

A New Solid-Phase Reaction System Utilizing a Temperature-Responsive Catalyst: Oxidative Cyclization with Hydrogen Peroxide

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Abstract: A switchable catalyst based on temperature change provides a novel solid-phase reaction system in water. An increase in catalyst affinity for organic substrates at higher temperature led to efficient activity driving the solid inner-phase reaction, and loss of affinity at lower temperature allowed easy separation of organic products upon completion of the reaction. Application of this catalyst intelli-

gence to design a novel catalytic system brought about an efficient oxidative cyclization with hydrogen peroxide, a useful method of accessing oxygen heterocycles.

Keywords: oxidation; oxygen heterocycles; polymers; supported catalysts; tungsten

Introduction

Solid-phase catalysts offer a number of important advantages over their homogeneous counterparts.^[1,2] For example, their separation from reaction products is easy and their subsequent recycling steps have the potential for green chemical processes. In addition, the immobilization of the solid phase often stabilizes sensitive catalysts and has potential applicability to intelligent materials. In spite of these advantages, solid-phase catalysts, in which the reaction occurs on the surface, show low reactivity due to weak affinity between the substrate and catalyst under heterogeneous conditions. Because of this significant disadvantage, the synthetic utility of solid-phase reaction systems is decreased in many cases. On the other hand, organic reactions in aqueous media may lead to several unforeseen reactivities or selectivities due to strong affinity between the substrate and catalyst based on hydrophobic effects.^[3,4] However, this strong interaction may cause difficulties in the separation of organic materials when the reaction is completed. In addition, subsequent clean-up of the used water-containing surfactants and inorganic agents may also be problematic.

Due to the points mentioned above, the use of an intelligent solid phase that can change the affinity to an organic substrate in aqueous media would be an ideal approach to form efficient, recyclable catalytic

systems. Here we describe a new approach to a solid-phase reaction system in aqueous media utilizing a switchable solid-phase catalyst. The property of the solid phase in water is controlled by the temperature-responsive nature of the polymer support, and the reaction system driving the inner phase of the solid state based on hydrophobic effects was designed for efficient catalytic activity.

Results and Discussion

Due to their characteristic temperature-responsive intelligence, poly(*N*-isopropylacrylamide) (PNIPAAm) polymers and polymer gels have been applied in various fields such as drug-delivery systems, column packing materials, and cell culture substrates using external temperature changes.^[5–7] PNIPAAm polymers undergo thermally reversible changes between the water-soluble and -insoluble states across a lower critical solution temperature (LCST) from 30 to 40 °C. Thus, the polymer chains of PNIPAAm are hydrated below the LCST and dehydrated with aggregation above the LCST.^[6] The efficient applications of soluble PNIPAAm supported catalyst to biphasic system have already been reported by Bergbreiter.^[8] We have investigated the self-assembly of PNIPAAm polymer and an inorganic species (Figure 1A).^[9] Recently, we have found that the use of the intelligence of

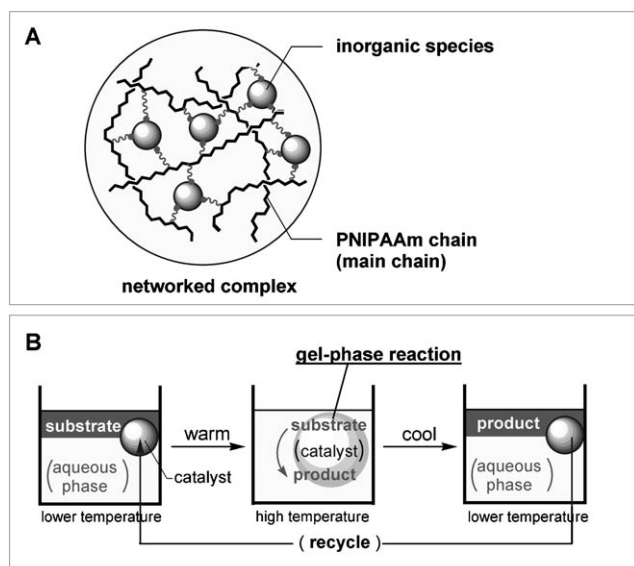
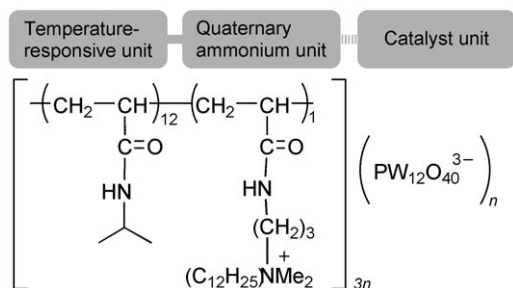


