Reaction Mechanisms

DOI: 10.1002/anie.201103860

Metal-Mediated Deformylation Reactions: Synthetic and Biological Avenues**

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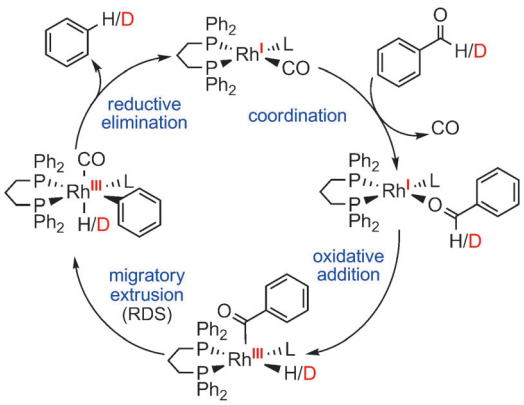
aldehydes · cytochromes · oxygenation · rhodium · synthetic methods

Methods for the removal of functional groups from organic molecules are immensely important in synthesis and biology. Synthetically, the utility of functional groups is mainly due to their ability to act as directing groups as well as their high reactivity and selectivity in a wide variety of transformations. In this regard, metal-mediated deformylation reactions have attracted the attention of chemists for decades since such processes enable temporary use of the beneficial features of the CHO functionality.[1] Also the majority of C–C bond-cleavage reactions catalyzed by cytochrome P450 (CYP) in nature[2] are deformylation reactions.[3] Interestingly, the biosynthesis of alkanes and alkenes from cyanobacteria has been recently suggested to occur through deformylation as one of the key steps.[4]

In 2008, Madsen and co-workers reported detailed mechanistic studies on the decarbonylation of aldehydes catalyzed by a bidentate phosphine ligated rhodium complex (Scheme 1).[1a] Linear Hammett plots having positive slopes



Scheme 1. Catalytic cycle for the rhodium-catalyzed decarbonylation of aldehydes.[1a]

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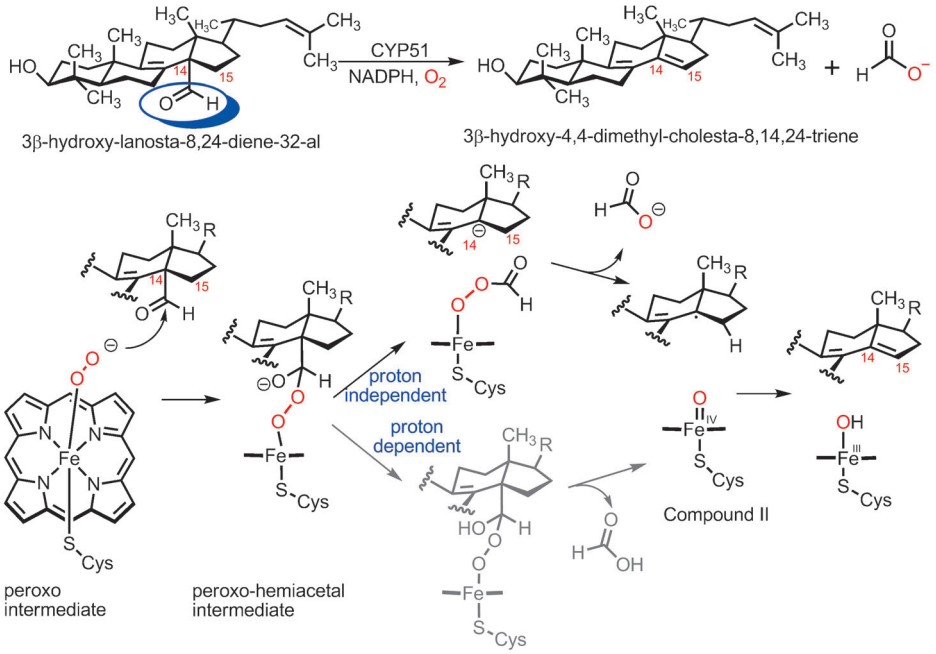
[**] Support by the IIT Bombay Seed Grant is gratefully acknowledged. D.M. thanks Reviewer 1 for insightful discussions.

of +0.79 and +0.43 were obtained for both the benzaldehyde derivatives and the phenyl acetaldehyde derivatives, respectively. These values suggest that there is a build up of a negative charge in the selectivity determining steps in both cases. The observed kinetic isotope effect values of 1.73 for benzaldehyde and 1.77 for phenyl acetaldehyde indicate a similarity in their reaction mechanisms. A detailed density functional theory (DFT; B3LYP) study of the catalytic cycle suggested a rapid oxidative addition into the C(O)–H bond followed by the rate-limiting elimination of CO and product formation. Furthermore, the theoretical kinetic isotope effects matched well with the observed experimental values for both benzaldehyde and phenyl acetaldehyde, provided removal of carbon monoxide was selected as the rate-determining step. Based on this information, the deformylation mechanism by rhodium complexes are suggested to be as follows: 1) coordination of the aldehyde substrate to the metal complex, 2) oxidative addition of the aldehydic C–H bond to form a metal acyl complex ($Rh^{I} \rightarrow Rh^{III}$), 3) migratory extrusion of carbon monoxide, 4) reductive elimination of the product ($Rh^{III} \rightarrow Rh^{I}$).

