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Nitrogen-Centered Nucleophile Catalyzed Thiol-Vinylsulfone Addition, Another Thiol-ene "Click" Reaction

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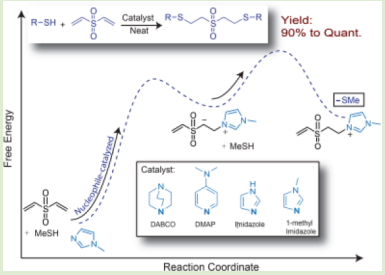
Supporting Information

ABSTRACT: A new group of nitrogen-centered nucleophilic catalysts for the thiol-Michael addition "click" reactions is examined. These nucleophiles showed efficient catalytic activities as compared with traditional base catalysts, such as triethylamine, and are demonstrated to be a viable strategy for cross-linking polymerization reactions. Additionally, an experimental and computational mechanistic study was performed, suggesting a pathway for the nitrogen-centered catalyst to undergo the nucleophilic addition mechanism.



The thiol-vinyl "click" reaction is one of the most powerful and popular organic reactions in polymer chemistry owing to ease of implementation, rapid reaction kinetics, and high yields.[1] This reaction has been used in numerous macromolecular synthetic strategies, such as polymer functionalization, network formation, and dendrimer synthesis.[2,3] The thiol-vinyl reaction typically proceeds via one of two pathways: (i) radical-mediated anti-Markovnikov addition, commonly referred to as the thiol-ene reaction, or (ii) base- or nucleophile-catalyzed thiol-Michael addition.[4−8] Recently, Chan et al. highlighted phosphine-containing species (specifically, organophosphine(III)) as highly efficient catalysts for the thiol-Michael addition reaction, including for the synthesis of star polymers.[9] Phosphine reagents (e.g., dimethylphenylphosphine or tri-*n*-butyl phosphine) were found to have far superior reaction kinetics as compared to amine-based catalysts for several thiol-vinyl combinations, demonstrating excellent activity at extremely low concentrations.[10−13] However, one must exercise extreme care when handling organophosphines owing to their potential reactivity and toxicity, especially trialkylphosphines.[12] Therefore, a nontoxic, efficient catalyst for thiol-Michael addition remains an important challenge for the development of thiol-vinyl chemistry.

Nitrogen-centered nucleophiles, such as 1,4-diazabicyclo[2.2.2]octane (DABCO) and 4-dimethylaminopyridine (DMAP), are often used as catalysts of the oxa-Michael addition in the Baylis−Hillman reaction.[14−17] Inspired by this reaction, we hypothesize that nitrogen-centered reagents will also catalyze the thiol-Michael addition through a nucleophilic addition pathway. To evaluate this hypothesis, we used 1-hexane thiol and divinylsulfone as a model thiol and as a Michael-type vinyl. The vinylsulfone has been used in applications, such as protein conjugation, and is orthogonal to the vinyl species typically employed in the radical-mediated thiol-ene reaction.[18−20] Here, we examine the catalytic activity of four nitrogen-centered catalysts: DABCO, DMAP, imidazole, and 1-methyl imidazole. These catalysts were selected based on their pK_a values (i.e., lower than the pK_a of hexane thiol), and they have all been shown to be good nucleophiles for oxa-Michael addition as indicated by Mayr and co-workers.[21,22] The reaction time and yields were monitored using Fourier transform infrared (FTIR) spectroscopy and are shown in Table 1 for the four nitrogen-centered catalysts. DABCO and DMAP exhibited excellent thiol-Michael catalysis, achieving quantitative yields within 5 min. 1-Methyl imidazole and imidazole also demonstrated good catalytic behavior for the thiol-Michael addition. The catalysis of the thiol−vinylsulfone addition reaction for these four nitrogen-centered compounds is superior to the primary amine (hexylamine) and secondary amine (diethylamine) (see Table 1) catalysis. Interestingly, the opposite is true for the thiol−acrylate addition reaction, demonstrating the importance of pairing the appropriate catalyst with the thiol and vinyl functional groups (see the Supporting Information). The reaction utilizing 1-methyl imidazole is particularly noteworthy as it is a liquid at ambient temperature, which aids in dispersing the catalyst into the monomer mixture.

To investigate the mechanism for the highly effective catalysis of the above reactions, we performed both experimental and theoretical investigations. 2,6-Lutidine was

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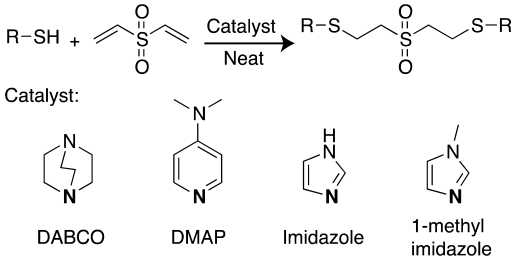
Table 1. Addition of Thiols to Divinylsulfone Catalyzed by Various Nitrogen-Centered Nucleophiles (1 mol % unless Otherwise Indicated)



