Direct synthesis of poly(*N*-alkyl acrylamide) (co)polymers with pendant reactive amino groups by organocatalyzed amidation of polymethylacrylate

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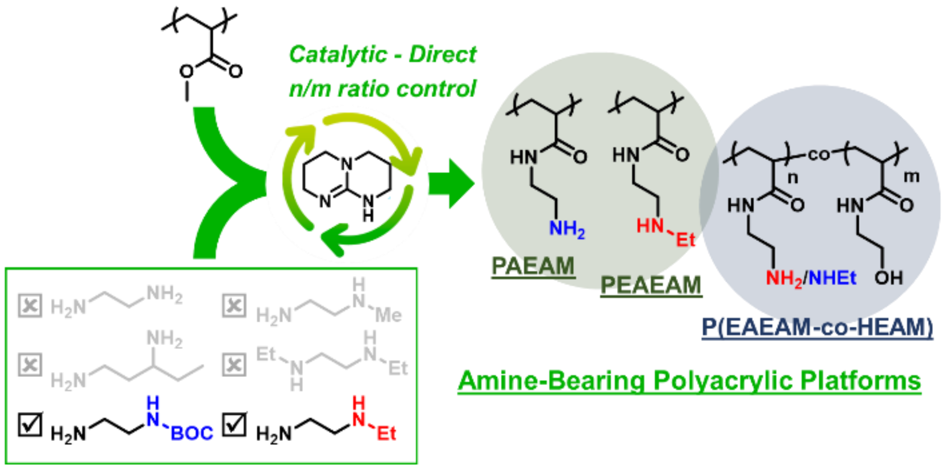


ABSTRACT: Post-polymerization modification of poorly reactive polyacrylates using efficient catalytic transesterification and amidation reactions has recently emerged as a valuable tool to access diversely functionalized poly(meth)acrylates and poly(meth)acrylamides. The method is particularly useful to introduce functional groups incompatible with the polymerization mechanism, such as non-protected reactive amino groups. In this work, we explored the TBD-catalyzed amidation of polymethylacrylate (PMA) with various difunctional amines to obtain polyacrylamide homo- and copolymers with a pendant reactive amine group. As anticipated, functional polymers could not be attained from amidation with ethylenediamine, because of competing cross-linking side reactions, but could be prepared from the mono-Boc-protected ethylenediamine instead, requiring, however, addition unwanted protection and deprotection steps. More interestingly, we found that the direct amidation of PMA with unprotected *N*-ethylethylenediamine is an efficient method for preparing secondary amine functionalized polymers, without the occurrence of crosslinking side-reaction even at lower catalyst loading. The crucial role of the ethyl group to prevent side reactions was clearly demonstrated as the use of *N*-methyl ethylenediamine led to crosslinking. The utility of the developed platform for the rapid preparation of a series of hydrophilic copolymers and hydrogel materials is also demonstrated. The hydrogels were prepared by reacting the secondary amine side chains with methacrylic anhydride, followed by photocuring in the presence and absence of dithiols.

1. INTRODUCTION

Post-polymerization modification, *i.e.* chemical manipulation of functionalities on polymers, has been historically seen as a method to overcome restrictions imposed by the polymerization method. This is well-illustrated for polyallylacrylamide (PAllAM) which cannot be prepared by radical polymerization, but could be obtained by amidation of poly(*N*-succinimidyl acrylate) (PNHSA)[1,2] or polymethylacrylate (PMA).[3] Post-polymerization modification is also increasingly addressed from another perspective, *i.e.* as a complementary tool to prepare functional polymers of equal viability than direct polymerization, but also for upcycling of low value commodity polymers into higher value specialty polymers.[4–8] This has been partly favored by the concomitant recent development of polyvalent and controllable polymerization techniques such as reversible-deactivation radical polymerization (RDRP),[9] among others, giving access to controlled, "ready-to-be-modified" polymers, paired with the advent of highly directional click-type reactions, including, CuAAC, thiol-ene, thiol-yne and several others.[4,10,11] This judicious combination is ideal to synthesize macromolecules with precise architectures and modular composition, functionality, topology.

Although post-polymerization modification seems to be a limitation-free method, the chemical method employed needs to be quantitative, chemoselective, and proceed under mild conditions to avoid side-reactions and polymer backbone transformation. Hence, many post-polymerization approaches employ highly reactive groups such as *N*-hydroxysuccinimidyl (NHS) and pentafluorophenyl (PFP) activated esters,[12,13] epoxides, anhydrides as well as the aforementioned click methods,[10,11] and sequential methods.[14] Even though these methods are without a doubt interesting and useful, they can, however, not be implemented for commodity polymers, apart from unsaturated polymers like polybutadiene,[15] thus requiring the preparation of "activated" polymeric precursors such as PNHSA.[1] Therefore, the development of economic and versatile routes, *i.e.* activation/protection free methods, to directly convert industrial commodity polymers into functional materials appears as a relevant alternative for various applications.

Although poorly reactive, some recent reports have shown that unactivated ester side-chains of widely available poly(alkyl)acrylates and poly(alkyl)methacrylates could be efficiently converted through transesterification[16–21] or amidation[22–29] reactions under mild conditions, assisted by the use of specific reagents, activating agents or catalysts. Metal-based catalysts have been employed by Terashima et al. to modify poly(meth)acrylates through transesterification,[17,20] whilst Sumerlin et al., as well as our group employed triazabicyclodecene (TBD) as an organocatalyst for the efficient transesterification or amidation of polyacrylates.[18,21,28] Other groups reported the stoichiometric use of metallo-[17] or organo-activators,[23,24] or strong reactants such as metal alkoxides or metal amides.[19,27,29] Catalytic systems are clearly the most advantageous, and among them, organo-catalysts possess several advantages such as low price and water insensitivity. Additionally, we recently demonstrated that substrates bearing an hydrogen-bonding group, such as amino-alcohols and dialkyamino groups, have a favorable impact on the reaction kinetics in TBD-catalyzed amidations of PMA, leading to an "autocatalytic accelerated" amidation process, resulting from intramolecular hydrogen-bonding of the formed amide units with the catalyst or with the neighboring esters groups, thereby reducing the activation energy barrier through the stabilization of intermediate transition states.[30] The combined effects were found to reduce the overall amidation reaction time, enabling quantitative transformation with lower catalyst loading, and enabling the introduction of various functional groups. In this work, this approach is extended towards the introduction of more challenging reactive primary and secondary amino-groups through amidation.

Among the many functionalities that could be introduced on a polymeric structure, amino groups are one of the most popular as they provide unique features, including pH responsivity, as cationic polyelectrolyte, as well as for further functionalization *via* acylation or alkylation by reaction with carboxyl, carbonyl, epoxy, Michael acceptors,[31] to access more complex structures.[32–34] Representative examples of amine-containing polymers are polyethyleneimine (PEI), poly-L-lysine (PLL), and polyvinylamine (PVAm). Amine-bearing poly(meth)acrylates and poly(meth)acrylamides are also of prime importance for the development of new materials for various biomedical applications including drug and gene delivery,[32,35–40] responsive systems,[34,41] and antimicrobial agents.[42–44]

The rapid and straightforward introduction of amine functionalities in polymeric structures, particularly reactive primary and secondary amines, is frequently hampered by their incompatibility with most of the polymerization or post-polymerization modification methods, therefore requiring the non-ideal use of protecting groups. Notably, primary and secondary amines are incompatible with (meth)acrylate and (meth)acrylamide monomers as they react with the vinyl double bond through Michael addition.[45,46] Therefore, poly(*N*-alkyl acrylamide)s (PAM) bearing primary or secondary amino groups in the side chain are usually prepared by polymerization of *tert*-butyl-2-acrylamido(alkyl)carbamates (Boc-AMA),[43] or 2-amino(alkyl)methacrylamide hydrochloride salts (AMA.HCl),[37,39,41,47–50] in which the amino group is either BOC-protected or protonated. Both routes request multiple steps, including protection/deprotection or protonation/deprotonation sequences. Moreover, these protected and protonated monomers have rather poor solubility in organic solvents. However, the direct amidation of PMA or other polyacrylates, which introduce protected or even unprotected primary of secondary amino groups into the side chain have not been reported, to the best of our knowledge.

Within this contribution, we explored the possibilities to prepare PAM containing a primary or secondary amine reactive handle in the side chain directly from PMA, especially aiming to identify, if possible, a method that omits activation/(de)protection steps, through a catalytic and solvent-free method. We used the TBD-catalyzed amidation with various symmetrical or asymmetrical bifunctional amines, such as BED that can give access to poly(*N*-aminoethyl acrylamide)s (PAEAM) homo- and copolymers with a pendant primary amine group after cleavage of the Boc-protecting group. Based on our previous research, we rationalized that the steric features of alkyldiamines could be exploited to enable chemoselective formation of the desired PAM through selective amidation of the primary amino-group, and thus avoiding crosslinking side-reactions. In this work, we indeed identified that the amidation with *N*-ethyl ethylenediamine (NEED) as a relevant protection-free modification strategy to access novel poly(*N*-(2-(ethylamino)ethyl) acrylamide) (PEAEAM) polymers and copolymers, which contain a pendant secondary amine group. As a proof of concept, the reactive poly(*N*-(2-(ethylamino)ethyl-co-*N*-hydroxyethyl acrylamide) P(EAEAM-co-PHEAM) copolymer was subsequently derivatized with methacryloyl groups to induce radical network formation in the presence of a bifunctional thiol in order to obtain hydrogels.

