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Introducing Mercaptoacetic Acid Locking Imine Reaction into Polymer Chemistry as a Green Click Reaction

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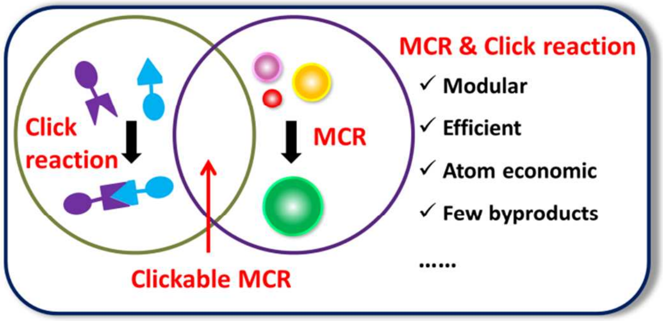
Some multicomponent reactions (MCRs) are similar to the click reactions to give highly selective products with reliable high yield and effective atom utilization, implying they can also be recognized as click reactions. The addition of mercaptoacetic acid to imine bond can be considered as a clickable MCR since this catalyst-free reaction can happen smoothly under benign condition in short time with water as the only byproduct. This reaction has thus been introduced into polymer chemistry and different functional polymers have been successfully synthesized through modification of polymer chain-end, linkage of two polymer chains and polycondensation.

Introduction

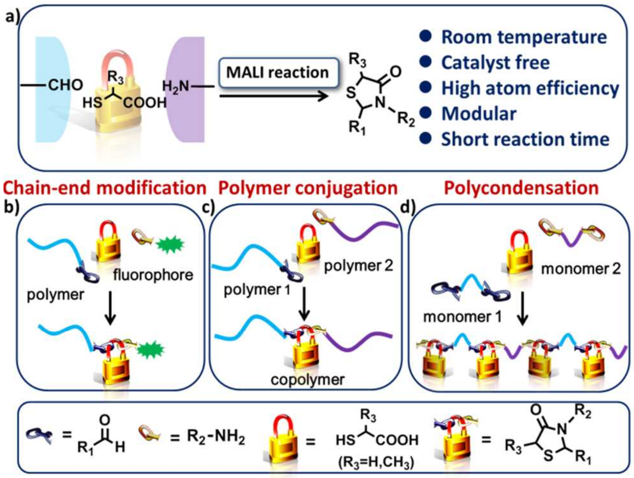
Click reactions are powerful tools for chemists to combine atoms together to achieve new structural and functional compounds. Click reactions should be modular, facile, highly efficient, atom-economical and generate no or only inoffensive byproducts such as H_2O[1]. Cu(I)-catalyzed azide-alkyne cycloaddition (CuAAC) is the most famous click reaction, and the concept of click chemistry is also derived therefrom[2, 3]. Followed the philosophy of click chemistry, several 'old' chemical reactions such as thiol-ene addition reactions[4, 5], (hetro) Diels-Alder (D-A) reactions[6], etc., have been developed as click reactions with optimized catalysts or conditions. Due to their attractive advantages, these click reactions have been wildly used in drug discovery[7, 8], material science[9-12], life science[13-15], and especially polymer chemistry[16-18]. Introducing these efficient click reactions into polymer chemistry leads to the development of new synthetic strategies to effectively prepare condensed polymer, modify polymer side-chain[19] or chain-end[20-22], and synthesize dendrimers[23-25] and other polymers with sophisticated architectures[19, 26, 27], enriching the horizon of functional polymers and materials. For example, novel furan–maleimide monomers have been polycondensed as thermoreversible, mendable and recyclable materials by means of the D-A reaction[28]. CuAAC has also been successfully applied to synthesize conjugated condensed polymers[29, 30].

Similar to click reactions, multicomponent reactions (MCRs) which combine three or more reactants sequentially to give single products are also modular, effective and atom economical[31, 32]. With the understanding of mechanism and optimation of reaction conditions, some MCRs can also be carried out under benign conditions with reasonable high yield. Therefore, those MCRs possess almost all the features of click reaction and can be recognized as new members of click family (**Scheme 1**). Very recently, our group found a 120 years old MCR, Biginelli reaction, may also be considered as a click reaction under certain condition, expanding the click reaction from two-component to multicomponent style[33]. However, Biginelli reaction still needs catalyst (normally Lewis acid) and uncommon starting materials (urea and ß-dione), more or less limiting the utilization of this new click reaction by wider range researchers. Thus, we hope to find other clickable MCRs using common reactants under even greener conditions (catalyst free & room temperature).



