Poly(*N*-allyl acrylamide) as a reactive platform towards functional hydrogels.

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ABSTRACT: The synthesis of poly(*N*-allyl acrylamide) (PNAllAm) as a platform for the preparation of functional hydrogels is described. The PNAllAm was synthesized via organocatalyzed amidation of poly(methyl acrylate) (PMA) with allylamine and characterized by ^{1}H NMR spectroscopy, size exclusion chromatography (SEC) and turbidimetry, which allowed an estimation of the lower critical solution temperature (LCST) of ~26 °C in water. The PNAllAm was then used to make functional hydrogels via photo-initiated thiol-ene chemistry, where dithiothreitol (DTT) was used to crosslink the polymer chains. In addition, mercaptoethanol (ME) was added as a functional thiol to modulate the hydrogel properties. A decrease of the volume-phase transition temperature (VPTT) of the resulting hydrogels was observed with increasing ME content. Altogether this work introduces a straightforward way for the preparation of PNAllAm from PMA and demonstrates its value as reactive polymer platform for the generation of functional hydrogels.

Hydrogels are hydrophilic polymeric 3D-networks resembling soft biological tissue and are capable of absorbing large amounts of water. They provide a versatile platform for the development of functional materials with a wide range of applications including tissue engineering,[1,2] drug delivery,[3,4] energy storage[5,6] and self-healing materials.[7,8]

Based on the type of crosslinks, two major classes of hydrogels can be identified, *i.e.* physically and covalently crosslinked hydrogels. In physical hydrogels, the polymer chains are linked together by non-covalent interactions like ionic interactions, hydrogen bonding or hydrophobic interactions, and they generally result in materials with dynamic properties.[9–11] In contrast, covalent hydrogels are covalently crosslinked polymer networks that are typically employed in applications where mechanical stability is of interest.[12] Additionally, both physical and chemical crosslinking can be combined to create hybrid materials with stimuli-responsive properties derived from the non-covalent bonds while the mechanical strength is provided by the covalent crosslinks.[13]

When choosing a polymer platform for the preparation of hydrogels, the hydrophilicity is an important property to allow the uptake of water. A wide range of hydrophilic polymers are available including biopolymers, like alginate,[14–16] chitosan[17–19] and gelatin,[20–22] as well as synthetic polymers, such as poly(ethylene glycol),[23–25] poly(hydroxyethyl methacrylate),[26–28] poly(vinyl alcohol),[29–31] poly(2-oxazoline)s,[32–35] polyacrylamides,[36–38] and recently poly(2-isopropenyl-2-oxazoline)s.[39–42]

N-substituted polyacrylamides are an interesting polymer scaffold where variation of the side-chains results in highly tunable properties, *e.g.* self-healing,[43,44] pH-,[45,46] light-[47,48] and thermoresponsive behavior.[49–52] These functional polyacrylamides are commonly synthesized by direct polymerization of a functional acrylamide monomer. Although monomer synthesis and subsequent polymerization are generally employed, the polymerization mechanism often poses limitations towards reactive monomers with interfering functional groups. In this case, post-polymerization modification (PPM) can provide a solution by introducing the desired functionalities to a readily available precursor polymer.[53–55] For radical polymerization, additional unsaturated functionalities in the monomer can interfere with the polymerization by causing side reactions, as exemplified by the polymerization of *N*-allyl acrylamide (NAllAm) that results in the formation of polymer networks.[56–62] Although Schubert *et al.* reported the synthesis of copolymers consisting of *N*-isopropylacrylamide (NiPAm) and NAllAm *via* atom transfer radical polymerization under mild conditions, the NAllAm monomer feed was limited to 30% to avoid crosslinking, indicating the occurrence of radical coupling on the side-chain allyl groups.[63]

With its large abundance of allyl groups, PNAllAm is a versatile platform to design functional polyacrylamides by variation of the added thiols that can be coupled to the polymers with thiol-ene reactions.[64–66] In addition, multifunc-

