studies focus on mapping out the various mechanistic pathways available for the Et\textsubscript{3}N promoted addition of methyl mercaptan (1) to N-methyl maleimide (NMM) in chloroform (CHCl\textsubscript{3}). With mechanistic insights gained from these initial investigations, computational studies are then extended to include four additional bases/nucleophiles (ethylamine, diethylamine, 1,8-diazabicyclo[5.4.0]undec-7-ene, and dimethylphenylphosphine), two additional solvents (ethyl mercaptan and \textit{N},\textit{N}-dimethylformamide), and six additional thiols (β-mercaptoethanol, thioacetic acid, methyl thioglycolate, methyl 3-mercaptopropionate, cysteine methyl ester, and thiophenol), all shown in Figure 2.1. Computational investigations suggest that, under most conditions, the first step along the base-initiated mechanism does not involve the direct deprotonation of a thiol by base as is commonly shown and discussed in the literature. Nucleophile-initiated pathways, often believed to be inoperative for thiol-maleimide additions, are computationally predicted to contribute to product formation in the presence of primary and secondary amines, a result that is supported
experimentally. Rates of thiol-maleimide additions are found to increase substantially in highly polar solvents (e.g. DMF), and these rate increases can be attributed to differences in the reaction mechanism under different solvent conditions. The reactivity of different thiols is predicted to vary in accordance with thiol pKa’s, and to be independent of their nucleophilicity. Computational results are supported by experimental investigations of reactions between NMM and two different thiols that demonstrate the influence of different experimental conditions on thiol-maleimide selectivity in ternary reactions. The results provide not only a significantly more detailed understanding of thiol-maleimide reactions but also provide a path toward a greater understanding of thiol-Michael reactions in general and the design of selective thiol-maleimide reactions in particular.

**Figure 2.1:** Chemical structures of the maleimide, bases/nucleophiles, thiols, and solvents investigated in the current study, as well as the dielectric constant of each solvent.
2.2. Et₃N-Initiated Mechanism in Chloroform

The Et₃N-initiated addition of methyl mercaptan (1) to NMM in CHCl₃ was chosen as a starting point for investigating the energetics, kinetics, and mechanism of thiol-maleimide reactions. As discussed above thiol-maleimide reactions are ideally suited to display rapid reaction kinetics given (i) the nucleophilicity of thiolate anions, (ii) the highly activated π-bond of maleimide derivatives, (iii) the strong basicity of the enolate intermediate, and (iv) the general acidity of most thiols. Indeed, the computed energetics of the catalytic addition of methane thiolate (1⁻) to NMM in CHCl₃ (Figure 2.2) indicate a propagation step free energy barrier of $\Delta G^\ddagger = 8.1$ kcal/mol (TS8) leading to the slightly endergonic ($\Delta G^o = 3.7$ kcal/mol) formation of resonance-stabilized enolate intermediate 9. Deprotonation of another equivalent of thiol by this enolate intermediate, i.e. the chain-transfer step, requires an additional free energy barrier of $\Delta G^\ddagger = 4.8$ kcal/mol (TS10). The reaction generates thiol-maleimide addition product 11 along with another equivalent of thiolate anion, and is predicted to be exergonic overall by -11.7 kcal/mol. This catalytic cycle assumes that sufficient quantities of thiolate anion have been formed, either from the acid-base equilibrium established between 1 and Et₃N or from deprotonation of 1 by the enolate anion formed upon nucleophilic addition of Et₃N to NMM (Scheme 2.1b,c). Given that one or both of these processes is believed to occur in order to enter into the catalytic cycle shown in Scheme 2.1a it is important to compare their relative energetics.
Figure 2.2: Calculated relative free energies of stationary points along the thiolate-catalyzed mechanism of methane thiolate (1⁻) addition to NMM. Free energies are expressed in kcal/mol and were calculated at 298 K in a solvent model for CHCl₃. Distances of bonds breaking or forming in TS8 and TS10 are given in angstroms (Å).

It is often assumed that the equilibrium between methyl mercaptan (I) and Et₃N will provide initial quantities of methyl thiolate (1⁻) and Et₃NH⁺ in solution, noting that the pKₐ of methyl mercaptan (~10.5) is slightly lower than the pKₐ of Et₃N (10.65). These values refer, of course, to their acid dissociation constants in water. When thiol-maleimide additions are used to prepare organic materials, however, the reactions are most commonly carried out as neat solutions or in organic solvents such as CHCl₃, which are considerably less able to stabilize the formation of 1⁻ and Et₃NH⁺ as compared to water. Lowe et al. have suggested²⁻¹¹a that attack on the π-bond of a Michael acceptor may initially occur by a thiolate/Et₃NH⁺ ion pair, such as 1⁻/Et₃NH⁺. Scheme 2.2 shows the calculated structures and relative energetics.
corresponding to proton transfer from 1 to Et₃N in CHCl₃, resulting in the formation of an ion pair as well as isolated ions. The free energy barrier for proton transfer from 1 to Et₃N is relatively low (ΔG° = 8.4 kcal/mol, TS12), however, the formation of a 1⁻/Et₃NH⁺ ion pair is calculated to be endergonic by 7.7 kcal/mol (Kₑq = 2.3x10⁻⁶). The formation of isolated thiolate and ammonium ions 1⁻ and Et₃NH⁺ is significantly less favored at ΔG° = 33.4 kcal/mol. Qi et al. computationally studied the energetics of the trimethylamine (Me₃N)-mediated addition of 1 to divinylsulfone and noted similar energetics for proton transfer from 1 to Me₃N.²²⁸ Computational results therefore suggest that (i) the equilibrium between 1 and Et₃N in CHCl₃ strongly favors the neutral reactants, (ii) very little of the 1⁻/Et₃NH⁺ ion pair will be present in solution, and (iii) essentially no free thiolate anion will be formed by direct deprotonation of 1 by Et₃N.

**Scheme 2.2:** Energetics of the acid-base equilibrium between methyl mercaptan (1) and triethylamine (Et₃N) calculated in CHCl₃. The relative free energy (ΔG° and ΔΔG‡, kcal/mol) of each species or pair of species is given in parentheses. Dashed lines indicate bonds being broken/formed while dotted lines indicate noncovalent interactions. Distances are given in Å.
2.2.1. Ion-Pair Pathway

While very little of the $\text{1}^-/\text{Et}_3\text{NH}^+$ ion pair is predicted to be present in CHCl$_3$, only a small amount of nucleophilic thiolate is necessary to initiate the self-sustaining catalytic cycle shown in Scheme 2.1a. The lowest energy transition state$^{2,29}$ found for the reaction between a $\text{1}^-/\text{Et}_3\text{NH}^+$ ion pair and NMM, TS13, is shown in Figure 2.3 and has a free energy barrier of $\Delta G^\ddagger = 22.8$ kcal/mol. The resulting enolate intermediate 14 can abstract a proton from either Et$_3$NH$^+$ or from another equivalent of 1 (both pathways are shown in Figure 2.3). Interestingly, the highest free energy barrier along the pathway for proton transfer from Et$_3$NH$^+$ corresponds to the energy required to disrupt the noncovalent interaction between the ammonium center and its carbonyl hydrogen bond acceptor (TS15). Once this noncovalent interaction is broken the transfer of a proton from Et$_3$NH$^+$ to the enolate proceeds energetically downhill through transition state TS16 to give thiol addition product 11 and Et$_3$N. The free energy of transition state TS15 is found to be 5.3 kcal/mol above enolate intermediate 14, indicating an overall free energy barrier of $\Delta G^\ddagger = 24.7$ kcal/mol for Et$_3$N-mediated addition of 1 to NMM along this pathway.
Figure 2.3: Relative free energies (kcal/mol) of stationary points for the addition of a $\text{I}^-/\text{Et}_3\text{NH}^+$ ion pair to NMM. Two mechanistic possibilities follow the initial propagation transition state ($\text{TS}_{13}$): one involving proton transfer from $\text{Et}_3\text{NH}^+$ ($\text{TS}_{15}-\text{TS}_{16}$) and another involving proton transfer from methyl mercaptan ($\text{TS}_{17}$). Only the latter results in formation of thiolate anion $1^-$. Dashed lines indicate bonds being broken/formed. Dotted lines indicate noncovalent interactions. Distances are given in Å.

Alternatively, enolate intermediate $14$ can abstract a proton from $1$ as shown in chain transfer transition state $\text{TS}_{17}$. Proton transfer from $1$ is found to require $\Delta G^\ddagger = 7.6$ kcal/mol relative to enolate intermediate $14$, indicating that proton transfer from $\text{Et}_3\text{NH}^+$ ($\text{TS}_{15}-\text{TS}_{16}$) is energetically more favorable by 2.3 kcal/mol. However, only catalytic amounts of $\text{Et}_3\text{N}$ are used to promote thiol-maleimide reactions and therefore the concentration of $1$ will almost always exceed the concentration of $\text{Et}_3\text{NH}^+$ in the reaction mixture. This is especially true in the early stages of thiol-maleimide reactions when the concentration of thiol is at its greatest. Therefore, while
proton transfer from Et₃NH⁺ to enolate intermediate 14 is favored energetically, the transfer of a proton from 1 may still be favored kinetically depending on the relative concentrations of Et₃NH⁺ and 1 in solution. This difference is important because proton transfer from Et₃NH⁺ does not produce any of the strongly nucleophilic thiolate anion 1⁻ whereas proton transfer from 1 does. Because no thiolate anion is formed in the first scenario, subsequent thiol-maleimide reactions must proceed along the same mechanistic pathway starting from the formation of a 1⁻/Et₃NH⁺ ion pair and proceeding through TS15, with an overall free energy barrier of ΔG‡ = 24.7 kcal/mol. The alternative pathway involving proton transfer from 1 to enolate 14 through TS17 does result in the formation of nucleophilic 1⁻, which can react directly with NMM along the catalytic cycle shown in Scheme 2.1a with a free energy barrier of ΔG‡ = 8.5 kcal/mol. This second scenario is more consistent with the experimentally observed rapid kinetics of Et₃N-mediated thiol-maleimide reactions. Which mechanistic pathway(s) is taken will depend on the relative concentrations of starting materials and intermediates as a function of time and, therefore, benefits significantly from kinetic analysis, as will be discussed in subsequent sections.

2.2.2. Nucleophilic Addition of Et₃N

One other potential means of forming the thiolate anion 1⁻ involves the nucleophilic addition of Et₃N to NMM. Et₃N is generally considered a poor nucleophile as a result of steric crowding around its central nitrogen atom. The transition state for
nucleophilic addition of Et$_3$N to NMM in CHCl$_3$ is shown as TS19 in Figure 2.4, and is found to have a barrier of $\Delta G^\ddagger = 24.5$ kcal/mol. Surprisingly, this free energy barrier is only 1.7 kcal/mol less favored than the free energy barrier for attack of NMM by a 1$^-$/Et$_3$NH$^+$ ion pair (TS13, Figure 2.3). The zwitterionic intermediate 20 formed following nucleophilic attack is found to be only 0.7 kcal/mol more stable than TS19. Deprotonation of 1 by zwitterionic enolate intermediate 20 requires an additional 10.8 kcal/mol (TS21), indicating that unimolecular $\beta$-scission of the N–C bond is energetically and kinetically more favored than the bimolecular chain-transfer pathway. The overall free energy barrier of $\Delta G^\ddagger = 34.6$ kcal/mol required to form 1$^-$ along a nucleophile-initiated mechanism is 7.6 kcal/mol greater than the free energy barrier to its formation along a base-initiated mechanism (TS17, Figure 2.3) and is therefore unlikely to contribute significantly to the overall reaction mechanism. It should be reiterated, however, that all potential mechanistic pathways leading to the formation of a nucleophilic thiolate anion should be considered because once even small quantities of thiolate are available to react with NMM the rapid, catalytic thiolate addition mechanism shown in Scheme 2.1a becomes viable.
Figure 2.4: Relative free energies (kcal/mol) of stationary points located along the nucleophile-initiated mechanism leading to methane thiolate formation (I⁻). Dashed lines indicate bonds being broken/formed, and distances are given in Å.

2.3. Kinetic Modeling

Reaction energetics presented in Figures 2.2-2.4 and Scheme 2.2 were used to calculate reaction rates using activated complex theory. Rate constants for individual mechanistic steps are provided in Table 2.7. Both forward and reverse rate constants were calculated for each individual step and modeled for all reactions. Kinetic modeling of thiol-maleimide addition reactions was performed with the initial concentrations of both thiol 1 and NMM taken to be 3.0 M and the concentration of Et₃N taken to be 0.3 M (10 mol%). With these initial conditions and the rate constants calculated for each possible mechanistic step, the concentrations of all starting materials, intermediates, and products were modeled as a function of time using the
program Kintecus.\textsuperscript{2,30} Including and simultaneously modeling all mechanistic pathways that can potentially lead to the formation of addition product 11, however favorable or unfavorable they may be, should result in the most accurate model of the thiol-maleimide reaction mechanism and kinetics. Furthermore, significant insights can be gained by selectively including or excluding individual reaction pathways from the overall kinetic model. For example, the influence of chain transfer from thiol 1 to intermediate 14 through TS17 (Figure 2.3) on overall reaction kinetics can be assessed by including or excluding that specific mechanistic pathway in the kinetic model. This creates an artificial yet informative means of evaluating the relative contributions of different mechanistic pathways to overall reaction kinetics and product formation.

Results from computational and kinetic modeling of the Et\textsubscript{3}N-promoted addition of 1 to NMM in CHCl\textsubscript{3} are shown in Figure 2.5. Four different mechanistic scenarios are overlaid on the same plot. For each mechanistic scenario the formation of addition product 11 is plotted as a function of time. All four mechanistic scenarios include the catalytic thiolate addition pathway shown in Figure 2.2. Where the pathways differ is in the process by which thiolate anion 1\textsuperscript{−} is formed. The green trace, labeled “Acid-Base Pathway,” plots product formation when the only mechanism available for thiolate formation is by deprotonation by Et\textsubscript{3}N (Scheme 2.2). Each of the other three scenarios include attack of NMM by a 1\textsuperscript{−}/Et\textsubscript{3}NH\textsuperscript{+} ion pair through TS13 and leading to intermediate 14 (Figure 2.3). The red trace plots product formation when chain-transfer occurs only from Et\textsubscript{3}NH\textsuperscript{+} through TS15, while
the black trace plots product formation when chain-transfer occurs only from 1 through TS17. Lastly, the blue trace is a “fully inclusive” mechanism wherein all possible reaction paths are included in the kinetic model.

![Graph of alkene conversion over time](image)

**Figure 2.5:** Results of kinetic modeling of the Et$_3$N-mediated addition of methyl mercaptan (1) to NMM in CHCl$_3$. The blue trace plots alkene conversion when all potential mechanistic pathways discussed in Figures 2.2-2.4 and Scheme 2.2 are included in the model. The black, red, and green traces selectively exclude specific pathways as a means of evaluating their influence on the overall reaction kinetics.

With all mechanistic pathways included in the kinetic model (Figure 2.5, blue trace) the Et$_3$N-promoted addition of 1 to NMM is predicted to reach 50% within 93 seconds. Interestingly, only 2% of 11 is predicted to form by 30 minutes when the only pathway available for thiolate formation is the direct deprotonation of 1 by Et$_3$N (green trace). Increasing the molar equivalents of Et$_3$N by a factor of 100 does not substantially change this observation, as the predicted yield of 11 after 30 minutes only increases to 7% when 10 molar equivalents of Et$_3$N are included in the model.
This prediction indicates that even a 10-fold excess of Et$_3$N cannot shift the acid-base equilibrium in CHCl$_3$ toward the formation of sufficient I$^-$ to drive the reaction forward. Overall, these results strongly suggest that, in nonpolar solvents, the mechanism of Et$_3$N-promoted thiol-maleimide reactions begins with the attack of the maleimide $\pi$-bond by a thiolate/Et$_3$NH$^+$ ion pair rather than direct deprotonation of the thiol by Et$_3$N.

As noted earlier, two different pathways are possible following the attack of NMM by a 1$^-$/Et$_3$NH$^+$ ion pair and the subsequent formation of enolate intermediate 14. Chain-transfer can occur by deprotonation of Et$_3$NH$^+$ or by deprotonation of thiol 1. The influence of chain-transfer from Et$_3$NH$^+$ can be examined by removing the pathway involving the thiol chain-transfer pathway from the kinetic model. The results of this scenario are shown as the red trace in Figure 2.5. When chain-transfer from Et$_3$NH$^+$ (TS15) is the only chain-transfer pathway available the formation of 11 is predicted to be quite slow, reaching less than 20% conversion within 30 minutes. By contrast, the black trace plots product formation when the only chain-transfer pathway included in the kinetic model is through TS17, i.e. chain-transfer from thiol 1. Under this hypothetical scenario the rate of product formation increases significantly, reaching 50% conversion in only 18 seconds. These results suggest that chain-transfer from 1 to 14 plays a more significant role in the formation of thiol-maleimide addition product 11 than chain-transfer from Et$_3$NH$^+$, despite the fact that chain-transfer from Et$_3$NH$^+$ is predicted to have a lower free energy barrier (TS15 vs TS17, Figure 2.3). The key difference between the two pathways being that chain-
transfer from 1 to 14 does produce nucleophilic thiolate 1− whereas chain-transfer between Et3NH+ and 14 produces Et3N and addition product 11 but no thiolate. It should be reiterated that the formation of thiolate 1− is necessary for the characteristically rapid kinetics of thiol-maleimide click additions to be observed, as the rate-determining step in the thiol-maleimide catalytic cycle is predicted to have a free energy of only $\Delta G^\ddagger = 8.5$ kcal/mol (Figure 2.2). Once initial quantities of thiolate are formed the catalytic cycle can become self-sustaining. Calculations and kinetic analysis presented herein suggest that neither the acid-base equilibrium between 1 and Et3N nor the chain-transfer from Et3NH+ to enolate 14 are able to form sufficient free thiolate 1− and therefore do not contribute significantly to the formation of thiol-maleimide addition product 11. It is also predicted that the nucleophilic pathway does not contribute to thiolate formation. This prediction is not surprising given that the rate-determining step along the nucleophilic pathway (Figure 2.4) is 7.6 kcal/mol less favorable than the rate-determining step to thiolate formation along the ion pair pathway (Figure 2.3).

Collectively the kinetic results presented in Figure 2.5 provide significant insights into the role that Et3N plays in promoting thiol-maleimide click reactions. The insights and conclusions drawn from the above discussion, however, refer specifically to computational and kinetic modeling of the Et3N-mediated addition of methane thiolate (1) to NMM in CHCl3. Several researchers have noted that the kinetics of thiol-Michael reactions can vary significantly with different combinations of solvent, initiator, and thiol. Even greater insights into thiol-maleimide
click chemistry can be obtained by extending the above analysis to include a wider variety of solvents, bases/nucleophiles, and thiols. The next few sections will summarize results of modeling thiol-maleimide reactions under these different reaction conditions.

2.4. Influence of Different Solvents

Two additional solvent models were investigated to examine their role in the Et$_3$N-mediated addition of 1 to NMM: ethyl mercaptan (EtSH) and $N,N$-dimethylformamide (DMF). The use of the PCM solvent model for EtSH is expected to provide a reasonable representation of the energetics and kinetics of thiol-maleimide reactions run under neat conditions, while the solvent model for DMF was chosen to better understand the effects of running thiol-maleimide reactions in a polar solvent. Stationary points found along the reaction paths shown in Scheme 2.2 and Figures 2.2-2.4 were each conformationally searched and re-optimized in EtSH and DMF. The resulting energetics calculated for the acid-base reaction between 1 and Et$_3$N are shown in Table 2.1 while the energetics of the catalytic addition of 1$^-$ to NMM, the addition of an 1$^-$/Et$_3$NH$^+$ ion pair to NMM, and the nucleophilic addition of Et$_3$N to NMM are all summarized in Table 2.2.
Table 2.1: Comparison of the calculated free energies ($\Delta G^\circ$)$^a$ and equilibrium constants for the formation of a $1^-/Et_3NH^+$ ion pair and free ions $1^-$ and $Et_3NH^+$ in solvent models for CHCl$_3$, EtSH, and DMF. Also included are the free energies of proton transfer from $1$ to DMF in the absence of $Et_3N$ (DMF-catalysis).

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Ion Pair</th>
<th>Free Ions</th>
<th>$K_{eq}$ ion pair</th>
<th>$K_{eq}$ free ions</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHCl$_3$</td>
<td>7.7</td>
<td>33.4</td>
<td>$2.3 \times 10^{-6}$</td>
<td>$3.3 \times 10^{-25}$</td>
</tr>
<tr>
<td>EtSH</td>
<td>7.0</td>
<td>27.4</td>
<td>$7.9 \times 10^{-6}$</td>
<td>$9.0 \times 10^{-21}$</td>
</tr>
<tr>
<td>DMF</td>
<td>5.7</td>
<td>13.1</td>
<td>$6.6 \times 10^{-5}$</td>
<td>$2.6 \times 10^{-10}$</td>
</tr>
<tr>
<td>DMF catalysis</td>
<td>14.4</td>
<td>19.4</td>
<td>$2.7 \times 10^{-11}$</td>
<td>$6.6 \times 10^{-15}$</td>
</tr>
</tbody>
</table>

$^a$Free energies are given in kcal/mol at 298.15 K and 1.0 atm pressure.

As shown in Table 2.1, more polar solvents are better able to stabilize the formation of methane thiolate ($1^-$) and $Et_3NH^+$ from the acid-base reaction between $1$ and $Et_3N$. In all three solvents the formation of the $1^-/Et_3NH^+$ ion pair is predicted to be endergonic, however the relative free energy of the ion pair decreases from 7.7 kcal/mol in CHCl$_3$ to 7.0 kcal/mol in EtSH and ultimately 5.7 kcal/mol in DMF. A greater difference in calculated free energies is observed for the formation of free ions $1^-$ and $Et_3NH^+$, where the acid-base reaction is notably more favored in DMF ($\Delta G^\circ = 13.1$ kcal/mol) than in EtSH or CHCl$_3$ ($\Delta G^\circ = 27.4$ and 33.4 kcal/mol, respectively). Such a large difference is significant because any solvent that sufficiently stabilizes the formation of $1^-$ provides a direct pathway to the rapid catalytic cycle of thiolate addition to NMM (Scheme 2.1a), bypassing the less energetically favorable ion pair mechanism. It is known$^{2,20}$ that high-dielectric constant solvents such as DMF can promote thiol-maleimide reactions in the absence of a catalyst. In such cases it is the solvent itself that promotes deprotonation of a thiol to give a nucleophilic thiolate anion. The free energy of proton transfer from $1$ to DMF is also included in Table 2.1.
so that the kinetics of DMF-catalyzed thiol-maleimide reactions can be modeled as well.

2.4.1. Formation of Thiolate in DMF

The free energy required to form an ion pair between a given thiol and DMF (Scheme 2.3a) was calculated by first optimizing a complex between the starting thiol along with two explicit DMF molecules, all in a solvent model for DMF. The suprastructure of the complex was fully conformationally searched using the program Maestro\textsuperscript{2,43} and the global energy minimum was optimized to full convergence using the program Gaussian09\textsuperscript{2,23} Similarly, the ion pair complex between a thiolate and a proton solvated by two molecules of DMF was conformationally searched and optimized in a solvent model for DMF. Two molecules of DMF were found to be necessary to form a stable ion pair complex. The inclusion of a third molecule of DMF did not influence the free energies calculated. If the three species are not optimized together then a large entropic penalty is incurred upon bring together three separate molecules (the thiol and two equivalents of DMF) into one ion pair complex. It is therefore necessary to optimize all three species together in both their neutral and ion pair arrangements. The model is justified because there should not be an entropic cost associated with bringing molecules of DMF near the thiol when DMF is present throughout as the solvent medium.
**Scheme 2.3:** General model for transfer of a proton from a thiol to a dimer of DMF.

(a) Formation of an ion pair:

![Diagram of ion pair formation](image)

(b) Formation of isolated thiolate anion and solvated proton:

![Diagram of thiolate and proton formation](image)

The free energy required to form a free thiolate anion and a solvated proton in DMF was calculated as shown in Scheme 2.3b. The primary difference between the two models being that in the ion pair the thiolate anion is stabilized by the nearby protonated DMF dimer whereas in Scheme 2.3b the thiolate is modeled as infinitely separated from the protonated DMF dimer, though both species are in an implicit solvent model for DMF. The optimized geometries and energetics outlined in Scheme 2.3a-b for 1 are shown in Figure 2.6a-b, respectively. For comparison, the optimized geometries and energetics following Scheme 2.3a-b for 7 are shown in Figure 2.7a-b, respectively. Further, a kinetic comparison of the DMF-catalyzed addition 1 and 7 to NMM is shown in Figure 2.8.
Figure 2.6: Optimized structures and energetics for proton transfer between 1 and DMF to give (a) an ion pair and (b) free ions as described above.

\[ \Delta H^\circ_{(\text{ion pair})} = 9.6 \text{ kcal/mol} \]
\[ \Delta G^\circ_{(\text{ion pair})} = 14.4 \text{ kcal/mol} \]

\[ \Delta H^\circ_{(\text{free ions})} = 15.3 \text{ kcal/mol} \]
\[ \Delta G^\circ_{(\text{free ions})} = 19.4 \text{ kcal/mol} \]

Figure 2.7: Optimized structures and energetics for proton transfer between 7 and DMF to give (a) an ion pair and (b) free ions as described above.

\[ \Delta H^\circ_{(\text{ion pair})} = 3.5 \text{ kcal/mol} \]
\[ \Delta G^\circ_{(\text{ion pair})} = 8.0 \text{ kcal/mol} \]

\[ \Delta H^\circ_{(\text{free ions})} = 7.0 \text{ kcal/mol} \]
\[ \Delta G^\circ_{(\text{free ions})} = 10.6 \text{ kcal/mol} \]
Figure 2.8: Comparison of the DMF-catalyzed addition of methyl mercaptan (1) to NMM versus the DMF-catalyzed addition of thiophenol (7) to NMM in the absence of an initiator. The difference in predicted kinetics reflects the difference in the calculated free energy required for DMF to deprotonate 1 versus 7 (Figures 2.6 and 2.7 on the previous page).

2.4.2. Energetics and Kinetics

Table 2.2 summarizes the influence of solvent on the free energies of stationary points along the catalytic thiolate addition, ion pair addition, and nucleophile-initiated mechanistic pathways shown in Figures 2.2-2.4, respectively. For each solvent modeled the overall free energy barrier along the nucleophile-initiated pathway is at least 7.2 kcal/mol higher than the overall free energy barrier along the ion pair pathway to thiolate formation. The nucleophile-initiated mechanism is therefore not predicted to contribute significantly to thiolate formation in any of the three solvents investigated. For all stationary points along each of the three pathways summarized in
Table 2.2 the free energies of stationary points in EtSH are predicted to be within 0.8 kcal/mol of those modeled in CHCl₃. This observation suggests that the kinetics of thiol-maleimide reactions run as neat mixtures are likely to be similar to the same reactions run in CHCl₃, though the reaction concentration and the dielectric constant of a given neat reaction solution will influence experimental results. The relative energetics of stationary points along both the ion pair and nucleophile-initiated pathways are predicted to decrease with increasing solvent dielectric, i.e. progressing from CHCl₃ to DMF. For the catalytic addition of thiolate to NMM, however, the opposite is true. The predicted free energy barrier to chain-transfer, which is rate-determining in each solvent, increases from $\Delta G^\ddagger = 8.5$ kcal/mol in CHCl₃ to 9.2 kcal/mol in EtSH and finally 12.3 kcal/mol in DMF. This trend results primarily from differences in the free energy of solvation of methane thiolate 1⁻. Nonpolar solvents such as CHCl₃ are less able to solvate small, highly charged species such as 1⁻, whereas DMF solvates such species quite well. A free thiolate anion is therefore predicted to be more reactive in CHCl₃ than in DMF. Upon addition of 1⁻ to NMM the negative charge once localized on 1⁻ becomes a resonance stabilized enolate intermediate with its net negative charge distributed across several atoms. The solvation free energies of these more delocalized anions (e.g. the propagation transition state, enolate intermediate, and chain-transfer transition state) were each found to be more similar across the three different solvents investigated.
Table 2.2: Relative free energies ($\Delta G^\circ$)$^a$ of stationary points along catalytic cycle,$^b$ ion pair,$^c$ and nucleophile-initiated$^d$ reaction pathways involved in the Et$_3$N-mediated addition of 1 to NMM as a function of solvent (CHCl$_3$, EtSH, and DMF).

