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# Communications to the Editor

## Controlled Radical Polymerization of Active Ester Monomers: Precursor Polymers for Highly Functionalized Materials

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Recently, atom transfer radical polymerization (ATRP) has gained a lot of attention as a versatile polymerization technique.[1−3] It is one of the most successful methods to polymerize a variety of monomers under controlled conditions. The control in this polymerization process results from the fast exchange reaction between propagating radicals and dormant species. Thereby the concentration of propagating radicals is kept sufficiently low, suppressing termination and transfer reactions. The resulting polymers are well-defined with a good control over molecular weight, and low polydispersities (PDI < 1.3) can be obtained. Successful preparation of various functional polymers and block copolymers, as described in the literature, proved the potential of ATRP.

Active esters proved exceedingly useful in synthetic peptide chemistry.[4] Aminolysis of active esters proceeds by nucleophilic displacement at the carbonyl group, i.e., by acyl−oxygen fission. Various active ester polymers have been described by Ringsdorf et al.,[5,6] but most of them did not find broad scientific application. Mainly active esters based on *N*-hydroxysuccinimide (NHS) are in use in polymer science in the form of NHS−(meth)-acrylates.[7−9] Precursor polymers based on NHS−(meth)-acrylates offer the possibility to obtain multifunctional polyacrylamides simply by a polymer analogous reaction.[8] However, poly(*N*-hydroxysuccinimide (meth)acrylates) (pNHS) suffer from the fact of their poor solubility; i.e., polymer analogous reactions can only be performed in DMF or DMSO solution.[10] Hence, there is still a great interest in novel active ester polymers.

Nevertheless, NHS−methacrylates have been polymerized under controlled radical conditions.[11,12] ATRP showed good results regarding the control of molecular weight and polydispersities. However, the initiator efficiency in these systems was typically below 50%.[11] Attempts to polymerize NHS−methacrylate by RAFT have not been satisfactory.[12] In comparison, 2-vinyl-4,4-dimethyl-5-oxazolone had been polymerized by RAFT with control of molecular weight and polydispersities around 1.1.[12]

To the best of our knowledge, other active ester monomers have not been investigated by any controlled radical polymerization method. To develop novel polymer structures with their application in biopolymer science, we examined within this study the controlled radical polymerization by ATRP of two different active ester acrylates: 2,4,5-trichlorophenol acrylate (**1**)[13] and endo-*N*-hydroxy-5-norbornene-2,3-dicarboxyimide acrylate (**2**),[14] as shown in Scheme 1. All polymerizations were conducted under similar conditions. 2-Bromoisobutyric ethyl ester, CuBr, and 2,2′-biypyridine (bipy) initiated each monomer at 90 °C.[15] Monomer **2** was polymerized in DMSO solution, similar to the description of NHS−methacrylate by Müller et al.[11] Monomer **1** was polymerized in bulk, resulting in a better control than in DMSO. The polymers were isolated by precipitation into 2-propanol. While p(NHS) is only soluble in DMSO or DMF, the polymers **P1** and **P2** show a better solubility and can be dissolved in most common organic solvents, such as $CHCl_3$, THF, etc. In other words, **P1** and **P2** are already superior to p(NHS) considering any following polymer analogous reaction.