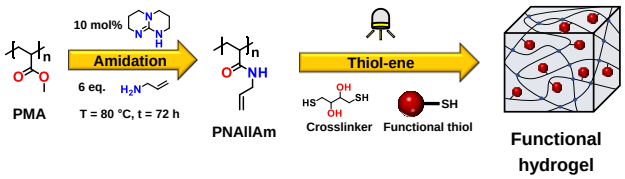
tional thiols enable crosslinking, and therefore the synthesis of functional hydrogels, which has not been previously reported for this polymer platform. Subsequently, the remaining alkenes in the hydrogel can be further functionalized with thiols, which has been reported for hydrogels with latent allyl groups that were introduced in the form of allyl methacrylate[67] or norbornene.[68,69]

The first reported synthesis of PNAllAm dates back to 1972 where Ferruti *et al.* synthesized the polymer from poly(*N*-hydroxysuccinimide acrylate) (PNHSA) by reacting the activated ester side-chains with allylamine, which was later reproduced by Lou *et al.*[59,61] Activated esters have been a valuable tool in the development of functional poly(meth)acrylates and poly(meth)acrylamides, with *N*-hydroxysuccinimide (NHS) and pentafluorophenol (PFP-OH) esters as the most popular examples.[70] Although activated esters are successfully applied in multiple applications, direct modification of unactivated poly(meth)acrylates remains relatively uncharted territory and offers a couple of advantages over the activated ester approach. Firstly, the catalytic conversion of unactivated polymeric esters enables the synthetic upcycling of commodity polymers such as poly(methyl acrylate) (PMA), poly(ethyl acrylate), poly(*n*-butyl acrylate) and poly(2-ethylhexyl acrylate), and holds a large potential towards upcycling strategies of plastic waste into chemicals, fuels and materials.[71] Secondly, the catalytic pathway offers a superior atom efficiency over the activated ester approach, which involves relatively large leaving groups. Finally, the synthesis of conventional unactivated poly(alkyl acrylate)s and subsequent catalytic modification is more cost-effective than the synthesis and conversion of the more expensive activated ester alternatives.

Recently, several research groups started exploring the catalytic upcycling of poly(meth)acrylates *via* transesterification and amidation.[62,72–76] Our group developed a direct amidation and transesterification protocol for the modification of polyacrylates by the application of catalytic bases.[62,76,77] Here, triazabicyclodecene (TBD) enables transesterification and amidation of the polymeric esters with alcohols and amines respectively, yielding a wide variety of functional polyacrylates and polyacrylamides using PMA as unactivated base polymer. In addition, this catalytic approach was also applied to poly(2-alkyl-2-oxazoline)s comprising 2-methoxycarboxypropyl-2-oxazoline.[35]

In this work, the synthesis of PNAllAm is reported based on the post-polymerization modification of PMA through the TBD catalyzed amidation (**Scheme 1**).[62] Subsequently, PNAllAm was employed to prepare functional hydrogels using thiol-ene chemistry with dithiotreitol (DTT) as a crosslinker, which was also performed in presence of mercaptoethanol (ME) to modulate the hydrogel properties. A two-step sequential approach was also considered (i.e. first crosslinking the PNAllAm with DTT followed by functionalization of the obtained hydrogel with a functional thiol), but the poor mechanical properties of the hydrogel obtained in the first step did not allow physical manipulation without damaging the gels. Therefore, only the one-pot approach is reported (i.e. simultaneous addition of crosslinker and functional thiol), which is also more simple as both the crosslinking and functionalization can be combined in one step, which presumably also leads to more homogeneous functionalization.

Scheme 1. Synthesis of poly(*N*-allyl acrylamide) (PNAllAm) with subsequent synthesis of the functional hydrogels. The displayed equivalents are relative to the molar amount of methyl esters of PMA.



The synthesis of PNAllAm was adapted from Van Guyse *et al.*[62] In short, PMA, TBD and allylamine were heated to 80 °C for 3 days, after which the polymers were precipitated in diethyl ether. The TBD was efficiently removed by addition of an acidic exchange resin (Dowex) to an aqueous solution of the polymer, yielding the purified PNAllAm as confirmed by ^{1}H NMR spectroscopy (**Figure 1**). Full conversion of the methyl ester groups to *N*-allyl amides was confirmed by the absence of the methyl ester peak ^{1}H NMR spectrum as well as the integrals of the allyl side-chain signals and the polymer backbone.