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Propagation T.S.</th>
<th>Intermediate</th>
<th>Chain Transfer T.S.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Thiolate addition to NMM (catalytic cycle)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHCl$_3$</td>
<td>8.1</td>
<td>3.7</td>
<td>8.5</td>
</tr>
<tr>
<td>EtSH</td>
<td>8.7</td>
<td>4.3</td>
<td>9.2</td>
</tr>
<tr>
<td>DMF</td>
<td>11.2</td>
<td>6.6</td>
<td>12.3</td>
</tr>
<tr>
<td></td>
<td>Ion pair pathway to thiolate formation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHCl$_3$</td>
<td>22.8</td>
<td>19.4</td>
<td>27.0</td>
</tr>
<tr>
<td>EtSH</td>
<td>22.0</td>
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</tr>
<tr>
<td>DMF</td>
<td>19.9</td>
<td>16.6</td>
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<tr>
<td></td>
<td>Nucleophile initiated pathway to thiolate formation</td>
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<td></td>
</tr>
<tr>
<td>CHCl$_3$</td>
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<td>23.8</td>
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<tr>
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<tr>
<td>DMF</td>
<td>23.5</td>
<td>21.7</td>
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</tr>
</tbody>
</table>

$^a$Energies are reported in kcal/mol. $^b$See Figure 2.2. $^c$See Figure 2.3. $^d$See Figure 2.4.

The kinetics of Et$_3$N-mediated addition of 1 to NMM in EtSH and DMF were modeled using the same procedure as described in the previous section, and the results are plotted in Figure 2.9. The predicted rate of alkene conversion in CHCl$_3$ and the DMF-catalyzed addition of 1 to NMM are also included in Figure 2.9 for comparison. Two mechanistic scenarios were modeled for each solvent: solid lines in Figure 2.9 correspond to the rate of product formation when all possible mechanistic pathways were included in the kinetic model while dashed lines plot product formation when the only pathway available for thiolate formation is by the acid-base reaction between 1 and Et$_3$N. Only one plot is presented for the DMF-catalyzed addition of 1 to NMM formation because no Et$_3$N is included in the model.
Figure 2.9: Results of kinetic modeling of the Et₃N-mediated addition of methyl mercaptan (1) to NMM in DMF (purple traces), CHCl₃ (blue traces), and EtSH (red traces). Solid lines indicate that all potential pathways to methane thiolate formation (acid-base, ion pair, and nucleophilic) are included in the model. Dashed lines indicate that the only pathway to thiolate formation included in the model is from the direct deprotonation of 1 by Et₃N. The dotted purple trace corresponds to the DMF-catalyzed addition of 1 to NMM in the absence of Et₃N.

As can be seen in Figure 2.9 the solid and dashed purple lines corresponding to Et₃N-mediated thiol-maleimide reactions in DMF, overlap with each other. This result indicates that the rates of thiol-maleimide reactions in DMF are predicted to be the same regardless of whether thiolate (1⁻) is formed through the acid-base reaction between 1 and Et₃N or along an ion pair addition pathway. DMF is therefore predicted to be sufficiently polar that the ion pair addition pathway to thiolate formation is completely bypassed in DMF and thiol-maleimide reactions do occur following direct deprotonation of a thiol by a base, as commonly described in the literature. As noted above, however, highly polar solvents such as DMF are able to
promote thiol-Michael reactions in the absence of an initiator. Therefore the kinetics of DMF-catalyzed addition of 1 to NMM was also examined, and the results are shown as the dotted purple trace in Figure 2.9. Results of kinetic modeling show that the DMF-catalyzed thiol-maleimide reaction requires 3 minutes to reach 50% conversion, as compared to only 6 seconds in the presence of 10 mol% Et₃N. This result is not surprising given that the formation of an ion pair between DMF and 1 requires $\Delta G^\circ = 14.4$ kcal/mol, and separation of that ion pair to give free thiolate 1⁻ requires $\Delta G^\circ = 19.4$ kcal/mol (Table 2.1). The formation of free thiolate 1⁻ by proton transfer to DMF is therefore calculated to be 6.3 kcal/mol less favored than proton transfer to Et₃N in DMF. Computational results differ somewhat from experimental investigations by Du Prez that demonstrated the catalyst-free addition of isooctyl-3-mercaptopropionate to NMM in DMF is complete within one minute.²,2₀ This difference between computational and experimental results may be expected, however, because mercaptopropionates are known²,¹₈-²,¹⁹ to undergo thiol-Michael reactions faster than alkane thiols. Differences in thiol reactivity will be evaluated and discussed in a later section.

The kinetics of thiol-maleimide reactions in EtSH are predicted to be similar to their kinetics in CHCl₃. One significant difference between EtSH and CHCl₃ is apparent in Figure 2.9, namely that the direct formation of thiolate 1⁻ through deprotonation by Et₃N is predicted to contribute somewhat to product formation in EtSH (dashed red line) whereas the acid-base pathway is not predicted to contribute to product formation when the reaction is carried out in CHCl₃ (dashed blue line).
This observation results from the fact that the formation of free ions $1^-$ and $\text{Et}_3\text{NH}^+$ in EtSH is predicted to be 6.0 kcal/mol more favored than in CHCl$_3$ ($\Delta G^o = 27.4$ vs 33.4 kcal/mol, Table 2.1). It is therefore possible that the acid-base reaction between $1$ and Et$_3$N plays some role in thiol-maleimide additions in EtSH, however reaction kinetics based on thiolate formation along this acid-base reaction alone are not in agreement with experimental observations. Computational predictions only agree with experimental observations when the mechanistic pathway involving attack of NMM by a $1^-$/Et$_3$NH$^+$ ion pair, followed by chain-transfer from another equivalent of thiol, is included in the model. These results further support the conclusion that thiol-maleimide reactions in less polar solvents, likely including those carried out as neat solutions, follow an ion pair mechanism for initial thiolate formation.

2.5. Influence of Different Initiators

It has been widely demonstrated$^{2,3,10,11,15,20}$ that the choice of initiator can influence the kinetics and yields of thiol-Michael reactions. The current study was therefore expanded beyond Et$_3$N to examine the influence of four additional initiators: EtNH$_2$, Et$_2$NH, DBU, and DMPP. The energetics of proton transfer between each initiator and methyl mercaptan ($1$) were calculated in solvent models for both CHCl$_3$ and DMF, and the results are summarized in Table 2.3. As may be expected, proton transfer from $1$ to phosphine-centered initiator DMPP is found to be highly endergonic with the free energy of forming a $1^-$/DMPPH$^+$ ion pair calculated to be $\Delta\Delta G^o = 27.6$ kcal/mol in CHCl$_3$. Across the series of amine bases,
computational results in CHCl₃ predict the free energy of transferring a proton from 1 to base decrease with greater amine substitution from ΔG° = 11.2 kcal/mol for the formation of a 1⁻/EtNH₃⁺ ion pair to ΔG° = 7.7 kcal/mol for the formation of a 1⁻/Et₃NH⁺ ion pair. It’s noteworthy that the calculated free energies of proton transfer between 1 and the series of amines do not correlate with the amine pKa’s. Lowe and Haddleton have observed experimentally that the kinetics of amine-initiated thiol-acrylate reactions also do not correlate with the pKa’s of each amine, further highlighting that acid-base reactivity alone often cannot explain thiol-Michael reaction kinetics. Lastly, proton transfer from 1 to the amidine base DBU is predicted to be the most favorable of the series, with ΔG° = 6.0 kcal/mol for the formation of 1⁻/DBUH⁺ in CHCl₃. Importantly, the formation of free ions 1⁻ and DBUH⁺ in CHCl₃ is predicted to require 22.4 kcal/mol. This value is lower than the rate-determining step of the ion pair mechanism involving Et₃N (ΔG‡ = 27.0 kcal/mol, Table 2.2) suggesting that very strong bases such as DBU may be able to bypass the ion pair mechanism and contribute to thiol-maleimide reactions by the direct deprotonation of thiols, even in nonpolar solvents.

2.5.1. Ion Pair Formation

As can be seen in Table 2.3, the transfer of a proton from 1 to each of the nitrogen-centered bases is more favorable in DMF than in CHCl₃. This observation is most pronounced when comparing the free energy required to form free ions in solution,
where switching to DMF is predicted to stabilize the formation of free thiolate by 20-23 kcal/mol relative to CHCl$_3$. Computational and kinetic$^{2,34}$ results predict that, in DMF, all four nitrogen-centered bases are able to directly deprotonate enough of thiol 1 to initiate the catalytic thiol-maleimide cycle shown in Scheme 2.1a. In short, the kinetics of thiol-maleimide reactions in highly polar solvents such as DMF are predicted to be largely independent of the base used because the polarity of the solvent is able to promote the formation of sufficient free thiolate to bypass the ion pair mechanism. Furthermore, as shown in the preceeding section, DMF is able to catalyze thiol-maleimide reactions itself, absent any base. In nonpolar solvents such as CHCl$_3$, however, the ion pair mechanism and/or nucleophile-initiated mechanism are predicted to be necessary for the formation of initial quantities of thiolate, except in the cases of highly basic species such as DBU.

Table 2.3: Free energies ($\Delta G^\circ$)$^a$ calculated for the formation of an ion pair between 1 and each initiator as well as for the formation of free ions 1$^-$ and Initiator-H$^+$. pKa’s of nitrogen-centered bases are provided for reference.

<table>
<thead>
<tr>
<th>Initiator</th>
<th>CHCl$_3$</th>
<th>DMF</th>
<th>pKa$^b$</th>
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<td></td>
<td>Ion Pair</td>
<td>Free Ions</td>
<td>Ion Pair</td>
</tr>
<tr>
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<td>Et$_3$N</td>
<td>7.7</td>
<td>33.4</td>
<td>5.7</td>
</tr>
<tr>
<td>DBU</td>
<td>6.0</td>
<td>22.4</td>
<td>1.9</td>
</tr>
<tr>
<td>DMPP</td>
<td>27.6</td>
<td>42.5</td>
<td>28.8</td>
</tr>
</tbody>
</table>

$^a$Free energies are reported in kcal/mol. $^b$pKa values taken from reference 2.33.
2.5.2. Energetics and Kinetics

Listed in Table 2.4 are the relative free energies calculated for the formation of methane thiolate (1⁻) along both the ion pair and nucleophile-initiated mechanisms for each of the five initiators investigated. The one exception is that no propagation transition state could not be located along the ion pair pathway involving DMPP.\textsuperscript{2,35} Computations predict that the overall free energy barrier to forming thiolate 1⁻ along an ion pair mechanistic pathway is lowest for DBU (ΔG\textsuperscript{‡} = 18.9 kcal/mol) and highest for EtNH\textsubscript{2} (ΔG\textsuperscript{‡} = 29.7 kcal/mol). The overall free energy barriers for secondary and tertiary amine bases Et\textsubscript{2}NH and Et\textsubscript{3}N are predicted to be identical within error (ΔG\textsuperscript{‡} = 26.7-27.0 kcal/mol). This predicted similarity in reaction energetics between Et\textsubscript{2}NH and Et\textsubscript{3}N comes despite the fact that the formation of an ion pair between 1 and Et\textsubscript{3}N is calculated to be 2.5 kcal/mol more favorable than the formation of an ion pair with Et\textsubscript{2}NH. The discrepancy can be explained upon examination of the propagation transition states involving 1, each of the different nitrogen-centered bases, and NMM (Figure 2.10). Primary and secondary amine bases EtNH\textsubscript{2} and Et\textsubscript{2}NH, though less energetically favored to deprotonate methyl mercaptan 1, are able to simultaneously hydrogen bond with both the nucleophilic thiolate anion and the amide carbonyl of NMM as shown in propagation transition states TS\textsubscript{23} and TS\textsubscript{24} (Figure 2.10a,b), respectively. Tertiary Et\textsubscript{3}N, by contrast, can only form one hydrogen bond between the Et\textsubscript{3}NH\textsuperscript{+} and the nucleophilic thiolate as shown in TS\textsubscript{13}. Similar differences in hydrogen bonding are observed in the enolate intermediates and chain transfer
transition states involving each of the three amines. This balance between basicity and hydrogen-bonding ability helps explain the different reaction energetics summarized in Table 2.4.

Table 2.4: Calculated reaction and transition state free energies ($\Delta G^o$, $\Delta G^\ddagger$)$^a$ for the ion pair and nucleophile-initiated pathways leading to thiolate formation for each of the five initiators investigated.

<table>
<thead>
<tr>
<th>Initiator</th>
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<th>Enolate Int</th>
<th>Chain Transfer TS (from 1)</th>
</tr>
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<tbody>
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<tr>
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<tr>
<td>Et$_3$N</td>
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<td>19.4</td>
<td>27.0</td>
</tr>
<tr>
<td>DBU</td>
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<td>12.1</td>
<td>18.9</td>
</tr>
<tr>
<td>DMPP</td>
<td>$b$</td>
<td>–</td>
<td>–</td>
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</tbody>
</table>

<table>
<thead>
<tr>
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<th>Initiator Addition TS</th>
<th>Zwitterion Int</th>
<th>Chain Transfer TS</th>
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<td>EtNH$_2$</td>
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<tr>
<td>Et$_2$NH</td>
<td>22.3</td>
<td>20.2</td>
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<td>Et$_3$N</td>
<td>24.5</td>
<td>23.8</td>
<td>34.6</td>
</tr>
<tr>
<td>DBU</td>
<td>21.5</td>
<td>16.4</td>
<td>24.2</td>
</tr>
<tr>
<td>DMPP</td>
<td>21.7</td>
<td>14.9</td>
<td>24.5</td>
</tr>
</tbody>
</table>

$^a$Free energies reported in kcal/mol using a solvent model for CHCl$_3$. $^b$No propagation transition state could be found for attack of the $\pi$-bond of NMM by the 1-/DMPPH$^+$ ion pair.

DBU is also only able to form one hydrogen bond in its propagation transition state (TS25, Figure 2.10d). It’s interesting to note that in TS25 the DBUH$^+$ ion is found to hydrogen bond with the NMM carbonyl rather than thiolate anion 1-. This difference in hydrogen bonding interactions between Et$_3$NH$^+$ in TS13 and DBUH$^+$ in TS25 reflects the fact that DBU is the stronger base and separation of the 1-/DBUH$^+$ ion pair is less energetically costly than separation of the 1-/Et$_3$NH$^+$ ion pair (Table
The strength of DBU also results in the lowest calculated free energy barrier to thiolate formation along the DBU-mediated ion pair pathway ($\Delta G^\dagger = 18.9$ kcal/mol).

**Figure 2.10:** Propagation transition states EtNH$_2$-mediated (a), Et$_2$NH-mediated (b), Et$_3$N-mediated (c), and DBU-mediated (d) addition of 1 to NMM in CHCl$_3$. Dashed lined indicate bonds being broken/formed while dotted lines indicate hydrogen bonding interactions. Distances are given in Å.

Also shown in Table 2.4 are the relative energetics of nucleophilic pathways involving each of the five initiators. The propagation transition state free energy barriers for addition of each initiator to NMM are all predicted to fall within the relatively small range of $\Delta G^\dagger = 21.5-24.5$ kcal/mol. Much greater differences are observed when comparing the stabilities of resulting zwitterionic intermediates and subsequent chain-transfer free energy barriers. Each of the amine bases form largely unstable zwitterionic intermediates that are only slightly more stable than their propagation transition states. Furthermore, chain-transfer transition states between 1 and each of the amonium intermediates are predicted to be quite high, ranging from $\Delta G^\dagger = 32.1-34.6$ kcal/mol. DBU and DMPP are both predicted to form more stable zwitterion intermediates and have chain-transfer free energy barriers between $\Delta G^\dagger = 24-25$ kcal/mol. These computational results are consistent with observations by
Lowe\textsuperscript{2,11a} and Mayr\textsuperscript{2,36} that the high catalytic activity of DBU is best explained by a model wherein DBU is able to react both as a base and as a nucleophile.

While it’s interesting to compare the nucleophile-initiated free energy barriers of different initiators it is more instructive to compare the relative free energy barriers of nucleophile-initiated versus ion pair mechanistic pathways for each individual initiator. For example, DMPP will only follow a nucleophile-initiated pathway because its ion pair pathway is so energetically unfavorable it could not be located. More subtle trends are observed for the nitrogen-centered initiators. The rate-determining steps along the ion pair and nucleophile-initiated pathways involving EtNH\textsubscript{2} are within 3.6 kcal/mol of each other at $\Delta G^\dagger = 29.7$ kcal/mol (ion pair) and $\Delta G^\dagger = 33.3$ kcal/mol (nucleophile-initiated). It is therefore possible that the nucleophile-initiated EtNH\textsubscript{2} pathway may contribute to thiolate formation. For the more sterically bulky Et\textsubscript{3}N the nucleophile pathway is 7.6 kcal/mol less favored than the ion pair pathway, and earlier kinetic analysis (Figure 2.5) indicated that the nucleophile-initiated pathway does not contribute to thiolate formation or overall thiol-maleimide reactivity. Et\textsubscript{2}NH and DBU fall in between EtNH\textsubscript{2} and Et\textsubscript{3}N with the free energy difference between their ion pair and nucleophile-initiated pathways to thiolate formation calculated to be $\Delta \Delta G^\dagger = 5.4$ and 5.3 kcal/mol, respectively. It is therefore possible that Et\textsubscript{2}NH may also follow a hybrid mechanism involving some thiolate formation by both the ion pair and nucleophile-initiated pathways. DBU may also follow a hybrid mechanism, however DBU is the only initiator for which both the ion pair ($\Delta G^\dagger = 18.9$ kcal/mol) and direct deprotonation ($\Delta G^\circ = 22.4$ kcal/mol)
pathways are predicted to be more favorable than its nucleophilic addition pathway. It is therefore less likely that the nucleophile-initiated pathway for DBU will contribute to the overall thiol-maleimide reaction mechanism.

Figure 2.8 shows a plot of alkene conversion versus time for each of the five initiators studied. For nitrogen-centered initiators the kinetic modeling conditions used in Figure 2.8 were identical to those used previously in Figures 2.5 and 2.6. For DMPP the only difference in modeling conditions was in the initial quantity of initiator, which was reduced to 1% as is more typical\[^{2,3,10,21b}\] for nucleophilic thiol-Michael initiators. As before, solid lines indicate that all possible mechanistic pathways were included in the kinetic model for each initiator. Dashed lines correspond to kinetic results when the only available pathway for thiolate formation is the direct deprotonation of 1, i.e. the acid-base pathway. Kinetic modeling of computational results suggest that DMPP exhibits the fastest overall reaction kinetics, a result that is in broad general agreement with experimental observations of DMPP-initiated thiol-Michael reactions.\[^{2,10,21b,2,16,2,17,2,20}\] One of the primary reasons DMPP-mediated thiol-maleimide reactions are predicted to be so rapid is because they follow a nucleophile-initiated mechanism exclusively. No protic species are formed along a nucleophile-initiated pathway and therefore the reaction proceeds along an anion chain-like mechanism. Protic species (e.g. Et\(_3\)NH\(^+\)) have the effect of slowing down product formation at longer reaction times because they can undergo a rapid and exergonic acid-base reaction with any thiolate (e.g. 1\(^-\)) present, especially in nonpolar solvents. The consumption of 1\(^-\) by conjugate acid species causes the initially rapid
kinetics of thiol-maleimide reactions to level off over time. Along a nucleophile-initiated reaction pathway, by contrast, all nucleophile $1^-$ anions formed are available to react with NMM along the rapid catalytic cycle shown in Scheme 2.1a and alkene conversion does not slow dramatically as a function of time. This distinction can be applied broadly to thiol-Michael reactions that follow a nucleophile-initiated mechanism: because they do not produce protic species nucleophile-initiated thiol-Michael additions typically exhibit exceptionally rapid kinetics.

![Kinetic modeling of the addition of 1 to NMM in the presence of five different initiators: EtNH$_2$ (green traces), Et$_2$NH (red traces), Et$_3$N (blue traces), DBU (orange traces), and DMPP (black trace). Solid lines indicate that all potential pathways to methane thiolate formation (acid-base, ion pair, and nucleophilic) are included in the model. Dashed lines indicate that the only pathway to thiolate formation included in the model is the acid-base pathway involving direct deprotonation by a nitrogen-centered base. All results are modeled in CHCl$_3$.](image)

**Figure 2.11:** Kinetic modeling of the addition of 1 to NMM in the presence of five different initiators: EtNH$_2$ (green traces), Et$_2$NH (red traces), Et$_3$N (blue traces), DBU (orange traces), and DMPP (black trace). Solid lines indicate that all potential pathways to methane thiolate formation (acid-base, ion pair, and nucleophilic) are included in the model. Dashed lines indicate that the only pathway to thiolate formation included in the model is the acid-base pathway involving direct deprotonation by a nitrogen-centered base. All results are modeled in CHCl$_3$.

The relative kinetics of product formation using nitrogen-centered initiators are more nuanced. DBU is predicted, by far, to exhibit the most rapid thiol-maleimide
kinetics (Figure 2.11, solid orange line). Additionally, as indicated by the dashed orange line in Figure 2.11, DBU is the only nitrogen-centered base capable of initiating the thiol-maleimide reaction by its direct deprotonation of 1 in CHCl₃. Each of the other three amine bases must follow an ion pair mechanism, nucleophile-initiated mechanism, or some combination of both in order to produce initial quantities of thiolate 1⁻. When comparing the three amine bases, the initial rate of alkene conversion is most rapid with Et₃N followed by Et₂NH and finally EtNH₂. The initial rate therefore appears to follow the calculated trend in acid-base reactivity (Table 2.3). At longer reaction times, however, this ordering is switched as EtNH₂ is the first amine predicted to reach >90% alkene conversion, followed by Et₂NH and finally Et₃N. A closer examination of the kinetics of EtNH₂-mediated thiol-maleimide reactions can help explain this observation. The kinetic profile of the EtNH₂-mediated addition of 1 to NMM has a short induction period wherein less than 10% alkene conversion is observed within the first minute. This slow induction period is the result of the high free energy barriers to both the ion pair and nucleophile-initiated pathways for EtNH₂ (ΔG⁺ = 29.7 and 33.3 kcal/mol, respectively). After the first minute, however, the rate of EtNH₂-mediated alkene conversion increases rapidly and does not level off significantly. This rapid rate increase and lack of leveling suggests that the nucleophilic pathway is contributing to product formation in EtNH₂-mediated thiol-maleimide reactions. The kinetic profile of Et₂NH-mediated addition of 1 to NMM, while slightly slower by comparison, also does not level off significantly at longer reaction times. As noted earlier the nucleophile-initiated pathway for Et₂NH is
calculated to be within 5.4 kcal/mol of its ion pair mechanism, which is not as close as for EtNH\textsubscript{2} ($\Delta \Delta G^\ddagger = 3.6$ kcal/mol) but closer than for Et\textsubscript{3}N ($\Delta \Delta G^\ddagger = 7.6$ kcal/mol). Alkene conversion as promoted by Et\textsubscript{3}N does level off at longer reaction times likely because little, if any, thiolate is formed by the nucleophilic addition of Et\textsubscript{3}N to NMM. Figure 2.12 shows a similar plot of alkene conversion versus time for each of the five initiators studied in DMF.

**Figure 2.12:** Plot of alkene conversion versus time for the addition of methyl mercaptan (1) to NMM as catalyzed by ethylamine (green trace), diethylamine (red trace), triethylamine (blue trace), and DBU (orange trace) in DMF. In each case the only pathway available for initial thiolate formation is through the direct deprotonation of 1 by each N-centered base. Kinetic modeling indicates that, in DMF, all four N-centered bases are able to directly deprotonate enough of 1 to initiate the catalytic thiol-maleimide cycle. Inclusion of the ion pair addition, nucleophile-initiated, and DMF-catalyzed pathways would further increase the rate of alkene conversion for each initiator.
2.5.3. Amine Addition to Maleimide

Computational results indicating that EtNH$_2$ and Et$_2$NH may nucleophilically add to NMM as a means of producing thiolate $I^-$ complement experimental studies of amine-mediated thiol-Michael reactions.$^{2,10,2,11}$ As noted earlier, Lowe and Haddleton have discussed the nucleophilic behavior of primary amines in thiol-acrylate reactions.$^{2,11}$ Several amines have also been shown to nucleophilically add to $N$-substituted maleimides. O’Dell et al. have synthesized$^{2,37}$ a variety of linear and crosslinked polymers by reacting bismaleimides with oligomeric bisamines. Schlup et al. have extensively studied$^{2,38}$ the addition of primary amines and aniline to maleimide derivatives using mid- and near-IR spectroscopy. More recently, Du Prez et al. have studied$^{2,20}$ the addition of both $n$-propyl and $n$-octyl amines to NMM in DMF by both $^1$H NMR spectroscopy and LC-MS. Experimental studies have shown that secondary amines also undergo Michael addition to maleimides, though the addition of secondary amines is notably slower than the addition of primary amines.$^{2,37-2,38}$ To the best of our knowledge, tertiary amines (e.g. Et$_3$N) have not been shown to undergo nucleophilic addition to maleimide derivatives. To more directly compare computational studies presented herein and experimental investigations of amine additions to NMM, each amine initiator was stirred in a 1:1 molar ratio with NMM in CHCl$_3$ at ambient temperature (Scheme 2.4). In the case of Et$_3$N, 1.0 equiv. of tert-butanol was added to the reaction mixture as a non-nucleophilic proton source. The nucleophilic Michael addition of hexylamine to NMM was obtained in $>95\%$ yield, in contrast to 79\% addition of Et$_2$NH and 0\% addition of Et$_3$N.$^{2,39}$ These
experimental results support computational predictions that EtNH₂, and to a lesser extent Et₂NH, can nucleophilically add to NMM, even in a nonpolar solvent and at ambient temperature while the nucleophilic addition of Et₃N is not observed under these conditions.

**Scheme 2.4:** Spectroscopic investigation of the ability of hexylamine, diethylamine, and triethylamine to nucleophilically add to NMM in CHCl₃.

Overall, computational modeling of the influence that initiators have on thiol-maleimide reactions helps explain the varying relationships between initiator pKa, nucleophilicity, and reaction kinetics. DMPP exclusively follows a nucleophilic pathway, inducing the very rapid formation of thiol-maleimide addition product 11. DBU is strong enough to directly deprotonate 1, however the overall mechanism of DBU-mediated thiol-maleimide reactions is predicted to involve a combination of direct deprotonation and ion pair addition. A full understanding of the kinetics and mechanism of amine-mediated addition of 1 to NMM requires consideration of (i) the pKa of the amine, (ii) hydrogen-bonding interactions observed along ion pair reaction
pathways (Figure 2.10), and (iii) the favorability of forming catalytic thiolate $1^-$ along a nucleophile-initiated pathway.

### 2.6. Influence of Different Thiols

Results so far have all used methyl mercaptan (1) as the representative thiol. To extend the current results beyond methyl mercaptan six additional thiols were investigated (2-7, Figure 2.1). To reduce the overall computational burden of studying each mechanistic pathway for every combination of thiol, initiator, and solvent the seven different thiols were evaluated by comparing their acid-base reactivity with $\text{Et}_3\text{N}$ in CHCl$_3$ along with the nucleophilicity of their resulting thiolate anions. Table 2.5 summarizes the relative free energies of hydrogen atom transfer transition states between thiols 1-7 and $\text{Et}_3\text{N}$, the formation of each thiolate/$\text{Et}_3\text{NH}^+$ ion pair, the formation of isolated thiolate and $\text{Et}_3\text{NH}^+$ ions, and calculated nucleophilicity $N$ indicies$^{2,40}$ for each thiol anion.

**Table 2.5:** Calculated reaction and transition state free energies ($\Delta G^\circ$, $\Delta G^\ddagger)$ for hydrogen transfer between thiols 1-7 and $\text{Et}_3\text{N}$ in CHCl$_3$ as well as the calculated nucleophilicity $N$ index$^b$ for each thiol.

