Summary, online thesis

Title: Supramolecular Orientation of Substrates in the Transition Metal Catalyzed Asymmetric Hydrogenation Reaction

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Summary:

This thesis describes a detailed study of a catalytic system in which hydrogen bonds are formed between two ligand building blocks as well as between the catalyst and the substrate during the asymmetric hydrogenation reaction catalyzed by rhodium complexes. We present detailed studies on the reaction mechanism of the asymmetric hydrogenation reaction catalyzed by such a complex, based on a rhodium complex formed by the assembly of a urea-functionalized phosphine and a phosphoramidite. This complex is highly selective in the asymmetric hydrogenation of methyl 2-hydroxymethacrylate (ee up to 99%), which is a precursor of the so-called “roche ester”, an important intermediate in the preparation of several biologically active compounds. An in-depth study of the reaction mechanism has been carried out in order to detect if such interactions were actively involved during the reaction. The identification of several intermediates in the early stages of the reaction using NMR spectroscopy and X-ray crystallography revealed the involvement of hydrogen bonds at a key step of the reaction, i.e. the coordination of the substrate to the catalyst. Two hydrogen bonds between the catalyst and the substrate were identified in the catalyst-substrate complex, which play a crucial role in the stabilization of this important intermediate in the early stages of the reaction. Further kinetic experiments combining gas-uptake experiments and stopped-flow kinetics to evaluate the substrate coordination demonstrate that the rate determining step of the reaction is at the late stages of the reaction. Also, kinetic results based on the application of the Michaelis-Menten rate equation to describe this catalytic system highlighted the crucial role of the hydrogen bonding during catalysis at the late stages of the reaction. Then, we performed a detailed computational study of the reaction mechanism. We demonstrate that the reaction follows an unsaturated pathway in which the hydride migration step is rate determining. The study of the different paths leading to products with opposite absolute configurations revealed that the hydrogen bonds...
between the catalyst and the substrate are also involved in the high selectivity observed experimentally. Based on these findings, a new series of ligand building blocks for the formation of supramolecular rhodium complexes have been designed and evaluated in the asymmetric hydrogenation reaction. We created a series of bisphosphine monoxide ligands that act as hydrogen bond acceptors to form hydrogen bonding with the PNH group of a phosphoramidite, resulting in the formation of new bidentate ligands. Kinetics studies show that these supramolecular complexes display higher rates of hydrogenation and have an improved robustness toward the reaction conditions compared to the first generation of urea-based catalysts. Also, we describe the formation of supramolecular iridium complexes, that most likely operate via similar hydrogen bond controlled mechanisms.