2. EXPERIMENTAL SECTION

2.1. Materials.

The following chemicals were purchased from various providers (Sigma Aldrich, TCI Europe, Fluka) and used as received, unless otherwise stated: acetonitrile (MeCN, ≥ 99%), acetone (≥ 99%), methanol (MeOH, ≥ 99 %) chloroform (≥ 99%), diethylether (Et_2O, ≥ 99%), tetrahydrofuran (THF, ≥ 99%), triazabicyclodecene (TBD, 98%), ethylenediamine (ED, ≥ 99%), N-ethyl ethylenediamine (NEED, >99.0%), *N*-methyl ethylenediamine (NMED, >97.0%), 1,3-pentanediamine (PD, >97%), *N,N'*-diethyl ethylenediamine (DEED, >98%), di-*tert*-butyl dicarbonate (≥ 95 %), hydrochloric acid (37%), methacrylic anhydride (>94.0%), trimethylamine (>99%) DL-Dithiothreitol (DTT) (≥ 98%). Irgacure® 2959 was kindly donated by BASF. PMA was purchased from Scientific Polymer Products (40.08% solution in toluene, Approx. Mw: 40,000 g.mol^{-1}). The toluene from PMA was removed by evaporation under vacuum using a rotary evaporator until no toluene signal was visible by ^{1}H-NMR analysis. *N*-Boc-ethylenediamine was synthesized from ethylenediamine and di-*tert* butyl dicarbonate according to a previously published method.[51] Dialysis membranes (regenerated cellulose – MWCO 3.5 kDa) were acquired from Roth. Acidic resin (Dowex®, 50W X8, hydrogen form, strongly acidic, 16-50 mesh) was purchased from Sigma Aldrich and washed with methanol and then water before use.

2.2. Methods.

Proton nuclear magnetic resonance (^{1}H-NMR) spectra were measured at room temperature with a Bruker Advance MSL 400 MHz or 300 MHz NMR spectrometer. All chemical shifts are given in parts per million (δ, ppm) relative to tetramethylsilane. Deuterated solvents, such as chloroform-d ($CDCl_3$) and dimethylsulfoxide-d_6 (DMSO-d_6) were purchased from Eurisotop. Size exclusion chromatography (SEC) was performed on an Agilent 1260-series HPLC system equipped with a 1260 online degasser, a 1260 ISO-pump, a 1260 automatic liquid sampler (ALS), a thermostatted column compartment (TCC) set at 50 °C equipped with two PLgel 5 μm mixed-D columns (7.5 mm × 300 mm) and a precolumn in series, a 1260 diode array detector (DAD) and a 1260 refractive index detector (RID). Distilled *N*,*N*-dimethyl acetamide (DMA) containing 50 mM of LiCl was used at eluant at a flow rate of 0.500 mL.min^{-1}. Number-averaged molar mass (M_n), *weight-averaged molar mass* (M_w) and molar mass distribution (dispersity, *Đ*) values were calculated against narrow dispersity polymethylmethacrylate (PMMA) standards from PSS. FTIR spectra were measured on a PerkinElmer 1600 series FTIR spectrometer and are reported in wavenumber (cm^{-1}). In situ infrared spectra or kinetics measurements were obtained with ReactIR 4000 instrument (Mettler Toledo) using a silicone probe (SiComp, optical range 4400-650 cm^{-1}). For on-line monitoring, the silicon probe was introduced into a two-necked glass flask, equipped with a stir bar. Centrifugation was performed on an ALC multispeed refrigerated centrifuge PK 121R from Thermo Scientific using 15 mL or 50 mL high clarity polypropylene conical tubes from

Falcon. Lyophilization was performed on a Martin Christ freeze-dryer, model Alpha 2–4 LSC plus. Ultrapure deionized water (Milli Q) was prepared with a resistivity less than 18.2 MΩ x cm using an Arium 611 from Sartorius with the Sartopore® 2 150 (0.45 + 0.2 μm pore size) cartridge filter. Photocrosslinking kinetics were studied by performing small strain oscillatory shear experiments on an Anton Paar MCR302 Rheometer with 25 mm parallel plate-plate geometry at R.T. Samples were irradiated using an Omnicure Series 2000 ultraviolet light source with 365 nm filter and a fiber optic probe fitted under the quartz bottom plate of the rheometer.

2.3. Experiments

General procedure for (co-)amidation reaction with ED, NMED, NEED, PD, DEED, BED, EA and copolymers thereof. Amidation reactions were conducted in sealed microwaves tubes. PMA (0.5 g, 40 kDa according to supplier, corresponding to approx. 5.81 mmol of methyl ester group) was weighed in 5 mL crimp vials (5 mL Biotage microwaves tubes). Amines (EA, ED, BED, NMED, NEED, PD or DMED) of predetermined ratio (34.88 mmol, 6 eq. per methyl ester group) were introduced in the flasks and the solutions were degassed by argon bubbling for 15 min. TBD (0.05-0.25 eq. per methyl ester) was then added to the mixtures and the flasks were flushed with Argon, capped and heated at 80 °C over a period of 72 h. To evaluate the reaction conversion, a sample (100 μL) was precipitate in cold diethyl ether (5 mL), centrifuged, dried under vacuum at 40 °C for 2 h, and analyzed by FTIR and/or by ^{1}H-NMR spectroscopy in dmso-d_6 (for BED) or D_2O.

General work-up procedure after amidation with NMED, NEED, EA and copolymers thereof. After return to room temperature, the mixture was poured into 30 mL of cold acetone to precipitate the polymer. The solution was centrifuged, and the liquid supernatant discarded. The polymer was further precipitated twice by dissolving in a minimal amount of methanol (1-3 mL) and pouring in cold acetone (30 mL). The polymer was dried under vacuum (R.T., 2h) to remove residual solvent. To remove TBD and residual traces of amines, the resultant polymer was dissolved in water (around 20 mL), and for each sample, Dowex (80-400 mg, corresponding to twice the mass of TBD) was added. After stirring for 5 hours and filtration to remove the Dowex, water was removed by freeze-drying and the resultant solid was dried in a vacuum oven at 40°C overnight to yield the desired pure polymer as a white powder. The absence of polymer protonation was confirmed by ^{1}H NMR spectroscopy.

General work-up procedure after amidation with BED and EA/BED mixtures. After return to room temperature, the mixture was poured into 40 mL of cold diethyl ether to precipitate the polymer. The solution was centrifuged, and the liquid supernatant discarded. The polymer was further precipitated twice by dissolving in a minimal amount of MeOH (1-3 mL) and pouring in cold diethyl ether (30 mL). The polymer was dried under vacuum (R.T., 2h) to remove residual solvent. The polymer was dissolved in water and the pH was adjusted to 5 with diluted HCl (0.1 M). The mixture was put in a 3.5 kDa Mw cutoff dialysis bag and dialyzed 3 times against deionized water. Water was removed by freeze drying and the resultant solid was dried in a vacuum oven at 40 °C overnight to yield the desired pure polymer as a white powder.

General procedure for the deprotection of Boc-protected polymers. 100 mg of Boc-protected homo- or copolymer was dissolved in 10 mL methanol and 1 mL of concentrated hydrochloric acid was added dropwise and the resulting mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure, and the residue was dissolved in water. The pH was adjusted to pH 7 with diluted NaOH (0.1 M), and the mixture was put in a 3.5 kDa Mw cutoff dialysis bag and dialyzed 3 times against deionized water. Water was removed by freeze drying and the resultant solid was dried in a vacuum oven at 40 °C overnight to yield the desired pure polymer as a white powder.

General procedure for the derivatization by acetylation for the SEC analysis. A homo- or copolymer sample (100 mg) was poured in 1 mL acetic anhydride (around 15 eq. per functional group, *i.e.* OH groups + NH groups) in presence of a catalytic amount of *N,N*-dimethylaminopyrridine (DMAP) (11 mg, 0.1 eq. per functional group). The reaction was stirred at 40°C overnight. After return to room temperature, the mixture was poured into 10 mL of cold diethyl ether to precipitate the polymer. The solution was centrifuged, and the liquid supernatant discarded. The polymer was further precipitated twice by dissolving in a minimal amount MeOH (1 mL) and adding to cold diethyl ether (10 mL). The polymer was dried under vacuum (R.T., 2h) and then analyzed.

General procedure for the acylation of PEAEAM-co-PHEAM copolymers with methacrylic anhydride. 0.5 g of the polymer was poured in 5 mL of dry DMF under inert atmosphere. A little amount of hydroquinone was added to the mixture. Then dry triethylamine (4 eq. per amine group) followed by methacrylic anhydride (2 eq. per amine group) were added, and the mixture was stirred at room temperature in the dark overnight. The following purification steps were also conducted as much as possible in the dark. The mixture was poured into 20 mL of cold diethyl ether to precipitate the polymer. The solution was centrifuged, and the liquid supernatant discarded. The polymer was further precipitated twice by dissolving in a minimal amount MeOH (2-3 mL) and pouring in cold counter-solvent (20 mL). The polymer was then poured into a 1M KOH/MeOH mixture (50:50, 5 mL) and the mixture was stirred at room temperature for 5h to cleave the O-acetylated by-product. The methanol was evaporated, and the resultant aqueous solution was neutralized to pH 7 with 1 M HCl. The mixture was put in a 3.5 kDa Mw cutoff dialysis bag and dialyzed 3 times against deionized water. Water was removed by freeze drying and the resultant solid was dried in a vacuum oven at 40 °C for 2 h to yield the desired pure polymer as a white powder.

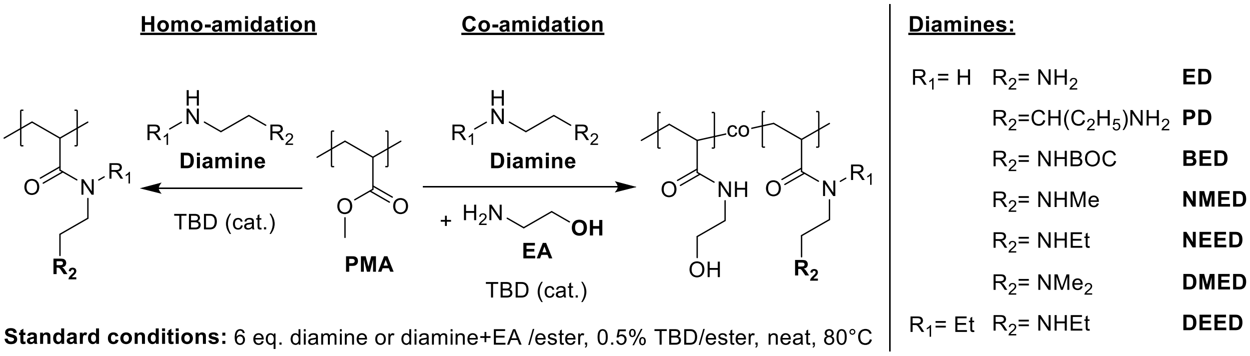
Reaction kinetics. The reaction kinetics were followed via ReactIR, using the ester peak (C=O stretching, 1770-1700 cm^{-1}) for quantification of the amount of starting esters function in the reaction, and the amide product peak (C=O stretching, 1698-1645 cm^{-1}) for quantification of the amount of amide function formed in the reaction.

