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Ultrasound Promoted Step-Growth Polymerization and Polymer Crosslinking Via Copper Catalyzed Azide-Alkyne 'Click' (CuAAC) Reaction.

Hemakesh Mohapatra, Jorge Ayarza, Emily C. Sanders, Angelique M. Scheuermann, Philip J. Griffin, Aaron P. Esser-Kahn*

Abstract: Mechano-activated chemistry is a powerful tool for remodeling of synthetic polymeric materials, however few reactions are currently available. Here we show that using piezochemical reduction of a Cu^{II}-based pre-catalyst, a step-growth polymerization occurs via the copper catalyzed azide-alkyne cycloaddition (CuAAC) reaction to form a linear polytriazole. Furthermore, we show that a linear polymer can be crosslinked mechanochemically using the same chemistry to form a solid organogel. We envision that this chemistry can be used to harness mechanical energy for constructive purposes in polymeric materials.

Biological materials such as bones, muscles, and skin can adapt in response to mechanical stimuli by changing their composition and structure through a process called mechanotransduction.[1] These cellular systems convert mechanical stimuli into chemical signals that deposit or remove material and change their structure.[2] Currently, synthetic polymeric materials mostly lack similar adaptability, resulting in the need to replace them repeatedly. Recently, we and others have started investigating methods to use mechanical energy, in the form of ultrasound, to conduct controlled chain-growth polymerization with the goal of allowing structural changes through the conversion of mechanical energy to chemical energy.[3, 4] Here we show that we can use ultrasound to promote step-growth polymerization and polymer crosslinking, adding to our ability to use mechanical energy for the construction of new polymeric materials.

To harness the energy of ultrasound in order to promote polymerization we rely on piezoelectric nanoparticles which can directly convert mechanical stress into electrochemical activity. Previously, we used ultrasonic agitation of piezoelectric nanoparticles ($BaTiO_3$) to mechanically activate a Cu^{I}-based catalyst that could then promote atom transfer radical polymerization (ATRP) of acrylate monomers. [3a] The process of mechanotransduction in this context is believed to be mediated through the reduction of Cu^{II} complex to Cu^{I}-based polymerization promoter on the surface of the nanoparticles. Others have since shown that ATRP is compatible with other monomers and other piezoelectric nanoparticles.[3b,c]

The ease with which Cu^{II} can be reduced to Cu^{I} via ultrasound under amenable conditions prompted us to look into other reactions promoted by Cu^{I}. Notably, the copper-catalyzed azide-alkyne cycloaddition, commonly referred to as copper 'Click' reaction[5, 6] (Figure 1) would lead to the potential control of both step-growth and crosslinking reactions owing to the A+B type coupling reaction.[7] Ultrasound has been used previously to promote 'Click' reaction in the context of small molecules, where ultrasound promotes reaction through enhanced diffusion or depassivation of metallic surfaces.[8] In this study, we conducted a step-growth linear polymerization via ultrasound promoted copper 'Click' reaction (i.e., mechano-click reaction) to synthesize a polytriazole. Moreover, we took one step forward in transitioning away from linear polymerizations to crosslinking polymer chains – leading to the formation of solid polymeric composites upon mechanical stimulation. We synthesized a linear polyurethane with azide containing pendant groups. This polymer was then crosslinked with tripropargyl amine via the mechano-click reaction. The approach of using the piezoelectric effect to activate catalysts for CuAAC-mediated reactions in polymeric materials complements others approaches of mechano-click reactions that are mediated by mechanophores.[9]

