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Pericyclic Reactions

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Using Theory and Experiment to Discover Catalysts for Electrocyclizations

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Huge numbers of pericyclic reactions have been carried out synthetically and studied theoretically. These reactions, which are characterized by highly delocalized, often nonpolar, transition-state structures and the absence of intermediates, present a particular challenge for catalysis. Several strategies have been put forth, some purely theoretical and others validated by experiment, for accelerating pericyclic reactions. In some cases, the reaction rate has been accelerated by using a catalyst, while in other cases only the use of stoichiometric amounts of reagents has been successful.

A generic representation of a transition-state structure for a pericyclic reaction is shown in Figure 1 (blue). If such a transition-state structure bears no substituents, then acceleration of the reaction rate would likely involve direct interactions between a promoter and the electrons that rearrange during the pericyclic reaction (Figure 1, green). Jiao and Schleyer have predicted that such an acceleration of the reaction rate will occur for some sigmatropic shifts and electrocyclizations in the presence of inorganic cations (M^{n+}, Figure 1).[1] Here, rate acceleration is achieved as a result of the favorable electrostatic interactions between the cation and the rearranging electrons being stronger for the transition-state structure than for the reactant.[1] It has also been predicted that halogen-containing molecules can reduce the energy barriers for [3,3] sigmatropic shifts through a combination of electrostatic and orbital interactions, which are again stronger for complexes of transition-state structures (Hal-X, Figure 1) than reactants.[2] Transition-metal-containing groups (ML_n, Figure 1; L: ligand) have also been shown to be capable of such selective transition-state complexation.[3] In many cases where transition-metal catalysts or promoters are involved, however, a concerted pericyclic reaction is converted into a nonpericyclic stepwise process.[4]

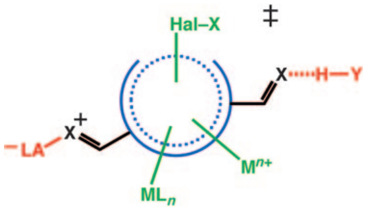

Figure 1. Types of groups (green: groups that interact directly with rearranging electrons; red: groups that interact with substituents) that could bind selectively to a pericyclic transition-state structure (blue) and accelerate the rearrangement.

If the pericyclic transition-state structure of interest bears substituents, then additional opportunities for rate acceleration exist. It is well-known that substituents by themselves can affect the rates of pericyclic reactions,[5] and their effects can be magnified by interactions with catalysts or promoters (Figure 1, red). Consider the generic electron-withdrawing substituents shown in Figure 1 (black, C=X). The electron-withdrawing ability of these substituents can be enhanced by binding to a Lewis acid (LA) or a hydrogen-bonding organocatalyst (H-Y). Examples of this strategy include Lewis acid, Brønsted acid, and antibody-catalyzed Diels–Alder reactions.[6,7]

The class of pericyclic reactions for which the most catalysts have been described by far is cycloadditions.[4,6–8] Some catalyzed sigmatropic shifts have also been described.[7,9] However, aside from Nazarov cyclizations (four-electron electrocyclizations in which oxy-pentadienyl cations are generated in situ),[10] electrocyclizations have generally resisted catalysis. Recently, though, Bergman, Trauner, and co-workers have demonstrated for the first time that six-electron electrocyclizations can be catalyzed by Lewis acids (Scheme 1).[11]

Using the knowledge that 1,3,5-hexatrienes with electron-withdrawing substituents located at the 2-position cyclize with lower energy barriers than analogous systems lacking such susbtituents,[5b] Bergman, Trauner, and co-workers set out to catalyze six-electron electrocyclizations of 2-substitued systems by transient binding of these substituents with Lewis acids, thereby enhancing their rate-accelerating effects. First, the viability of this strategy was assessed by using quantum chemical calculations (at the B3LYP/6-31G** level of theory), which predicted that protonation (which is likely to have a larger effect than complexation with a Lewis acid) lowered the energy barrier for electrocyclization of 2-carbomethoxy-

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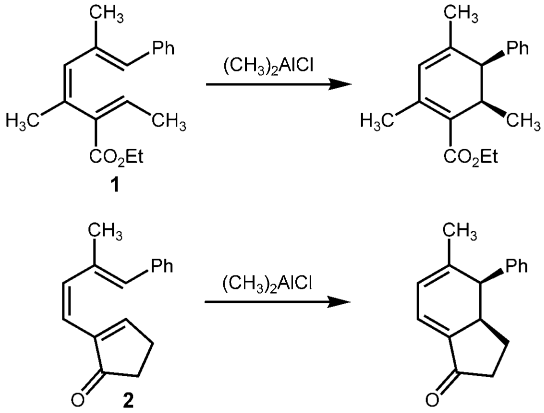

Scheme 1. Lewis acid catalyzed six-electron electrocyclizations.

1,3,5-hexatriene by approximately 10 kcal mol^{-1}. A variety of Lewis acids were subsequently examined, and $(CH_3)_2AlCl$ was found to be an effective catalyst for the reactions shown in Scheme 1; note that one system involves an ester substituent, while the other involves a ketone. Significantly, the Bergman and Trauner research groups demonstrated that: 1) the rates of these electrocyclization reactions were increased in the presence of $(CH_3)_2AlCl$ (by a factor of up to 55 for the rearrangement of **2** in the presence of one equivalent of $(CH_3)_2AlCl$ at 28 °C), and 2) the reaction rates were accelerated when using *substoichiometric* amounts of $(CH_3)_2AlCl$. Although approximately 20 mol % or more of $(CH_3)_2AlCl$ was generally necessary for significant rate acceleration to be observed, these results provide proof-of-principle that the substituent-enhancing strategy can be used to catalyze six-electron electrocyclizations. A variety of experiments were also performed that indicated that 1:1 substrate/catalyst binding occurs, and Eyring plots were used to determine activation parameters for the reactions shown in Scheme 1 when performed in the presence and absence of $(CH_3)_2AlCl$; decreases of approximately 2 kcal mol^{-1} in the free energies of activation (at 298 K; predominantly an enthalpic effect) were observed.

Although there is room for improvement in terms of the magnitude of the rate acceleration and turnover efficiency, as noted by Bergman, Trauner, and co-workers, their results provide a starting point for developing not only more efficient catalysts, but also chiral Lewis acid catalysts (the relative configuration of the products of these reactions is controlled by classical orbital symmetry effects[12] and traditional torquoselectivity effects,[5a] but chiral catalysts would allow for the control of the absolute configuration), as well as organocatalysts that enhance the effects of substituents. The systems already examined are fairly complex, which bodes well for the use of such reactions in the synthesis of complex molecules. The combined theoretical/experimental approach to catalyst design employed in this case has tremendous potential as it is applicable to many other systems.[13]

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