Macromolecules
ARTICLE

Macromolecules **2010**, *43*, 6381–6388 **6381**
DOI: 10.1021/ma101069c

Nucleophile-Initiated Thiol-Michael Reactions: Effect of Organocatalyst, Thiol, and Ene

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Received May 13, 2010; Revised Manuscript Received June 28, 2010

ABSTRACT: A detailed evaluation of the kinetics of the thiol-Michael reaction between hexanethiol and hexyl acrylate is described. It is shown that primary amines are more effective catalysts than either secondary or tertiary amines with, for example, quantitative conversion being achieved within 500 s in the case of hexylamine with an apparent rate constant of 53.4 mol L^{-1} s^{-1} at a catalyst loading of 0.057 mol %. Certain tertiary phosphines, and especially tri-*n*-propylphosphine and dimethylphenylphosphine, are shown to be even more effective species even at concentrations 2 orders of magnitude lower than employed for hexylamine and performed in solution with quantitative conversions reached within ca. 100 s for both species and apparent rate constants of 1810 and 431 mol L^{-1} s^{-1}, respectively. The nature of the thiol is also demonstrated to be an important consideration with mercaptoglycolate and mercaptopropionate esters being significantly more reactive than hexanethiol with reactivity mirroring the pK_a of the thiols. Likewise, it is shown that the structure of the activated ene is also crucial with the degree of activation and ene-substitution pattern being important features in determining reactivity. In terms of reaction with hexanethiol in the presence of hexylamine as catalyst, it is shown that propylmaleimide > diethyl fumarate > diethyl maleate > dimethylacrylamide > acrylonitrile > ethyl crotonate > ethyl cinnamate > ethyl methacrylate.

Introduction

The thiol−ene click[1] reaction has recently drawn a great deal of attention given its exceptional utility in organic synthesis, polymer functionalization, and network synthesis/modification. The well-known radical-mediated thiol−ene reaction involves the hydrothiolation of an alkene, commonly in a terminal position, and has been studied/utilized for decades. Such addition reactions can be readily initiated thermally or photochemically (with or without added photoinitiator) and proceed via thiyl radical addition to the C=C bond followed by a chain transfer reaction with additional thiol affording the corresponding thioether in essentially quantitative yield with anti-Markovnikov orientation. Recently, the radical thiol−ene reaction has been widely investigated for its general applicability in a wide range of fields, including, but not limited to, biocompatible network materials,[2] dendrimer synthesis,[3] nanoimprinting and lithography,[4] liquid crystal and holographic materials, glycopolymer synthesis,[5] protein immobilization,[6] and in the modification of low molecular weight polyisobutylene.[7] While there is little doubt that it is a highly efficient click process, one drawback of the radical-mediated thiol−ene reaction is the nonquantitative formation of target thioether with α,β-unsaturated *electron-deficient* alkenes, such as acrylates and acrylamides. With such substrates the addition of a thiyl radical across the C=C bond yields an intermediate carbon-centered radical that is able to undergo the desired chain transfer reaction *but* can also add across another C=C bond; i.e., the radical can propagate, giving oligomers/polymer as a contaminant in the final product. As such, the radical-mediated thiol−ene click reaction is best conducted with *electron-rich* double bonds, thus ensuring quantitative formation of the target thioether.

As with many addition reactions, the thiol−ene reaction is not limited to a radical-mediated process and can also proceed via an ionic mechanism and typically via anionic reactive centers. The common base-catalyzed addition of thiols to activated C=C bonds, i.e., the thiol-Michael reaction, has been investigated extensively in small molecule synthesis, polymer modification,[8] tissue engineering,[9] and step-growth polymerizations and can result in relatively high yields of thioether product by optimizing conditions such as the nature of the base catalyst, solvent, and chemical structures of the ene and thiol components. Many base-catalyzed systems, however, result in less than quantitative conversion and require lengthy reaction times, high polarity low volatile solvents, high catalyst concentrations, and elevated reaction temperatures. For a detailed description of Michael addition reactions, and particularly in the macromolecular field, the interested reader is directed to an excellent review by Mather et al.[10] Aside from the traditional base-catalyzed reaction, such hydrothiolations can be catalyzed/initiated with certain strong *nucleophiles* although less is known about such reactions in general even though evidence of the potential of primary amines as effective thiol-Michael catalysts was presented over 40 years ago by Saniu and Ogata.[11] Interestingly, and importantly from a practical standpoint, *nucleophile*-initiated thiol-Michael reactions possess the same general features as a typical radical-mediated thiol−ene click reaction, facilitating the rapid, modular, orthogonal addition of thiols to *electron-deficient* enes in a quantitative manner, under nondemanding conditions (no heat or light needed), with minimal amounts of simple, cheap, commercially available catalysts.

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Published on Web 07/14/2010

While the potency and synthetic potential of nucleophile-initiated thiol-Michael reactions are not yet fully appreciated, there are recent literature examples that clearly demonstrate the high efficacy and ease of execution of such reactions. For example, Chan et al. described nucleophile-mediated hydrothiolations as a route to branched molecules[12] and in convergent star polymer syntheses[13] using dimethylphenylphosphine (DMPP) as a catalyst, while Rim and Son recently detailed the synthesis of star-shaped oligomers in which one of the key building steps was an *n*-propylamine-mediated thiol-Michael addition reaction.[14] Haddleton and co-workers[15] described the synthesis of glycopolymers via catalytic chain transfer polymerization in which the end-chain ene functionality was modified to the corresponding thioether by phosphine-initiated addition of either benzylmercaptan or 2-mercaptoethanol. The same group also disclosed a facile route to polymer−protein conjugates composed of salmon calcitonin (sCT) and poly(ethylene glycol) (PEG) obtained by the addition of thiol groups in sCT to acrylic PEG macromonomers.[16] Hong, Kislukhin, and Finn[17] described the synthesis of a new class of fluorogenic probes for thiols based on thiol-Michael addition to a heavily activated ene bond in a series of 7-oxanorbornadienes. A recent review highlights these, and other, contributions in more detail.[1b] However, while such nucleophile-initiated thiol-Michael reactions are clearly beginning to attract the attention of researchers in various fields, currently there is little in the literature regarding a detailed evaluation of reaction components. In an attempt to address this deficiency herein, we detail our findings regarding the model reaction of hexanethiol with hexyl acrylate in the presence of a series of nucleophilic initiators. The primary emphasis will be on an evaluation of a series of amine and phosphine initiators although we will also highlight the effect of thiol and ene structure.