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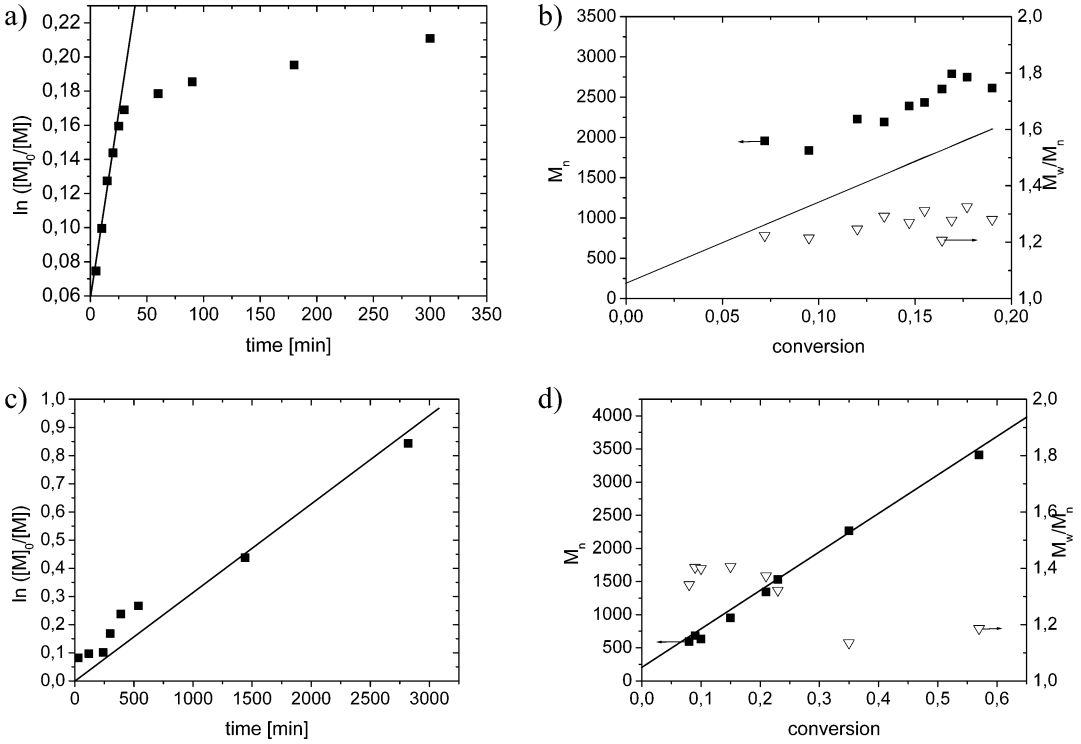
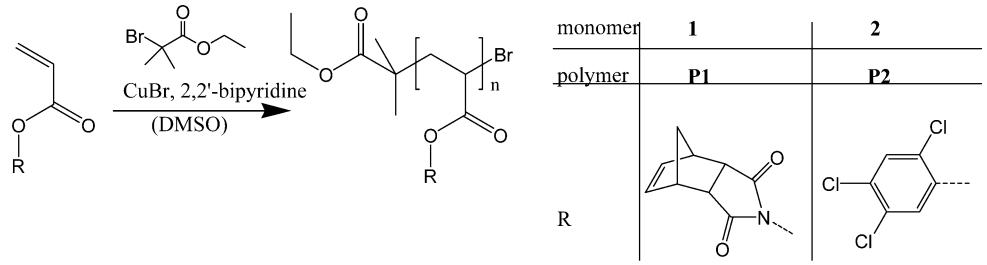



**Figure 1.** (a) Kinetics for the ATRP of **1** in bulk at 100 °C. (b) $M_n$ and $M_w/M_n$ vs conversation for ATRP of **1**. (c) Kinetics for the ATRP of **2** in DMSO at 90 °C. (d) $M_n$ and $M_w/M_n$ vs conversation for ATRP of **2**.

**Scheme 1**




The first-order plots of the respective polymerizations of **1** and **2** are shown in Figure 1. The polymerization of NHS−methacrylate proceeds rapidly; as reported, the polymerization is complete after 15 min.[11] Probably due to the reactive character of NHS−methacrylate a perfect control could not be achieved, as indicated by the low initiator efficiency, even though low polydispersities could be obtained.

In comparison, the polymerization of **1** proceeded slower, and we hoped with better control. Within the first 30 min the first-order plot was linear (Figure 1a). Afterward, a deviation from the linear variation of conversion with time in semilogarithmic coordinates occurred, indicating that the constant concentration of active species in the polymerization decreased. Then the kinetic of the polymerization seemed to show a linear behavior again. The evolution of the molecular weight (Figure 1b) seemed to follow a linear progress, and the initiator efficiency was between 50% and 70%. This can be seen by the straight line representing the theoretical molecular weight which was consistently smaller than the actual molecular weight. Even though the initiator efficiency was better than for the polymerization of NHS−methacrylates (12%−61%), it is not completely satisfying yet. Nevertheless, narrow molecular weight distributions ($M_w/M_n = 1.2-1.3$) of **P1** could be obtained.

