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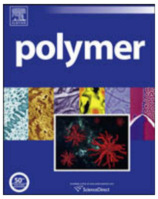

# Catalytic activity of a thermosensitive hydrophilic diblock copolymer-supported 4-*N*,*N*-dialkylaminopyridine in hydrolysis of *p*-nitrophenyl acetate in aqueous buffers

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## ABSTRACT

This article reports on the synthesis of a thermosensitive hydrophilic diblock copolymer with the thermosensitive block containing a catalytic 4-*N*,*N*-dialkylaminopyridine and the study of the effect of thermo-induced micellization on its catalytic activity in the hydrolysis of *p*-nitrophenyl acetate (NPA). The block copolymer, poly(ethylene oxide)-*b*-poly(methoxydi(ethylene glycol) methacrylate-*co*-2-(*N*-methyl-*N*-(4-pyridyl)amino)ethyl methacrylate), was synthesized by ATRP. The critical micellization temperatures (CMTs) of this block copolymer in the pH 7.06 and 7.56 buffers were 40 and 37 °C, respectively. The polymer was used as the catalyst for the hydrolysis of NPA. We found that below CMT, the logarithm of initial hydrolysis rate changed linearly with inverse temperature. With the increase of temperature above CMT, the plot of logarithm of reaction rate versus $1/T$ leveled off, i.e., the hydrolysis rate did not increase as much as anticipated from the Arrhenius equation. This is likely because the reaction rate at temperatures above CMT was controlled by mass transport of NPA from bulk water phase to the core of micelles where the catalytic sites were located.

## 1. Introduction

Polymer-supported organic catalysts have been a subject of intensive research in the past decades [1–3]. In addition to offering the advantages of facile recovery and reuse of the catalysts, polymers create a distinct microenvironment, which can be tailored by varying polymer structures, allowing the tuning of catalytic activities of supported catalysts and the control of the compatibility between different types of catalytic groups [1–22]. Of great interest are stimuli-responsive polymer catalysts, which exhibit tunable or switchable catalytic activities in response to environmental stimuli [23–25]. These catalysts are highly desired for many applications as the reaction rates can be conveniently controlled by environmental stimuli. Up to date, there are only a few examples of such polymer organocatalysts in the literature. Tanaka and coworkers reported an imidazole-containing polymer gel consisting of *N*-isopropylacrylamide (NIPAm), 4(5)-vinylimidazole, and a crosslinker [23]. The gel can undergo reversible swelling and shrinking in response to the composition changes of the mixed solvent of water and methanol. They observed that when the gel collapsed, the catalytic activity for esterolysis was dramatically enhanced, which was believed to result from the increased affinity of the substrate to the collapsed hydrophobic network. Khokhlov et al. synthesized thermosensitive random copolymers of 1-vinylimidazole and *N*-vinylcaprolactam or NIPAm, and found that above the lower critical solution temperatures (LCSTs) of the copolymers, the hydrolysis rates of an activated ester were higher than predicted from the Arrhenius equation, presumably because both the substrate and the catalytic imidazole units were enriched at the interface of polymer aggregates [24]. The observed effect was larger for the copolymer of NIPAm and 1-vinylimidazole than for the copolymer of *N*-vinylcaprolactam and 1-vinylimidazole. With further increasing temperature, the aggregates became unstable and the activities decreased appreciably.

Compared with thermosensitive catalyst-containing random copolymers, which form unstable large aggregates at temperatures above the LCSTs, block copolymers are more advantageous for developing polymer catalysts with tunable or switchable activities as they can self-assemble into well-defined stable micelles upon application of external stimuli. Patrickios et al. synthesized poly(2-(*N*,*N*-dimethylamino)ethyl methacrylate)-*b*-poly(2-(1-imidazolyl)-ethyl methacrylate) (PDMAEMA-*b*-PImEMA) by group transfer polymerization [26–28]. Different from their original speculation that the micellization of block copolymers with PImEMA forming the core would accelerate the reaction, they did not observe

