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Non-traditional hydrogen bond explanation of asymmetric catalysis of Mukaiyama aldol reactions by dinuclear zinc semi-crown ligands

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Introduction

The Pollution Prevention Act of 1990 put green chemistry at the forefront of chemical design and synthesis to ensure the sanctity and sustainability of the environment.¹ Yet, a majority of catalysts employed today are metal based and continue to be dangerously toxic. Consequently, the dream of green chemistry is far from reaching its full potential. Our work on metal free catalysis is to first understand the mechanistic and electronic control of metals in catalysis. The foundation of our work has been possible through combining the advances of two renown scientists: E. J. Corey, 1990 Nobel Laureate, who has contributed to the development of the theory, methodology, and stereochemical control of organic reactions important to society, and Trost and co-workers, whom have proposed semi-crown catalysts to improve upon the otherwise limited aldol synthesis. We integrate ideas and advances from both of these two fields with a goal to create a predictive scheme for designing selective green catalysts for a variety of important organic reactions. To achieve this goal, we investigate the role of the semi-crown catalyst in the Mukaiyama aldol reaction, as depicted in Figure 1.

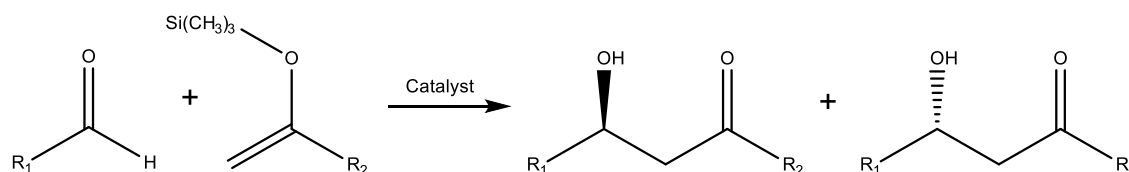


Figure 1. Mukaiyama Aldol Addition.

Motivation

The aldol reaction is a versatile reaction used to synthesize many valuable medications and important industrial chemicals such as: Lipitor, a drug for lowering blood cholesterol and cardiovascular disease by Roth in 1985;² Amphotericin B, an antifungal drug used to treat fungal infections by Nicolaou

in 1987;³ and even pentaerythritol, a biodegradable and non-hazardous alternative for transformer fluids by Tollens 1891.⁴ Green catalysts could have massive impact in designing new medications, as well as in other vital products, while maintaining the environmental sanctity. Since the aldol reaction plays an integral role in the synthesis of important products, we decided to understand the structural and mechanistic features that enable the semi-crown to behave as an affective catalyst.

Background

Our idea originated from an analysis on the catalysis of the Diels-Alder reaction with chiral Lewis acids. Koga and co-workers were the first researchers to achieve stereoselectivity with an aluminum-based chiral Lewis acid in 1979.⁵ Two decades later, Corey and co-workers found X-ray evidence that suggested the presence of an “induced, nontraditional” hydrogen bond.⁶ This hydrogen bond was called a “formyl hydrogen bond,” since it occurred between the formyl hydrogen on the dienophile and the oxygen on the chiral Lewis acid. Corey and co-workers hypothesized that this two-point interaction could form a ring that restricts conformational freedom, thereby explaining the reported selectivity by Koga. Corey contrasted the novel formyl hydrogen bond with the water dimer hydrogen bond, as seen in Figure 2.

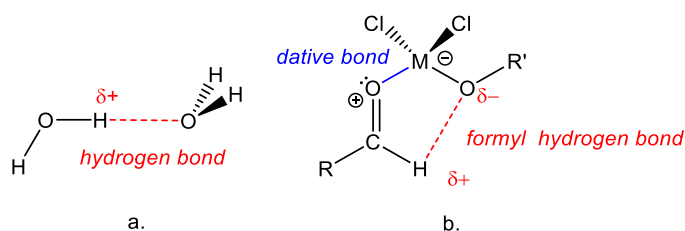


Figure 2. Hydrogen (a), formyl hydrogen (b), and alpha hydrogen bond (c).

Corey and co-workers used the formyl hydrogen bond to explain the mechanisms behind of other important asymmetric Diels-Alder reaction systems with this concept.⁶ Although the formyl hydrogen bond hypothesis explains most of the data, it does not explain all of Koga’s original experimental results. This leaves an opportunity to make a complete explanation for understanding stereochemical control.