Photocuring experiment. In situ photo-crosslinking experiments were conducted with 10 wt% solutions of (*PEAEAM-co-PHEAM*) copolymers with 14% functionalization degree of methacryloyl groups in water as solvent, in presence of photo-initiator (Irgacure2959) (0.05 eq. per methacryloyl groups) and eventually (2S,3S)-1,4-Bis-sulfanylbutane-2,3-diol (DTT) (0.5 eq. per methacryloyl group). The solution (around 0.2 mL) was pipetted onto the rheometer glass plate and the gap was fixed at 0.4 mm (25 mm diameter upper profile). The storage and loss modulus were measured over a total period over 665 sec with a gamma amplitude for the (oscillating) shear deformation at 0.1 % and a deformation frequency of 1 Hz. The baseline was measured during 1 min, then the solution was irradiated with the UV lamp at room temperature.

Polymer characterizations. The polymers were generally characterized by FTIR and ^{1}H-NMR spectroscopy and SEC analysis with DMA/ 1 wt% LiCl as the eluent. The spectra and corresponding values are presented and described in the supplementary data.

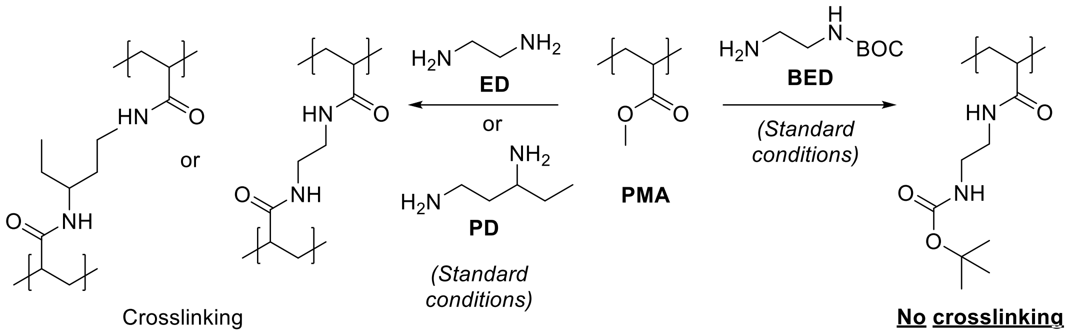
3. RESULTS AND DISCUSSION

Aiming for the modification of bulk, commodity polymers, we used commercially available PMA (around 40 kDa average molar mass (M_w)) as a starting material. The TBD-catalyzed amidation was explored with bifunctional amines, *i.e.* ethylenediamine (ED), 1,3-pentanediamine (PD) mono-Boc-protected ethylene diamine (BED) and alkylated diamines, including *N*-methyl ethylene diamine (NMED), N-ethyl ethylene diamine (NEED), and *N,N'*-diethyl ethylenediamine (DEED) (Scheme 1). The relevance of the transformations was evaluated according to a set of criteria for an ideal modification approach, which should 1) allow the introduction of a reactive amino group without any crosslinking between polymers chains, 2) be efficient enough to achieve full conversion of the methyl ester, 3) eliminate the need for protecting groups, 4) limit the price and the production of waste by minimization of amounts of catalyst and solvent, and 5) allow "homo-amidation" as well as controllable co-amidation with ethanolamine (EA) to yield water-soluble amine-functional polymers. Indeed, co-amidation with EA could give access to functionalized PHEAM, which are valuable water soluble, non-ionic anti-fouling polymers found in various biomedical applications.[52–59] Such a copolymer, therefore, represents a promising reactive platform for a large range of applications.



Scheme 1. *Overview of the investigated post-polymerization modification reactions of PMA with various amines to gives poly(N-alkyl acrylamide)s homo- and copolymers.*

We firstly explored the amidation reaction of PMA with ED, as the most direct and simple route to introduce an *N*-aminoethyl side-chain group. As standard conditions, 0.05 equivalents (5 mol%) of TBD were used together with 6 equivalents of the amine, both related to the methyl ester groups, and the reaction was performed at 80°C. In our previous work, these conditions were previously found to be optimal to reach a full conversion of the methyl ester groups using ethanolamine (EA) as reactant.[30] As a preliminary amidation reaction of PMA with ED led to crosslinking, only co-amidations with EA were further explored, in order to reduce crosslinking through the amidation reaction from both amines of ED. The reaction conversions were evaluated by FTIR, by comparison of the methyl ester peak ($C=O_{(vibration)}$ at 1726 cm^{-1}) and the amide peak ($C=O_{vibration}$ at 1642 cm^{-1}) from a reaction sample that was precipitate in diethyl ether, centrifuged and dried (Figure S1). Although we could easily reach full conversion after 24 hours of reaction, it was clear that the reactions led to undesired crosslinking (Scheme 2. left) regardless of the reaction conditions, even with the use of an excess of EA as a co-reactant, either in neat conditions or diluted in MeCN (Table S1). The propensity to crosslink was judged qualitatively (SEC was not measured because of insolubility of the samples), by visual observation of an eventual insoluble fraction in the reaction bulk or during work-up. A set of PMA amidation reactions with an asymmetric diamine (PD) containing two primary amines, of which one is sterically less accessible due to its connection to a secondary carbon, was also carried out aiming to achieve selective amidation with the less sterically hindered amino group (Table S2). However, insoluble material was again formed in the reaction, demonstrating the inability of PD to avoid the crosslinking side-reaction.



Scheme 2. *Post-polymerization modification of PMA with unprotected vs protected ethylenediamine leading to crosslinking (left) or no crosslinking (right).*

Therefore, the amidation of PMA with BED appears as the most evident approach (Scheme 2, right) to introduce a primary amine side-chain and to prevent crosslinking, although the use of a protecting group is not ideal. Nonetheless, amidation reactions of PMA were conducted with BED alone as well as in a coamidation of BED with EA at various ratio. Here, the conversion was evaluated by ^{1}H-NMR spectroscopic analysis of the samples, by looking at the methyl ester peak disappearance (at around 3.58 ppm), because the signal of the Boc-group overlaps with the methyl ester group signal in FTIR spectroscopy. The fully converted polymers were purified by precipitation in diethyl ether followed by dialysis at acidic pH (5) to remove the catalyst. As one could expect, no significant crosslinking was observed. However, it was rather difficult to obtain full conversion, particularly for high BED contents (EA/BED > 3:3 or BED alone) (Table S3). This lower reactivity for BED compared to EA is most likely due to the high steric bulk of the Boc-group, hampering the amidation of neighboring ester groups. To push the reactions at high BED content to full conversion, it was necessary to increase the TBD loading to 20 mol% per methyl ester (when EA/BED ≥ 3:3) and increase the reaction times (up to 96 h, for EA/BED 1:6 and for BED alone). Increasing the temperature to 120 °C was found to be detrimental for the polymer dispersity, probably due to, partial, thermally induced Boc-cleavage leading to crosslinking. In contrary, the Boc-group remains relatively stable for the reactions at 80°C and during workup, as shown by the SEC analysis of the isolated polymers (Figure 1.A.; Mn, Mw and Đ of the products are provided in the Table S4), except for the polymers made with BED/EA 5:1 and 6:0 (29% and 100% Boc-aminoethylacrylamide ((BOC)AEAM) units content) that gives a high molar mass shoulder on the SEC, presumably due to a slight BOC cleavage as a consequence of prolonged reaction time. All polymers show a clear and similar shift in retention time compared to PMA, confirming the transformation into PAM. The corresponding fraction of (BOC)AEAM units in the final P(HEMA-co-(BOC)AEAM) copolymers as a function of the stoichiometric ratio of amine used is shown in Figure 1.B. The values were calculated from the ^{1}H-NMR spectra, by comparison of the integral of the protons of the Boc-group (k) with signal of the backbone protons (a+b) (Figure 1.C.). The lower incorporation degree of BED compared to EA is in line with an expected difference in reactivity during TBD-catalyzed amidation reactions, because of their difference in steric bulk and hydrogen-bonding capability. Indeed, the hydroxyl group in EA is able to lower some transition states via hydrogen-bonding,[60] whereas the amino-*N*-Boc-group in BED probably cannot. For example, the use of equal amount of BED and EA (eq. ratio 0.5) gives a polymer with only 7 mol % of (BOC)AEM units. However, the variation of this amine ratio is a direct and straightforward means to control the percentage of incorporated (BOC)AEM functional groups.