Experimental Section

All reagents were purchased from the Aldrich Chemical Co. at the highest available purity and used as received unless noted otherwise.

Synthesis. All reactions were performed at room temperature under a normal air atmosphere; i.e., no special precautions were taken. Below is detailed a typical procedure for the reaction between hexanethiol and hexyl acrylate in the presence of hexylamine. All other experimental details and NMR spectroscopic data can be found in the Supporting Information.

Hexylamine-Catalyzed Reaction of Hexanethiol with Hexyl Acrylate. To a 20 mL glass scintillation vial was added hexanethiol (0.590 g, 5.0 mmol) and hexylamine (10 μL, 0.55 wt %). To this was added hexyl acrylate (0.781 g, 5.0 mmol), and the mixture quickly agitated. ^{1}H NMR: yield >99% (a) δ 4.07−4.03 ppm (t, 2H); (b) δ 2.77 −2.71 ppm (t, 2H); (c) δ 2.58−2.46 ppm (m, 4H); (d) δ 1.63−1.49 ppm (hept, 4H); (e) δ 1.39−1 0.27 ppm (broad m, (14+) H, hexylamine region); (f) δ 0.87−0.83 ppm (broad t, 6H). ^{13}C NMR: (a) δ 171.97 ppm; (b) δ 64.72 ppm; (c) δ 34.87 ppm; (d) δ 32.04 ppm; (e) δ 31.33 ppm; (f) δ 29.43 ppm; (g) δ 28.45 ppm; (h) δ 26.93 ppm; (i) δ 25.48 ppm; (j) δ 22.50−22.47 ppm; (k) δ 13.92−13.89 ppm (neat, 3 h, RT).

Instrumentation. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker 300 MHz spectrometer. Samples were prepared in $CDCl_3$ at 15% v/v. Chemical shifts are reported in parts per million (ppm) relative to TMS. Thiol (2570 cm^{-1}) and acrylate (1640 cm^{-1}) conversions were monitored by real-time Fourier transform infrared (RTIR) spectroscopy using a modified Bruker 88 spectrometer. Reactions were conducted in a cell prepared by sandwiching samples between two sodium chloride salt plates at a thickness of 250 μm. IR absorption spectra were obtained at a scan rate of 5 scans/s.

Results and Discussion

Recently there has been renewed interest in the materials arena in the hydrothiolation of C=C bonds as a means of preparing advanced and complex materials. The most common form of this reaction, the radical-mediated thiol−ene reaction, has been shown to be a highly efficient reaction and its use demonstrated in a range of synthetic applications. The hydrothiolation of activated C=C bonds via a nonradical pathway, i.e., the thiol-Michael reaction, has also recently garnered attention in polymer synthesis and modification although the effect of basic reaction components is less well documented.

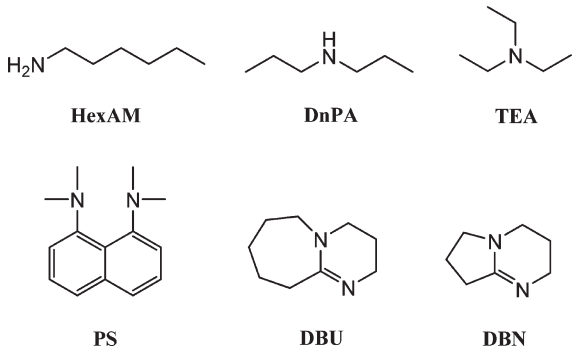


Figure 1. Chemical structures of amines employed as catalysts for thiol-Michael reactions.

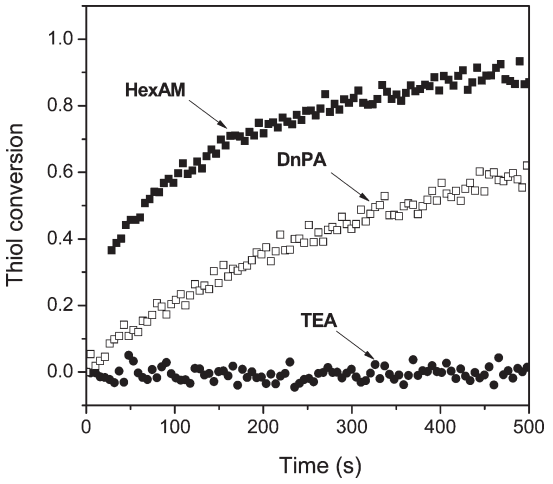


Figure 2. Thiol conversion vs time kinetic profiles using amine catalysts. 5 mmol of hexanethiol with 5 mmol of hexyl acrylate with 0.057 mol % catalyst: (■) hexylamine, (□) di-*n*-propylamine, and (●) triethylamine. Conversion determined by monitoring the disappearance of the thiol peak at 2570 cm^{-1}.

Initially the catalytic behavior of three simple amines (one each of a 1°, 2°, and 3° species), namely hexylamine (HexAM, pK_a = 10.6), di-*n*-propylamine (DnPA, pK_a = 11.00), and triethylamine (TEA, pK_a = 10.75) (Figure 1), were evaluated in the room temperature, bulk reaction of hexanethiol with hexyl acrylate at a catalyst loading of 0.057 mol %.