We extend the formyl hydrogen bond hypothesis to include two new, novel competing interactions between the enal vinylic alpha- and beta-hydrogens and the Group 13 chiral Lewis acids, MCl_2OR ($M = B, Al, Ga$), depicted in Figure 3. We found that these new types of so-called hydrogen bonds were favorable and have potential to compete with the formyl hydrogen bond, especially with the alpha hydrogen bond.

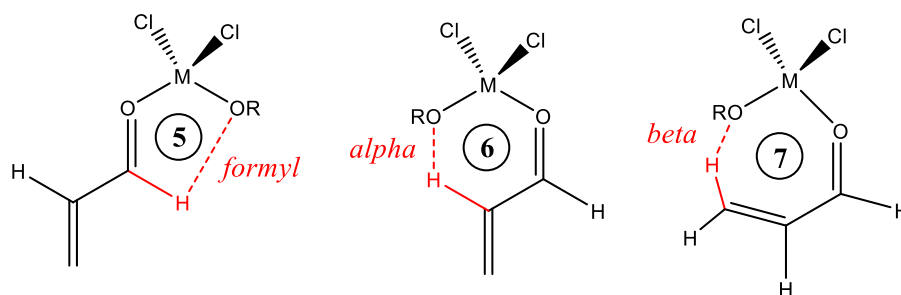


Figure 3. Depictions of formyl-, alpha-, and beta-hydrogen bond complexes ($M = B, Al, Ga$).

The energy difference between the complexes were computed utilizing M06-2X theory and the aug-cc-pvTz basis set for acrolein and MCl_2OCH_3 ($M = B, Al, Ga$). The energy differences reduced as the metal size increased, where the boron complex resulted in an alpha interaction of 1.7 kcal/mol and beta interaction of 8.1 kcal/mol over the formyl hydrogen bond. The aluminum complex resulted with an alpha interaction of 0.3 kcal/mol and beta interaction of 5.0 kcal/mol greater in energy over the formyl hydrogen bond. Gallium was further reduced with an alpha interaction of 0.5 kcal/mol and beta interaction of 5.2 kcal/mol over the formyl hydrogen bond.

We expanded our scope to further test this interaction in other versatile aldol reactions. It occurred to us that our ideas on the nontraditional hydrogen bond could help bring clarity to the Mukaiyama aldol reaction discovered by Teruaki Mukaiyama in 1973.⁹ This reaction involves aldehydes and silyl enol ethers in an aqueous environment, making it an important green reaction. Trost has synthesized a semi-crown catalyst for this reaction that can be utilized in an aqueous environment.¹¹ Trost advocates two possible structures, referred to as Structures 3a and 4a, as shown in Figure 4.

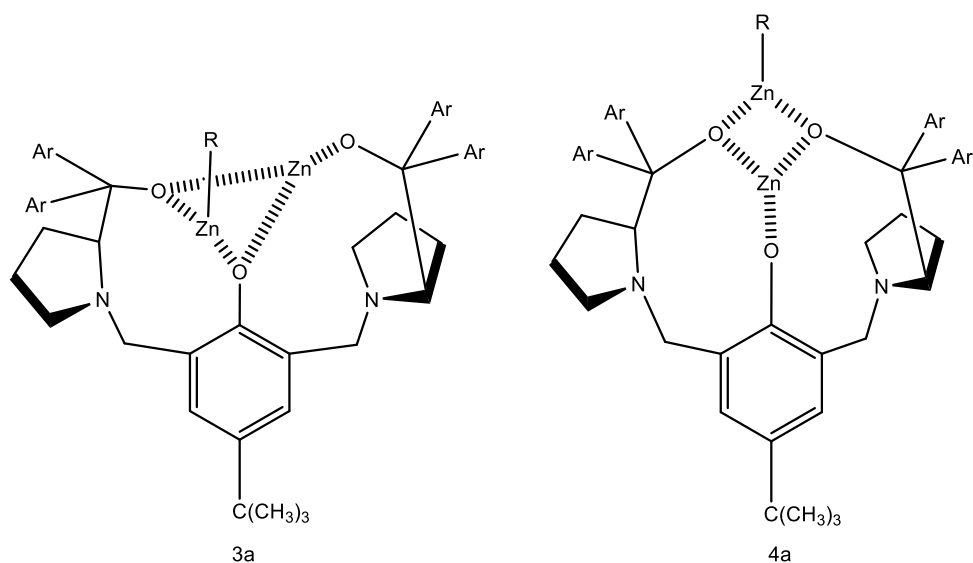


Figure 4. Definition of Structures 3a and 4a.

