

## ORIGINAL ARTICLE

# Polymer microgel particles as basic catalysts for Knoevenagel condensation in water

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The catalytic activities of basic and thermoresponsive microgel particles for the Knoevenagel condensation reaction in water at ambient temperature were evaluated. The gel particles (GPs) were incorporated with primary-amino, tertiary-amino, imidazole or pyridyl groups. In the Knoevenagel condensation between benzaldehyde and ethyl cyanoacetate, the GPs that had no basic group did not exhibit any catalytic activity. The GPs that had primary-amino, tertiary-amino and imidazole groups exhibited catalytic activity. The catalytic activity of the basic GPs depended on their base strength. The tertiary-aminated microgel particles had quadruple and double the activities of tertiary-aminated silica gel and trimethylamine, respectively. The higher catalytic activity may be attributable to the local enrichment effect of ethyl cyanoacetate. In terms of gel geometry, the activity of the tertiary amines in the microgel particles was higher than that in the bulk gel. The geometry of the microgel particles allowed the rapid uptake of the substrates. Because the base strength of the tertiary amines in the microgel particles decreased with increasing temperature, the catalysts and residual active methylene substrates were separated by dialysis at 80 °C. The recovered microgel particle catalysts were recyclable for an additional Knoevenagel condensation.

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## INTRODUCTION

Catalysts are important materials for chemical transformations in the laboratory and in industrial processes. In particular, polymer catalysts have been extensively studied and rapidly developed.<sup>1–4</sup> Polymer catalysts are broadly classified into two categories: molecular catalysts that are prepared by the polymerization of monomers with catalytic groups on their side chains and polymer-supported catalysts that are loaded with catalysts, such as metals. The catalytic sites are covalently incorporated in the former and non-covalently incorporated into the latter. The improvement in the activity, specificities of the substrate and reaction, and stabilization of the catalysts are provided by the appropriate design of the polymeric structure.

One of the advantages of polymer catalysts is the enrichment effect of the catalytic groups and substrates. The substrate concentration around the active site is locally enhanced by uptake of the substrate in the polymer. This effect is well known for micellar catalysts.<sup>5–8</sup> Polymer gels are also superior materials that exert a local enrichment effect. Tanaka and co-workers have reported that the catalytic activity of the imidazole group in a gel for the hydrolysis of *p*-nitrophenyl esters was higher than that in the monomer solution, when the gel was shrunken.<sup>9</sup> The adsorption of the substrate in the gel network through hydrophobic interactions leads to an enhancement of the catalytic activity. Wang *et al.*<sup>10</sup> have demonstrated the local enrichment effect for transition metal catalysts supported by a chelating hydrogel. Compared with a palladium complex in water, the coupling reactions using palladium in the hydrogel were accelerated as a result of the

enrichment of the hydrophobic reactants and the palladium catalysts, in which the gel became a suitable reaction vessel.

Another advantage of polymer catalysts is the easy separation and recovery of the catalyst from the reaction mixture using filtration or precipitation techniques, allowing the catalyst to be recycled.<sup>2–4,11</sup> This advantage is important in terms of the application of these catalysts in green chemistry. Although the separation and recovery of catalysts is easier with increasing sizes of the catalytic matrices, such as bulk gels and latex beads, the diffusion of the substrates into the matrices is limited. The operability and reactivity of a catalyst have a trade-off relationship. Therefore, the appropriate size of polymer catalysts is from tens to hundreds of nanometers. Because the catalyst that is not reused may be a waste, the establishment of a recycling system is necessary for catalytic chemistry. The design of the polymer has a great effect on the establishment of a recycling system.

*N*-isopropyl acrylamide (NIPAm) polymer is well known as a thermoresponsive polymer with a steric structure that drastically changes at the phase transition temperature. When crosslinkers and surfactants are added during NIPAm polymerization, gel particles (GPs), which also have thermoresponsive properties, with diameters of tens to hundreds nanometers are formed.<sup>12,13</sup> Hoshino *et al.* have synthesized conformation-tuned GPs by the copolymerization of NIPAm, a saccharide monomer, a hydrophobic monomer, and a crosslinker and have succeeded in controlling the binding kinetics of lectin recognition.<sup>14,15</sup> GP catalysts, which were incorporated with tertiary amines and immobilized with palladium nanoparticles, have been developed for hydrogenation and Suzuki coupling reactions.<sup>16,17</sup>

Numata and co-workers have optimized amidolytic activity using imidazole-incorporated GPs to mimic hydrolase.<sup>18</sup> Because the GPs have a high dispersity and a small diameter, the uptake of the substrates into the GPs is kinetically favorable. It is not inaccurate to say that the NIPAm-based GPs have a major role as ‘smart’ catalysts, in which the catalytic activity and selectivity are tuned by a stimulus-responsive behavior, such as a volume phase transition in response to a change in pH, ionic strength or temperature.<sup>19</sup> It is consistently important to suggest novel ‘smart’ functionalities of GP catalysts.

Recently, it has been reported that the base strength of tertiary-aminated GPs in water depends on the temperature.<sup>20</sup> The mechanism for the thermoresponsive change in the base strength of the GPs is based on hydration-dehydration. Protonation of the amine groups, which are located in an environment with a low dielectric constant (that is, in the dehydrated GPs), is suppressed.<sup>21</sup> Similarly, this phenomenon also occurred in the case of acidic GPs. The  $pK_a$  of the carboxylate in the GPs increased with increasing temperature.<sup>22</sup> Dissociation of the carboxylic groups, which are located in the dehydrated GPs, is suppressed, resulting in a weaker acid strength of the GPs. These basic and acidic GPs have been applied as a carbon dioxide gas absorbent<sup>20</sup> and a proton transporter,<sup>22</sup> respectively.