The SEC analysis of PNAllAm and the starting PMA is depicted in **Figure S1**. The shift towards lower retention times after post modification confirms the chemical transformation of the polymeric chain, indicating larger hydrodynamic volume of the PNAllAm compared to the starting PMA. The presence of a minor high molecular weight fraction after Dowex purification compared to the crude reaction mixture might be attributed to minor coupling of allyl groups during the aqueous work-up of the crude polymers, more specifically the freeze-drying step after the Dowex treatment.[78,79]

It is worth mentioning that during purification, the cloud point temperature (T_{cp}) (defined by the temperature where 50% transmittance is reached) of PNAllAm dropped significantly, as is displayed in **Figure S2**. This "salting-in" effect of PNAllAm in the presence of TBD may be attributed to direct interactions of TBD with the polymer, presumably by hydrogen bonding of the guanidine moiety with the polymeric amide groups.[80,81] In addition, with each heating-cooling cycle the transmittance decreased, indicating incomplete solubilization of the polymer during the cooling cycle for the polymer that still contained TBD.

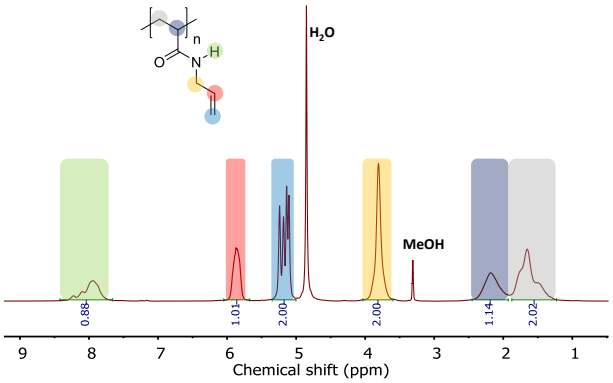


Figure 1. ^{1}H NMR spectrum of the purified PNAllAm recorded in methanol-d_4.

After the polymer was purified from TBD, the turbidimetry measurements in water were repeated to determine the lower critical solution temperature (LCST) of PNAllAm, revealing reversible phase transitions. **Figure S3**a shows the third heating and cooling curves of an aqueous PNAllAm solution for a range of concentrations revealing a gradual decrease in T_{cp} when increasing the concentration from 5 to 40 mg/mL. When further increasing the polymer concentration to 60 to 100 mg/mL, the trend is reversed and the T_{cp} increases again. **Figure S3**b shows the average T_{cp} and clearance point temperature (T_{cl}) from three heating and cooling cycles, respectively, which evolve to a minimum around 50 mg/mL, indicating similar LCST behavior as other poly(*N*-alkyl acrylamide)s.[49]

Both the T_{cp} and T_{cl} are in relatively good agreement for polymer concentrations of 5 to 40 mg/mL and with an acceptable standard deviation. However, from 60 mg/mL the standard deviations on the T_{cp} become significantly higher resulting in less defined T_{cp}s, which might be attributed to the presence of hydrogen bonded polymer clusters at these higher concentrations that required a lower cooling temperature, or more time to completely redissolve. Nonetheless, the data allow for a reliable estimation of the lower critical solution temperature (LCST, defined as the minimum of the curve through the cloud points) for PNAllAm in water around 26 °C at a polymer concentration of approximately 50 mg/mL, which is close to the LCST of poly(*N*-(*n*-propyl) acrylamide) (PNnPAm, LCST ≈ 24 °C)[82,83] and about 6 °C below poly(*N*-isopropyl acrylamide) (PNiPAm, LCST ≈ 32 °C).[84,85] By applying molecular dynamics calculations to investigate NnPAm, NiPAm and *N*-isopropyl methacrylate (NiPMAm) monomers and short oligomers, Pang and coworkers found that the difference in LCST between PNnPAm and PNiPAm was mainly related to the monomer side-chains.[86] Considering these findings, the allyl groups of PNAllAm appear to be more closely related to the *n*-propyl groups and probably behave in a similar manner, although the sp^2 hybridization of the alkene group introduces a larger electron density and rigidity to the PNAllAm side-chains, which results in a slightly higher LCST for PNAllAm compared to PNnPAm.

