Thermoresponsive Polymer-Bound Substrates

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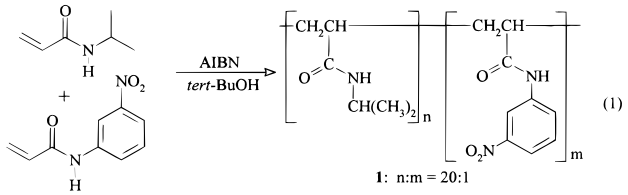
Polymers are now widely used in synthesis.[1−5] This use is most commonly seen in the synthesis of bioorganic materials like peptides and nucleotides.[1,2] Continuing advances in areas like catalysis[4] and combinatorial chemistry[5] have also led to the ever increasing use of polymer supports in more conventional organic chemistry. The main role of the polymer in much of this chemistry is that of separation. The polymer separates a substrate or catalyst from other products or facilitates separation of library members from one another. However, the intrinsic differences between polymers and small molecules mean that there are other significant ways in which polymers can be used to affect the reactivity of pendant substrate groups. Here we describe a polymer that can be used to separate and recover reagents and whose inverse temperature dependent solubility affects a substrate's solubility in useful ways. Specifically, we show how a polymer can affect a bound substrate's reactivity toward a heterogeneous hydrogenation catalyst in a reversible, responsive way by virtue of the polymer support's inverse temperature dependent solubility.

Unlike small molecules, most polymers phase separate from solution when the solution is heated.[6] In the case of a hydrocarbon polymer in organic solvents, this effect occurs above the boiling point of the solvent (e.g. poly(isobutylene) in pentane at 75 °C).[7] Water soluble polymers, however, phase separate in more accessible temperature ranges. Moreover, the temperature at which this phase separation occurs can be tuned by altering the structure of the polymer in predictable ways.[8] Recently we described examples of homogeneous catalysis in water where we used this effect to prepare so-called "smart" catalysts.[9,10] In these cases, soluble polymer-bound catalysts were prepared using polymeric ligands that possessed inverse temperature dependent solubility. The resulting catalysts were active when in solution and inactive when phase separated. This report extends and expands on this chemistry to include other polymers and polymer-bound substrates. Kinetic studies of the effects of very modest changes in temperature on these reducible polymer-bound substrates under "normal" solvent/temperature conditions and under "inverse" solvent/temperature conditions illustrate the difference from normal temperature dependent kinetic behavior. Our results suggest that poly(*N*-isopropylacrylamide) (PNIPAM) copolymer-bound substrates should be most useful in this regard. In addition, PNIPAM-bound substrates can be isolated and separated from soluble reagents simply by heating and decantation of excess water from the resulting polymer suspension.

The principle polymer substrate support used for the chemistry described below was a copolymer produced by radical polymerization of *N*-isopropylacrylamide and acrylic acid or derivatives. The most detailed kinetic studies used the copolymer **1** prepared by AIBN-initiated copolymerization of *N*-isopropylacrylamide and the *m*-nitroaniline amide of acrylic acid (eq 1). The product copolymer was characterized by ^{1}H and



(1)

^{13}C NMR and FT-IR spectroscopy. The M_v of **1** was measured and was 3.2×10^5 Da using values of 9.59×10^{-3} mL/g and 0.65 for *K* and *a* in THF at 27 °C.[11] The homopolymer poly(*N*-isopropylacrylamide) is known to have inverse temperature dependent solubility with a lower critical solution temperature (LCST) of 31−32 °C.[9,11] Variable temperature UV−visible spectroscopy studies of 0.1 N aqueous solutions of **1** at 700 nm (where there was no initial absorbance) demonstrated opacity which became apparent at 24 °C. The solution was visually opaque at 27 °C.

Other PNIPAM copolymers more appropriate for use as supports in synthesis have solubility like **1**. Copolymers prepared using 5 mol % of acrylic acid, *p*-acrylamidobenzoic acid, *p*-acrylamidophenol, and *p*-acrylamidohydroxymethylbenzene as comonomers had LCSTs of 31, 29, 27, and 38 °C, respectively. Each of these polymers can be dissolved in water and recovered by gentle heating and decantation of the water and any soluble impurities.