If the substrates or products have a strong interaction with the polymer catalysts during the catalytic reaction, the separation and recovery of the catalyst from the reaction mixture is complicated; catalyst poisoning may also occur. When the substrates or products are adsorbed in ionic GPs through electrostatic interactions, those interactions are disrupted by the thermoresponsive changes in the acid/base strength of the GPs. As a result, the substrates or products are effectively released from the GP catalysts. It is expected that a novel recycling system can be established using the thermoresponsive properties of the GPs.

The Knoevenagel condensation is an alkene-producing reaction between a carbonyl compound and an activated methylene

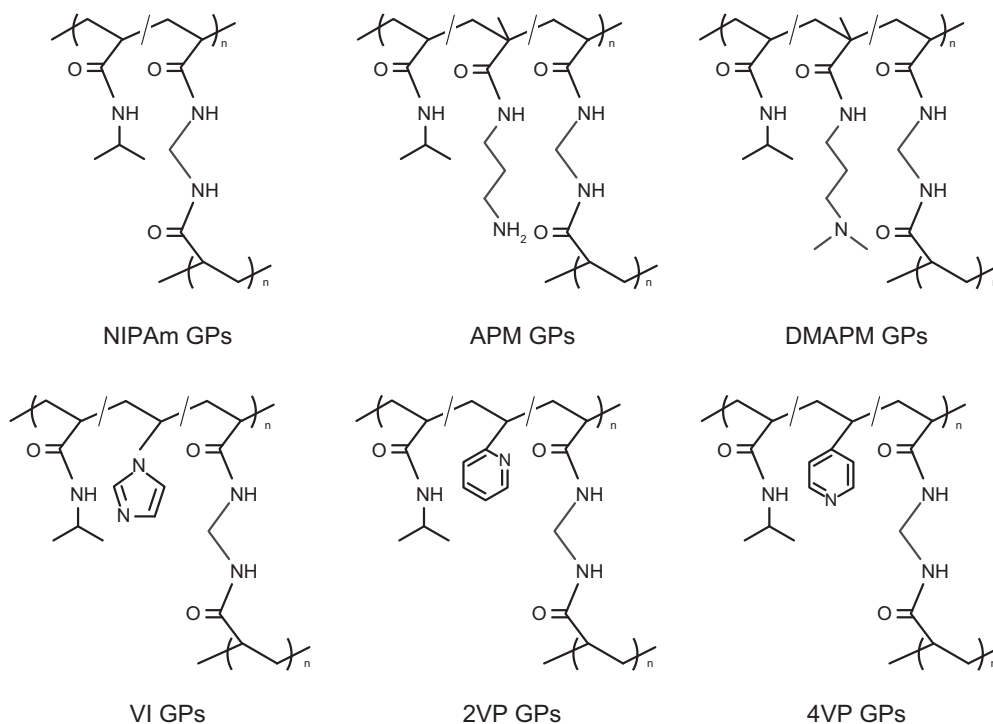
compound, which has a methylene group sandwiched between two electron-withdrawing groups, such as CN, COOR, CONH<sub>2</sub> and NO<sub>2</sub>.<sup>23</sup> In general, basic catalysts, such as amines, are used for the Knoevenagel condensation. There is great variety in the geometries of basic catalysts, for example, amino acids,<sup>24</sup> surfactants,<sup>25</sup> ion liquids,<sup>26</sup> dendrimers,<sup>27</sup> metal-organic frameworks,<sup>28</sup> resins,<sup>29</sup> cellulose paper,<sup>30</sup> polyacrylonitrile fibers<sup>31</sup> and silicates.<sup>32</sup> The Knoevenagel condensation has been reported to proceed in partially or fully aqueous media<sup>24–26,30–35</sup> and has attracted attention as a sustainable organic synthesis reaction. The current goals for improving this reaction are to find milder reaction conditions, such as at ambient temperature, as well as environmentally benign reaction conditions.

In the present study, PNIPAm-based GPs incorporating basic groups that exhibit activity for the Knoevenagel condensation in fully aqueous media at ambient temperatures were developed. We chose to use the GPs as a catalyst matrix from the standpoint of exploiting the local enrichment effect and recyclability. This study has two focuses: (1) the evaluation of the catalytic activity of the basic GPs; and (2) the establishment of a recycling system for the catalyst using the thermoresponsive properties of PNIPAm-based GPs. Primary-amino, tertiary-amino, imidazole and pyridyl groups, which have different base strengths, were incorporated in the GPs. The effects of the basic species and the catalyst geometry on the catalytic activity for the condensation reaction were investigated. Using the change in the base strength of the amines in the swelled and shrunken states of the GPs, the basic GPs were regenerated and reused for the catalytic reaction.

## EXPERIMENTAL PROCEDURE

### Reagents

*N*-(3-Aminopropyl) methacrylamide (APM) hydrochloride (Polysciences Inc, Warrington, PA, USA), *N*-(3-dimethylaminopropyl) methacrylamide (DMAPM, Tokyo Chemical Industry Co., Ltd, Tokyo, Japan), 1-vinylimidazole (VI, Tokyo Chemical Industry Co.), 2-vinylpyridine (2VP, Tokyo Chemical Industry Co, Ltd. and 4-vinylpyridine (4VP, Tokyo Chemical



**Figure 1** Chemical structures of the GPs used as catalysts for the Knoevenagel condensation reaction.

Industry Co., Ltd.) were used as the basic monomers. NIPAm (Wako Pure Chemical Industries Ltd., Osaka, Japan), *N,N'*-methylenebisacrylamide (BIS, Tokyo Chemical Industry Co., Ltd.), cetyltrimethylammonium bromide (Wako Pure Chemical Industries Ltd.) and 2,2'-azobis(2-amidinopropane) dihydrochloride (Wako Pure Chemical Industries Ltd.) were used as the GP matrix, crosslinker, surfactant and polymerizing initiator, respectively. Benzaldehyde (Tokyo Chemical Industry) and ethyl cyanoacetate (Tokyo Chemical Industry) were used as the substrates for the Knoevenagel condensation.