Figure 2 shows the kinetic profiles for these amine-mediated thiol-Michael reactions. The kinetic profiles were obtained by real-time FTIR spectroscopy by monitoring the disappearance of the thiol peak centered about 2570 cm^{-1} with reactions intentionally monitored for only 500 s. In the case of the TEA-mediated reaction essentially 0% conversion is observed during this time period. In contrast, the DnPA and HexAM-mediated reactions reach ~60% and 90% conversion, respectively, over the same time period. Traditionally, such reactions are assumed to proceed via a purely base-mediated process (vide infra); however, in the context of a purely *base*-catalyzed process this observed order of activity is inconsistent with the pK_a's of the amine catalysts. Indeed, given the pK_a's noted above the predicted order of activity would be DnPA > TEA > HexAM. Additionally, the pK_a's of these three

Table 1. Effect of Amine Catalyst on the Apparent Rate Constant[a]

thiol	ene	catalyst	pK_a[b]	mol % catalyst	$k_{app}/10^{-4}$ (mol L^{-1} s^{-1})[c]
hexanethiol	hexyl acrylate	HexAM	10.6	0.057	53.4
hexanethiol	hexyl acrylate	DnPA	11.00	0.057	8.02
hexanethiol	hexyl acrylate	TEA	10.75	0.057	0.028[d]

[a] 5.0 mmol of hexanethiol mixed with 0.057 mol % catalyst, 5.0 mmol of hexyl acrylate added just before RTIR measurement. [b] Hexanethiol pK_a = 10.3. [c] Rate constant taken at 30% conversion unless otherwise noted. [d] Rate constant taken over 500 s.

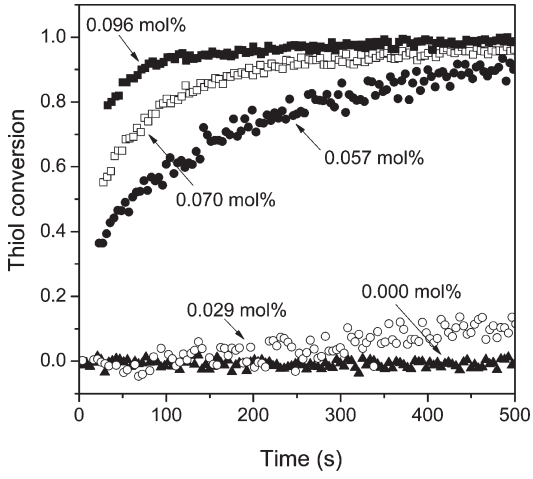


Figure 3. Thiol conversion vs time kinetic profiles: 5.0 mmol of hexanethiol with 5.0 mmol of hexyl acrylate with (▲) 0, (○) 0.029, (●) 0.057, (□) 0.070, and (■) 0.096 mol % hexylamine catalyst. Conversion determined by monitoring the disappearance of the thiol peak at 2570 cm^{-1}.

amines span only ~0.4 units, and such a large difference in the kinetic profiles would not be expected.

The apparent rate constants (k_{app}) were also evaluated for these reactions and are listed in Table 1. Importantly, HexAM and DnPA have k_{app} values 2 and 3 orders of magnitude larger than the more commonly employed TEA. While these kinetic measurements and k_{app} values do not coincide with the basic character of the amines, the data are consistent with the *nucleophilicity* of the catalysts (vide infra). Of course, it can be argued that steric impedance to protonation is also playing a role in the observed order of activity with the more sterically hindered amines exhibiting reduced catalytic activity relative to HexAM; i.e., a basic or hybrid process is in operation. However, given the use of TEA as a common base catalyst and as a means of quenching liberated H^+ in a variety of organic reactions, it seems such an effect is likely minimal and cannot, alone, account for the observed differences in the kinetics.

Having established that HexAM is the most potent of the three amine catalysts examined, the effect of [HexAM] was evaluated next. Figure 3 shows the experimentally determined kinetic profiles for the bulk reaction of hexanethiol with hexyl acrylate in the presence of 0−0.096 mol % HexAM. As expected, increasing the catalyst concentration results in an increase in the rate of reaction with, for example, reactions run at 0.096 mol % HexAM, resulting in essentially quantitative reaction in ~120 s.

In addition to the simple alkylamines, the effectiveness of three additional amine-based species was evaluated, also in the reaction of hexanethiol with hexyl acrylate, namely *N,N,N′,N′*-tetramethyl-1,8-naphthalenediamine (proton sponge, (PS)), and the bicyclic amidines 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and 1,5-diazabicyclo[4.3.0]non-5-ene (DBN). Initially, DBU was employed at the same concentration as the alkylamines, i.e., 0.057 mol %; however, the reaction profile was too fast to be measured by RTIR spectroscopy, indicating a quantitative reaction in < 10 s.

In order to be able to conveniently monitor the reaction kinetics, the concentration of DBU and DBN was reduced by 2 orders of magnitude (Table 2). Under these conditions the thiol-Michael reaction still proceeds rapidly with k_{app} values, determined at 30% conversion, of 5.34 and 54.9 mol L^{-1} s^{-1} for DBU and DBN, respectively—values essentially identical to DnPA and HexAM at the higher catalyst loadings. The exact nature of the role of DBU and DBN is however less clear than with the alkylamines. While both these bicyclic amidines are well-known *basic* catalysts for reactions such as dehydrohalogenation and Michael addition reaction of β-ketoesters,[18] being commonly described as "non-nucleophilic strong bases", there are also reports demonstrating that they possess significant nucleophilic character and are, for example, able to readily undergo aza-Michael reactions.[19] So while both DBU and DBN are clearly highly efficient catalysts relative to the simple alkylamines, it is not immediately evident if this is due to their enhanced basic character or to their potential to serve as nucleophiles or, indeed, if a hybrid process/mechanism is in operation. An indication that the enhanced activity of DBU and DBN is due, at least in part, to their nucleophilic character is evident from the result obtained using PS as a catalyst—a well-established non-nucleophilic organobase. With a pK_a of 12.1 PS is more basic than HexAM, DnPA, or TEA and intermediate of DBU (pK_a = 11.6) and DBN (pK_a = 13.5). As such, if the enhanced activity of DBU and DBN were due to their strong basic nature, then it would be expected that the use of PS would likewise result in a similar increase in catalytic activity relative to the alkylamines. However, even at a concentration identical to the simple alkylamines the use of PS results in a measured k_{app} of only 0.02 mol L^{-1} s^{-1}—a value lower than that determined for TEA. This result, at least qualitatively, suggests that it is the enhanced nucleophilic character of DBU and DBN that is responsible for the observed increase in catalytic activity.