Substrates supported on these PNIPAM copolymers react normally under homogeneous conditions. For example, the polymer-bound nitroarene **1** was readily hydrogenated using Pt/C in ethanol with a rate of 3.7×10^{-2} mL of H_2/min at 0 °C. This rate was comparable to the rate of hydrogenation of this same polymer-bound sample in H_2O (4.9×10^{-2} mL of H_2/min) at 0 °C. A low molecular weight substrate *m*-acetamidonitrobenzene, was hydrogenated to form an aminoamide with a rate of 3×10^{-2} mL of H_2/min in ethanol with the same catalyst under the same conditions. These data show that attachment of the substrate to this polymer had little effect on its reactivity toward the heterogeneous Pt/C catalyst when the solution of the polymer-bound arene was homogeneous.

The consequences of phase separation of the polymer-bound substrate on hydrogenation rate are shown in Figure 1. As illustrated, hydrogenation proceeded when the polymer was in solution (0−33 °C) but decreased at least 50-fold (no hydrogenation was detected for 4 h) when the polymer-bound substrate was phase separated (>39 °C). This demonstrates that the temperature dependent polymer solubility controls the reactivity and kinetic accessibility of bound substrates in appropriate solvents. We also used NMR spectroscopy to verify that hydrogenation had occurred in reactions below 33 °C. The product polymer-bound aryl amine was distinguishable from the starting nitro compound, based on the changes in the aromatic region of the ^{1}H NMR spectrum. The starting polymer had broad peaks at δ 8.6, 7.9, and 7.4 while the product had similar peaks at δ 7.0, 6.8, and 6.3.

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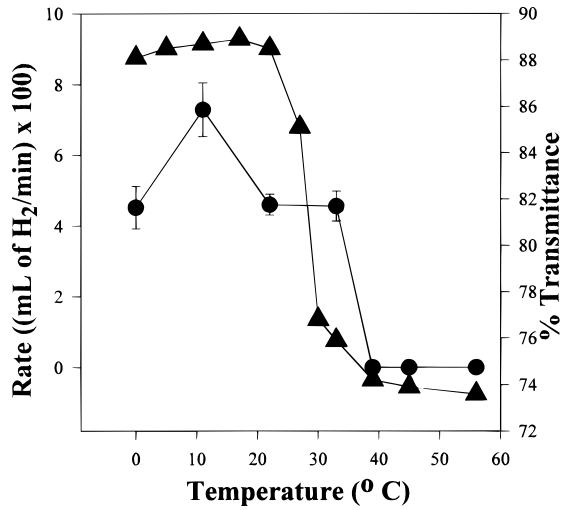


Figure 1. Plot of absorbance of a solution of **1** in water (▲) measured at 240 nm as a function of temperature superimposed on a plot showing the rate of hydrogenation of **1** at the same temperatures (●) using 5% Pt/C and H_2 at atmospheric pressure.

