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Smart Ligands That Regulate Homogeneously Catalyzed Reactions

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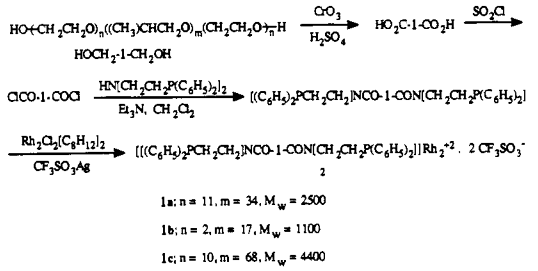
Developments that have led to control over function and physical properties in materials have led to an exciting concept—smart materials.[1,2] Such materials undergo some physical property change, such as a phase change, in response to a stimulus. In materials science, a desirable outcome might be a change in a material's tensile strength, resistivity, or some other mechanical property. In this work, we have extended this concept to include ligand chemistry. The utility of ligands in modifying the steric and electronic environment of homogeneous catalysts is well established. Likewise, there has been considerable effort since the late 1960s to develop ligands that alter a catalysts' solubility. These latter efforts have generally focused on using insoluble polymers to phase-isolate a catalyst. The use of soluble polymers to effect phase isolation with minimal alteration of a catalyst's activity is also known.[3] In each instance, the underlying idea was to use the properties of macromolecules to control the physical properties of a catalyst. Here we describe our initial work that extends this idea in a novel way through the synthesis of "smart" ligands—ligands that control a catalyst's activity as a function of temperature.

The synthesis of catalyst ligands from polymers that possess a property termed inverse temperature-dependent solubility illustrates the potential of this concept. Such polymers have the unusual property of undergoing a temperature-dependent phase change wherein they dissolve on cooling and phase separate on heating above the lower critical solution temperature. In a common example, polyacrylamides or poly(alkene oxides) precipitate or phase separate from water on heating and redissolve on cooling.[4-6] Several explanations for these phenomena have been offered. The simplest rationalizes these solubility changes in terms of the entropy effects arising from desolvation of the polymer by water at higher temperatures. In this case, the polymer becomes increasingly more hydrophobic as the temperature is increased. By varying the polymer microstructure and hydrophobicity, we can control the temperature of this phase change. As is shown below, this property can be designed into a catalyst ligand and hence into a catalyst to yield catalysts that respond in a regulatory way to increases in reaction temperature.

Our initial efforts at syntheses of smart ligands focused on modification of known polymers. Poly(alkene oxides) and, more specifically, block copolymers of ethylene oxide, propylene oxide, and ethylene oxide are known and commercially available materials having inverse temperature dependence in water.[7] We have found that the end group of these polymers can be chemically modified either by oxidation and subsequent amide formation or by mesylation and nucleophilic substitution with $LiPPh_2$ to yield phosphine ligands that are soluble at low temperatures but which phase-separate at higher temperatures. For example, the bis(2-diphenylphosphinoethyl)amide derivative of the PEO–PPO–PEO oligomer (**1**) has inverse temperature-dependent solubility in water (eq 1). While the exact lower critical solution temperature varied with the proportion of PEO/PPO in the starting oligomer, a typical oligomer having a molecular weight of 2500 and 20 mol % ethylene oxide was soluble at 0 °C in water but was insoluble above room temperature based on the observation of a distinct cloud point on warming from 0 °C to room temperature. A similar solubility change of **3** (*n* = ca. 2000) occurred above 95 °C (eq 2).



$$\underset{\text{HOCH}_2\text{-}\mathbf{1}\text{-CH}_2\text{OH}}{\text{HO}\!-\!(\text{CH}_2\text{CH}_2\text{O})_n((\text{CH}_3)\text{CHCH}_2\text{O})_m(\text{CH}_2\text{CH}_2\text{O})_{\overline{n}}\text{H}} \xrightarrow[\text{H}_2\text{SO}_4]{\text{CrO}_3} \text{HO}_2\text{C-}\mathbf{1}\text{-CO}_2\text{H} \xrightarrow{\text{SO}_2\text{Cl}}$$