<table>
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<th>Thiol</th>
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<th>6</th>
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</table>

$^a$Free energies are reported in kcal/mol. $^b$Nucleophilicity $N$ indicies are given in eV, see reference 2.40 additional details.
Calculations show that thiol functionality can significantly impact the favorability of Et$_3$N-mediated thiol-maleimide reactions. The free energy of forming an ion pair between thiols 1-7 and Et$_3$N in CHCl$_3$ is predicted to span a range of over 11 kcal/mol, from $\Delta G^\circ = -2.0$ kcal/mol (thioacetic acid, 3) to $\Delta G^\circ = 9.3$ kcal/mol (cysteine methyl ester, 6). Thioacetic acid 3 is the only thiol for which the formation of an ion pair, i.e. 3$^-$/Et$_3$NH$^+$, is predicted to be exergonic. Relative energies of ion pair formation are also found to correlate relatively well with their S•••H hydrogen-bond distances (Figure 2.13): more stable ion pairs are observed to have longer S•••H hydrogen-bond distances and vice versa. Overall the favorability of forming an ion pair with Et$_3$N follows the following trend from lowest to highest relative free energy: thioacetic acid (3), thiophenol (7), methyl thioglycolate (4), β-mercaptoethanol (2), methyl mercaptan (1), methyl 3-mercaptopropionate (5), and cysteine methyl ester (6). The trend in the relative free energy of forming free ions upon deprotonation of thiols 1-7 by Et$_3$N in CHCl$_3$ is quite similar, with only the order of the last three thiols being switched.

The free energy of forming an ion pair between thiols 1-7 and Et$_3$N was found to correlate approximately with the S•••H hydrogen bond distance in each ion pair (Figure 2.13). Two notable outliers are methyl mercaptan (1) and cysteine methyl ester (6): the S•••H distance observed in the ion pair 1$^-$/Et$_3$NH$^+$ was found to be shorter than the trend (1.98 Å) while the S•••H distance in the ion pair 6$^-$/Et$_3$NH$^+$ was found to be longer than the trend (2.03 Å). The likely explanation for methyl mercaptan as an outlier is its size, as 1 represents the smallest thiol possible. Cysteine
methyl ester has a notably long S⋯H distance because the sulfur anion is able to hydrogen bond with the NH₂ moiety of ₆⁻ as shown in Figure 2.14. With the two outliers the correlation has an R² value of 0.816, if thiols ₁ and ₆ are excluded from the set the correlation increases to R² = 0.992.

![Figure 2.13: General correlation between the free energy of ion pair formation between thiols 1-7 and Et₃N and the S⋯H hydrogen bond distances in each ion pair.](image)

Recently Bowman and coworkers have taken advantage of differences in reactivity between two or more thiols and Michael acceptors to achieve selective thiol-Michael reactions in ternary²,¹⁶,¹⁷ and even quaternary²,¹⁸,¹⁹ mixtures. One study in particular¹⁹ evaluated the relative reactivities of ₄, ₅, ₇, and 1-hexanethiol (a longer chain analogue of ₁) by setting up competition reactions between pairs of thiols and methyl acrylate in CDCl₃ using 10 mol% Et₃N as a catalyst. These experiments revealed the following order of Et₃N-mediated thiol-Michael reactivity toward methyl acrylate: ⁷ > ⁴ > ⁵ > 1-hexanethiol (most rapid to least rapid). This
trend observed experimentally by Bowman agrees well with the trend in calculated free energies of ion pair formation (Table 2.5), supporting the theory that differences in thiol reactivity in thiol-Michael reactions are primarily related to the pKa of the thiol. The one discrepancy between experimental and computational results is found in the ordering of 5 and 1-hexanethiol (modeled computationally as methyl mercaptan 1). Experiments suggest 5 is more reactive than 1-hexanethiol in thiol-acrylate reactions while computations predict the formation of an ion pair between 1 and Et₃N is more favorable than between 5 and Et₃N. This discrepancy suggests that 1 may not be a perfect model for 1-hexanethiol. The discrepancy may also reveal differences in the reactivity of methyl acrylate relative to NMM. It is also noteworthy that the experimental and computational trends match exactly when comparing experimental selectivities to the calculated free energies of forming free thiolate ions.

![Figure 2.14: Global free energy minimized structure of the 6/Et₃NH⁺ ion pair with hydrogen bonding interactions between S•••H_ammonium and S•••H_amide indicated by dotted lines. Distances are given in Å.](image)
2.6.1. Nucleophilicity $N$ Indices

No correlation is observed between the experimental trend in thiol reactivity and calculated nucleophilicity $N$ indices. This is likely because all seven thiolate anions are considered strong nucleophiles given that each has an $N$ index between 4.7-5.4 (Table 2.6), where any organic molecule with an $N$ index greater than 3.0 is considered a strong nucleophile. Any of the strongly nucleophilic thiolate anions, once formed, will react readily and rapidly with the highly electrophilic NMM. The key to differences in thiol reactivity therefore appears to be the ease (or difficulty) of forming initial quantities of thiolate anions rather than the nucleophilicity of the thiolate itself. This observation again highlights the importance that the pKa of a thiol will play in the overall kinetics of thiol-maleimide reactions, though previous insights regarding the influences of solvent and initiator will also need to be taken into account (e.g. all thiols are predicted to react rapidly with NMM when DMF is the solvent or when DBU is the base, etc.).

The nucleophilicity of each thiolate anion was calculated using the formula:

$$N = E_{\text{HOMO(Na)}} \text{(eV)} - E_{\text{HOMO(TCE)}} \text{(eV)}$$

where tetracyanoethylene (TCE) was taken as a reference. Nucleophilicity $N$ indices calculated using equation (1) have shown good general agreement with the nucleophilicity scales developed by Mayr and coworkers based on experimentally measured rate constants of various nucleophiles.$^{244}$ To keep consistent with all other
computational results presented in the current work, \( E_{\text{HOMO}} \) values for each thiol and TCE were calculated at the M06-2X/6-311G(2D,P)//B3LYP/6-31+G(D) level.

**Table 2.6:** Calculated values of \( E_{\text{HOMO}} \) for TCE and thiolates of 1-7 used to calculate nucleophilicity \( N \) indices.

<table>
<thead>
<tr>
<th></th>
<th>TCE</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>( E_{\text{HOMO}} )</td>
<td>-0.38278</td>
<td>-0.18627</td>
<td>-0.19497</td>
<td>-0.21007</td>
<td>-0.19689</td>
<td>-0.19050</td>
<td>-0.19452</td>
<td>-0.18496</td>
</tr>
<tr>
<td>( N ) (eV)</td>
<td>–</td>
<td>5.35</td>
<td>5.11</td>
<td>4.70</td>
<td>5.06</td>
<td>5.23</td>
<td>5.12</td>
<td>5.38</td>
</tr>
</tbody>
</table>

\( E_{\text{HOMO}} \) values are given in Hartrees.

**2.7. Experimental Investigations of Ternary Thiol-Maleimide Reactions**

A primary aim of this manuscript, in addition to providing a deeper understanding of thiol-maleimide reactions, is to elucidate how different reaction conditions can be used to promote selectivity in thiol-Michael, and particularly thiol-maleimide, reactions. To date we are unaware of any examples of selective thiol-maleimide reactions involving ternary mixtures of a maleimide derivative with two different thiols.\(^2,41\) The high reactivity of maleimide toward a wide range of thiols can make the selective addition of one thiol in the presence of another particularly challenging. Insight from computational investigations of the influence of solvent, initiator, and thiol on thiol-maleimide reactions can aid significantly in developing and understanding selective thiol-maleimide reactions in ternary mixtures. The results of ternary reactions run under different reaction conditions also provide a means of experimentally evaluating computational results discussed in this manuscript.
Thiophenol (7) and 1-hexanethiol (HT, a model for methyl mercaptan 1) were chosen for model ternary reactions with NMM. The two thiols were mixed in equimolar ratios with NMM in either CDCl₃ or DMF in the presence or absence of different initiators (Chart 2.1). Each mixture was stirred at ambient temperature until complete consumption of NMM was observed by ¹H NMR spectroscopy. Percent yields of thiophenol addition product A and 1-hexanethiol addition product B were calculated by ¹H NMR spectroscopy and are provided in Chart 2.1.

When NMM, 7, and HT are mixed in CHCl₃ in the presence of 0.1 equiv Et₃N the thiophenol addition product A is produced in 94% yield along with 6% of HT addition product B (Entry 1). Computational and kinetic modeling have shown that methyl mercaptan 1 must initially follow an ion pair mechanism with an overall barrier of ΔG‡ = 27.0 kcal/mol in order to form thiolate 1⁻ because the direct deprotonation by Et₃N in CHCl₃ requires ΔG° = 33.4 kcal/mol. Deprotonation of the more acidic thiophenol 7 by Et₃N in CHCl₃, by contrast, requires only ΔG° = 24.2 kcal/mol, with an ion pair mechanism involving 7 and Et₃N likely to have an even lower free energy barrier. Experimental results are therefore in line with the conclusion that thiols react in order of their acidity. The use of a stronger base in the same solvent should increase the relative favorability of deprotonating HT, leading to an increase in the formation of product B. Indeed, when 0.1 equiv of DBU is used as the base the percent of product B formed increases almost four-fold from 6% to 23% (Entry 2). Computational results suggest the use of DBU drops the overall free energy barrier required to form thiolate 1⁻ considerably (ΔG‡ = 18.9 kcal/mol, Table 2.4) and
similarly increases the favorability of directly deprotonating the alkane thiol ($\Delta G^\circ = 22.4$, Table 2.3). Therefore a greater quantity of hexanethiolate is present when DBU is used rather than the same quantity of Et$_3$N, which enables the formation of product B to be more competitive with the formation of product A. This effect can be mitigated, however, by reducing the equivalents of DBU as shown in Entry 3. When 0.01 equiv of DBU is used to initiate the reaction a small but reproducible increase in selectivity is observed, with the yield of product A increasing to 83%.\textsuperscript{2.42}

**Chart 2.1:** Ternary reactions\textsuperscript{a} between NMM, 7, and HT given different ratios\textsuperscript{b} of thiol-maleimide addition products depending on the choice of solvent and initiator.\textsuperscript{c}

![Chart 2.1](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Initiator</th>
<th>Product A (%)</th>
<th>Product B (%)</th>
<th>A/B</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CDCl$_3$</td>
<td>0.1 Et$_3$N</td>
<td>94</td>
<td>6</td>
<td>16</td>
</tr>
<tr>
<td>2</td>
<td>CDCl$_3$</td>
<td>0.1 DBU</td>
<td>77</td>
<td>23</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>CDCl$_3$</td>
<td>0.01 DBU</td>
<td>83</td>
<td>17</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>CDCl$_3$</td>
<td>0.01 DMPP</td>
<td>96</td>
<td>4</td>
<td>24</td>
</tr>
<tr>
<td>5</td>
<td>DMF</td>
<td>none</td>
<td>97</td>
<td>3</td>
<td>32</td>
</tr>
<tr>
<td>6</td>
<td>DMF</td>
<td>0.1 Et$_3$N</td>
<td>85</td>
<td>15</td>
<td>6</td>
</tr>
<tr>
<td>7</td>
<td>DMF</td>
<td>0.1 DBU</td>
<td>36</td>
<td>64</td>
<td>0.6</td>
</tr>
</tbody>
</table>

\textsuperscript{a}All reactions were run at room temperature with equimolar amounts of NMM, 7, and HT. \textsuperscript{b}Product ratios determined by $^1$H NMR spectroscopy. \textsuperscript{c}Full experimental details can be found in section 2.4 Experimental and Computational Methods.

Switching to a non-basic initiator, DMPP (Entry 4), results in an increase of selectivity above that of Et$_3$N: 96% A and 4% B. This result is further supportive of the conclusion that the difference in selectivity between Et$_3$N and DBU in CHCl$_3$ is a
result of the higher pKa of DBU. The trace amounts of product B formed when DMPP is used as the initiator must result from deprotonation of HT by the zwitterionic enolate formed upon nucleophilic addition of DMPP to NMM. This enolate intermediate is more basic (pKa ≈ 25) than Et₃N and DBU and can readily deprotonate both thiols 7 and HT. The observation that product A is dominant when DMPP is used as the initiator further corroborates the conclusion that the concentration of strong base (in this case enolate) influences selectivity in ternary reactions involving two different thiols. Decreasing the concentration of strong base, whether DBU as in Entries 2 and 3 or enolate (via DMPP in Entry 4), will result in greater observed selectivity.

Lastly, the role of solvent was investigated. Mixing NMM, 7, and HT in DMF in the absence of an initiator resulted in higher selectivity than any of the results in CHCl₃: 97% A and 3% B (Entry 5). This result is an interesting case where the solvent itself is able to act as a selective initiator for ternary thiol-maleimide reactions. Selectivity is explained by the difference in the ability of DMF to deprotonate 1 versus its ability to deprotonate 7. As seen in Table 2.1, proton transfer from 1 to DMF to give free thiolate 1⁻ requires ΔG° = 19.4 kcal/mol. Kinetic modeling predicts that DMF can catalyze the addition of 1 to NMM in the absence of an initiator, however the reaction is relatively slow (3 minutes to reach 50% conversion, Figure 2.9). Proton transfer from 7 to DMF is calculated to be notably more favorable, requiring only ΔG° = 10.6 kcal/mol to form free thiolate 7⁻. Kinetic analysis of the DMF-catalyzed addition of 7 to NMM is predicted to be rapid (90%
conversion within 100 seconds), results that agree well with the experimental observations of DMF-catalyzed thiol-maleimide reactions by Du Prez\textsuperscript{2,20} noted earlier. The difference in thiol pKa is again found to be the primary factor determining selectivity.

Adding 10 mol% Et\textsubscript{3}N to the DMF mixture of NMM, 7, and HT results in a reduction of selectivity, giving 85% product A and 15% product B (Entry 6). The free energy required for Et\textsubscript{3}N to deprotonate 1 in DMF is predicted to be $\Delta G^\circ = 13.1$ kcal/mol (Table 2.1), which is 6.3 kcal/mol lower than the free energy necessary for DMF itself to deprotonate 1. Again, the greater ease of forming hexanethiolate makes formation of product B more competitive with product A, though product A is still favored under these conditions. To further investigate the influence of initiator pKa in polar solvents, 0.1 equiv of DBU was used to initiate the ternary reaction in DMF. With DBU present as the initiator (Entry 7) a reversal of selectivity is observed, with 36% formation of product A and 64% formation of product B. The combined influences of high solvent polarity and 10% of a strong base result in facile formation of significant quantities of both thiophenolate and hexanethiolate. With significant quantities of both thiolates present the observed yields of products A and B no longer reflect differences in thiol pKa. The observation that products A and B are formed in nearly equal amounts in DMF with 10% DBU implies that the thermodynamic and kinetic differences giving rise to the product yields in Entry 6 are subtle and may be outside the scope and error limits of the computational methods used herein. These results highlight the importance of understanding and optimizing reaction conditions.

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when selective thiol addition is desired. Simply choosing a polar solvent and strong base with the intention of increasing reaction kinetics can, as demonstrated in Chart 2.1, significantly disfavor selectivity.

The experimental results summarized in Chart 2.1 corroborate many of the computational and kinetic results discussed throughout this study. Furthermore, they highlight several of the means by which the selective addition of one thiol to maleimide can be achieved in the presence of another thiol. Of primary importance is a sufficient difference in the pKa of the two thiols. Second, weakly basic or strictly nucleophilic initiators promote greater selectivity. If a strong base is necessary then it should be used at very low catalyst loading to promote greater selectivity. Lastly, nonpolar solvents can help accentuate differences in thiol pKa, promoting greater selectivity. If a highly polar solvent capable of catalyzing the thiol-maleimide reaction itself is necessary (e.g. DMF, H$_2$O, or DMSO) then greater selectivity can be expected in the absence of any catalyst.

2.8. Conclusions

The energetics and mechanism of base- and nucleophile-initiated thiol additions to maleimide has been fully explored using computational methods. While the catalytic cycle of thiolate addition to maleimide is straightforward, the mechanism leading to initial formation of catalytic thiolate can follow a combination of several potential mechanistic pathways: direct deprotonation of the thiol by an initiator, attack of the maleimide $\pi$-bond by a thiol-initiator ion pair, and/or nucleophilic attack of
maleimide by the initiator. Which mechanism(s) is dominant depends on the specific combination of solvent, initiator, and thiol. Understanding how each of these reaction parameters influences the mechanism and, therefore, kinetics of thiol-maleimide addition enables the design and tuning of selective thiol-maleimide reactions. The results are important for understanding and developing optimal means of using thiol-maleimide additions in the synthesis of organic materials and macromolecules, and can also enable the design of selective thiol-maleimide reactions. Conclusions from this study are expected to have broader implications in thiol-Michael in general. Investigations of the influence of different Michael acceptors in thiol-Michael reactions are currently underway.

2.9. Experimental and Computational Details

**Computational Details**

All calculations were performed within the Gaussian09 suite of programs. Initial conformational searches of all species were performed by scanning all freely rotating dihedral angles at the HF/6-31G(D) level of theory to locate their approximate global energy minimum structures prior to full geometry optimization. Approximate locations of transition states were determined by performing relaxed potential energy surface scans (B3LYP/6-31G(D)) along the internal coordinates corresponding to bond breaking and/or bond formation. Potential transition state structures were then refined by performing a Berney optimization at a higher level of theory (discussed below). Transition states were confirmed by IRC calculations and were distinguished
as having a single imaginary vibrational frequency. All potential energy surface scans, geometry optimizations, and single-point calculations were performed at 298.15 K, 1.0 atm pressure, and in a PCM solvent model\textsuperscript{24} for chloroform, ethyl mercaptan, or N,N-dimethylformamide.

Theoretical investigations of methane thiolate additions to N-allyl and N-propargyl maleimide have been carried out previously\textsuperscript{2,25} using the compound CBS-QB3 method developed by Petersson and co workers\textsuperscript{2,26} and results were found to agree well with experimental observations. Similarly, computational investigations of radical-initiated thiol-ene reactions have been carried out\textsuperscript{2,14} at the CBS-QB3 level and were found to predict reaction enthalpies within ±0.5 kcal/mol mean absolute deviation (MAD) of experimental data. The number of heavy atoms present in large initiators (e.g. DBU, PMe\textsubscript{2}Ph) and thiols (e.g. thiophenol) investigated in the current study render these systems unsuitable for study at the CBS-QB3 level. Recent computational investigations by Houk\textsuperscript{2,27} and Qi\textsuperscript{2,28} have found that a combination of geometry optimizations at the B3LYP/6-31+G(D) level\textsuperscript{2,22} followed by single-point energy calculations using Truhlar’s MO6-2X functional\textsuperscript{2,21} with a large basis set provide thiol-Michael reaction energetics that are in good agreement with CBS-QB3 benchmarks. All reaction and transition state enthalpies and free energies reported herein were obtained at the MO6-2X/6-311G(2D,P)//B3LYP/6-31+G(D) level of theory.
Materials and Instrumentation

Chemicals were purchased from Aldrich, Acros, TCI America, or Cambridge Isotope Labs and used as received. All $^1$H NMR spectra were recorded with a Varian Mercury (300 MHz) or Varian Unity Plus (400 MHz) spectrometer using residual solvent as the internal standard. All chemical shifts are quoted using the $\delta$ scale and all coupling constants are expressed in Hertz (Hz).

General procedure for ternary thiol-maleimide reactions in CDCl$_3$

Ternary reactions between thiophenol (7), 1-hexanethiol (HT), and N-methyl maleimide (NMM) were carried out in CDCl$_3$ in the presence of three different initiators: Et$_3$N, DBU, or DMPP. In each case 7 (30 mg, 0.27 mmol), HT (32 mg, 0.27 mmol), and NMM (30 mg, 0.27 mmol) were added to a 2-dram vial. To each vial was added 0.2 mL of a stock solution of Et$_3$N (0.135 M), DBU (0.135 M or 0.0135 M), or DMPP (0.0135 M) in CDCl$_3$ to initiate the reaction. Each mixture was stirred at ambient temperature for a minimum of 30 minutes and then diluted with additional CDCl$_3$ and used directly for $^1$H NMR spectroscopic analysis to determine the percent formation of thiophenol addition product versus 1-hexanethiol addition product. Spectra of ternary reactions were compared to $^1$H NMR spectra of pure thiophenol addition product and 1-hexanethiol addition product. The chiral methine signals and the N-methyl signals of the two different addition products were well isolated and therefore used to calculate the relative percentages of the two addition products.
General procedure for ternary thiol-maleimide reactions in DMF

Ternary reactions of 7, HT, and NMM were similarly run in anhydrous DMF under three different scenarios: initiator free, 0.1 equiv Et₃N, and 0.1 equiv DBU. Stock solutions of Et₃N (0.135 M) and DBU (0.135 M) in anhydrous DMF were prepared so that both the initiator and DMF would be introduced at the same time to avoid preemptive DMF-catalyzed initiation of thiol-maleimide reactions prior to addition of the initiator. Equimolar quantities of 1-hexanethiol, thiophenol, and N-methyl maleimide were added to a 2-dram vial followed by the addition of DMF either with or without an initiator as described. The ternary reactions were stirred at ambient temperature for at least 30 minutes to ensure complete reactions. Mixtures were then concentrated under reduced pressure and the resulting residue was placed under high vacuum for 30 minutes. The reaction mixtures were diluted with CDCl₃ and used for ¹H NMR spectroscopic analysis to determine the percent formation of thiophenol addition product versus 1-hexanethiol addition product.

Nucleophilic addition of amine bases to NMM in CDCl₃

To a 0.1 M CDCl₃ solution of N-methyl maleimide (50 mg, 0.45 mmol) was added either hexylamine (46 mg, 0.45 mmol), diethylamine (33 mg, 0.45 mmol) or triethylamine (46 mg, 0.45 mmol) and the reaction mixtures were stirred overnight at ambient temperature. Separately, to a 0.1 CDCl₃ solution of N-methyl maleimide (50 mg, 0.45 mmol) was added triethylamine (46 mg, 0.45 mmol) and tert-butanol (33 mg, 0.45 mmol) and the reaction mixture stirred overnight at ambient temperature.
Each reaction mixture was then diluted with CDCl₃ and used for ¹H NMR spectroscopic analysis to determine the extent of nucleophilic addition of each amine to NMM.

**Calculated Rate Constants**

Rate constants were calculated at 298.15 K using the transition state free energies ($\Delta G^\ddagger$) for every elementary step of each reaction mechanism according to conventional activated complex theory: $k(T) = (k_B T/h)e^{(-\Delta G^\ddagger/RT)}$. Two general classes of reactions were considered to be barrierless: (i) the association of free thiolate and a protonated base to give an ion pair, and (ii) the association of a protonated base and thiol-maleimide addition product (Scheme 2.5).

**Scheme 2.5:** Generic examples of the two classes of reactions that were considered to be barrierless in all kinetic models.

(i) 

\[
\begin{align*}
\text{R-S} \cdots \text{H-Initiator} & \quad \text{Ion Pair} \quad \text{Barrier} \propto \Delta G^\circ \quad \text{Barri} \\
\text{R-S}^- & + \text{H-Initiator} \quad \text{Free Ions}
\end{align*}
\]

(ii) 

\[
\begin{align*}
\text{R-S} & \quad \text{Barri} \\
\text{R-S}^- + \text{H-Initiator} & \quad \text{Barri} \\
\text{R-S}^- & + \text{H-Initiator}
\end{align*}
\]

The rate constant for the above barrierless processes was taken to be $k = 6.21 \times 10^{12}$ M⁻¹ s⁻¹ (i.e. $k_B T/h$). All other calculated rate constants are summarized in the Tables below.
Table 2.7: Calculated rate constants for all forward and reverse elementary steps of every mechanism discussed in the main text.

<table>
<thead>
<tr>
<th>Process</th>
<th>Solvent</th>
<th>Initiator</th>
<th>Thiol</th>
<th>$k_{\text{forward}}$</th>
<th>$k_{\text{reverse}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formation of a thiolate/initiator ion pair (e.g. $1^-\cdots\text{Et}_3\text{NH}^+$)</td>
<td>CHCl₃</td>
<td>Et₃N</td>
<td>1</td>
<td>4.32x10⁶</td>
<td>1.87x10¹²</td>
</tr>
<tr>
<td></td>
<td>CHCl₃</td>
<td>Et₃N</td>
<td>2</td>
<td>4.83x10⁷</td>
<td>4.05x10¹²</td>
</tr>
<tr>
<td></td>
<td>CHCl₃</td>
<td>Et₃N</td>
<td>3</td>
<td>2.90x10¹⁰</td>
<td>9.33x10⁸</td>
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<td>Et₃N</td>
<td>4</td>
<td>7.89x10⁷</td>
<td>2.00x10¹¹</td>
</tr>
<tr>
<td></td>
<td>CHCl₃</td>
<td>Et₃N</td>
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<td>1.55x10⁵</td>
<td>4.52x10¹¹</td>
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<tr>
<td></td>
<td>CHCl₃</td>
<td>Et₃N</td>
<td>6</td>
<td>1.96x10⁵</td>
<td>1.19x10¹²</td>
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<tr>
<td></td>
<td>CHCl₃</td>
<td>Et₃N</td>
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<td>EtNH₂</td>
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</tr>
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<td>DMF</td>
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<td>DMF</td>
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<td>1</td>
<td>1.57x10³</td>
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2.8. The growing applications of click chemistry in macromolecular and materials synthesis has lead to a recommendation that the criteria for classifying reactions as “click” in such applications be updated to better reflect the challenges specific to materials synthesis, see: Barker-Kowollik, C.; Du Prez, F. E.; Espeel, P.; Hawker, C. J.; Junkers, T.; Schlaad, H.; Van Camp, W. Angew. Chem., Int. Ed. 2011, 50, 60-62.


2.29. Three unique propagation transition states for the attack of the NMM π-bond by a 1/*Et3NH* ion pair were found, with TS13 being the most energetically favorable. The next most energetically favorable propagation transition state found has a relative free energy of ΔG‡ = 26.1 kcal/mol.

2.31. A combination of explicit and implicit solvation was used to calculate the free energy of proton transfer from 1 to DMF, see Figure 2.6-2.7 for structures and a complete explanation of the modeling details.

2.32. In the case of DMF, the solid and dashed lines also include the pathway wherein DMF itself deprotonates 1 to give free thiolate 1-. The concentration of DMF used in the kinetic model was taken to be 12.9 M, corresponding to the concentration of pure DMF at room temperature.


2.34. See Figure 2.12 for a plot of alkene conversion versus time for the four nitrogen-centered bases as modeled in DMF.

2.35. All attempts to locate the propagation transition state for addition of a 1-/DMPPH+ ion pair to NMM optimized to give starting materials 1, DMPP, and NMM. It was therefore concluded that DMPP is not able to act as a base along an ion pair reaction pathway such as the one shown in Figure 2.3.


2.39. Yields of nucleophilic Michael-addition products were calculated from relative integration ratios of 1H NMR spectroscopic signals corresponding to starting materials (NMM and amines) and the product.


2.41. Thiol-Michael selectivity within ternary mixtures of N-propyl maleimide, thiol 5, and an additional Michael acceptor (phenyl vinyl sulfonate, methyl acrylate, or methyl methacrylate) have been carried out and thiol addition to N-propyl maleimide is preferred, see reference 1.19.

2.42. Increasing the equivalents of DBU decreases the selectivity in the ternary mixture; however high loading (e.g. 0.5 equiv) of DBU also promotes side reactions such as the Michael addition of DBU to NMM.

Chapter 3

Investigation and Demonstration of Catalyst/Initiator Driven Selectivity in Thiol-Michael Reactions
This Chapter is based on the following work:


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Thiol-Michael ‘click’ reactions are essential synthetic tools in the preparation of various materials including polymers, dendrimers, and other macromolecules. In spite of 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 the 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 (TEA, DBU, and DMPP) 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 selectivity 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.
3.1. Introduction

While known for over a century, the thiol-Michael addition reaction\(^3\) — generally classified as a “click” reaction\(^3,2\) between a thiol and an \(\alpha,\beta\)-unsaturated carbonyl-containing compound — has recently generated high levels of interest and implementation across many areas of materials chemistry.\(^3,3\) 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,\(^3,4\) dendrimers and hyperbranched polymers,\(^3,5\) copolymers\(^3,6\) and crosslinked networks,\(^3,7\) and hydrogels.\(^3,8\) Thiol-Michael reactions have also proven very useful for the post-synthetic modification of polymers through side chain\(^3,9\) and end group functionalization,\(^3,10\) with particular utility in the functionalization of reversible addition-fragmentation chain transfer (RAFT) polymers.\(^3,10b-e\) 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 their 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.
3.1.1. Preparation of Advanced Materials

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 that are initiated by a nucleophile. Bowman and coworkers 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. 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 coworkers, for example, have made use of thiol additions to divinylsulfones to prepare a range of high refractive index materials. Thiol-acrylate reactions have also been used to prepare a variety of biodegradable polymers and dendrimers with potential use as drug carriers and in the controlled release of therapeutics. Hubbell and coworkers 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. Bowman and coworkers 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. Bowman has also shown that photoinitiated thiol-Michael reactions can be applied to lithographic photopatterning. 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 field of thiol-Michael “click” reactions only appears to be expanding its reach and impact.

