Investigation into thiol-(meth)acrylate Michael addition reactions using amine and phosphine catalysts†

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This work describes a study into thiol–ene based Michael addition reactions. Different catalysts, primary and tertiary amines and phosphines, were investigated for the reaction of a range of thiols with dimers and oligomers of some (meth)acrylates. Primary and tertiary amines are efficient catalysts for the thiol–ene reaction, although these catalysts require several hours to reach high conversion. Moreover, the phosphine catalysts, dimethylphenylphosphine (DMPP) and tris-(2-carboxyethyl)phosphine (TCEP), were investigated in detail. DMPP is an efficacious catalyst yielding complete conversion in few minutes under optimized conditions. Importantly, the concentration of DMPP should be kept at catalytic levels to avoid the formation of by-products, originating from the addition of DMPP to the vinyl group. Furthermore, TCEP is an efficient catalyst for thiol–ene reactions in aqueous media when the pH of the medium is higher than 8.0 since at acidic pH the formation of by-products is observed.

Introduction

Over the last decade, click chemistry has opened new avenues to design and synthesize tailor-made macromolecules for different applications in chemistry as well as for the functionalization of nanoparticles and polymers.[1–5] Although, numerous organic reactions have been described in the literature as "click reactions", the copper catalyzed [3 + 2] Huisgen cycloaddition reaction has been widely employed in conjunction with metal-mediated controlled radical polymerization.[6–9] However, the residual amount of copper and the ligand content in the final product give constraints and limit the application of Huisgen cycloaddition, especially for biological applications. This has directed research towards metal-free synthesis techniques.[10–12] One of the most attractive and long time known organic reactions, thiol–ene addition, has become popular in polymer chemistry.[13–18]

Thiol–ene addition reactions can proceed by two routes: (i) anti-Markovnikov radical addition and (ii) base or nucleophile catalyzed Michael addition reaction, Scheme 1.[19–26] The thiol–ene/yne radical addition mechanism requires an external radical source and energy to generate radicals, which may be azo-initiators or photo-initiators using thermal or UV light energy.[27–32] Moreover, it should be noted that thiol compounds may react non-selectively with any type of vinyl bond within the polymer. Despite the few drawbacks of thiol–ene radical addition
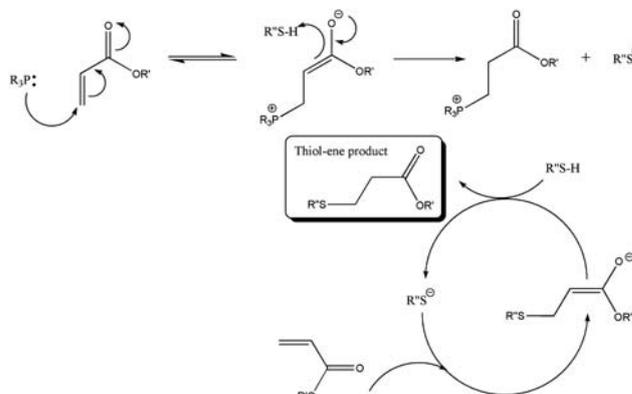
Scheme 1 Proposed mechanism for the nucleophile mediated hydro-thiolation of an acrylic carbon–carbon bond under phosphine catalysis.

reactions, it is possible to reach near quantitative conversions in relatively short periods by its high reactivity for low molecular weight compounds, as described recently.[33]

In the case of the Michael addition reaction, this is a facile reaction between nucleophilic species and activated olefins under basic conditions.[34] The Michael reaction benefits from mild reaction conditions, minimal by-product formation, high functional group tolerance and high conversions when optimized. Various amines, enolates, thiols and phosphines can react with (meth)acrylates, (meth)acrylamides, maleimides, acrylonitriles and cyanoacrylates, which are Michael donors and Michael acceptors, respectively.[35,36] There are a few parameters that should be taken into account when optimizing the synthetic protocol, such as the nucleophile type, solvent and substrate, all of which have been systematically investigated in this present study.

The synthesis of end functional polymers with high fidelity is challenging even though several controlled radical

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polymerization techniques have been developed.[37] Metal mediated radical polymerization techniques have been widely employed to obtain bromide or chloride end-functionalized polymers that can be converted into azide groups to subsequently facilitate Cu-catalyzed azide–alkyne click reactions. Similarly, reversible addition-fragmentation chain transfer (RAFT) polymerization has been used to give thiol terminated polymers following the cleavage of the chain transfer agent.[38–42] In general practice, amines have been used in excess to cleave the chain transfer agent from the chain end, however, the bulky structure of the polymer may reduce the cleavage efficiency. Additionally, the free thiol terminal-groups can be oxidized to disulfides. To avoid this side reaction, CAMD has developed a strategy proposing the *in situ* aminolysis of RAFT end-groups in the presence of pyridyl disulfide to yield a thiol protected polymer.[43] In addition, RAFT polymerization requires dedicated chain transfer agents (CTA) designed according to the monomer structure and also optimized reaction conditions such as initiator/CTA ratio, solvent type and reaction temperature.[44–51] Nevertheless, thiol terminated polymers have been successfully used in thiol–ene, thiol–yne, thiol–bromo, thiol–isocyanate and thiol–maleimide click reactions.[52–60]

Alternatively, vinyl terminated polymers have been prepared to react with thiol compounds.[61–63] One of the most successful techniques to obtain vinyl-terminated polymers is catalytic chain transfer polymerization (CCTP) that proceeds *via* a free-radical mechanism in the presence of certain Co(II) catalysts.[64–68] In particular, this is an ideal technique to synthesize very short oligomers, *i.e.* dimer, trimer and tetramer, with very high fidelity. This technique has been generally employed for the preparation of macromonomers and has been used successfully for a wide range of methacrylates. Advantageously, CCTP requires a very low amount of catalyst (in low ppm levels), yielding quasi-pure polymers with a very low amount of residual catalyst.

