

Orlando Acevedo

Yale University, Department of Chemistry, New Haven, CT 06520-8107

Essay

The Diels-Alder reaction, first discovered in 1928, is one of the most commonly utilized carbon-carbon bond forming processes in organic synthesis. Its significance is so great, that Otto Diels and Kurt Alder were awarded the Nobel Prize in 1950 for its discovery. The present understanding of how to control this important reaction is formed from a huge amount of experimental work, yet there are a number of unresolved problems that need further scientific investigation to develop a complete understanding of the Diels-Alder reaction.

My Ph.D. dissertation investigates three different external influences on the reaction, which are known experimentally but poorly understood theoretically, by using large-scale quantum mechanical computations. The three studied external influences upon chemical reactivity and stereochemistry are ionic liquids, Lewis acid catalysts and bis(oxazoline) copper(II) catalysts. In each of the categories it is necessary to understand the microscopic details and intermolecular interactions in order to access their role in the rate and selectivity enhancement.

Ionic liquids. Room temperature ionic liquids are a novel and exciting class of solvents that have the potential to accelerate and control a vast range of reactions in an environmentally safe manner. Ionic liquids are defined as organic salts or mixtures containing only ionic species with a melting point at or below room temperature. The four-stereospecific Diels-Alder transition structures for the cyclopentadiene and methyl acrylate cycloaddition have been computed within different basic and acidic ionic melt approximations, where the ionic liquid, 1-ethyl-3-methylimidazolium cation (EMI⁺) acts

as a Lewis acid and is modulated by surrounding chloroaluminate counterions. Evidence from NMR and experimental densities suggest that the ionic interactions resulting from cation-to-anion ratios are crucial to understanding the physical and chemical properties of the ionic melts.

In calculating activation energies for the transition structure of cyclopentadiene and methyl acrylate in both basic and acidic environments, a model was sought which delivers a realistic picture of the energetic behavior. A new model using the 2:1 anion-to-cation ratio was found to reproduce experimental data best. The 2:1 ratio lends the ability to satisfy more key electrostatic interactions on the diene and dienophile, while further stabilizing the transition structure. The transition structure with two Al_2Cl_7^- anions complexed to the EMI^+ cation was found to have excellent agreement with experimental data such as vibrational frequencies, x-ray crystal structures and thermodynamic properties. The correct experimental trend of the acidic melt having a lower activation barrier than the basic melt was reported for the first time.

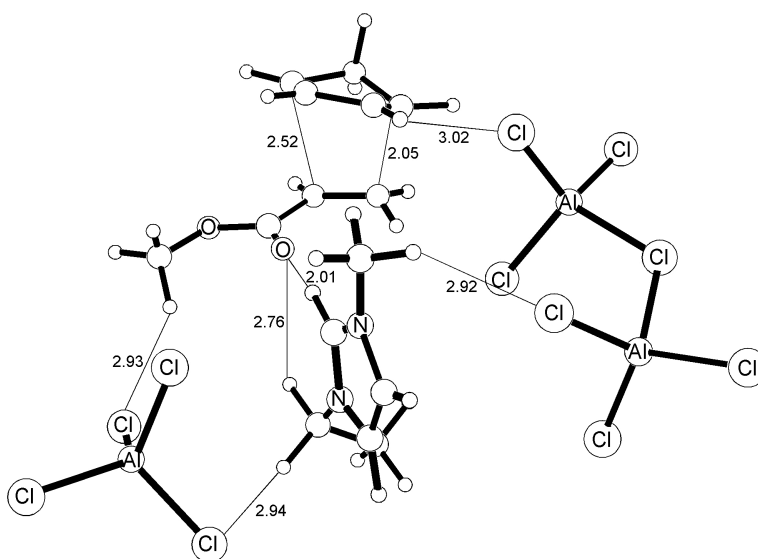


Figure 1. The endo-cis transition structure for cyclopentadiene and methyl acrylate with an acidic approximated 2:1 ratio anion-cation environment computed using the B3LYP/6-31G(d) level of theory. Distances in Å.

Our computations yield a new understanding of the local microscopic interactions occurring at the transition structure that give ionic liquids the ability to impact the rates based on their acidity and ion pair ratios.

Lewis Acids. Lewis acids are known to influence strongly the rate and *endo/exo* selectivities of the Diels-Alder reaction. Asymmetric catalysis using chiral Lewis acids provides a crucial tool in the enantioselective synthesis of chiral organic compounds. My efforts were directed at uncovering the intermolecular forces responsible for the rate and stereoselective enhancements, by studying the transition structures of chiral Lewis acid catalyzed Diels-Alder reactions. Density functional theory was used to investigate the effect BF_2OCH_3 has on the activation energies and *endo/exo* selectivity of the four transition structures comprised of 1,3-butadiene and acrolein. A novel combination of two simultaneous intermolecular interactions has been identified to contribute to the rate enhancement of the system: *nontraditional hydrogen bonding* ($\text{O}=\text{C}-\text{H}\cdots\text{X}$) and the *through-space electrostatic interaction*, as illustrated below.