Figure 1. **A:** Simplified structure of networked PNIPAAm-inorganic complex. **B:** Simplified representation of thermomorphic catalysis.

PNIPAAm is important in the creation of valuable catalyst recycling strategies in water^[10] and established a facile oxidation system *via* the thermoregulated formation of stable emulsion species.^[10a,11] The present study focused on the use of the temporarily formed specific hydrophobic PNIPAAm gel phase holding the flexible solid state as a specific organic reaction medium to provide a novel recyclable catalytic oxidation system in water (Figure 1B). The utilization of the inner site of such a networked complex would be more effective than the conventional solid-phase reaction on the surface.

Previously, a small amount (0.1 mol %) of PNIPAAm-based solid-phase catalyst **1** (Scheme 1), a complex of PNIPAAm polymer with a quaternary ammonium and phosphotungstate anion ($\text{PW}_{12}\text{O}_{40}^{3-}$), in the presence of organic substrates caused thermoregulated formation of stable emulsion species at 90 °C in water. To explore the phase transformation mode of **1** in greater detail, the quantity of **1** used was increased from 0.1 mol % equivalent to 0.4 mol %



Scheme 1. Networked PNIPAAm- $\text{PW}_{12}\text{O}_{40}^{3-}$ complex (**1**).

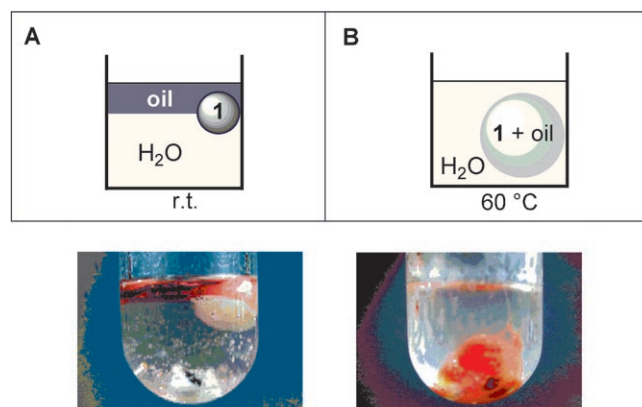


Figure 2. Photographs of a mixture of pent-4-en-1-ol and **1** in water (with magnetic stir bar). **A:** at room temperature; **B:** at 60 °C. The oil phase was stained with dye (oil red O).

Table 1. Oxidative cyclization of pent-4-en-1-ol.

$\text{CH}_2=\text{CH}(\text{CH}_2)_3\text{OH} \xrightarrow[60^\circ\text{C, 6 h}]{\text{1 (0.4 mol \%), 30\% aq. H}_2\text{O}_2 \text{ (2.0 equiv.)}} \text{HO-CH}_2\text{-(CH}_2)_3\text{-O-CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$			
Entry	Catalyst	Solvent	Conversion [%] ^[a]
1	none	H ₂ O	< 5
2	1	H ₂ O	83 ^[b]
3	1	H ₂ O	87 ^[b] (2 nd use)
4	1	H ₂ O	88 ^[b] (3 rd use)
5	1	CH ₃ CN	25 ^[b]
6	1	<i>t</i> BuOH	48 ^[b]

^[a] Determined by ¹H NMR (300 MHz) and GC.

^[b] Selectivity: > 95 %.

equivalents, and the effect of temperature on the phase transformation was investigated. Although the organic substrate, pent-4-en-1-ol (**2**), was separately floating on the water surface at room temperature (Figure 2A), the osmosis of organic substrate to **1** gradually proceeded with heating and full absorption into the solid gel phase was achieved at around 60 °C (Figure 2B), while additional heating^[10] to more than 70 °C tended to induce the generation of emulsion species.