In this present work, the effect of different catalysts for the nucleophilic mediated thiol–ene reaction is described using model compounds, both monomers and oligomers obtained by CCTP. Different catalysts, including pentylamine and hexylamine (primary amines), triethyl amine (tertiary amine), and two different phosphines, dimethylphenylphosphine (DMPP) and tris(2-carboxyethyl)phosphine (TCEP), were investigated in the presence of different thiols, Scheme 2. This study had the objective to determine the optimum reaction conditions for nucleophile mediated thiol–ene click reactions.

Experimental part

Materials

Methyl methacrylate (MMA, 99%, Sigma-Aldrich), 2-hydroxyethyl methacrylate (HEMA, 97%, Sigma-Aldrich), poly(ethylene glycol) methylether acrylate (PEGMEA$_{454}$, Sigma-Aldrich), poly(ethylene glycol) methylether methyacrylate (PEGMEMA$_{475}$, Sigma-Aldrich), 2,2′-azoisobutyronitrile (AIBN), 2-mercaptoethanol (2-ME, 99%, Fluka, Sigma-Aldrich), 1-thioglycerol (TG, 98%, Sigma-Aldrich), 1-propanethiol (PT, 99%, Sigma-Aldrich), 1-dodecanethiol (DT, 98+%, Sigma-Aldrich), benzyl mercaptan (BT, 99%, Sigma-Aldrich), glutathione (98%, Sigma-Aldrich), 1-thiol-β-D-glucose sodium salt (thiol–glucose, 99%, Sigma-Aldrich), 3-mercaptopropanoic acid (3-MPA, 99%, Sigma-Aldrich), dimethylphenylphosphine (DMPP, 99%, Aldrich), tris(2-carboxyethyl)phosphine hydrochloride (TCEP, 98%, Alfa Aesar), triethylamine (TEA, 99%, Fisher Scientific UK Ltd.), pentylamine (PAm, 99%, Sigma-Aldrich), hexylamine (HA, 99%, Sigma-Aldrich), dimethyl sulfoxide-d_6 (DMSO-d_6) and acetone-d_6 (99.9% atom %D, Sigma-Aldrich) and acetonitrile-d_3 (ACN, 99.8% atom %D, Sigma-Aldrich) were used as received. PBS buffer (pH 7.0, 0.5 M) was made of NaH$_2$PO$_4$ (99.85%, Fisher Scientific UK Ltd.), carbonate–bicarbonate (CBB) buffer (pH 9.2, 0.2 M) was made of Na$_2$CO$_3$ (0.2 M) (99%, BDH, VWR International Ltd.) and NaHCO$_3$ (0.2 M) (99%, Fisher Scientific UK Ltd.).

Bis(boron difluorodimethylglyoximate) cobaltate(II) bis(methanol) complex, (CH$_3$OH)$_2$Co-(dmgBF$_2$)$_2$ (CoBF), as prepared according to the method of Bakac *et al.*[69] The activity
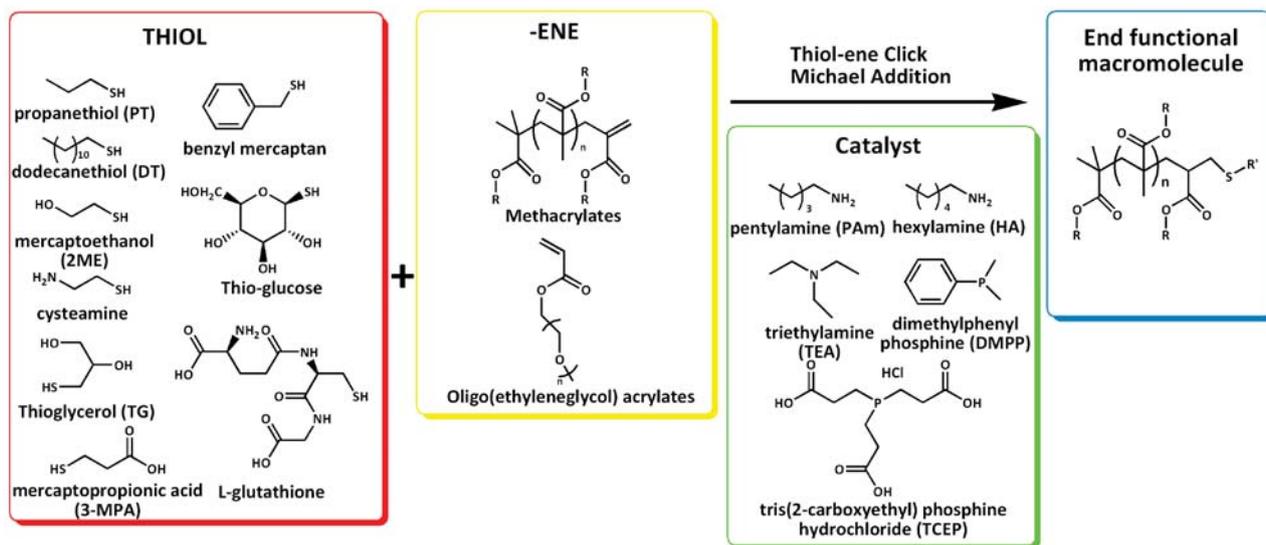
Scheme 2 Summary of the different thiols, thiol–enes and catalysts investigated in this study.

of the synthesized CCT agent was tested with CCTP of MMA yielding a C_s value = 25 000.

Characterization

^{1}H NMR spectroscopy was used to determine the monomer conversion. NMR spectra were recorded on a Bruker DPX-300 MHz and a Bruker DPX-400 MHz spectrometer at 25 °C on approximately 10% w/v solutions in deuterated NMR solvents from Sigma-Aldrich. All chemical shifts are reported in ppm (δ) relative to tetramethylsilane (TMS), referenced to the chemical shifts of residual solvent resonances (^{1}H and ^{13}C). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, dd = doublet of doublets, t = triplet, m = multiplet.