This semi-crown catalyst is the first to demonstrate high yields up to 89% and stereoselectivity up to 91% for the important aldol reaction.¹¹ Trost further reports that the reaction requires nearly stoichiometric amounts of both reactant, making the catalyst highly efficient.¹¹ Although Trost was able to demonstrate the synthetic utility of the semi-crown catalyst, he was not able to explain the specific catalytic elements and molecular interactions that made the reaction successful. This leaves an opportunity to test the impact of nontraditional hydrogen bonding upon the observed catalysis and stereoselectivity of this system.

Methodology and Results

In order to investigate the role of non-traditional hydrogen bonding in the aldol reaction catalysis, we developed a computational model for the semi-crown catalyst. Our initial geometry optimization involved the Parametric Method 6 (PM6)⁷ and M06-2X Minnesota functional¹³ with Dunning⁸ cc-pvDz basis set. Using the non-augmented model optimized geometry as a starting point, we developed a model using the jul-cc-pvDz basis set.¹⁵ The most favorable placements will be identified for the aldol and enol ether reactants using the computed model. Once these sites are identified, the reactant-catalyst transition state structure can be computed to investigate the role of the non-traditional hydrogen bonds.

Hypothesis

Our hypothesis is that the dinuclear zinc semi-crown ligands catalyze the stereoselective Mukaiyama aldol reaction in aqueous solutions by employing the nontraditional *formyl*, *alpha*, and *beta* hydrogen bonding. The Zn-O bond lengths are critical to our hypothesis, since the aldol and silyl enol ether reactant geometry should roughly match the geometry of those docking sites on the catalyst.

Specific Aim 1

The first aim is to construct a three-dimensional structure of Structure 3a using quantum chemistry, since its three-dimensional structure has not been determined by experiment.¹² Both the 3a and 4a conformations were constructed for geometry optimization; however, we focus on the 3a conformation in our current studies. We computed five potential sites with separation distances of 2.0 Å (pink and purple), 2.1 Å (green), 3.2 Å (blue), and 3.8 Å (orange), where the electron-rich oxygen of the aldehyde or silyl enol can bind then form a nontraditional *formyl*, *alpha*, or *beta* hydrogen bond. As seen in Figure 5, the nontraditional hydrogen bonds are proposed to form with the catalyst Structure 3a to allow preorganization and produce the final aldol product. Understanding both the geometry and critical molecular interactions will help us design a predictive scheme to produce powerful and efficient catalysts for other important organic reactions.

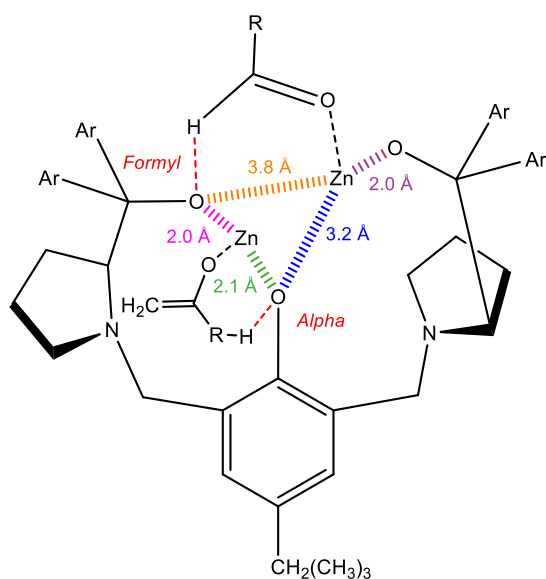


Figure 5. Proposed *formyl-alpha* hypothesis on 3a semi-crown.