### Preparations of basic catalysts

Basic GPs (Figure 1) incorporated with primary-amino, tertiary-amino, imidazole and pyridyl groups were synthesized (see the Supplementary Information). The mole fractions of the basic and crosslinking monomers were 10 and 5 mol%, respectively. The obtained basic GPs were treated with an anion-exchange resin (Muromac A2004-OH, Muromachi Chemicals Inc, Fukuoka, Japan). For comparison, GPs that do not contain any basic monomers (NIPAm GPs, NIPAm:BIS = 95:5) were synthesized using the same method. Using ultrafiltration and a size exclusion chromatography, it was confirmed that the main component in the solutions was GP (Supplementary Figure S1). The hydrodynamic diameters of the GPs in water were determined using dynamic light scattering (DLS; Zetasizer Nano ZS, Malvern Instruments Ltd., Worcestershire, UK) at 30 °C. The GP concentrations in the DLS measurements were adjusted to 1 g l<sup>-1</sup>. The hydrodynamic diameters of the GPs in the presence of ethyl cyanoacetate (11 mmol l<sup>-1</sup>) were also determined. The base densities in the GPs were determined by acid–base titrations, where it was defined that the pH value of the half equivalence point is the pK<sub>a</sub> value.<sup>20</sup> Tertiary-aminated silica gel (that is, DMAP silica gel) was prepared using a previously reported method,<sup>36</sup> and its physical properties are summarized in Supplementary Figure S2 and Table S1. The DMAPM bulk gel was synthesized by redox polymerization at room temperature (see the Supplementary Information).

### Knoevenagel condensation using basic catalysts

The catalytic activities of the GPs were evaluated in the Knoevenagel condensation between benzaldehyde and ethyl cyanoacetate (Figure 2). The basic GP aqueous solutions were purged with N<sub>2</sub> gas for at least 30 min. The catalytic reaction was performed in a polypropylene vessel. The Knoevenagel condensations were initiated by the addition of ethyl cyanoacetate and benzaldehyde to the GP solutions, and the mixture solutions were stirred at 30 °C. The final concentrations of the GPs, benzaldehyde, and ethyl cyanoacetate were adjusted to 1 g l<sup>-1</sup>, 10 mmol l<sup>-1</sup> and 11 mmol l<sup>-1</sup>, respectively. The benzaldehyde concentrations in the mixture solutions were determined using a high-performance liquid chromatography system (LC-2000Plus, JASCO Co., Tokyo, Japan) with a reverse phase column (Mightysil RP-18 GP 250-4.6, Kanto Chemical Co., Inc., Tokyo, Japan) and a UV detector (UV-2007 Plus, JASCO Co.). A mixture solution of acetonitrile and water (50:50) with 0.1 v/v% trifluoroacetic acid was used as the mobile phase at a flow rate of 1 ml min<sup>-1</sup>. Conversion percentages of benzaldehyde were estimated using equation (1):

$$\text{Conversion percentage (\%)} = 100 \times \frac{[\text{Benzaldehyde}]_0 - [\text{Benzaldehyde}]}{[\text{Benzaldehyde}]_0} \quad (1)$$

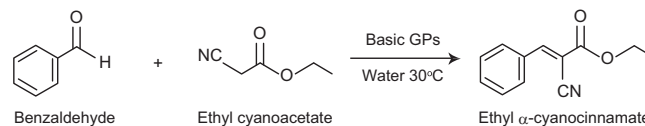
where the subscript 0 denotes the initial conditions. The reaction rates (*V*) and the apparent reaction rate constants (*k*) in the Knoevenagel condensation were estimated by the second-order reaction model from the conversion up to 3 h.

$$V = k [\text{Benzaldehyde}] \times [\text{Ethyl cyanoacetate}] \quad (2)$$

$$\frac{1}{[\text{Ethyl cyanoacetate}]_0 - [\text{Benzaldehyde}]_0} \ln \left( \frac{[\text{Benzaldehyde}]_0 \times [\text{Ethyl cyanoacetate}]}{[\text{Ethyl cyanoacetate}]_0 \times [\text{Benzaldehyde}]} \right) = kt \quad (3)$$

where *t* is the reaction time. The ethyl cyanoacetate concentration was estimated as follows:

$$[\text{Ethyl cyanoacetate}] = (a - 1)[\text{Benzaldehyde}]_0 + [\text{Benzaldehyde}] \quad (4)$$



**Figure 2** Knoevenagel condensation between benzaldehyde and ethyl cyanoacetate using basic GPs.

where *a* is the feed ratio of ethyl cyanoacetate to benzaldehyde. Therefore, equation (3) was converted as follows:

$$\frac{1}{(a - 1)[\text{Benzaldehyde}]_0} \ln \left( \frac{(a - 1)[\text{Benzaldehyde}]_0 + [\text{Benzaldehyde}]}{a[\text{Benzaldehyde}]} \right) = kt \quad (5)$$

The solutions were shaken for 48 h. Likewise, catalytic reactions for the Knoevenagel condensation were performed using the DMAP silica gel and trimethylamine. The turnover number was defined as the following:

$$\text{TON (-)} = \frac{\text{Amount of benzaldehyde converted}}{\text{Amount of tertiary amine}} \quad (6)$$

The initial turnover frequency was estimated from the reaction rate and the amine density. The catalytic activity of the DMAPM bulk gel was also evaluated (see the Supplementary Information).