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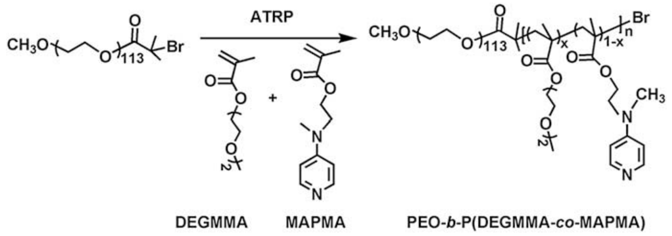
enhanced catalytic activities of the block copolymers compared with the random copolymers, likely because the hydrophobicity of short PImEMA blocks was not sufficient for extensive micellization. Using reversible addition–fragmentation chain transfer polymerization, Liu et al. synthesized doubly hydrophilic thermosensitive diblock copolymers, PNIPAm-*b*-poly(*N*-vinylimidazole), which self-assembled into micelles with the PNIPAm block forming the core and the catalytic block forming the corona at elevated temperatures [25]. They found that the esterolysis rates were enhanced pronouncedly at temperatures above the critical micellization temperatures (CMTs).

Despite these efforts, the issue, how the micellization affects the catalytic activity of a stimulus-responsive block copolymer with an organic catalyst being incorporated into the core-forming block, has not been elucidated. Understanding this issue will enable a rational design of stimuli-responsive polymeric catalysts. One can envision that if the partition coefficient of the substrate between micelles and bulk water phase is sufficiently high, it could be concentrated in the core of micelles, resulting in a higher reaction rate. On the other hand, the formation of micelles with the catalyst buried inside the core could impose a mass transport limitation, which might suppress the reaction rate. In the present work, we synthesized a thermosensitive hydrophilic diblock copolymer with the thermosensitive block containing catalytic 4-*N*,*N*-dialkylaminopyridine (DAAP) units and studied the effect of thermo-induced micellization of the block copolymer on the hydrolysis rate of *p*-nitrophenyl acetate (NPA), an activated ester, in aqueous buffers. DAAPs are highly efficient nucleophilic catalysts for many organic reactions, including acylation of sterically hindered alcohols, hydrolysis of activated esters, and Baylis–Hillman reaction [6–22,29–32]. Scheme 1 illustrates the synthesis of block copolymer poly(ethylene oxide)-*b*-poly(methoxydi(ethylene glycol) methacrylate-*co*-2-(*N*-methyl-*N*-(4-pyridyl)amino)ethyl methacrylate) PEO-*b*-P(DEGMMA-*co*-MAPMA) from a PEO macroinitiator by atom transfer radical polymerization (ATRP). PDEGMMA is a thermosensitive water-soluble polymer with a LCST of 25 °C in water; it belongs to a new family of thermosensitive hydrophilic polymers that contain a short oligo(ethylene glycol) pendant in each monomer unit [33–42]. The thermo-induced micellization of the block copolymer in aqueous buffers (Scheme 2) was studied by dynamic light scattering. The block copolymer was then used as catalyst for the hydrolysis of NPA at various temperatures from below to above the CMT and the hydrolysis rates of NPA were measured by UV–vis spectrometry.