Given that catalyst nucleophilicity appears to be a crucial factor with respect to reaction kinetics in the thiol-Michael reaction, at least in the case of simple alkylamines and also possibly for DBU and DBN, additional simple nucleophilic organocatalysts were evaluated. In addition to amines, tertiary phosphines, PR_3, represent some of the most commonly employed nucleophilic organocatalysts. Indeed, trialkylphosphines are well-known to catalyze Michael and oxa-Michael reactions[20] as well as being able to undergo direct conjugate addition with acrylates.[21] Four different tertiary phosphines, namely tri-*n*-propylphosphine (P(*n*-Pr)$_3$), dimethylphenylphosphine (PMe_2Ph), methyldiphenylphosphine ($PMePh_2$), and triphenylphosphine (PPh_3) (Figure 4), were evaluated in the reaction between hexanethiol and hexyl acrylate. As with the alkylamine catalysts, the reactions were intentionally only monitored for 500 s.

Figure 5 shows the kinetic profiles obtained by RTIR spectroscopy by monitoring the disappearance of the thiol band at 2570 cm^{-1}. Two important experimental points are worth noting. First, to facilitate ease of monitoring, the thiol-Michael reactions were conducted in solution in 45 wt % benzene, and second the concentration of phosphine catalyst had to be dropped to ~0.0004 mol %, 2 orders of magnitude lower than for the simple alkylamines (and similar to the concentrations employed for DBU and DBN), in both instances to allow for convenient evaluation of the reaction kinetics. The kinetic profiles for these reactions indicate that the reactions can be extremely rapid with certain phosphine catalysts even at such low catalyst loadings. For example, in the case of the P(*n*-Pr)$_3$-mediated reaction $>92\%$ conversion is observed in ~80 s. It should be noted,

Table 2. Effect of Amine Catalyst (pK_a Values) on Apparent Rate Constant[a]

thiol	ene	catalyst	pK_a[b]	mol % catalyst	$k_{app}/10^{-4}$ (mol L^{-1} s^{-1})[c]
hexanethiol	hexyl acrylate	PS	12.1	0.053	0.020[d]
hexanethiol	hexyl acrylate	DBU	11.6	0.057	*e*
hexanethiol	hexyl acrylate	DBU	11.6	0.0005	5.24
hexanethiol	hexyl acrylate	DBN	13.5	0.0005	54.9

[a] 5.0 mmol of hexanethiol mixed with catalyst, 5.0 mmol of hexyl acrylate added just before RTIR measurement. [b] Hexanethiol pK_a = 10.3. [c] Rate constant taken at 30% conversion unless otherwise noted. [d] Rate constant taken over 500 s (PS = proton sponge). [e] Too fast to measure.

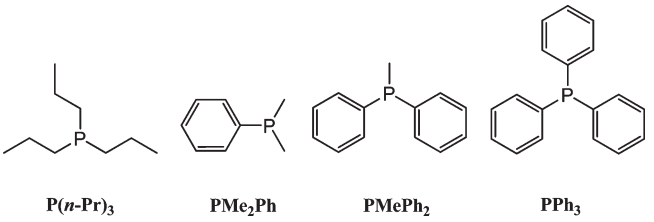


Figure 4. Chemical structures of tertiary phosphines evaluated as catalysts for thiol-Michael reactions.

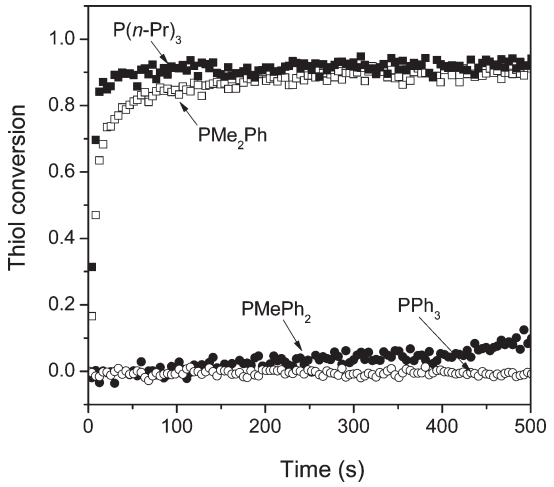


Figure 5. Thiol conversion vs time kinetic profiles using phosphine catalysts. 2.0 M hexanethiol with 2.0 M hexyl acrylate with 0.0004 mol % catalyst: (■) P(*n*-Pr)$_3$, (□) PMe$_2$Ph, (●) PMePh$_2$, and (○) PPh$_3$. Conversion determined by monitoring the disappearance of the thiol peak at 2570 cm^{-1}.

however, that the real conversion is likely higher than this since it takes a short period of time after mixing of all the reagents to load them into the spectrometer and begin the acquisition process. Again, in the context of a purely base-catalyzed reaction, it is difficult to reconcile these kinetic characteristics with the basic nature of the phosphines. First, the pK_a's of the conjugate acids of the two most active species, P(*n*-Pr)$_3$ and PMe$_2$Ph, are 8.64 and 6.49, respectively (Table 3), 2−4 pK_a units lower than the most active alkylamines and approximately 5−7 pK_a units lower than DBN; i.e., these phosphines are relatively weak bases. Second, the pK_a of hexanethiol (10.66, Table 4) suggests that the phosphines are not strong enough bases to deprotonate the thiol to any appreciable degree. So, while the observed activity does coincide with the basic nature of the phosphines, they are not sufficiently strong bases to account for their enhanced activity as such low concentrations relative to the amine-based species. However, in keeping with the observations made for the alkylamine catalysts, and for such organocatalysts serving not as bases but as nucleophiles, the order of activity also increases in order of increasing nucleophilicity of the phosphine, i.e., P(*n*-Pr)$_3$ > PMe$_2$Ph ≫ PMePh$_2$ > PPh$_3$.[20c] It should also be noted that the much larger phosphorus atom, relative to nitrogen, also helps minimize any steric effects that may be contributing to their observed order of activity.