Mass spectra were recorded on either Bruker UHR-Q-TOF MaXis or Thermo Finnigan LCQ. ESI-MS was obtained using Thermo Finnigan LCQ Deca quadrupole ion trap mass spectrometer (Thermo Finnigan, San Jose, CA), equipped with an atmospheric pressure ionization source operating in the nebulizer assisted electrospray mode and was used in positive ion mode. Mass calibration was performed using caffeine, MRFA, and Ultramark 1621 in the m/z range of 195–1822 Da. All spectra were acquired within the m/z range of 150–2000 Da, and typical instrumental parameters were a spray voltage of 4.5 kV, a capillary voltage of 44 V, a capillary temperature of 275 °C and flow rate of 5 µL min^{-1}. Nitrogen was used as sheath gas (flow: 50% maximum) and helium was used as auxiliary gas (flow: 5% maximum), 30 microscans, with maximum inject time of 10 ms per microscan. For each respective scan, approximately 35 scans were signal averaged to obtain the final spectrum. Solvent used was 3 : 1 mixture of DCM : methanol with sodium acetate concentration of 0.3 µM. Sodium acetate was added to the solvent prior to analysis to ensure that ionization would occur and to suppress potassium salt peaks. All data processing was done using Xcalibur™ included together with Thermoproducts. Mass spectra were recorded on a Bruker UHR-Q-TOF MaXis equipped with electrospray ionisation source in positive mode; samples were directly infused at 2 µL min^{-1} with a syringe pump. Nitrogen was used as nebulizer gas (0.4 bar) and dry gas (4 L min^{-1} at 180 °C). Capillary voltage was set at −3000 V. Data were acquired in the 50–2000 m/z range. Calibration was carried out with sodium formate solution (10 mM in 50% IPA). Mass spectra were acquired by MALDI-ToF (matrix-assisted laser desorption and ionization time-of-flight) mass spectrometry using a Bruker Daltonics Ultraflex II MALDI-ToF mass spectrometer, equipped with a nitrogen laser delivering 2 ns laser pulses at 337 nm with positive ion ToF detection performed using an accelerating voltage of 25 kV.

Catalytic chain transfer polymerization (CCTP)

Preparation of MMA dimer. Methyl methacrylate dimer macromonomer was prepared by CCTP of MMA with CoBF as chain transfer agent and AIBN as the initiator. MMA (250 mL) was used as supplied and degassed by bubbling through with nitrogen for at least 2 hours prior to use, then CoBF (0.25 g) and AIBN (0.5 g) were added to the Schlenk tube filled with nitrogen prior to addition of MMA. The reaction was carried out in an oil bath at 60 °C for three days, after which the unreacted MMA was

removed using a rotary evaporator. Hydroquinone (100 ppm) was added to inhibit subsequent polymerization of products during the removal of MMA dimer. A crude separation was carried out using a Kugelrohr apparatus and MMA dimer was collected at 125–135 °C, 0.12 mbar. MMA dimer was further purified by reduced pressure distillation at 130 °C, 0.12 mbar. The purity of the macromonomers was verified by ^{1}H NMR, ^{13}C HMR and ESI-MS (see ESI†).

Preparation of HEMA dimer. Hydroxyethyl methacrylate dimer macromonomer was prepared by CCTP of HEMA in the presence of CoBF as chain transfer agent initiated by AIBN. CoBF (0.1 g) and AIBN (0.5 g) were dissolved in a mixture of HEMA (150 mL) and methyl ethyl ketone (MEK) (150 mL). All reagents were degassed by three freeze–pump–thaw cycles prior to use. The reaction mixture was placed in an oil bath at 60 °C for 48 h under nitrogen, and then the MEK was removed by rotary evaporation. Hydroquinone (100 ppm) was added to inhibit subsequent polymerization of products during the removal of both HEMA and HEMA dimer. A crude separation was carried out using a Kugelrohr apparatus, HEMA was collected at 60–150 °C, 0.3 mbar, HEMA dimer was collected at 170–180 °C, 0.4 mbar. HEMA dimer was further purified by reduced pressure distillation, HEMA removed at 113 °C, 1 mbar, and HEMA dimer was collected at 202 °C, 1 mbar. The purity of the macromonomers was verified by ^{1}H NMR and ESI-MS (see ESI†).

Preparation of PEGMEMA$_{475}$ oligomers. The monomer, PEGMEMA$_{475}$ (5 g, 10.5 mmol), in acetonitrile (5 mL) was deoxygenated by purging with N$_2$ gas for at least one hour prior to use. A stock solution of CoBF was prepared by dissolving CoBF (1.3 mg) in acetonitrile (10 mL) followed by purging with N$_2$ gas for at least one hour. AIBN (12.5 mg, 0.0761 mmol) was then weighed in a Schlenk flask and mixed with the deoxygenated PEGMEMA$_{475}$ and the CoBF stock solution (4 mL). The mixture was then subjected to three freeze–pump–thaw cycles to ensure removal of oxygen. The mixture was then placed in an oil bath at 70 °C for 14 hours. The reaction was stopped by exposure to air and quenched in ice bath. The resulting product was a mixture of PEGMEMA monomer, dimer, and trimer.

TEA catalyzed thio-click reactions. The MMA, MMA dimer, HEMA, PEGMEA$_{454}$ or PEGMEMA$_{475}$, thiols, TEA were added into an NMR tube containing acetone-d_6 or actonitrile-d_3 or DMSO-d_6. The reactions were carried out at ambient temperature and monitored by ^{1}H NMR spectroscopy. In a typical reaction, 1 eq. (0.05 g) of monomer, 1.5 eq. thiol, 0.5 eq. (13 mg) of TEA were added into an NMR tube containing deuterated solvent (0.5 mL).

HA catalyzed thio-click reactions. The PEGMEMA$_{475}$ oligomers were placed in glass vials with hexylamine, water or acetonitrile as solvent, and thiol. In a typical reaction, 100 mg of PEGMEMA$_{475}$ oligomers, 5 eq. thiol, and 5 eq. hexylamine were mixed in a flask and then purged for 15 minutes with N$_2$ and placed into 40 °C oil bath and reacted for 14 hours before and the products were purified using dialysis.