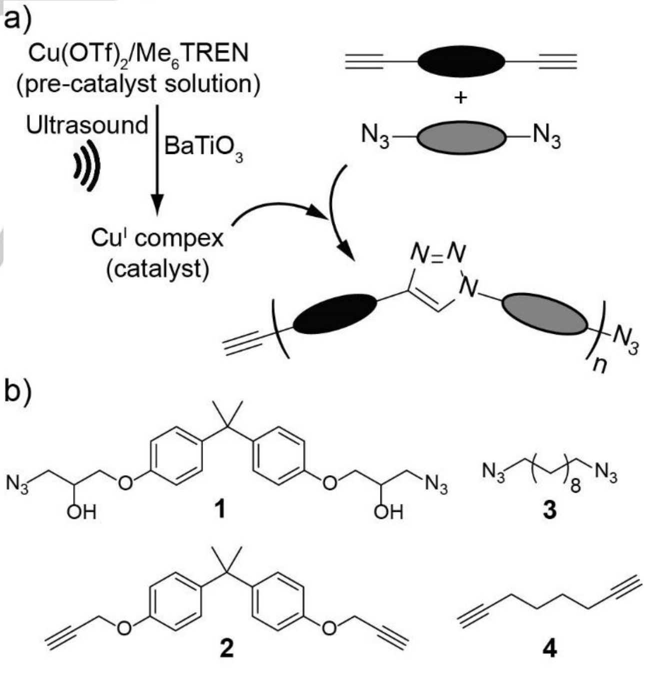

Figure 1. (a) Representation of 'Click' polymerization catalyzed by Cu^{I} generated through ultrasonic reduction of Cu^{II} precursor (Cu(OTf)$_2$/Me$_6$TREN). The reaction mixture contains a divalent azide, a divalent alkyne, substoichiometric Cu^{II} precursor salt with ligand Me$_6$TREN, and piezoelectric nanoparticle $BaTiO_3$. Under ultrasonic activation piezoelectric nanoparticles provide an interface where ligand stabilized Cu^{II} salts are reduced to Cu^{I}-based catalysts for 'Click' reaction; (b) Structures of diazides and dialkynes used for mechano-click reaction.

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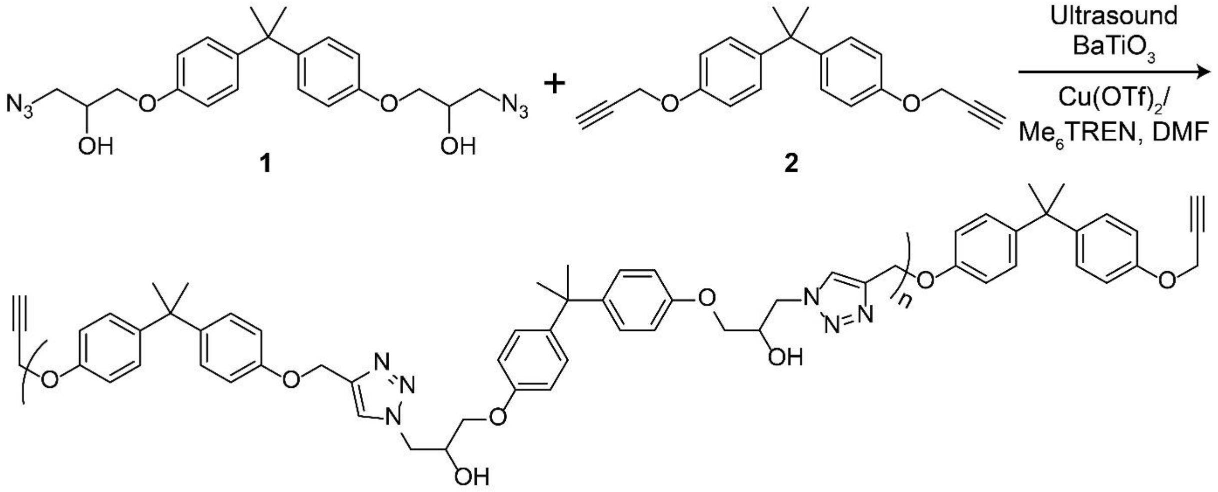

Scheme 1. Representative example of mechano-click polymerization.

