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Living Ring-Opening Metathesis Polymerization in Water

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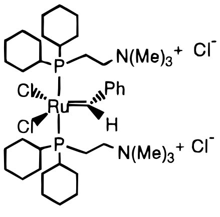
The development of functional group tolerant, late transition metal polymerization catalysts has recently enabled living ring-opening metathesis polymerization (ROMP),[1a−c] free-radical polymerization,[1d] and polymerization of isocyanides[1e] in wet organic media. Although these examples represent significant advances toward entirely aqueous systems, the catalysts (and often the monomers) are insoluble in water, and the polymerization reactions take place in the organic phase. The development of water-soluble catalysts that will polymerize monomers in a living fashion[2] in entirely aqueous solution has remained a principal synthetic goal, particularly in light of emerging biomedical applications for water-soluble polymers which demand precise control over polymer length and polydispersity.[3] We report the first example of a living polymerization taking place in entirely aqueous solution, in the absence of surfactants or organic solvents, using ROMP initiated by water-soluble ruthenium alkylidene complexes.

The aqueous ROMP of strained, cyclic olefins initiated by group VIII salts and coordination complexes is well-documented.[4] Although these complexes serve as robust polymerization catalysts in water, the polymerizations are not living and inefficient initiation steps produce erratic results (typically less than 1% of metal centers are converted to catalytically active species). Recently, we reported water-soluble ruthenium complexes **1** and **2**, containing preformed alkylidene fragments that initiate rapidly and quantitatively.[5] This dramatic increase in initiation efficiency prompted us to investigate the potential for these alkylidenes to initiate living polymerizations in entirely aqueous solution.



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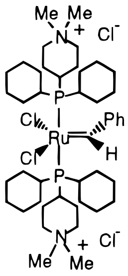

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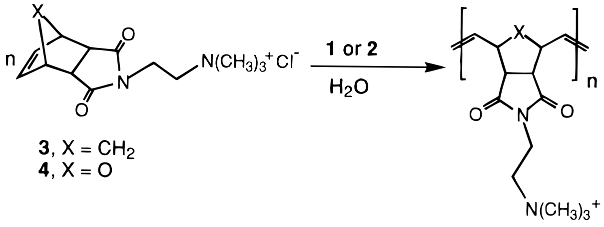
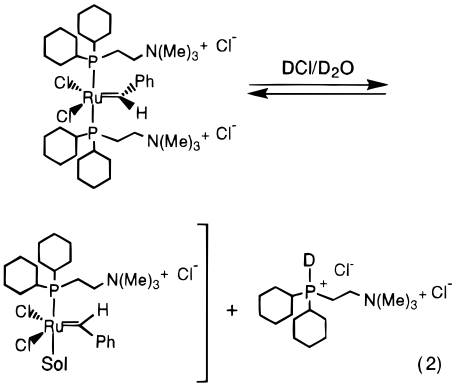
Although complexes **1** and **2** initiate ROMP in a well-defined manner, further investigations indicated that the propagating species in these reactions decomposed before polymerization was complete. For example, in the ROMP of water-soluble monomers **3** and **4** (eq 1), conversions of up to 45−80% were typically observed. Consistent with data obtained for earlier "classical" aqueous ROMP systems,[6] we determined that the presence of hydroxide ions in aqueous solutions of **1** and **2** resulted in rapid decomposition. In an attempt to eliminate small concentrations of hydroxide ions which could result from the autoprotolysis of water, or from the basic nature of the phosphines employed, we investigated the compatabilities of **1** and **2** with Brønsted acids.



(1)

3, X = CH$_2$
4, X = O

Upon addition of 0.3 equiv of DCl to a solution of complex **1** in D$_2$O, a new alkylidene species was generated, in addition to the parent carbene, which has been identified *via* ^{1}H and ^{31}P NMR spectroscopies as a monophosphine derivative of **1** (eq 2).