Table 3 shows the k_{app} values, determined at 30% conversion for P(*n*-Pr)$_3$, PMe$_2$Ph, PMePh$_2$, and after 500 s for PPh$_3$. To reiterate, not only are P(*n*-Pr)$_3$ and PMe$_2$Ph clearly far superior organocatalysts than the simple alkylamines, they are also more effective than DBU and DBN even though they were employed with a somewhat lower catalyst loading and were used in solution. Indeed, the k_{app} for P(*n*-Pr)$_3$ is 2 orders of magnitude larger than for DBN and highlights the potent nature of trialkylphosphines as catalysts for such reactions. However, from a practical standpoint it is worth noting that many trialkylphosphines are pyrophoric and readily oxidized and thus can be difficult to handle and their use difficult to justify in the context of a "click" reaction. In contrast, PMe$_2$Ph, while marginally less active than P(*n*-Pr)$_3$, is considerably easier to handle, and no special precautions need to be employed in its use and should therefore be considered as the "catalyst of choice" for such reactions.

Mechanistic Considerations. The *base*-catalyzed thiol-Michael reaction has been studied extensively for decades. There is no dispute that in a given system a thiol (−SH) can behave as a Brønsted acid and will readily donate a proton to a stronger Brønsted base (catalyst) such as a tertiary amine. Such acid−base reactions are thermodynamically controlled and can proceed essentially spontaneously. The resulting thiolate anion is a potent nucleophile and can easily add into an electron-deficient C═C bond, a kinetically controlled process, and can proceed to high conversions with appropriate choice of substrate, thiol, and catalyst. However, the thiolate anion is not completely free to react in every given system with reactivity depending on factors such as base strength and solvent polarity.[10,22] The accepted base-catalyzed mechanism for a thiol-Michael reaction is shown in Scheme 1. The first step involves the formation of the thiolate anion, or ion pair, by reaction with the base, the extent and rate of which will clearly depend on both the pK_a of the thiol and the strength of the base. The free thiolate anion, or ion pair, subsequently attacks the activated ene at the more favorable β-position, forming an intermediate carbanion or enolate (pK_a ∼ 25) in the case of the acrylic substrate shown. In the final step, the enolate is protonated at the α-carbon of the original C═C bond. As a very strong base, the enolate can abstract a proton from any acidic species in the reaction medium including the thiol, conjugate acid, or protic solvent (if present). Protonation is shown here to occur via abstraction from the conjugate acid with concurrent regeneration of the base catalyst.

Given the lower basicity of phosphines compared to amines of a similar substitution pattern (see pK_a values in Tables 1 and 3),[23] the order of activity observed for HexAM, DnPA, and TEA (assuming steric effects are essentially negligible), the enhanced activity of phosphines in general, and the extremely rapid rates observed for such reactions, an alternative mechanism can be considered.

Scheme 2 shows a plausible mechanism that accounts for the observed activity in terms of the nucleophilic character of the amines/phosphines as well as accounting for the overall rapid rates of reaction. The reaction using a phosphine with an acrylic substrate is highlighted, but a similar mechanism can also be drawn for the 1° and 2° amine species. The process is initiated by nucleophilic attack of the phosphine at the β-carbon of the acrylic C═C bond to give the phosphonium−enolate zwitterionic

Table 3. Effect of Phosphine Catalyst on Apparent Rate Constant for the Reaction between Hexanethiol and Hexyl Acrylate[a]

thiol	ene	catalyst	pK_a	mol % catalyst	$k_{app}/10^{-4}$ (mol L^{-1} s^{-1})[b]
hexanethiol	hexyl acrylate	P(n-Pr)$_3$	8.64	0.0004	1810
hexanethiol	hexyl acrylate	PMe_2Ph	6.49	0.0004	430
hexanethiol	hexyl acrylate	$PMePh_2$	4.59	0.0004	0.987
hexanethiol	hexyl acrylate	PPh_3	2.73	0.0004	0.0125[c]

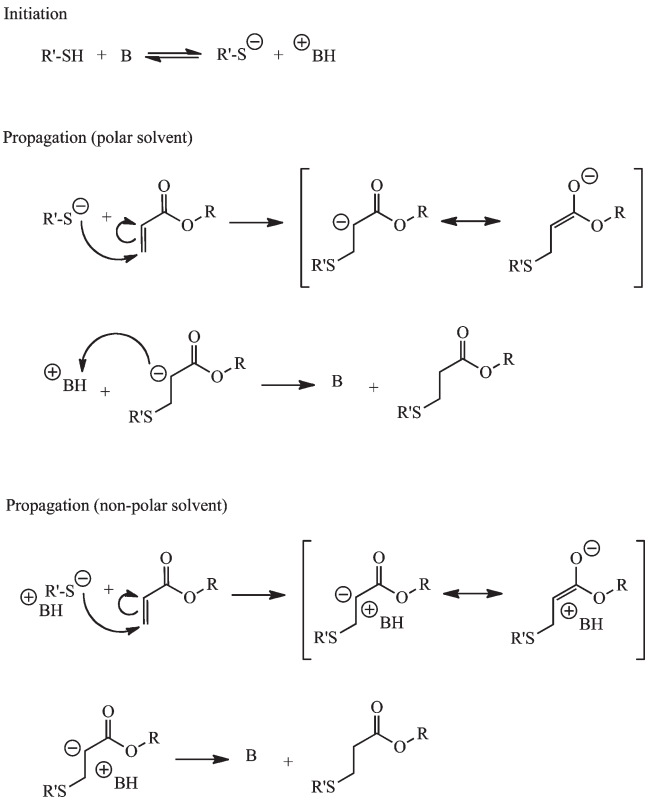
[a] 2.0 M hexanethiol mixed with 0.0004 mol % phosphine catalyst in 45 wt % benzene, 2.0 M hexyl acrylate added just before RTIR measurement. [b] Rate constant taken at 30% conversion unless otherwise noted. [c] Rate constant taken at 500 s.