Specific Aim 2

The goal for Specific Aim 2 was to find the most stable placements for each aldol reactant on semi-crown Structure 3a. There are five such sites where the reactant can coordinate to one of the two Zn atoms and form a second interaction point with the oxygen atom on the catalyst. This second point is where the competing *formyl*, *alpha*, and *beta* hydrogen bond concept is implemented. Once the semi-crown three-dimensional structure was determined in Specific Aim 1, the aldol reactants were complexed onto the ligand individually, as guided by a simple geometric estimation, as described below.

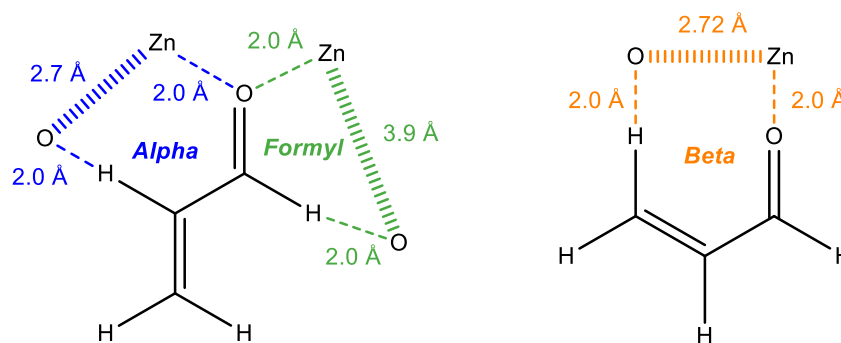


Figure 6. Required bond length for *formyl*, *alpha*, and *beta* aldol docking.

We employed simple geometry to estimate expected Zn-O distances in the *formyl*, *alpha*, and *beta* hydrogen bonds. By using ideal angles of 120° and hydrogen bond distances of 2 \AA , we estimate that the aldol reactant requires a 3.9 \AA distance to accommodate its formyl hydrogen bond, as seen in Figure 6. We also calculate that 2.7 \AA is required for both alpha and beta interactions, as indicated in Figure 6. The catalytic surface Zn-O distances allow coordination of the reactants with ease if the zinc-oxygen bond length matches the predicted aldol reactant length of either 2.7 or 3.9 \AA . Based off of this initial estimate, we identify two competing sites, as shown in Figure 5.

Although we have narrowed down the potential sites based off our estimated distances, we will investigate if any induced fit effects are occurring when the reactants bind to the catalytic surface. Six binding positions test where the reactants can form the most stable *alpha*, *beta*, and *formyl* hydrogen bonding. In Figure 5, two such placements are depicted. The lowest energy and most stable positions can be used in the next stage where both reactants will be complexed onto the semi-crown simultaneously.

We successfully computed a complexation between an enol reactant and the semi-crown with M06-2X theory and Dunning's cc-pvDz basis set, using the sites that matched with the predicted 2.7 Å or 3.8 Å Zn-O bond length. The bond distance for the *alpha* hydrogen bond was roughly 3.05 Å and can be visualized in Figure 7. The catalytic surface Zn-O bond length was 2.1 Å, which was smaller than the required *alpha* bond length of 2.7 Å, as indicated in Figure 6. Zinc-oxygen bond lengths will be compared between the reactant-catalyst surface and the isolated semi-crown surface to understand the induced fit. If a difference between the isolated catalyst Zn-O distances and the reactant-catalyst complex Zn-O distances are noted, then it can be stated that the catalyst undergoes an induced fit during the reaction.

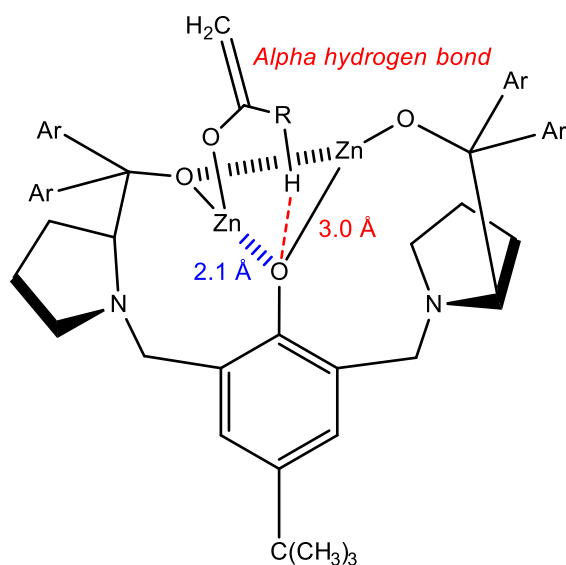


Figure 7. Enol-Semi Crown Complexation (*alpha* hydrogen bond).