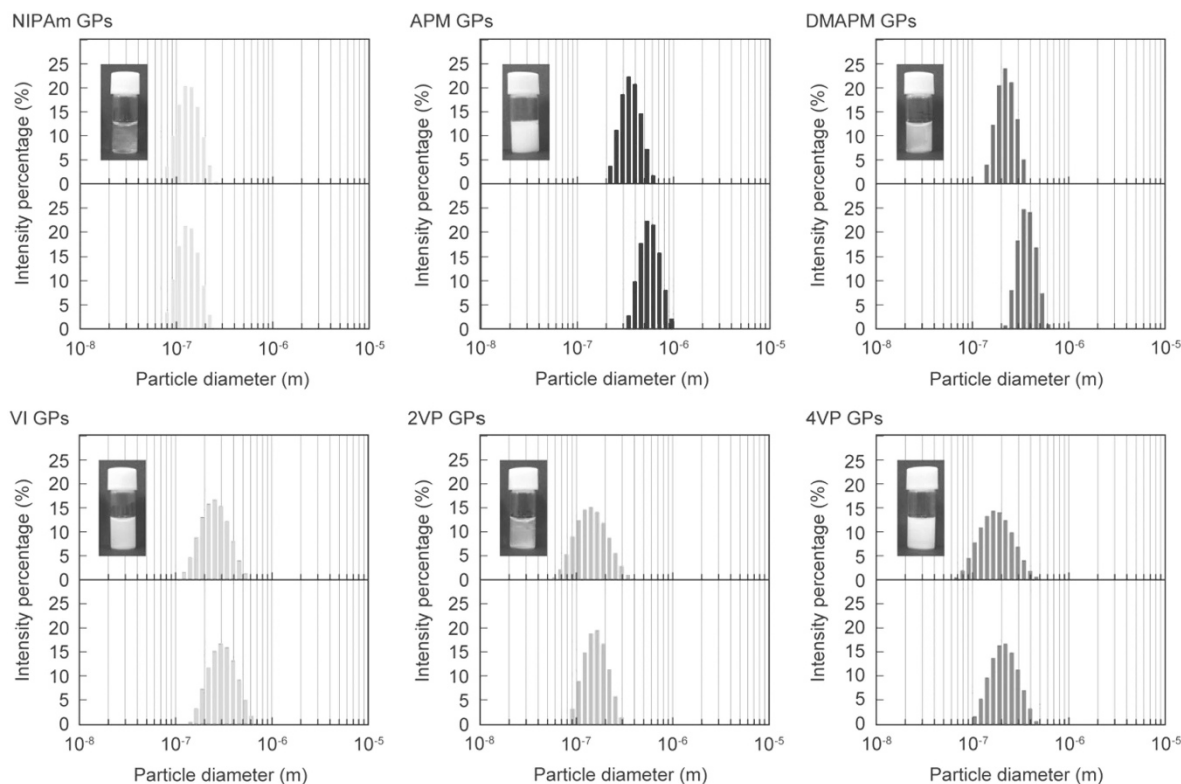
### Regeneration of GP catalysts used in Knoevenagel condensations

The DMAPM GP solution used in the Knoevenagel condensation between benzaldehyde and ethyl cyanoacetate was filtered to recover the product. After the filtrate was washed with *n*-hexane, the GP solution was dialyzed against a 100-fold volume of hot water (80 °C) for 1 day. The hydrodynamic diameters of the spent and dialyzed GPs in water were determined using DLS at various temperatures. After freeze drying, the DMAPM GPs were recovered as a white powder. The removal of ethyl cyanoacetate from the GPs was confirmed using an infrared (IR) spectrometer (Spectrum 100 FTIR spectrometer, PerkinElmer Inc., Waltham, MA, USA). Pellet samples were prepared using KBr with a 100-fold amount of the GPs. The IR spectra were obtained at room temperature in air, with 2 cm<sup>-1</sup> spectral resolution and 32 scans. The baseline of the obtained spectra was adjusted using Spectrum software (v6.3.5, PerkinElmer Inc.). The peak assignment of the PNIPAm film, which has previously been reported,<sup>37</sup> was used as a reference for the IR spectra of the GPs, consisting of (meth)acrylamides containing NIPAm, DMAPM and BIS. The regenerated GPs were redispersed in water and then reused for the next Knoevenagel condensation. The relative activity and relative conversion of the regenerated GPs were evaluated by comparison with the reaction rate constants and the conversion percentages of the original GPs, respectively.

## RESULTS AND DISCUSSION

### Characterizations of basic GPs

The GPs were obtained as white- or bluish-colored solutions and were homogeneously dispersed without precipitation. The dispersed GP solutions were stable for more than 1 year. The size distributions of the NIPAm, APM, DMAPM, VI, 2VP and 4VP GPs in water at 30 °C are shown in Figure 3. The hydrodynamic diameters of the GPs were several hundred nanometers (Table 1). When ethyl cyanoacetate (11 mmol l<sup>-1</sup>) was added as an acidic substrate, aggregation of the GPs was not observed. The diameter of the NIPAm GPs was not changed by the addition of ethyl cyanoacetate, whereas the diameters of the basic GPs increased with the addition of ethyl cyanoacetate. The increase in the diameter of APM and DMAPM GPs was particularly noticeable. The APM and DMAPM GPs swelled, with a four- to five-fold increase in the volume of the GP. The amine groups in the APM and DMAPM GPs were protonated by trapping protons from ethyl cyanoacetate, and as a result, the GPs swelled owing to electrostatic repulsion.



**Figure 3** Size distributions of GPs in water at 30 °C, in the absence (above) and presence (below) of ethyl cyanoacetate. The photographs show the GP solutions after dialysis, in which the GP concentrations were without any change. A full color version of this figure is available at *Polymer Journal* online.