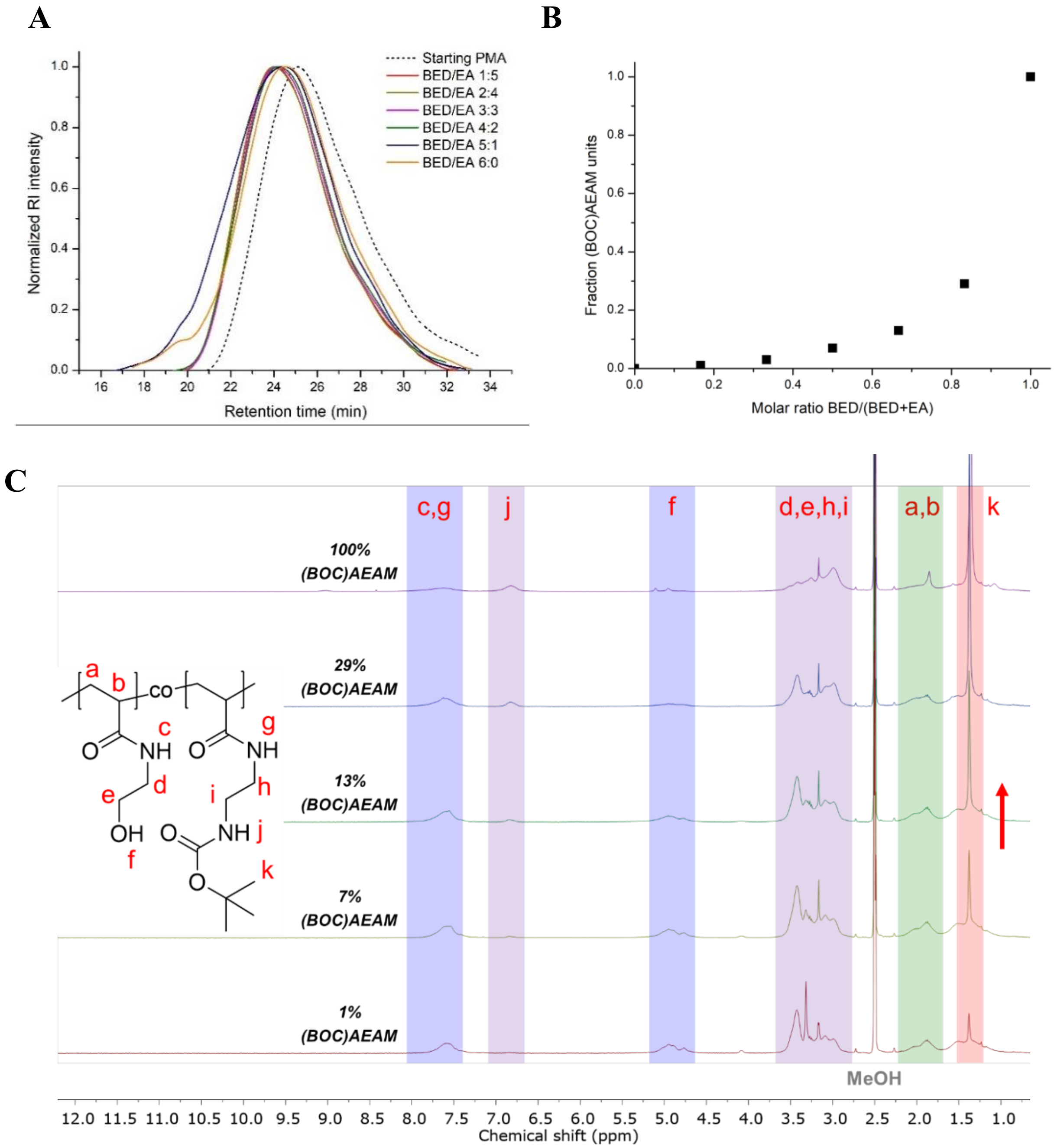
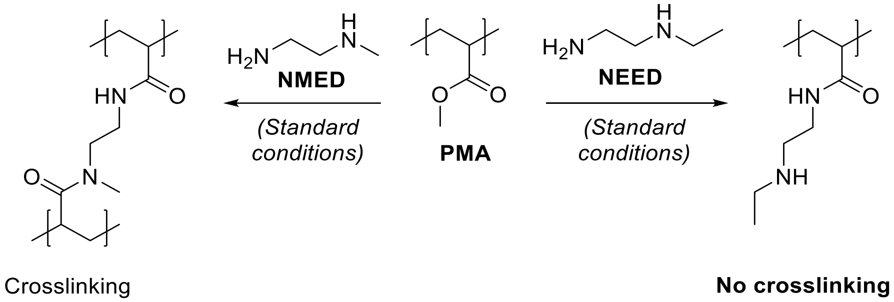


Figure 1. *A) Overlay of SEC-RI traces of the starting PMA and the PHEAM-co-P(BOC)AEAM copolymers obtained after amidation with BED/EA ratios ranging from 1:5 to 6:0. B) The fraction of (BOC)AEAM units in the corresponding copolymers as a function of the stoichiometric BED/EA ratio. C) The corresponding* ^{1}*H-NMR spectra (MeOD, 300 MHz) of the*

obtained purified P(HEMA-co-(BOC)AEAM) and P((BOC)AEAM) polymers (the spectrum for ratio 1:5 is not showed as (BOC)AEAM content is below 1%).

The deprotection of the Boc-group that leads to PAEAM homo- and copolymers was then investigated using standard acidic conditions. It was found that stirring 24 hours in acidic media allows a complete cleavage of the Boc-group as no *tert*-butyl protons were observed by ^{1}H-NMR spectroscopic analysis (Figure S2). At this stage, we have shown that reactive primary amine containing poly(*N*-alkylated acrylamide) homopolymers and copolymers can be prepared by amidation of PMA. Therefore, the method provides rapid access to water-soluble functional copolymers from commercial PMA or for potential upcycling of PMA containing waste. However, the usefulness of the method remains moderate because 1) it utilizes a protecting group, 2) it requests a high catalyst loading and prolonged reaction times, hence inducing visible cross-linking for high BED/EA ratios, 3) the incorporation degree of the amine group is relatively low and 4) the same polymers could be obtained from the monomer approach, *i.e.* starting from BOC-AMA or AMA.HCl, as discussed in the introduction.

Therefore, we continued our investigations to study the modification of PMA with mono-*N*-alkylated diamines, *i.e*. NMED and DMED, in order to discriminate between the reactivity of a primary amine and a secondary amine, thus potentially eliminating the need of a protecting group if sufficient selectivity is achieved (Scheme 3). We previously observed that secondary amines (diethylamine, pyrrolidine) display lower reactivity in the amidation reaction of PMA compared to primary amines (allylamine, benzylamine).[28] Therefore, we hypothesized that primary amines could be selectively incorporated in the presence of an alkyl-substituted secondary amine. We also anticipated that these diamines could react faster compared to BED, because of their reduced steric hindrance, as well as a restored activation/transition state stabilization of neighboring ester groups, as the secondary amine in NMED and NEED is expected to act as a hydrogen-bond donor. To assess the latter, we compared the reactivity of ED, NMED, dimethylethylenediamine (DMED) and propylamine (PA) in DMSO through *in situ* following of the conversion by FTIR using a reactIR (Figure 2.A). It is clearly demonstrated that the reaction is faster for NMED compared to amines with no hydrogen-bonding units, *i.e.* DMED or PA, but slower compared to ED or EA. Although NMED could react efficiently, the visual observations and SEC analysis of the polymers made by amidation of PMA with NMED highlighted the poor capability of this amine to prevent cross-linking (Table S5, figure 2.B). Indeed, when NMED is used either alone or in combination with EA at a ratio of NMED:EA of 3:3: or 1:5, a broad molar mass distribution with a large high molar mass shoulder is observed on the SEC chromatogram, indicative of chain-coupling side reactions. Quite surprisingly, the SEC traces that were obtained for analogous amidation reactions of PMA with NEED, instead of NMED, revealed well-defined peaks with a molar mass distribution similar to that of the starting PMA. Moreover, there was no visual evidence of crosslinking for the amidation reactions with NEED either. The differences in reactivity between NMED and NEED clearly highlight that the nature of the alkyl group that substitutes the secondary amine is primordial to steer the selectivity of the amidation reaction. A recent report from *Yuan et al.*,[61] indeed observed a similar difference for amidation of plant oils with methyl and ethyl *N*-substituted ethanolamines, whereby a four-time slower reaction was observed for the *N*-ethyl-ethanolamine substrate. Here, we can hypothesize that the *N*-ethyl substituted secondary amine could still provide the beneficial stabilization of the transition states through hydrogen-bonding, but would be too sterically hindered to sufficiently compete (kinetically) with the primary amine for the amidation reaction itself, or would impose too much steric hindrance to enable stabilization of the transition state by the primary amine, probably resulting in increased thermodynamic and kinetic barriers. To further prove this hypothesis, we also performed the amidation reaction under the same experimental conditions with the symmetrical *N*,*N'*-disubstituted DEED (Scheme S8). In this situation, crosslinking was visually observed in the bulk, indicating reaction on both sides of the DEED. Therefore, we reasonably concluded that, although the *N*-ethyl group is sufficiently reactive to react with PMA, the large difference in reactivity compared to the primary amine in the NEED promotes the quantitivate amidation of the primary amines, whilst the crosslinking involving the secondary amine is kinetically disfavored. In contrast, the reactivity difference is probably reduced in the case of NMED, which leads to inevitable crosslinking indicating the delicate balance in reactivity that is required for selective amidation on one of the amines.



Scheme 3. *Post-polymerization modification of PMA with secondary amines leading either to, partial, crosslinking (NMED) or no crosslinking (NEED).*