We first sought to extend the Cu^{I} generation to step-growth polymerization, however, using the copper 'Click', reaction requires divalent azides and divalent alkynes. Based on safety concerns,[10] previous work,[11] and creating compatibility with current commercial resins, we synthesized diazide **1** in one step from commercial bisphenolic epoxides.[11] **1** also has alcoholic functionality that we used for further urethane polymerization. The dialkyne **2** was also synthesized by single synthetic step from bisphenol A.[12]

For our initial attempts at step-growth polymerization promoted by ultrasound (i.e., mechano-click polymerization), we used equimolar amounts of **1** and **2** as the co-monomers. The model reaction mixture contained **1** (1 M in DMF), **2** (1 M), Cu(OTf)$_2$/Me$_6$TREN (50/55 mM respectively), and BaTiO$_3$ (10 wt%). The reaction mixture was degassed and sonicated using an ultrasonic bath. The preliminary reaction conditions were adapted from the mechano-ATRP polymerization.[3a] Our preliminary experiments with a reaction time of 24 h provided high conversions of the azide (> 95%), as determined by proton nuclear magnetic resonance (^{1}H-NMR), and linear polymers of average molecular weights of ~18 kDa (Table 1), as determined by gel permeation chromatography (GPC).

To investigate the feasibility of the mechano-click method to synthesize other linear polytriazoles, we conducted polymerization reactions using two different diazide-dialkyne pairs. However, we obtained short polymers, even though conversion of the starting diazide was high (Table 1, entry 2). For each of these reactions, we observed precipitation, leading us to the conjecture that poor solubility of the products limits the molecular weight. Similarly, when two aliphatic co-monomers were used (Table 1, entry 3) we could not measure the molecular weight of the resulting polymers due to the poor solubility of the reaction mixture. These observations support our conclusion that poor solubility might be preventing formation of longer polymers even when the consumption of the diazide was high. Similar solubility problems have also been observed when polytriazoles were prepared by conventional 'Click' reaction.[13] Therefore, we continued our investigation using **1** and **2**.

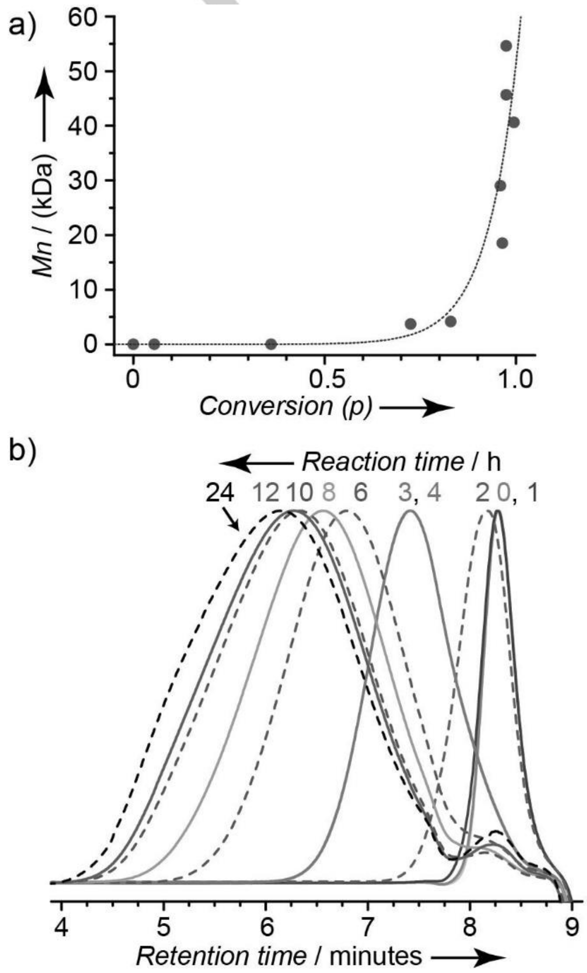

Figure 2. Ultrasound mediated 'Click' polymerization. a) Evolution of the number average molecular weight (M$_n$) over increasing monomer conversion (dashed line showing trend); b) GPC trace depicting the evolution of polymer molecular weight over time. The polymerization mixture contained **1** (1 M in DMF), **2** (1 M), Cu(OTf)$_2$/Me$_6$TREN (50/55 mM) and BaTiO$_3$ nanoparticles (tetragonal, 200 nm, 10 wt%). The mixture was sonicated at 40 kHz using an ultrasonic cleaner. Aliquots from the reaction were analyzed by ^{1}H-NMR, and GPC with polystyrene standards.