**Table 1** Hydrodynamic diameters of GPs in the absence and presence of ethyl cyanoacetate and apparent  $pK_a$  of GPs.

GPs	Without ethyl cyanoacetate		With ethyl cyanoacetate		Relative GP volume ( $-^d$ )	$pK_a$ ( $-^e$ )
	Diameter (nm) <sup>a</sup>	PDI ( $-^b$ )	Diameter (nm) <sup>a</sup>	PDI ( $-^b$ )		
NIPAm	128	0.059	127	0.031	1.0	–
APM	345	0.049	553	0.008	4.1	6.6
DMAPM	219	0.006	365	0.038	4.6	7.4
VI	230	0.144	280	0.147	1.8	4.9
2VP	135	0.124	153	0.054	1.5	<3.5
4VP	162	0.132	201	0.089	1.9	<3.5

Abbreviations: APM, *N*-(3-aminopropyl) methacrylamide; DLS, dynamic light scattering; DMAPM, *N*-(3-dimethylaminopropyl) methacrylamide; GP, gel particle; NIPAm, *N*-isopropyl acrylamide; VI, 1-vinylimidazole; 2VP, 2-vinylpyridine; 4VP, 4-vinylpyridine.

<sup>a</sup>Hydrodynamic diameters were determined using DLS at 30 °C.

<sup>b</sup>Relative GP volumes are defined as (diameter in the presence of ethyl cyanoacetate)<sup>3</sup>/(diameter in the absence of ethyl cyanoacetate)<sup>3</sup>.

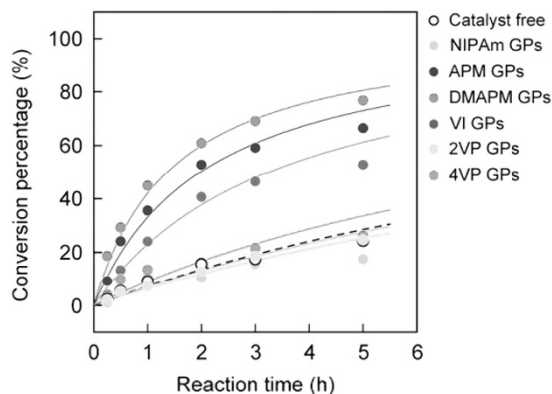
<sup>c</sup>Apparent  $pK_a$  was determined by acid–base titration with HCl under  $N_2$  gas purge.

The actual densities of the basic groups in the GPs were determined by acid–base titrations (Supplementary Figure S3). The base densities in the APM, DMAPM and VI GPs, which were obtained from neutralization points in the titrations, were 858, 886 and 897  $\mu\text{mol g}^{-1}$ , respectively, and were close to the theoretical values. The apparent  $pK_a$  values were estimated from the pH value of the half equivalence point in the titrations (Table 1). In general, the  $pK_a$  of a basic polymer is lower than its basic monomer because the basic

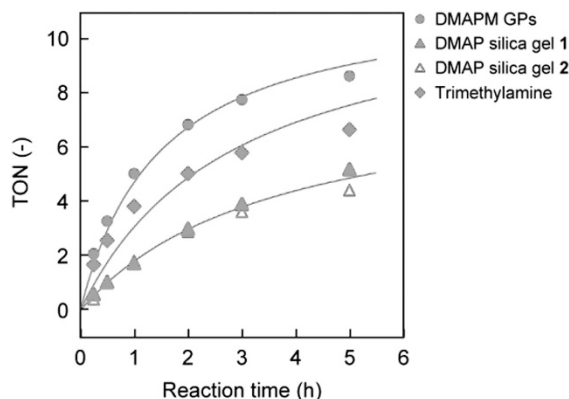
groups in the polymer are significantly closer than those of the monomers in solution.<sup>38</sup> Although the neutralization points were not observed in the titrations of 2VP and 4VP GP solutions, the VP GPs showed a buffering effect in the pH range of 2.0–3.5, which was consistently lower than the  $pK_a$  value of VI GPs. The  $pK_a$  values of VP monomers are also lower than the others; the  $pK_a$  values of APM, DMAPM, VI, 2VP and 4VP monomers are  $\sim 10$ ,<sup>39</sup> 9.8,<sup>40</sup> 5.8,<sup>41</sup> 4.9<sup>42</sup> and 5.6,<sup>42</sup> respectively. Therefore, the base strength order of the GPs is estimated to be DMAPM > APM > VI > VPs. The  $pK_a$  difference between the APM and DMAPM GPs may be attributable to the particle sizes of the GPs.<sup>43</sup>

#### Knoevenagel condensations using various basic GPs

The catalytic activities of the various basic GPs for the Knoevenagel condensation were evaluated. The conversion percentages of benzaldehyde in the Knoevenagel condensation using the GPs are shown in Figure 4. The GPs without basic groups (that is, the NIPAm GPs) did not exhibit catalytic activity for the Knoevenagel condensation, indicating that the basic groups are necessary for the Knoevenagel condensation. The 2VP and 4VP GPs had no activity for the Knoevenagel condensation. The apparent reaction rate constants for the Knoevenagel condensation were estimated as second-order reactions (Supplementary Table S2). The catalytic activities of the basic GPs increased in the order corresponding to DMAPM > APM > VI > > 4VP  $\approx$  2VP, which depends on the base strength, that is, the  $pK_a$  value. Catalysts with a higher base strength facilitate the deprotonation of activated methylene compound. It has been suggested that a proton sponge with a high  $pK_a$  value is a



**Figure 4** Conversion of benzaldehyde in the Knoevenagel condensation reaction using various GPs. [Benzaldehyde]:  $10 \text{ mmol l}^{-1}$ , [Ethyl cyanoacetate]:  $11 \text{ mmol l}^{-1}$ , [GPs]:  $1 \text{ g l}^{-1}$ , reaction temperature:  $30^\circ\text{C}$ . A full color version of this figure is available at *Polymer Journal* online.