The attractive properties of **1** prompted us to develop a novel reaction system using the PNIPAAm gel phase in catalytic oxidative cyclization with hydrogen peroxide, a useful method of accessing oxygen heterocycles.^[12] In the oxidation of **2** in water, the absorption of organic materials in the catalyst phase was similarly detected at 60 °C, and higher reactivity and selectivity were observed although the oxidation barely proceeded in the absence of catalyst (Table 1, entries 1 and 2). The recovery of catalyst was easy; the organic materials retained were released by cooling the reaction mixture and the organic/aqueous/solid phases were cleanly separated after the addition of diethyl ether. The re-

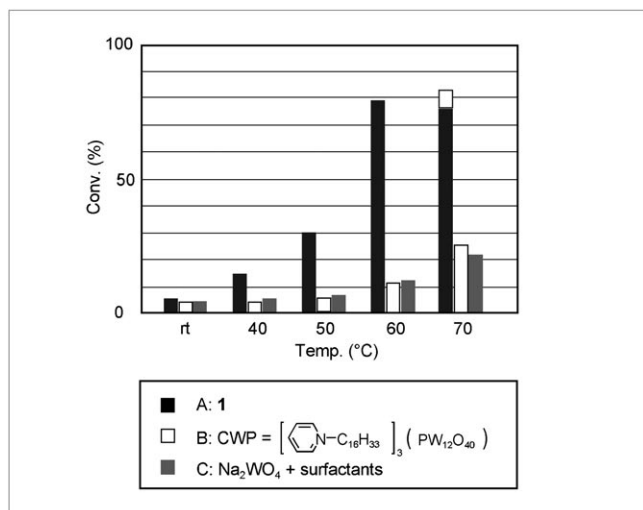


Figure 3. Oxidative cyclization of **2a** in the presence of various tungsten catalyst systems. *Conditions:* A) **1** (0.4 mol %), 10 % aqueous H₂O₂, 6 h; B) CWP (0.4 mol %), 10 % aqueous H₂O₂, 6 h; Na₂WO₄·2H₂O (4.8 mol %), [CH₃(*n*-C₈H₁₇)₃N] HSO₄, NH₂CH₂PO₃H, 10 % aqueous H₂O₂, 6 h (□ = undesired product).

covered **1** could be used for subsequent reactions without any significant loss of catalytic efficacy (Table 1, entries 3 and 4). The present system afforded higher reactivity than a homogeneous system utilizing acetonitrile or *tert*-butyl alcohol (Table 1, entries 5 and 6), indicating that the utilization of the reaction with the PNIPAAm phase *via* the thermoregulated formation is effective in increasing the activity of **1** in water.

To estimate the utility of the present system, further investigation of the effects of the PNIPAAm chain was performed using other conventional tungsten oxidation systems, employing cetylpyridinium peroxotungstophosphate (CWP)^[13] and sodium tungstate in the presence of surfactants^[14] for comparison (Figure 3). When the oxidation was carried out at lower temperature, no significant dominance was observed. On the other hand, catalyst **1** showed remarkable acceleration in reactivity at higher temperature (60 °C), with generation of the adsorption of **2a** into the PNIPAAm gel phase, whereas undesired products were detected with additional heating (higher than 70 °C), attributable to the subsequent partial formation of emulsion species.^[15] The results demonstrate that the acceleration caused by **1** in water is novel and the intelligence of the polymer chain plays an important role in the activation. Thus, higher catalytic activity exerted over other versatile tungsten systems with the advantage of easy catalyst recycling was noted, and this concept might be helpful in tailoring other polyoxometalate reaction systems.

The scope of this oxidation system was studied further with various open-chain precursors (Table 2). Organic substrates were similarly absorbed onto the cat-

alyst phase with heating and smoothly converted into the corresponding oxygen heterocycles *via* oxidative cyclization in each case.^[16] Thus, this method provides a useful tool for the process design of various types of oxygen heterocycle syntheses.

