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Enamine Organocatalysts for the Thiol-Michael Addition Reaction and Cross-Linking Polymerizations

Jasmine Sinha,[§] Shafer Soars,[§] and Christopher N. Bowman*

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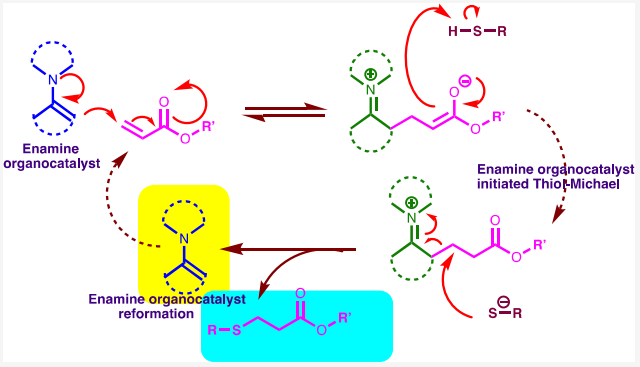
ABSTRACT: This article describes an efficient enamine organocatalyzed thiol-Michael click reaction and its broad application in cross-linking polymerizations. A series of enamines was shown to catalyze the thiol-Michael reaction via a nucleophilic pathway. By varying the amines as well as the ring size of the ketones, enamines were designed with broad ranges of nucleophilic character ranging from 11 to 17 on the Mayr nucleophilicity scale. Upon evaluating the enamines' organocatalytic effect on the kinetics of reactions involving a thiol and Michael acceptor, wherein butyl 3-mercaptopropionate and 1-hexyl acrylate were used as model reactants, enamines were shown to outperform their base analogs. The efficiency and overall reaction yields, ranging from 11 to 92% based on the thiol conversion, were highly dependent upon the nucleophilicity of the enamines employed. Interestingly, *in situ* formation of an enamine via photo-deprotection of an amine in the presence of cyclic ketones facilitated the thiol-Michael reaction efficiently while simultaneously enabling higher functional group conversion. This efficiency in the reaction kinetics and conversion was extended to multifunctional derivatives, which resulted in the formation of highly cross-linked polymers.



INTRODUCTION

The thiol-Michael "click" reaction was first reported by Allen et al. in the 1960s.[1] The reaction is broadly characterized as the addition of a thiol into an α,β-unsaturated ketone and also other electron-deficient vinyls such as acrylamides, vinyl sulfones, and malemides.[2] It is often facilitated by a catalyst such as a base or a nucleophile.[3] In addition to extensive utility in organic synthesis, it has been widely implemented in the field of material chemistry for surface modification, adhesives, polymerization reactions, polymer conjugation, dendrimer formation, and biomolecular synthesis.[4−6] Chan et al. demonstrated that the effectiveness and rate of the thiol-Michael reaction are largely dependent on several factors such as the acidity of the thiol, basicity/nucleophilicity of the catalyst, and the electrophilicity of the vinyl group.[3]

With facile access to various bases, the base-catalyzed thiol-Michael reactions have been extensively studied; however, these reactions have several drawbacks which include limited spatial and temporal control in bulk polymerizations, non-orthogonality that a base catalyst imparts, and disulfide formation under basic conditions.[5] To circumvent the drawbacks associated with base catalysis, more attention has recently been given to the study of nucleophile-catalyzed thiol-Michael addition reactions. The mechanism by which nucleophiles catalyze the thiol-Michael addition has been shown to involve the generation of a zwitterion resulting from the nucleophilic attack of the Michael acceptor which is then responsible for deprotonating a thiol, instigating a repeating cycle of addition and deprotonation (Scheme 1).[5,7,8] Compared with the base-catalyzed thiol-Michael additions, nucleophile-catalyzed reactions result in less undesired disulfide formation, and the rate of the reaction varies with the nucleophilicity of the nucleophile in use.[3,5,7]

The most studied nucleophilic catalysts investigated for the thiol-Michael reaction are phosphine and amine catalysts.[7−9] The application of some phosphine catalysts (trimethylphosphine, triisopropylphosphine) results in rates substantially greater than even the most effective amine base catalysts (1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and 1,5-diazabicyclo[4.3.0]non-5-ene (DBN)).[3] The primary concern with the application of these nucleophilic reaction initiators in thiol-Michael additions is the generation of undesirable side products. Specifically, the nucleophiles add into the vinyl group to form stable byproducts.[9,10] Some of the side products produced via phosphine-catalyzed additions have been shown to be toxic to cells, preventing many biological applications of

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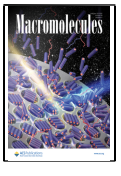

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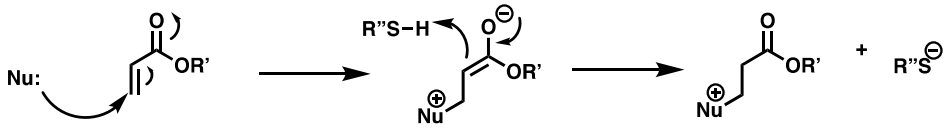
Scheme 1. Reaction Mechanism of the Nucleophile-Initiated Thiol-Michael Addition Reaction



these reactions.[11] Most recently, the Michael addition reaction facilitated by photolatent tertiary amines was found to be highly efficient; however, most photolatent tertiary amines are associated with limited solubility and stability of the formulations of low polarity which then leads to non-orthogonality of the reaction.[12,13]

Herein, a series of enamines are investigated for their potential as nucleophilic catalysts for the thiol-Michael addition. It is proposed that enamines are capable of overcoming some of these limitations of the thiol-Michael "click" reaction, while also mitigating the formation of potentially toxic and otherwise undesirable byproducts. Enamines have been extensively used in organocatalysis for transformations such as the aldol, Mannich, Michael-addition, and Diels–Alder reactions.[14−18] Chiral amines have also been extensively studied as asymmetric organocatalysts for similar transformations.[19] The strong nucleophilic character of enamines has been demonstrated and studied in regards to reactivity toward Michael acceptors, acceptor-activated aryl halides, and electron-deficient dienes. More importantly, Mayr et al. demonstrated that the nucleophilicity of enamines is tailored by modulating the ring size and electron density of the corresponding enamine.[20]