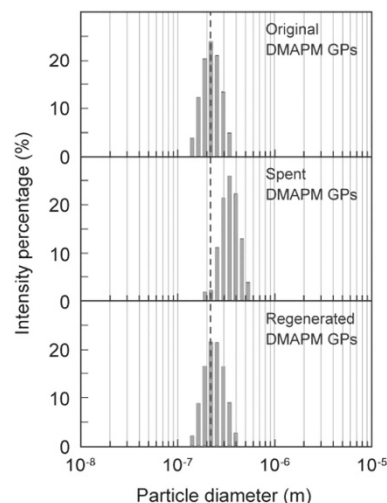


**Figure 5** Turnover numbers in the Knoevenagel condensation using the DMAPM GPs, the DMAP silica gels and trimethylamine. [Benzaldehyde]:  $10 \text{ mmol l}^{-1}$ , [Ethyl cyanoacetate]:  $11 \text{ mmol l}^{-1}$ , reaction temperature:  $30^\circ\text{C}$ . DMAP silica gels **1** and **2** were adjusted for comparisons of molar and mass concentrations, respectively. A full color version of this figure is available at *Polymer Journal* online.

more effective catalyst for the Knoevenagel condensation than 1,8-diaminonaphthalene, *N,N*-dimethylaniline, and pyridine.<sup>44</sup> Note, however, that a very high base strength leads to catalyst poisoning, in which the subsequent return of the proton to the condensed product is inhibited. Kasinathan *et al.* have also reported that the catalytic activity shows a correlation with the  $\text{p}K_{\text{a}}$  values of diamines on metal-organic frameworks, although there is a small structural influence on the reactivity.<sup>45</sup>

#### DMAPM GPs catalysts versus other basic catalysts

The catalytic activities of tertiary-amine groups incorporated in the various matrices were compared with investigate the availability of the GP geometry for catalytic activity. The turnover numbers in the Knoevenagel condensation using the DMAPM GPs, the DMAP silica gels, and trimethylamine are shown in Figure 5. The DMAPM GPs had the largest turnover number out of the basic catalysts that were used. The apparent reaction rate constants for the Knoevenagel condensation were estimated from the time course curves for the conversion of benzaldehyde (Supplementary Figure S4 and Table S2). The initial turnover frequencies using the DMAPM GPs, the DMAP silica gels, and trimethylamine were  $7.9$ ,  $2.3$  and  $4.2 \text{ h}^{-1}$ , respectively.

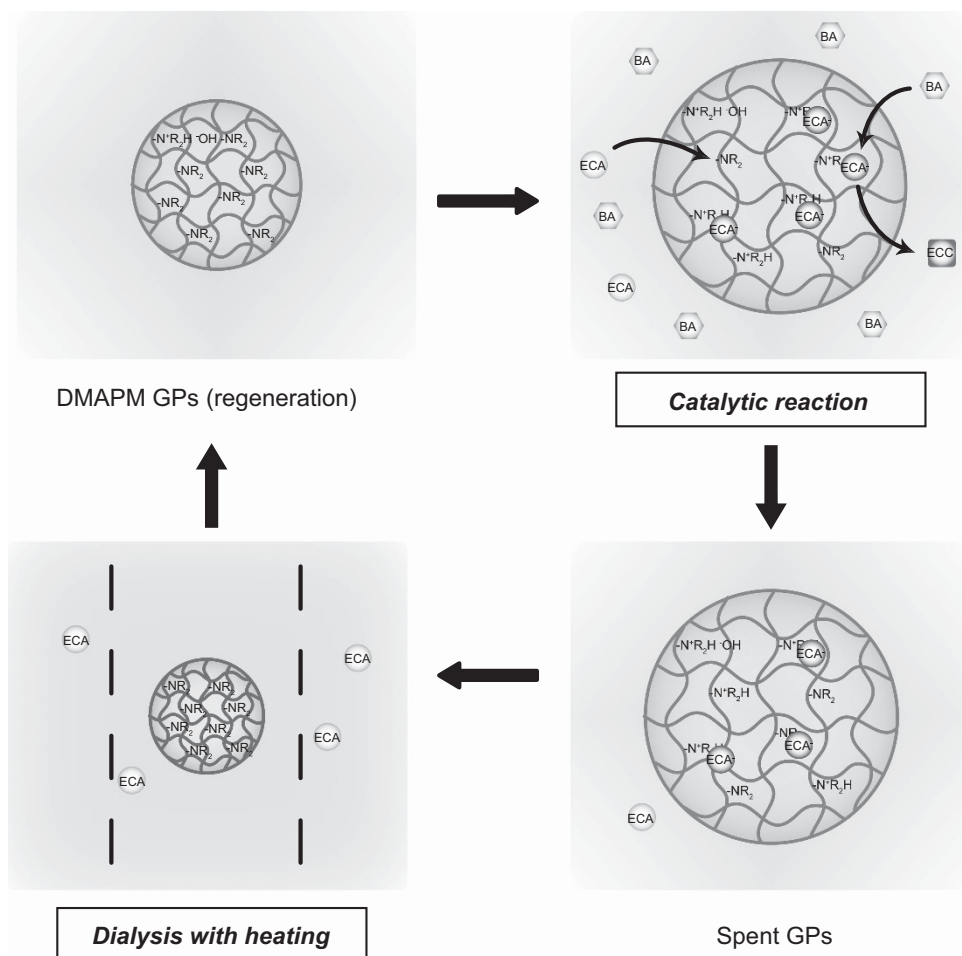


**Figure 6** Size distributions of the original, spent, and regenerated DMAPM GPs in water at  $30^\circ\text{C}$ . The dashed line represents the mean diameter of the original DMAPM GPs. A full color version of this figure is available at *Polymer Journal* online.