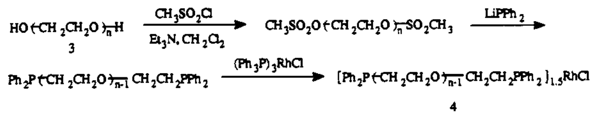
$$\text{ClCO-}\mathbf{1}\text{-COCl} \xrightarrow[\text{Et}_3\text{N, CH}_2\text{Cl}_2]{\text{HN[CH}_2\text{CH}_2\text{P(C}_6\text{H}_5)_2]_2} [(\text{C}_6\text{H}_5)_2\text{PCH}_2\text{CH}_2]\text{NCO-}\mathbf{1}\text{-CON[CH}_2\text{CH}_2\text{P(C}_6\text{H}_5)_2] \qquad (1)$$

$$\xrightarrow[\text{CF}_3\text{SO}_3\text{Ag}]{\text{Rh}_2\text{Cl}_2[\text{C}_8\text{H}_{12}]_2} \underset{\mathbf{2}}{[[(\text{C}_6\text{H}_5)_2\text{PCH}_2\text{CH}_2]\text{NCO-}\mathbf{1}\text{-CON[CH}_2\text{CH}_2\text{P(C}_6\text{H}_5)_2]]\text{Rh}_2^{+2}\cdot 2\,\text{CF}_3\text{SO}_3^-}$$

1a; n = 11, m = 34, M_w = 2500

1b; n = 2, m = 17, M_w = 1100

1c; n = 10, m = 68, M_w = 4400



$$\underset{\mathbf{3}}{\text{HO}\!-\!(\text{CH}_2\text{CH}_2\text{O})_{\overline{n}}\text{H}} \xrightarrow[\text{Et}_3\text{N, CH}_2\text{Cl}_2]{\text{CH}_3\text{SO}_2\text{Cl}} \text{CH}_3\text{SO}_2\text{O}(\text{CH}_2\text{CH}_2\text{O})_{\overline{n}}\text{SO}_2\text{CH}_3 \xrightarrow{\text{LiPPh}_2} \qquad (2)$$

$$\text{Ph}_2\text{P}(\text{CH}_2\text{CH}_2\text{O})_{\overline{n-1}}\text{CH}_2\text{CH}_2\text{PPh}_2 \xrightarrow{(\text{Ph}_3\text{P})_3\text{RhCl}} \underset{\mathbf{4}}{[\text{Ph}_2\text{P}(\text{CH}_2\text{CH}_2\text{O})_{\overline{n-1}}\text{CH}_2\text{CH}_2\text{PPh}_2]_{1.5}\text{RhCl}}$$

Typical synthetic routes to ligands (and catalysts) that phase-separate on heating are shown in eqs 1 and 2.[8] In a typical ligand synthesis, a PEO–PPO–PEO triblock oligomeric surfactant was first oxidized with CrO_3 in sulfuric acid. The dicarboxylic acid so formed was isolated and purified by flash chromatography using acetone as the eluting solvent to yield 70% of the diacid that was characterized by ^1H NMR and IR spectroscopy (1710 cm^{-1}). The diacid (2 g) was then treated with 40 mL of $SOCl_2$ containing a few drops of DMF. After the solution was stirred overnight at 25 °C, the excess thionyl chloride was removed under reduced pressure to yield a crude diacid chloride (IR 1810 cm^{-1}). This crude acid chloride was directly used in the next step without further purification to form an amide by reaction of 0.29 mmol of the diacid chloride with 0.58 mmol of bis(2-diphenylphosphinoethyl)amine. In forming the amidophosphine, the acid chloride was dissolved in CH_2Cl_2 along with DMF and excess triethylamine (to take up any HCl formed). Other phosphine-containing ligands with inverse temperature-dependent solubility were also accessible from poly(ethylene oxide) using the route shown in eq 2. However, since the ligand **3** exhibited inverse temperature-dependent solubility only at high temperatures, (between 95–100 °C), we focused our attention on catalyst studies on derivatives of **1a**.

Cationic rhodium(I) complexes prepared using ligands derived from **1** have inverse temperature-dependent solubility and an LCST like that of the starting ligand. The practical implications of this solubility can be seen in hydrogenations in water using the cationic rhodium complex **2**. Figure 1 shows the results of hydrogenations carried out through a series of temperature regimes. In Figure 1, the catalytic hydrogenation reaction of allyl alcohol in water proceeded at a rate (2 mmol of H_2/mmol of Rh/h) comparable to that of a similar catalyst ligated by a poly(ethylene glycol)-derived phosphine ligand at 25 °C.[8] While this rate for a hydrogenation reaction occurring in water is not of particular interest, the behavior of this catalyst on heating is

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(1) Whitesides, G. M. *Angew. Chem., Int. Ed. Engl.* **1990,** *29,* 1209–18.

(2) Yanagida, H. *Angew. Chem., Int. Ed. Engl.* **1988,** *27,* 1389–92. Garnier, F. *Angew. Chem., Int. Ed. Engl.* **1989,** *28,* 513–7.