Herein, the potential of a series of enamines formed from different amines and cyclic ketones of varying ring sizes to act as a catalyst for the thiol-Michael "click" reaction was investigated. A detailed kinetic study with systematically varying enamine structures led to successful employment in the thiol-Michael reaction. Furthermore, enamines were generated *in situ* by the reaction of a photocleaved amine with equimolar amounts of cyclic ketone present in a monomer mixture of a stoichiometric ratio of monofunctional thiol and acrylate. The amine, formed after irradiation, preferentially reacts with ketones to form an enamine over deprotonation of the thiol, which would further catalyze the reaction. The success of utilizing enamines to catalyze the reaction was further extended to bulk network polymerization.

MATERIALS AND METHODS

Materials. Butyl 3-mercaptopropionate (BMP), *n*-hexyl acrylate (HA), imidazole (Im), cyclohexanone (CyHex), cyclopentanone (CyPent), 2-(2-nitrophenyl)propyl chloroformate (NPPOCl), pyrrolidine (Pyr), morpholine (Mor), diethylamine (DEA), pentaerythritol tetrakis(3-mercaptopropionate) (PETMP), trimethylolpropane triacrylate (TMPTA), anhydrous toluene, and anhydrous dichloromethane were purchased from Sigma-Aldrich. Sulfuric acid (H_2SO_4) was purchased from fisher scientific. NPPOC-DEA was synthesized according to the previously reported procedure.[21] All other chemicals were of reagent grade and used without further purification.

Methods. *General Synthesis of Enamines (1, 2, 4).* To a round-bottom flask equipped with a magnetic stir bar and Dean–Stark apparatus was added an equimolar amount of the corresponding amine and ketone in toluene (0.5 M). A catalytic amount of sulfuric acid was added, and the reaction was heated to reflux overnight. The reaction was then concentrated under reduced pressure to afford enamines, which was then used without further purification.

4-Cyclohexen-1-ylmorpholine (Enamine 1). Brown liquid. Yield 98%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.66 (t, 1H), 3.73 (m, 4H), 2.77 (m, 4H), 2.04 (m, 4H), 1.66 (m, 2H), and 1.54 (m, 2H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 145.6, 100.6, 67.1, 48.6, 27.0, 24.5, 23.3, and 22.9.

1-(1-Cyclohexen-1-yl)pyrrolidine (Enamine 2). Brown liquid. Yield 99%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.28 (t, 1H), 2.98 (m, 4H), 2.18 (m, 2H), 2.09 (m, 2H), 1.83 (m, 4H), 1.67 (m, 2H), and 1.54 (m, 2H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 143.4, 93.6, 47.6, 27.6, 27.1, 25.3, 25.0, 24.5, 23.4, and 23.0.

1-(1-Cyclopent-1-yl)pyrrolidine (Enamine 4). Brown liquid. Yield 97%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.07 (s, 1H), 3.10 (m, 4H), 2.47 (m, 2H), 2.37 (m, 2H), and 1.88 (m, 6H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 149.5, 92.1, 48.9, 48.6, 46.9, 33.0, 30.8, 25.5, 25.2, 25.0, 23.3, and 23.0.

Synthesis of 1-(9-Fluorenylmethoxycarbonyl)-diethylamine (Fmoc-DEA). To a round-bottom flask equipped with a magnetic stir bar was added the corresponding amine (14.1 mmol) and fluorenylmethyloxycarbonyl chloride (14.1 mmol) in dichloromethane (0.3 M) at 0°C. The reaction was then allowed to slowly warm to room temperature and stirred overnight. The mixture was diluted with dichloromethane and transferred to a separatory funnel and washed with water, saturated aq. ammonium chloride, brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the product was purified by column chromatography to yield colorless viscous liquid. Yield 70%; ^{1}H NMR (400 MHz, $CDCl_3$): 7.78 (d, J = 7.89 Hz, 2H), 7.61 (d, J = 7.67 Hz, 2H), 7.42 (dd, J = 7.24 Hz, 2H), 7.34 (dd, J = 7.56 Hz, 2H), 4.48 (d, J = 6.5 Hz, 2H), 4.28 (t, J_1 = 7.3 Hz, J_2 = 6.76 Hz, 1H), 3.27 (m, 4H), and 1.07 (m, 6H). ^{13}C NMR (400 MHz, $CDCl_3$): 155.80, 144.30, 141.42, 127.62, 127.02, 119.95, 66.93, 47.53, 41.82, 41.27, 13.92, and 13.53.

2-(2-Nitrophenyl)propoxycarbonyl Pyrrolidine (NPPOC-Pyr). To a round-bottom flask equipped with a magnetic stir bar was added pyrrolidine (14.1 mmol) and 2-(2-nitrophenyl)propyl chloroformate (14.1 mmol) in dichloromethane (0.3 M) at 0 °C. Triethylamine (28.2 M) was then added dropwise to the solution. The reaction was then allowed to slowly warm to room temperature and stirred overnight. The mixture was diluted with dichloromethane and transferred to a separatory funnel and washed with water, saturated aq. ammonium chloride, brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure to afford clean products. Yield 90%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (m, 1H), 7.56 (m, 2H), 7.37 (m, 1H), 4.23 (m, 2H), 3.72 (m, 1H), 3.17 (m, 4H), 1.82 (m, 4H), and 1.37 (d, 2H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 154.7, 150.5, 137.8, 132.5, 128.3, 127.3, 124, 69.1, 46.0, 33.5, 25.4, and 17.9. HRMS-ESI+ (m/z) $[M + H]^+$ calculated at 279.1345, found 279.1371.

Characterization. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 400 MHz NMR spectrometer. Proton chemical shifts are expressed in parts per million (δ). The δ scale was referenced to deuterated solvents, indicated in the respective measurement.