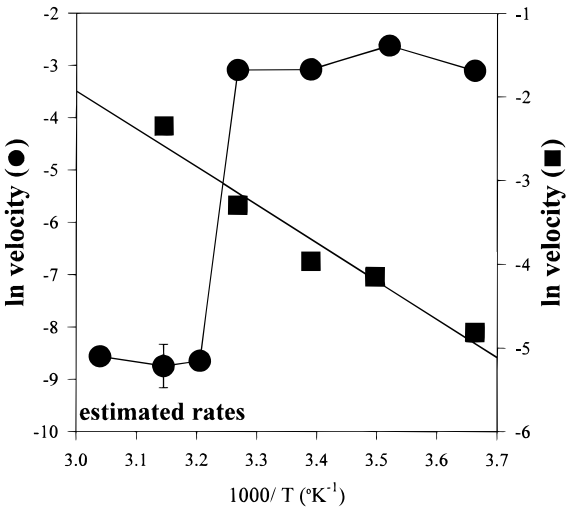


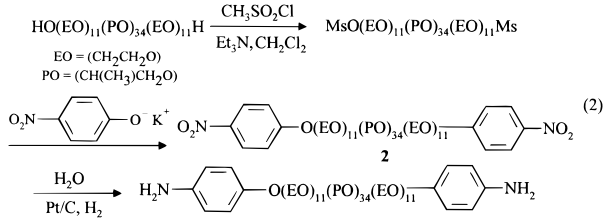
Figure 2. Plots of the dependence of hydrogenation rate with temperature for hydrogenations carried out in EtOH (■) or water (●) at temperatures from 0 to 50 °C.

Arrhenius plots in Figure 2 for hydrogenation reactions in water or ethanol clearly show the contrast between the normal effects of temperature on these rates and the effects of temperature on rates when a temperature responsive polymer support is used. In ethanol, normal Arrhenius behavior is seen and the rate is linearly correlated with $1/T$. However, in water, phase separation of the polymeric catalyst from water effectively removes the substrate from solution and leads to no detectable hydrogenation. In these cases, we estimated a minimal rate for hydrogenation and used this rate (1×10^{-3} mL of H_2/min) in the plot. The actual rate could be less than this estimate, but this would only mean that the anomalous effects of temperature shown in Figure 2 would be greater. Equally noteworthy is the fact that this behavior is completely reversible. The solutions that were inactive in hydrogenation reactions above 39 °C could simply be cooled whereupon the substrate redissolved and the hydrogenation continued as before.

As shown in Figure 2, the rate dependence on temperature of the water solution is not at all Arrhenius-like. The inactivity above the LCST point presumably reflects the fact that the polymer under these conditions is essentially out of solution. Before that point, the rate changes little over the range 0−33 °C with a slight increase followed by slight decrease in rate as the LCST point is approached. This behavior may reflect a combination of normal Arrhenius behavior and the effects seen in Figure 1 that were ascribed to aggregation preceding supraaggregation and phase separation.

Substrates bound to other PNIPAM copolymers have similar behavior. For example, CBZ-protected glycine attached to the phenolic hydroxyl group of a PNIPAM copolymer (LCST of 29 °C) containing *N*-(*p*-hydroxyphenyl)acrylamide was inert to hydrogenolysis above 38 °C. However, this polymer-bound amino acid was readily hydrogenolyzed at 10 °C. The ready availability of other PNIPAM copolymers (*vide supra*) and their similar temperature dependent solubility suggest that this sort of kinetic behavior should be general.

We also briefly examined other polymers that phase separate from water solutions with increases in temperature. For example, we briefly examined the polymer-bound substrate **2**. This material was prepared by alkylation of a commercially available triblock surfactant with the potassium salt of *p*-nitrophenol as shown in equation 2. However, while this



(2)

polymeric substrate did exhibit phase separation and an LCST as did **1**, phase separation in this case produced an oil-in-water emulsion. The rate of heterogeneous hydrogenation of this substrate by Pt/C did not uniformly increase with temperature past the LCST point. Kinetics studies here were complicated by catalyst fouling by the oily hydrophobic polymer above the LCST point. While we did not see Arrhenius-like kinetics in this case, the decrease in the hydrogenation rate with temperature varied from run to run.

In summary, it is possible to use the inverse temperature dependent solubility of polymers to control the reactivity of bound substrates toward phase-separated catalysts. Such temperature dependent kinetic isolation may have analogies in systems where pH, ionic strength, or polarity vary. As illustrated here, such phase separation behavior can turn reaction rates on and off. Such behavior in other systems could be used to kinetically isolate reagents in multistep syntheses and to generally affect reactions that depend on the presence of a soluble substrate. This solubility change with temperature also provides a mechanism to recover polymer-bound substrates from an aqueous solution. Given the resurgence of interest in the use of polymer supports in synthesis of organic and biological substrates and the fact that many easily accessible copolymers of N-isopropylacrylamide exhibit this sort of phase separation, this type of phenomenon could be useful both in controlling reactivity and in synthesis.

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