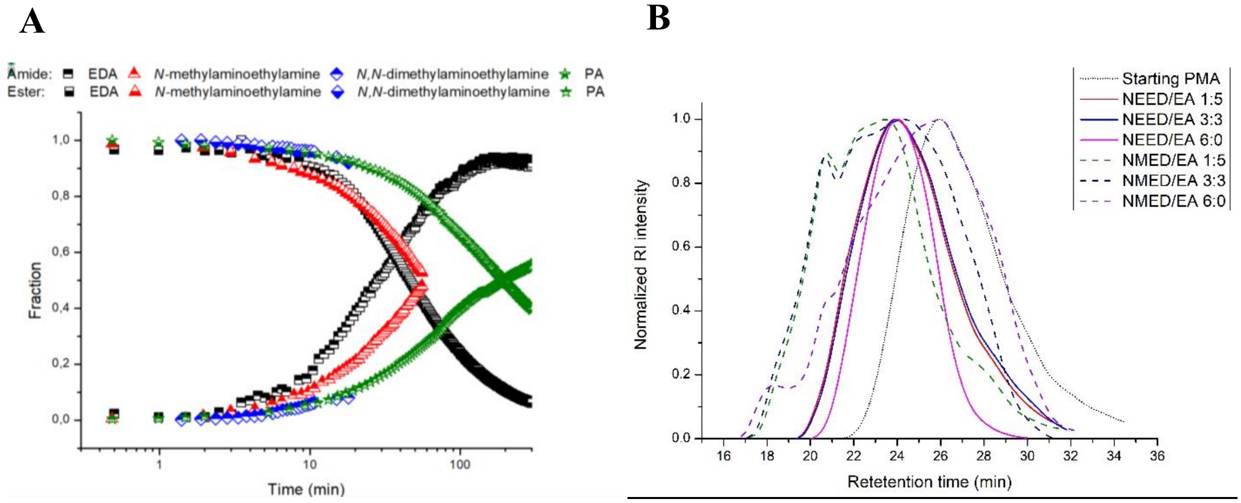
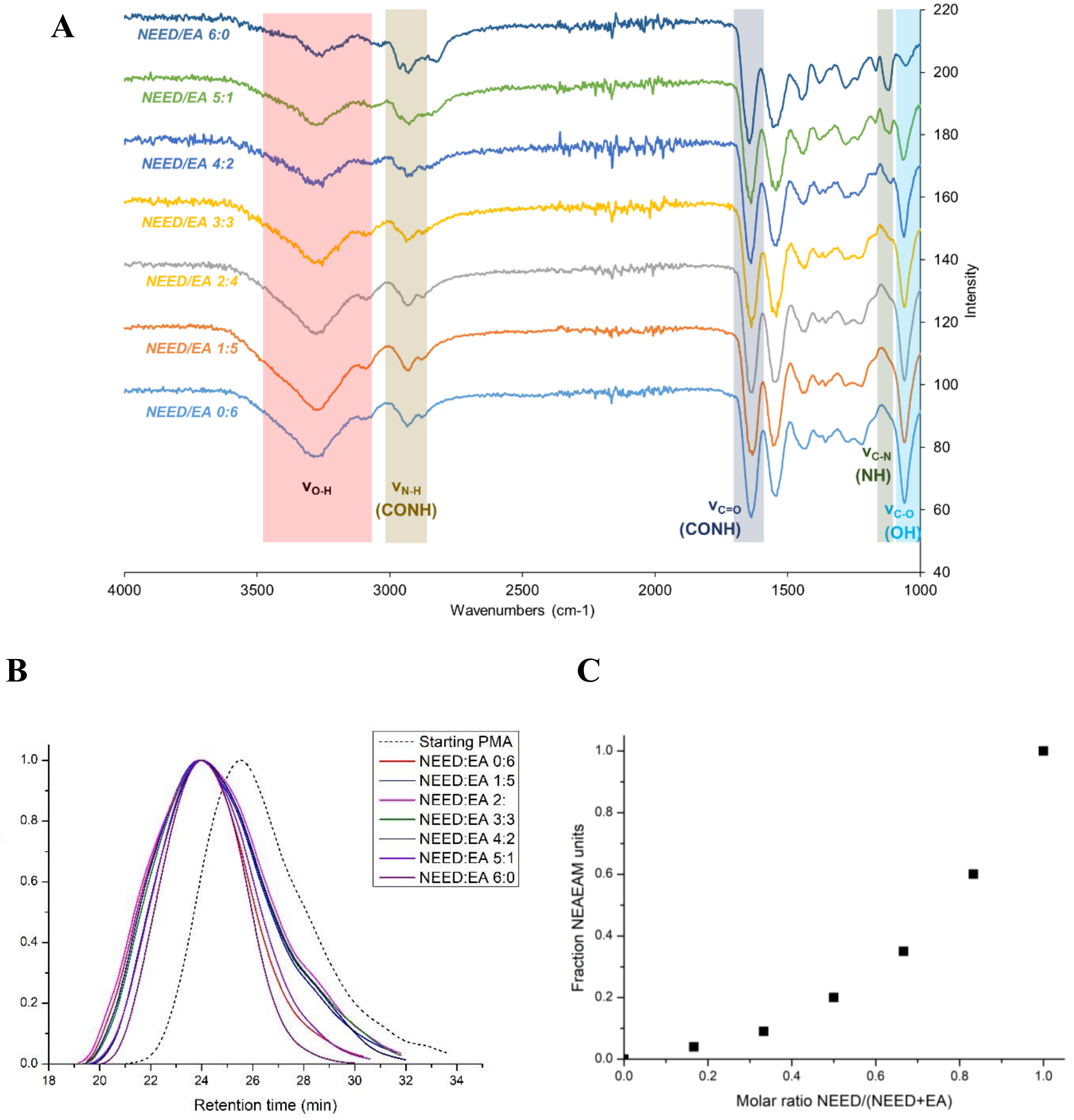


Figure 2. *A) Kinetic curves obtained by in situ FTIR monitoring of the methyl ester consumption (lower-part marked symbols) and amide formation (upper-part marked symbols) B) Overlay of SEC-RI traces of the starting PMA and the PMA modified either with EA/NMED mixtures or with EA/NEED mixtures*

It is worth mentioning that for the SEC experiments, the polymers were derivatized before analysis, *i.e.* they were fully acylated (*O*- and *N*- acylated) using acetic anhydride in presence of DMAP, as the SEC method we employed is unsuitable for polymers with high amine content. The derivatization through acylation was monitored by ^{1}H-NMR spectroscopy (Figure S4).

Then, we extended the method involving NEED to prepare a range of copolymers of PEAEAM and PHEAM with various compositions, as well as the PEAEAM homopolymer, by simple modulation of the amine proportions. For every amine ratio, a reaction time of 18h, in neat conditions, at 80°C and using only 5 % of TBD per methyl esters were sufficient conditions to attain the full conversion of the methyl ester, which was confirmed by FTIR spectroscopy (Figure 3A, Table S6,), except for the reaction with 100% NEED as a reactant which requested a longer reaction time (40 h). This is consistent with the expected higher reactivity of NEED compared to

BED, but lower reactivity compared to EA. All obtained polymers revealed SEC elution peak profiles similar to that of the starting PMA, with a clear shift in retention time (Figure 3.B, Figure S5). An even narrower dispersity compared to PMA was measured for the polymers with high EAEAM contents, probably because of the applied purification method. The PEAEAM containing polymers were purified by precipitation in acetone, which might partially dissolve the low molar mass polymers and lead to a change in molar mass, which is not the case for the P(BOC)AEAM polymers that were precipitated in diethyl ether and therefore keep a similar dispersity as the starting PMA (Figure 1.A). The higher reactivity of NEED compared to BED is also well visible when looking at the EAEAM functional group incorporation degree (Figure 3.C.) calculated from the ^{1}H-NMR analysis (Figure 3.D.). For an equimolar amount of EA and NEED (stoichiometric ratio 0.5), a polymer with 20 % EAEAM functionality is obtained (to be compared with 7 % functionality for (BOC)AEAM) at the same stoichiometric ratio). Although stabilization of the transition state occurs for both EA and NEED, EA still stabilizes the transition state more efficiently.[60] While the acceleration phenomenon due to the ester activation by neighboring EAEAM or HEAM units is present in both cases, still a difference exists for the stabilization of the transition state by the incoming amine, which is most likely the cause of the reactivity difference.


A
NEED/EA 6:0
NEED/EA 5:1
NEED/EA 4:2
NEED/EA 3:3
NEED/EA 2:4
NEED/EA 1:5
NEED/EA 0:6
ν_{O-H}
ν_{N-H} (CONH)
$\nu_{C=O}$ (CONH)
ν_{C-N} (NH)
ν_{C-O} (OH)
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)
Intensity
220
200
180
160
140
120
100
80
60
40
B
Starting PMA
NEED:EA 0:6
NEED:EA 1:5
NEED:EA 2:
NEED:EA 3:3
NEED:EA 4:2
NEED:EA 5:1
NEED:EA 6:0
Normalized RI Intensity
1.0
0.8
0.6
0.4
0.2
0.0
18
20
22
24
26
28
30
32
34
Retention time (min)
C
Fraction NEAEAM units
1.0
0.8
0.6
0.4
0.2
0.0
0.0
0.2
0.4
0.6
0.8
1.0
Molar ratio NEED/(NEED+EA)

D

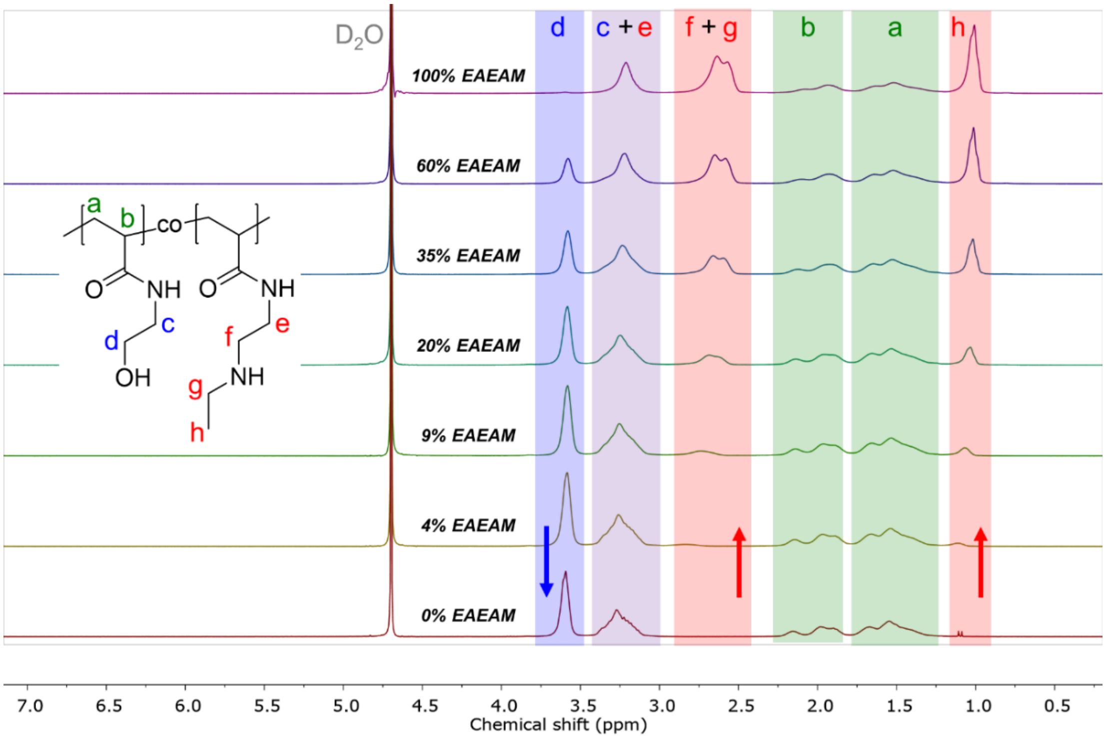
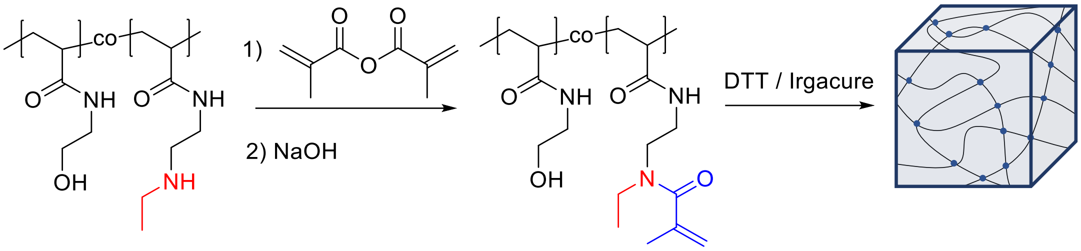


Figure 3. *A) Overlay of FTIR spectra after 24h of amidation of PMA with NEED/EA ratio ranging from 0:6 to 6:0. B) Overlay of SEC-RI traces of the starting PMA and the PHEAM-co-PEAEAM copolymers obtained after amidation with NEED/EA ratio ranging from 0:6 to 6:0 and derivatization by acylation B) The fraction of EAEAM units in the corresponding copolymers as a function of the stoichiometric NEED/EA ratio. D) The corresponding ^{1}H-NMR spectra of the obtained purified polymers.*

To remove the TBD catalyst, dialysis after acidic treatment could be used (Figure S6

). Alternatively, the employment of an acidic resin (Dowex) in water turned out be more straightforward and offers the possibility to recover and reuse the catalyst. Overall, the use of NEED is very beneficial, and allowed us to access novel PEAEAM homopolymers and (PHEAM-co-PEAEAM) copolymers in a controllable, economic and straightforward manner.