Scheme 1. Similar features between Click reaction and MCRs.

In the current research, we chose the mercaptoacetic acid locking imine (MALI) reaction to describe its 'clickable' characteristics. MALI reaction is an excellent method to prepare 4-thiazolidinones which have interesting activity profiles, such as anti-HIV[34-36], antituberculotic[36, 37], anticonvulsant[38, 39], etc.. In typical MALI reaction, mercaptoacetic acid covalently binds amine and aldehyde substrates together like a lock (**Scheme 2a**). Since its birth in 1947, this three component reaction has been continually optimized under various conditions, such as different reactants, solvents and catalysts[40, 41]. Up to now, MALI reaction can be carried out efficiently under environment friendly condition (catalyst free & room temperature) with water as the only byproduct, implying it a possible new click reaction. In this article, we introduced MALI reaction into polymer chemistry like other click reactions to prepare new functional polymers (**Scheme 2**): (1) The polymer chain-end has been modified efficiently with fluorescent group through MALI reaction to get chain-end fluorescent polymer. (2) Two different polymer chains have been rapidly stitched together to achieve copolymer by the addition of mercaptoacetic acid on imine bond. (3) Room temperature polycondensation of dialdehyde, diamine, and 2-mercaptopropionic acid has been performed to generate a new type of sequence regulated polymer. All these reactions take place at room temperature (25 °C) in short time without external added catalyst, suggesting the MALI reaction could be reconsidered as a new catalyst free MCR click reaction.



Scheme 2. a) ‘Clickable’ features of the MALI reaction and its applications in polymer chemistry (25 °C, catalyst free). b) Fluorescent polymer by polymer chain-end modification. c) Copolymer synthesis by polymer conjugation. d) Condensed polymer by polycondensation of dialdehyde, diamine, and 2-mercaptopropionic acid.

Results and Discussion

Chain-end modification is one of the most common methods to get terminal functionalized polymers. The highly efficient click reactions have been proven facile and powerful tools to add new function groups on polymer chain ends and many completely chain-end modified polymers have been successfully prepared[12, 22, 42]. In current work, MALI reaction has also been employed as a click reaction to modify polymer chain-end.

N-(2-aminoethyl)-5-(dimethylamino)-naphthalene-1-sulfonamide (dansyl ethylenediamine) was chosen as the fluorescent group and amino source to modify the benzaldehyde terminated methoxypolyethylene glycol (mPEG-CHO, M_{nNMR} ~ 5000, M_{nGPC} ~ 26300, PDI: 1.03) in the present of mercaptoacetic acid. The reaction was carried out at 25 °C using dimethylsulfoxide (DMSO) as solvent (**Fig. 1a**) (excess mercaptoacetic acid was added to ensure the quick cyclization. Results not presented). ^{1}H NMR was used to monitor the reaction and the characteristic –CHO peak of mPEG was nearly disappeared within 1.5 h, indicating the almost complete MALI reaction in such short time(**Fig. S1, ESI†**). After simple precipitation, the pure fluorescent terminated polymer was facilely obtained. From ^{1}H NMR spectrum, it is clearly to see the signals of the fluorescent moiety at 7.23–8.43 ppm and the characteristic –NCHS- peak of MALI reaction products at 5.78 ppm. The integral ratio between –NCHS- and the ester methylene ($I_{5.78}/I_{4.42}$) is 0.50, consistent with theoretical value, indicating the complete modification of the polymer chain end (**Fig. 1b**). Meanwhile, the fluorescent group terminated polymer has an excitation wavelength at 340 nm and an emission wavelength at 547 nm (**Fig. S2, ESI†**). Through the gel permeation chromatography (GPC) with an UV detector, the original mPEG-CHO only has absorption at 250 nm while the fluorescent group terminated polymer has absorption at both 250 nm and 350 nm (**Fig. 1c**), confirming the polymer chain end has been successfully transferred from benzaldehyde to a fluorescent group. Therefore, MALI reaction can work like other click reactions to highly efficient modify polymer chain-end with new functionality.