### 3.1.2. Selective, Orthogonal Thiol-Michael Reactions

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. 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. While 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 3.1) or two Michael acceptors with one thiol is far from 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 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.

**Scheme 3.1:** General representation of unselective versus selective thiol–Michael reactions originating from a ternary mixture of two thiols and one Michael acceptor (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).

Previous investigations of the selectivity of alkenes for different thiols are summarized in Table 3.1a, while the selectivities of thiols for different alkenes are summarized in Table 3.1b. As noted earlier, Bowman and coworkers have pioneered many of the early studies of selectivity within ternary thiol-Michael reactions under both base-catalyzed and nucleophile-initiated conditions. 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. The high selectivity for the vinyl sulfone over the acrylate
was used to control the gelation behavior of a crosslinked polymer network comprised of a tetrafunctional thiol, bifunctional alkene, and a monofunctional acrylate. In a subsequent work, Bowman and coworkers 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.³⁵e³ 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 3.1, entry 1), while 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 7-8).³¹¹e 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%.
Table 3.1: Summary of previous investigations\textsuperscript{3.5c,3.11d-e} of selectivity within ternary mixtures of one Michael acceptor and two thiol components. TEA = triethylamine, DBU = 1,8-diazabicyclo(5.4.0)undec-7-ene.
Table 3.2: Summary of previous investigations$^{3.5e,3.12c}$ of selectivity within ternary mixtures composed of one thiol and two different Michael acceptors. MDPP = methyldiphenylphosphine.

For reactions involving two Michael acceptors, the selective addition of 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 3.2, entries 2-5). High selectivity is even observed for the addition of 3-mercaptopropionate to methyl acrylate in the presence of methyl methacrylate (entry 6). Taken together, the selectivities demonstrated in
Tables 3.1 and 3.2 were used to design A*A₂ and B*B₂ monomers for the efficient, sequential, and selective syntheses of dendrimers.³,⁵e The A*A₂ monomer contained a highly reactive vinyl sulfonate focal point (A) and two less reactive methacrylate branches (A₂), while the B*B₂ monomer contained a more reactive thiolglycolate focal point (B) and two less reactive alkanethiol branches (B₂). The A*A₂ and B*B₂ monomers were used to grow a fifth generation dendrimer rapidly and efficiently, requiring less than 12 hours time. Bowman’s research on controlling the gelation of crosslinked polymer networks³,⁷d and streamlining dendrimer growth³,⁵e 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 3.1. 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.

![Chemical structures of (a) alkenes 1-6, (b) thiols 7-11, and (c) catalysts/initiators used in the current study.](image)

**Figure 3.1:** Chemical structures of (a) alkenes 1-6, (b) thiols 7-11, and (c) catalysts/initiators used in the current study.

### 3.2. 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 3.1). 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. To fully explore 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 CDCl₃ 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 one hour as determined by the disappearance of vinylic signals by ¹H NMR spectroscopy. Thiol-isocyanate reactions involving n-butyl isocyanate (3) were also complete within one hour, 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 3.2. The remaining selectivity tables are provided in 2.4 (Figures 3.8-3.15). The selectivity table shown in Figure 3.2a represents ternary mixtures of N-methyl maleimide (1) and two different thiols (7-11) as catalyzed by TEA. The table in Figure 3.2b 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. To further aid visualization the percentages are color-coded as shown in the Figure inset.

**Figure 3.2:** 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.

Comparing the results summarized in Figures 3.2a and 3.2b 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 3.8). 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 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 selectivity for all thiols as compared to 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 methacrylate 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-mercaptpropiolate (8) in roughly that order, while hexanethiol (11) was the least reactive in nearly all cases.

It’s important to reiterate that all ternary results discussed above refer to reactions carried out in chloroform. The selectivity tables shown in Figure 3.2 and Figure 3.8-3.15 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. 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. 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 pKa’s 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 while all the results presented herein are for the thiol-Michael addition reaction in chloroform, the selectivity of the thiol-Michael addition was also examined in tetrahydrofuran. In general, and as expected, the selectivity decreased in tetrahydrofuran, likely due to the higher dielectric constant enabling alternative reaction pathways that are less accessible in chloroform.
3.3. 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 3.3, 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 3.3a 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 3.3b) 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 ppm to 2.92 ppm. Acrylate signals are unchanged in Figure 3.3b 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 3.3c). 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 ppm, 6.18 ppm, and 5.87 ppm concomitant with the appearance of product peaks at 2.92 ppm and 2.68 ppm.
Figure 3.2: $^1$H NMR spectra showing (a) the ternary mixture of isocyanate (3), methyl acrylate (4), and hexanethiol (11) prior to 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 ppm, 3.68 ppm, and 3.28 ppm.

3.3.1. *Ex Situ* Tuning of Reactivity

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 Figures 3.4a and 3.4b. In Figure 3.4a, $N$-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. 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 3.3 and the sequence shown in Figure 3.4a. In Figure 3.3, TEA is sufficiently basic to catalyze the addition of the 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 3.4a). The nucleophilic initiator DMPP is known to afford quantitative conversion of acrylates with various thiols in less than an hour. 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 3.4b to carry out an alternative two-step quaternary thiol-Michael reaction sequence, however, the order of thiol addition is reversed. Hexanethiol (11) reacts 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 highlight again 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 3.4b, or between a sufficiently reactive thiol (7) and a less reactive Michael acceptor (4) as shown in Figure 3.4a.

**Figure 3.3:** $^1$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.

### 3.3.2. Importance of Initiator

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 3.4. 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 3.4a 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, while maleimide is fully consumed its thiol-Michael product with thioglycolate (7) is not cleanly observed as noted by the disappearance of $\alpha$ and $\beta$ methine and methylene protons of thiol-maleimide product (Figure 3.5). 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 3.2. McCormick has recently shown$^{3,16}$ 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.
Figure 3.5: $^1$H NMR spectrum obtained upon addition of 10 mol% DBU to a ternary mixture of $N$-methyl maleimide (1), methyl acrylate (4), and methyl thioglycolate (7). The disappearance of the methine doublet of doublets (4.08 ppm) and methylene doublet of doublets (3.20 and 2.57 ppm) of the initially formed 1-7 product suggests that the thiol-maleimide product is deprotonated by DBU, which is consistent with observations of McCormick et al.3.16 The resulting enolate intermediate is hypothesized to react with acrylate present in the mixture as shown in Scheme 3.2.

Scheme 3.2: 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.

3.4. 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 3.7 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 thioglycolate-acrylate adduct and the 6-11 hexaenethiol-crotonate adduct in a nearly 50:50 ratio. Overlap of several spectroscopic signals in the $^1$H NMR spectrum of the products prevented the direct spectroscopic assessment of selectivity by $^1$H NMR as in the sequential quaternary reactions. In order to evaluate and quantify the relative amounts of the four potential thiol-Michael products the reaction mixture was purified by silica gel chromatography 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 the total isolated mass respectively.\textsuperscript{3,17} 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 3.7 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 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.

**Figure 3.6:** 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.\(^{3,17}\)

### 3.5. 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 3.7). 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 3.7a) along with the appearance of two sets of doublet of doublets (4.06 ppm...
and 3.17 ppm) indicative of thiol-maleimide product formation. Following the formation of the 1-7 adduct, hexanethiol 11 and DMPP were 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. Figures 3.6b-c 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 3.7d) 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 ppm, 6.15 ppm, and 5.85 ppm and the 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.
Figure 3.7: $^1$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.

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 Figures 3.8-3.15. 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.

3.6. Conclusions

The results presented herein provide a deeper understanding of the selectivities 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, while 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 3.8-3.15) 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 given 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.

3.7. Experimental Methods

General Information

Unless otherwise stated chemicals were purchased from commercial suppliers and used as received. Thiol-Michael products except thiol-maleimide adducts 1-7 and 1-
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 $\delta$ scale and all coupling constants are expressed in Hertz (Hz).

**Compound 1-7:** An equimolar mixture of N-methyl maleimide (50 mg, 0.45 mmol) and methyl thioglycolate (47.8 mg, 0.04 mL, 0.045 mmol) were 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 minutes. 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]$^+$ Calculated for C$_8$H$_{12}$NO$_4$S, 218.0487, found 218.0482. $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 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), 3.43 (d, 1H, $J = 15.8$ Hz), 3.20 (dd, 1H, $J = 19.0, 9.0$ Hz), 3.04 (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$_3$): $\delta$ 176.3, 174.4, 170.0, 52.6, 38.4, 35.4, 32.8, 25.1 ppm.
**Compound 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) were 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 minutes. After 30 minutes 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]$^+$ Calculated for C$_{11}$H$_{20}$NO$_2$S, 230.1215, found 230.1224. The product was isolated as a light yellow oil. $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 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): $\delta$ 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 either 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 allowed to stir at ambient temperature for one hour. The ternary reaction mixtures were evaporated to dryness overnight before further drying under high vacuum for one minute. The ternary reaction mixtures were then diluted with CDCl$_3$ and analyzed by $^1$H NMR.
spectroscopy. Relative ratios of thiol-Michael products were determined by integrating signals that are distinctive of 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 3.8-3.15). 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. The 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 TEA and DBU, and 0.1 equiv DMPP) were used to ensure complete consumption of the desired Michael acceptor before addition of any subsequent thiols. Upon completion of the first selective thiol-Michael reaction (as judged by $^1$H 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 CDCl₃ 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 $^1$H NMR spectroscopy. Upon completion the mixture was concentrated under reduced pressure and dried under high vacuum.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Mass</th>
<th>Absolute Yield</th>
<th>Normalized Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-Hexanethiol</td>
<td>3.0 mg</td>
<td>0.2%</td>
<td>0.3%</td>
</tr>
<tr>
<td>6-11</td>
<td>488.0 mg</td>
<td>34.8%</td>
<td>44.1%</td>
</tr>
<tr>
<td>6-7</td>
<td>78.0 mg</td>
<td>5.6%</td>
<td>7.0%</td>
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<tr>
<td>4-7</td>
<td>537.0 mg</td>
<td>38.2%</td>
<td>48.6%</td>
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The same one-pot quaternary reaction was run a second time at the same scale to investigate its reproducibility:

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<thead>
<tr>
<th>Compound</th>
<th>Mass</th>
<th>Absolute Yield</th>
<th>Normalized Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-Hexanethiol</td>
<td>53.0 mg</td>
<td>3.8%</td>
<td>4.8%</td>
</tr>
<tr>
<td>6-11</td>
<td>529.0 mg</td>
<td>37.7%</td>
<td>47.7%</td>
</tr>
<tr>
<td>6-7</td>
<td>23.0 mg</td>
<td>1.6%</td>
<td>2.1%</td>
</tr>
<tr>
<td>4-7</td>
<td>503.0 mg</td>
<td>35.8%</td>
<td>45.4%</td>
</tr>
</tbody>
</table>

**Average yield over two runs:** 1-Hexanethiol (2.6%), 6-11 (46%), 6-7 (4.6%), 4-7 (47%).

**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 $^1$H 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.

3.8. Complete Selectivity Charts

Ternary thiol-Michael reactions were carried out as described in the main text. Relative integrations of $^1$H NMR spectroscopic signals corresponding to both potential thiol-Michael products were used to quantify the relative amounts of each product and determine the selectivity for one thiol-Michael product over the other. Complete results are summarized in the charts below and follow the same format as the representative example discussed in Figure 3.2 of the main text. An entry of “I,” meaning inconclusive, is used for ternary reactions that were clearly unselective as indicated by multiple product signals however overlap of diagnostic signals complicated or prevented quantitative evaluation. An entry of “X” indicates little to no thiol-Michael reactivity within one hour. Such reactions were therefore considered unsuitable for the goals of this investigation.
**Figure 3.8:** Selectivity charts for ternary thiol-Michael reactions involving $N$-methyl maleimide (I) and pairs of thiols 7-11 as catalyzed by TEA (A), DBU (B), or initiated by DMPP (C). Entries report the ratio of the product obtained from $N$-methyl maleimide reacting with thiol A versus reacting with thiol B, expressed as a percentage and color coded as indicated below the charts.
Figure 3.9: Selectivity charts for ternary thiol-Michael reactions involving ethyl vinyl sulfone (2) and pairs of thiols 7-11 as catalyzed by TEA (A), DBU (B), or initiated by DMPP (C). Entries report the ratio of the product obtained from ethyl vinyl sulfone reacting with thiol A versus reacting with thiol B, expressed as a percentage and color coded as indicated below the charts.
**Figure 3.10:** Selectivity charts for ternary thiol-Michael reactions involving $n$-butyl isocyanate (3) and pairs of thiols 7-11 as catalyzed by TEA (A), DBU (B), or initiated by DMPP (C). Entries report the ratio of the product obtained from $n$-butyl isocyanate reacting with thiol A versus reacting with thiol B, expressed as a percentage and color coded as indicated below the charts.
Figure 3.11: Selectivity charts for ternary thiol-Michael reactions involving methyl acrylate (4) and pairs of thiols 7-11 as catalyzed by TEA (A), DBU (B), or initiated by DMPP (C). Entries report the ratio of the product obtained from methyl acrylate reacting with thiol A versus reacting with thiol B, expressed as a percentage and color coded as indicated below the charts.
**Figure 3.12**: Selectivity charts for ternary thiol-Michael reactions involving methyl methacrylate (5) and pairs of thiols 7-11 as catalyzed by TEA (A), DBU (B), or initiated by DMPP (C). Entries report the ratio of the product obtained from methyl methacrylate reacting with thiol A versus reacting with thiol B, expressed as a percentage and color coded as indicated below the charts. Instances where product percentages do not total 100% indicate some unreacted starting materials existed after one hour.
Figure 3.13: Selectivity charts for ternary thiol-Michael reactions involving ethyl crotonate (6) and pairs of thiols 7-11 as catalyzed by TEA (A), DBU (B), or initiated by DMPP (C). Entries report the ratio of the product obtained from ethyl crotonate reacting with thiol A versus reacting with thiol B, expressed as a percentage and color coded as indicated below the charts. Instances where product percentages do not total 100% indicate some unreacted starting materials existed after one hour.
Figure 3.14: Selectivity charts for ternary thiol-Michael reactions involving methyl thioglycolate (7) and pairs of electron-withdrawn alkenes 1-6 as catalyzed by TEA (A), DBU (B), or initiated by DMPP (C). Entries report the ratio of the product obtained from methyl thioglycolate reacting with alkene A versus reacting with alkene B, expressed as a percentage and color coded as indicated below the charts.
Instances where product percentages do not total 100% indicate some unreacted starting materials existed after one hour.

**Figure 3.15**: Selectivity charts for ternary thiol-Michael reactions involving hexanethiol (11) and pairs of electron-withdrawn alkenes 1-6 as catalyzed by TEA
(A), DBU (B), or initiated by DMPP (C). Entries report the ratio of the product obtained from methyl thioglycolate reacting with alkene A versus reacting with alkene B, expressed as a percentage and color coded as indicated below the charts. Instances where product percentages do not total 100% indicate some unreacted starting materials existed after one hour.
3.9. Notes and References


3.13. The orthogonal reactivity of base/nucleophile promoted thiol-Michael and radical catalyzed thiol-ene click chemistries has also been demonstrated. See, for example: (a) Stolz, R. M.; Northrop, B. H. *J. Org. Chem.* **2013**, *78*, 8105-8116; (b) Peng, H.; Wang, C.; Xi, W.; Kowalski, B. A.; Gong, T.; Xie, X.;

3.14. It should be noted that the quote from Hoyle et al. refers to thiol-ene click chemistry in general, including the radical-catalyzed addition of thiols to a wider spectrum of alkenes including those that are electron poor as well as those that are electron rich. The work presented herein focuses more narrowly on thiol-Michael reactions.


3.17. Yields are averages of two runs, see section **2.3 Experimental Methods** “Quaternary Reactions” for full details.


Chapter 4

Evaluating Nucleophile Byproduct Formation During Phosphine- and Amine-Catalyzed Thiol-Methyl Acrylate Reactions
This Chapter is based on the following work:

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4.0. Abstract

The commonly accepted mechanism of nucleophile-catalyzed thiol-acrylate reaction requires the formation of undesired nucleophile byproducts. A systematic evaluation of the formation of such nucleophile byproducts has been carried out to gain an understanding of the relationships between byproduct formation and nucleophile structure, catalyst loading, solvent, and reaction type. Three common nucleophiles for thiol-Michael reactions were investigated: dimethylphenylphosphine (DMPP), diethylamine (DEA), and hexylamine (HA). The formation of phosphonium ester and aza-Michael byproducts upon initiating a representative thiol-acrylate reaction between 1-hexanethiol and methyl acrylate at a range of catalyst loading (0.01 equivs up to 10.0 equivs) and in different solvents (neat, DMSO, THF, and CHCl₃) was determined quantitatively by ¹H NMR spectroscopy. The influence of reaction type was investigated by expanding from small molecule reactions to the end group thiol-acrylate functionalization of PEG-diacylate polymers and through investigations of polymer-polymer coupling reactions. Results indicate that the propensity of forming nucleophile byproducts varies significantly with nucleophile type, solvent, and reaction type. Interestingly, for all but polymer-polymer ligation reactions, nucleophile byproduct formation is largely unobserved for nitrogen-centered nucleophiles DEA and HA, and essentially nonexistent for the phosphorous-centered nucleophile DMPP even in the presence of a large excess of DMPP initiator. A rationale for the differences in nucleophile byproduct formation for DMPP, DEA, and HA is proposed and supported by experimental and computational analysis. Results
have implications for the use of different nucleophile initiators for promoting thiol-
acrylate and other thiol-Michael reactions.

4.1. Introduction

4.1.1. Base versus Nucleophile Catalysis

The thiol-Michael reaction\(^ {4.1-4.3}\) involves the anti-Markovnikov addition of a thiol
across the vinyl group of an electron-withdrawn alkene. Thiol-Michael reactions
represent a subset of thiol-ene reactions,\(^ {4.4}\) which generally exhibit the characteristics
of “click” chemistry\(^ {4.5-4.6}\) such as high to quantitative yields, rapid kinetics, high
selectivity, facile purification, and broad functional group tolerance. Over the past
fifteen years, thiol-Michael reactions have found particular utility in macromolecular
synthesis and functionalization. While thiol-Michael reactions can be carried out
using radical initiators they are more commonly promoted in the presence of
substoichiometric base or nucleophile. The base catalyzed pathway involves direct
deprotonation of a thiol (Scheme 4.1a) while the nucleophilic pathway involves
addition of a nucleophile to the Michael acceptor to form a strongly basic enolate
intermediate,\(^ {4.1}\) which then deprotonates an available thiol (Scheme 4.1b). Both
pathways lead to the formation of a strongly nucleophilic thiolate anion that enters
into the catalytic anionic chain mechanism shown in Scheme 4.1c.
Scheme 4.1: (a) Acid-base equilibrium resulting in the formation of a thiolate anion in the presence of base. (b) General mechanism for the formation of thiolate and nucleophile byproduct resulting from the addition of a nucleophile to the vinyl group of an acrylate followed by deprotonation of thiol by the resulting enolate intermediate. (c) Catalytic cycle for the reaction of thiolate with acrylate to give a thiol-Michael addition product.

Several studies have investigated the kinetics and/or energetics of base and nucleophile-promoted thiol-Michael reactions, most commonly involving phosphine or amine catalysts. Phosphine catalyzed thiol-Michael reactions have been consistently shown to exhibit faster reaction kinetics than the same reactions catalyzed by amines. Some of the variation in overall kinetics arises because of differences in the reaction mechanism under phosphine versus amine catalysis:
phosphines are known to follow a nucleophilic mechanism similar to phosphine-initiated oxa-Michael reactions\textsuperscript{4,15} while amines may act as a base, a nucleophile, or a combination of both. The presence of any protic species other than thiol, such as a protonated ammonium, will slow down thiol-Michael reaction kinetics and can even inhibit product formation. Though the nucleophilic pathway is also adversely impacted by protic species, the issue is naturally more intrinsic to the base catalysis pathway. Indeed Chan et al. have shown\textsuperscript{4,7} that when thiol-acrylate reactions are catalyzed by primary, secondary, or tertiary amines the resulting reaction kinetics correlate with the relative nucleophilicity of the amines rather than their pKa. One possible disadvantage of the otherwise efficient nucleophilic pathway is the formation of nucleophile addition byproducts, e.g. “inert” phosphonium esters and aza-Michael adducts (Scheme 4.1b). Several researchers, including us, have cautioned that low equivalents (e.g. <1 wt\%) of nucleophiles should be used in order to limit the formation of such nucleophile side products.\textsuperscript{4.1,4.7-4.8,4.12-4.14} Given the prominent and expanding role of thiol-Michael reactions in macromolecular chemistry, and the superior kinetics observed when nucleophiles are used to carry out thiol-Michael reactions, it is important to develop a thorough understanding of the reaction pathways available to different nucleophile initiators with the aim of retaining their efficiency while eliminating the potential formation of nucleophile addition byproducts.
4.1.2. Observation of Nucleophile Byproducts

The first detailed investigations of the nucleophilic mechanism of thiol-Michael reactions were reported in 2010 by Chan et al. and by Li et al. These two studies show quite definitively that dimethylphenylphosphine (DMPP), hexylamine (HA), and diethylamine (DEA) can initiate thiol-methyl acrylate reactions along the nucleophilic pathway shown in Scheme 4.1b, though 1° and 2° amines may also follow the base-catalysis mechanism (Scheme 4.1a) to some extent. Triethylamine (TEA), by contrast, follows the base catalyzed mechanism of Scheme 4.1a exclusively and has been shown incapable of promoting thiol-methyl acrylate reactions along the nucleophilic mechanism. More recently, combined theoretical and experimental investigations involving maleimide, acrylate, and vinylsulfone derivatives further support the different means by which phosphines and amines promote thiol-Michael reactivity. In support of the recommendation against high catalyst loading Li et al. have shown ESI-MS evidence of nucleophile byproduct formation when excess DMPP (2.5 equiv) or pentyamine (40 equiv) is used to catalyze the addition of β-mercaptoethanol to a methyl methacrylate functionalized poly(ethylene glycol) (PEG). The ratio of thiol to nucleophile was also found to play a role in the formation of nucleophile byproducts, with more byproduct formed at high [nucleophile]/[thiol] ratios. Several critical questions naturally arise, such as: at what level of catalyst loading does the formation of nucleophile byproduct become a concern (e.g. represent >1-2% of the overall product yield)? Does the threshold loading level vary with different nucleophiles? Does it vary with solvent?
Scheme 4.2: The reaction between 1-hexanethiol (1) and methyl acrylate (2) to give addition product 4 was investigated as a representative thiol-Michael reaction in different solvents (DMSO, THF, CHCl₃, or solvent free) as catalyzed by different nucleophiles (DMPP, DEA, or HA, 3a-c respectively) that were present in varying molar equivalents (0.01–10.0 equiv) while monitoring the formation of nucleophile byproducts 5a-5c.

In response to these questions, herein we report a systematic investigation of the influence of reaction conditions on the formation of nucleophile side products during phosphine and amine-initiated thiol-methyl acrylate reactions. The addition of 1-hexanethiol (1) to methyl acrylate (2) was investigated as a representative model thiol-Michael reaction (Scheme 4.2). Three different nucleophile initiators were investigated: dimethylphenylphosphine (DMPP, 3a), hexylamine (HA, 3b), and diethylamine (DEA, 3c). Reactions were carried out neat with varying equivalents of nucleophile as well as in three different solvents (DMSO, THF, and CHCl₃), with the formation of the desired thiol-Michael product and undesired nucleophile byproduct quantified by ¹H NMR spectroscopy. These investigations were then extended to two synthetic transformations of particular interest and utility in polymer chemistry: end group functionalization and polymer-polymer coupling. Under almost all
conditions the amount of nucleophilic byproduct was found to be minimal (<1% yield), a notable exception being polymer-polymer ligation reactions. We propose a rationale for the observation of minimal byproduct formation, a rationale that is different for the phosphine initiator DMPP than for amine initiators HA and DEA.

4.2. Small Molecule Thiol-Acrylate Reactions

Initial experiments focused on the addition of 1-hexanethiol to methyl acrylate in the absence of solvent (Table 4.1). Equimolar amounts of thiol and acrylate were added to a 3-dram vial followed by the addition of DMPP, HA, or DEA. As noted in Table 4.1, the amounts of nucleophile added ranged from 0.01–10.0 molar equivalents when catalyzed by DMPP and 0.01-10.0 equiv when catalyzed by DEA or HA. Reaction mixtures were mechanically stirred at ambient temperature and pressure, open to atmosphere, for 30 minutes after which an aliquot was removed for analysis by $^1$H NMR spectroscopy. Spectral signals were compared to analytical standards of the target thiol-acrylate product (4), nucleophile byproducts (5a-c), and the diaddition product between HA and two equivalents of methyl acrylate, each of which were synthesized separately. No signals corresponding to phosphonium ester 5a could be observed by $^1$H NMR spectrometry when the thiol-Michael reaction was catalyzed by DMPP at any level of catalyst loading (0.01–10.0 equiv, see Figure 4.7). This observation does not rule out the possibility that trace quantities of byproduct 5a are formed, though it does demonstrate that any such quantities are below the level necessary for detection and quantitative assessment by $^1$H NMR spectroscopy.
Table 4.1: Results of solvent free reactions between 1 and 2 to give 4 as catalyzed by varying amounts of nucleophiles DMPP, DEA, HA, and propylamine (PA).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nucleophile</th>
<th>Equivalents</th>
<th>% Product 4&lt;sup&gt;b&lt;/sup&gt;</th>
<th>% Byproduct&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DMPP</td>
<td>0.01</td>
<td>&gt;99</td>
<td>_&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>DMPP</td>
<td>0.1</td>
<td>&gt;99</td>
<td>_&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>DMPP</td>
<td>0.25</td>
<td>&gt;99</td>
<td>_&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>DMPP</td>
<td>0.5</td>
<td>&gt;99</td>
<td>_&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td>DMPP</td>
<td>1.0</td>
<td>&gt;99</td>
<td>_&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>6</td>
<td>DMPP</td>
<td>10.0</td>
<td>&gt;99</td>
<td>_&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>7</td>
<td>DEA</td>
<td>0.1</td>
<td>99</td>
<td>trace&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>8</td>
<td>DEA</td>
<td>0.25</td>
<td>99</td>
<td>trace&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>9</td>
<td>DEA</td>
<td>0.5</td>
<td>99</td>
<td>trace&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>10</td>
<td>DEA</td>
<td>1.0</td>
<td>&gt;98</td>
<td>trace&lt;sup&gt;d&lt;/sup&gt;</td>
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<td>DEA</td>
<td>10.0</td>
<td>&gt;98</td>
<td>trace&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
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<td>trace&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>13</td>
<td>HA</td>
<td>0.25</td>
<td>99</td>
<td>trace&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
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<td>HA</td>
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<td>&gt;98</td>
<td>&lt;2</td>
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<tr>
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<td>HA</td>
<td>1.0</td>
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<td>4</td>
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<tr>
<td>16</td>
<td>HA</td>
<td>10.0</td>
<td>e</td>
<td>e</td>
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<tr>
<td>17</td>
<td>PA</td>
<td>10.0</td>
<td>95</td>
<td>4</td>
</tr>
</tbody>
</table>

<sup>a</sup>All reactions were run at room temperature with equimolar amounts of 1 and 2. <sup>b</sup>Percent yields determined by 1H NMR spectroscopy. <sup>c</sup>No trace of signals corresponding to nucleophile byproduct could be observed above the NMR baseline. <sup>d</sup>Byproduct signals could be observed by 1H NMR spectroscopy but were so minor that they could not be integrated reliably. <sup>e</sup>Yields could not be determined because diagnostic signals were overwhelmed by residual HA.