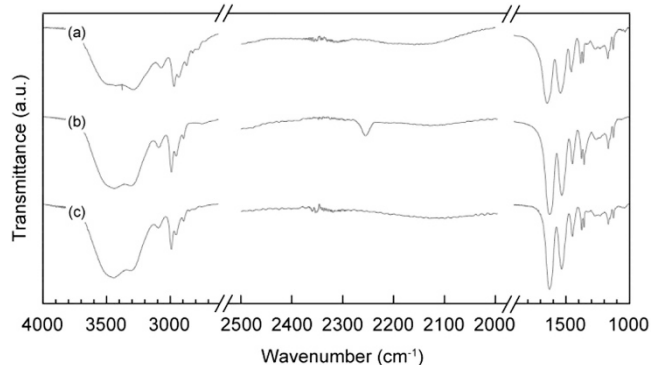
The catalytic reaction rate using the DMAPM GPs was four times higher than that using the DMAP silica gel for the same molar concentrations of tertiary-amine groups. In addition, the DMAPM GPs had an advantage in the catalytic reaction, although the tertiary-amine density in the DMAP silica gel was twice that in the DMAPM GPs for the same mass concentrations. The Knoevenagel condensation using the DMAPM GPs progressed more rapidly than the DMAPM bulk gel (Supplementary Figures S5 and S6). When silica gels and bulk gels were used as a matrix, the mass transport of the substrate to the pores and internal part of the gels was limited, and it was difficult for the substrate to access the basic groups on the surface. By contrast, the GPs were highly dispersed and had a small diameter; therefore, the accessibility of the GPs to the substrate was high. The GPs acted like a homogeneous catalyst. The final conversion percentage using the DMAPM GPs was the highest out of the basic catalysts that were used.

The catalytic activity of the DMAPM GPs was also compared with that of the homogeneous basic catalyst. Interestingly, the DMAPM GPs showed two-fold higher activity than trimethylamine, which has a higher base strength ( $\text{p}K_{\text{a}}$ : 9.8). This may be attributable to the local enrichment effect of ethyl cyanoacetate, which has often been observed in micellar catalysts.<sup>5–8</sup> When the DMAPM GPs and ethyl cyanoacetate were mixed in solution, the amount of ethyl cyanoacetate taken up by the DMAPM GPs was equal to the tertiary-amine density (Supplementary Figure S7). The polymer density of the PNIPAm-based microgels with a hydrodynamic diameter of  $\sim 120 \text{ nm}$  in the shrunken state at temperatures above the volume phase transition temperature has been suggested to be  $\sim 0.8 \text{ g cm}^{-3}$ , in which the dependency of the polymer density on the mole fraction of the crosslinker was low in the shrunken state.<sup>46</sup> The DMAPM GPs were shrunken to a hydrodynamic diameter of  $120 \text{ nm}$  at temperatures above the volume phase transition temperature (Supplementary Figure S8). Assuming that the polymer densities of the NIPAm and DMAPM GPs with the same diameter in the shrunken state are equal, the polymer density of the DMAPM GPs in the swollen state can be estimated from the hydrodynamic diameters:

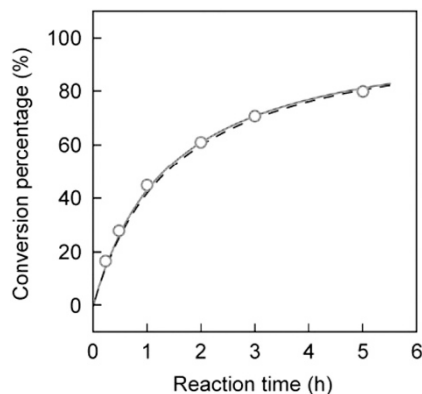
$$\rho_{\text{swollen}} (\text{g cm}^{-3}) = \rho_{\text{shrunken}} \times \left( \frac{D_{\text{shrunken}}}{D_{\text{swollen}}} \right)^3 \quad (7)$$



**Figure 7** Schematic representation of the regeneration of the GP catalysts using their thermoresponsive property. BA, ECA, ECA<sup>-</sup> and ECC represent benzaldehyde, ethyl cyanoacetate, dissociated ethyl cyanoacetate and ethyl  $\alpha$ -cyanoacrylate, respectively. A full color version of this figure is available at *Polymer Journal* online.



**Figure 8** Transmittance IR spectra of the (a) original, (b) spent and (c) regenerated DMAPM GPs. The spectra in the wavenumber range of 2500–2000  $\text{cm}^{-1}$  are enlarged four times. Assignments: 3600–3200  $\text{cm}^{-1}$  (N–H stretching vibration), 2975 and 2937  $\text{cm}^{-1}$  ( $\text{CH}_3$  and  $\text{CH}_2$  asymmetric stretching vibration, respectively), 2877  $\text{cm}^{-1}$  ( $\text{CH}_3$  and  $\text{CH}_2$  symmetric stretching vibration), 1643  $\text{cm}^{-1}$  (C=O stretching vibration, Amide I), 1547  $\text{cm}^{-1}$  (N–H deformation vibration, Amide II), 1462  $\text{cm}^{-1}$  ( $\text{CH}_3$  and  $\text{CH}_2$  asymmetric deformation vibration), and 1388 and 1368  $\text{cm}^{-1}$  ( $\text{CH}_3$  and  $\text{CH}_2$  symmetric deformation vibration, respectively). The broad peak associated with the N–H stretching vibration may be overlapped by the O–H stretching band in water. The peak at 2257  $\text{cm}^{-1}$  corresponds to C $\equiv$ N. The noise at 2350  $\text{cm}^{-1}$  corresponds to  $\text{CO}_2$ . A full color version of this figure is available at *Polymer Journal* online.