entry	catalyst	pK_a[a]	R	reaction time (min)	yield[b] (%)
1	DABCO	8.8	$CH_3(CH_2)_4CH_2$	5	quant.
2	DMAP	9.7	$CH_3(CH_2)_4CH_2$	5	quant.
3	imidazole	7.0	$CH_3(CH_2)_4CH_2$	15	90
4	1-methyl imidazole	7.0	$CH_3(CH_2)_4CH_2$	5	96
5	DABCO	8.8	$^nBuOCOCH_2CH_2$	5	quant.
6	DABCO	8.8	$MeOCOCH_2CH_2$	5	quant.
7	DABCO	8.8	furyl	5	quant.
8	diethylamine	11.0	$CH_3(CH_2)_4CH_2$	60	90
9	hexylamine	10.6	$CH_3(CH_2)_4CH_2$	20	66[c]
10	hexylamine	10.6	$CH_3(CH_2)_4CH_2$	120	15
11	triethylamine	10.8	$CH_3(CH_2)_4CH_2$	30	90
12			$CH_3(CH_2)_4CH_2$	120	0

[a]Refers to the pK_a of the corresponding conjugate acid in H_2O at 20 °C. [b]^1H NMR yield. [c]Hexamine catalyst loading is 5 mol %.

utilized as a negative control catalyst, because its pK_a value (6.7) is quite similar as 1-methyl imidazole (7.0), but the steric hindrance at the nitrogen position decreases its nucleophilic character. The reaction kinetics comparing the catalytic activity of 1-methyl imidazole, triethylamine (TEA), and 2,6-lutidine are shown in Figure 1. While the 1-methyl imidazole catalyzed reaction achieved over 90% conversion after only 2 min, no thiol conversion was observed in the reaction catalyzed by 2,6-lutidine in this same time period. Consistent with Chan et al.,[12] this significant difference suggests that the nucleophilicity of the catalyst is one of the critical parameters in this thiol-Michael

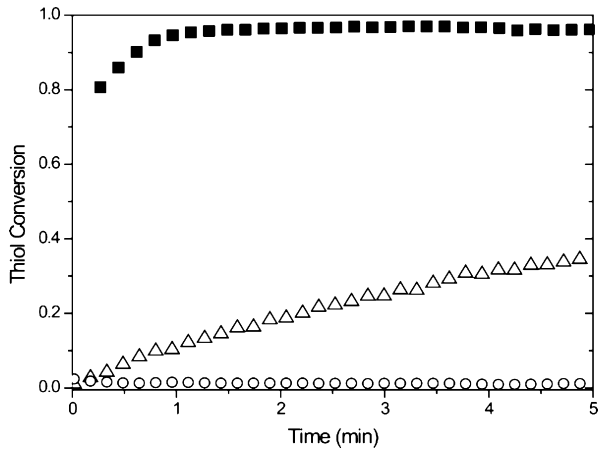
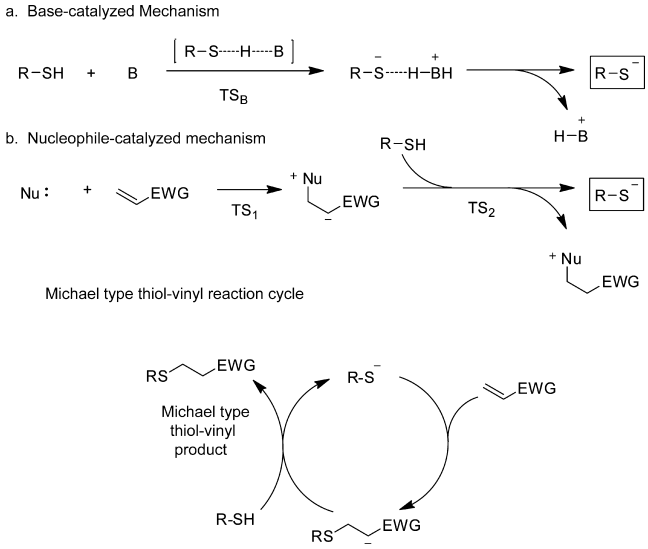


Figure 1. Thiol conversion versus time for a stoichiometric mixture of 1-hexane thiol and vinylsulfone using 1 mol % 1-methylimidazole (filled square), TEA (open triangle), and 2,6-lutidine (open circle).

reaction. We also compared the reaction kinetics of 1-methyl imidazole with TEA, which is a commonly used base catalyst in the thiol-Michael reaction. As shown in Figure 1, 1-methyl imidazole exhibits significantly faster reaction kinetics for these reactants as compared to TEA; this result further indicates a nucleophile- rather than base-catalyzed pathway since the pK_a of 1-methyl imidazole is significantly lower than TEA (7.0 versus 10.8, respectively) and TEA is a comparatively poor nucleophile.