The applicability of this PEAEAM reactive platform to access hydrogel materials was then explored. The reactive nature of the secondary amine groups was exploited to install methacryloyl groups, which would enable facile photo-initiated network formation via either free radical or thiol-ene chemistry. Thiol–ene click reactions are attractive tools for hydrogel materials preparation owing to their rapid reaction rate and efficiency under mild aqueous conditions, enabling the formation of gels with well tunable properties.[62,63] For this purpose, a PHEAM-co-PEAEAM copolymer (with 20 % EAEAM units) was reacted with methacrylic anhydride in presence of triethylamine, followed by basic hydrolysis of the O-acetylated by-product (Scheme 4). After dialysis, a polymer with 14% functionalization degree was obtained, as determined by integration of the protons signal of the methacrylamide side-groups *versus* the signal of the protons from the backbone in the ^{1}H-NMR spectrum (Figure S9, Table S7). The polymer (10 wt% in water) was subsequently subjected to photo-initiated curing with and without dithiol crosslinker, in presence of Irgacure 2959 as a photoinitiator. The tests were performed by strain oscillatory shear photorheological experiments with *in situ* irradiation. For both experiments, a clear crossover point highlights the sol-gel transition, although it is reached faster for the experiment with DDT (Figure 4). The storage modulus attained is also higher for this latter experiment, reaching up to 10 kPa, indicating that the thiol-ene photocrosslinking is more efficient than the radical chain coupling of the methacrylamide side chain units. It should be noted that it can not be excluded that during thiol-ene photocrosslinking also some radical polymerization of methacrylamide units occurs.



Scheme 4. *Post-polymerization modification of P(EAEAM-co-HEAM) with methacrylic anhydride and subsequent photocrosslinking.*

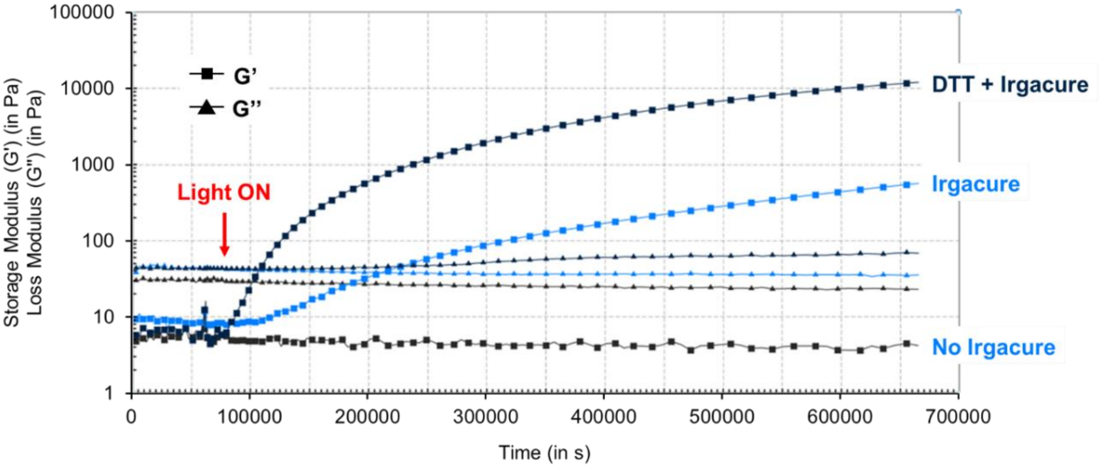


Figure 4. *Storage modulus and loss modulus evolution over time as measured by rheology during the in situ photocrosslinking experiments of P(EAEAM-co-HEAM) modified with methacrylic anhydride (10 wt% in water), with or without DTT in presence of Irgacure 2959 as photoinitiator.*

Conclusion

To summarize, we have explored the direct TBD-catalyzed amidation of commercial PMA with difunctional amines, aiming for the preparation of poly(*N*-alkylated) acrylamides bearing pendant reactive primary or secondary amino groups. Whilst we observed inevitable cross-linking when performing the reaction with ED or PD, the employment of mono-Boc-protected BED provides access, after deprotection, to PAEAM containing homo- and co-polymers with reduced side reactions. However, the method is limited when high degree of amine content is targeted because of the low reactivity of BED as well as the occurrence of some side-reactions due to more harsh reaction conditions. Therefore, the employment of monoalkylated diamines, *i.e.* NEED, is clearly more advantageous because it omits protecting group strategies, uses a low catalyst loading, does not need solvent, reduces reaction time and excludes side-reactions, overall reducing energy cost and waste production, whilst allowing the reliable preparation of the desired functionalization degree simply by modulating the ratio between different amine reactants. The comparison of the amidation of PMA with NEED to amidation with other amines (NMED, DMED, PA) have clearly highlighted the beneficial role of the *N*-ethyl substituted secondary amino group. Its hydrogen bonding capability is hypothesized to favor the fast amidation at the primary amine side by stabilization of the transition states, while the bulky *N*-ethyl substituent is essential to dramatically reduce its reactivity toward amidation and consequently suppress cross-linking side-reactions. However, the secondary amine remains sufficiently reactive for later modification. Along this line, we demonstrated the potential of the reactive P(EAEAM-co-HEAM) platform to conduct further modification reactions to prepare a methacrylated polymer precursors for hydrogel materials.

Beyond this proof of concept, the presented approach appears powerful as a simple method to access novel amine-containing homo- and copolymers that could find place in several applications, such as hydrogels and biomaterials, and therefore extending the range of applications of polyacrylamides in general.

ABBREVIATIONS

Polymethylacrylate (PMA), ethanolamine (EA), ethylenediamine (ED), 1,3-pentanediamine (PD), *N*-(tertbutoxycarbonyl)ethylenediamine (BED), *N*-methylethylenediamine (NMED), *N*-

ethylethylenediamine (NEED), *N*,*N*-dimetylethylenediamine (DMED), propylamine (PA), polyhydroxethylacrylamide (PHEAM), polyaminoethylacrylamide (PAEAM), poly(*N*-Boc-aminoethylacrylamide (P(BOC)AEAM), Poly(*N*-methyl aminoethylacrylamide) (PMAEAM), Poly(*N*-ethyl aminoethylacrylamide) (PEAEAM), Poly(*N*,*N*-dimethyl aminoethylacrylamide) (PDMAEAM), polypropylamine (PPAM).

ASSOCIATED CONTENT

Supporting Information. Additional experiments, procedures and characterization data are described in the Supporting Information

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. All authors contribute equally to this work.

Conflict of interest: JVG and RH are listed as inventors on patent WO2019224356A1 that covers part of the side-chain amidation that is used in this work. YB, JVG and RH are listed as inventor on a priority patent application that covers the reported polyacrylamides with secondary amino groups in the side chains. The other authors have no conflicts to declare.

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REFERENCES

(1) Ferruti, P.; Bettelli, A.; Feré, A. High Polymers of Acrylic and Methacrylic Esters of N-Hydroxysuccinimide as Polyacrylamide and Polymethacrylamide Precursors. *Polymer* **1972**, *13* (10), 462–464. https://doi.org/10.1016/0032-3861(72)90084-5.

(2) Batz, H.-G.; Franzmann, G.; Ringsdorf, H. Model Reactions for Synthesis of Pharmacologically Active Polymers by Way of Monomeric and Polymeric Reactive Esters. *Angew. Chem. Int. Ed. Engl.* **1972**, *11* (12), 1103–1104. https://doi.org/10.1002/anie.197211031.

(3) Verjans, J.; Sedlačík, T.; Jerca, V. V.; Bernhard, Y.; Van Guyse, J. F. R.; Hoogenboom, R. Poly(N-Allyl Acrylamide) as a Reactive Platform toward Functional Hydrogels. *ACS Macro Lett.* **2023**, *12* (1), 79–85. https://doi.org/10.1021/acsmacrolett.2c00650.

(4) Blasco, E.; Sims, M. B.; Goldmann, A. S.; Sumerlin, B. S.; Barner-Kowollik, C. 50th Anniversary Perspective: Polymer Functionalization. *Macromolecules* **2017**. https://doi.org/10.1021/acs.macromol.7b00465.

(5) Günay, K. A.; Theato, P.; Klok, H.-A. History of Post-Polymerization Modification. In *Functional Polymers by Post-Polymerization Modification*; Theato, P., Klok, H.-A., Eds.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2013; pp 1–44. https://doi.org/10.1002/9783527655427.ch1.

(6) Günay, K. A.; Theato, P.; Klok, H.-A. Standing on the Shoulders of Hermann Staudinger: Post-Polymerization Modification from Past to Present. *J. Polym. Sci. Part Polym. Chem.* **2013**, *51* (1), 1–28. https://doi.org/10.1002/pola.26333.