Table 4. Effect of Thiol pK_a on the Degree of Conversion for the Reaction between a Series of Thiols and Hexyl Acrylate in the Presence of 0.057 mol % Hexylamine

thiol	pK_a	conversion (%)[a]
ethyl thioglycolate	7.95	99
ethyl 2-mercaptopropionate		95
methyl 3-mercaptopropionate	9.33	61
hexanethiol	10.66	19

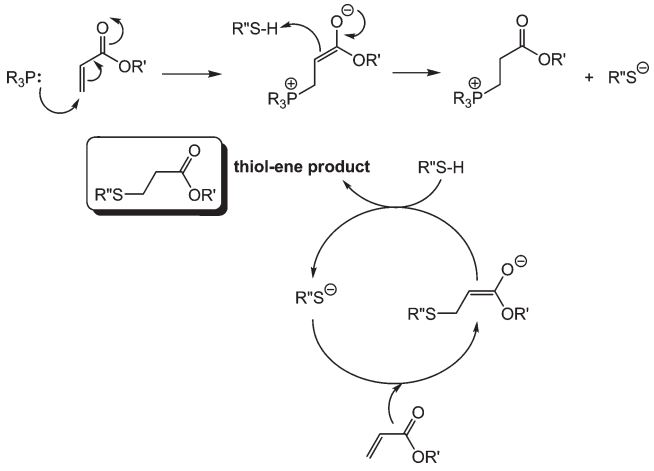
[a] This kinetic data is consistent with the pK_a values of the different thiols, with the more acidic thiols exhibiting faster rates of reaction.

Scheme 1. Mechanism for the Base-Catalyzed Thiol-Michael Addition Reaction



intermediate, and is formally a phospha-Michael addition reaction. This strong enolate base will abstract any available acidic hydrogens—the only source of which, in this instance, is the thiol. Deprotonation of the thiol yields the thiolate anion and an inert phosphonium ester. The soft, strongly nucleophilic thiolate anion is able to undergo direct conjugate addition with the soft, activated acrylic C=C bond yielding an enolate intermediate that deprotonates additional thiol generating more thiolate anion. It is this resulting anionic chain process that is responsible for the extremely rapid rates of reaction that are observed. Such a mechanism has been proposed previously by Toste et al. for the hydration and hydroalkoxylation of activated olefins, i.e., oxa-Michael reactions,[20a] and also noted by Methot and Roush in Michael addition reactions of carbon acids.[24] It should be noted, however, that the inert phosphonium ester formed from the

Scheme 2. Proposed Anionic Chain Mechanism via Nucleophilic Initiation for the Phosphine-Mediated Thiol-Michael Reaction with an Acrylic Substrate



zwitterionic enolate after hydrogen abstraction from thiol subsequently exists as an impurity in the final product, with the same being true of such species derived from initiation by amines (the use of these amines/phosphines at the concentrations described herein ensures a negligible amount of such impurity).

Clearly, an important observation regarding the anionic chain mechanism is the presence of the phospha- or aza-Michael products resulting from the proposed nucleophilic initiation reaction. While we have not investigated this in the present study, a recent report from Li et al. demonstrates that both primary amines and Me_2PPh do undergo such hetero-Michael additions forming the proposed inert intermediates, as evidenced by detailed mass spectrometry studies, when employed as organocatalysts in thiol-Michael reactions.[25] This, in conjunction with the kinetic studies noted above, indicates that the proposed anionic chain mechanism is a plausible mechanism that can account for the observed activity of the organocatalysts. However, we cannot entirely neglect the possibility of a base or hybrid mechanism also being in operation in such systems and especially where amines of reduced nucleophilicity are employed.

One key and distinguishing feature of the nucleophile-initiated thiol-Michael reaction, compared to traditional Michael or oxa-Michael reactions, is the ability to conduct such chemistry even in the presence of trace amounts of water. This is a direct result of the large difference in the pK_a values of most common thiols and water. In the case of Michael reactions with carbon acids or oxa-Michael reactions with alcohols, for example, the pK_a of water is significantly lower or comparable to the primary, desired proton source—the carbon acids or alcohols, respectively. As such, the presence of even trace amounts of water can result in competitive reactions yielding nondesired products.

Effect of Thiol Structure. While there is a clear, and in some instances dramatic, effect associated with the type of amine or phosphine organocatalyst employed in the above

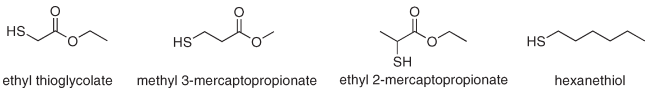


Figure 6. Chemical structures of thiols examined in the thiol-Michael reaction with hexyl acrylate in the presence of hexylamine.