Real-Time Fourier Transform Infrared (FT-IR) Spectroscopy. Reaction kinetics were analyzed using a FT-IR spectrometer (Nicolet 8700) in transmission mode to monitor real-time functional group conversions. Samples were interposed between two NaCl windows and placed into a horizontal transmission apparatus. Irradiation was performed using a mercury-lamp (Acticure 4000) with a 365 nm band gap filter after 1 min and continued for 60 min. The light intensity was kept at 50 mW/cm^2, which was measured by an International Light. Inc., model IL 1400A radiometer. By measuring the IR peak area decreasing at 3100 and 2560 cm^{-1}, the real-time functional group conversions of vinyl and thiol groups were monitored and calculated as the ratio of the real-time peak area to the peak area of the initial spectra. The real-time analysis to compare enamines with amine

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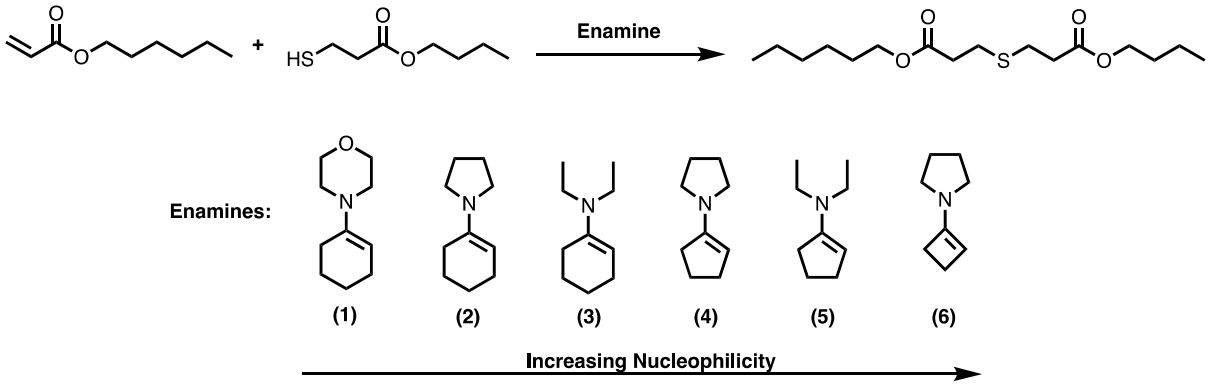

Figure 1. Representation of the thiol-Michael addition reaction composed of 1:1 stoichiometric ratio of butyl 3-mercaptopropionate and *n*-hexyl acrylate in the presence of enamines as the organocatalyst. A list of different enamines employed are listed in order of increasing nucleophilicity. Enamine **6** (Mayr nucleophilicity, N = 16.9) could not be synthesized due to its unstable nature though it is listed to enable comparison of the variation in the nucleophilicity trend upon introduction of different ring sizes of the cyclic ketone to form the enamine.

analogues was performed at ambient temperature and recorded immediately after interposing the sample between NaCl plates where the mixture consists of an initial stoichiometric ratio of 1:1 thiol to vinyl functional groups and catalyst.

RESULTS AND DISCUSSION

A series of enamines were synthesized according to procedures previously described utilizing a Dean−Stark apparatus to drive the reaction to completion,[22] and the potential of each enamine to act as a potent nucleophile was investigated in the thiol-Michael reaction (Figure 1). It is well documented that base catalysts undergo the thiol-Michael reaction efficiently; however, disulfide formation and slower rates of the reaction have been previously found as potential limiting factors.[5] More recently, nucleophiles have been studied as the catalyst for the thiol-Michael reaction and have been systematically studied for phosphine-based nucleophiles.[3]

Enamines were designed with varying nucleophilicity and pK_a to assess their influence on conversion and yield. The reactivity of enamines is expected to be dependent on the choice of amine, which would then influence the electron density around C-α and reactivity at C-β by hyperconjugation and inductive effects. For example, the lone pair on the nitrogen for Enamine **1** is expected to have less p-orbital character when compared to enamines **2**−**6**. As a result, it contributes toward the reduction of its capability to act as a potent nucleophile.[19,20] One approach to introduce variation in the nucleophilicity of enamines is to derive enamines from cyclic ketones. As previously reported, spectroscopic evidence suggested that the reactivity of enamines may vary with the ring size of the ketone in the order of 5 > 12 > 8 > 6 > 7, which would subsequently influence the nucleophilicity of enamines.[16,17] In addition, another factor that influences the nucleophilicity of enamines is the bond angle upon the formation of the iminium cation.[23] For example, with enamines 2, 4, and 6, the amine employed is cyclic, resulting in the formation of a higher energy intermediate iminium cation as opposed to the less restricted compounds 3 and 5.

The synthesized enamines were subjected to investigation for their catalytic potential in the thiol-Michael addition reaction and were compared to base analogs. First, it was demonstrated that some enamines successfully catalyze the thiol-Michael reaction more rapidly when compared to their base analogs (Figure 2). Figure 2 shows that 1-pyrrolidinocyclopent-1-ene, enamine **2**, performed better than the

