A Novel Nickel Pincer Complex in the Active Site of Lactate Racemase

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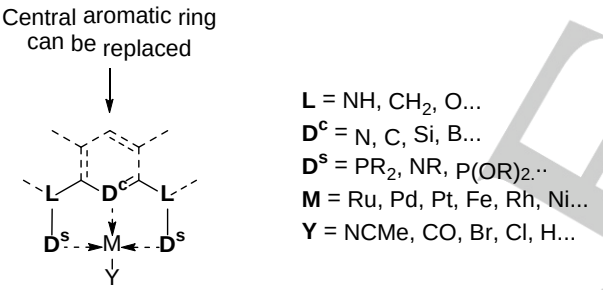
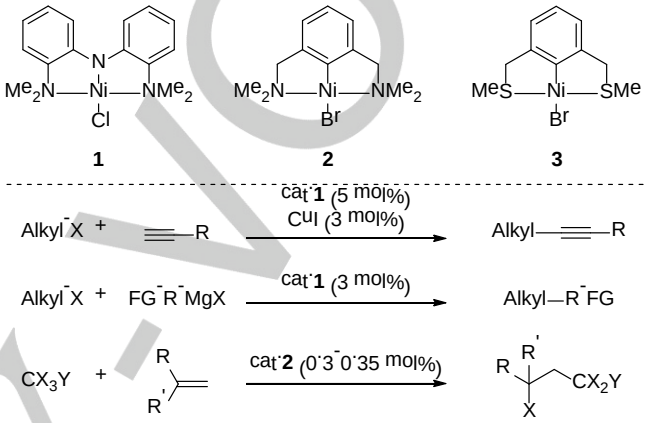
Dedication ((optional))

Pincer and pincer-like complexes, with their well-defined structures and high thermal stability, have been established as important catalysts in many organic reactions such as hydrogenation, cross-coupling, and C-H activation.[1] The first pincer complexes were described in the early 1970's,[2a] while the name "pincer" was coined by Van Koten in 1989.[2b] Although there is no strict definition, a pincer ligand traditionally consists of a central benzene ring, which is 1,3-disubstituted with two chelating side arms (Scheme 1).[3] The central atom ($\mathbf{D^c}$) together with the two donor groups on the side arms ($\mathbf{D^s}$) bind to the metal ion in a meridional fashion, which provides both structural and thermal stability. The two flanking side arms are connected to the central atom with a linker (**L**). All parameters ($\mathbf{D^c}$, $\mathbf{D^s}$ and **L**) can be freely changed, so is the whole ligand backbone. Indeed, newer versions of pincer ligands based on a central pyridinyl or diarylamido unit are widely studied in recent years.[4] The modularity of pincer ligands makes it possible to synthesize an almost endless amount of ligands with varying electronic and steric properties.[5]



Scheme 1. Generalized structure of a pincer complex.

Nickel catalysis has drawn much attention due to the unique reactivity of nickel as well as the economic advantage of nickel over precious metals such as palladium and platinum.[6] To stabilize nickel ion and control its reactivity, many nickel pincer complexes have been synthesized (**1**-**3**, Scheme 2).[7] Some of them exhibit high catalytic activity. For example, complex **1**, Nickamine, catalyzes many cross-coupling reactions of alkyl halides, and complex **2** catalyzes Kharasch addition reactions.



Scheme 2. Selective nickel pincer complexes and their catalytic applications. X = halogen, Y = H, halogen, CF_3, FG = functional groups.

Even though pincer complexes are ubiquitous in synthetic chemistry, they had not been encountered in the natural world. There was no report of a pincer complex in the active site of a native metalloenzyme. Until now! The groups of Hausinger and Hu just discovered a tethered niacin-derived nickel pincer complex in the active site lactate racemase (Figure 1).[8]