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To further investigate the mechano-click polymerization, we followed the progress of the polymerization. Aliquots of the reaction mixture were analyzed by ^{1}H-NMR and GPC at set intervals. We observed that the diazide was consumed quickly (Table S1), about 85% of it was consumed within 4 h. The mechano-click polymerization followed similar kinetics to conventional catalyzed step-growth polymerization, i.e. high values of M_n were only obtained at very high conversion. (Figure 2a). There was no significant increase of polymer M_n beyond 24 h. The polydispersity (Đ) of the polymer was around 2.9, which is expected for a step-growth polymerization.For comparative purposes, we ran a control experiment where we used 10 mM of $Cu^I(OTf)/Me_6TREN$, instead of 50 mM of $Cu^{II}(OTf)_2/Me_6TREN$ in the mechano-click polymerization (Figure S2). Understandably, the kinetics of the polymerization were extremely fast and polytriazoles of very high M_n formed in a shorter reaction time.

Table 1. Results of preliminary screening of comonomers for mechano-click polymerization.[a]

No.	Diazide[a]	Dialkyne[a]	% conversion[b]	M_w (kDa)[c]	Đ[d]
1	**1**	**2**	98	17.7	1.47
2	**1**	**4**	47	0.5	1.12
3	**3**	**4**	20	–[e]	–[e]

[a] Reaction conditions: 5/5.5 mol% $Cu(OTf)_2/Me_6TREN$, 10 wt% $BaTiO_3$ in DMF; Concentrations of each of the monomers were 1 M, 0.8 M, and neat for entry 1, 2, and 3 respectively; reaction mixture was sonicated using a benchtop ultrasonic cleaner (40 kHz) for 24 h. [b] % conversion of diazide as determined using ^{1}H-NMR. [c] Weight average molecular weight (M_w) as determined using GPC with polystyrene standards. [d] Polydispersity (Đ) as determined using GPC. [e] Not determined.

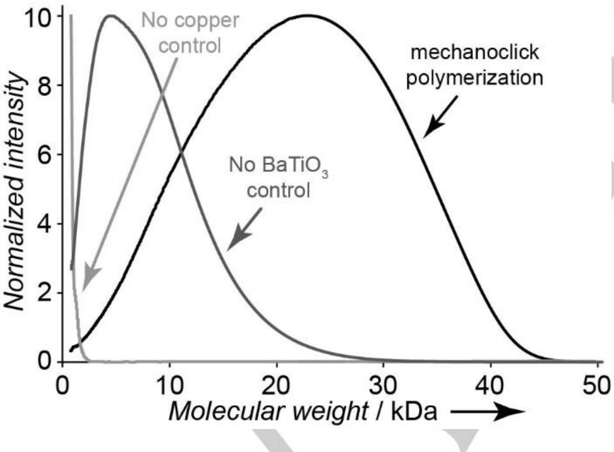

Figure 3. Analysis of polymers obtained in control experiments. GPC traces of aliquots from mechano-click polymerization where either copper precursor solution or $BaTiO_3$ nanoparticles were absent. GPC trace of a representative mechano-click polymerization is shown for comparison. The polymerization mixture contained **1** (1 M in DMF), **2** (1 M), $Cu(OTf)_2/Me_6TREN$ (0/0 or 50/55 mM) and $BaTiO_3$ nanoparticles (0 or 10 wt%). The mixture was sonicated at 40 kHz using a benchtop ultrasonic cleaner.

Finally, to demonstrate that the 'Click' polymerization is indeed mediated by piezoelectric reduction of Cu^{II} to active Cu^I catalyst, we conducted control experiments. The polymerizations were repeated in the absence of either Cu^{II} salt or $BaTiO_3$ nanoparticles. As shown in the GPC traces of reaction mixtures obtained after a reaction time of 24 h, no polymerization is observed in the absence of Cu^{II} precursor salt (Figure 3). This supports the hypothesis that thermal energy generated during ultrasonic agitation of solution is not sufficient to account for the observed polymerization. However, we observed the formation of short polymers when Cu^{II} was present in the reaction mixture but $BaTiO_3$ was absent. This observation suggests that there is a mode of reduction of Cu^{II} that is not mediated by the piezoelectric effect of $BaTiO_3$. A possible source of background reactivity could be the generation of radicals through non-specific homolytic bond cleavage in Me_6TREN or DMF as observed elsewhere.[14] In a control experiment where Me_6TREN was absent in the polymerization mixture, we saw a small amount of polymerization consistent with non-specific background polymerization observed previously (Figure S2). This suggests degradation of DMF through ultrasound could be responsible for the background reactivity. Further experiments to support these assertions will be reported in future publications.