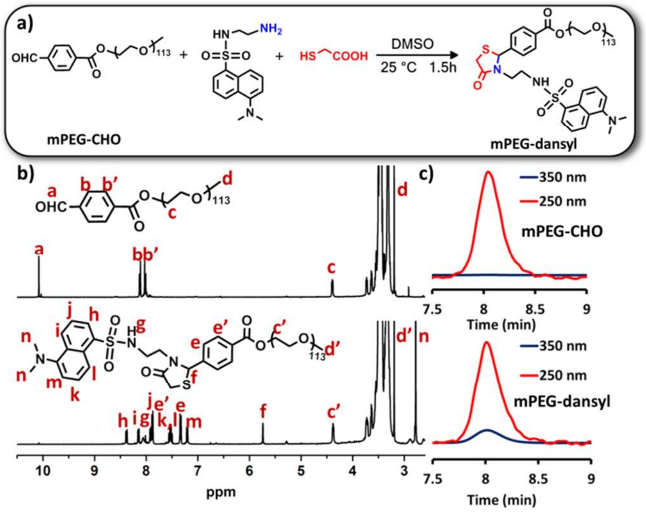


Fig. 1. Polymer chain-end modification through MALI reaction. a) Reaction conditions: [mPEG-CHO]/ [dansyl ethylenediamine]/ [mercaptoacetic acid] = 1/1/10, DMSO as solvent, 25 °C, 1.5 h. b) ^{1}H NMR spectra (DMSO-d_6, 400 MHz, portion) of the polymers before and after MALI reaction. c) GPC *via* UV-detector of the polymers before and after MALI reaction.

Copolymer synthesis through traditional chemical reactions to link two different polymer chains together is often slow and inefficient, usually leading to the partially modified products because of the intrinsic steric hindrance of the polymer chain. Click reactions are the key to this thorny problem, and two different polymer chains can be efficiently stitched together to generate the target copolymers[43-45]. Herein, MALI reaction has also performed like other click reactions for polymer conjugation. A benzaldehyde terminated poly (methyl methacrylate) (PMMA-CHO, M_{nNMR} ~ 6300, M_{nGPC} ~ 23900, PDI: 1.09) through atom transfer radical polymerization (ATRP) and a commercially available amino terminated methoxypolyethylene glycol (mPEG-NH_2, M_{nNMR} ~ 2000, M_{nGPC} ~ 13100, PDI: 1.04, ~ 80% NH_2 loaded) were used (CHO/NH_2 = 1/1) as parent polymers. The two polymer chains were locked by mercaptoacetic acid to generate the daughter PMMA-*b*-mPEG copolymer through MALI reaction (catalyst free, 25 °C) while GPC and ^{1}H NMR were utilized to monitor the process (**Fig. 2a**).

The GPC curves of the parent polymers, PMMA-CHO and mPEG-NH_2, show peaks at 8.14 min and 8.78 min, respectively. After adding mercaptoacetic acid, the peaks of parent polymers decreased gradually while a new peak corresponding to the daughter copolymer generated smoothly. After 1.5 hours, almost all the parent polymer chains were locked by mercaptoacetic acid according to GPC analysis (**Fig. S3, ESI†**), and the ^{1}H NMR spectrum also showed no -CHO peak or -N=CH- peak left, suggesting the nearly complete MALI process (**Fig. S4, ESI†**). The impurities (excess mercaptoacetic acid and non-amino terminated mPEG) were easily removed after precipitation into cold isopropanol. The ^{1}H NMR spectrum of purified polymer showed there is no characteristic peaks of parent polymer chain ends while the –NCHS- peak (~ 6.01 ppm) could be clearly observed. The integral ratio between –NCHS- and ester metheylene ($I_{6.01}/I_{4.37}$) is 0.50 (theoretical value = 0.5), indicating the complete MALI reaction between parent polymer chain ends (**Fig. 2b**). The GPC trace of daughter copolymer has a peak at 8.05 min with higher molecular weight and narrow PDI (M_{nGPC}: ~26600, PDI: 1.09. **Fig. 2c**), which further suggests the rapid addition of mercaptoacetic acid to the imine bond and the successfully preparation of PMMA-*b*-mPEG copolymer, confirming MALI reaction can behave like other click reactions to efficiently prepare copolymers.