Previous work on catalysis of the thiol-Michael addition suggests that there are two possible mechanisms, as shown in Scheme 1. The principle difference in these thiol-Michael

Scheme 1. Base- (a) and Nucleophile- (b) Catalyzed Pathway for Generating the Thiolate Anion, Which Initiates the Michael Type Thiol–Vinyl Reaction Cycle



addition reactions is the pathway for generating the alkyl thiolate anion.[14,23,24] To examine the energy difference, we used the catalyst 1-methyl imidazole as an example for theoretical assessment of these two pathways. The calculated relative free energies at 298 K for the two possible pathways are shown in Figure 2. Utilizing quantum level calculations (see the Supporting Information), the free energy was determined for the nitrogen-centered catalysis of the thiol-Michael reaction for both the nucleophile- and the base-mediated pathways. As an example, the energy profile is shown below in Figure 2 for 1-methyl imidazole as the nitrogen-centered catalyst. Here, it was determined that the nucleophile-catalyzed pathway has an energy difference necessary to form the thiolate anion that is ~9 kcal/mol lower than that for the base-catalyzed pathway. Similar results were also obtained for other catalysts which indicated that the nucleophilic pathway is thermodynamically favored for these catalyst-reactant combinations as the means for generating the alkyl thiolate anion (Table S1, SI).

Finally, we demonstrated utilization of a nitrogen-centered nucleophilic catalyst to catalyze cross-linked polymer formation from multifunctional thiol and divinyl monomers. A tetrathiol (PETMP) and divinylsulfone were mixed in the presence of 1 mol % 1-methyl imidazole as catalyst. The thiol conversion reached in excess of 92% after 20 min (Figure S3 of the Supporting Information), likely limited by vitrification and mobility rather than any reaction limitation. DMA results (Figure 3) confirmed the formation of cross-linked polymer

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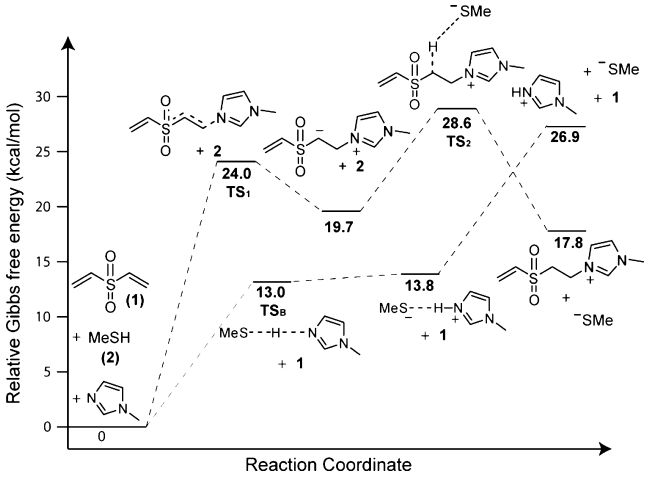

Figure 2. Free energy profiles of the base- and nucleophile-catalyzed pathways for 1-methyl imidazole calculated at the B3LYP/6-31+G(d) level of theory.

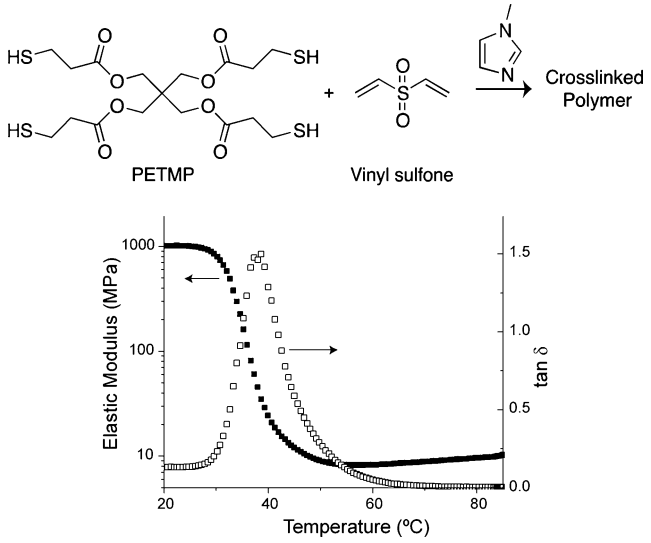

Figure 3. The tan δ and elastic modulus plots versus temperature for networks formed from a stoichiometric mixture of PETMP and divinyl sulfone.

network having a glass transition temperature of 41 °C, which most likely accounts for the decreased conversion relative to the model compounds shown in Table 1. The cross-linking density (ρ) was determined based on rubber elasticity theory according to this equation[25]

$$\rho = \frac{E}{2(1+\gamma)RT}$$

where E is the modulus in the rubbery state, T is the absolute temperature, R is the ideal gas constant, and γ is Poisson's ratio which is assumed to be 0.5 for incompressible networks. The calculated cross-linking density based on the mechanical property measurement is 1.1 M.

In summary, it has been found that nitrogen-centered nucleophiles such as DABCO, DMAP, and 1-methyl imidazole catalyze the rapid, efficient thiol-Michael addition under mild conditions. Both experimental and theoretical results demonstrated that the nucleophilic pathway is favored to catalyze the thiol-Michael addition. We further demonstrate that nitrogen-centered nucleophiles are excellent catalysts for thiol-ene polymerizations. These catalysts are an attractive alternative to traditional base or phosphine catalytic systems for the initiation of the Michael-type thiol-ene addition reaction.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental data, computational data, molecular characteristics of model reaction, and kinetics of polymerization. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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