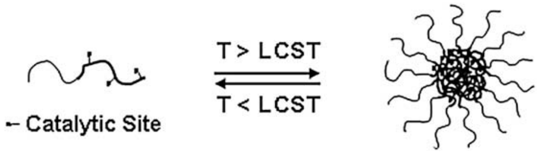
## 2. Experimental section

### 2.1. Materials

Methoxydi(ethylene glycol) methacrylate (DEGMMA, or di(ethylene glycol) methyl ether methacrylate, 95%, Aldrich) was dried with calcium hydride, distilled under a reduced pressure, and stored in a refrigerator prior to use. CuCl (99.995%, Aldrich) was purified according to the procedure described in the literature [43–45] and stored in a desiccator. $CuCl_2$ (anhydrous, 99%), *p*-nitrophenyl acetate (NPA, 97%), acetonitrile (99.5%), *N*,*N*-dimethylformamide (extra dry, with molecular sieves), and sodium tetraborate decahydrate were purchased from Acros and used as-received. Potassium dihydrogen phosphate (≥99%) and 1,1,4,7,10,10-hexamethyltriethylenetetramine (97%) were obtained from Aldrich–Sigma and used as-received. Ethyl 2-bromoisobutyrate (98%, Aldrich) was dried over calcium hydride, distilled under a reduced pressure, and stored in a desiccator prior to use. The synthesis and characterization of 4-(*N*-methyl-*N*-(2-hydroxyethyl)amino)pyridine, 2-(*N*-methyl-*N*-(4-pyridyl)amino)ethyl methacrylate (MAPMA), and macroinitiator PEO-Br (PEO with molecular weight of 5000 Da and one end functionalized with an ATRP initiator) can be found in previous publications [32,46,47].



**Scheme 1.** Synthesis of thermosensitive block copolymer PEO-*b*-P(DEGMMA-*co*-MAPMA) with the thermosensitive block containing a catalytic 4-*N*,*N*-dialkylaminopyridine by atom transfer radical polymerization.



**Scheme 2.** Thermo-induced micellization of PEO-*b*-P(DEGMMA-*co*-MAPMA) in an aqueous buffer.

### 2.2. Characterization

Size exclusion chromatography (SEC) was carried out at ambient temperature using PL-GPC 50 Plus (an integrated GPC/SEC system from Polymer Laboratories, Inc) with a differential refractive index detector, one PSS GRAL guard column (50 × 8 mm, 10 μm particles, Polymer Standards Service-USA, Inc.), and two PSS GRAL linear columns (each 300 × 8 mm, 10 μm, molecular weight range from 500 to 1,000,000 according to Polymer Standards Service-USA, Inc.). The data were processed using Cirrus™ GPC/SEC software (Polymer Laboratories, Inc.). *N*,*N*-Dimethylformamide (DMF) was used as the carrier solvent at a flow rate of 1.0 mL/min. Standard monodisperse polystyrenes (Polymer Laboratories, Inc.) were used for calibration. $^1H$ NMR (300 MHz) spectra were recorded on a Varian Mercury 300 NMR spectrometer and the residual solvent proton signal was used as the internal standard.

The cloud points of poly(methoxydi(ethylene glycol) methacrylate-*co*-2-(*N*-methyl-*N*-(4-pyridyl)amino)ethyl methacrylate) (P(DEGMMA-*co*-MAPMA)) in 10 mM aqueous phosphate buffers with pH of 7.06 and 7.56 at a concentration of 0.020 wt% were measured by turbidimetry. The optical transmittances of polymer solutions at various temperatures were recorded at wavelength of 500 nm with a UV–vis spectrometer (Biomate 5 from Thermospectronic, Inc.). The sample cell was thermostated with an external water bath of a Fisher Scientific Isotemp refrigerated circulator. At each temperature, the solutions were equilibrated for 5 min.

### 2.3. Synthesis of PEO-b-P(DEGMMA-co-MAPMA)

Copper (I) chloride (4.9 mg, $4.9 \times 10^{-5}$ mol), copper (II) chloride (2.9 mg, $2.2 \times 10^{-5}$ mol), macroinitiator PEO-Br (223.6 mg, $4.34 \times 10^{-5}$ mol), DEGMMA (1.005 g, 5.34 mmol), MAPMA (82.7 mg of a 53.0 wt% solution of MAPMA in DMF, 43.8 mg MAPMA, $1.99 \times 10^{-4}$ mol), and DMF (1.004 g) were added into a two-necked flask. The reaction mixture was stirred under a dry nitrogen atmosphere. 1,1,4,7,10,10-Hexamethyltriethylenetetramine (HMTETA, 16.2 mg, $7.03 \times 10^{-5}$ mol) was injected via a microsyringe; the