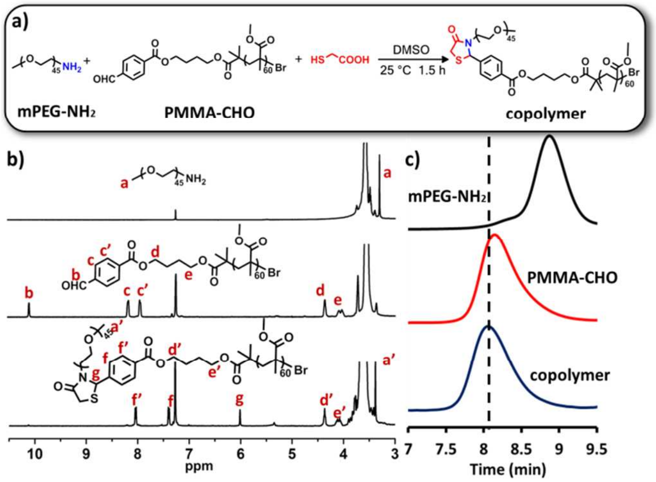


Fig. 2. The locking of two polymers *via* MALI reaction to get copolymer. a) Reaction conditions: [mPEG-NH_2]/[PMMA-CHO]/[mercaptoacetic acid] = 1.25/1/7, DMSO as solvent, 25 °C, 1.5 h. b) ^1H NMR spectra ($CDCl_3$, 400 MHz, portion) of the two parent polymers (top to bottom): mPEG-NH_2 and PMMA-CHO and the purified daughter copolymer. c) GPC curves (top to bottom) of the two parent polymers: mPEG-NH_2 and PMMA-CHO and the purified locked daughter copolymer.

Polycondensates, such as Nylon, polyester etc., are most useful polymers. Some click reactions[28, 45, 46] and MCRs[47-51] have been employed to prepare new functional condensation polymers. Although the clickable and MCR monomers are not common and normally synthesized through organic method, polycondensation through click reactions and MCRs still open a new door to new functional polymers. In the current research, we used commercially cheap terephthalaldehyde, hexamethylenediamine and 2-mercaptopropionic acid (aldehyde/amine/2-mercaptopropionic acid = 1/1/4) as starting materials to prepare condensation polymer under benign condition (catalyst free, 25 °C) (**Fig. 3a**). GPC and ^1H NMR were utilized to monitor this process. The conversion was calculated by comparing the integral ratio of the phenyl protons to those methine protons (-C(=O)CHS, ~ 3.84-4.10 ppm). As can be seen, a time-dependent increase of molecular weight was observed. Oligomers formed rapidly at the beginning of the polymerization (3 h, ~ 78%) (**Fig. S5, ESI†**). Afterwards, the conversion reached maximum (~ 100%) in 12 h (**Fig. 3b**). The continuous increase of viscosity of the polymerization system was observed, and only at the later stage of the polymerization, the molecular weight increased rapidly (**Fig. 3c**, M_{nGPC} ~ 18800, PDI: ~ 1.49), confirming the mechanism of conventional step-growth polymerization. The polymer could be simply purified by precipitation into cold ethyl ether and the ^1H NMR spectrum demonstrated the characteristic –NCHS- peaks of MALI products at 5.71 ppm (**Fig. 4d**). Considered the commonplace starting reactants and benign reaction condition (catalyst free, room temperature), MALI reaction is a facile and efficient method for polycondensation which might has potential to prepare new functional polycondensates like other click reactions.