DMPP or TCEP catalyzed thio-click reactions. The MMA, MMA dimer, HEMA, HEMA dimer, PEGMEA$_{454}$, PEGMEMA$_{475}$ or oligo(PEGMA$_{475}$), thiols, DMPP or TCEP were added into an NMR tube containing acetone-d_6, actonitrile-d_3 or DMSO-d_6. The reactions were carried out at ambient temperature and monitored by ^{1}H NMR spectroscopy. In a typical reaction, 1 eq. (0.05 g) of monomer, 1.5 eq. thiol and 0.05 eq. (1.7 mg) of DMPP were added into an NMR tube containing deuterated solvent (0.5 mL).

Results and discussion

The optimal conditions for the thiol–ene reaction were investigated using primary amines, tertiary amine and phosphines at different temperatures and in different solvents using a broad range of monomers or oligomers. The synthesis of short oligomers bearing a terminal vinyl group was carried out using CCTP.[23,61,62,70–75] This method has been successfully exploited for the synthesis of MMA and HEMA dimers (after separation from higher adducts) and OEGMA oligomers. The oligomers were tested using different thiol–ene reactions with a large range of thiol compounds and catalyst systems.

Triethylamine catalyzed thiol–ene reactions

The Michael addition between a thiol and an activated vinyl group was carried out in the presence of triethylamine as catalyst at ambient temperature. Table 1 presents the results from using MMA dimer (dMMA), poly(ethylene glycol) acrylate (PEGMEA$_{454}$) and poly(ethylene glycol) methacrylate (PEGMEMA$_{475}$) in the presence of 2-mercaptoethanol.

A relatively fast reaction rate was observed for PEGMEA$_{454}$ with the reaction **T2** catalyzed by a [TEA]/[thiol] ratio of 1.2/0.3 reaching quantitative conversions after 2 hours. However, in the case of methacrylates, even at extended reaction periods, *i.e.* 72 h, it was not possible to reach quantitative conversion values. Nevertheless, more than 80% conversion was measured for PEGMEMA$_{475}$ using a [thiol]/[TEA] ratio equal to 1.2/1.1 after 3 days. To accelerate this reaction, the [monomer]/[thiol]/[TEA] ratio was varied from 1.0/1.2/1.1 to 1.0/1.2/9.0 (**T3–T6**) and the kinetics followed by ^{1}H NMR, Fig. 1. There was no significant difference in the kinetic behavior as the ratios were varied. Thus, excess TEA does not accelerate the thiol–ene reaction with

Table 1 Optimization reactions using triethylamine as catalyst with different monomers/dimers and thiols

Run	Monomer/dimer	Thiol	Ratios [M] : [T] : [cat]^a	React. time/h	Conv. (%)
T1	dMMA	2-ME	1 : 1.5 : 0.1	15	42
T2	PEGMEA$_{454}$	2-ME	1 : 1.2 : 0.3	2	97
T3	PEGMEMA$_{475}$	2-ME	1 : 1.2 : 1.1	72	81
T4	PEGMEMA$_{475}$	2-ME	1 : 1.2 : 2.2	72	89
T5	PEGMEMA$_{475}$	2-ME	1 : 1.2 : 4.5	72	88
T6	PEGMEMA$_{475}$	2-ME	1 : 1.2 : 9.0	72	88

^{a} [M] : [T] : [cat] = monomer/dimer : thiol : triethylamine. All reactions were performed at ambient temperature in d_6-acetone. Conversion values were calculated by ^{1}H NMR following the disappearance of the vinyl bond.
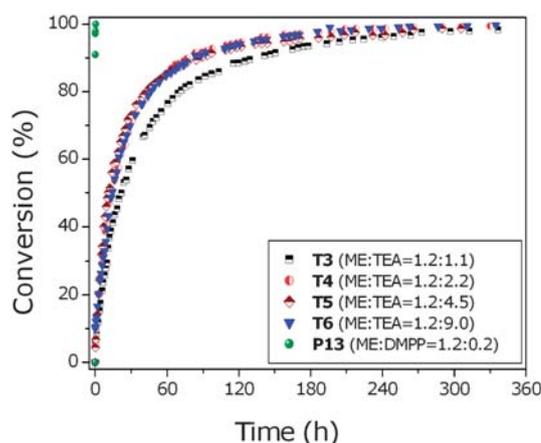

Fig. 1 Conversion *vs.* time plot for the reaction of PEGMEMA$_{475}$ with 2-ME in the presence of varying concentrations of TEA or DMPP. Conversion values were calculated by ^{1}H NMR following the disappearance of the vinyl group.

methacrylic vinyl groups. ^{1}H NMR and ESI-MS does not show any formation of side products. The DMPP catalyzed reaction **P13** is included as a comparison in Fig. 1, which reached quantitative conversions in few minutes; this will be discussed further in following sections.

Primary amine catalyzed thiol–ene reactions

In order to accelerate the rate of reaction, we examined primary amines as catalysts at ambient temperature. Primary amines are more nucleophilic than tertiary amines. The formation of thiolate should be followed by a nucleophilic addition onto the vinyl group. PEGMEA$_{454}$, PEGMEMA$_{475}$ and PEGMEMA$_{2080}$ monomers were reacted with 2-ME, 3-MPA and 1-dodecanethiol

Table 2 Optimized reactions using *n*-pentylamine as catalyst with different monomers and thiols

Run	Monomer	Thiol	Ratios [M] : [T] : [cat]^a	React. time/h	Conv. (%)
PAm1	PEGMEA$_{454}$	DT	1 : 1.2 : 0.1	24	10
PAm2	PEGMEA$_{454}$	3-MPA	1 : 1.2 : 0.1	24	20
PAm3	PEGMEA$_{454}$	BM	1 : 1.2 : 0.1	24	78
PAm4	PEGMEA$_{454}$	2-ME	1 : 1.2 : 0.1	24	93
PAm5	PEGMEA$_{454}$	2-ME	1 : 1.2 : 0.3	0.5	93
PAm6	PEGMEMA$_{475}$	DT	1 : 1.2 : 1.7	4	5
PAm7	PEGMEMA$_{475}$	3-MPA	1 : 1.2 : 1.4	4	3
PAm8	PEGMEMA$_{475}$	BM	1 : 1.2 : 1.4	4	17
PAm9	PEGMEMA$_{475}$	TG	1 : 1.2 : 1.4	4	77
PAm10	PEGMEMA$_{475}$	2-ME	1 : 1.2 : 1.3	4	33
PAm11	PEGMEMA$_{475}$	2-ME	1 : 1.2 : 2.7	4	49
PAm12	PEGMEMA$_{475}$	2-ME	1 : 1.2 : 5.4	4	74
PAm13	PEGMEMA$_{475}$	2-ME	1 : 1.2 : 10.8	4	95
PAm14	PEGMEMA$_{2080}$	2-ME	1 : 1.2 : 5.0	4	60
PAm15	PEGMEMA$_{2080}$	2-ME	1 : 1.2 : 10.0	4	69
PAm16	PEGMEMA$_{2080}$	2-ME	1 : 1.2 : 20.0	4	87
PAm17	PEGMEMA$_{2080}$	2-ME	1 : 1.2 : 40.0	4	99