A closer visual of the two-interaction ring system is depicted in Figure 8, where the *alpha* hydrogen bond interaction is highlighted. The complexation shows the model is beginning to show promise. More placements will be done and at higher computational methods at M06-2X with jul-cc-pvDz. These complexations were made so the catalyst was fixed and the reactant could complex freely. Next, the whole complex will be released and allowed to converge to investigate induced fit effects.

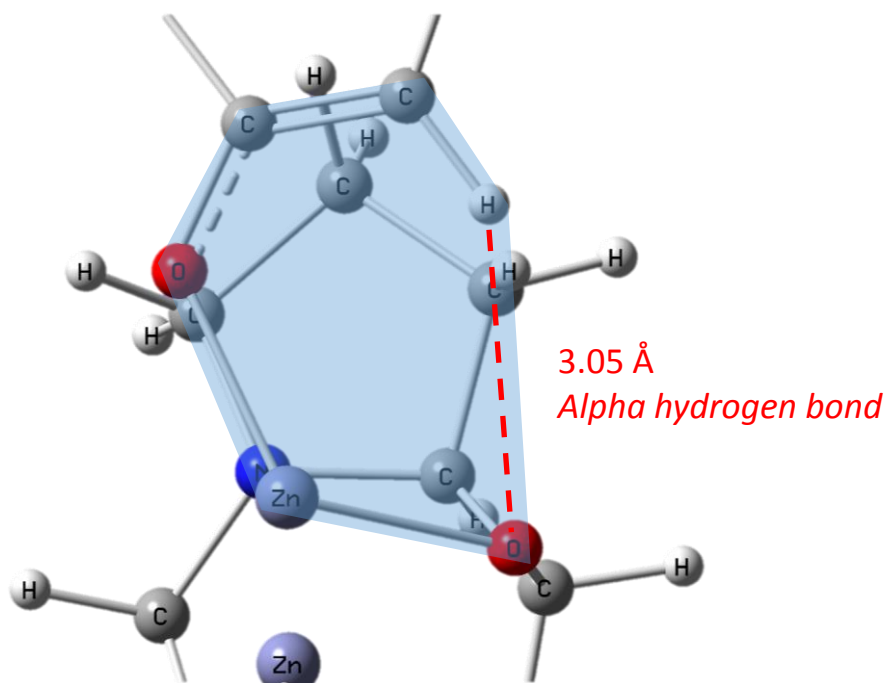


Figure 8. Enol – Semi Crown ring formation site with *alpha hydrogen bond*.

Specific Aim 3

Once the most favorable reactant placements are identified, the semi-crown model can be complexed with both reactants in the most favorable positions for analysis of the critical interactions. This coordination may have a barrier to aldol formation, so the transition state will be determined. Trost's experimental stereochemistries and ees can be compared with the computational results to verify the model and strengthen our hypothesis that the *formyl*, *alpha*, and *beta* hydrogen bonding explain the catalytic elements in the semi-crown assisted Mukaiyama aldol reactions. By examining the most stable compounds, we will be able to identify the correct stereochemistry of the products and compare with experimental results.

Conclusion and Future Directions

Understanding the critical molecular elements in the semi-crown assisted aldol reaction will give us insight into developing a predictive scheme to design powerful green catalysts applicable to other chemical systems and important reactions. Our goal is to achieve this through continuing research on this

project, as we have over the past two years. With an increasing need for viable green catalysts to replace traditional toxic catalysts, we hope to alleviate this issue after continuous research through our work on non-traditional hydrogen bonding. The foundation for remainder of the research project has been built. The 3a semi-crown catalyst model has been developed and is now implemented in testing various aldehyde docking placements. The next stage is to determine the optimal placements of the silyl enol, followed by an examination of the transition structure of the catalyst and reactants. We firmly believe in the principles of green chemistry and aim to integrate it in catalyst design for a better and much cleaner, sustainable future. If successful, we can develop a scheme to design catalysts for other organic reactions, while retaining the green chemistry principles and high performance.

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