Catalysis of the reaction between thiol 1 and acrylate 2 by DEA resulted in near quantitative formation of desired thiol-Michael product 4, however signals at 2.90 ppm also indicated the formation of trace quantities of aza-Michael byproduct 5b. Attempts to quantify the amounts of nucleophile byproduct 5b by integration proved unreliable given that byproduct signals could barely be seen above the baseline, even at a 10-fold excess of DEA (see Figure 4.8). Furthermore, increasing the molar equivalents of DEA from 0.1 to 10.0 did not result in an observable trend of
increasing signal intensity corresponding to byproduct 5b, though conceptually one would expect that to be the case. This observation was taken as further evidence that the quantity of aza-Michael byproduct 5b, though more apparent than in the case of phosphonium ester 5a, is also below the limit necessary for quantitative assessment by $^1$H NMR spectroscopy.

In the case of HA, quantifiable amounts of the nucleophile byproduct methyl 3-(hexylamino)propionate (5c) could be observed when equimolar or greater quantities of HA were used to catalyze the thiol-acrylate reaction. Mixing thiol, acrylate, and HA in a 1:1:1 molar ratio resulted in 96% conversion to thiol-acrylate product 4 along with 4% of aza-Michael byproduct 5b (Table 4.1, entry 15). At a 10-fold excess of HA the intensity of residual amine signals overwhelmed nearby signals, preventing quantitative determination of the amount of nucleophile byproduct (Table 4.1, entry 16). Therefore an analogous reaction was run using 10.0 molar equiv of propylamine as the nucleophile catalyst, after which excess propylamine could be removed under reduced pressure. $^1$H NMR analysis of the resulting product mixture again revealed about 4% of the methyl 3-(propylamino)propionate nucleophile byproduct. From these results it was clear that stoichiometric or greater quantities of primary amine did result in small, but quantifiable, amounts of nucleophilic byproduct.

The influence of solvent was investigated, and the results are provided in Table 4.2. Solvent polarity has been shown to influence thiol-Michael reaction kinetics,\textsuperscript{4,8,4,10,4,13} with faster rates observed in more polar solvents. Three solvents were chosen based on their polarity and utility in polymer synthesis: CHCl$_3$ ($\varepsilon =$
4.71), THF (\(\varepsilon = 7.43\)), and DMSO (\(\varepsilon = 46.83\)). Thiol-acrylate reactions were carried out at a concentration of 1.0 M using equimolar quantities of thiol, acrylate, and nucleophile. It should be noted that an equimolar amount of catalyst represents a significantly greater catalyst load than what is typically used to promote thiol-Michael reactions. However 1.0 molar equiv of nucleophile was chosen because 1.0 equiv marked the onset of observation of quantifiable nucleophile byproducts for HA as noted earlier.

Table 4.2: Relative yields\(^a\) of product (4) and byproducts (5a-c) upon DMPP, DEA, or HA catalyzed thiol-Michael reactions between 1 and 2 when carried out in CHCl\(_3\), THF, or DMSO.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nucleophile</th>
<th>Solvent</th>
<th>% Product 4(^b)</th>
<th>% Byproduct(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DMPP</td>
<td>CHCl(_3)</td>
<td>&gt;99</td>
<td>(-^c)</td>
</tr>
<tr>
<td>2</td>
<td>DMPP</td>
<td>THF</td>
<td>&gt;99</td>
<td>(-^c)</td>
</tr>
<tr>
<td>3</td>
<td>DMPP</td>
<td>DMSO</td>
<td>&gt;99</td>
<td>(-^c)</td>
</tr>
<tr>
<td>4</td>
<td>DEA</td>
<td>CHCl(_3)</td>
<td>99</td>
<td>trace</td>
</tr>
<tr>
<td>5</td>
<td>DEA</td>
<td>THF</td>
<td>99</td>
<td>trace</td>
</tr>
<tr>
<td>6</td>
<td>DEA</td>
<td>DMSO</td>
<td>99</td>
<td>trace</td>
</tr>
<tr>
<td>7</td>
<td>HA</td>
<td>CHCl(_3)</td>
<td>95</td>
<td>5</td>
</tr>
<tr>
<td>8</td>
<td>HA</td>
<td>THF</td>
<td>99</td>
<td>trace</td>
</tr>
<tr>
<td>9</td>
<td>HA</td>
<td>DMSO</td>
<td>99</td>
<td>trace</td>
</tr>
</tbody>
</table>

\(^a\)All reactions were run at room temperature at a concentration of 1.0 M with equimolar amounts of 1, 2, and nucleophile. \(^b\)Percent yields determined by \(^1\)H NMR spectroscopy. \(^c\)No trace of signals corresponding to nucleophile byproduct could be observed above the NMR baseline.

Again, no evidence of phosphonate ester byproduct 5a could be observed by \(^1\)H NMR spectroscopy in any of the three solvents. Only trace quantities of aza-Michael nucleophile byproducts 5b and 5c were observed in the more polar solvents THF and DMSO. In CHCl\(_3\), thiol-acrylate additions promoted by DMPP and DEA
again showed full conversion (≥99%) to the thiol-Michael product 4. Using HA to carry out the thiol-acrylate reaction in CHCl₃, by contrast, resulted in approximately 5% of the aza-Michael byproduct 5c.

Cumulatively, the results of both neat and solvated thiol-Michael reactions between the small molecules hexanethiol 1 and methyl acrylate 2 indicate that only trace (or undetectable) quantities of nucleophile byproduct are observed under the majority of conditions outlined in Tables 4.1 and 4.2. Quantifiable amounts of nucleophile byproduct are only observed when HA is used in stoichiometric or greater amounts to promote thiol-acrylate reactions in the absence of solvent or in a nonpolar solvent such as chloroform. For DMPP and DEA no quantifiable amounts of phosphonium ester 5a or aza-Michael byproduct 5b were observed under any conditions. Importantly, any of the three nucleophiles investigated is able to promote the near quantitative addition of hexanethiol 1 to methyl acrylate 2 in any of the three solvents studied, or solvent free, at up to 0.5 equivalents of nucleophile without concern of forming quantifiable amounts of unwanted nucleophile byproducts. Researchers commonly use even lower catalyst loading, and under such conditions the formation of nucleophile byproducts is even less of a concern.

While testing thiol-Michael conditions on small molecules such as 1 and 2 facilitates straightforward and, generally, quantitative analysis, much of the recent interest in thiol-Michael reactions stems from their utility in polymer chemistry. It is well known that chemical transformations that can be carried out reliably on small molecules are not always as successful when applied to polymers.⁴,¹⁶,⁴,²¹
Incorporation of a given functionality into a polymer or other macromolecule often decreases its reactivity. This is one of several reasons why polymer-polymer ligations are some of the most challenging reactions in macromolecular synthesis. It is important to determine whether the results noted in Table 4.1 extend to thiol-acrylate reactions involving polymers. Therefore two general classes of polymer reactions were investigated: end group functionalization and polymer-polymer ligation.

4.3. Polymer End Group Functionalization

End group functionalization was investigated using poly(ethylene glycol) diacrylate (6, PEG-diacylate) as a representative difunctional polymer (Figure 4.1). A PEG-diacrylate of average Mn 700 was chosen to be large enough to react as a representative polymer yet low enough molecular weight to allow for quantitative or semi-quantitative analysis of byproduct formation by 1H NMR spectroscopy. PEG-diacrylate 6 was reacted at both ends with methyl 3-mercaptopropionate (7) in the presence of DMPP, DEA, or HA (1:2:2:2 acrylate:thiol:nucleophile)4,22 both in the absence of solvent and in THF, resulting in thiol-acrylate product polymer 8. For end group functionalization reactions carried out in solvent, THF was chosen because of its prominence as one of the most commonly used solvents in polymer synthesis and functionalization. Thiol 7 was chosen for polymer functionalization investigations because it allows for greater differentiation4,23 between starting materials and products as compared to hexanethiol 1. End group functionalization results are summarized in Figure 4.1. Figure 4.1a shows an initial spectrum of a 1:2.2 mixture of
PEG-diacrylate 6 and thiol 7 prior to the addition of any catalyst. Figures 4.1b-d show the products obtained upon addition of DMPP, DEA, or HA, respectively. Spectra for end group functionalization in the presence of DMPP or HA (Figures 4.1b and 4.1d, respectively) show complete consumption of acrylate signals $H_{ac}$ between 5.80-6.50 ppm, the thiol methylene quartet $H_f$ at 2.80 ppm, and an upfield shift of PEG-diacrylate methylene $H_d$ from 4.33 to 4.28 ppm. End group functionalization promoted by DEA under the same conditions, however, did not result in complete consumption of the acrylate signals of PEG-diacrylate 6 as shown by residual vinylic signals between 5.80-6.50 ppm (inset, Figure 4.1c) and methylene $H_d$ at 4.33 ppm. This observation is consistent with previous experiments showing reduced reactivity of DEA in thiol-acrylate reactions compared to DMPP and HA.4,7

The observation of acrylate consumption is helpful for determining which reactions proceed to completion within 30 minutes, however the consumption of acrylate is not indicative of byproduct-free thiol-acrylate reactions as both the desired thiol-Michael product and undesired nucleophile byproduct require the consumption of acrylate end groups. Evidence of nucleophile byproduct formation, or lack thereof, can be evaluated upon examination of the 2.50-3.00 ppm regions of spectra that are also shown as insets in Figures 4.1b-d. Consistent with small molecule investigations in THF, only trace signals of aza-Michael byproducts can be observed upon significant enlargement (Figure 4.1c-d, arrows at approximately 2.95 ppm). No discernable phosphonium ester byproducts could be observed when the reaction was catalyzed by DMPP (Figure 4.1b). Similar results are obtained under solvent-free
conditions (Figure 4.2) with the most prominent difference being that all end group 
functionalization reactions reach full conversion, including when promoted using 
DEA. In short, the results of Figures 4.1 and 4.2 indicate quantitative end group thiol- 
acrylate functionalization of PEG-diacrylate 6 in the presence of DMPP or HA 
whether carried out in THF or solvent-free, and near-quantitative functionalization in 
the presence of DEA in THF along with complete conversion when solvent-free. In 
each case end group functionalization proceeded without significant or quantifiable 
formation of nucleophile byproducts even though a stoichiometric amount of 
nucleophile was used to carry out each reaction. Nucleophile byproduct formation can 
be expected to be even less of a concern at lower catalyst loading (e.g. 0.01-0.1 
equiv), which is more common for promoting thiol-Michael reactions. However, such 
reactions carried out at low catalyst loading may require longer reaction times to 
reach full conversion in some solvents when promoted by HA and, especially, DEA.
**Figure 4.1:** End group functionalization of PEG-diacrylate polymer 6 with thiol 7. (a) Starting mixture of 6 and 7 (1:2.2). (b)-(d) Resulting polymer 8 when catalyzed by 2.2 equiv DMPP, DEA, or HA, respectively, in THF. Residual DMPP can be observed between 7.26-7.50 ppm in spectrum (b) while arrows in spectra (c)-(d) indicate trace quantities of aza-Michael byproduct signals.
Figure 4.2: Compiled $^1$H NMR results for the reaction between PEG-diacrylate polymer 6 and methyl 3-mercapropionoate (7) (4.2a) initiated by either DMPP, DEA, or HA (4.2b-d, respectively) in the absence of solvent. Unlike the solvated results highlighted in Figure 4.1, all reactions go to completion as indicated by the lack of any vinylic protons between 5.8-6.5 ppm. Only trace amounts of byproduct are observed in the Figure 4.2c and 4.2d (DEA and HA, respectively), and no byproduct is observed in Figure 4.2b (DMPP).
4.4. Polymer-Polymer Ligation

Polymer-polymer ligation investigations were carried out by reacting PEG-diacylate (6) with poly(ethylene glycol) methyl ether thiol (PEG-thiol, 9, average Mn 2000). Product and nucleophile byproduct formation were monitored by $^1$H NMR spectroscopy (see section 4.9.) and GPC. Reactions were carried out along a similar procedure as end group functionalization: a 1:2 molar ratio of PEG-diacylate 6 and PEG-thiol 9 was dissolved in THF, after which 2.0 molar equiv of DMPP, DEA, or HA was added (Figure 4.3a). Polymer-polymer ligation reactions were allowed to stir for three days to account for the reduced reactivity of polymer chain ends. After stirring for three days each reaction mixture was concentrated and analyzed. Figure 4.3b-c show GPC traces of starting polymers 6 and 9 (black and purple, respectively) as well as the products of polymer-polymer ligation reactions as promoted by DMPP, DEA, and HA (red, blue, and green, respectively).

Before discussing the results of polymer-polymer ligation reactions it is worthwhile to note both the goals and limitations of these experiments. First, the sizes of PEG-diacylate 6 and PEG-thiol 9 were chosen such that differences in the molecular weights of residual starting polymers, desired polymer product 10, and undesired nucleophile addition byproduct polymers should be distinguishable by GPC. More specifically the Mn of polymers 6, 9, and 10 are approximately 700, 2000, and 4700, respectively, while nucleophile byproduct formation during polymer-polymer ligation would result in polymer side products with Mn of approximately 2700 (mono-byproduct 11) or 700 (dibyproduct 12) depending on whether
nucleophile addition occurred at one or both ends of PEG-diacylate 6. However there exist a few experimental and analytical challenges inherent to the thiol-Michael polymer-polymer ligation reactions as outlined above.

As indicated in the reaction scheme of Figure 4.3a, PEG-thiol 9 exists as a mixture of thiol and disulfide species, 9-disulfide. The presence of the disulfide is evident in the purple GPC trace of Figure 4.3a, which consists of a dominant peak at 20.8 min corresponding to PEG-thiol 9 as well as a minor though still significant peak at 19.7 min corresponding to 9-disulfide. Care was taken to minimize the amount of disulfide present by synthesizing 9 under anaerobic, non-oxidizing conditions, however all attempts resulted in a mixture of approximately 70% PEG-thiol (9) and 30% disulfide (9-disulfide), which is typical of 2000 Mn PEG-thiol.4,24 The presence of 9-disulfide complicates GPC analysis because the disulfide Mn of 4000 is quite close to the 4700 Mn of target polymer 10. Furthermore, any disulfide present can be expected to reduce the yield of target polymer 10 because less thiol will be present to react with PEG-diacylate 6. Methods for reducing 9-disulfide in situ were considered but each also present their own complications. For example, the most common and reliable means of chemically reducing disulfide bonds involve the addition of other thiol species such as β-mercaptoethanol or dithiothreitol, which could also undergo thiol-acrylate reactions with PEG-diacylate 6, or phosphines such as tris(2-carboxyethyl)phosphine, which can act as nucleophiles in thiol-Michael reactions and would introduce uncertainty into the analysis of nucleophile byproducts. Alternative synthetic strategies such as RAFT polymerization are highly useful for preparing
protected thio-polymers that can be deprotected in situ for thiol-Michael reactions,\textsuperscript{4,25} however RAFT deprotection is most commonly carried out using primary amines that would again introduce additional nucleophiles into the reaction mixture and complicate byproduct analysis.

While the use of PEG-thiol 9 has its complications and limitations, the reactions outlined in Figure 4.3 are still informative for comparing the efficiency and utility of using DMPP, DEA, and HA to carry out polymer-polymer ligation reactions. Figure 4.3c shows an overlay of the products obtained upon reacting PEG-diacylate 6 with two equivalents of PEG-thiol 9 in the presence of the three different initiators. Several clear differences in the GPC traces of Figure 4.3c are readily apparent. The blue and green traces obtained from polymer-polymer ligation in the presence of DEA and HA, respectively, both indicate a more complex mixture of products than that obtained in the presence of DMPP (red trace). The largest peak in both the DEA and HA traces occurs at 19.9 min, however both appear bimodal with a broad shoulder or subpeak at approximately 20.4 min. In addition, residual PEG-diacylate 6 at 22.1 min is apparent in the results for both DEA and HA (Figure 4.18-4.19, respectively). The DMPP trace, by contrast, is less bimodal with a peak at 19.7 min, a smaller shoulder around 20.4 min, and no residual PEG-diacylate starting material.

The broad shoulders of the DEA and HA traces likely indicate the formation of a nucleophile byproduct polymer 11 resulting from a thiol-Michael reaction at one acrylate end of PEG-diacylate 6 and an aza-Michael reaction at the other. As noted
above the resulting polymer would have an Mn of approximately 2700, and would be expected to elute at a retention time in between PEG-thiol 9 and target polymer 10. Given that unreacted PEG-diacrylate 6 is also observed in the DEA and HA results it is likely that residual 9-disulfide and, possibly, PEG-thiol 9 also contribute to the breadth of the DEA and HA traces. Overall it is quite clear that the use of DEA or HA (1 molar equivalent per acrylate) to promote polymer-polymer ligation between 6 and 9 is inefficient, as indicated by incomplete conversion after 3 days, and results in a substantial quantity of undesired nucleophile addition byproduct polymer.

Notably better results are obtained with DMPP as the initiator. DMPP is known to reduce disulfide bonds. Therefore, when stoichiometric amounts of DMPP are used to initiate the polymer-polymer coupling there is ample DMPP available to both promote the thiol-Michael reaction between 6 and 9 as well as reduce the disulfide present in the starting material. This dual role likely explains the fact that no residual PEG-diacrylate 6 is observed in the red DMPP GPC trace. The shoulder at approximately 20.4 min in the DMPP results, however, indicates the likely formation of nucleophile byproduct polymer as is observed in the DEA and HA results. Byproduct formation in the presence of DMPP is reduced relative to results with DEA and HA, though the simple observation that some nucleophile addition byproduct is formed is in stark contrast to small molecule and end group functionalization results where no evidence of phosphonium ester byproduct formation could be found. A potential explanation for this contrast is the reduced reactivity of polymer chain ends that makes polymer-polymer ligation reactions
particularly challenging. If the rate of the thiol-Michael reaction between PEG-thiol 9 and PEG-diacrylate 6 is slow relative to the rate of small molecule Michael addition then it is likely that DMPP, which can diffuse much faster throughout the reaction mixture than the end groups of PEG derivatives, is kinetically competitive with the thiol-Michael reaction between polymers 6 and 9. The same rationale can help explain the increase in nucleophile byproduct formation during polymer-polymer ligation in the presence of DEA or HA.
Figure 4.3: (a) Reaction of PEG-diacrylate polymer 6 with 2.0 equiv of PEG-thiol 9 as catalyzed by 2.0 equivs of nucleophiles 3a-c to give target polymer 10 as well as potential formation of nucleophile byproduct polymers 11 and 12. (b) GPC traces of polymer starting materials 6 (black) and 9 (purple), with 9-disulfide indicated. (b) Overlay of the products of polymer-polymer ligation as catalyzed by DMPP (red), DEA (blue), or HA (green).
Polymer-polymer ligation results at higher catalyst loading (solid lines) corroborate several of the conclusions reached from results at lower catalyst loading (dashed lines) (Figure 4.4). Increasing catalyst loading from 1:1 with respect to acrylate to 5:1 does measurably impact results when amine-based DEA or HA are used to initiate polymer-polymer ligation but does not measurably impact the results when phosphine-based DMPP is used. As noted earlier and observed in Figures 4.18-4.19, not all acrylate functionalities are consumed when polymer-polymer ligation is carried out in the presence of DEA or HA at 1:1 nucleophile:acrylate loading. This remains true at 5:1 loading as indicated by peaks around 22 min. In the case of DMPP, however, no residual acrylate starting material is observed at either level of catalyst loading (Figure 4.17 and the absence of signal around 22 min in Figure 4.4). These observations are consistent with the fact that some percentage of PEG-thiol 9 exists as a disulfide that is unable to undergo the desired thiol-acrylate reaction with PEG-diacrylate 6. DMPP, however, is able to reduce disulfides and therefore push the reaction further toward completion while DEA and HA are not. Therefore, even with a large excess of amine-initiator, some amount of unreacted PEG-diacrylate 6 remains.

An increase in catalyst loading also has the effect of increasing the amount of nucleophile byproduct in the presence of DEA or HA, but not in the presence of DMPP. As noted earlier, the more polydisperse and somewhat bimodal traces of polymer-polymer ligation products observed for DEA and HA likely indicate the formation of nucleophile byproduct polymer 11 (Figure 4.3). These nucleophile
byproducts appear around approximately 20.5 min in Figure 4.4. Increasing from a 1:1 ratio of DEA:acrylate or HA:acrylate to a 5:1 ratio gives rise to an increase in this byproduct signal. Importantly, the increase in nucleophile byproduct formation is greater in the case of HA (solid purple line versus dashed green line) than it is for DEA (solid red line versus dashed blue line), which is consistent with all other results indicating a greater amount of nucleophile byproduct formation in the presence of the more nucleophilic HA versus less nucleophilic DEA. It is also noteworthy that there is no observable increase in the amount of nucleophile byproduct at higher catalyst loading of DMPP (solid turquoise line versus dashed orange line).

Attempts were also made to carry out the same polymer-polymer ligation reactions at lower catalyst loading (0.2:1 catalyst:acrylate) to decrease the amount of nucleophile byproduct obtained. However ligation reactions at such low catalyst loading gave little to no product formation in the presence of HA and especially DEA, even after 10 days. These results further highlight the difficulties of carrying out polymer-polymer ligation reactions. Further experiments will be necessary to test for and determine the optimal balance of catalyst loading, solvent, concentration, thiol polymer structure, etc. for achieving high conversion and minimal byproduct formation. Still, the current results indicate that nucleophile byproduct formation is a greater concern in polymer-polymer ligation reactions than it is in small molecule or end group functionalization reactions.
Figure 4.4: Compiled GPC results for reaction between PEG-diacrylate polymer \( 6 \) and PEG-thiol \( 9 \) as promoted by 2.0 equivalents of DMPP, DEA, or HA (i.e. 1:1 nucleophile:acrylate) or 10.0 equivalents of DMPP, DEA, or HA (5:1 nucleophile:acrylate).

4.5. Kinetic and Mechanistic Considerations

The general lack of observable nucleophile byproduct formation appears to be at odds with the generally accepted mechanism of nucleophile catalyzed thiol-Michael reactions as shown in Scheme 4.1. The nucleophilic pathway requires the production of at least some nucleophile byproduct in order for initial quantities of thiolate to be formed and enter the catalytic anionic cycle. The question then becomes, why aren’t quantifiable amounts of this nucleophile byproduct observed? Two possible explanations may account for the lack of nucleophile byproduct formation.
One potential explanation relates to the relative kinetics of nucleophile-acrylate versus thiolate-acrylate reactions. It is well known that the catalytic cycle of thiolate anion addition to an electron withdrawing alkene (Scheme 4.3, right) is very rapid and that the addition of a nucleophile such as DMPP, DEA, or HA to the same alkene is slow by comparison (Scheme 4.3, left). Nguyen et al. have experimentally compared the kinetics of a variety of thiol-Michael and aza-Michael reactions and found that, with the exception of iso(thio)cyanates, Michael acceptors react faster with thiols than with amines. Desmet et al. have recently carried out a thorough computational investigation of the thiol-Michael reaction between ethanethiol and ethyl acrylate as initiated by triethylphosphine (TEP), ethylamine (EA), and DEA in a solvent model for THF. Free energy barriers for addition of TEP, EA, and DEA were each computationally predicted to fall between 21-23 kcal/mol whereas the propagation step for addition of ethane thiolate to ethyl acrylate was predicted to be 15.6 kcal/mol. This difference in free energy barriers suggests that the rate constant for addition of thiolate to acrylate is greater than that for addition of TEP, EA, or DEA to acrylate by factor of \(10^4\) (Scheme 4.3). These experimental results and computational predictions suggest that trace, catalytic quantities of thiolate \(1^-\) formed along the nucleophilic mechanism may react so rapidly with acrylate \(2\) that essentially all remaining acrylate is consumed along the catalytic anionic cycle before measurable quantities of nucleophile addition byproducts can accumulate. Relative rates and free energy barriers vary with solvent, which
may help explain the greater amounts of nucleophilic byproduct 5c observed in CHCl₃ in comparison to THF, DMSO, and solvent free conditions. However further experiments and/or computational modeling are necessary to distinguish which process, i.e. the anionic cycle or nucleophilic attack, is sped up or slowed down relative to the other as a factor of solvent. These investigations will be the subject of future work.

**Scheme 4.3:** General comparison of the pathways and relative rates for consumption of acrylate by a nucleophile (left cycle) leading to an undesired nucleophile byproduct, or by a thiolate (right cycle), which leads to a desired thiol-Michael product. Relative magnitudes of the rates of nucleophile initiation and catalytic anionic cycle pathways are adapted from reference 4.14.

Chan et al. have shown that thiol-acrylate reactions promoted using primary amines (e.g. HA) proceed faster than those promoted by secondary amines (e.g. DEA).⁴ ⁷ This result is consistent with the greater nucleophilicity of HA relative to DEA, and it can be expected that more nucleophile byproduct will be formed when a
stronger nucleophile is used as a catalyst. Indeed, as noted in Table 4.1, greater quantities of the nucleophile byproduct 5c (from HA) are formed relative to byproduct 5b (from DEA) under identical reaction conditions. However, this line of reasoning breaks down when considering DMPP, which is an even stronger nucleophile and known to catalyze thiol-acrylate reactions at much faster rates than either HA or DEA. Some of the rate enhancement under DMPP catalysis can be attributed to the fact that phosphonium ester byproducts (e.g. 5a) are not protic species whereas aza-Michael reactions initially form protic ammonium species that compete with thiols and slow down thiol-Michael reaction rates.\textsuperscript{4,12} Still, DMPP is also known to be a more effective catalyst than other amine nucleophiles that do not produce protic aza-Michael intermediates, such as DBU or DBN.\textsuperscript{4,7} Therefore, it is surprising that under all conditions the least amount of nucleophile byproduct is observed when DMPP is used as a catalyst. A second potential explanation that further distinguishes the reactivity and results observed for DMPP versus amine initiators is therefore hypothesized.

As noted above the nucleophile byproduct formed during DMPP-catalyzed thiol-acrylate reactions is a cationic phosphonium ester, such as 5a. Obviously, these cationic byproducts cannot persist in the absence of a balancing anion. The thiol-Michael reaction involves the formation of two prominent anions: enolate and thiolate species. Enolates are strongly basic and are most favored to deprotonate available thiol as shown in Scheme 4.1c. Thiolate anions are strong nucleophiles that are known to add rapidly to available Michael acceptors, also shown in Scheme 4.1c.
Along the mechanism summarized in Scheme 4.1, more thiolate will exist than acrylate because some initial quantity of acrylate was consumed by DMPP to form phosphonium ester byproduct 5a. The end result will be the formation of the desired product 4 as well as a salt comprised of phosphonium ester cation 5a and thiolate anion 1−, which theoretically must be present in equimolar amounts as required for charge balance. It is therefore worth considering the potential reactions that could occur between the thiolate and phosphonium ester species.

4.5.2. Reactivity of Phosphonium Ester Byproducts

Scheme 4.4 summarizes potential reactions that could occur between a thiolate anion and a phosphonium ester cation. Three reaction pathways are shown as they were considered to be the most likely possible reactions between a thiolate anion and a phosphonium ester cation. Of the three pathways one is classified as an elimination-addition process (Scheme 4.4a, blue arrows) while the remaining two involve nucleophilic substitution (Scheme 4.4b-c, purple arrows). The elimination-addition pathway first involves deprotonation of the phosphonium ester by thiolate and subsequent elimination of DMPP. The first two steps of this elimination route are the reverse of the nucleophile initiation pathway shown in Scheme 4.1b and, therefore, produce the starting materials DMPP, methyl acrylate, and thiol. The acrylate formed along this route is then favored to react rapidly with available thiolate to give the same enolate intermediate as is observed along the catalytic anionic cycle. This
enolate can abstract a proton from the thiol formed upon deprotonation of the phosphonium ester, giving the desired thiol-Michael product and a thiolate anion.