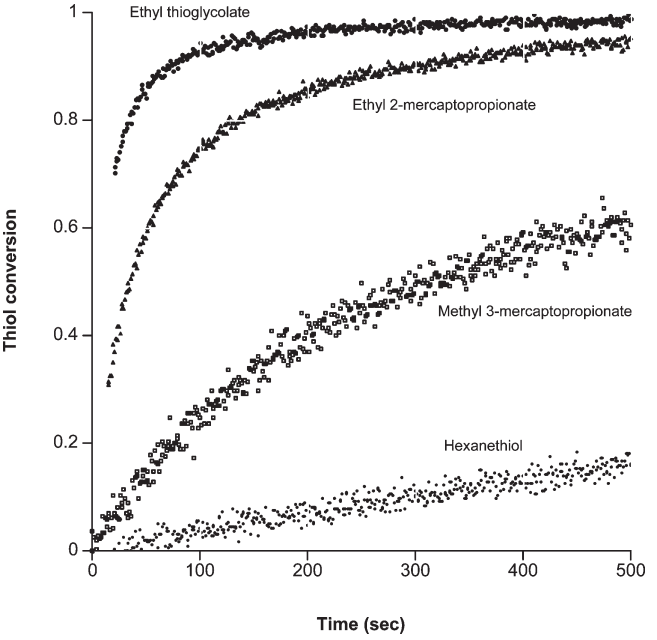


Figure 7. Thiol (2570 cm^{-1}) conversion vs time for reaction of 5.0 mmol of thiols—(●) ethyl thioglycolate, (▲) ethyl 2-mercaptopropionate, (□) methyl 3-mercaptopropionate, and (○) hexanethiol—with 5.0 mmol of hexyl acrylate with 0.0057 mol % hexylamine at room temperature determined by RTIR.

thiol-Michael addition reactions, it should be noted that not all thiols are created "equal" and significant differences in reactivity are observed. There are four common classes of thiols: alkylthiols, thioglycolate esters, thiopropionate esters, and aromatic species such as thiophenol. To evaluate the effect of thiol structure, four different mercaptans (5.0 mmol) (Figure 6) were examined in the thiol-Michael reaction with hexyl acrylate (5.0 mmol) under bulk conditions in the presence of hexylamine (0.5 wt %).

It is clear that there are significant differences in the kinetic characteristics of these reactions. For example, in the case of the reaction with ethyl thioglycolate ~100% conversion is attained within ~2 min, whereas in the case of hexanethiol only ~19% conversion is reached after 500 s. After the glycolate ester, the next fastest reaction is observed with ethyl 2-mercaptopropionate (~95%), a secondary thiol, followed by methyl 3-mercaptopropionate (~61% conversion) (Figure 7).

Effect of Ene Structure. In addition to the nature of the amine/phosphine and the structure of the thiol, the inherent propensity of an activated ene to undergo conjugate addition is also an important consideration in thiol-Michael reactions. Figure 8 shows the chemical structures of a range of activated enes that were examined in their reaction with hexanethiol in the presence of hexylamine.

Figure 9 shows the real-time kinetic data for the reaction of hexanethiol with the activated enes shown in Figure 8 in the presence of hexylamine as a catalyst, with conversions and apparent rate constants listed in Table 5. Parent solutions were prepared, and a sample was removed and immediately loaded into the IR spectrometer and monitored for 500 s. In instances where little, or no, apparent reaction had occurred

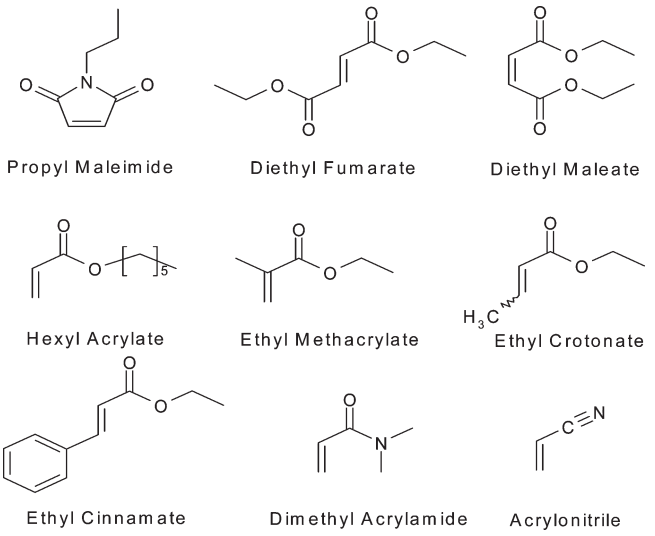


Figure 8. Chemical structures of electron-deficient enes.

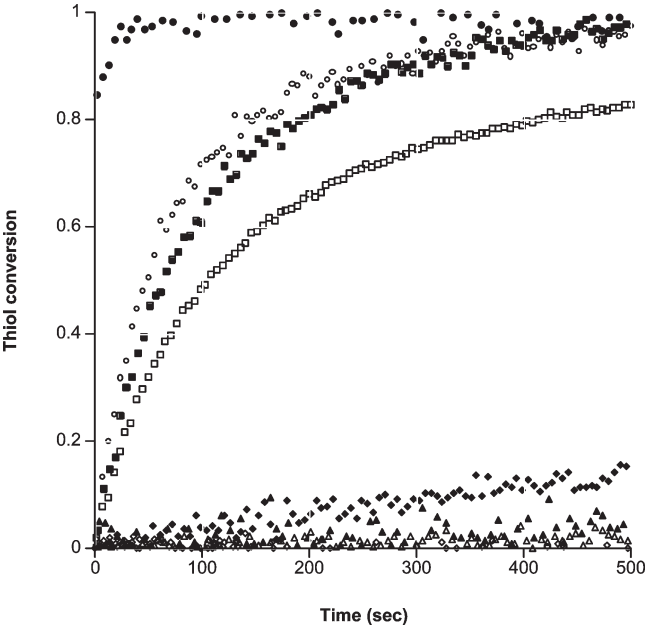


Figure 9. Thiol conversion vs time kinetic profiles comparing various activated alkenes. Reaction between 5.0 mmol of hexanethiol with 5.0 mmol of each alkene with 2 wt % hexylamine: (●) propylmaleimide; (○) diethyl fumarate; (■) diethyl maleate; (□) dimethylacrylamide; (◆) acrylonitrile; (▲) ethyl crotonate; (△) ethyl cinnamate; and (◇) ethyl methacrylate (RTIR conversion monitored by following the disappearance of the thiol band at 2570 cm^{-1}).