^{a} [M] : [T] : [cat] = monomer : thiol : *n*-pentylamine. All reactions were performed at ambient temperature in d_6-acetone as solvent. Conversion values were calculated by ^{1}H NMR based on the consumption of the vinylic bonds.
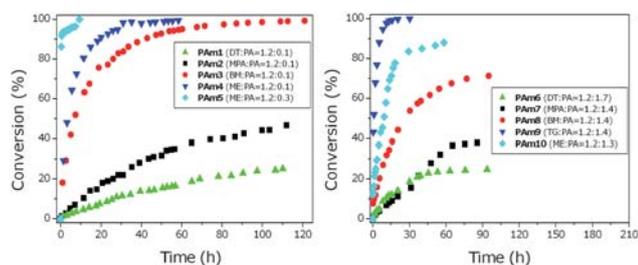
Fig. 2 Vinyl bond conversion *vs.* time plots for PEGMEA$_{454}$ (left) and PEGMEMA$_{475}$ (right) reacting with different thiols in the presence of *n*-pentylamine as catalyst. *Note: conversion values were calculated by ^1H NMR based on the consumption of the vinylic bonds.*

(DT), Table 2. Higher ratios of catalyst were used to compensate for the lower reactivity of methacrylates relative to acrylates.

Different thiol–ene reactions were conducted using 4 different thiols in the presence of a low concentration of *n*-pentylamine as the catalyst ([M]/[T]/[amine] = 1.0/1.1/0.1), Fig. 2. The reactions were monitored for up to 5 days and the vinyl bond conversion *versus* time was plotted, Fig. 2. The reaction rates differ depending on the thiol structure. For example, 1-dodecanethiol (DT) has the slowest rate (10% conversion in 24 h) in comparison to all other thiols used in this study. The reaction with 3-mercaptopropionic acid (3-MPA), **PAm2**, did not exceed 50% conversion, even after 4 days of reaction. However, benzyl mercaptan (BM) had a faster reaction rate **PAm3** with 78% after 24 hours. One explanation of the low reactivity of 3-MPA is the presence of carboxylic acid functionality (**PAm2**) resulting in potentially the enolate quenching and the subsequent non-generation of thiolate.

It is evident that benzyl mercaptan (BM) and 2-ME react with PEGMEA$_{454}$ relatively faster than DT and 3-MPA, **PAm3–PAm5**, **PAm1** and **PAm2**, respectively. Quantitative conversions were obtained in less than 3 days by reacting BM in the presence of *n*-pentylamine, **PAm3**. The final product of **PAm3** was characterized using MALDI-TOF MS confirming the expected structure, Fig. 3. All peaks are assigned and the main distribution (labeled as A and B ionized with Na$^+$ or K$^+$ salt, respectively) can be assigned to BM conjugated PEGMEA$_{454}$ (a trace amount of un-reacted monomer (labeled as C) is also detected).

The catalyst concentration was varied as 0.1 **PAm4** and 0.3 **PAm5** for the reaction of PEGMEA$_{454}$ and 2-ME. The reactions reached ~90% conversion after 24 hours and 0.5 hours using
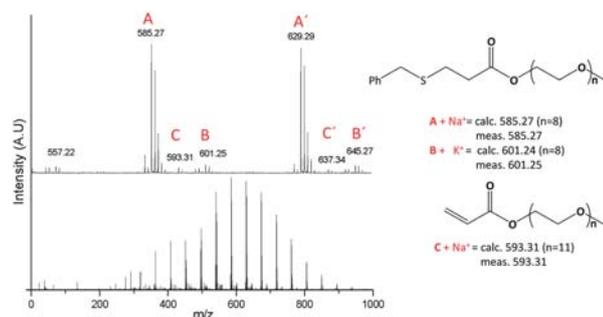

Fig. 4 ^1H NMR spectra for Michael addition of PEGMEA$_{454}$ and ME, using 0.1 eq. of *n*-pentylamine in d_6-acetone, **PAm4**.

0.1 and 0.3 equivalents of PA, respectively. There is a significant difference in the reaction rate by changing the catalyst concentration (in contrast to the TEA catalyzed reactions). The reaction kinetics with acrylates was followed by ^1H NMR and all corresponding peaks of the starting material and the products are assigned, Fig. 4. Using relatively short oligomer chains has facilitated the characterization of both the products and the side products in detail.

The effect of the pentylamine concentration on the Michael addition reaction of 2-ME in the presence of PEGMEMA$_{475}$ or PEGMEMA$_{2080}$ was investigated in experiments, **PAm6–PAm17**, Table 2. The reaction kinetics of methacrylates with 2-ME **PAm10–PAm17** was followed using ^1H NMR, Fig. 5. A large excess of catalyst was used in these experiments for two reasons: (i) it has been shown that methacrylates react very slowly with thiols in the presence of amines, (ii) PEGMEMA$_{2080}$ is a more sterically hindered molecule with reduced accessibility to the vinyl bonds. In these experiments, it is shown that the reaction proceeds much faster with a higher amount of catalyst present.