(2)

Remarkably, the acid did not react with the ruthenium−carbon bond, but rather protonated an equivalent of phosphine to form a phosphonium salt.[7] This monophosphine derivative was surprisingly stable—addition of excess phosphine to the reaction mixture up to 1.5 h after addition of acid reversed the equilibrium in eq 2, reforming **1** with less than 5% detectable decomposition. We believe that water may coordinate to the monophosphine species, stabilizing it toward bimolecular decomposition.[8] Protonation of phosphine in this manner is not stoichiometric. For instance, the addition 1.0 equiv of DCl yielded an equilibrium mixture of monophosphine and bisphosphine alkylidene species in a ratio

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(5) Mohr, B.; Lynn, D. M.; Grubbs, R. H. *Organometallics* **1996**, *15*, 4317−4325.

(6) Initiation periods for the classical catalysts are sometimes shorter at lower pH, while rapid catalyst deactivation occurrs in alkaline solution. Novak, B. M. Ph.D. Thesis, California Institute of Technology, 1989.

(7) The phosphonium salt generated *in situ* has been identified through comparison to spectroscopic data characteristic of the independently synthesized material.

(8) A well-known decomposition pathway for metal alkylidenes is bimetallic coupling. For ruthenium alkylidenes of the type (PR$_3$)$_2$Cl$_2$Ru=CHR, this coupling is sterically discouraged by the two coordinated phosphines. A monophosphine complex, having a more sterically exposed metal center, might be expected to decompose more rapidly, although this is not observed in aqueous solution. Coordination of water could yield a more protected 16- or 18-electron species, although no direct evidence for this type of coordination has been observed.

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of 1:2. The alkylidenes decomposed more rapidly under these conditions in the absence of monomer.

As anticipated, we found that monomers **3** and **4** could be completely polymerized when up to 1.0 equiv of DCl was added to the reaction mixture. Additionally, the presence of acid also had a profound effect on the reaction rate: the polymerizations were up to 10 times faster than those to which no acid had been added. More significantly, two propagating alkylidenes, corresponding to both bisphosphine and monophosphine species, were observed by ^{1}H NMR spectroscopy following complete consumption of monomer,[9] and the addition of more monomer to the reaction mixture resulted in further quantitative polymerization. The direct observation of propagating species is important, as it allows the extent of chain termination, a key factor in defining a living system, to be easily and directly addressed throughout the course of the reaction.[10]

The alkylidenes observed in the above reactions are significantly more stable than the initiating species **1** and **2**. In fact, at ambient temperature, the propagating species in these reactions can be observed for over three months. In addition to the relatively low concentration of the monophosphine species dictated by the equilibrium in eq 2, stability toward bimolecular decomposition is presumably imparted *via* the relative steric bulk of the propagating alkylidene. The ^{1}H NMR resonances for the two propagating alkylidenes coalesce at higher temperatures, indicating rapid equilibration *via* phosphine scrambling.

To probe the living nature of the aqueous polymerizations conducted in the presence of acid, an NMR-scale polymerization of monomer **3** was conducted employing DCl (1.0 equiv relative to alkylidene), and the relative amount of propagating species was quantified by integration of the alkylidene protons against the aromatic protons of the polymer endgroups. After 15 min at 45 °C, the reaction was >95% complete and the relative integration of the alkylidene protons of the two propagating species (coalesced as a broad singlet at 19.2 ppm) did not decrease either during the reaction or after all monomer had been consumed (Figure 1).[11] In fact, the propagating species remained intact for an additional 15 min in the absence of monomer before slowly decomposing.

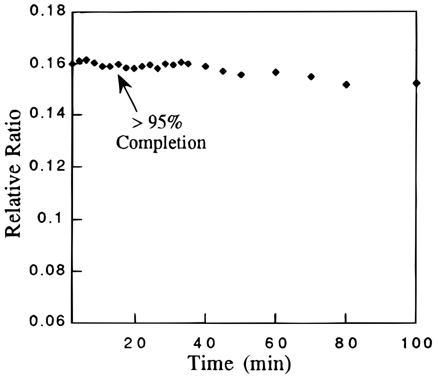

Figure 1. Ratio of propagating alkylidene, relative to polymer endgroups, over time for the polymerization of monomer **3** initiated by **1** in the presence of 1.0 equiv of DCl at 45 °C.