The polytriazoles were soluble in polar, aprotic solvents including DMF and DMSO. These solvents, allowed us to solvent cast these polymers for materials testing. We also conducted mass spectrometric analysis (MALDI-TOF) to confirm the chemical identity of the polymer. We obtained a set of MALDI peaks (Figure S3a) separated by 734 Da, matching the weight of a single repeat unit. We also obtained a set of MALDI peaks of lower molecular weight fragments (Figure S3b) separated by 426 and 304 Da. These peak separations suggest fragments corresponding to the pattern A-B and A-B-A respectively, where A and B refer to the dialkyne and the diazide respectively. Polytriazoles, obtained through 'Click' reactions are expected to have rigid polymeric chains leading to high materials strength. During the mechano-click reaction the suspension turns into a highly viscous fluid (Figure S1b). However, when the reaction mixture is dried under reduced pressure, we obtained a tough and rigid glassy polymer (Figure S1c). We performed a temperature ramp shear rheology measurement between the temperature range of 50–180 °C at a constant frequency of 1 Hz (Figure S5). At temperatures below 75 °C, the polymer is in the glassy state, exhibiting a storage modulus (G') in the range of 10^9 Pa. In the range of 75–120 °C, the polymer shows a considerably sharp decrease in G' from 10^9 to 10^7 Pa, indicating the formation of a rubbery state. Finally, at temperatures above 150 °C, the loss modulus (G'') overcomes G', indicating the formation of a polymer melt.

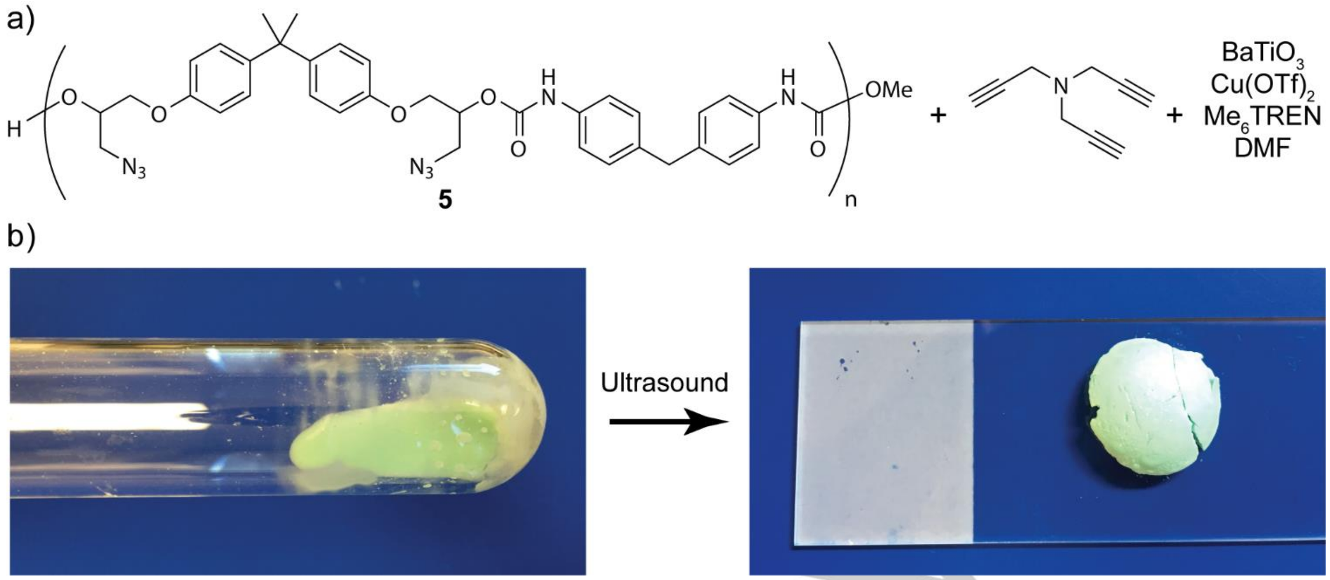

Figure 4. Ultrasound mediated polymer crosslinking using mechano-click reaction (a) Components of pre-crosslinked polyurethane-trialkyne mixture; (b) Photographs depicting the starting reaction mixture (left) and the solid polymer gel obtained after sonication (right).