It is noted that using a large excess of *n*-pentylamine provides an observation of intermediate species in the nucleophile mediated hydrothiolation reaction. These intermediates were

Fig. 3 MALDI-TOF MS analysis of the final product of PEGMEA$_{454}$ reacted with benzyl mercaptan **PAm3** in the presence of *n*-pentylamine.
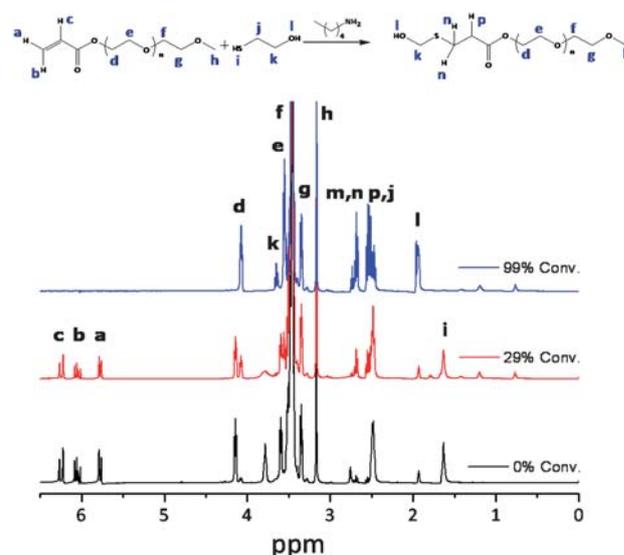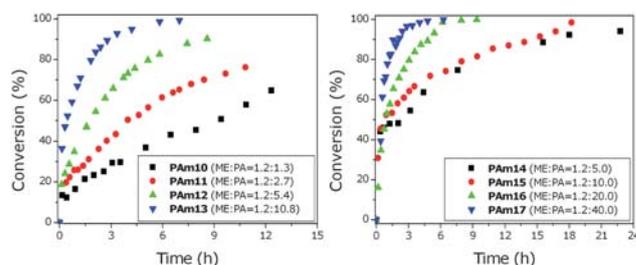

Fig. 5 Michael addition of PEGMEMA$_{475}$ (left) or PEGMEMA$_{2080}$ (right) with 2-ME in different amounts of *n*-pentylamine. The reaction was performed in 0.5 mL d_6-acetone and monitored *via* ^1H NMR.
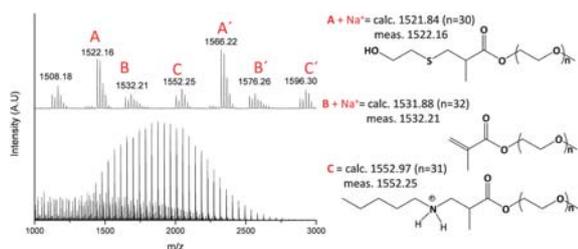
Fig. 6 MALDI-TOF MS spectrum of PEGMEMA$_{2080}$ reacted with 2-ME in the presence of 40.0 eq. of *n*-pentylamine **PAm12**.

identified using MALDI-TOF MS from the reaction of PEG-MEMA$_{2080}$ and 2-ME, Fig. 6. The main distribution (labeled as A and A′) belongs to the product at 1521.9 Da (*n* = 30) and 1565.9 Da (*n* = 31). Moreover, starting material can be identified (labeled as B and B′, 1531.9 Da and 1575.9 Da) and the intermediates (labeled as C and C′, 1552.2 Da and 1596.3 Da) observed in the spectrum. The intermediate is assigned as a compound formed from the reaction of PEGMEMA$_{2080}$ and *n*-pentylamine. Thiols are better nucleophiles than amines, however, in a large excess of amine (or for a higher [amine]/[thiol] ratio), such as in **PAm12**, these intermediates are visible by this technique. *It is noted that MALDI-TOF MS does not provide quantitative information due to different ionization efficiencies of each compound.* For instance, compound C is protonated and ionizes without forming a sodium adduct, as calculated from the spectra. It is interesting to note that MALDI-TOF analysis shows the presence of starting material, while almost full conversion was calculated from ^{1}H NMR. Based on these results, it appears that vinyl terminated species ionizes more efficiently than the thiol or amine substituted species.

CCTP was used to synthesize oligo(PEGMEMA$_{475}$) to give mixtures of dimers, trimers, tetramers and higher adducts, that were used directly for subsequent thiol addition reactions. The CCTP product mixture was reacted with six different thiols, 2-ME, BM, 3-MPA, cysteamine, glutathione and thiol–glucose, Table 3. The mixtures were reacted overnight at 40 °C. To improve the yield of the reaction using primary amine, reactions were carried out using [ene]/[thiol]/[amine] = 1/5/5 at 40 °C in organic solvents and aqueous solution. After 14 hours, a complete conversion of oligo(PEGMEMA$_{475}$) was observed by ^{1}H NMR, Table 3, and by ESI-MS, Fig. 7. ESI-MS spectra show

Table 3 Optimization reactions using *n*-hexylamine as catalyst with oligo(PEGMEMA)$_{475}$ and various thiols

Run	Oligomer	Thiol	Ratio [M] : [T] : [cat]^a	Solvent	Conv. (%)
HA1	Oligo(PEGMEMA$_{475}$)	2-ME	1 : 5 : 5	MeCN	100
HA2	Oligo(PEGMEMA$_{475}$)	BM	1 : 5 : 5	MeCN	100
HA3	Oligo(PEGMEMA$_{475}$)	3-MPA	1 : 5 : 5	MeCN	100
HA4	Oligo(PEGMEMA$_{475}$)	Cysteamine	1 : 5 : 5	D$_2$O	100
HA5	Oligo(PEGMEMA$_{475}$)	Glutathione	1 : 5 : 5	D$_2$O	100
HA6	Oligo(PEGMEMA$_{475}$)	HS-Glc	1 : 5 : 5	D$_2$O	100

^{a} [M] : [T] : [cat] = oligo(PEGMEMA$_{475}$) : thiol : hexylamine. Conversion values were calculated by ^{1}H NMR with respect to vinyl peaks. All reactions were performed at 40 °C for 14 hours.
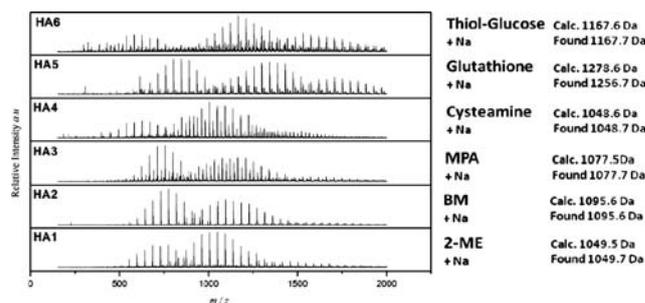

Fig. 7 ESI-MS result of oligo(PEGMEMA475) reacted with various thiol compounds. Identified peaks of products are tabulated in Table S2, see ESI† (**HA1–HA6**).

the quantitative formation of expected product, *i.e.* thiol conjugated to oligo(PEGMEMA$_{475}$), without the formation of by-products, Table 3.