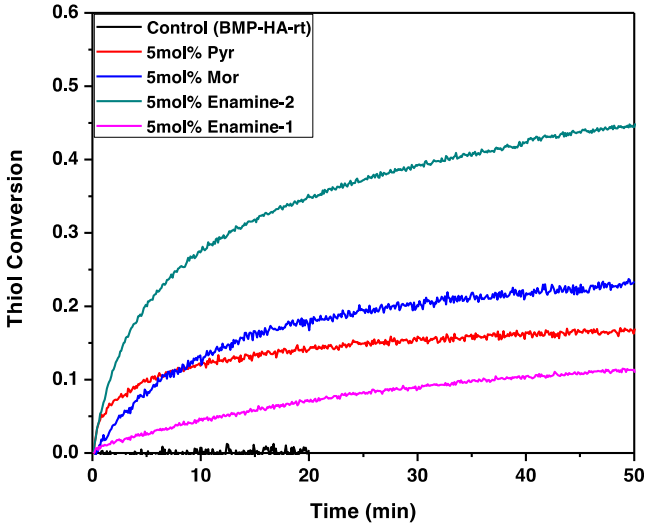

Figure 2. Thiol conversion versus time as monitored by FT-IR for the model reaction between butyl 3-mercaptopropionate (BMP) and 1-hexyl acrylate (HA). The plot illustrates the comparison of different bases and enamines, i.e., 5 mol % Pyr (pyrrolidine), 5 mol % Mor (morpholine), 5 mol % enamine **2** (1-(1-cyclohexen-1-yl)-pyrrolidine), and 5 mol % enamine **1** (4-cyclohexen-1-ylmorpholine) and a control experiment of 1:1 BMP and HA without a catalyst. The mixture consisted of an initial stoichiometric ratio of 1:1 thiol to vinyl functional group concentrations and organocatalyst. Each sample was run at ambient temperature and recorded immediately after interposing the sample between NaCl plates.

pyrrolidine base analog in both rate of reaction, as well as overall yield; however, 4-cyclohexen-1-ylmorpholine, enamine **1**, when compared to morpholine resulted in a lower reaction rate which could be attributed to the reduced p-orbital character of the lone pair on nitrogen for enamine **1**. In addressing the catalytic mechanism, it should be noted that the enamine (pK_a ∼ 9) will not deprotonate the thiol (pK_a ∼ 11) to any appreciable degree, and the reaction must be following predominately a nucleophilic pathway. In addition, to further test the proposed nucleophilic mechanism, a catalytic amount of 2,4,6-trimethylpyridine (pK_a = 7.5) was mixed with *n*-hexyl acrylate and butyl 3-mercatopropionate. Due to a pK_a value well below the employed thiol, no reaction occurred, which further supports the proposed nucleophilic pathway (Figure S1). Since enamines with similar pK_a values were capable of

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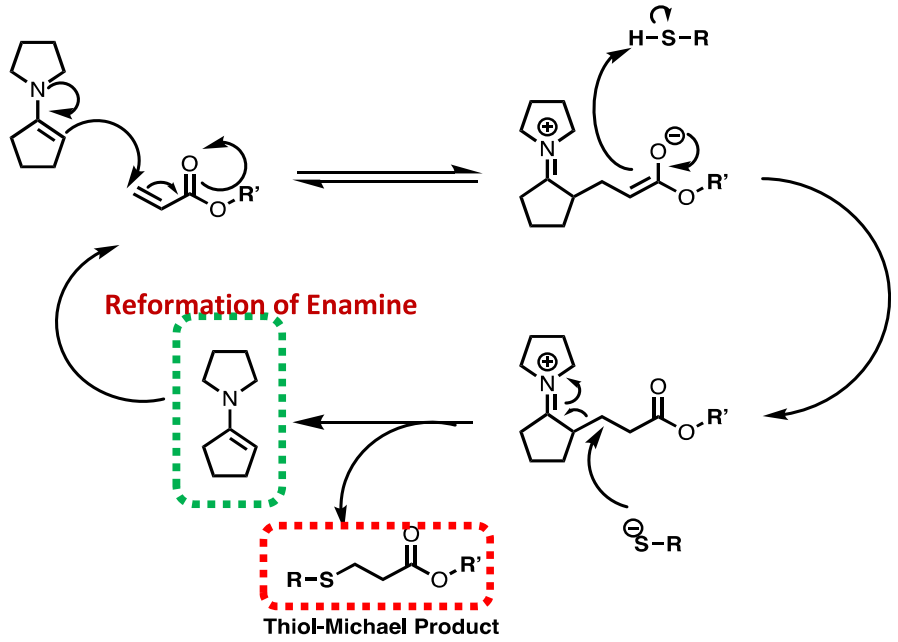
Scheme 2. Proposed Catalytic Cycle of the Enamine-Catalyzed Thiol-Michael Reaction[a]



[a]Enamine addition to acrylates generates a basic Zwitterion that deprotonates the thiol that attacks the β-C of the ester and regenerates the enamine catalyst.

catalyzing the thiol-Michael reaction, it follows that the reaction must be occurring primarily through a nucleophilic pathway (Scheme 2).

Additionally, the proposed mechanism results in the regeneration of the catalyst which is advantageous over the tertiary phosphine as the latter sometimes results in phosphonium ester side products, which may be difficult to remove from polymeric materials.[10] Some of these side products have been reported to exhibit toxicity and are nonbiodegradable,[11] whereas enamines are known to exhibit biodegradability.[24]

Next, a variation in the nucleophilicity of enamines was introduced by deriving enamines from cyclic ketones, enamines **1**−**5**. It was found that with the change in the ketone ring size, a trend occurred in which the most nucleophilic enamine catalyst formed from cyclopentanone exhibited the highest overall conversion (Table 1 and Figure 3). For example, enamine **1**, which exhibited the weakest nucleophilic character, resulted in only 11% final thiol conversion, whereas catalyst enamine **4** exhibited a greater nucleophilic character and resulted in roughly 82% thiol conversion. The thiol-Michael reaction was also conducted with less polar thiol, 1-hexanethiol, with HA in the presence of organocatalyst enamine **4**, which resulted in an overall yield of 75% (Figure S9). This behavior further demonstrates that the proposed catalytic cycle does indeed go primarily through a nucleophilic pathway, with the conversion highly dependent on the nucleophilicity of the enamine employed.

Additionally, the *in situ* formation of an enamine via photodeprotection of an amine in the presence of a ketone was demonstrated as a viable means to catalyze the thiol-Michael reaction. It was hypothesized that the enamine formation was more rapid than the thiol-Michael reaction, and therefore the photo-deprotected amine would preferentially react with the ketone to form an enamine before undergoing base catalysis of the thiol-Michael reaction to any appreciable degree.

