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Dynamic Measurements of Aqueous Lanthanide Triflate-Catalyzed Reactions Using Luminescence Decay

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Carbon−carbon bond forming reactions are of paramount significance in synthetic chemistry. A wide range of important carbon−carbon and carbon−heteroatom bond-forming reactions can be catalyzed with water-tolerant lanthanide triflates, $Ln(OTf)_3$.[1−3] Attempts to use these water-tolerant precatalysts in stereoselective reactions have been successful only in cases of limited substrate scope.[1,4] A major hindrance preventing the widespread use of lanthanide triflates in aqueous asymmetric carbon−carbon bond formation is the nominal mechanistic understanding of the catalysts in aqueous solution. Specifically, an unanswered question in aqueous lanthanide triflate-based catalysis is if complete loss of triflate from the precatalyst occurs during catalysis: is x greater than zero in Scheme 1? While knowledge of triflate dissociation should aid in the design of catalysts for aqueous asymmetric reactions, inconclusive support both for and against complete dissociation exists.[2,5]

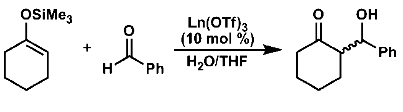
Scheme 1. Hydration of the Precatalyst[a]

$$Ln(OTf)_3 \xrightarrow[\text{conditions}]{\text{aqueous catalysis}} Ln(H_2O)_q(OTf)_x + (3-x)OTf$$

[a] Charges have been omitted for simplification.

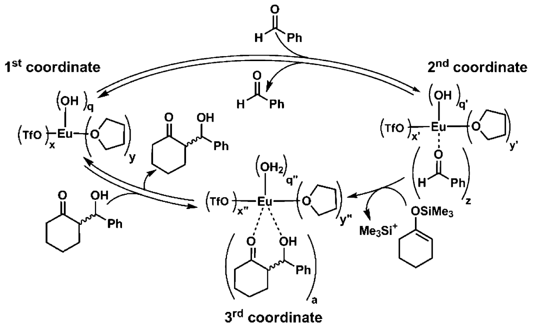
Our strategy for examining triflate dissociation was to use luminescence-decay measurements, which are commonly used to study water-coordination number with lanthanide-based contrast agents for magnetic resonance imaging.[6,7] In using this technique, two solutions of a europium (or terbium) complex are prepared: one in a solution containing H_2O and one in a solution containing D_2O. These two solvents are used because lanthanide-based luminescence is quenched at different rates by O−H and O−D vibrations near the metal ion. The luminescence-decay rates of the two solutions are measured using a spectrofluorometer. These rates are used to determine the number of water molecules, q, coordinated to the lanthanide ion using equations developed by Horrocks and co-workers (see Supporting Information for details).[8] Compared to other methods, such as X-ray crystallography and infrared spectroscopy, this characterization method is advantageous because it allows for the direct, quantitative observation of reactions in aqueous solution. In addition to being water-tolerant, luminescence-decay measurements are fast (∼10 ms) and dynamic, making them perfectly suited for the study of lanthanide-based aqueous catalysis. We hypothesized that these properties would allow us to examine discrete reaction coordinates without perturbing the system being studied. To the best of our knowledge, the use of luminescence-decay measurements to study catalytic bond-forming reaction mechanisms has not been reported. As proof of the applicability of luminescence-decay measurements to study lanthanide-based catalysts, we examined the Mukaiyama aldol reaction in Scheme 2 because the Mukaiyama aldol reaction is one of the most important carbon−carbon bond-forming reactions.[9]

Scheme 2. $Ln(OTf)_3$-Catalyzed Mukaiyama Aldol Reaction



To answer the question of triflate dissociation in the Mukaiyama aldol reaction using luminescence-decay measurements, we divided the catalytic cycle of the reaction into three reaction coordinates (Scheme 3). This division made possible the separate examination of each reaction coordinate. The first reaction coordinate was generated by dissolving $Eu(OTf)_3$ in mixtures of water and tetrahydrofuran (THF). While many water-miscible solvents can be used for these reactions, we chose THF to avoid complications that could arise from solvents containing O−H or N−H oscillators.[8] The second and third reaction coordinates were generated by adding benzaldehyde or 2-(hydroxyphenylmethyl)cyclohexanone to the first reaction coordinate solutions. For each reaction coordinate, the concentration of precatalyst and substrate matched reported reaction conditions.[2] The amount of water was varied from 1 to 100%, and the validity of the method in each solvent was confirmed by measuring the water-coordination number of 2,2′,2″-(10-(2-hydroxyethyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetoeuropium(III). This complex has a water-coordination number of 1,[6] and a water-coordination number of 1 was determined using luminescence-decay measurements in every ratio of water to THF used (Supporting Information, Table S1, Page S7).[6] The Eu^{3+} ion was used in these studies because it has a large energy gap between its emissive and ground states ($\Delta E = 1.23 \times 10^4$ cm^{-1}) and a long-lived (9.67 ms) excited state in aqueous media.[10] Further, Eu^{3+} is commonly used to represent all of the lanthanides because it is centrally located in the series and, like all lanthanides, has a maximum water-coordination number, q, between 8 and 9.[8,11]

Scheme 3. Catalytic Cycle of an Aqueous $Eu(OTf)_3$-Catalyzed Mukaiyama Aldol Reaction[a]



[a] The subscripts a, q, x, y, and z represent the number of 2-(hydroxyphenylmethyl)cyclohexanone, water, triflate, THF, and benzaldehyde ligands, respectively. Charges have been omitted for simplification.