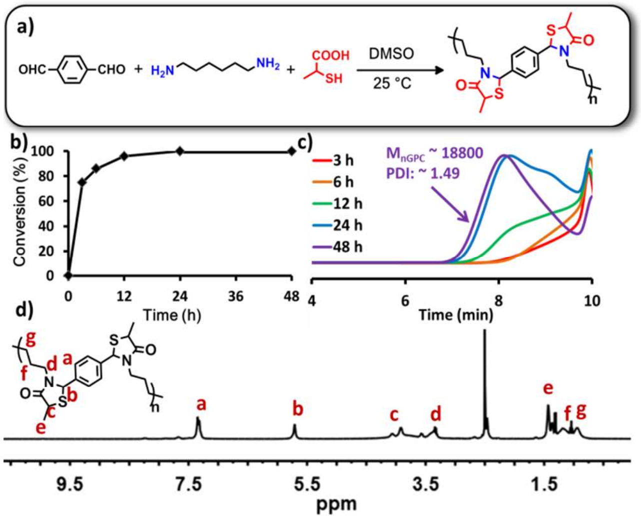


Fig. 3. Condensation polymerization of terephthalaldehyde, hexamethylenediamine and 2-mercaptopropionic acid. a) Reaction conditions: [terephthalaldehyde]/[hexamethylenediamine]/[2-mercaptopropionic acid] = 1/1/4, DMSO as solvent, 25 °C. b) The conversions of MALI reaction. c) GPC tracking of the condensation polymerization. d) ^1H NMR spectrum (DMSO-d_6, 400 MHz) of the final polymer.

Conclusions

Through the MALI reaction under benign condition (catalyst free, room temperature (25 °C)), a series of functional polymers have been successfully synthesized: 1) chain-end of polymer has been completely modified with a fluorescent group within short time; 2) two different polymer chains can be quickly and completely stitched together to generate a new copolymer by the MALI reaction; 3) mercaptoacetic acid locking the dialdehyde and diamine to form polymer main chain, leading to the formation of new structural polycondensate. All those experiments suggest the MALI reaction is a modular, efficient and high atom economic multicomponent reaction which behaves like other well-known two-component click reactions such as thiol-ene and CuAAC reactions. Furthermore, the MALI reaction need only common starting compounds (aldehyde, amine and mercaptoacetic acid) and can be carried out under benign reaction condition, the MALI reaction should be possibly considered as a green click reaction. The application of this new click reaction in other fields such as material surface modification, protein conjugation and synthesis of new polymers with sophisticated structures are under our research.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Detailed experimental procedures, ^{1}H NMR spectrum during polymer modification, ^{1}H NMR spectrum and GPC trace during polymer conjugation, ^{1}H NMR spectrum during polycondensation. See DOI: 10.1039/b000000x/

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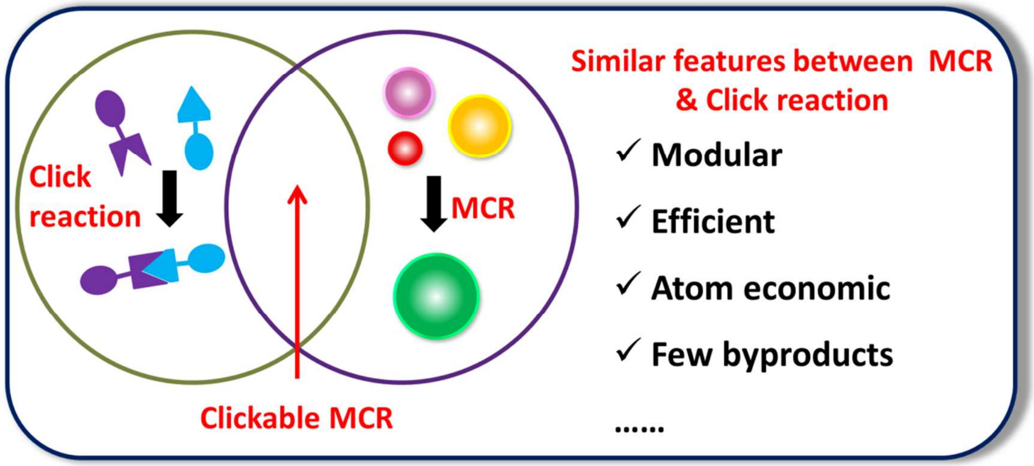

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