Table 1. Thiol Conversion, Nucleophilicity (N), and pK_a of Different Enamines and 2,4,6-Trimethylpyridine under Investigation for Thiol-Michael Addition Reaction[21,a]

Enamine	%Thiol Conversion (60 min)	*N*	pKa
(**1**)	11	11.4	6.3
(**2**)	44	14.9	8.9
(**3**)*	71	16.9	8.9
(**4**)	82	15.9	8.9
(**5**)*	92	16.5	8.9
	0%	9.3	7.5

[a]A clear trend is observed between nucleophilicity and thiol conversion. pK_a of all of the mentioned compounds are below the pK_a of butyl 3-mercaptopropionate (BMP). * Enamines **3** and **5** were generated in situ via photo-deprotection of NPPOC-DEA in the presence of the cyclic ketones, cyclohexanone, and cyclopentanone, respectively.

To investigate the potential of photogenerated enamines to catalyze the thiol-Michael addition reaction, different catalyst loadings (5−10 mol % NPPOC-amine) and cyclic ketones (cyclopentanone and cyclohexanone) were investigated and monitored using Fourier transform infrared (FT-IR) spectroscopy (Table 2). NPPOC-Pyr was utilized as a photobase generator to form identical enamines **2** and **4** *in situ*, to enable the direct comparison of the efficiency of initiation of the thiol-Michael reaction with the *in situ* formed enamine and presynthesized enamine. The real-time kinetics study of a mixture of butyl 3-mercaptopropionate and *n*-hexyl acrylate in a 1:1 thiol/vinyl stoichiometric ratio was subjected to the reaction in the presence of both 10 mol % of NPPOC-Pyr and two different ring sizes of cyclic ketone, cyclohexanone, or cyclopentanone (5 or 10 mol %, Figures S2 and 4a). Upon

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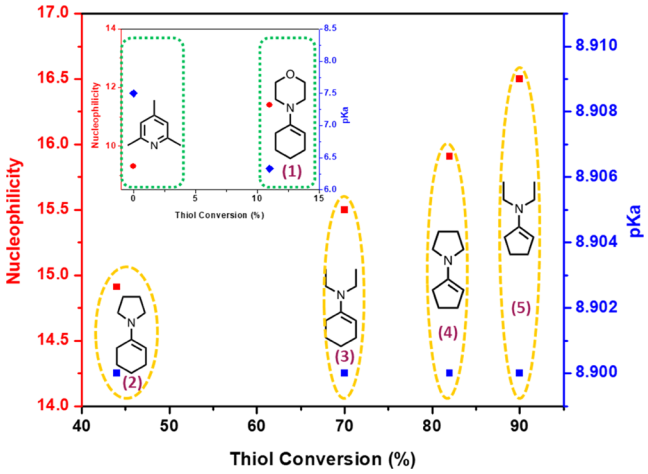

Figure 3. Thiol conversion for different enamines employed in the reaction for 60 min. A clear trend develops in which the more nucleophilic (N) enamines correspond to higher thiol conversion (nucleophilicity is based on the Mayr scale). In addition, enamine pK_a values are shown to demonstrate that the deprotonation of thiol (pK_a = 12) with these enamines is essentially nonexistent.

evaluation, a thiol conversion of >60% was obtained in the presence of 5 mol % CyPent and >40% in the presence of 5 mol % CyHex in the system after 60 min of continuous irradiation. In addition, a mixture of butyl 3-mercaptopropionate and *n*-hexyl acrylate in a 1:1 thiol/vinyl stoichiometric ratio was subjected to an addition reaction in the presence of NPPOC-Pyr (5 or 10 mol %) and resulted in only ∼40% of thiol conversion under similar irradiation condition. Furthermore, in the presence of 10 mol % of NPPOC-Pyr and 10 mol % of CyPent, the reaction system resulted in >70% thiol conversion upon continuous irradiation for 60 min which could be attributed to the highly nucleophilic enamines generated *in situ* (Figure 4a). This behavior clearly indicates the influence of the ketone ring size, which influences the efficiency of the thiol-Michael addition reaction. However, the bulky nature NPPOC-Pyr results in reduced molecular interactions and mobility, limiting the ability of enamine formation to occur before the base-catalyzed thiol-Michael reaction. Figures 4a and S4 clearly indicate the deviation in overall reaction yield upon using presynthesized enamine **4** directly and *in situ* formed enamine **4**. The lowering of molecular interaction and mobility would result in complexities due to the presence of amine, ketone, and enamine at a given point of time, resulting in two competing catalytic reactions: (1) the photolysis of photocaged amines (NPPOC-amines) liberates the base and initiates the base-catalyzed thiol-Michael reaction and (2) the photolysis of photocaged amines (NPPOC-amines) liberates the base that reacts with the cyclic

Table 2. Scope of Different Organocatalyst Enamines Generated for the *In Situ* Thiol-Michael Addition Reaction[a]