Searching for less reactive monomers with even a better control during the polymerization, we investigated monomer **2**, which is a sterically hindered NHS−acrylate. Because of the bulkiness of the norbonene group, we expected a lower polymerization rate and therefore a better control. Figure 1c shows the first-order plot of **2**. A linear behavior could be observed for up to 40 h. In the same time the evolution of molecular weight increased linearly with conversion, while the polydispersity leveled off at 1.1−1.2. As the straight line for the theoretical molecular weight showed, the initiator efficiency was satisfactory. Quantitative efficiencies could be realized within the error range. Comparing the polymerizations of **1** and **2** under ATRP conditions, only **2** showed a satisfactory controlled radical polymerization. Nevertheless, **1** could be polymerized under ATRP conditions, even though the control is not accurate.

As the conversion and the molecular weight of the polymer were kept low despite the repetitive polymerization using bipy as a ligand, other ligands, such as 1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane (**4N**) and 1,1,4,7,7-pentamethyldiethyleneamine (**3N**), which are known to increase the rate of the polymerization, were investigated. The polymerizations of **1** and **2** using the ligands **3N** or **4N** were performed under the same conditions as in the case of bipy.

**Table 1. Conditions and Results for the ATRP of Monomer 2 Varying the Initiator Ratio**[a]

| $[M]_0/[I]_0$ | time [h] | conv [%] | $M_n$[b] | PDI | $M_n$(theo)[c] |
|---|---|---|---|---|---|
| 150 | 19.5 | 13.0 | 4360 | 1.34 | 4547 |
| 100 | 18 | 14.0 | 3420 | 1.27 | 3264 |
| 50 | 18.5 | 21.7 | 2550 | 1.34 | 2530 |
| 28 | 24 | 35.0 | 2260 | 1.14 | 2285 |

[a] Reaction conditions: 90 °C, DMSO, [bipy]:[CuBr]:[I] = 2:1:1. [b] The molecular weights were calculated by end-group analysis by $^1$H NMR. [c] $[M]_0/[I]_0$ × conversion × 233.2 g/mol.

However, despite higher conversions of the polymerization with **3N** or **4N**, a narrow polydispersity was not achieved. For example, in the case of polymerization of monomer **1** with **3N** at room temperature, a bimodal GPC curve was obtained (PDI ∼ 2), while the conversion was very high (>95%). Therefore, **3N** and **4N** ligands seemed not to be adequate for the controlled polymerization of monomers **1** and **2**.

Table 1 summarizes the monomer to initiator dependence for constant reaction conditions of the polymerization of **2** (∼20 h, 90 °C). As expected with increasing monomer concentration higher molecular weights could be obtained. The polymerization of **2** occurred slower compared to NHS−methacrylate or monomer **1**. After 20 h of polymerization time conversions up to 20% were obtained, except for the very low monomer-to-initiator ratio of 28. Thus, experiments to increase the conversion were made. As reported for the polymerization of NHS−methacrylate, the concentration of DMSO influenced the polymerization. Varying the solvent-to-monomer ratio, similar effects were found. The conversion of polymerizations performed under constant reaction conditions (90 °C, 19 h) varied dramatically with the solvent-to-monomer ratio. At least a monomer concentration higher than 25 wt % was needed for the polymerization of monomer **2**. There appears to be a threshold concentration (25−50 wt %) for successful polymerization. At concentrations higher than 70 wt % the conversion decreased again. Thus, it is quite certain that the polymerization rate increased as the concentration increased, however only up to a certain value. Evidently, increasing the temperature increased the polymerization rate likewise. Even though the overall conversions are not very high, reasonable molecular weights can be obtained. Further studies to increase the conversion are in progress.