Characterization was also performed using ESI-MS, Fig. 7. The top spectra show the presence of monomer, dimer, trimer and also tetramer distributions modified by thiol–glucose (**HA6**). Similar results were obtained for the glutathione, cysteamine, BM, 2-ME and 3-MPA conjugated oligomers **HA1–HA5**. ESI-MS results confirm the synthesis of expected products. The presence of two main distributions observed for **HA1**, **HA2**, **HA3** and **HA6** can be attributed to the expected products. The two populations can be assigned to differently ionized forms (ionized with sodium or hydrogen). The calculated and measured molecular weight was found to have maximum error of 0.2 Da, well within the inherent 0.3 Da error of the instrument. Moreover, it can also be seen from the mass spectra that there is no starting material or side products (see ESI-MS spectrum, Fig. S4 in the ESI†). As explained above, mass spectroscopy is more sensitive than ^{1}H NMR analysis, giving confidence that the reactions were complete, without detectable side products. The absence of addition of amine onto methacrylic bonds can be explained by the use of low [thiol]/[amine] ratio = 1 at 40 °C. In summary, hexylamine is an efficient catalyst for the Michael reaction of thiol/acrylates at ambient temperature without observation of any side products when the [amine]/[thiol] ratio is kept close to 1.0. The use of a higher ratio yields a side product which can be attributed to the addition of amine onto vinyl bonds. A slight increase of the temperature (at 40 °C) and the amount of thiol allow us to obtain a quantitative reaction with monomer or oligomer bearing a methacrylic double bond.

Phosphine catalyzed thiol–ene reactions

Lowe has reported that phosphine based catalysts are known as very reactive catalysts for Michael addition reactions.[18] However, the highly reactive phosphine compound can also react with the vinyl group (methacrylate or acrylate) resulting in the formation of side reactions. Therefore, we initially performed some test reactions **P1** and **P2** by mixing MMA in the presence of different amounts of dimethylphenylphosphine (DMPP) in acetone, Table 4. The expected reaction is the nucleophilic addition of the phosphine to the vinyl group. After 4 days, the presence of vinyl group was monitored by ^{1}H NMR and it was found that 4% and 23% of vinyl groups were reacted with

Table 4 Optimization reactions using DMPP as catalyst with different monomers and thiols

Run	Monomer/ oligomer	Thiol	Base	Ratios [M] : [T] : [cat][a]	Solvent	React. time/h	Conv. (%)
P1	MMA	—	DMPP	1 : 0 : 0.1	Acetone	96	4
P2	MMA	—	DMPP	1 : 0 : 1.0	Acetone	96	23
P3	MMA	TG	DMPP	1 : 1 : 0.05	Acetone	1	100
P4	MMA	DT	DMPP	1 : 1 : 0.05	Acetone	3.5	93
P5	dMMA	TG	DMPP	1 : 1 : 0.05	Acetone	1	97
P6	dMMA	DT	DMPP	1 : 1 : 0.05	Acetone	4	81
P7	dMMA	DT	DMPP	1 : 1.5 : 0.05	MeCN	2	83
P8	dMMA	DT	DMPP	1 : 1.5 : 0.05	DMSO	2	95
P9	dMMA	PT	DMPP	1 : 1.5 : 0.05	Acetone	9	72
P10	dMMA	PT	DMPP	1 : 2.5 : 0.05	Acetone	8	85
P11	dMMA	PT	DMPP	1 : 1.5 : 0.05	MeCN	9	98
P12	dMMA	PT	DMPP	1 : 1.5 : 0.05	DMSO	1	100
P13	PEGM EMA$_{475}$	2-ME	DMPP	1 : 1.2 : 0.2	Acetone	0.5	100

[a] [M] : [T] : [cat] = monomer or oligomers : thiol : DMPP. Conversion values were calculated by ^{1}H NMR. All reactions were performed at ambient temperature.
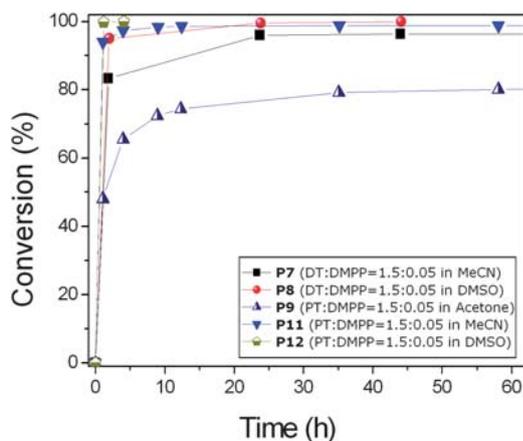

Fig. 8 Vinyl bond conversion *vs.* time for MMA dimer in the presence of different thiols and solvents.