(7) Gauthier, M. A.; Gibson, M. I.; Klok, H.-A. Synthesis of Functional Polymers by Post-Polymerization Modification. *Angew. Chem. Int. Ed.* **2009**, *48* (1), 48–58. https://doi.org/10.1002/anie.200801951.

(8) Jehanno, C.; Alty, J. W.; Roosen, M.; De Meester, S.; Dove, A. P.; Chen, E. Y.-X.; Leibfarth, F. A.; Sardon, H. Critical Advances and Future Opportunities in Upcycling Commodity Polymers. *Nature* **2022**, *603* (7903), 803–814. https://doi.org/10.1038/s41586-021-04350-0.

(9) Braunecker, W. A.; Matyjaszewski, K. Controlled/Living Radical Polymerization: Features, Developments, and Perspectives. *Prog. Polym. Sci.* **2007**, *32* (1), 93–146. https://doi.org/10.1016/j.progpolymsci.2006.11.002.

(10) Fournier, D.; Hoogenboom, R.; Schubert, U. S. Clicking Polymers: A Straightforward Approach to Novel Macromolecular Architectures. *Chem. Soc. Rev.* **2007**, *36* (8), 1369. https://doi.org/10.1039/b700809k.

(11) Goldmann, A. S.; Glassner, M.; Inglis, A. J.; Barner-Kowollik, C. Post-Functionalization of Polymers via Orthogonal Ligation Chemistry. *Macromol. Rapid Commun.* **2013**, *34* (10), 810–849. https://doi.org/10.1002/marc.201300017.

(12) Das, A.; Theato, P. Activated Ester Containing Polymers: Opportunities and Challenges for the Design of Functional Macromolecules. *Chem. Rev.* **2016**, *116* (3), 1434–1495. https://doi.org/10.1021/acs.chemrev.5b00291.

(13) Eberhardt, M.; Mruk, R.; Zentel, R.; Théato, P. Synthesis of Pentafluorophenyl(Meth)Acrylate Polymers: New Precursor Polymers for the Synthesis of Multifunctional Materials. *Eur. Polym. J.* **2005**, *41* (7), 1569–1575. https://doi.org/10.1016/j.eurpolymj.2005.01.025.

(14) Kubo, T.; Easterling, C. P.; Olson, R. A.; Sumerlin, B. S. Synthesis of Multifunctional Homopolymers *via* Sequential Post-Polymerization Reactions. *Polym. Chem.* **2018**, *9* (37), 4605–4610. https://doi.org/10.1039/C8PY01055B.

(15) Arslan, M.; Acik, G.; Tasdelen, M. A. The Emerging Applications of Click Chemistry Reactions in the Modification of Industrial Polymers. *Polym. Chem.* **2019**, *10* (28), 3806–3821. https://doi.org/10.1039/C9PY00510B.

(16) Sun, L.; Du, Z.; Wang, W.; Liu, Y. Synthesis and Self-Assembly Behavior of Comb-Like Surfactant Polymethyl Methacrylate-g-Methoxy Polyethylene Glycol. *J. Surfactants Deterg.* **2011**, *14* (2), 161–166. https://doi.org/10.1007/s11743-010-1235-2.

(17) Kim, J. G. Direct Transesterification of Poly(Methyl Acrylate) for Functional Polyacrylate Syntheses. *J. Polym. Sci. Part Polym. Chem.* **2017**, *55* (15), 2554–2560. https://doi.org/10.1002/pola.28659.

(18) Easterling, C. P.; Kubo, T.; Orr, Z. M.; Fanucci, G. E.; Sumerlin, B. S. Synthetic Upcycling of Polyacrylates through Organocatalyzed Post-Polymerization Modification. *Chem Sci* **2017**, *8* (11), 7705–7709. https://doi.org/10.1039/C7SC02574B.

(19) Fleischmann, C.; Anastasaki, A.; Gutekunst, W. R.; McGrath, A. J.; Hustad, P. D.; Clark, P. G.; Laitar, D. S.; Hawker, C. J. Direct Access to Functional (Meth)Acrylate Copolymers through Transesterification with Lithium Alkoxides. *J. Polym. Sci. Part Polym. Chem.* **2017**, *55* (9), 1566–1574. https://doi.org/10.1002/pola.28524.

(20) Ito, D.; Ogura, Y.; Sawamoto, M.; Terashima, T. Acrylate-Selective Transesterification of Methacrylate/Acrylate Copolymers: Postfunctionalization with Common Acrylates and Alcohols. *ACS Macro Lett.* **2018**, *7* (8), 997–1002. https://doi.org/10.1021/acsmacrolett.8b00502.

(21) Van Guyse, J. F. R.; Bernhard, Y.; Hoogenboom, R. Stoichiometric Control over Partial Transesterification of Polyacrylate Homopolymers as Platform for Functional Copolyacrylates. *Macromol. Rapid Commun.* **2020**, *41* (19), 2000365. https://doi.org/10.1002/marc.202000365.

(22) Gunes, D.; Batu Kurtarel, O.; Bicak, N. Poly(*N* -Hydroxyethyl Acrylamide)- *b* -Polystyrene by Combination of ATRP and Aminolysis Processes. *J. Appl. Polym. Sci.* **2013**, *127* (4), 2684–2689. https://doi.org/10.1002/app.37604.

(23) Kakuchi, R.; Wongsanoh, K.; Hoven, V. P.; Theato, P. Activation of Stable Polymeric Esters by Using Organo-Activated Acyl Transfer Reactions. *J. Polym. Sci. Part Polym. Chem.* **2014**, *52* (9), 1353–1358. https://doi.org/10.1002/pola.27124.

(24) Krappitz, T.; Theato, P. Comparative Study on Post-Polymerization Modification of C1 Poly(Benzyl 2-Ylidene-Acetate) and Its C2 Analog Poly(Benzyl Acrylate). *J. Polym. Sci. Part Polym. Chem.* **2016**, *54* (5), 686–691. https://doi.org/10.1002/pola.27891.

(25) Schöbel, J.; Karg, M.; Rosenbach, D.; Krauss, G.; Greiner, A.; Schmalz, H. Patchy Wormlike Micelles with Tailored Functionality by Crystallization-Driven Self-Assembly: A Versatile Platform for Mesostructured Hybrid Materials. *Macromolecules* **2016**, *49* (7), 2761–2771. https://doi.org/10.1021/acs.macromol.6b00330.

(26) Yoshida, K.; Tian, L.; Miyagi, K.; Yamazaki, A.; Mamiya, H.; Yamamoto, T.; Tajima, K.; Isono, T.; Satoh, T. Facile and Efficient Modification of Polystyrene- *Block* -Poly(Methyl Methacrylate) for Achieving Sub-10 Nm Feature Size. *Macromolecules* **2018**, *51* (20), 8064–8072. https://doi.org/10.1021/acs.macromol.8b01454.

(27) Schöbel, J.; Hils, C.; Weckwerth, A.; Schlenk, M.; Bojer, C.; Stuart, M. C. A.; Breu, J.; Förster, S.; Greiner, A.; Karg, M.; Schmalz, H. Strategies for the Selective Loading of

Patchy Worm-like Micelles with Functional Nanoparticles. *Nanoscale* **2018**, *10* (38), 18257–18268. https://doi.org/10.1039/C8NR05935G.

(28) Van Guyse, J. F. R.; Verjans, J.; Vandewalle, S.; De Bruycker, K.; Du Prez, F. E.; Hoogenboom, R. Full and Partial Amidation of Poly(Methyl Acrylate) as Basis for Functional Polyacrylamide (Co)Polymers. *Macromolecules* **2019**, *52* (14), 5102–5109. https://doi.org/10.1021/acs.macromol.9b00399.

(29) Hils, C.; Fuchs, E.; Eger, F.; Schöbel, J.; Schmalz, H. Converting Poly(Methyl Methacrylate) into a Triple-responsive Polymer. *Chem. – Eur. J.* **2020**, chem.202000485. https://doi.org/10.1002/chem.202000485.

(30) Van Guyse, J. F. R.; Leiske, M. N.; Verjans, J.; Bernhard, Y.; Hoogenboom, R. Accelerated Post-Polymerization Amidation of Polymers with Side-Chain Ester Groups by Intramolecular Activation. *Angew. Chem. Int. Ed.* **2022**, *61* (29), e202201781. https://doi.org/10.1002/anie.202201781.

(31) Read, E. S.; Thompson, K. L.; Armes, S. P. Synthesis of Well-Defined Primary Amine-Based Homopolymers and Block Copolymers and Their Michael Addition Reactions with Acrylates and Acrylamides. *Polym. Chem.* **2010**, *1* (2), 221. https://doi.org/10.1039/b9py00320g.

(32) Ahmed, M.; Narain, R. Progress of RAFT Based Polymers in Gene Delivery. *Prog. Polym. Sci.* **2013**, *38* (5), 767–790. https://doi.org/10.1016/j.progpolymsci.2012.09.008.

(33) Su, Z.; Jiang, X. Multi-Stimuli Responsive Amine-Containing Polyethers: Novel Building Blocks for Smart Assemblies. *Polymer* **2016**, *93*, 221–239. https://doi.org/10.1016/j.polymer.2016.04.034.

(34) Hu, J. Stimuli-Responsive Tertiary Amine Methacrylate-Based Block Copolymers: Synthesis, Supramolecular Self-Assembly and Functional Applications. 107.

(35) Gao, W.; Chan, J. M.; Farokhzad, O. C. PH-Responsive Nanoparticles for Drug Delivery. *Mol. Pharm.* **2010**, *7* (6), 1913–1920. https://doi.org/10.1021/mp100253e.

(36) Zhu, C.; Jung, S.; Si, G.; Cheng, R.; Meng, F.; Zhu, X.; Park, T. G.; Zhong, Z. Cationic Methacrylate Copolymers Containing Primary and Tertiary Amino Side Groups: Controlled Synthesis via RAFT Polymerization, DNA Condensation, and in Vitro Gene Transfection. *J. Polym. Sci. Part Polym. Chem.* **2010**, *48* (13), 2869–2877. https://doi.org/10.1002/pola.24064.