Conclusions

We have devised a novel catalytic system in water based on the intelligence of a thermomorphic catalyst. The reaction driving the inner phase of the solid state based on the thermoregulated control of affinity for the organic substrate in water led to a unique acceleration of the reactivity and ease in catalyst recycling in the oxidative cyclization with hydrogen peroxide. The utilization of intelligent polymeric catalysts may offer many advantages in both biochemical and industrial applications. In addition, the results described here will enhance the utility of PNIPAAm polymers in the field of organic synthesis. More detailed investigations into the catalytic features of **1** and efforts to extend this system to other types of reactions are currently ongoing.

Experimental Section

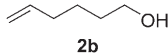
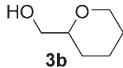
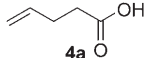
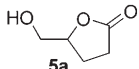
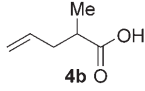
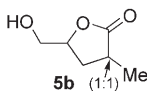
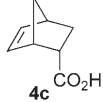
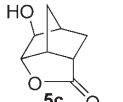
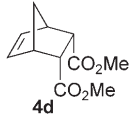
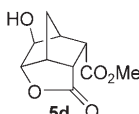
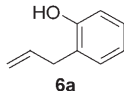
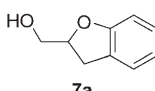
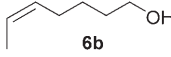
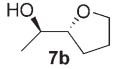
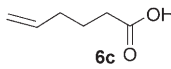
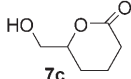
All melting points are uncorrected. ¹H NMR spectra were recorded at 300 MHz. All NMR spectra were recorded in CDCl₃ with either TMS or residual CHCl₃ as the internal standard. IR absorption spectra were recorded as a KBr pellets. Silica gel 60N (Kanto Chemical Company) was used for column chromatography. The organic layer was dried with anhydrous MgSO₄ or Na₂SO₄. All chemicals were purchased commercially and use as received. Poly(*N*-isopropylacrylamide) (PNIPAAm) based tungsten catalyst (**1**) was synthesized by an improvement of the previously reported method.^[9d]

Typical Experimental Procedure for the 1-Catalyzed Oxidative Cyclization in Aqueous Media

A mixture of **1** (160 mg, 0.02 mmol) and open-chain precursor (5 mmol) in 30 % aqueous H₂O₂ (10–15 mmol) was heated to 60 °C and stirred for 6–12 h. After the reaction mixture had been allowed to cool, Et₂O (5 mL) was added. The organic and aqueous phases were removed and the recovered **1** was washed with ether and distilled water, which were then added to the aqueous phase. The recovered **1** was reused for subsequent catalytic experiments. The aqueous phase was extracted three times with Et₂O and the combined organic extracts were washed with brine. The organic phase was then dried over MgSO₄ and concentrated under reduced pressure. The products were purified by on column chromatography with silica gel and isolated yields were determined.

Tetrahydrofurfuryl alcohol (3a):^[17] Colorless liquid; ¹H NMR: δ = 1.55–1.67 (m, 1H), 1.83–1.93 (m, 3H), 3.46 (dd, *J* = 6.1, 11.5 Hz, 1H), 3.63 (dd, *J* = 3.2, 11.5 Hz, 1H),

Table 2. Oxidative cyclization promoted by **1**.^[a]

Entry	Substrate	<i>t</i> [h]	Product	Yield ^[b] [%]
1	 2b	6	 3b	70
2	 4a	6	 5a	82
3	 4b	6	 5b (1:1)	85
4	 4c	6	 5c	89
5	 4d	6	 5d	92
6	 6a	12	 7a	71
7	 6b	6	 7b	85
8	 6c	12	 7c	46 ^[c]

^[a] **1** (0.4 mol %), 30 % H₂O₂ (2.0–3.0 equivs.), 60 °C.^[b] Yield of isolated products.^[c] See ref. ^[16]

3.70–3.78 (m, 1H), 3.80–3.86 (m, 1H), 3.95–4.01 (m, 1H); IR (KBr): ν = 3451, 2951, 2876, 1181, 1039 cm⁻¹; CAS registry number [97–99–4].