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Water-coordination numbers, q, were determined for the three reaction coordinates using luminescence-decay measurements. For the first reaction coordinate (Figure 1, solid dots), water saturation ($q = 8.3$)[12] of the Eu^{3+} precatalyst was determined by measurements in 100% water, and the results matched expected values.[6] Furthermore, q values near the saturation level were observed in solvents composed of 20−90% water.[13] Below 20% water, q values decreased to 5.1 at 1% water. These results indicate that triflate is almost completely dissociated from the precatalyst in H_2O−THF solutions containing over 20% H_2O ($x + y \approx 0$ in Scheme 3) and at least partially dissociated in solutions containing over 1% H_2O ($x + y \geq 0$ in Scheme 3). Upon addition of benzaldehyde, a decrease of up to 0.34 in water-coordination number was observed for each solution containing greater than 1% water (Figure 1, hollow dots), indicating that water is partially displaced by benzaldehyde at water concentrations above 1% ($z > 0$ in Scheme 3). The differences in water-coordination numbers between the first and second reaction coordinates are significant at a 95% confidence interval from 2 to 90% H_2O (Student t test). Finally, the water-coordination numbers of the third reaction coordinate were not significantly different from the values of the first reaction coordinate (Figure 1, solid dots; Supporting Information, pp S6−S9). These data indicate that product inhibition does not occur to a measurable extent in the aqueous $Ln(OTf)_3$-catalyzed Mukaiyama aldol reaction ($a = 0$ in Scheme 3).

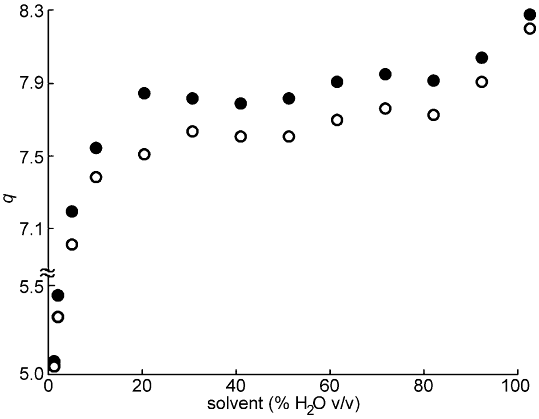

Figure 1. Water-coordination number, q, of Eu^{3+} in solvents containing different amounts of H_2O before (●) and after (○) the addition of benzaldehyde. Standard error bars are smaller than the data points.

These observations of the reaction coordinates of the catalytic cycle of the Mukaiyama aldol reaction are important because they provide support for a reaction mechanism that involves triflate dissociation. These measurements represent time averaged values, and there may be minor amounts of other species that could be active catalysts in solution including hydroxides.[14] However, it has been shown that protons produced from aqua acid complexes of lanthanides are not active catalytic species in the reaction.[2]

Interestingly, the maximum yield for the reaction that we studied was reported in a solution containing 20% water.[2] Our observations suggest that maximum yields are observed in 20% water solution because that is where the largest opportunity for benzaldehyde activation occurs; in our data, 20% water represents the largest difference in water-coordination number between the first and second reaction coordinates (Figure 1, largest difference between solid and hollow dots). Additionally, in this solvent the inner-sphere environment of Eu^{3+} is nearly saturated with water before the addition of substrate. High yields in 20% water may also be because at this concentration of water an advantageous dynamic occurs leading to open coordination sites on the metal for benzaldehyde coordination.

We have demonstrated the applicability of luminescence-decay measurements as a dynamic tool that is useful in mechanistic studies of water-tolerant lanthanide-based catalytic systems. This method should be widely applicable for the study of other important water-tolerant lanthanide-catalyzed reactions, including solid-supported catalysts.[15] Additionally, the use of this method to study reactions in other solvents and asymmetric variations of these reactions should allow for the design of powerful water-tolerant asymmetric catalysts with wide substrate scopes. These studies are currently underway in our laboratory.

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Supporting Information Available: Synthetic methods, experimental details, and tables of q values. This material is available free of charge via the Internet at http://pubs.acs.org.

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[12] Integer water-coordination numbers are not always observed because the bound water residency lifetime (10^{-8}−10^{-9} s) is shorter than the luminescence-decay measurements (~10 ms) resulting in time-averaged values. See ref 8 and Kobayashi, S.; Nagayama, S.; Busujima, T. *J. Am. Chem. Soc.* **1998**, *120*, 8287–8288.

[13] We were unable to determine if the observed decrease in water-coordination number was due to triflate or THF coordination.

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