A block copolymerization of monomers **3** and **4** was carried out, by sequential monomer addition, to demonstrate the robust nature of the propagating species in these reactions. After complete polymerization of monomer **3**, the reaction was allowed to sit for 5 min before 20 equiv of monomer **4** were injected. Monomer **4** was rapidly and completely consumed, and the concentration of the propagating species remained constant both during and after the polymerization of the second block. Within the limits of NMR sensitivity, the direct observation and quantification of the propagating alkylidenes in the above experiments demonstrates the absence of chain termination in these reactions. The fact that the alkylidene resonance does not disappear over a time period twice as long as the time scale of the reaction indicates that these systems are indeed living.

Gel permeation chromatography (GPC) analysis of these polymers yields a symmetric, monomodal peak with a polydispersity index (PDI) as low as 1.3. The reasons for this broadening are unclear at this point, although in aqueous GPC artificial peak broadening may occur due to ionic interactions between charged polymers and charged species on the gel phase.[12] Additionally, the equilibrium between the bisphosphine propagating species and the monophosphine propagating species could be responsible for the observed broadening, as the monophosphine species is a more active polymerization catalyst (see below).[13] We are currently investigating the factors governing peak broadening in these systems.

The equilibrium represented in eq 2 provides a straightforward explanation for the rate enhancements in the polymerizations described above. For alkylidene complexes of the type $(PR_3)_2Cl_2Ru{=}CHR$, olefin metathesis has been shown to proceed through a mechanism in which a phosphine dissociates from the metal center.[14] Rates of olefin metathesis in organic systems have been increased by the addition of phosphine scavengers, although the catalyst rapidly decomposes under these conditions. In aqueous systems employing complexes **1** and **2**, protons act as phosphine scavengers, increasing the rate of olefin metathesis without concomitant acceleration of catalyst decomposition. The differences in the rates of propagation and termination under these conditions facilitates rapid, quantitative conversion of monomer in a living manner.[15]

In summary, we have reported the first example of a homogeneous living polymerization in water. In the presence of a Brønsted acid, alkylidene complexes **1** and **2** will quickly and quantitatively initiate the living polymerization of water-soluble monomers in the absence of surfactant or organic solvents. These systems represent significant improvements over "classical" aqueous ROMP catalysts. The stabilities of the propagating species in these reactions have been demonstrated, and the synthesis of water-soluble block copolymers has been achieved by sequential monomer addition. Notably, the polymerizations are not living in the absence of acid. The effect of the acid in these systems appears to be two-fold—in addition to eliminating hydroxide ions, which would cause catalyst decomposition, catalyst activity is also enhanced by protonation of phosphine ligands. Remarkably, the acids do not react with the ruthenium alkylidene bond. Ongoing efforts focus on lowering polydispersities in these systems, as well as the synthesis of water-soluble polymers with biomedical relevance.

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Supporting Information Available: Experimental details (2 pages). See any current masthead page for ordering information and Web access instructions.

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[9] In "classical" aqueous systems, propagating species have never been observed.

[10] For leading references on experimental criteria for the determination of living polymerizations, see: (a) Quirk, R. P.; Lee, B. *Polym. Inter.* **1992**, *27*, 359−367. (b) Matyjaszewski, K. *Macromolecules* **1993**, *26*, 1787−1788.

[11] The slight deviation from the theoretical ratio of 0.2 observed in Figure 1 is also observed for complexes **1** and **2**, as well as other ruthenium carbene complexes.

[12] Barth, H. G. *J. Chromatogr. Sci.* **1980**, *18*, 409−429.

[13] Matyjaszewski, K. *J. Phys. Org. Chem.* **1995**, *8*, 197−207.

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[15] The activation of these complexes with strong acids does not preclude application to the ROMP of acid-sensitive monomers. The stoichiometric acid initially added to the alkylidene complex reacts to form a phosphonium salt, and acid-labile monomers can be added to this significantly less-acidic solution of activated catalyst to effect polymerization.