entry	catalyst/catalyst loading (mol %)	cyclic ketone (mol %)	irradiation time	yield (%)
1	no catalyst		60 min	35 ± 5
2	5 mol % NPPOC-Pyr		60 min	41 ± 3
3	10 mol % NPPOC-Pyr		60 min	44 ± 4
4	10 mol % NPPOC-Pyr	5 mol % CyHex	60 min	41 ± 5
5	10 mol % NPPOC-Pyr	5 mol % CyPent	60 min	59 ± 3
6	10 mol % NPPOC-Pyr	10 mol % CyHex	5 min	22 ± 1
7	10 mol % NPPOC-Pyr	10 mol % CyHex	60 min	50 ± 11
8	10 mol % NPPOC-Pyr	10 mol % CyPent	5 min	24 ± 4
9	10 mol % NPPOC-Pyr	10 mol % CyPent	60 min	67 ± 4
10	5 mol % NPPOC-DEA		60 min	44 ± 6
11	5 mol % NPPOC-DEA	5 mol % CyHex	30 s	12 ± 5
12	5 mol % NPPOC-DEA	5 mol % CyHex	60 s	22 ± 7
13	5 mol % NPPOC-DEA	5 mol % CyHex	300 s	42 ± 9
14	5 mol % NPPOC-DEA	5 mol % CyHex	60 min	71 ± 8
15	10 mol % NPPOC-DEA	10 mol % CyHex	5 min	67 ± 2
16	5 mol % NPPOC-DEA	5 mol % CyPent	30 s	38 ± 1
17	5 mol % NPPOC-DEA	5 mol % CyPent	60 s	51 ± 3
18	5 mol % NPPOC-DEA	5 mol % CyPent	300 s	55 ± 5
19	5 mol % NPPOC-DEA	5 mol % CyPent	60 min	90 ± 3
20	5 mol % NPPOC-DEA−1 mol % Fmoc-DEA	5 mol % CyHex	300 s	70 ± 6
21	5 mol % NPPOC-DEA−1 mol % Fmoc-DEA	5 mol % CyHex	60 min	84 ± 1
22	5 mol % NPPOC-DEA−0.5 mol % Fmoc-DEA	5 mol % CyHex	300 s	55 ± 2
23	5 mol % NPPOC-DEA−0.5 mol % Fmoc-DEA	5 mol % CyHex	60 min	69 ± 6
24*	5 mol % NPPOC-DEA−1 mol % Fmoc-DEA	5 mol % CyPent	300 s	73 ± 3
25*	5 mol % NPPOC-DEA−1 mol % Fmoc-DEA	5 mol % CyPent	30 min	86 ± 5
26*	5 mol % NPPOC-DEA−0.5 mol % Fmoc-DEA	5 mol % CyPent	300 s	57 ± 1
27*	5 mol % NPPOC-DEA−0.5 mol % Fmoc-DEA	5 mol % CyPent	30 min	71 ± 3
28	10 mol % NPPOC-DEA−1 mol % Fmoc-DEA	10 mol % CyHex	5 min	98 ± 1
29	10 mol % NPPOC-DEA−1 mol % Fmoc-DEA	10 mol % CyHex	20 s	51 ± 2

[a]Reaction conditions: BMP (1 mmol), HA (1 mmol), and photolabile catalysts/photobase amplifier with cyclic ketones irradiated using a Hg source with 365 nm band-pass filter at 50 mW/cm^2 for 60 min (or as indicated). Each sample was stabilized in the dark for 1 min and then irradiated. For demonstrating dark cure, the sample was irradiated only for an initial few seconds (irradiation time varied from 20 to 300 s, as indicated). * These samples were run for 30 min.

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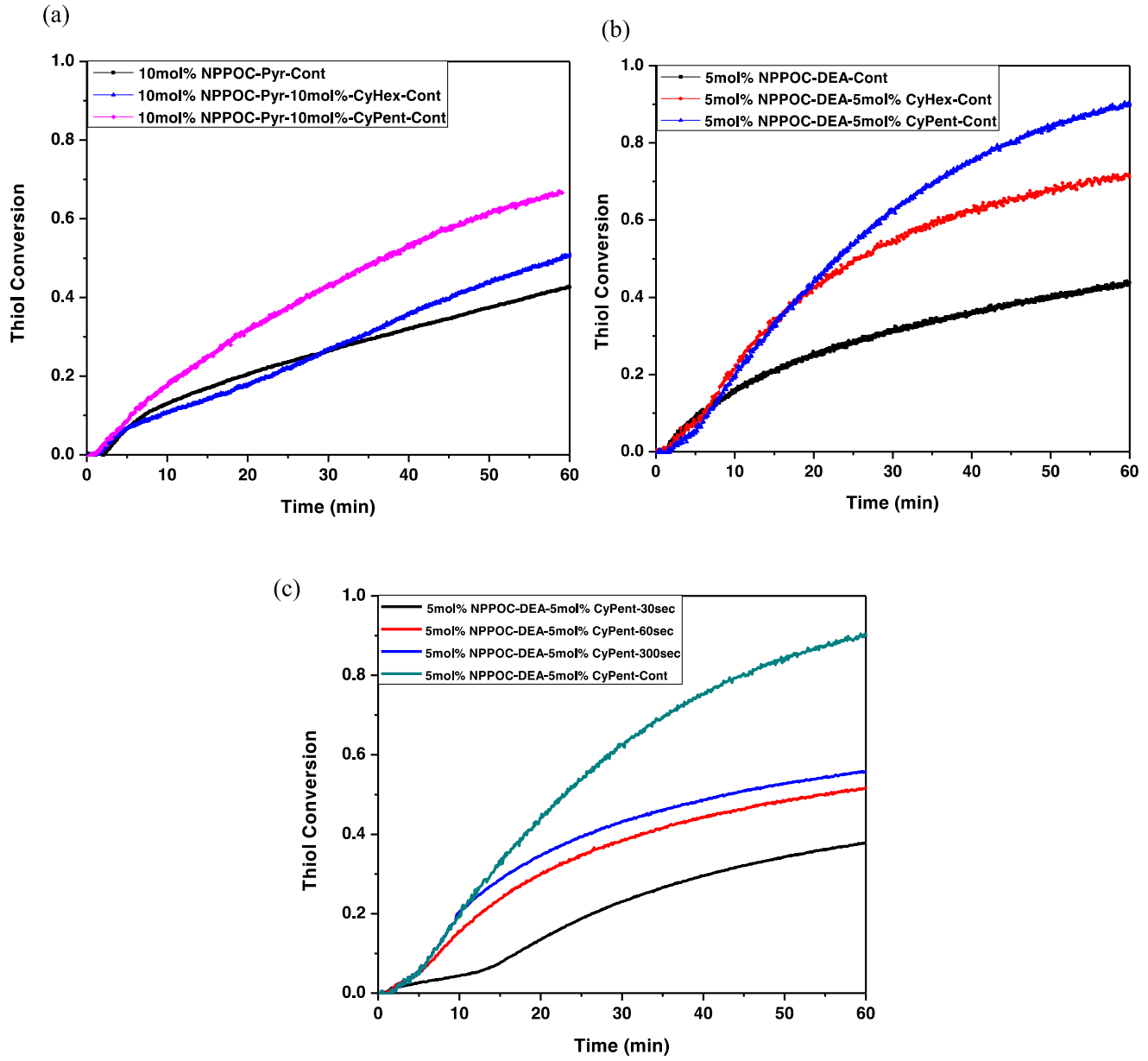