Tetrahydropyran-2-methanol (3b):^[18] Colorless liquid; ¹H NMR: δ = 1.29–1.35 (m, 1H), 1.42–1.61 (m, 4H), 1.80–1.85 (m, 1H), 3.40–3.60 (m, 4H), 4.00–4.11 (m, 1H), IR (KBr): ν = 3455, 2945, 2862, 1203, 1091, 1047 cm⁻¹; CAS registry number [100–72–1].

5-Hydroxymethylbutyrolactone (5a):^[12d] Colorless liquid; ¹H NMR: δ = 2.06–2.15 (m, 1H), 2.18–2.27 (m, 1H), 2.45–2.63 (m, 2H), 3.60 (dd, *J* = 4.6, 12.5 Hz, 1H), 3.85 (dd, *J* = 2.9, 12.5 Hz, 1H), 4.57–4.62 (m, 1H); IR (KBr): ν = 3400, 2941, 1740, 1460, 1358, 1200, 937, 806 cm⁻¹; CAS registry number [10374–51–3].

5-Hydroxymethyl-2-methylbutyrolactone (5b):^[12d] Colorless liquid; ¹H NMR (*cis* and *trans*): δ = 1.21 and 1.22 (d, *J* = 7.3 and 7.1 Hz, 3H), 1.65–1.91 (m, 1H), 2.29–2.37 (m, 1H), 2.63–2.73 and 2.71–2.82 (m, 1H), 3.55–3.61 (m, 1H), 3.75–3.85 (m, 1H), 4.42–4.48 and 4.52–4.57 (m, 1H); IR (KBr): ν = 3495, 2936, 1751, 1456, 1379, 1201, 927 cm⁻¹; CAS registry number [51577–65–2].

5-Hydroxy-2,6-norbornanecarbolactone (5c):^[12d] Colorless solid; mp 150–152 °C (lit. 157–158 °C^[19]); ¹H NMR (*cis* and *trans*): δ = 1.55–1.58 (m, 1H), 1.59–1.64 (m, 1H), 1.92–2.02

(m, 2H), 2.12 (dd, *J* = 1.7, 11.2 Hz, 1H), 2.38–2.39 (m, 1H), 2.50 (dd, *J* = 4.6, 11.2 Hz, 1H), 3.13–3.16 (m, 1H), 3.94 (s, 1H), 4.40 (d, *J* = 5.1 Hz, 1H); IR (KBr): ν = 3320, 1782, 1348, 1304, 1178, 1059, 1022, 895 cm⁻¹; CAS registry number [92343–46–9].

3-Carbomethoxy-5-hydroxy-2,6-norbornanecarbolactone (5d):^[20] Colorless liquid; ¹H NMR: δ = 1.55–1.58 (m, 1H), 2.17–2.23 (m, 2H), 2.58–2.63 (m, 1H), 2.74 (dd, *J* = 4.6, 10.7 Hz, 1H), 3.02 (dd, *J* = 4.4, 10.7 Hz, 1H), 3.22–3.28 (m, 1H), 3.67 (s, 3H), 4.30–4.34 (m, 1H), 4.46–4.50 (m, 1H); IR (KBr): ν = 3400, 2990, 1780, 1437, 1363, 1200, 1150, 1076 cm⁻¹; CAS registry number [5826–29–9].

2,3-Dihydro-2-benzofuran-2-ylmethanol (7a):^[21] Colorless liquid; ¹H NMR: δ = 2.50 (bs, 1H), 3.00 (dd, *J* = 7.3, 15.6 Hz, 1H), 3.23 (dd, *J* = 9.5, 15.6 Hz, 1H), 3.60 (dd, *J* = 6.3, 15.6 Hz, 1H), 3.82 (dd, *J* = 4.0, 15.6 Hz, 1H), 4.86–4.92 (m, 1H), 6.75–6.85 (m, 2H), 7.07–7.12 (m, *J* = 7.3 Hz, 2H); IR (KBr): ν = 3426, 2932, 1780, 1597, 1481, 1460, 1099, 1053, 1014, 989, 752 cm⁻¹; CAS registry number [66158–96–1].

erythro-Tetrahydro-2-furan-1-ethanol (7b):^[22] Colorless liquid; CAS registry number [16765–41–6].

6-Hydroxymethyltetrahydropyran-2-one (7c):^[12d] Colorless liquid; CAS registry number [81683–96–7].

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