The outstanding advantage of the active ester polymers **P1** and especially **P2** is the possibility to transform them to polyacrylamides simply by a polymer analogous reaction.[17] As the polymers **P1** and **P2** are soluble in organic solvents, e.g., chloroform, the preparation of water-soluble functionalized polyacrylamides may be carried out under phase-transfer conditions. The precursor polymer **P2** was dissolved in the chloroform phase, and an amine (as an example ammonia) was dissolved in the upper water phase. Both phases were clear before mixing. After the phases were stirred the mixture turned turbid and then within 5 min milky. After an additional 10 min the solution turned clear again. During the vigorous stirring of the phases, the precursor polymer **P2** partly reacted with ammonia forming an intermediated amphiphilic polymer that emulsified the solution. The amphiphilic character could be assigned to the existence of units of acrylamide and **2** in the polymer. As the reaction proceeded this intermediate amphiphilic polymer converted completely to polyacrylamide, which only dissolved in the upper water phase. This could be observed as the emulsion broke down forming the two clear phases. The released endo-*N*-hydroxy-5-norbornene-2,3-dicarboxyimide remained in the chloroform phase. Thus, the separation of the resulting polymer was very convenient, and the endo-*N*-hydroxy-5-norbornene-2,3-dicarboxyimide could be reused since it is the only compound in the chloroform phase, which offers an environment-friendly reaction cycle.

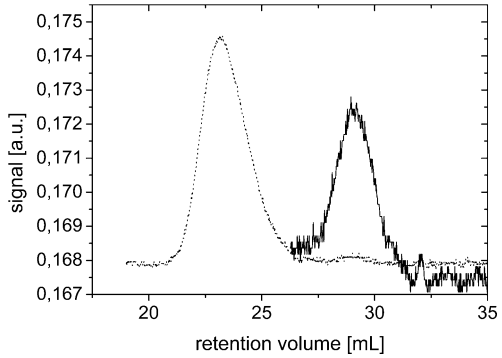



**Figure 2.** SEC traces of block copolymer **P2**-*b*-PMMA (dotted line) and macroinitiator **P2**-Br (solid line) obtained by ATRP.

Block copolymers of monomer **2** and MMA were prepared. Monomer **2** was first polymerized under the established optimum conditions. After precipitation and purification the homopolymer was used as a macroinitiator to initiate the polymerization of MMA in DMSO. After 2 h of polymerization the block copolymer was precipitated into 2-propanol.[16] Figure 2 plots the GPC curves of the homopolymer **P2** and the resulting block copolymer **P2**-*b*-PMMA (solid line and dotted line, respectively). **P2** had a molecular weight of $M_n = 3550$ with a polydispersity of 1.33. The block copolymer had a molecular weight of $M_n = 13\,950$ with a polydispersity of 1.7. Clearly, the polymerization conditions seemed not to be optimal and will be tuned in ongoing experiments. Nevertheless, the initiation of **P2** was quantitative, as no low molecular weight homopolymer **P2** could be detected after polymerization of MMA (dotted line in Figure 2). $^1$H NMR analysis showed signals for MMA and monomer **2** units, thus supporting the obtained block copolymer structure.[16] This may lead to a variety of novel functionalized block copolymers as the active ester group can be transformed to polyacrylamides by simple polymer analogous reactions. Reaction of the block copolymer **P2**-*b*-PMMA with ammonia in THF solution at room temperature led to the block copolymer PAAM-*b*-PMMA,[17] showing that the ester group of PMMA was not reacting through a competitive nucleophilic attack. Further studies to quantify the polymer analogous reactions are in progress and will be published elsewhere.

In summary, two reactive ester monomers **1** and **2** were polymerized by ATRP. Monomer **2** was polymerized with 100% initiator efficiency. Additionally, polymerization kinetics proved the controlled polymerization behavior. Further this method offered the possibility to prepare block copolymers. These resulting precursor polymers could successfully react with amines in a polymer analogous reaction under homogeneous or heterogeneous conditions. Thus, this strategy offers not only the possibility to prepare highly functionalized homopolymers but also highly functionalized block copolymers.