(37) York, A. W.; Zhang, Y.; Holley, A. C.; Guo, Y.; Huang, F.; McCormick, C. L. Facile Synthesis of Multivalent Folate-Block Copolymer Conjugates via Aqueous RAFT Polymerization: Targeted Delivery of SiRNA and Subsequent Gene Suppression †. *Biomacromolecules* **2009**, *10* (4), 936–943. https://doi.org/10.1021/bm8014768.

(38) York, A. W.; Huang, F.; McCormick, C. L. Rational Design of Targeted Cancer Therapeutics through the Multiconjugation of Folate and Cleavable SiRNA to RAFT-Synthesized (HPMA- *s* -APMA) Copolymers †. *Biomacromolecules* **2010**, *11* (2), 505–514. https://doi.org/10.1021/bm901249n.

(39) Ahmed, M.; Bhuchar, N.; Ishihara, K.; Narain, R. Well-Controlled Cationic Water-Soluble Phospholipid Polymer−DNA Nanocomplexes for Gene Delivery. *Bioconjug. Chem.* **2011**, *22* (6), 1228–1238. https://doi.org/10.1021/bc2001159.

(40) Truong, N. P.; Jia, Z.; Burgess, M.; Payne, L.; McMillan, N. A. J.; Monteiro, M. J. Self-Catalyzed Degradable Cationic Polymer for Release of DNA. *Biomacromolecules* **2011**, *12* (10), 3540–3548. https://doi.org/10.1021/bm2007423.

(41) Xu, X.; Smith, A. E.; Kirkland, S. E.; McCormick, C. L. Aqueous RAFT Synthesis of PH-Responsive Triblock Copolymer MPEO−PAPMA−PDPAEMA and Formation of Shell Cross-Linked Micelles †. *Macromolecules* **2008**, *41* (22), 8429–8435. https://doi.org/10.1021/ma801725w.

(42) Judzewitsch, P. R.; Corrigan, N.; Trujillo, F.; Xu, J.; Moad, G.; Hawker, C. J.; Wong, E. H. H.; Boyer, C. High-Throughput Process for the Discovery of Antimicrobial Polymers and Their Upscaled Production via Flow Polymerization. *Macromolecules* **2020**, *53* (2), 631–639. https://doi.org/10.1021/acs.macromol.9b02207.

(43) Judzewitsch, P. R.; Nguyen, T.-K.; Shanmugam, S.; Wong, E. H. H.; Boyer, C. Towards Sequence-Controlled Antimicrobial Polymers: Effect of Polymer Block Order on Antimicrobial Activity. *Angew. Chem. Int. Ed.* **2018**, *57* (17), 4559–4564. https://doi.org/10.1002/anie.201713036.

(44) Barbon, S. M.; Truong, N. P.; Elliott, A. G.; Cooper, M. A.; Davis, T. P.; Whittaker, M. R.; Hawker, C. J.; Anastasaki, A. Elucidating the Effect of Sequence and Degree of Polymerization on Antimicrobial Properties for Block Copolymers. *Polym. Chem.* **2020**, *11* (1), 84–90. https://doi.org/10.1039/C9PY01435G.

(45) Genest, A.; Portinha, D.; Fleury, E.; Ganachaud, F. The Aza-Michael Reaction as an Alternative Strategy to Generate Advanced Silicon-Based (Macro)Molecules and Materials. *Prog. Polym. Sci.* **2017**, *72*, 61–110. https://doi.org/10.1016/j.progpolymsci.2017.02.002.

(46) Wu; Liu, Y.; He; Chung; Goh. Effects of Chemistries of Trifunctional Amines on Mechanisms of Michael Addition Polymerizations with Diacrylates. *Macromolecules* **2004**, *37* (18), 6763–6770. https://doi.org/10.1021/ma0493832.

(47) Mendonça, P. V.; Serra, A. C.; Popov, A. V.; Guliashvili, T.; Coelho, J. F. J. Efficient RAFT Polymerization of N-(3-Aminopropyl)Methacrylamide Hydrochloride Using Unprotected "Clickable" Chain Transfer Agents. *React. Funct. Polym.* **2014**, *81*, 1–7. https://doi.org/10.1016/j.reactfunctpolym.2014.04.001.

(48) Deng, Z.; Bouchékif, H.; Babooram, K.; Housni, A.; Choytun, N.; Narain, R. Facile Synthesis of Controlled-Structure Primary Amine-Based Methacrylamide Polymers via the Reversible Addition-Fragmentation Chain Transfer Process. *J. Polym. Sci. Part Polym. Chem.* **2008**, *46* (15), 4984–4996. https://doi.org/10.1002/pola.22826.

(49) Dubey, A.; Burke, N. A. D.; Stöver, H. D. H. Preparation and Characterization of Narrow Compositional Distribution Polyampholytes as Potential Biomaterials: Copolymers of *N* -(3-Aminopropyl)Methacrylamide Hydrochloride (APM) and Methacrylic Acid (MAA). *J. Polym. Sci. Part Polym. Chem.* **2015**, *53* (2), 353–365. https://doi.org/10.1002/pola.27377.

(50) Xu, X.; Flores, J. D.; McCormick, C. L. Reversible Imine Shell Cross-Linked Micelles from Aqueous RAFT-Synthesized Thermoresponsive Triblock Copolymers as Potential Nanocarriers for "PH-Triggered" Drug Release. *Macromolecules* **2011**, *44* (6), 1327–1334. https://doi.org/10.1021/ma102804h.

(51) Kiyose, K.; Kojima, H.; Urano, Y.; Nagano, T. Development of a Ratiometric Fluorescent Zinc Ion Probe in Near-Infrared Region, Based on Tricarbocyanine Chromophore. 2.

(52) Albarghouthi, M. N.; Buchholz, B. A.; Huiberts, P. J.; Stein, T. M.; Barron, A.E.; Poly-N-hydroxyethylacrylamide (polyDuramide): a novel, hydrophilic, self-coating polymer matrix for DNA sequencing by capillary electrophoresis. *Electrophoresis*. **2002**, 10, 1429-40. https://doi-org./10.1002/1522-2683(200205)23:10<1429::AID-ELPS1429>3.0.CO;2-A.

(53) Narumi, A.; Chen, Y.; Sone, M.; Fuchise, K.; Sakai, R.; Satoh, T.; Duan, Q.; Kawaguchi, S.; Kakuchi, T. Poly(*N* -Hydroxyethylacrylamide) Prepared by Atom Transfer Radical

Polymerization as a Nonionic, Water-Soluble, and Hydrolysis-Resistant Polymer and/or Segment of Block Copolymer with a Well-Defined Molecular Weight. *Macromol. Chem. Phys.* **2009**, *210* (5), 349–358. https://doi.org/10.1002/macp.200800509.

(54) Albarghouthi, M. N.; Stein, T. M.; Barron, A. E. Poly-N-Hydroxyethylacrylamide as a Novel, Adsorbed Coating for Protein Separation by Capillary Electrophoresis. *Electrophoresis* **2003**, *24* (78), 1166–1175. https://doi.org/10.1002/elps.200390150.

(55) Zhao, C.; Li, X.; Li, L.; Cheng, G.; Gong, X.; Zheng, J. Dual Functionality of Antimicrobial and Antifouling of Poly(*N* -Hydroxyethylacrylamide)/Salicylate Hydrogels. *Langmuir* **2013**, *29* (5), 1517–1524. https://doi.org/10.1021/la304511s.

(56) Zhao, C.; Patel, K.; Aichinger, L. M.; Liu, Z.; Hu, R.; Chen, H.; Li, X.; Li, L.; Zhang, G.; Chang, Y.; Zheng, J. Antifouling and Biodegradable Poly(N-Hydroxyethyl Acrylamide) (PolyHEAA)-Based Nanogels. *RSC Adv.* **2013**, *3* (43), 19991. https://doi.org/10.1039/c3ra42323a.

(57) Zhao, C.; Chen, Q.; Patel, K.; Li, L.; Li, X.; Wang, Q.; Zhang, G.; Zheng, J. Synthesis and Characterization of PH-Sensitive Poly(N-2-Hydroxyethyl Acrylamide)–Acrylic Acid (Poly(HEAA/AA)) Nanogels with Antifouling Protection for Controlled Release. **2012**, 11.

(58) Zhao, C.; Zheng, J. Synthesis and Characterization of Poly(*N* -Hydroxyethylacrylamide) for Long-Term Antifouling Ability. *Biomacromolecules* **2011**, *12* (11), 4071–4079. https://doi.org/10.1021/bm2011455.

(59) Chen, J.; Liu, M.; Liu, H.; Ma, L. Synthesis, Swelling and Drug Release Behavior of Poly(N,N-Diethylacrylamide-Co-N-Hydroxymethyl Acrylamide) Hydrogel. *Mater. Sci. Eng. C* **2009**, *29* (7), 2116–2123. https://doi.org/10.1016/j.msec.2009.04.008.

(60) Horn, H. W.; Jones, G. O.; Wei, D. S.; Fukushima, K.; Lecuyer, J. M.; Coady, D. J.; Hedrick, J. L.; Rice, J. E. Mechanisms of Organocatalytic Amidation and Trans-Esterification of Aromatic Esters As a Model for the Depolymerization of Poly(Ethylene) Terephthalate. *J. Phys. Chem. A* **2012**, *116* (51), 12389–12398. https://doi.org/10.1021/jp304212y.

(61) Yuan, L.; Wang, Z.; Trenor, N. M.; Tang, C. Amidation of Triglycerides by Amino Alcohols and Their Impact on Plant Oil-Derived Polymers. *Polym. Chem.* **2016**, *7* (16), 2790–2798. https://doi.org/10.1039/C6PY00048G.

(62) Hoyle, C. E.; Bowman, C. N. Thiol–Ene Click Chemistry. *Angew. Chem. Int. Ed.* **2010**, *49* (9), 1540–1573. https://doi.org/10.1002/anie.200903924.

(63) Kalaoglu-Altan, O. I.; Verbraeken, B.; Lava, K.; Gevrek, T. N.; Sanyal, R.; Dargaville, T.; De Clerck, K.; Hoogenboom, R.; Sanyal, A. Multireactive Poly(2-Oxazoline) Nanofibers through Electrospinning with Crosslinking on the Fly. *ACS Macro Lett.* **2016**, *5* (6), 676–681. https://doi.org/10.1021/acsmacrolett.6b00188.