Alternatively, thiolate may react with the phosphonium ester as a nucleophile as shown in Scheme 4.4b and 4.4c. In Scheme 4.4b the nucleophilic thiolate attacks the β-carbon of the phosphonium ester, displacing DMPP as a leaving group. This process results in the formation of the desired thiol-Michael product. Alternatively, the nucleophilic thiolate may be envisioned to attack one of the phosphonium methyl groups as shown in Scheme 4.4c. This reaction pathway results in the formation of a tertiary phosphine and a methyl thioether rather than the desired thiol-Michael product. While the pathway shown in Scheme 4.4c does not produce any thiol-Michael product it is worth considering because nucleophilic attack at a phosphonium methyl is presumably less sterically hindered than attack at the the β-carbon of the phosphonium ester. Some combination of the mechanisms shown in Scheme 4.4 may also be possible.

It should be noted that similar substitution and elimination processes are not available for aza-Michael byproducts 5b and 5c as they are neutral amines incapable of being displaced as leaving groups. Protonation of aza-Michael byproducts 5b and 5c would result in ammonium salts that would not function as leaving groups because the most favored reaction between such ammonium species and thiolate would involve diffusion-controlled deprotonation\textsuperscript{4,14} by thiolate rather than substitution or elimination processes. This highlights a significant difference between the reactivity of amine nucleophiles HA and DEA as compared to the phosphine nucleophile.
DMPP that helps explain experimentally observed differences in their propensity to form nucleophile byproducts in thiol-Michael reactions.

**Scheme 4.4:** Potential pathways for reactions between a thiolate and phosphonium ester salt. (a) A multi-step elimination-addition pathway wherein thiolate initially deprotonates the phosphonium ester resulting in elimination of DMPP and a subsequent thiol-acrylate reaction. (b) Direct substitution wherein thiolate acts as a nucleophile, displacing DMPP and resulting in the desired thiol-Michael product. (c) Substitution involving nucleophilic attack of a phosphonium methyl group by thiolate to give a methyl thioether and tertiary phosphine byproduct.

Model phosphonium ester byproduct **13** (Figure 4.5a), the bromide salt of byproduct **5a**, was synthesized to investigate its potential reactivity with a thiolate nucleophile. Phosphonium ester **13** was reacted with the sodium salt of methyl 3-mercaptopropionate **7**

, which had been freshly prepared in anhydrous CDCl₃ under a nitrogen atmosphere to limit disulfide formation. Upon completion of the reaction,
the mixture was condensed under reduced pressure and analyzed by $^1$H NMR spectroscopy without any workup or purification so that all species could be accounted for. The resulting crude NMR spectrum is shown in Figure 4.5b.

![Chemical scheme and NMR spectroscopic results](image)

**Figure 4.5:** (a) Chemical scheme and (b) $^1$H NMR spectroscopic results of a model for the reaction of a phosphonium ester with a nucleophilic thiolate. Addition of the bromide salt of phosphonium ester 5a (i.e. model compound 13) to the sodium salt of methyl 3-mercaptopropionate (7–), which was formed *in situ* upon the addition of NaH to 7, in CDCl$_3$ results in the predominant formation of thiodipropionate 14, indicating that phosphonium-thiolate salts are capable of reacting to give thiol-Michael products.

The DMPP moiety of 13 is highlighted in red in Figure 4.5a, as are its corresponding proton signals in Figure 4.5b. Similarly, the methyl propionate moiety of 13 is highlighted in blue. The spectrum in Figure 4.5b is not phosphorous decoupled, therefore methylene protons of 13 that appear at 3.35 and 2.75 ppm show the expected $^2$J$_{PH}$ and $^3$J$_{PH}$ coupling to the phosphonium. Upon reaction with thiolate
these methylene signals appear as two sets of uncoupled triplets and are shifted upfield to 2.83 and 2.64 ppm. These changes in chemical shift and splitting are consistent with the formation of symmetric thiodipropionate product 14. Furthermore, the singlet of the methyl ester is observed to shift downfield from 3.59 to 3.72 ppm. Small amounts of residual phosphonium ester byproduct 13 can still be seen in the crude product, suggesting the conversion of 13 to 14 either did not go to completion or could be attributable to error in the reaction stoichiometry. While only a model reaction, the results of Figure 4.5 support the hypothesis that thiolate and phosphonium ester byproduct species formed in the course of DMPP initiated thiol-Michael reactions are capable of reacting with each other, and that the product of their reaction is a thiol-Michael adduct. Notably, no evidence of tertiary phosphine or methyl thioether byproducts are observed in the product mixture, suggesting that the \(S_N2\) reaction outlined in Scheme 4.4c is not competitive with the pathways shown in Scheme 4.4a and 4.4b.

### 4.5.3. Computational Modeling of Phosphium Ester Byproduct Reaction Paths

While the model reaction summarized in Figure 4.5 indicates that the reaction of a thiolate with a phosphonium ester does lead to the predominant formation of a thiol-Michael adduct, the results of the model reaction do not clarify whether the elimination-addition pathway of Scheme 4.4a or the substitution pathway of 4b is dominant, or if both pathways contribute to the formation of product 14. Computational modeling was therefore used to gain insight into the relative
favorability of the elimination and substitution pathways outlined in Scheme 4.4. The relative enthalpies and free energies of all stationary points along reaction pathways in Scheme 4.4a-c were located and optimized using methods we and others have previously applied to thiol-acrylate, thiol-vinylsulfone, and thiol-maleimide reactions, and have been shown to correlate well with experimental results. In short, all minima and transition states were optimized at the M06-2X/6-311G(2D,P)//B3LYP/6-31+G(D) level at 298.15 K in PCM solvent models for both DMSO and CHCl₃ using the program Gaussian09 (see Table 4.3 for full computational results). A summary of key computational insights in CHCl₃ is provided in Figure 4.6. In solvent models for both DMSO and CHCl₃ the most favored reaction pathway was predicted to be elimination followed by addition (blue and green profiles in Figure 4.6). The rate determining steps along the elimination-addition pathway in DMSO and CHCl₃ are predicted to have free energy barriers of 20.7 and 14.0 kcal/mol, respectively. Both the elimination and addition steps are predicted to be exergonic in both solvents, supporting the favorability of forming a thiol-Michael product as was observed experimentally. Reaction pathways where thiolate acts as a nucleophile, Figure 4.6a-b, were also predicted to be exergonic. However their free energy barriers were each predicted to range from 30.0 to 37.7 kcal/mol depending on which substitution pathway is followed and in which solvent. The free energy barriers for nucleophilic substitution are therefore predicted to be 1.8-2.2 times greater than the free energy barriers along the elimination-addition pathway. This is taken as strong support that the reaction between residual thiolate
and phosphonium ester byproducts follows the elimination-addition pathway outlined in Scheme 4.4a. Additional experimental and computational investigations involving a wider range of possible nucleophiles are being carried out to help answer this question further.

![Chemical structures and energy profiles](image)

**Figure 4.6:** Summary of substitution and elimination-addition pathways studied computationally. At the top are rate-determining steps for substitution at a DMPP methyl group (a), substitution at the β-carbon of the phosphonium ester (b), and for the deprotonation of the phosphonium ester by thiolate (c). Transition state free energies for each rate-determining step are given in kcal/mol and are relative to the starting phosphonium ester/thiolate salt in a solvent model for CHCl₃. At the bottom is the computed profile for each pathway in CHCl₃ with rate-determining steps a-c labeled. Complete computational results in both CHCl₃ and DMSO are in section 4.10.

The observation of phosphonium ester–thiolate reactivity, in conjunction with the fact that the kinetics of the catalytic anionic chain mechanism are several orders
of magnitude faster than the kinetics of DMPP addition to acrylate, helps explain the lack of observable nucleophile byproduct 5a. Thiol-Michael initiation by nucleophilic amines DEA and HA results in the formation of neutral aza-Michael byproducts 5b and 5c that are not subsequently consumed because (i) they are not capable of acting as leaving groups, and (ii) no residual thiolate anion is formed along the aza-Michael pathway. Therefore it is not surprising that aza-Michael byproducts were more observable than phosphonium ester byproducts both in some of the small molecule experiments and especially during polymer-polymer ligation reactions. It is still the case that, for all but polymer-polymer ligation reactions, the rate of nucleophilic addition of DEA or HA to acrylate is much slower than that of the catalytic addition of thiolate to acrylate. Hence only trace quantities of aza-Michael byproducts are observed even at stoichiometric catalyst loading.

It is important to recognize and reiterate that nucleophile byproducts have been observed previously by Li et al.\textsuperscript{4,8} A primary difference between the previous work and the current work centers on the methods of analysis used. More specifically, Li et al. observed aza-Michael and phosphonium ester byproducts by MALDI-TOF MS and ESI-MS, which do not provide quantitative analysis of the relative amounts of different species. This is in contrast to the current study wherein both \textsuperscript{1}H NMR and GPC are able to provide relative measures of the amounts of nucleophile byproducts. Furthermore, in the previous work\textsuperscript{4,8} nucleophilic addition of pentyamine to methyl methacrylate was observed in the presence of a larger excess of the primary amine (40.0 equivs) than was used in the current study. This is consistent with the results
presented herein, namely that a large excess of primary amine can lead to observable quantities of aza-Michael byproducts.

4.6. Conclusions

Several factors underlying the formation of undesired nucleophile byproducts during nucleophile-initiated thiol-acrylate reactions have been explored, leading to the conclusion that nucleophile byproduct formation is less of a concern than previously believed. Still, the amount of byproduct formation is found to vary as a function of both the type and equivalents of initiator and as a function of solvent and reaction type. For the different initiators investigated – dimethylphenylphosphine (DMPP), diethylamine (DEA), and hexylamine (HA) – no evidence of nucleophile byproduct could be observed for the phosphine initiator, even at stoichiometric and greater amounts, when catalyzing the addition of thiols to methyl acrylate or functionalizing the end groups of PEG-diacrylate polymers, regardless of the solvent chosen. Results are more mixed for the use of primary and secondary amines as nucleophilic initiators, which are shown to be more likely to result in undesired aza-Michael byproducts, particularly for primary amines at stoichiometric or greater catalyst loading in nonpolar solvents (e.g. CHCl₃). Reasons underlying the general lack of nucleophile byproduct formation at lower (<50 mol%) catalyst loading are explored, as are reasons for the dramatic difference in likelihood of nucleophile byproduct formation in the presence of P-centered DMPP versus N-centered DEA and HA. Importantly, experimental and computational investigations demonstrate that
phosphonium ester byproducts formed following thiol-acrylate initiation by DMPP can react with residual thiolate anions to form the desired thiol-Michael product and regenerate the DMPP catalyst. This new insight provides a greater understanding of the reaction pathways available to phosphorous nucleophiles in thiol-acrylate reactions and helps further elucidate the superior performance of DMPP as a thiol-Michael catalyst. Conclusions from this study help expand our understanding of the various roles nucleophiles can play in thiol-acrylate reactions, and thiol-Michael reactions more broadly, specifically with respect to the formation and potential consumption of undesired nucleophile byproducts. Given the variation in reaction kinetics and byproduct formation with different nucleophile structures it is likely that these new insights can be expanded to other nucleophile types and Michael acceptor structures to continue to fine-tune our understanding of their reactivity and simplify the choice of specific nucleophile initiators for the optimization of all types of thiol-Michael reactions.

4.7. Experimental and Computational Details

Materials

1-Hexanethiol, methyl acrylate, dimethylphenylphosphine, and diethylamine were purchased from Alfa Aesar. Poly(ethylene glycol) diacrylate and poly(ethylene glycol) methyl ether were purchased from Sigma-Aldrich. Hexylamine, propylamine, and methyl 3-mercaptopropionate were purchased from Acros Organics. Methyl 3-bromopropionate was purchased from Ark Pharma. All chemicals were used as
received. Methyl 3-(hexylthio)propionate (4), methyl 3-(diethylamino)propionate (5b), methyl 3-(hexylamino)propionate (5c), methyl 3-(dihexylamino)propionate, and poly(ethylene glycol) methyl ether thiol were synthesized according to previously reported literature procedures.

**Methods**

Thin layer chromatography (TLC) was performed on alumina-backed sheets coated with silica gel 60 F254. TLC plates were visualized using a UV 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). Gel permeation chromatography (GPC) was performed on a Viscotek TDA 305 eluting with THF at 35 °C at 1.0 mL min$^{-1}$. The Viscotek TDA 305 was arranged with one guard column (particle size 8 micron, dimensions 10x4.6 mm) and a series of two identical SEC columns (particle size 10 micron, max pore size 5,000 Å, dimensions 300x7.8 mm). The number average molecular weight ($M_n$), molecular weight ($M_w$), and polydispersity index (PDI) were determined using the Viscotek RI detector and OmniSEC software, and calculated relative to linear poly(methyl methacrylate) (PMMA) standards in the range of $M_p$ 1,960-903,000 purchased from Polymer Standards Service.
**General procedure for solvent free thiol-acrylate reactions**

An equimolar mixture of methyl acrylate (50.0 mg, 0.58 mmol) and 1-hexanethiol (68.7 mg, 0.58 mmol) was added to each of nineteen separate three-dram vials. To each vial was added a specific amount of DMPP, DE, HA, or propylamine: DMPP (0.01-10.0 equivs), DE or HA (0.01-10.0 equivs), or propylamine (10.0 equiv). The mixtures were magnetically stirred for 30 minutes at ambient temperature open to the atmosphere. Each reaction mixture was then diluted with CDCl$_3$ and analyzed by $^1$H NMR spectroscopy, which confirmed the completion of each reaction as indicated by the absence of methyl acrylate vinylic protons.

**General procedure for solvated thiol-acrylate reactions**

Equimolar amounts of methyl acrylate (50.0 mg, 0.58 mmol), 1-hexanethiol (68.7 mg, 0.58 mmol), and either DMPP (80.1, 0.58 mmol), DE (42.4 mg, 0.58 mmol), or HA (58.7 mg, 0.58 mmol) were taken up in CDCl$_3$, THF, or DMSO-d$_6$ to make 1.0 M solutions and stirred for 30 minutes. After 30 minutes, reactions carried out in CDCl$_3$ or DMSO-d$_6$ were analyzed directly by $^1$H NMR spectroscopy. Thiol-acrylate reactions carried out in THF were concentrated under reduced pressure and then taken up in CDCl$_3$ for spectroscopic analysis. As before the completion of each reaction was shown by the absence of vinylic protons by $^1$H NMR spectroscopy.
**Polymer end-group functionalization**

End group functionalization reactions were carried out both in the absence of solvent and in THF. For solvent free reactions, poly(ethylene glycol) diacrylate (average Mn 700, 94.0 mg, 0.13 mmol, 1.0 equiv) and methyl 3-mercaptopropionate (34.8 mg, 0.29 mmol, 2.2 equiv) were added to a three-dram vial and stirred. To this mixture was added 2.2 equiv of either DMPP (40.1 mg, 0.29 mmol), DEA (21.2 mg, 0.29 mmol), or HA (29.3 mg, 0.29 mmol). The reactions were allowed to continue stirring at ambient temperature open to the atmosphere for 30 minutes. A sample of the reaction mixture was removed and taken up in CDCl₃ for analysis by ¹H NMR spectroscopy. Reactions carried out in THF followed the same general procedure with the exception that the poly(ethylene glycol) diacrylate and methyl 3-mercaptopropionate mixture was diluted with 1.3 mL of THF to make a 0.1 M solution prior to the addition of nucleophile. Following completion of the thiol-acrylate reactions the THF was removed under reduced pressure and the resulting residue was dried further under high vacuum prior to analysis by ¹H NMR spectroscopy in CDCl₃.

**Polymer-Polymer Ligation**

Poly(ethylene glycol) diacrylate (average Mn 700, 35.0 mg, 0.05 mmol) and poly(ethylene glycol) methyl ether thiol (average Mn 2000, 200.0 mg, 0.1 mmol) were added to a three-dram vial and dissolved in THF. The reaction was initiated upon the addition of either DMPP, DEA, or HA (2.0 equv). Reactions were stirred
at ambient temperature under nitrogen for 3 days, after which they were each concentrated under reduced pressure and dried further under high vacuum. Each mixture was then diluted with CDCl₃ and analyzed by ¹H NMR spectroscopy and GPC.

**Synthesis of (3-methoxy-3-oxopropyl)dimethyl(phenyl)phosphonium bromide (13)**
Methyl 3-bromopropionate (300.0 mg, 1.8 mmol) was added to a 10 mL round bottom flask and dissolved in acetonitrile (0.4 M). Dimethylphenylphosphine (248.0 mg, 1.8 mmol) was added to the round bottom flask and the mixture was allowed to stir at ambient temperature open to atmosphere overnight. The mixture was concentrated under reduced pressure and dried further under high vacuum. Yield: 540 mg (99%). The product was isolated as a white crystalline solid. TOF MS ES (m/z) [M]+ Calculated for C₁₂H₁₈O₂P, 225.1044, found 225.1049. ¹H NMR (CDCl₃, 500 MHz): δ 8.02-7.97 (m, 2H), 7.75-7.72 (m, 1H), 7.69-7.66 (m, 2H), 3.58 (s, 3H), 3.32 (dt, 2H, J = 13.0, 7.5 Hz), 2.74 (dt, 2H, J = 18.0 Hz, 7.5 Hz), 2.65 (d, 6H, J = 14.0 Hz). ¹³C NMR (125 MHz): δ 171.32, 134.36, 131.75, 130.00, 52.23, 26.91, 20.08, 9.10.

**Procedure for thiolate-phosphonium ester reactions**
Sodium hydride (40.0 mg, 0.1 mmol) was added to a round bottom flask under inert atmosphere. Anhydrous CDCl₃ (1.0 mL, 0.10 M) was added and the solution was
cooled down to 0 °C using an ice bath. Methyl 3-mercaptopropionate (120.2 mg, 0.1 mmol) was added to the NaH solution dropwise and the mixture was stirred for 2 hrs at 0 °C. An equimolar amount of (3-methoxy-3-oxopropyl)dimethyl(phenyl)phosphonium bromide (13) (305.2 mg, 0.1 mmol) was added to a separate round bottom flask under inert atmosphere. Dry CDCl₃ (1.0 mL, 0.10 M) was added and the resulting solution was taken up by syringe and added dropwise to the NaH mixture at 0 °C. The ice bath was then removed and the reaction was stirred overnight at ambient temperature. The reaction mixture was passed through a short pad of celite, concentrated under reduced pressure, and dried further under high vacuum. The residue was diluted with CDCl₃ and analyzed by ¹H NMR spectroscopy.

### 4.8. ¹H NMR Results of Hexanethiol-Methyl Acrylate Reactions

The NMR spectra in the following section correspond the results highlighted in Tables 4.1 and 4.2 of the main text for reactions between 1-hexanethiol (1) and methyl acrylate (2) under neat and solvated conditions. As may be expected given the results in Tables 4.1 and 4.2, many of the product spectra are redundant. Therefore, for entries that afford the same amount of byproduct (e.g. Table 4.1, entries 1-6), only the spectrum that corresponds to the highest amount of initiator loading, and therefore the highest expected amount of nucleophile byproduct, is shown (e.g. Table 4.1, entry 6).
**Figure 4.7:** $^1$H NMR spectrum (500 MHz) obtained upon the addition of 10.0 equivalents of DMPP to a mixture of 1-hexanethiol and methyl acrylate, solvent free (Table 4.1, entry 6). Residual DMPP signals are observable just above the baseline between $\delta$ 7.0-7.8 ppm and as a doublet at $\delta$ 1.8 ppm.

**Figure 4.8:** $^1$H NMR spectrum (500 MHz) obtained upon the addition of 10.0 equivalents of DEA to a mixture of 1-hexanethiol and methyl acrylate, solvent free (Table 4.1, entry 11). Trace 1,2-dihexyl disulfide peaks are observed just above the baseline at 2.7 and 1.7 ppm.
Figure 4.9: $^1$H NMR spectrum (500 MHz) obtained upon the addition of 0.25 equivalents of HA to a mixture of 1-hexanethiol and methyl acrylate, solvent free (Table 4.1, entry 13). The methylene protons $\beta$ to the byproduct ester appear as a triplet at 2.90 ppm. Poor signal to noise prevents the meaningful integration of the byproduct triplet as can be seen above (-0.02).

Figure 4.10: $^1$H NMR spectrum (500 MHz) obtained upon the addition of 0.50 equivalents of HA to a mixture of 1-hexanethiol and methyl acrylate, solvent free (Table 4.1, entry 14). The methylene protons $\beta$ to the ester appear as a well-resolved triplet observed just above the baseline at 2.90 ppm. A comparison of the integrations
of the methylene protons β to the ester in both the byproduct (0.04) and product (2.21) affords a byproduct to product ratio of <2:>98.

**Figure 4.11:** $^1$H NMR spectrum (500 MHz) obtained upon the addition of 1.0 equivalent of HA to a mixture of 1-hexanethiol and methyl acrylate, solvent free (Table 4.1, entry 15). In this case the integrations of the methyl protons of the byproduct and product were compared to determine product ratios. The greater integration of the methyl group (3 protons) as compared to the methylene protons β to the ester (2 protons) provides greater signal to noise and a more reliable integration. The byproduct to product ratio was determined to be approximately 4:96.
Figure 4.12: $^1$H NMR spectrum (500 MHz) obtained upon the addition of 10.0 equivalents of PA to a mixture of 1-hexanethiol and methyl acrylate, solvent free (Table 4.1, entry 17). Propylamine was chosen in addition to hexylamine because of its lower boiling point. Again, the integrations of the methyl protons of the byproduct and product were compared to determine product ratios. The inset shows two resolved singlets at 3.71 (byproduct) and 3.72 (product) ppm. The byproduct to product ratio was determined to be 4:96.

Figure 4.13: $^1$H NMR spectrum (500 MHz) obtained upon the addition of 1.0 equivalent of DMPP to a mixture of 1-hexanethiol and methyl acrylate in CDCl$_3$ (1.0 M). Signals corresponding to the phosphonium ester byproduct are not observed.
Identical results were obtained when the same reaction was carried out in DMSO and THF. (Table 4.2, entries 1-3)

**Figure 4.14:** $^1$H NMR spectrum (500 MHz) obtained upon the addition of 1.0 equivalent of DEA to a mixture of 1-hexanethiol and methyl acrylate in CDCl$_3$ (1.0 M). The methylene protons $\beta$ to the ester are observed slightly above the baseline at 2.90 ppm. Poor signal to noise prevented a more accurate determination of the product to byproduct ratio. Identical results were obtained when the same reaction was carried out in DMSO and THF. (Table 4.2, entries 4-6)

**Figure 4.15:** $^1$H NMR spectrum (500 MHz) obtained upon the addition of 1.0 equivalent of HA to a mixture of 1-hexanethiol and methyl acrylate in CDCl$_3$ (1.0 M).
The methylene protons β to the ester of byproduct 5c are observed at 2.90 ppm and provide a product to byproduct ratio of approximately 5:95. (Table 4.2, entry 7)

**Figure 4.16:** $^1$H NMR spectrum (500 MHz) obtained upon the addition of 1.0 equivalent of HA to a mixture of 1-hexanethiol and methyl acrylate in THF (1.0 M). After the completion of the reaction the mixture was concentrated under reduced pressure and analyzed by $^1$H NMR in CDCl$_3$. The methylene protons β to the ester of byproduct 5c are observed slightly above the baseline at 2.90 ppm. While byproduct is observed, poor signal to noise complicates an accurate determination of the product to byproduct ratio. Similar results were observed in DMSO. (Table 4.2, entries 8-9)
Figure 4.17: $^1$H NMR spectrum (500 MHz) obtained upon the addition of 2.0 equivalents of DMPP to a 2:1 mixture of PEG-diacrylate 6 and PEG-thiol 9. The absence of any vinyllic signals from PEG-diacrylate 6 between 5.8-6.5 ppm indicates complete consumption of acrylate moieties.

Figure 4.18: $^1$H NMR spectrum (500 MHz) obtained upon the addition of 2.0 equivalents of DEA to a 2:1 mixture of PEG-diacrylate 6 and PEG-thiol 9. Unreacted PEG-diacrylate 6 is observed as indicated by the vinyllic signals between 5.8-6.5 ppm.
Figure 4.19: $^1$H NMR spectrum (500 MHz) obtained upon the addition of 2.0 equivalents of HA to a 2:1 mixture of PEG-diacylate 6 and PEG-thiol 9. Unreacted PEG diacrylate is observed as indicated by the vinylic signals between 5.8-6.5 ppm.

4.9. Computational Results Summary

The following reaction sequences were modeled computationally to gain insight into the relative favorability of different reaction pathways involving the phosphonium ester–thiolate salt:
**Pathway A:** Phosphonium ester deprotonation followed by DMPP elimination:

![Pathway A diagram]

**Pathway B:** Anionic cycle of thiolate addition to methyl acrylate:

![Pathway B diagram]

**Pathway C:** Nucleophilic attack of thiolate at the phosphonium ester β-carbon:

![Pathway C diagram]

**Pathway D:** Nucleophilic attack of thiolate at a phosphonium ester methyl group:

![Pathway D diagram]
Table 4.3: Calculated transition state and reaction enthalpies and free energies for each step of the elementary reactions summarized in Pathways A-D. All values are given in kcal/mol at 298.15 K as calculated at the M06-2X/6-311G(2D,P)//B3LYP/6-31+G(D) level\textsuperscript{4,29,4,30} using the program Gaussian09.\textsuperscript{4,32} Values for each pathway A-D are reported relative to their respective starting materials.

<table>
<thead>
<tr>
<th>Pathway A: phosphonium ester deprotonation followed by DMPP elimination</th>
<th>T.S. 1</th>
<th>Rxn 1</th>
<th>T.S. 2</th>
<th>Rxn 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHCl\textsubscript{3}</td>
<td>$\Delta H^\circ$ or $\Delta H^\ddagger$</td>
<td>14.2</td>
<td>17.9</td>
<td>22.7</td>
</tr>
<tr>
<td></td>
<td>$\Delta G^\circ$ or $\Delta G^\ddagger$</td>
<td>14.0</td>
<td>8.1</td>
<td>12.1</td>
</tr>
<tr>
<td>DMSO</td>
<td>$\Delta H^\circ$ or $\Delta H^\ddagger$</td>
<td>11.1</td>
<td>15.3</td>
<td>22.0</td>
</tr>
<tr>
<td></td>
<td>$\Delta G^\circ$ or $\Delta G^\ddagger$</td>
<td>19.1</td>
<td>13.9</td>
<td>20.7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pathway B: Anionic cycle of thiolate addition to methyl acrylate</th>
<th>T.S. 3</th>
<th>Rxn 3</th>
<th>T.S. 4</th>
<th>Rxn 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHCl\textsubscript{3}</td>
<td>$\Delta H^\circ$ or $\Delta H^\ddagger$</td>
<td>2.0</td>
<td>2.1</td>
<td>-5.0</td>
</tr>
<tr>
<td></td>
<td>$\Delta G^\circ$ or $\Delta G^\ddagger$</td>
<td>13.4</td>
<td>12.8</td>
<td>16.5</td>
</tr>
<tr>
<td>DMSO</td>
<td>$\Delta H^\circ$ or $\Delta H^\ddagger$</td>
<td>5.3</td>
<td>4.2</td>
<td>-1.5</td>
</tr>
<tr>
<td></td>
<td>$\Delta G^\circ$ or $\Delta G^\ddagger$</td>
<td>16.42</td>
<td>14.8</td>
<td>19.2</td>
</tr>
</tbody>
</table>

| Pathway C: Nucleophilic attack of thiolate at the phosphonium ester $\beta$-carbon | T.S. 5 | Rxn 5 |
|---|---|
| CHCl\textsubscript{3} | $\Delta H^\circ$ or $\Delta H^\ddagger$ | 31.7 | -8.8 |
| | $\Delta G^\circ$ or $\Delta G^\ddagger$ | 29.9 | -19.9 |
| DMSO | $\Delta H^\circ$ or $\Delta H^\ddagger$ | 30.14 | -8.5 |
| | $\Delta G^\circ$ or $\Delta G^\ddagger$ | 37.7 | -10.5 |

| Pathway D: Nucleophilic attack of thiolate at a phosphonium ester methyl group | T.S. 6 | Rxn 6 |
|---|---|
| CHCl\textsubscript{3} | $\Delta H^\circ$ or $\Delta H^\ddagger$ | 32.3 | -8.8 |
| | $\Delta G^\circ$ or $\Delta G^\ddagger$ | 31.1 | -19.4 |
| DMSO | $\Delta H^\circ$ or $\Delta H^\ddagger$ | 29.7 | -8.5 |
| | $\Delta G^\circ$ or $\Delta G^\ddagger$ | 37.5 | -10.2 |


4.20. Thiol-acrylate reactions catalyzed by 0.01 molar equiv of DEA and HA were attempted, however the reactions did not reach completion within 30 minutes.