(3) Bergbreiter, D. E. *ACS Symp. Ser.* **1986,** *308,* 17–41.

(4) Bailey, F. E.; Koleske, J. V. *Poly(ethylene oxide)*; Academic Press: New York, 1976.

(5) Clinton, N.; Matlock, P. In *Encyclopedia of Polymer Science and Engineering, Vol. 6*; John Wiley & Sons: New York, pp 225–73.

(6) Winnik, F. M.; Ottaviani, F. M.; Bossmann, S. H.; Garcia-Garibay, M.; Turro, N. J. *Macromolecules,* **1992,** *25,* 6007–17.

(7) These surfactants are commercially available through BASF and have the Pluronics tradename.

(8) The syntheses of **1** and **3** were modeled on a synthesis of a water-soluble PEO-bound cationic rhodium(I) complex, cf.: Nuzzo, R. G.; Haynie, S. L.; Wilson, M. E.; Whitesides, G. M. *J. Org. Chem.* **1981,** *46,* 2861–7. Nuzzo, R. G.; Feitler, D.; Whitesides, G. M. *J. Am. Chem. Soc.* **1979,** *101,* 3683–5.

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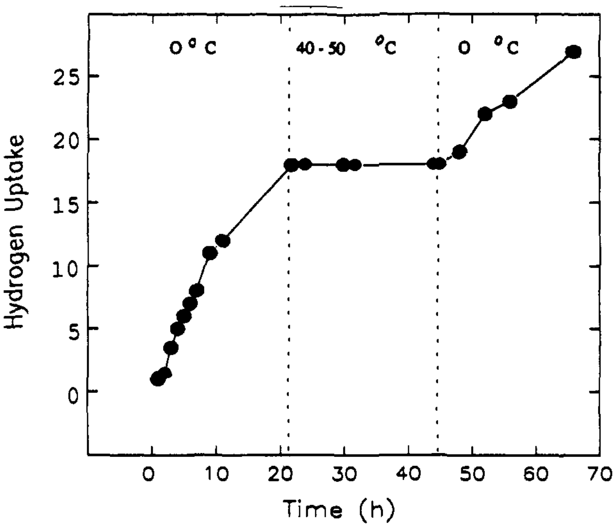

Figure 1. Hydrogenation of allyl alcohol using a cationic rhodium(I) hydrogenation catalyst that contains a "smart ligand" showing the effect on hydrogenation rate of different reaction temperatures. Anti-Arrhenius behavior is illustrated by the cessation of hydrogen uptake when the temperature was raised and the resumption of the reaction on recooling.

striking. On heating of the sample to 40–50 °C, the reaction stops. Although normal Arrhenius-type kinetics suggest that this temperature change should lead to a reaction occurring ca. 20-fold faster, the reaction rate *decreased* by a factor of 20 or more. This ca. 400-fold change in rate is due to the solubility changes that the complex **2** experiences on heating. This effect is reversed on cooling to 0 °C, where the ligand is rehydrated and where the catalyst redissolves. These effects were also observed in hydrogenations of other substrates and could be observed through a series of up to four heating/cooling cycles. However, gradual catalyst deactivation appeared to occur over long-term experiments that exceeded 1 week.

This same effect can be seen in other solvents or solvent mixtures. Catalyst **2** was ineffective in hydrogenations of α-acetamidoacrylic acid in pure water because of the low solubility of the substrate. However, use of a pH 8 buffer and a 1:1 (v/v) ethanol–water mixture produced solutions of the catalyst **2** and the substrate. Active hydrogenation occurred in such solutions at 0 °C. As was true in water, a cessation of the hydrogenation reaction occurred on heating (50–60 °C). In these cases, catalyst phase separation produced a dispersion of clear oily droplets in the aqueous phase.

Inverse temperature-dependent solubility of polymers can be observed in both organic and aqueous solutions. This, coupled with results from our prior work with soluble oligomeric catalysts which have shown that oligomer ligands do not affect catalysts in other than physical ways,[3] suggests that these effects could be broadly applicable. Our limited experience and literature data show that the temperature of phase separation of these ligands and catalysts can be controlled through variations in the oligomer's microstructure. The idea of moderating a catalyst's activity through solubility changes resulting from a temperature change could be potentially useful in controlling exothermic reactions, controlling temperature-dependent selectivity changes in asymmetric catalysis, and controlling temperature throughout a reactor. It is an effect seen in a crude way in protein denaturation and likely also has some manifestation as a process affecting selectivity and/or rate in biological systems.

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