**Figure 9** Conversion of benzaldehyde in the Knoevenagel condensation using the regenerated DMAPM GPs. [Benzaldehyde]: 10  $\text{mmol l}^{-1}$ , [Ethyl cyanoacetate]: 11  $\text{mmol l}^{-1}$ , [GPs]: 1  $\text{g l}^{-1}$ , reaction temperature: 30  $^{\circ}\text{C}$ . The dashed line is the conversion curve, as estimated from the reaction rate constant of the original DMAPM GPs. A full color version of this figure is available at *Polymer Journal* online.

where  $\rho$  and  $D$  are the polymer density and the hydrodynamic diameter, respectively. From the hydrodynamic diameter of the DMAPM GPs determined using DLS, the polymer density of the DMAPM GPs at 30  $^{\circ}\text{C}$  was estimated to be 0.03–0.13  $\text{g cm}^{-3}$ . The

concentration of ethyl cyanoacetate in the gel phase is estimated using the amount of ethyl cyanoacetate adsorbed in the GPs ( $q$ , see the Supplementary Information) as follows:

$$\begin{aligned} &\text{Concentration of ethyl cyanoacetate in gel phase (mmol L}^{-1}\text{)} \\ &= q \times \rho_{\text{swollen}} \end{aligned} \quad (8)$$

It was found that 11 mmol l<sup>-1</sup> of ethyl cyanoacetate was enriched 2–10-fold in the DMAPM GPs.

### Recycling system of DMAPM GPs catalysts

The diameter of the DMAPM GPs increased after the reaction (Figure 6). In addition, the GPs were not completely shrunk even above the volume phase transition temperature, which was similar to the behavior of the DMAPM GPs in the presence of ethyl cyanoacetate (Supplementary Figure S8). In the mechanism of the Knoevenagel condensation, ethyl cyanoacetate is taken up by the basic GPs, resulting in the formation of a carbanion. The structure of the basic catalysts returned after two cycles of protonation and deprotonation, and the product was released from the GPs. Because the feed ratio of ethyl cyanoacetate to benzaldehyde was 1.1, at least 1 mmol l<sup>-1</sup> ethyl cyanoacetate remained in the solution after the reaction. The residual ethyl cyanoacetate must be released from the DMAPM GPs. Accordingly, we proposed to regenerate the catalyst using the thermoresponsivity of the DMAPM GPs (Figure 7). The apparent pK<sub>a</sub> value of the DMAPM GPs decreased with increasing temperature (Supplementary Figure S9). Hoshino *et al.* have developed reversible absorption-desorption materials for carbon dioxide gas using the thermoresponsive pK<sub>a</sub> shift of DMAPM GPs.<sup>20</sup> When the base strength of DMAPM GPs decreased, the electrostatic interaction with ethyl cyanoacetate was disrupted. The transmittance IR spectra showed that the released ethyl cyanoacetate and the DMAPM GPs were separated because the peak at 2257 cm<sup>-1</sup>, which corresponds to the cyano group, disappeared after dialysis (Figure 8). The particle size and swelling-shrinking behavior of the DMAPM GPs, regenerated by dialysis with heating, was recovered. Conversely, it was observed that the DMAPM GPs dialyzed at room temperature for only 1 day could not be regenerated (Supplementary Figure S8).

The diameter of the redispersed GPs was similar to that of the original GPs, and no aggregation was determined (Supplementary Figure S10). The DMAPM GPs solution was reused for the next Knoevenagel condensation. The conversion percentage of benzaldehyde in the Knoevenagel condensation using the regenerated DMAPM GPs is shown in Figure 9. The catalytic activity of the DMAPM GPs was maintained. The relative activity and relative conversion of the regenerated DMAPM GPs were 1.06 and 0.96, respectively. Because recovery of the DMAPM GPs from the substrate and product is easy, the DMAPM GPs can be used as an effective catalyst for green chemistry. A recycling system for the catalyst using the thermoresponsivity of the PNIPAm-based GPs has been proposed.

### CONCLUSIONS

Basic GP catalysts that catalyze the Knoevenagel condensation reaction in water at room temperature were developed. The catalytic activity for the Knoevenagel condensation depends on the base strength, that is, the pK<sub>a</sub> values of the GPs. The DMAPM GPs had the highest activity out of the prepared basic catalysts, including bulk gel and silica gel. The usefulness of the GP geometry as a polymer catalyst matrix was demonstrated. It is noteworthy that the DMAPM GPs had higher activity than trimethylamine because of the local enrichment effect of

ethyl cyanoacetate. Recycling of the catalyst is an important consideration for green chemistry. The regeneration of the catalyst using the thermoresponsivity of the DMAPM GPs was suggested as a smart functionality. When the reaction mixture solution of the GPs was dialyzed with heating, it was easy to recover the GP catalysts from the residual acidic substrates. The particle size and swelling-shrinking behavior of the DMAPM GPs was reversed. The catalytic activities in the second Knoevenagel condensation were maintained. The recycling system of the catalyst using the thermoresponsivity was established. Recently, polymer catalysts that catalyze the redox, transfer, and hydrolysis reactions in water have received much attention because of their ability to mimic enzymes. The hydrophilicity, hydrophobicity, functional group density, flexibility, acidity, and basicity of the GPs are tunable. Moreover, the molecular imprinting technique is also applicable to the design of GPs. The tuned GPs should deliver added value, that is, not only high activity but also specificity, stability and recyclability, which are important in catalytic chemistry.

### CONFLICT OF INTEREST

The authors declare no conflict of interest.

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