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**Supporting Information Available:** Experimental section. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Monomer **1** was synthesized by the reaction of 2,4,5-trichlorophenol with acryloyl chloride (1 equiv) in dried THF in the presence of triethylamine (1 equiv). The crude product was purified by recrystallization from ethanol. Yield: 67%; mp: 64.3 °C. $^1$H NMR (300 MHz, $CDCl_3$, $\delta$, ppm): 7.55 (s, 1H, arom H), 7.32 (s, 1H, arom H), 6.65 (d, 1 H, vinyl H), 6.31 (dd, 1H, vinyl H), 6.09 (d, 1H, vinyl H).
(14) Monomer **2** was synthesized by the reaction of endo-*N*-hydroxy-5-norbornene-2,3-dicarboxyimide with acryloyl chloride (1 equiv) in dried THF in the presence of triethylamine (1 equiv). The crude product was purified by recrystallization from ethanol. Yield: 84%, mp: 114.4 °C. $^1$H NMR (300 MHz, $CDCl_3$, $\delta$, ppm): 6.63 (d, 1H, vinyl H), 6.19 (m, 4H, vinyl H), 3.44 (s, 2H), 3.32 (s, 2H), 1.78 (d, 1H), 1.53 (dd, 1H).
(15) All polymerizations were performed under ATRP (atom transfer radical polymerization) conditions. Generally, in a polymerization of endo-*N*-hydroxy-5-norbornene-2,3-dicarboxyimide acrylate (**2**), copper(I) bromide (45 mg, 0.27 mmol), 2,2′-bipyridine (104 mg, 0.54 mmol), and monomer **2** (1.68 g, 7.5 mmol) were added to a flask, which was then sealed with a septum followed by drying in a vacuum for 30 min. After the flask was purged with nitrogen, distilled DMSO (0.3 mL) was then injected into the flask at 90 °C. The resulting mixture was magnetically stirred until the solution became homogeneous. A degassed solution of 2-bromoisobutyric ethyl ester (54 mg, 0.27 mmol) in DMSO (0.2 mL) was then injected into the mixture. The conversion of the polymerization and the number-average molecular weight ($M_n$) were calculated from $^1$H NMR of a sampled portion of the mixture by comparing of the integrals of the peaks corresponding to monomer, polymer, and initiator. Purification of the polymer was performed by precipitation the solution into 2-propanol. Monomer **1** was polymerized at 100 °C without solvent. Gel permeation chromatography (GPC) measurements were performed with a house-made GPC equipped with a PU-980 pump, a RI-930 detector, and a Jasco UV dectector using columns from PSS. THF was used as an eluent with a flow rate of 1.0 mL/min.
(16) The **P2**-*b*-PMMA diblock copolymer was synthesized using **P2** homopolymer as a macroinitiator. To the vial containing **P2** (30 mg, 0.01 mmol), CuBr (19 mg, 0.14 mmol), and bipy (42 mg, 0.28 mmol) in 0.3 mL of DMSO, 0.7 mL (6.6 mmol) of MMA was injected at 70 °C. After 2 h the solution was precipitated into cold 2-propanol to afford a white solid. **P2**-*b*-PMMA: $^1$H NMR (300 MHz, $CDCl_3$, $\delta$, ppm): 6.15, 3.57, 3.37, 3.27, 1.84, 1.42, 1.18, 0.99, 0.82.
(17) The polymer analogous reaction of **P2** and **P2**-*b*-PMMA under homogeneous conditions was performed as follows: to the vials containing the polymer in 5 mL of dried tetrahydrofuran, 1 equiv of ammonia was added. The mixtures were allowed to react at room temperature. After ammonia and THF were evaporated, the crude product was dissolved in THF and purified by precipitation into cold diethyl ether.

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