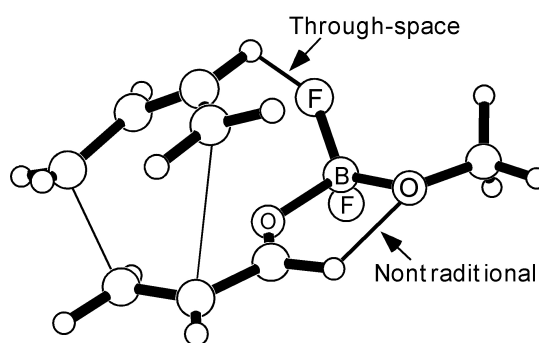
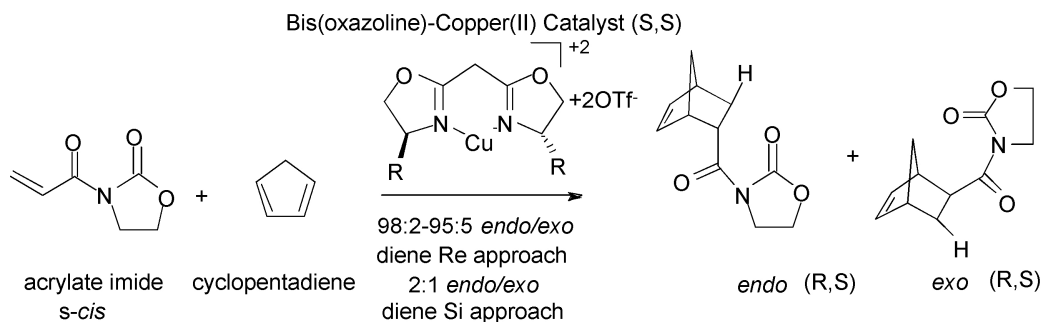


Figure 2. The two enhanced transition structure interactions between the Lewis acid, BF_2OCH_3 , and the Diels-Alder transition structure comprised of acrolein and 1,3-butadiene.

We found the *through-space electrostatic interaction* contributes 2-3 kcal/mol in lowering the activation barrier, and the *nontraditional hydrogen bond* contributes 1-3 kcal/mol in the gas phase, explaining which intermolecular interactions are responsible for the rate enhancements. Inclusion of bulk solvent effects through a continuum method, perturbs the reaction coordinate to proceed through the preferred *endo-cis* and *endo-trans* transition structures, explaining the *endo* selectivity observed experimentally.

Bis(oxazoline)-Cu(II) complexes. C_2 -symmetric bis(oxazoline)-Cu(II) complexes impact Diels-Alder reactions that typically involve α,β -unsaturated carbonyl compounds with electron rich olefins (Scheme 1). Despite intensive experimental efforts, the physical reasons for *endo* selectivity and rate enhancements for bis(oxazoline)-Cu(II) catalyzed Diels-Alder reactions are not completely clear.



Scheme 1. The acrylate imide and cyclopentadiene Diels-Alder reaction catalyzed by bis(oxazoline)-Cu(II) with representative products of the favorable stereochemical outcome (*S*) and unfavorable outcome of (*R*).

Our computed transition structures provide a novel explanation. The enhancements delivered can be attributed to the unique positioning of the *t*-butyl C_2 -substituent with respect to the diene, creating an “axial gateway” to the Cu(II) metal center, as shown in Figure 3. The solvent accessible area is tighter for an *endo* approach due to the constricted axial gateway opening as compared to an *exo* approach. Thus,

Cu(II) is more prone to attack in the *exo* approach, yielding *endo* selectivity. Shielding of the Cu(II) center from either solvent or nucleophilic counterions renders it a more powerful catalyst by withdrawing electron density from the dienophile.

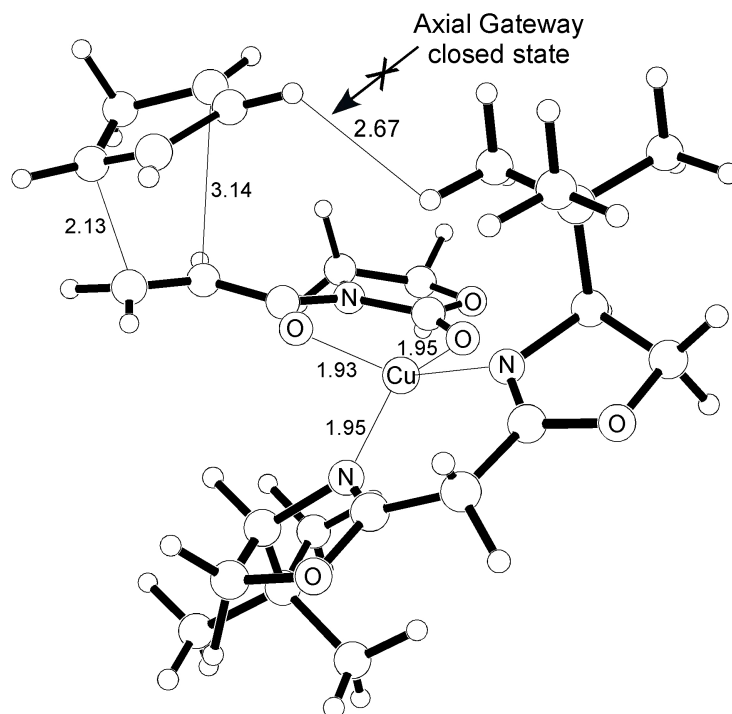


Figure 3. UB3LYP/6-31G(d) optimized transition structure of the NC Re Diels-Alder reaction between acrylate imide and cyclopentadiene catalyzed by bis(oxazoline)-Cu(II) with *t*-butyl substituents. Bond lengths in Å.

In summary, my doctoral work provides new insight into the effects of external influences on the geometry, flexibility and energy of the Diels-Alder transition structures and the influence of these factors on rate and selectivity. My thesis contributes to the understanding of the stereochemical and catalytic issues of solvent effects, in terms of ionic liquids and bulk phase effects, and important local electrostatic interactions, due to Lewis acid complexation. This work establishes a better understanding of intermolecular interactions occurring at Diels-Alder reactions, which will allow for opportunities in the design of future asymmetric catalytic systems.