4.22. Polydispersity inherent to the PEG-diacrylate introduces greater uncertainty regarding the number of equivalents of acrylate moieties present as compared to small molecule experiments. Therefore a slight molar excess of both thiol and nucleophile (1.1 equiv per acrylate) was used for end group functionalization to ensure complete consumption of all acrylate groups present. Residual, unreacted thiol was removed under reduced pressure followed by high vacuum.
4.23. Methylene signals α and β to the sulfur of end group functionalized polymer 8 were found to be more diagnostic due to symmetry than signals of the less symmetric end group functionalized polymer obtained when PEG-diacylate 6 is reacted with hexanethiol 1. Furthermore, the lower boiling point of methyl 3-mercaptopropionate relative to hexanethiol (55 °C versus 150 °C, respectively) aided in ensuring the removal of any excess starting thiol resulting from non-ideal reaction stoichiometry due to the inherent polydispersity of PEG-diacylate 6.

4.24. Commercial suppliers of 2,000 Mn poly(ethylene glycol) methyl ether thiol similarly report a disulfide content of approximately 30%. See, for example, Sigma Aldrich product no 729140.


Chapter 5

Structurally Diverse Dendritic Architectures by Orthogonal Thiol-Maleimide and Furan-Maleimide “Click” Chemistries
This Chapter is based on the following work:


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Orthogonal thiol-ene “click” chemistries can offer a promising route to rapid and efficient high generation dendrimers. A set of orthogonal reactions, the kinetically-driven thiol-maleimide and thermodynamically reversible furan-maleimide reactions, are used to synthesize 3rd generation dendrimers. Homogeneous (A-R-B₂/A-R-B₂/A-R-B₂) and random (A-R-B₂/A-R-B₂/A-R’-B₂) dendritic architectures – previously inaccessible by orthogonal click chemical approaches – have been synthesized to demonstrate the utility of thiol-maleimide/furan-maleimide chemistries in dendrimer synthesis. This new methodology affords an enhanced ability to control, and therefore tailor, the dendrimer architecture to match the intended application.

5.2. Introduction

Major macromolecular architectures (Figure 5.1) have evolved from linear structures, such as Nylon, to branched, such as low density polyethylene, hyperbranched, and most recently, dendritic.¹ Dendrimers are nano-sized, radially symmetric macromolecules

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**Figure 5.1:** Common macromolecular architectures: linear polymers comprised AB monomers, branched polymers comprised of AB monomers, and hyperbranched polymers comprised of ABₙ monomers.
with well-defined, monodisperse structures consisting of tree-like branches (Figure 5.2). Unlike the AB monomers used to produce linear polymers, dendrimers are synthesized from ABₙ monomers (n is usually 2 or 3) resulting in hyperbranched structures. Moreover, dendrimers are prepared in an iterative fashion which is a further point of divergence from traditional, linear polymers. The combination of these growth attributes affords a nonlinear, stepwise growth wherein the number of monomer units doubles (AB₂) or triples (AB₃) upon the addition of each layer of branches (exponential growth), or generation, to the dendrimer architecture. In other words, the generation of the dendrimer corresponds directly to the numbers of iterative cycles performed, and may be easily determined by counting the number of branching points moving from the core toward the periphery. While an appropriately activated ABₙ monomer may be polymerized in a single step, the resulting polymer will have a higher polydispersity index (PDI) and a lower degree of branching than the analogous dendrimer due to more random growth that leads to a hyperbranched polymer. It is also worth noting that the iterative synthesis of linear polymers, such as the Merrifield solid-phase peptide synthesis, while well known, is limited in the number of monomers that may be linked in high yield and purity. Thus, the hallmark of dendrimer synthesis is the ability to synthesize high molecular weight polymers with narrow molecular weight distributions (PDI > 1.1), representing a single compound (PDI ≈ 1.0) as opposed to a Gaussian distribution of polymer molecular weights.
Figure 5.2: Dendrimer and dendron architectures. Key structural motifs are highlighted. Surface groups (multivalency), branching units (de Gennes dense packing), and interior cavities (host-guest chemistry).

5.1.1. Dendrimer Synthesis

In 1978, Fritz Vögtle reported the first successful laboratory synthesis of dendrimers.\textsuperscript{5,8} Importantly, Vögtle’s synthesis represented the first time in the history of synthetic polymer chemistry that an abiotic macromolecule had been synthesized without the use of a biological system.\textsuperscript{5,9} Shortly thereafter, in 1985, Donald Tomalia and his group at Dow Chemical Co. reported the preparation of poly(amidoamine) (PAMAM) dendrimers;\textsuperscript{5,10} the same year that George Newkome separately reported the synthesis of his own take on dendrimers, called arborols.\textsuperscript{5,11} The ‘cascade’ approach, now called “convergent”, used by Newkome involving acrylonitrile for the preparation of poly(propyleneimine)\textsuperscript{5,11} (PPI) arborols suffered from low yields and difficult product isolations, and helped popularize the divergent approach employed by Tomalia for the
preparation of PAMAM dendrimers. Scheme 5.1 highlights the divergent approach to dendrimer synthesis where growth occurs outward from a central core resulting in an exponentially increasing number reactive sites at the periphery.

Scheme 5.1: The divergent growth of dendrimers emanates outward. Blue and red spheres react to afford a new generation (growth step), and pendant green spheres are subsequently converted to blue spheres (activation step). The number of reactive sites on the periphery grows exponentially with each generation. This iterative process is repeated to grow higher generation dendrimers.

It is important to note that ‘dendrimer’ refers to an architectural state, and not a compound. The so-called ‘dendritic state’ separates dendrimers from other hyperbranched small molecules and macromolecules, and it is characterized by features and properties that develop as a function of size (generation).\(^5.12\) Unfortunately, efforts to expand the divergent approach beyond the original PAMAM structure were largely unsuccessful resulting in problems of purification and stunted growth or structural defects, which necessitated the development of alternative approaches to dendrimer synthesis.\(^5.9\)

In 1990, Jean Fréchet published the synthesis of a poly(benzyl ether) dendrimer using a novel synthetic strategy, the convergent methodology.\(^5.13\) Unlike the divergent methodology, convergent syntheses proceed from the periphery inward to afford
building blocks (dendrons, Figure 5.2) that may be subsequently reacted with a branched core molecule (Scheme 5.2). Seminal examples of dendrimer synthesis following the convergent methodology can be found in the work of Frechet, Miller, and Moore. Importantly, the convergent approach mitigates defects by drastically limiting the amount of reagents used and enables the more facile purification after each growth step.

**Scheme 5.2:** The convergent growth of dendrimers emanates inward. Blue and red spheres react (growth step), and green spheres are subsequently converted to blue spheres (activation step). This iterative process is repeated to obtain a dendron. Growth is controlled: at most two reactions must occur in parallel. In a final step, the dendron is reacted with a branched core to afford the resulting dendrimer.

Although dendrimers are traditionally prepared via highly rational synthetic methods that employ structurally divergent or convergent approaches, both synthetic strategies of growing dendrimers from a central core (Scheme 5.1), or bringing dendrimer subunits together in a final step (Scheme 5.2), are not without their limitations. The convergent methodology is thought to produce more homogeneous (monodisperse) dendrimers because the number of coupling reactions needed to add each new generation is held constant (typically 2 or 3 depending on branching). On
the other hand, at higher generations the core becomes increasingly crowded by large dendrons, and steric hindrance results in low conversions.\textsuperscript{5,14} Unavoidable steric constraints relegate the convergent methodology to the preparation of lower generation dendrimers. Conversely, divergent growth strategies mitigate steric constraints but require an exponentially increasing number of reactions to occur for dendrimer growth to proceed from one generation to the next.\textsuperscript{5,20} An exponentially increasing number of reactive sites at the periphery greatly increases the propensity for incomplete conversions. Incomplete reactions introduce defects that contribute to already challenging purification steps, and ultimately hurt overall reaction yields. Despite these synthetic obstacles, commercially available PAMAM and PPI dendrimers are prepared by the divergent method.\textsuperscript{5,21-5,23} The challenge then becomes expanding the scope of the divergent method.

5.1.2. Orthogonal Coupling Strategies

To unlock their full practical potential, high generation dendrimers ideally should be synthetically attainable quickly, efficiently, and with little to no purification; attributes missing from many of the traditional convergent and divergent growth approaches. The importance of efficient dendrimer preparation\textsuperscript{5,24} is recognized in the field, and significant effort has been focused on developing accelerated and more efficient syntheses. Previous attempts to accelerate the synthesis of dendrimers relied on branched AB\textsubscript{4} monomers,\textsuperscript{5,25} where A represents a focal point and B represents four identical branching points, and various orthogonal coupling strategies.\textsuperscript{5,26} Early reports
of orthogonal coupling strategies by Zimmerman combined AB$_2$ and CD$_2$ monomers by Mitsunobu esterification and Sonogashira chemistry, enabling the growth of dendrimers by one generation per step in contrast to requiring sequential growth and deprotection steps.$^{5,26}$ Although accelerated as compared to the first reports of dendrimers, these strategies still require complicated purification steps that lead to a considerable time investment and inefficiency. More recently, the application of orthogonal click chemistries has been employed to overcome the tedious, expensive, and time-consuming syntheses of dendrimers.$^{5,27-5,28}$ Bowman and coworkers highlighted the ability of numerous orthogonal “click” chemistries to circumvent end-group protection/deprotection steps and achieve high end-group conversions with few to no side reactions, enabling highly efficient dendrimer synthesis.$^{5,29}$
Scheme 5.3: Dendrimer synthesis using orthogonal Sonogashira and Mitsunobu reactions. Adapted from reference 5.26.
5.1.3. Orthogonal Click Strategies

The emergence of click chemistry in 2001\textsuperscript{5,30} brought with it an entirely new set of tools to address the synthetic challenges associated with bio-organic and materials synthesis. Click reactions are highly efficient, robust, and orthogonal, making them particularly well-suited for the preparation of dendrimers.\textsuperscript{5,31} The application of orthogonal “click” chemistries to the divergent growth of dendrimers has largely necessitated at least two different reactions. Majoral and coworkers demonstrated the power of orthogonal coupling strategies in dendrimer growth by synthesizing a 4\textsuperscript{th} generation dendrimer using orthogonal condensation reactions between phosphorhydrazines and aldehydes as well as the Staudinger reaction between phosphines and azides.\textsuperscript{5,32} In 2008, Hawker and coworkers were the first to employ thiol-ene click reactions, paired with esterification reactions, for the synthesis of dendrimers.\textsuperscript{5,33} More recently, Hawker and coworkers were able to synthesize a 6\textsuperscript{th} generation dendrimer using orthogonal thiol-ene/CuAAC reactions (Scheme 5.4).\textsuperscript{5,34} The highly efficient reaction conditions used by both Majoral et al. and Hawker et al. were also limiting; AB\textsubscript{2} and CD\textsubscript{2} monomers reacted to afford a singly accessible sequentially layered dendrimer architecture as demonstrated in Scheme 5.4. The Bowman group successfully employed a single orthogonal reaction, using selective thiol-Michael additions, to growth a 5\textsuperscript{th} generation dendrimer (Scheme 5.5).\textsuperscript{5,29a} The implementation of A*A\textsubscript{2} and B*B\textsubscript{2} monomers, however, still limited Bowman et al. to a single sequentially layered dendritic architecture. The use of kinetically driven thiol-maleimide\textsuperscript{5,35} reactions and thermodynamically driven furan-maleimide\textsuperscript{5,36} reactions
may be a key to unlocking the full potential of dendrimers by providing access to
dendrimers of any desired layering architecture via a single set of orthogonal reactions.

**Scheme 5.4:** Orthogonal thiol-ene (AB₂ growth, green) and copper(I)-catalyzed azide
alkyne cycloaddition (CD₂ growth, blue) click reactions for the preparation of 6<sup>th</sup>
generation dendrimers.

**Scheme 5.5:** Orthogonal, selective thiol-Michael additions between alkyl thiols (teal)
and a sulfone (red), and a thioglycolate (blue) and methacrylates (pink) to afford the
rapid and efficient synthesis of a 5<sup>th</sup> generation dendrimer.

In this report, we present the synthesis of 3<sup>rd</sup> generation dendrimers using an A-
R-B₂/A-R′-B₂ approach employing orthogonal thiol-Michael click and dynamic
covalent furan-maleimide reactions. We present a new methodology for accessing
previously unattainable dendritic architectures whereby monomers containing a focal
thiol (‘A’) and pendant furan-protected maleimide groups (‘B’2) may be “clicked” together in any order to yield homogenous (e.g. A-R-B2/A-R-B₂₂/A-R-B₂), sequentially layered (e.g. A-R-B₂₂/A-R’-B₂₂/A-R-B₂), multilayered (e.g. A-R-B₂₂/A-R’-B₂₂/A-R”-B₂), and random dendritic architectures (e.g. A-R-B₂₂/A-R-B₂₂/A-R’-B₂). This methodology affords complete control over the resulting dendritic architecture and enables dendrimer properties, such as hydrophilicity/hydrophobicity, cavity size, and branching to be tailored specifically to match the intended application of the dendrimer.

5.2. Synthesis of A-R-B₂ and A-R’-B₂ Monomers

The A-R-B₂ and A-R’-B₂ monomers were each synthesized in 10 steps from 3,5-dihydroxybenzoic acid (see Schemes 5.6 and 5.7). The syntheses of A-R-B₂ and A-R’-B₂ monomers both begin with the acid catalyzed Fischer esterification of 3,5-dihydroxybenzoic acid to afford the corresponding benzoate. The phenolic alcohols are benzyl protected and the benzoate is oxidized back to the carboxylic acid so that it may serve as a handle for the Steglich amidation with ethanolamine. The benzyl groups are hydrogenated at atmospheric pressure, and the phenolic alcohols are selectively substituted with either the R or R’ (2 and 5, respectively) furan-maleimide linker following the Williamson coupling. The R and R’ linkers are considered especially ‘valuable’ because they contain furan-maleimide groups. As such, considerable effort went into optimizing this reaction in particular and it was found that the Finklestein reaction facilitated higher yields. Fréchet demonstrated the power of Williamson ether couplings between highly nucleophilic phenolates and benzylic bromides in his initial
report on the preparation of poly(benzyl ether) dendrimers.\textsuperscript{5,13} The modular synthesis of A-R-B\textsubscript{2} and A-R′-B\textsubscript{2} precursors enables their preparation in large scales. It should be noted however that yields were found to be scale dependent. In general, poorer yields were observed on gram and multi-gram scale reactions, and further optimization is necessary in order for the syntheses of branched monomer precursors and, ultimately, A-R-B\textsubscript{2} and A-R′-B\textsubscript{2}, to be prepared on a commercial scale. After the selective substitution with either R or R′, the alkyl alcohol is converted to the corresponding bromide by the Appel reaction. The bromide is converted to the corresponding thioester through a substitution reaction with potassium thioacetate. The final step involves the anaerobic reduction of the thioester to the thiol with hydrazine monohydrate. The benzyl amide thiol moiety is shared in A-R-B\textsubscript{2} and A-R′-B\textsubscript{2}, and was chosen for its stability under aerobic oxidations. Benzylic thiol versions of A-R-B\textsubscript{2} and A-R′-B\textsubscript{2} were prepared separately, and were found to readily oxidize to their corresponding disulfides which complicated their handling and application in dendrimer syntheses, further highlighting the importance of the benzyl amide thiol moiety’s stability.
Scheme 5.6: Synthesis of A-R-B₂ monomer in 9 steps from 3,5-dihydroxybenzoic acid.
Scheme 5.7: Synthesis of A-R′-B₂ monomer in 4 steps from 10.
The syntheses of A-R-B₂ and A-R’-B₂ diverge after intermediate 10, and differ solely in the choice of furan-maleimide linker used to functionalize the phenolic alcohols on the benzoic acid core. The modular syntheses of thiol monomers A-R-B₂ and A-R’-B₂ provides a simple and highly tailorable route to tune dendrimer properties. To demonstrate this concept, furan-maleimide linkers 2 and 5 were synthesized as hydrophobic (2) and hydrophilic (5) linkers (Scheme 5.8), and when combined with intermediate 10, afford unique thiol monomers A-R-B₂ and A-R’-B₂, respectively.

**Scheme 5.8:** Synthesis of hydrophobic, 2, and hydrophilic, 5, furan-maleimide linkers.
5.3. Synthesis of Maleimide-Functionalized Core

A tri-maleimide functionalized core, 19, is synthesized in three steps from mesitylene. Benzoyl peroxide readily undergoes hemolysis when heated forming benzoyloxyl radicals which lose carbon dioxide to afford phenyl radicals. The phenyl radicals serve as initiators for the radical, benzylic bromination of mesitylene with N-bromosuccinimide. The benzylic bromines serve as efficient leaving groups for the $S_N2$ substitution with 1 to afford 18. Compound 18 is activated through a heat-mediated retro Diels-Alder reaction to afford 19.

Scheme 5.9: Synthesis of tri-maleimide functionalized core, 19, in three steps from mesitylene.

The combination of thiol monomers A-R-B$_2$ and A-R′-B$_2$ with maleimide-functionalized cores enables the growth of a variety of layered dendrimer architectures.
(Scheme 5.10). Scheme 5.10 illustrates how the synthesis of a dendron (i.e. singly valent core) proceeds to afford a myriad of different dendron architectures. Initially, either A-R-B₂ or A-R’-B₂ is reacted with a core molecule to yield an unactivated, or protected, version of a first generation (G₁₅) dendron. The notation G₁₅ denotes a first generation (G₁) furan-capped (F) dendron. Next, an activation step occurs where the retro Diels-Alder reaction is carried out by heating the G₁₅ dendron to afford G₁₆ (i.e. first generation, maleimide-capped). The activated G₁₆ contains pendant maleimides, which may now undergo another growth step with either A-R-B₂ or A-R’-B₂ to afford an unactivated second generation dendrimer, G₂₅. Subsequent activation and growth steps are may be carried out in a step-wise fashion to afford higher generation dendrons.

**Scheme 5.10:** A-R-B₂ and A-R’-B₂ monomers can be mixed iteratively to afford any combination of dendritic architectures including homogenous (top) and specifically layered (bottom) structures.
5.4. Dendron Synthesis

An example of the stepwise growth of a $\text{G}_2\text{F}$ dendron is shown in Figure 5.3. Growth and activation steps are easily monitored by $^1\text{H}$ NMR spectroscopy. Figure 5.3a shows a mixture of a monovalent core, $\text{N}$-methyl maleimide, and $\text{A-R-B}_2$. The vinylic protons of $\text{N}$-methyl maleimide appear at 6.7 ppm, shown in blue, and the pendant furan groups of $\text{A-R-B}_2$ appear at 6.5 and 5.3 ppm, shown in purple. The addition of a catalytic amount of trimethylamine (TEA) initiates the thiol-maleimide click reaction (growth step) evidenced by the disappearance of the maleimide vinylic protons at 6.7 ppm concurrent with the appearance of a new doublet of doublets at 3.7 ppm, shown in red, resulting in a $\text{G}_1\text{F}$ dendron (Figure 5.3b). The retro Diels-Alder (activation step) is carried out by heating $\text{G}_1\text{F}$ at 140 °C for 1 hour. Figure 5.3c shows $\text{G}_1\text{M}$ marked by the appearance of the vinylic maleimide protons at 6.7 ppm, shown in blue, concurrent with the disappearance of furan signals at 6.5 and 5.3 ppm, shown in purple. An additional 2 equivalents of $\text{A-R-B}_2$ and a catalytic amount of TEA initiates the next growth step to afford $\text{G}_2\text{F}$, and the iterative process outlined above may be repeated to obtain up to 4th generation homogeneous dendrons.
**Figure 5.3:** $^1$H NMR highlighting the growth of a homogeneous 2nd generation Dendron using the A-R-B$_2$ monomer. Growth (a to b) and activation (b to c) steps are easily visualized by $^1$H NMR. Disappearance of N-methyl maleimide vinylic protons (blue, a to b) represents a complete growth step. Disappearance of furan allylic and vinylic protons (purple, b to c) concomitant with the appearance of maleimide vinylic protons (blue, b to c) marks a complete activation step.
5.5. Dendrimer Synthesis

Homogeneous and multilayered dendrimers, A-R-B₂/A-R-B₂/A-R-B₂ and A-R-B₂/A-R-B₂/A-R-B₂/A-R′-B₂, were also synthesized up to the 3rd generation. The connotation A-R-B₂/A-R-B₂/A-R-B₂ is used to denote a homogeneous 3rd generation dendrimer composed of A-R-B₂ monomers, while A-R-B₂/A-R-B₂/A-R′-B₂ is used to denote a dendrimer where the first and second generation are comprised of A-R-B₂ monomers while the third generation is A-R′-B₂. Dendrimers larger than the 3rd generation were not obtained due to their insolubility. The A-R-B₂/A-R-B₂/A-R-B₂ and A-R-B₂/A-R-B₂/A-R-B₂/A-R′-B₂ dendrimers are ~12,000 and ~15,000 Da respectively, and this likely contributes to their insolubility beyond the 3rd generation. In contrast to linear polymer growth which can theoretically continue ad infinitum, dendritic growth is mathematically limited. During the divergent growth of a dendrimer, the number of pendant groups at the periphery increases exponentially with each generation, while the volume available to the dendrimer only scales as the cube of its radius. As a result of this physical limitation, dendrimers become more globular and reach a steric limit to controlled growth, known as De Gennes dense packing, at higher generations. It is possible that De Gennes dense packing is also contributing to the insolubility of the A-R-B₂/A-R-B₂/A-R-B₂ and A-R-B₂/A-R-B₂/A-R′-B₂ G₃M dendrimers. However, the power of the orthogonal methodology presented herein is in its ability to unlock previously inaccessible dendrimer architectures. Previously, orthogonal thiol-ene chemistries had been limited to the synthesis of sequentially layered dendrimers composed of two types of branched monomers. With a library of thiol monomers,
the approach detailed herein may be used to synthesize $X^n$ unique dendrimers where $X$ is the number of different thiol monomers and $n$ is the generation (Figure 5.4).

![Figure 5.4: A subset of the various dendrimer architectures accessible with only four monomers (A, B, C, and D) using orthogonal thiol-maleimide and furan-maleimide chemistry.](image)

Dendrimers are prepared with a level of control absent many traditional, linear polymerizations, leading to highly monodisperse macromolecules. Characterization by gel permeation chromatography (GPC) showed narrow polydispersity peaks of homogeneous dendrons $G_1_F$ through $G_3_M$ (Figure 5.5). In addition to highly monodisperse GPC traces, number average molecular weight data ($M_n$) trends well with prediction. $M_n$ data from GPC shows the masses of each generation roughly doubling (exponential growth) after each growth step. Unfortunately, $M_n$ data from GPC cannot be used for the more precise determination of masses because the calibration curve is based on poly (methyl methacrylate) standards. The activation step at each generation is also supported by GPC. The difference between the apogees of the GPC curves within the same generation (e.g. $G_1_F$ and $G_1_M$) roughly double moving from one generation to the next (e.g. $G_1$ to $G_2$). This correlates to the fact that at each generation twice the number of furans are being lost to the retro Diels-Alder reaction. The polydispersity index (PDI) and mass spectroscopy data corresponding to the
homogeneous dendrons (Figure 5.5) are shown in Table 5.1. The PDI’s for each generation were shown to be highly monodisperse (<1.1) and ESI mass spectroscopy showed the molecular weights of each generation to agree well with their calculated mass. GPC was carried out using THF as a mobile phase, and solubility issues again hindered the characterizations at higher generations (>G3M). As such, samples for the dendrons shown in Figure 5.5, as well as A-R-B₂/A-R-B₂/A-R-B₂ and A-R-B₂/A-R-B₂/A-R'-B₂ dendrimers have been submitted to the Department of Polymer Science and Engineering at University of Massachusetts Amherst for further analysis by GPC with a mobile phase of dimethylformamide.

**Figure 5.5:** Gel permeation chromatography traces for G1ₕ through G3ₘ homogeneous dendrons built from A-R-B₂.
Matrix-assisted laser-desorption ionization (MALDI) and electrospray ionization (ESI) mass spectrometry were carried out to further support the formation of each ideal dendron and dendrimer generation. ESI was used to determine the exact mass of the small molecule precursors as well as smaller dendrons and dendrimers such as G1_F through G2_F. ESI mass spectroscopy supported the formation of G1_F, G1_M, and G2_F (see section 5.7 for mass spec results). High resolution accurate mass becomes increasingly challenging with larger ions, and for ions >2,500 Da the unambiguous assignment of the exact elemental formula is not possible. As such, low resolution MALDI was performed on dendron and dendrimer samples >2,500 Da. Despite being a soft ionization technique the intact molecular ions for dendron and dendrimer samples >2,500 Da were not observed under ionizations conditions with either dithranol or 2,5-dihydroxybenzoic acid (DHB) matrices. Bowman et al. observed similar difficulty observing the molecular ions for dendrimers prepared via orthogonal thiol-Michael click reactions.\textsuperscript{5,29a} It should be noted, however, that molecular fragments observed by MALDI did generally support the formation of each generation as did \textsuperscript{1}H NMR and GPC.

\textbf{Table 5.1:} The predicted masses, observed masses by ESI mass spectroscopy, and PDI’s for G1_F through G3_M homogeneous dendrons built from A-R-B\textsubscript{2}.

<table>
<thead>
<tr>
<th>Generation</th>
<th>M\textsubscript{calc}</th>
<th>M\textsubscript{obs}</th>
<th>PDI</th>
</tr>
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</tr>
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<td>4101.83</td>
<td>1.06</td>
</tr>
<tr>
<td>G3_M</td>
<td>3524.80</td>
<td>-</td>
<td>1.04</td>
</tr>
</tbody>
</table>
5.6. Conclusions

In conclusion we have demonstrated a new methodology capable of synthesizing previously inaccessible dendritic architectures by combining orthogonal thiol-maleimide click reactions with furan-maleimide chemistry. A-R-AB$_2$ and A-R’-B$_2$ monomers with propyl and tetraethylene glycol linkages, respectively, were designed, synthesized and applied to the dendron and dendrimer syntheses. To the best of our knowledge this is the first time that orthogonal chemistries have provided an efficient route to varied dendrimer structures. Although dendrons $>$G$_4$F and dendrimers $>$G$_3$F were not obtained, efforts are currently underway to design and synthesize more soluble analogues of the A-R-AB$_2$ and A-R’-B$_2$ monomers such that the resulting dendrimers are soluble. Additionally, syntheses of monomers with alternative thiol (A) and linker (R) functionalities are underway, and we anticipate that a library of unique monomers will afford previously unrecognized control of structure/function properties as they relate to dendrimers. Nevertheless, the ability to completely control the order in which monomers are layered onto the periphery of the dendrimer cannot be understated, and is the biggest contribution to the literature that the present work makes.

5.7. Materials and Methods

Materials

Unless otherwise stated chemicals were purchased from commercial suppliers and used as received. The syntheses of compounds 1, 2, 3, 4, 5, 6, 8, 10.
and 17\textsuperscript{5,48} were carried out according to modified literature procedures. Solvents were dried using an Innovative Technologies SPS-400-5 solvent purification system. All reactions were carried out under an anhydrous N\textsubscript{2} atmosphere unless otherwise noted. 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. Column chromatography was performed using glass columns over dynamic absorbents 60 Å, 32–63 μm silica gel. All \textsuperscript{1}H and \textsuperscript{13}C NMR spectra were recorded on with 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). Gel permeation chromatography (GPC) was performed on a Viscotek TDA 305 eluting with THF at 35 °C at 1.0 mL min\textsuperscript{-1}. The Viscotek TDA 305 was arranged with one guard column (particle size 8 micron, dimensions 10x4.6 mm) and a series of two identical SEC columns (particle size 10 micron, max pore size 5,000 Å, dimensions 300x7.8 mm). The number average molecular weight (\(M_n\)), molecular weight (\(M_W\)), and polydispersity index (PDI) were determined using the Viscotek RI detector and OmniSEC software, and calculated relative to linear poly(methyl methacrylate) (PMMA) standards in the range of Mp 1,960-903,000 purchased from Polymer Standards Service. APCI and MALDI high-resolution mass spectrometric analysis was performed at the University of Illinois at Urbana-Champaign and University of Massachusetts Amherst Mass Spec facilities.
**Compound 1:** Maleimide (20.0 g, 0.21 mol) was added to a round-bottom pressure flask, and suspended in diethyl ether (100 mL, 2.1 M). Furan (28.1 g, 0.41 mol) was added and the pressure flask was immediately sealed with the threaded Teflon cap. The reaction was heated at 100 °C overnight, and then allowed to cool to room temperature. After cooling to room temperature the reaction mixture was filtered through a fritted funnel and washed with excess diethyl ether. The solid was collected and dried under high vacuum to afford 33.7 g (99%) of compound 1 as a white solid. The product was used without further purification.