After demonstrating the synthesis of linear polymers using mechano-click polymerization, we looked into using this method to crosslink polymers. Crosslinking reactions mediated by mechanical force would provide us with the capability to fabricate polymers of a wider range of materials properties. We synthesized a linear polymer **5** containing 2 equivalents of azide per repeat unit providing multiple sites for potential crosslinking reactions. Polymer **5** was synthesized using conventional base-catalyzed polycondensation of **1** (which contains 2 alcohol functionalities in addition to being a diazide) and methylene diphenyl diisocyanate (MDI). The resulting polymer **5** (M_w = 21.5 kDa) was crosslinked using mechano-click reaction with tripropargyl amine as the crosslinker (Figure 4a). Briefly, a mixture containing **5** (c.a. 0.89 mmol N_3), tripropargyl amine (0.89 mmol alkyne), $BaTiO_3$ (10 wt%), $Cu(OTf)_2$/Me_6TREN (5/5.5 mol%) and DMF (0.5 mL) was degassed with three cycles of freeze-pump-thaw and was then sonicated for 24 h. At the end of the reaction, we obtained a gel that was resistant to flow (Figure 4b). The gel was brittle, but hardened to a tough plastic when the solvent was removed under reduced pressure (Figure S6a). In a control experiment in which we ran an equivalent crosslinking experiment in the absence of added Cu^{II} precursor, we observed no crosslinking (Figure S6b), supporting our previous hypothesis that Cu^{I} is necessary for the mechano-click chemistry to function. When the experiment was repeated with the Cu^{II} precursor present, but $BaTiO_3$ was absent we observed some crosslinking. The polymeric mixture obtained in this case was, however, a soft gel that disintegrated with compression. This observation suggests that a small amount of crosslinking likely occurs that is not mediated by piezocatalysis either through local increased temperatures or other means. This is consistent with the small amount of background we observed in the linear system (Figure 3).

In this communication, we demonstrated that we can use mechanical energy in the form of ultrasound to activate the Cu^{I} catalyzed 'Click' reactions of multivalent azides and alkyne. We showed here that we can synthesize linear polymers, as well as crosslinked polymers using a mechano-click reaction. This is the first example of a reaction where ultrasonic agitation mediates copper 'Click' polymerization through piezocatalysis. Ultrasonic energy is usually considered destructive in polymer chemistry, however, through the use of piezochemical activation of a copper-based catalyst we can design polymeric systems that can harness ultrasound and mechanical energy in a constructive role.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: mechanochemistry • copper 'Click' reaction • piezochemical reaction • step-growth polymerization • polymer crosslinking

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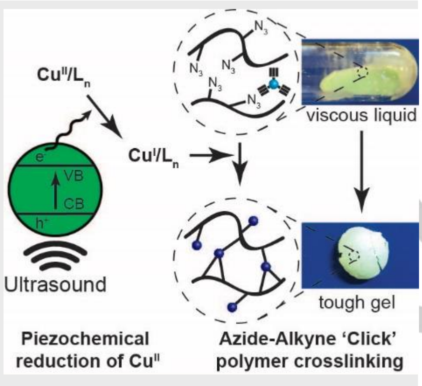
Layout 1:

COMMUNICATION

Mechano-Click polymerization: Mechanochemical polymerization using piezochemically driven copper catalyzed azide-alkyne 'Click' reaction has been shown here. Ultrasonic activation of piezoelectric nanoparticles was used to generate a Cu^{I} catalyst to promote click polymerization and polymer crosslinking. Sonochemical polymerization will provide us the tools to design polymeric materials that grow or become stronger with mechanical activation.



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