Racemization of lactic acid is part of lactate metabolism and is linked to the cell wall assembly of many microorganisms. Lactate racemase, which interconverts the D- and L-isomers of lactic acid, requires nickel as a cofactor, but the nickel-binding site was unclear.[9] In this highlighted contribution, Hausinger, Hu, and co-workers combined mass spectrometry (MS) and x-ray crystallography to reveal the composition and structure of the nickel-containing cofactor in lactase racemase. They found that niacin (nicotinic acid or nicotinamide) was necessary for lactate racemase activity, which suggested that niacin was a precursor of the cofactor. They used LC-ESI-MS to probe the composition of the cofactor. The MS data suggested that the cofactor consists of a nicotinic acid mononucleotide (NAMN) derivative attached to lysine[184] through its carboxylic acid group. In addition to the NAMN unit, there was a mass fragment of CS_2Ni^{2+} in the co-factor. To establish the detailed structure of the cofactor, the authors then solved the structure of the enzyme at 3.0 Å resolution. The crystallography revealed an active site consisting of a tethered niacin-derived nickel pincer complex (Figure 1). The pincer ligand acts as a SCS donor, and the nickel center is additionally coordinated to His[200]. Although (SCS)Ni pincer complexes have been synthesized (e.g., **3**),[7c] the particular SCS pincer ligand found in the enzyme is highly unusual.

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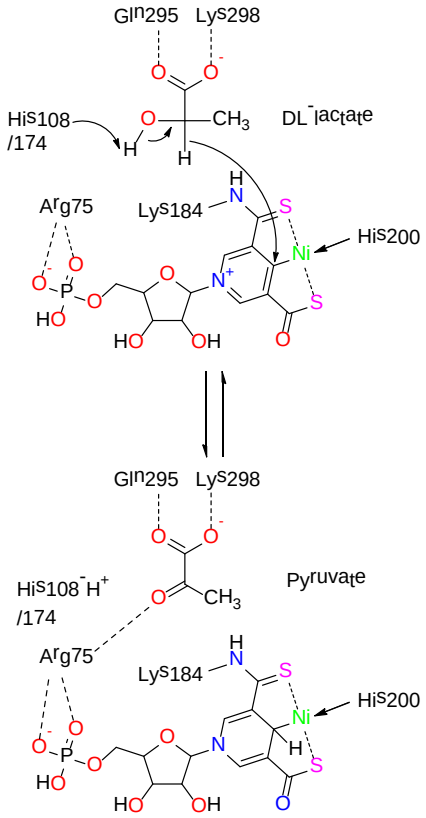

Figure 1. Putative catalytic mechanism of lactase racemase.

The catalytic mechanism of lactate racemase is yet unclear. It was previously suggested that a hydride transfer was involved in the lactate racemisation.[10] Based on this new structural insights, a more concrete mechanism is now proposed (Figure 1). The key step is a hydride transfer from lactic acid to the sp^2-C atom that is coordinated to the Ni ion. The resulting sp^3-C center remains coordinated to Ni, while the pyridinium ring is now in the reduced, dihydropyridine-derived form. This mechanism is analogous to those proposed for hydride transfer reactions involving nicotinamide adenine dinucleotide (NAD). The crystal structure also suggests that His^{108} and His^{174} may participate in the reaction as bases, and Arg^{75} may form hydrogen bond with the cofactor, which could stabilize the hypothesized pyruvate intermediate.

The discovery of Hausinger, Hu, and co-workers is exciting because it provides a hitherto missing link between synthetic chemistry and biological catalysis. It suggests that pincer complexes, much appreciated for homogeneous catalysis, can be attractive choices for enzymes as well. As the nickel pincer cofactor in lactate racemase is synthesized by proteins that are widely distributed in microorganisms, similar pincer complexes might be present in other enzymes. The discovery also motivates the biomimetic community to develop synthetic models for the elucidation of the mechanism of lactase racemase.

Acknowledgements

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Keywords: Nickel • pincer complex • Lactate racemase • hydride transfer

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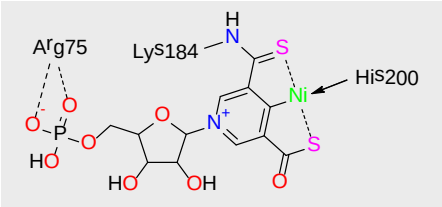
Entry for the Table of Contents (Please choose one layout)

Layout 1:

HIGHLIGHT

A recent study revealed the structure of the Ni-containing active site of lactate racemase. The Ni is coordinated by a SCS pincer ligand derived from a nicotinic acid mononucleotide.



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A novel nickel pincer complex in the active site of lactate racemase

Layout 2:

HIGHLIGHT