After successful synthesis and purification of PNAllAm, and with its thermoresponsive behavior in mind, we aimed to obtain functional hydrogels with tailored properties by using DTT as a crosslinker and mercaptoethanol (ME) as a functional thiol in a one-pot thiol-ene reaction. ME was specifically chosen to increase the hydrophilicity of the polymers and to tune the swelling properties of the final hydrogels. Photorheology was performed to determine the gel point (i.e. the time point where the storage modulus (G') starts to increase) for the synthesis of the hydrogels for mechanical characterization. To avoid LCST related solubility problems, the crosslinking of PNAllAm was performed in ethanol, which after solvent exchange will yield the final hydrogels. All experiments were performed at a polymer concentration of 10 wt%, a photoinitiator amount of 5 mol% relative to the total amount of thiols and a DTT content of 5 mol% relative to the amount of allyl groups on the polymer, while the amount of ME was varied from 0 to 40 mol% relative to the total amount of allyl groups. **Figure 2** shows that the gel points are similar for all samples with ME, while the gel point of the pure PNAllAm hydrogel (ME0) occurs at a later time. The faster gel points of the ME-containing gels could possibly be explained by the suppression of intramolecular coupling of DTT with the formation of loops rather than effective crosslinks by addition of the ME units that decrease the number of available allyl-groups. This hypothesis is supported by the observation of a lower gel yield for ME0 compared to the hydrogels prepared with ME (**Figure S4**). In addition, the plateau values of the G' increased up to 20 kPa with increasing ME content, which is possibly caused by the increasing amount of hydrogen bonds between the introduced OH groups from ME and the polymeric amides. Additionally, the photorheology experiment for 10 mol% ME was performed in triplicate, resulting in the almost complete overlap of the G' curves, indicating excellent reproducibility.

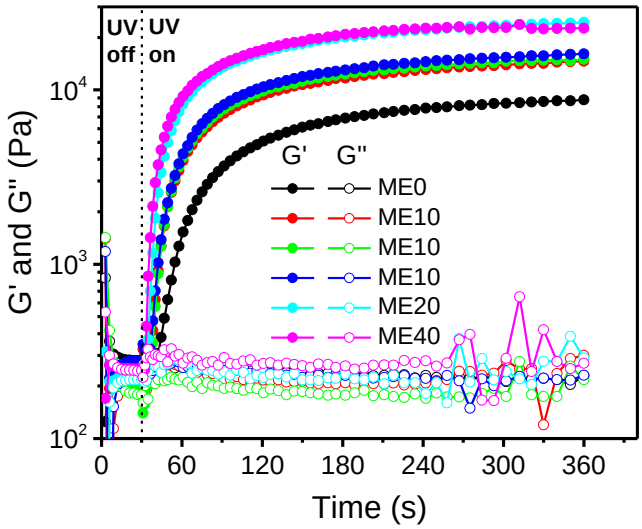


Figure 2. Photorheology of PNAllAm (10 wt%) with DTT (5 mol% to allyl groups) and mercaptoethanol (ME, 10 to 40 mol% to allyl groups) in ethanol, the UV lamp was turned on after 30 seconds. The measurement with 10 mol% ME was carried out in triplicate.

The photorheology data were used as a starting point to synthesize hydrogels on a larger scale, of which the reaction conditions are summarized in **Table 1**. Across the four different gels, the ME content was varied from 0% to 60% while keeping the other parameters constant. It should be noted that the UV intensity for the photorheology experiments was higher than for the hydrogel synthesis for mechanical characterization (7500 vs. 10 mW/cm², respectively), resulting in longer irradiation times to reach the plateau modulus in the large scale experiments. Therefore, the curing time for preparation of the macroscopic hydrogels was extended to 1 hour.

Table 1. Sample compositions for the synthesis of PNAllAm gels in ethanol. The UV intensity was 10 mW/cm².