after this time period samples were taken from the parent stock solution at 3 and 12 h and analyzed by ^1H NMR spectroscopy. Consider first propylmaleimide and the diethyl fumarate and maleate esters. These three enes, bearing two electron-withdrawing groups, are highly electron-deficient and, not surprisingly, exhibit the fastest rates of reaction. In the case of propylmaleimide the reaction is essentially complete before any significant kinetic data can be obtained, and as such an apparent rate constant could not be determined. For both the fumarate and maleate esters, reactions are rapid and reach quantitative conversion within the 500 s monitoring period with the fumarate reacting slightly faster (Table 5). Considering these reactions were performed with the *least* reactive type of thiol (an alkylthiol) with one of the

Table 5. Effect of Activated Ene Structure in Reactions with Hexanethiol in the Presence of Hexylamine as Catalyst[a]

thiol	activated ene	conversion (%)[b]	time (h)[c]	$k_{app}/10^{-4}$ (mol L^{-1} s^{-1})[d]
hexanethiol	propylmaleimide	99		*f*
hexanethiol	diethyl fumarate	99		40.0
hexanethiol	diethyl maleate	99		28.5
hexanethiol	dimethylacrylamide	99	3	18.6
hexanethiol	acrylonitrile	99	3	0.67
hexanethiol	ethyl crotonate	96	12	0.058[e]
hexanethiol	ethyl cinnamate	75	12	0.058[e]
hexanethiol	ethyl methacrylate	25	12	0.058[e]

[a] 5.0 mmol of hexanethiol mixed with (0.2 M) hexylamine, 5.0 mmol of hexyl acrylate and allowed to react at 25 °C without stirring. [b] Measured by ^{1}H NMR using $CDCl_3$ as solvent. [c] Products were analyzed by ^{1}H NMR at 3 and 12 h; final conversion may have been reached in shorter time. [d] Rate constant taken at 30% conversion unless otherwise noted. [e] Rate constant taken over 500 s. [f] Too fast to measure.

lesser effective catalysts, these rates of reaction are clearly impressive.

In the case of dimethylacrylamide, with only one activating functional group, the observed reaction is also rapid and approaches 80% conversion during the 500 s monitoring period with a calculated k_{app} of 18.6 mol L^{-1} s^{-1}. ^{1}H NMR analysis of the parent solution after 3 h indicated complete conversion to the thiol-Michael adduct although it is noted that this was almost certainly attained in a significantly shorter period of time. Similar observations were made in the case of acrylonitrile. While noticeably less reactive than dimethylacrylamide (ca. 15% conversion in 500 s with k_{app} = 0.67 mol L^{-1} s^{-1}), ^{1}H NMR analysis also indicated quantitative reaction after a 3 h time period. The least reactive of the series of enes were the crotonate, cinnamate, and methacrylate esters, with essentially zero conversion being reached after 500 s. Indeed, any appreciable conversion was only observed after a 12 h time period although in the case of the cinnamate and methacrylate esters conversions were still minimal (75 and 25% conversion, respectively). The reduced activity of the cinnamate and crotonate esters may be ascribed to either steric or weak electronic effects. Given the high activity of the other 1,2-disubstituted enes, it seems unlikely that the lower activity of the crotonate is due solely to sterics, although it is obviously a less activated ene. The reduced activity may be due to the positive inductive effect associated with the methyl group on the β-carbon that helps stabilize the electrophilic character ($\delta+$) of this carbon atom, reducing its reactivity toward nucleophilic attack. In the case of the cinnamate ester, the reduced activity is ascribed to a steric effect with the bulky phenyl ring serving as effective shield against nucleophilic attack at the β-carbon. For ethyl methacrylate the low reactivity is likely due to a destabilizing effect of the α-CH_3 group on the intermediate carbanion/enolate, again due to a positive inductive effect. While there is clearly no steric barrier to attack at the electrophilic β-carbon, nucleophilic addition to the C=C bond yields a less stable tertiary anion versus a secondary species in the case of all the other enes examined.

Summary and Conclusions

Herein we have described a detailed study on the effect of organocatalyst, thiol, and ene structure in the thiol-Michael conjugate addition reaction. We have demonstrated the potent nature of primary amines, but especially certain tertiary phosphines such as tri-*n*-propylphosphine and dimethylphenylphosphine with the latter highlighted as the catalyst of choice. Mechanistically, the observed activity has been rationalized in terms of a nucleophile-initiated anionic chain process although it is noted that the occurrence of a hybrid or purely base-catalyzed process may also be in operation in certain instances. The rates of reaction have also been shown to be highly dependent on the chemical structure of the thiol with simple alkyl thiols being significantly less reactive than both the mercaptoglycolate and mercaptopropionate esters and is in accord with the pK_a values of the thiols. The nature of the ene substrate is also an important variable with highly activated species such as maleimides, fumarates, and maleates exhibiting extremely rapid rates of reactions even with less reactive thiols and weaker catalysts. Less activated enes, including dimethylacrylamide and acrylonitrile, while giving quantitative yields of Michael adduct, undergo reaction at a significantly lower rate and is attributed simply to the less electron-deficient nature of the C=C bond. Cinnamates, crotonates, and methacrylates show drastically reduced reactivity, relative to the other enes, due to a combination of steric and inductive effects.

Acknowledgment. A.B.L. thanks UNSW for strategic funding.

Supporting Information Available: Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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