a monomer to DMPP ratio equal to 0.1 and 1.0, respectively. Subsequently, a 1 : 1 ratio of [MMA]/[thiols] (TG or DT) were reacted in the presence of [vinyl group]/[thiol]/[DMPP] = 1/1/0.05 as catalyst in acetone solution. Full conversion was obtained in an hour for the reaction of TG (**P3**) and ≥93% conversion was calculated for the reaction of DT (**P4**). Similar reaction rates were observed when the dimer of MMA was used instead of the monomer (**P5** and **P6**). As expected, solvent selection has a great influence on the reaction rates. Therefore, we tested acetonitrile (MeCN), acetone and DMSO with the reaction in DMSO displaying faster kinetics in comparison to MeCN and acetone (**P7** and **P8**) attributable to the higher polarity of DMSO. The high polarity of DMSO allows a better stabilization of thiolate ion, and favors its formation. Solvent effects were also tested by using 1-propanethiol (PT) in all three solvents. The reaction in acetone was the slowest and in DMSO the fastest (**P9**, **P11** and **P12**). In reactions **P9** and **P10**, a higher ratio of thiol provides higher conversion values at the same reaction time. Finally, PEG-MEMA$_{475}$ monomer was reacted with 2-ME in the presence of

Table 5 Michael addition reactions to show evidence of side reactions

Run	Oligomer	Ratios [M] : [T] : [B] : [P][a]	React. temp./°C	React. time/h	Cat.
S1	o(PEGMEMA $_{475}$)	1 : 5 : 0 : 2.5	Ambient	14	TCEP (pH 8)
S2	o(PEGMEMA $_{475}$)	1 : 5 : 0 : 2.5	Ambient	14	TCEP (pH 3)
S3	o(PEGMEMA $_{475}$)	1 : 5 : 2.5 : 2.5	40	14	DMPP/HA

[a] [M] : [T] : [B] : [P] = o(PEGMEMA$_{475}$) : 2-ME : hexylamine : phosphine.
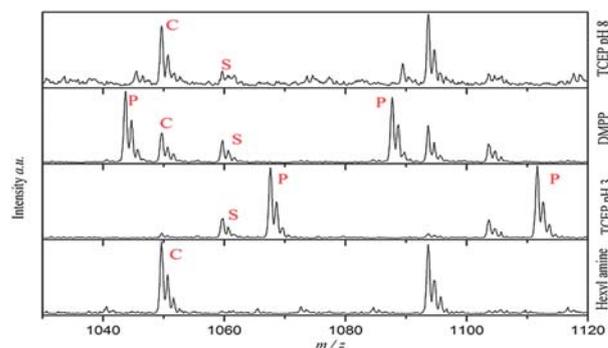
Fig. 9 ESI-MS of oligo(PEGMEMA$_{475}$) synthesized by CCTP used to identify the side reaction of phosphine catalyst. S = starting material, P = phosphine conjugated species, C = desired thiol–oligomer conjugate. Spectra were obtained with ESI-MS LCQ-Deca quadrupole. The list of corresponding compounds is given in the ESI†.

DMPP and full conversion was observed after 30 minutes **P13**, Fig. 8.

Furthermore, the addition reaction on oligo(PEGMEMA$_{475}$) was investigated using DMPP and TCEP as catalysts, Table 5. However, side reactions occur when an excess of catalyst is used and this should be taken into account when designing experimental conditions **S1–S3**. The presence of side reactions was investigated with ESI-MS, Fig. 9. In the presence of a large excess of DMPP or TCEP, by-products were clearly identified, corresponding to the presence of mono-addition of phosphine onto vinyl group for TCEP and DMPP.

In the case of TCEP, the pH has a large effect on the amount of side products formed. Indeed, at low pH, the major population observed corresponds to the presence of phosphine reacted polymers, while at high pH values the excepted product

Table 6 Optimization reactions with different monomers/dimers and thiols in the absence of catalysts

Run	Monomer/ dimer	Thiol	Ratios [M] : [T][a]	Solvent	React. time/h	Conv. (%)
N1[b]	HEMA	2-ME	1 : 1.5	D$_2$O	4	83
N2[c]	HEMA	2-ME	1 : 1.5	D$_2$O	4	100
N3[c]	dHEMA	2-ME	1 : 1.5	D$_2$O	0.5	60
N4[b]	dHEMA	HS-Glc	1 : 1.5	D$_2$O	44	91

[a] [M] : [T] = monomer or dimer : thiol. Conversion values were calculated by ^{1}H NMR. All reactions were performed at ambient temperature. [b] PBS buffer was used at a pH value of 7.1. [c] PBS buffer was used at a pH value of 9.2.

(thiol–oligomer conjugate) is present in large amounts. As expected, low pH does not favor the formation of thiolate anion (R–S⁻). These experiments show that the concentration of phosphine should be kept relatively low (or the [phosphine]/[thiol] ratio should be kept very low) to minimize side product formation.

Although the aim of this study was to investigate the effect of catalysts on thiol–ene click reactions, it was also observed that 2-hydroxyethyl methacrylate (HEMA, water soluble monomer) can react with 2-ME in water in the absence of catalyst, Table 6. However, it is crucial to control the pH of the solution in the right range.[76] For instance, when PBS buffer was used and the pH was set to 7.1 and 9.2 for the reaction of HEMA and 2-ME in D_2O after 4 hours 83% and 100% of conversion was observed for **N1** and **N2**, respectively. Pure dimer of HEMA synthesized by CCTP[77] was reacted with 2-ME under basic conditions in D_2O and 60% of conversion was obtained in 30 minutes **N3**. However, the reaction with thiol–glucose took relatively longer time to reach more than 90% conversion **N4**.

Conclusion

We present here a detailed study on the effect of catalyst on nucleophilic thiol–ene click reactions. It has been shown that when triethylamine is used as catalyst, even in excess amounts, it does not give any noticeable side reactions since mechanistically it is operating differently from pentylamine, DMPP and TCEP. Moreover, primary amines, pentylamine and hexylamine, were tested as appropriate catalysts. However, these can react with the vinyl group and form stable species which can also be monitored by ESI-MS. Phosphine catalysts provide the fastest reaction, which also brings the highest amount of side reactions. Nevertheless, using the catalyst in catalytic amounts provide relatively fast reaction rates for the desired compounds. It should also be noted that the effect of solvent, type of thiol and the basicity of the medium have a great role on this reaction and should be selected with care based on these optimization reactions. These model reactions were performed on monomers, dimers and oligomers and will form the basis of our following studies on thiol-click reactions with vinyl-terminated polymers.

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