Sample	PNAllAm (wt% in EtOH)	DTT (mol% to allyl groups)	ME (mol% to allyl groups)	Initiator (mol% to thiols)
ME0	10	5	0	5
ME20	10	5	20	5
ME40	10	5	40	5
ME60	10	5	60	5

After irradiation of the precursor solution in the mold, the gels were swollen in excess distilled water to extract residuals, such as any unreacted ME, and to replace ethanol with water. Interestingly, the resulting water-swollen hydrogels with ME became semi-transparent to opaque with increasing ME content as visualized in **Figure 3**, which indicates that the introduced hydroxyl groups reduced the overall hydrophilicity of the hydrogels, which was not anticipated. This observation might be attributed to intramolecular hydrogen bonding between the hydroxyl-groups and the amide groups in the hydrogels that compete with polymer hydration. Similar observations have been reported for sugar-modified poly(2-oxazoline)s in which higher sugar side-chain content led to a decrease in T_{cp}.[87] This trend was confirmed by a visual estimation of the volume phase transition temperature (VPTT), which identifies the temperature at which the hydrogel starts to become opaque. For ME0, the T_{cp} was 26 °C, and decreased to 11 °C, 7 °C and 1 °C for ME20, ME40 and ME60, respectively. The samples were fully transparent below the indicated temperatures.

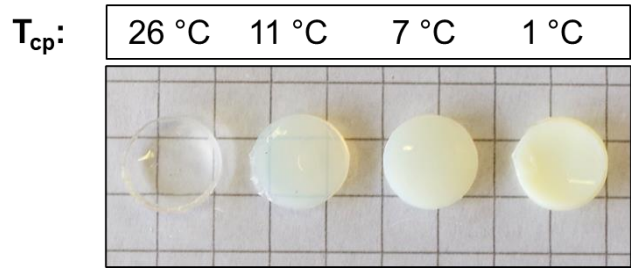


Figure 3. Pictures of the hydrogels after swelling in water taken at room temperature, with their respective cloud point temperatures (T_{cp}). From left to right: ME0 ME20, ME40 and ME60.

Furthermore, the swelling kinetics were evaluated at room temperature (21 °C) according to Equation 1 by weighing the hydrogels after drying and subsequent swelling in water (**Figure 4**). A significant difference in swelling kinetics was observed between ME0 and the other samples, which can be attributed to ME0 being the only sample below its VPTT under the swelling conditions. Hydrogel ME0 swelled to a higher extent and at a faster rate. While sample ME0 reached an equilibrium after about 3 hours, the samples that were swollen above their VPTT did not reach an equilibrium within the measurement time of 8 hours. When sample ME0 was measured at a higher temperature (i.e. 30 °C, above VPTT), the plateau was reached at about swollen weight twice lower than at 21 °C (**Figure S5**).