Figure 4. Thiol conversion versus time as monitored by FT-IR for the model reaction between butyl 3-mercaptopropionate (BMP) and 1-hexyl acrylate (HA). (a) Comparison of 10 mol % NPPOC-Pyr (NPPOC-pyrrolidine) with *in situ* generation of photobase using different ring size cycloketone, 10 mol % NPPOC-Pyr-10 mol % CyHex (cyclohexanone), and 10 mol % NPPOC-Pyr-10 mol % CyPent (cyclopentanone). (b) Comparison of 5 mol % NPPOC-DEA with 5 mol % NPPOC-DEA in the presence of 5 mol % CyHex (cyclohexanone) and 5 mol % CyPent (cyclopentanone), respectively, and irradiating continuously for 60 min. (c) Comparison of 5 mol % NPPOC-DEA with 5 mol % NPPOC-DEA in the presence of 5 mol % CyPent (cyclopentanone), irradiating for different time intervals, i.e., 30 s, 60 s, 300 s, and 60 min continuously. The mixture consists of an initial stoichiometric ratio of 1:1 thiol to vinyl functional group concentrations. Each sample was stabilized in the dark for 1 min and then irradiated with 50 mW/cm^2 365 nm wavelength at ambient temperature.

ketone to form enamine *in situ* followed by the initiation of the thiol-Michael reaction via a nucleophilic pathway. Due to the formation of a higher energy iminium cation intermediate and reaction complexities associated with NPPOC-Pyr, the kinetic studies were conducted with NPPOC-DEA, which is anticipated to generate an iminium cation with lower energy and less steric hinderance when reacted with the same cyclic ketones (resulting in enamines **3** and **5**) to efficiently facilitate the rapid enamine formation first. The kinetic profile for the thiol conversion of the model reactant, butyl 3-mercaptopropionate (BMP), and *n*-hexyl acrylate in a 1:1 thiol/vinyl stoichiometric ratio exhibited >70% in the presence of 5 mol % NPPOC-DEA and 5 mol % CyHex (*in situ* formation of enamine **3**) and >90% in presence of 5 mol % NPPOC-DEA and 5 mol % CyPent (*in situ* formation of enamine **5**) after 60 min of continuous irradiation as opposed to 44% with 5 mol % NPPOC-DEA (Figure 4b) and 50 and 60% in the presence of 10 mol % NPPOC-Pyr/10 mol % CyHex and 10 mol % NPPOC-Pyr/10 mol % CyPent (Figure 4a). It is important to note the lag time at the beginning of the reaction, as it is believed that this period correlates with the enamine formation prior to the catalysis of the thiol-Michael reaction. Figure 4b suggests that NPPOC-DEA in combination with CyPent is likely to rapidly form enamine **5** due to the planar

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conformation of CyPent as opposed to NPPOC-DEA in combination with CyHex. This result clearly indicates that the highly reactive nature of the five-membered ring cyclic enamines **4** and **5** associated with its maximally planar conformation at the nitrogen results in initiation of the thiol-Michael reaction via the nucleophilic pathway more rapidly than six-membered ring cyclic enamines **2** and **3**. The six-membered ring of CyHex tends to be in the more stable chair conformation, resulting in slower photoinduced *in situ* formation of enamines **2** and **3** as compared to enamines **4** and **5**. Due to the slower formation of enamines **2** and **3**, the base-catalyzed thiol-Michael reaction is expected upon photolysis of the photocaged amine. Once enamines **2** and **3** are formed through photoinduction, the progress of the reaction was observed to change which could be attributed to a more favorable enamine organocatalyzed thiol-Michael reaction.

This study supports the claim that the photoinduced *in situ* formation of enamines catalyze the thiol-Michael reaction. It is worth mentioning that the use of NPPOC-Pyr (Figure 4a) does not show a significant lag time at the beginning of the reaction to account for enamine formation, but a lag is observed upon the use of NPPOC-DEA (Figure 4b). This behavior clearly demonstrates that the choice of amine substituted on the photobase generator and the cyclic ketone are crucial to enable the rapid formation of enamine *in situ* prior to catalysis of the thiol-Michael reaction.

Because of the regeneration of the nucleophile, it is expected that the thiol-Michael reaction will continue in the dark even after cessation of the irradiation. To demonstrate this concept, a dark cure experiment was performed with model reactants, BMP and HA in the presence of 5 mol % NPPOC-DEA and 5 mol % CyPent or CyHex with different limited light exposure times as depicted in Figures 4c and S5. Although slower reaction kinetics are observed in the dark, when compared to continuous irradiation, 5 min of limited exposure time exhibited a distinctive and continuing reaction. It is believed that the longer light exposure would result in a higher overall conversion due to an increase in the photogenerated amine, which then reacts with the cyclic ketone to form enamine over time during the irradiation.

It has been previously shown for the thiol-Michael reaction that a catalytic amount of Fmoc-protected amine in the presence of a catalytic photoinducible base increases both the rate of the reaction and overall yield.[25] Therefore, the photo autocatalytic amplification of enamine formation for the catalysis of the thiol-Michael reaction was investigated by combining NPPOC-protected amines with Fmoc-protected amine analogs in the presence of a ketone to amplify the formation of enamines generated *in situ* (Figures 5, S6, and S7). Figure 5 shows an increase in the reaction kinetics and a drastic increase in overall yield with the Fmoc-protected amine analog going to completion. Interestingly, the thiol conversion after the light was turned off was only roughly 60%; however, the reaction continued until completion after irradiation had ceased. This observed "living" character has the potential to form cross-linked networks even with only limited light exposure and enhanced conversions.