**Compound 2:** A three-neck round-bottom flask was charged with compound 1,3-dibromopropane (61.1 g, 0.30 mol), potassium carbonate (41.0 g, 0.29 mol), potassium iodide (0.51 g, 31.0 mmol), and acetone (305 mL) under inert atmosphere. Compound 1 (10.0 g, 0.061 mol) was added and the solution was stirred at 50 °C for 8 hours. The solution was filtered through a fritted funnel and the filtrate was concentrated under reduced pressure. The resulting residue was purified on a silica plug using a mixture of EtOAc:Hex (1:1) to yield 15.4 g (89%) of compound 2 as a white solid.

**Compound 3:** Tetraethylene glycol (100.9 g, 520.0 mmol) was added to a round-bottom flask, dissolved in 100 mL of tetrahydrofuran, and cooled to 0 °C. Separately, sodium hydroxide (3.32 g, 83.0 mmol) was dissolved in 30 mL of water. The sodium hydroxide/water solution was added to the tetraethylene glycol solution at 0 °C, and the resulting mixture was stirred for 30 minutes at 0 °C. A solution of p-toluenesulfonyl chloride (9.90 g, 52.0 mmol) in tetrahydrofuran (30 mL) was added dropwise to the
solution of tetraethylene glycol solution at 0 °C over the course of 1 hour. The resulting mixture was warmed slowly to room temperature and stirred overnight at room temperature. The mixture was concentrated under reduced pressure, diluted with dichloromethane, and extracted three times with dichloromethane. The combined organic layers were washed three times with water, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to afford 18.0 g (99%) of compound 3 as a viscous oil.

**Compound 4:** Compound 1 (8.5 g, 51.0 mmol) and potassium carbonate (9.4 g, 68.0 mmol) were added to a three-neck round-bottom flask and placed under an inert N₂ atmosphere and dissolved in acetone (34 mL, 1.0 M). In a separate round-bottom flask, compound 3 (11.9 g, 34.0 mmol) was dissolved in acetone (34 mL, 1.0 M) under an N₂ atmosphere. The solution containing compound 3 was added to the three-neck round-bottom, and the resulting mixture was heated at 50 °C for 60 hours. Solids were removed by filtration through a fritted funnel, and the filtrate was concentrated under reduced pressure. The resulting residue was purified by column chromatography DCM:MeOH (98:2) to afford 11.1 g (95%) compound 4 as a viscous oil.

**Compound 5:** Triethylamine (13.2 g, 130.0 mmol) was added to a solution of compound 4 (11.1 g, 33.0 mmol) and p-toluenesulfonyl chloride (7.7 g, 41.0 mmol) in dichloromethane (66 mL, 0.5 M), and the resulting solution was stirred overnight at room temperature. The solution was diluted with water and extracted three times with dichloromethane. The combined organic layers were dried over magnesium sulfate,
filtered, and concentrated under reduced pressure. The resulting residue was purified by column chromatography using a mixture of DCM:Hex (80:20) to afford 10.7 g (66%) compound 5 as a viscous oil. $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 7.82 (d, 2H, J = 8.0 Hz), 7.37 (d, 2H, J = 8.5 Hz), 6.53 (s, 2H), 5.28 (s, 2H), 4.18 (t, 2H, J = 4.5 Hz), 3.70 (t, 4H, J = 5.0 Hz), 3.64 (t, 2H, J = 5.0 Hz), 3.62-3.57 (m, 8H), 2.88 (s, 2H), 2.47 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 176.1, 144.8, 136.5, 132.9, 129.8, 128.0, 80.9, 80.8, 70.7, 70.6, 70.5, 69.3, 68.6, 67.1, 47.5, 38.2, 21.6 ppm.

**Compound 6**: A catalytic amount of concentrated sulfuric acid (95-98%, 1 mL) was added to a solution of 3,5-dihydroxybenzoic acid (65.0 mmol, 10.0 g) in methanol (80 mL, 0.81 M). The solution was refluxed for 5 hours, concentrated under reduced pressure and diluted with ethyl acetate. The resulting solution was washed once each with saturated sodium bicarbonate, water, and brine. The organic layer was dried over magnesium sulfate, filtered, and concentrated under reduced pressure to yield 9.9 g (91%) of compound 6 as a white solid.

**Compound 7**: Compound 6 (9.9 g, 59.0 mmol) and potassium carbonate (37.0 g, 267.6 mmol) were added to a two-neck flask and placed under an inert N$_2$ atmosphere. Acetone (100 mL, 0.89 M) and benzyl bromide (45.8 g, 267.6 mmol) were added and the resulting solution was stirred overnight at room temperature. The solution was diluted with ethyl acetate and water, and extracted four time with ethyl acetate. The combined organic layer were washed once with brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was
recrystallized three times from ether to afford 21.0 g (67%) of compound 7 as a white solid. \(^1\)H NMR (CDCl\(_3\), 500 MHz): δ 7.46-7.35 (m, 10H), 7.32 (d, 2H, J = 2.0 Hz), 6.83 (t, 1H, J = 2.5 Hz), 5.10 (s, 4H), 3.93 (s, 3H). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): δ 166.8, 159.9, 136.6, 132.2, 128.7, 128.2, 127.6, 108.5, 107.3, 70.3, 52.3 ppm.

**Compound 8:** A mixture of compound 7 (21.0 g, 60.0 mmol), powdered potassium hydroxide (8.5 g, 151.0 mmol), and ethanol (200 mL, 0.3 M) were refluxed for two hours. The resulting mixture was diluted with ethyl acetate and acidified to pH 1 with 1N HCl. The organic layer was washed twice with water, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to yield 18.7 g (93%) of compound 8 as a white solid. \(^1\)H NMR (DMSO-d\(_6\), 500 MHz): δ 7.46-7.33 (m, 10H), 7.15 (d, 2H, J = 2.5 Hz), 6.92 (t, 1H, J = 2.5 Hz), 5.15 (s, 4H). \(^{13}\)C NMR (75 MHz, DMSO-d\(_6\)): δ 167.5, 159.9, 137.2, 133.7, 128.9, 128.3, 128.1, 108.6, 106.9, 70.0 ppm.

**Compound 9:** Compound 8 (18.0 g, 54.0 mmol), ethanolamine (4.0 g, 65.0 mmol), and trimethylamine (13.6 g, 135.0 mmol) were placed under an inert N\(_2\) atmosphere. Anhydrous dimethylformamide (54.0 mL, 0.5 M) and anhydrous dichloromethane (54.0 mL, 0.5 M) were added and the solution was cooled to 0 °C. N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (12.4 g, 65.0 mmol) was added portion-wise to the solution at 0 °C, the solution was slowly warmed to room temperature, and stirred further at room temperature for 24 hours. The resulting mixture was filtered through, diluted with water, and extracted five times with dichloromethane. The combined organic layers were dried over magnesium sulfate, filtered, and
The resulting residue was purified over a short plug of silica using a mixture of DCM:MeOH (97:3), and the residue was purified further by recrystallization from dichloromethane to yield 11.5 g (57%) of compound 9 as a white solid. $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 7.45-7.29 (m, 10H), 7.03 (d, 2H, J = 2.5 Hz), 6.76 (t, 1H, J = 2.5 Hz), 6.57 (s, 1H), 5.08 (s, 4H), 3.85 (q, 2H, J = 5.0 Hz), 3.64 (q, 2H, J = 5.0 Hz), 2.48 (t, 1H, 5.0 Hz). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 168.3, 160.0, 136.4, 128.6, 128.2, 127.6, 106.2, 105.3, 70.3, 62.0, 42.9 ppm.

**Compound 10:** 10 wt % palladium on carbon (1.15 g) was added to a solution of compound 9 (11.5 g, 30.0 mmol) in ethanol (60 mL) and ethyl acetate (40 mL) under a hydrogen atmosphere (1.0 atm). The suspension was stirred at room temperature for 16 hours, and filtered through celite while washing with excess ethyl acetate. The filtrate was concentrated under reduced pressure and recrystallized from warm methanol to afford 5.3 g (88%) of compound 10 as a brown solid.

**Compound 11:** A three-neck round-bottom flask was charged with compound 2 (7.02 g, 0.025 mol), potassium carbonate (3.4 g, 0.025 mol), potassium iodide (91 mg, 0.55 mmol), and acetone (22 mL) under inert atmosphere. After stirring for 10 minutes at room temperature, compound 10 (2.2 g, 0.011 mol) was added and heated overnight at 50 °C. The mixture was filtered through a fritted funnel and the filtrate was concentrated. The resulting residue was purified by column chromatography using a mixture of EtOAc:MeOH (96:4) to yield 4.2 g (62%) of 11 as a white solid. $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 6.88 (d, 2H, J = 2.4 Hz), 6.72 (s, 1H), 6.54 (t, 1H, J = 2.4 Hz),
6.51 (s, 4H), 5.25 (s, 4H), 3.96 (t, 4H, J = 6.8 Hz), 3.81 (q, 2H, J = 5.4 Hz), 3.69 (t, 4H, J = 6.8 Hz), 3.58 (q, 2H, J = 5.4 Hz), 2.85 (s, 4H), 2.75 (t, 1H, J = 5.7 Hz), 2.05 (p, 4H, J = 6.6 Hz). $^{13}$C NMR (75 MHz, CDCl3): $\delta$ 176.2, 168.3, 159.9, 136.5, 136.2, 105.9, 105.4, 80.9, 65.6, 62.6, 47.4, 43.0, 36.1, 27.1 ppm. TOF MS ESI (m/z) [M+H]$^+$ Calculated for C$_{31}$H$_{34}$N$_3$O$_{10}$, 608.2244, found 608.2250.

**Compound 12:** A three-neck round-bottom flask was charged with compound 11 (3.2 g, 0.0053 mol) and dry dichloromethane (27 mL) under inert atmosphere. The three-neck round-bottom flask was charged with carbon tetrabromide (2.1 g, 0.0063 mol) and triphenylphosphine (1.7 g, 0.0063 mol) and stirred at room temperature overnight. The solution was concentrated and purified by column chromatography using a mixture of EtOAc:Hex (3:1) to yield 3.0g (86%) of 12 as a white solid. $^1$H NMR (CDCl3, 300 MHz): $\delta$ 6.87 (d, 2H, J = 1.8 Hz), 6.63 (s, 1H), 6.54 (s, 1H), 6.51 (s, 4H), 5.25 (s, 4H), 3.96 (t, 4H, J = 6.0 Hz), 3.81 (q, 2H, J = 6.0 Hz), 3.69 (t, 4H, J = 6.0 Hz), 3.57 (t, 2H, J = 6.0 Hz), 2.85 (s, 4H), 2.06 (p, 4H, J = 6.6 Hz). $^{13}$C NMR (75 MHz, CDCl3): $\delta$ 176.1, 167.2, 159.9, 136.5, 136.1, 105.8, 105.0, 80.9, 65.5, 47.4, 41.6, 36.1, 32.2, 27.1 ppm. TOF MS ESI (m/z) [M+H]$^+$ Calculated for C$_{31}$H$_{33}$N$_3$O$_9$, 670.1400, found 670.1410.

**Compound 13:** A three-neck round-bottom flask was charged with compound 12 (2.0 g, 0.003 mol), potassium thioacetate (0.68 g, 0.006 mol), potassium iodide (25 mg, 0.15 mmol), and acetonitrile (15 mL) under inert atmosphere. The solution was stirred at room temperature for 5 hours before it was filtered through a fritted funnel. The filtrate was concentrated and purified by column chromatography using a mixture EtOAc:Hex
(2:1) to yield 1.4 g (71%) of 13 as a white solid. $^1$H NMR (CDCl$_3$, 300 MHz): δ 6.84 (d, 2H, J = 1.8 Hz), 6.61 (s, 1H), 6.53 (s, 1H), 6.51 (s, 4H), 5.26 (s, 4H), 3.96 (t, 4H, J = 5.9 Hz), 3.69 (t, 4H, J = 6.8 Hz), 3.59 (q, 2H, J = 6.5 Hz), 3.11 (t, 2H, J = 6.5 Hz), 2.85 (s, 4H), 2.37 (s, 3H), 2.06 (p, 4H, J = 6.2 Hz). $^{13}$C NMR (75 MHz, CDCl$_3$): δ 196.4, 176.1, 167.2, 159.8, 136.5, 136.2, 105.7, 105.1, 80.9, 65.5, 47.4, 40.0, 36.1, 30.7, 28.7, 27.2 ppm. 

TOF MS ESI (m/z) [M+H]$^+$ Calculated for C$_{33}$H$_{36}$N$_3$O$_{10}$S, 666.2121, found 666.2124.

**Compound A-R-B$_2$:** A three-neck round-bottom flask was charged with compound 9 (1.0 g, 0.0015 mol) and tetrahydrofuran under inert atmosphere. Hydrazine monohydrate (0.14 g, 0.0045 mol) was added, and the reaction was stirred at room temperature for 4 hours and quenched with acetic acid (0.27 g, 0.0045 mol). The solution was concentrated, and extracted three times from water using dichloromethane. The organic layers were collected and concentrated, and the residue was purified by column chromatography using a mixture of DCM/MeOH (99:1) to yield 0.7 g (78%) of A-R-B$_2$ as a white solid. $^1$H NMR (CDCl$_3$, 300 MHz): δ 6.87 (d, 2H, J = 2.4 Hz), 6.63 (s, 1H), 6.54 (s, 1H), 6.51 (s, 4H), 5.25 (s, 4H), 3.96 (t, 4H, J = 6.2 Hz), 3.69 (t, 4H, J = 7.1 Hz), 3.59 (q, 2H, J = 6.3 Hz), 2.84 (s, 4H), 2.76 (q, 2H, J = 6.3 Hz), 2.06 (p, 4H, J = 6.3 Hz), 1.41 (t, 1H, J = 8.4 Hz). $^{13}$C NMR (75 MHz, CDCl$_3$): δ 176.2, 167.3, 159.8, 136.5, 105.8, 104.8, 80.9, 65.5, 47.4, 43.0, 36.0, 27.1, 24.4 ppm.

**Compound 14:** A three-neck round-bottom flask was charged with compound 5 (9.9 g, 0.02 mol), potassium carbonate (2.8 g, 0.02 mol), and acetone (45 mL) under inert
atmosphere. After stirring for 10 minutes at room temperature, compound 10 (1.8 g, 0.009 mol) was added and heated overnight at 50 °C. The mixture was filtered through a fritted funnel and the filtrate was concentrated. The resulting residue was purified by column chromatography using a mixture of EtOAc:MeOH (96:4) to yield 1.2 g (16%) of 14 as a white solid. \(^1\)H NMR (CDCl\(_3\), 500 MHz): δ 7.02 (t, 1H, J = 5.5 Hz), 6.99 (d, 2H, J = 2.5 Hz), 6.63 (t, 1H, J = 2.5 Hz), 6.50 (s, 4H), 5.25 (s, 4H), 4.15 (t, 4H, J = 4.5 Hz), 3.85 (t, 4H, J = 4.5 Hz), 3.82 (t, 2H, J = 5.0 Hz), 3.72-3.60 (m, 26H), 3.09 (t, 1H, J = 5.5 Hz), 2.86 (s, 4H). \(^1\)C NMR (125 MHz, CDCl\(_3\)): δ 176.2, 168.0, 159.8, 136.5, 106.0, 104.6, 80.9, 80.8, 70.6, 70.5, 70.4, 70.0, 69.5, 67.6, 67.0, 61.8, 47.4, 43.0, 38.1 ppm.

**Compound 15:** A three-neck round-bottom flask was charged with compound 14 (1.2 g, 0.0014 mol) and dry dichloromethane (14 mL) under inert atmosphere. The three-neck round-bottom flask was charged with carbon tetrabromide (0.57 g, 0.0017 mol) and triphenylphosphine (0.45 g, 0.0017 mol) and stirred at room temperature overnight. The solution was concentrated and purified by column chromatography using a mixture of EtOAc:Hex (3:1) to yield 0.9 g (70%, crude yield) of 15 as a white solid. \(^1\)H NMR (CDCl\(_3\), 500 MHz): δ 7.12 (d, 2H, J = 2.0 Hz), 6.64 (s, 1H), 6.51 (s, 4H), 5.27 (s, 4H), 4.44 (t, 2H, J = 9.5 Hz), 4.15 (t, 4H, J = 5.0 Hz), 4.07 (t, 2H, J = 9.5 Hz), 3.86 (t, 4H, J = 5.0 Hz), 3.73-3.63 (m, 26H), 2.87 (s, 4H). \(^1\)C NMR (125 MHz, CDCl\(_3\)): δ 176.0, 164.2, 159.6, 136.5, 106.5, 105.3, 80.8, 80.7, 70.6, 70.5, 70.4, 70.0, 69.4, 67.6, 67.0, 54.7, 47.3, 38.1 ppm.
**Compound 16:** A three-neck round-bottom flask was charged with compound 15 (3.0 g, 0.0033 mol), potassium thioacetate (0.76 g, 0.0066 mol), potassium iodide (55 mg, 0.33 mmol), and acetonitrile (16.5 mL) under inert atmosphere. The solution was stirred at room temperature for 5 hours before it was filtered through a fritted funnel. The filtrate was concentrated and purified by column chromatography using a mixture EtOAc:Hex (2:1) to yield 0.8 g (27%) of 16 as a white solid. $^1$H NMR (CDCl$_3$, 500 MHz): \(\delta\) 6.98 (d, 2H, \(J = 2.0\) Hz), 6.80 (s, 1H), 6.65 (t, 1H, \(J = 2.0\) Hz), 6.50 (s, 4H), 5.26 (s, 4H), 4.16 (t, 4H, \(J = 5.0\) Hz), 3.86 (t, 4H, \(J = 5.0\) Hz), 3.73-3.61 (m, 28H), 2.87 (s, 4H), 1.45 (t, 1H, \(J = 8.5\) Hz). $^{13}$C NMR (125 MHz, CDCl$_3$): \(\delta\) 176.2, 167.2, 160.0, 136.5, 136.4, 106.0, 104.7, 80.6, 70.7, 70.6, 70.5, 70.1, 69.6, 67.7, 67.1, 47.4, 43.0, 38.2, 25.4 ppm.

**Compound A- R'-B2:** A three-neck round-bottom flask was charged with compound 16 (0.8 g, 0.88 mmol) and tetrahydrofuran under inert atmosphere. Hydrazine monohydrate (138.8 mg, 1.77 mmol) was added, and the reaction was stirred at room temperature for 4 hours and quenched with acetic acid (106.3 mg, 1.77 mmol). The solution was concentrated, and extracted three times from water using dichloromethane. The organic layers were collected and concentrated, and the residue was purified by column chromatography using a mixture of DCM/MeOH (99:1) to yield 0.6 g (65%) of A- R'-B2 as a white solid. $^1$H NMR (CDCl$_3$, 500 MHz): \(\delta\) 6.95 (d, 2H, \(J = 2.5\) Hz), 6.79 (t, 1H, \(J = 5.5\) Hz), 6.64 (t, 1H, \(J = 2.5\) Hz), 6.50 (s, 4H), 5.26 (s, 4H), 4.16 (t, 2H, \(J = 5.0\) Hz), 3.86 (t, 4H, \(J = 4.5\) Hz), 3.73-3.62 (m, 28H), 3.15 (t, 2H, \(J = 6.0\) Hz), 2.87 (s, 4H), 2.38 (s, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$): \(\delta\) 196.6, 176.2,
Compound 17: N-bromosuccinimide (NBS) was dissolved in near-boiling water, gravity filtered into a round-bottom flask at 0 °C, and allowed to recrystallize at 0 °C for 2 hours. The crystals were filtered through a Buchner funnel and washed with ca. 100 mL of ice water before drying under high vacuum. The freshly recrystallized NBS (6.7 g, 0.038 mol), mesitylene (1.3 g, 0.011 mol), and benzoyl peroxide (0.78 g, 0.003 mol) were dissolved in chloroform (16 mL, 0.7 M) and refluxed at 70 °C for 6 hours. The crude reaction mixture was filtered, washed with water, and extracted 3 times with DCM. The combined organic layers were washed once with brine, dried over MgSO₄, filtered, and condensed under reduced pressure. The residue was purified by column chromatography using mixture of Hexanes:EtOAc (98:2) to afford 2.8 g (72%) of 17 as a light yellow solid.

Compound 18: 1 (4.3 g, 0.026 mol) and potassium carbonate (4.3 g, 0.031 mol) were added to a 3-arm flask and placed under a N₂ atmosphere and dissolved in dry acetonitrile (9 mL, 0.87 M). Compound 17 (2.8 g, 0.0078 mol) was dissolved in acetonitrile (9 mL, 0.87 M) under N₂, and added to the 3-arm flask. The reaction mixture was heated at 50 °C for 48 hours, and the completion of the reaction was monitored by TLC. The reaction mixture was filtered and condensed under reduced pressure. The residue was purified by column chromatography using a mixture of EtOAc:MeOH (98:2) to afford 0.9 g (19%) of 18 as a white solid. ¹H NMR (CDCl₃,
500 MHz): δ 7.13 (s, 3H), 6.53 (s, 6H), 5.32 (s, 6H), 4.60 (s, 6H), 2.87 (s, 6H). $^{13}$C NMR (125 MHz, CDCl3): δ 175.8, 136.6, 136.3, 126.5, 80.9, 47.5, 42.0 ppm.

**Compound 19: 18** (0.9 g, 0.0015 mol) was added to a round-bottom flask and suspended in anisole (5 mL). The reaction mixture was heated at 140 °C for 1 hour, and then allowed to cool to room temperature. The crude reaction was added directly to a silica gel column. Excess anisole was removed by eluting with hexanes. The remaining residue was purified by gradually increasing the polarity of the elution mixture to DCM:MeOH (99:1) to afford 0.5 g (83%) of 19 as a white solid. $^1$H NMR (CDCl3, 500 MHz): δ 7.19 (s, 3H), 6.73 (s, 6H), 4.63 (s, 6H). $^{13}$C NMR (125 MHz, CDCl3): δ 170.3, 137.2, 134.2, 127.4, 41.0 ppm.

**General Procedure for Dendron Synthesis:**

**Growth step:** N-methylmaleimide (1.0 equiv) and either A-R-B$_2$ or A'-R'-B$_2$ (2.1 equivs) was added to a 3 dram vial and dissolved in 1.0 M deuterated chloroform. A catalytic amount of TEA was added and the reaction mixture was stirred under ambient atmosphere for 4 hours. The crude reaction mixture was added directly to a silica gel column and purified with a mixture of DCM/MeOH. **Activation step:** The dendron or dendrimer sample (1 equiv) was added to 10 mL round-bottom flask and suspended in 3 mL of anisole. The reaction mixture was heated at 140 °C for 1 hour. After cooling to room temperature the crude reaction mixture was added directly to a silica gel column. Anisole was removed by eluting with hexanes purified by column chromatography eluting with a mixture of DCM/MeOH. The above growth and activation steps were repeated sequentially,
doubling the molar equivalents of A-R-B₂ or A-R′-B₂ at each growth step, to obtain a G₄F dendron.

**General Procedure for Dendrimer Synthesis:** Dendrimer synthesis followed the same steps as Dendron synthesis with the key difference being that 19 is used as a core molecule in place of N-methylmaleimide. **Growth step:** Compound 19 (1.0 equiv) and either A-R-B₂ or A-R′-B₂ (2.1 equivs) was added to a 3 dram vial and dissolved in 1.0 M deuterated chloroform. A catalytic amount of TEA was added and the reaction mixture was stirred under ambient atmosphere for 4 hours. The crude reaction mixture was added directly to a silica gel column and purified with a mixture of DCM/MeOH. **Activation step:** The dendron or dendrimer sample (1 equiv) was added to 10 mL round-bottom flask and suspended in 3 mL of anisole. The reaction mixture was heated at 140 °C for 1 hour. After cooling to room temperature the crude reaction mixture was added directly to a silica gel column. Anisole was removed by eluting with hexanes purified by column chromatography eluting with a mixture of DCM/MeOH.
5.8. Note and References


Chapter 6

Conclusions and Future Directions
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6.0. Conclusions and Future Directions

The work discussed in this dissertation expands on the mechanistic understanding of the thiol-maleimide reaction (Chapter 2), ternary combinations of common Michael acceptors and thiols that afford selective products (Chapter 3), the formation – or lack thereof – of nucleophile byproducts during amine and phosphine initiated thiol-Michael reactions (Chapter 4), and presents a demonstration of how thiol-maleimide click reactions and furan-maleimide Diels-Alder chemistry may be exploited to afford previously inaccessible dendritic architectures (Chapter 5).

The mechanistic nuances of the thiol-maleimide reaction indicated an ion-pair promoted pathway in low dielectric solvents (e.g. CHCl₃), a conclusion that was supported with computational modeling of the reaction energetics and kinetics. Moreover, we observed that acid-base and/or nucleophile initiated pathways become competitive — and sometimes preferred — in high dielectric solvents. Proof-of-concept experiments involving the ternary combinations of two different thiols with maleimide validated the hypothesis that judicious choice of solvent and initiator influences reaction selectivity. The subtleties of selective thiol-Michael reactions were further explored through careful consideration of the ternary combinations of six common Michael acceptors (N-methylmaleimide, ethyl vinyl sulfone, n-butyl isocyanate, methyl acrylate, methyl methacrylate, and ethyl crotonate) and five thiols (methyl thioglycolate, methyl 3-(methylthio)propionate, benzenethiol, β-mercaptoethanol, and 1-hexanethiol). A more complete understanding of ternary selectivity enabled the design of one-pot quaternary, sequential quaternary, and senary
thiol-Michael reactions. Separately, we hypothesized, and support experimentally and by computational modeling, a rationale for the observation that no quantifiable amount of nucleophile byproduct was measured during phosphine initiated thiol-acrylate reactions; a result that differed from amine initiated thiol-acrylate reactions under some conditions.

Taken together, our mechanistic work designing selective thiol-Michael reactions led to the application of two orthogonal reaction paradigms — thiol-maleimide click and furan-maleimide Diels-Alder — to the synthesis of dendrimers. The combination of these orthogonal chemistries is a significant advancement in the field of dendrimer synthesis, as it provides previously inaccessible control and precision over the design of dendritic architectures, while still capitalizing on the efficiency afforded by click chemistry.

Future work will involve expanding the scope of the research presented in Chapter 1 on thiol-maleimide reactions to employ other common Michael acceptors, with the goal of better understanding the influence of solvent, initiator, and thiol in the context of those Michael acceptors. Moreover, the energetics associated with degradation pathways of ammonium byproducts produced following the nucleophile initiated thiol-Michael reaction — similar to the phosphonium byproduct discussed in Chapter 4 — will be studied computationally. The potential reactivity of ammonium byproducts will also be explored experimentally. In addition, considerable effort will be focused on designing more soluble analogues of A-R-B_2 and A-R’-B_2, so that generations in excess of G_3 may be obtained. When >G_4 dendrimers are prepared, they
will be functionalized with targeting ligands, imaging agents, drug molecules, or some combination thereof, and collaboration will be sought so that their pharmacologically relevant parameters may be measured to fully explored their medicinal potential.

In final summary, the work presented herein in partial fulfillment of the requirements for the degree of Doctor of Philosophy has contributed the following to the field of Chemistry: we (1) expanded mechanistic understanding of the ubiquitously useful thiol-maleimide reaction, and, using insights gained from this discovery, (2) designed complex thiol-Michael systems that afford selective products, (3) determined factors that influence the formation byproducts during amine and phosphine initiated thiol-Michael reactions, and (4) presented a demonstration of how thiol-maleimide and furan-maleimide chemistries afford orthogonality and efficiency enabling the synthesis of previously inaccessible dendritic architectures.