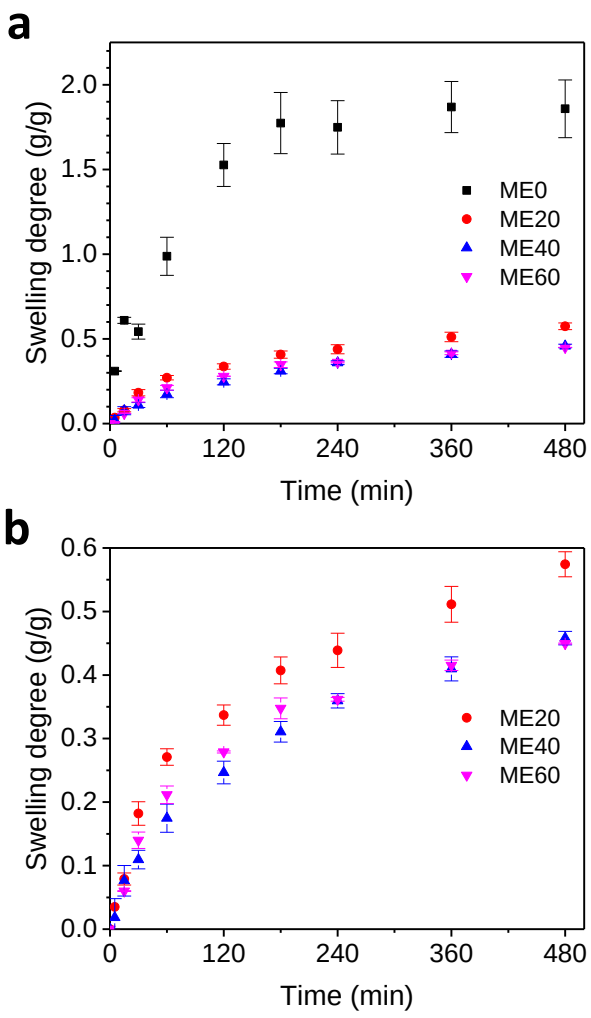


Figure 4. The swelling kinetics of the PNAllAm hydrogels. a) All samples; b) zoom of samples ME20, ME40 and ME60.

To determine the equilibrium swelling degree (ESD), the hydrogels were weighed after reaching equilibrium swollen state, and weighed again after drying in the oven at 70 °C. The calculated ESD of the hydrogels is depicted in **Figure 5**. The ESD of ME0 was significantly higher than the modified hydrogels (i.e. ME20, ME40 and ME60), which is explained by the fact that ME0 was the only sample that was swollen below its VPTT, while the other hydrogels were rather in their collapsed state and therefore less capable of absorbing water into the network. However, the re-swelling of the dried hydrogels was significantly reduced and might indicate further crosslinking of the hydrogel networks during drying at elevated temperatures, or any other structural changes, such as the formation of strong hydrogen bonds in the dry state, which can limit the access of water during subsequent swelling. The hydrogels should therefore be stored in their swollen state before use.

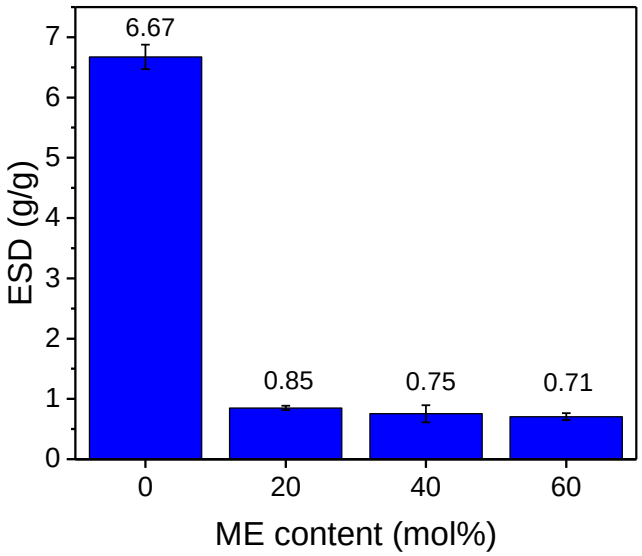


Figure 5. The equilibrium swelling degree (ESD) of PNAllAm-based hydrogels as a function of ME content.

From the VPTT and swelling kinetics, it can be concluded that an increase in ME content leads to a lower hydrophilicity of the polymer network, which was not anticipated as stated above.

In summary, we demonstrated the synthesis of PNAllAm *via* a TBD-catalyzed amidation from PMA followed by acidic work-up to obtain the pure polymer. Subsequently, the isolated PNAllAm was successfully used for the synthesis of hydrogels *via* thiol-ene coupling of DTT as a crosslinker and ME as a functional thiol to obtain functional hydrogels in a one-pot system. Due to the low LCST of PNAllAm (approx. 26 °C), the crosslinking was performed in ethanol, after which the resulting gels were swollen in excess water to obtain the hydrogels. However, increased ME incorporation resulted in a decrease of the VPTT and swelling properties of the hydrogels, presumably originating from a decreased hydration due to intramolecular hydrogen bonding. To address this issue, the hydrophilicity of the functional hydrogels can be increased by introduction of charged groups, as previously demonstrated for soluble PNAllAm.[61] Given the wide variety of commercially available thiols and dithiols, a broad range of functional hydrogels based on PNAllAm could be synthesized by simply changing the reactants and their relative ratios.

ASSOCIATED CONTENT

Materials, instrumentation, methods and turbidimetry of PNAllAm before and after removal of TBD. "This material is available free of charge via the Internet at http://pubs.acs.org."

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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.

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