The potential of enamines to act as potent organocatalysts in cross-linking polymerizations was also examined (Figure 6) with PETMP as a multifunctional thiol monomer and TMPTA as the vinyl monomer. Upon continuous irradiation or with a limited exposure time of 5 min for the PETMP/TMPTA system in a 1:1 thiol/vinyl stoichiometric ratio in the presence of 10 or 20 mol % NPPOC-DEA and 10 or 20 mol %, CyPent resulted in ~85% thiol conversion within 30 min. A limited exposure of 20 s resulted in relatively higher thiol conversion (70%) compared to the NPPOC base analogue (20%) after 30

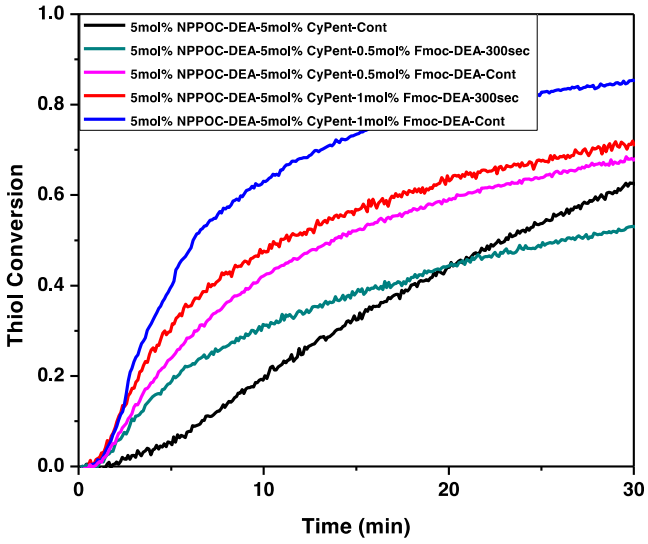

Figure 5. Thiol conversion versus time as monitored by FT-IR for the model reaction between butyl 3-mercaptopropionate (BMP) and 1-hexyl acrylate (HA). A comparison of 5 mol % of NPPOC-DEA in the presence of 5 mol % CyPent, and its comparison with 5 mol % NPPOC-DEA in the presence of both 0.5 or 1 mol % Fmoc-DEA and 5 mol % CyPent (cyclopentanone), irradiating for 5 and 30 min continuously. The mixture consists of an initial stoichiometric ratio of 1:1 thiol to vinyl functional group concentrations. Each sample was stabilized in the dark for 1 min and then irradiated with 50 mW/cm^2 365 nm wavelength at ambient temperature.

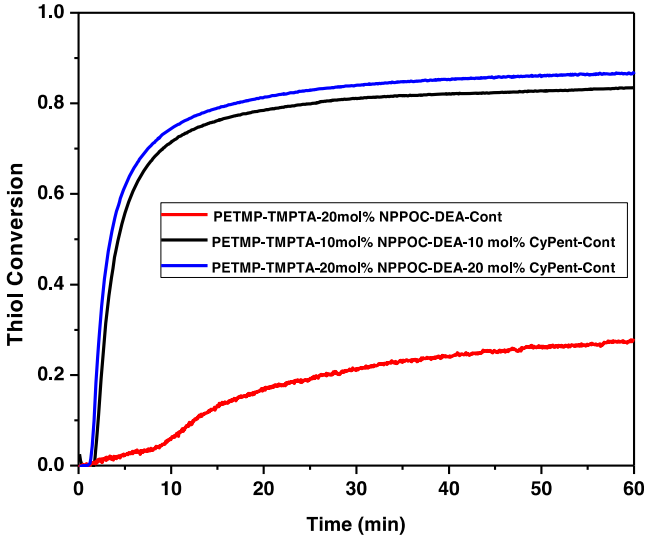

Figure 6. Thiol conversion versus time as monitored by FT-IR for photopolymerization between PETMP and TMPTA using 10 or 20 mol % NPPOC-DEA in the presence of 10 or 20 mol % CyPent(cyclopentanone), irradiating 60 min and its comparison with 20 mol % of NPPOC-DEA irradiated continuously for 60 min without cyclopentanone. The mixture consists of an initial stoichiometric ratio of 1:1 thiol to vinyl functional group concentrations. Each sample was stabilized in the dark for 1 min and then irradiated with 50 mW /cm^2 365 nm wavelength at ambient temperature.

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min (Figure S8), which clearly indicates the efficacy of enamines as organocatalysts toward thiol-Michael polymerizations in the formation of highly cross-linked networks with only limited light exposure.

CONCLUSIONS

In summary, it has been shown that the enamines employed in this study act as catalysts for the thiol-Michael reaction with improved yield and rates compared to the base analogs. It was also demonstrated that photo-protecting amines with NPPOC in the presence of a ketone results in enamine formation *in situ*. In addition, the photo autocatalytic amplification of the thiol-Michael reaction by adding in a Fmoc-protected amine could improve both the rate and the overall yield of the reaction. This novel organocatalyst for the thiol-Michael reaction proceeds via a nucleophilic pathway, producing byproducts that exhibit biodegradability, unlike previously reported catalysts of this nature. It is anticipated that the studies described herein will improve the (bio)material science applications of the thiol-Michael reaction.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.macromol.0c02128.

NMR spectra of model reactant, reaction kinetics, and NMR of the synthesized compounds (PDF)

AUTHOR INFORMATION

Corresponding Author

Christopher N. Bowman − *Department of Chemical and Biological Engineering, University of Colorado Boulder, Boulder, Colorado 80309, United States;* orcid.org/0000-0001-8458-7723; Email: Christopher.bowman@colorado.edu

Authors

Jasmine Sinha − *Department of Chemical and Biological Engineering, University of Colorado Boulder, Boulder, Colorado 80309, United States;* orcid.org/0000-0001-8396-1322

Shafer Soars − *Department of Chemistry, University of Colorado Boulder, Boulder, Colorado 80309, United States*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.macromol.0c02128

Author Contributions

[§]J.S. and S.S. contributed significantly to this work.

Notes

The authors declare no competing financial interest.

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