For the case of cytochrome-P450-catalyzed deformylation, methyl group hydroxylation occurs first to generate an alcohol and then a geminal diol.[3a,b] The diol intermediate then dehydrates to the aldehyde, which is removed by the enzyme. Sen and Hackett demonstrated the deformylation mechanism of the sterol 14α-demethylase (CYP51) from *Mycobacterium tuberculosis* by using a molecular dynamics simulation, DFT, and hybrid quantum mechanics/molecular mechanics methods.[5] A heme/peroxo intermediate has been established as the key active species in CYP-catalyzed deformylation (Scheme 2). Molecular dynamics simulations indicate that the hydrogen-bonded proton shuttle in this enzyme is diverted to the aldehyde oxygen atom from the peroxo intermediate, thus allowing the peroxo species to accumulate. In turn, the peroxo intermediate is trapped by the preorganized aldehyde substrate, thus resulting in a peroxo-hemiacetal without an apparent barrier. A transition state for the concerted rearrangement to produce the formate and the triene steroid was found; however, a stepwise mechanism involving heterolytic C–C bond cleavage is favored as a result of its lower energy, and thus a carbanion at C14 is generated along the way. The researchers also show that a homolytic C–C cleavage is favorable in the absence of the protein electrostatic background. According to them, this fact clearly



Scheme 2. Mechanisms for peroxo-mediated deformylation in sterol 14α-demethylase.[5a]

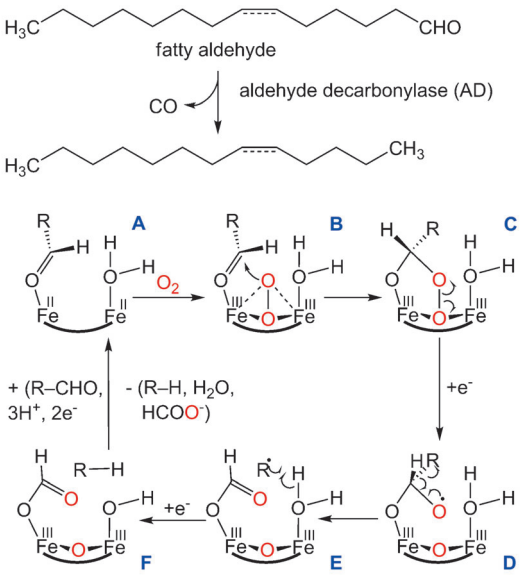
undermines the importance of the active site environment towards modulating the electronic structure of the peroxo-hemiacetal intermediate. With the proton channel directed toward the peroxo-hemiacetal oxygen atom, the possibility that the peroxo-hemiacetal was protonated prior to C–C bond cleavage was also considered. Albeit with higher energy barriers, this mechanism also converges on the Compound II species, which is oriented for abstraction of the 15α-hydrogen atom. Thus, both the proton-independent and proton-dependent pathways can form the double bond between C14 and C15 of the steroid skeleton.

Alternatively, nucleophilic addition of a hydroperoxo intermediate (Compound 0) to the aldehyde was found to proceed with high energy barriers. Notably, experimental work by Nam and co-workers on nonheme iron complexes demonstrates that although iron(III)-peroxo complexes are capable of deformylating aldehydes through a nucleophilic reaction, nonheme iron(III)-hydroperoxo complexes are sluggish oxidants.[6] The mechanism involving the high-valent oxo species (Compound I) mediated deformylation of the geminal diol was also studied in the context of the protein environment; however, in stark contrast to gas-phase calculations,[7] Compound I failed to initiate a concerted deformylation reaction. In this context, related synthetic work from Valentine and co-workers illustrated that a synthetic peroxo porphyrin complex $[Fe^{III}(TMP)(O_2)]^-$ can promote direct nucleophilic attack on an aldehydic substrate.[8] Thus Sen and Hackett's findings[5] are in accord with experimental observations by the groups of Nam[6] and Valentine.[8]

Alkanes are biosynthesized and are major constituents of gasoline, diesel, and jet fuels. However, nature's path to synthesizing alkanes are largely unknown. Consequently, efficient generation of renewable hydrocarbons remain challenging to date. A major breakthrough in this area has recently been reported by the Schirmer group.[4] They have established that upon generation of fatty aldehydes from saturated and unsaturated fatty acids, alkanes and alkenes can be biosynthesized. This critical step involving removal of the carbonyl moiety from the aldehyde (R-CHO) is catalyzed by an aldehyde decarbonylase (AD).

The Schirmer group has shown that cyanobacterial aldehyde decarbonylases are members of the ferritin-like or ribonucleotide reductase-like family of nonheme diiron enzymes. A carboxylate-bridged bimetallic center, similar to those in di-iron oxidases and oxygenases was suggested as the active species in the aldehyde decarbonylase. In vitro deformylation also has been found to give a positive result with purified aldehyde decarbonylase in the presence of reducing equivalents of ferredoxins, ferredoxin reductase, and NADPH.[4]

Related recent findings from Booker, Krebs, Bollinger, and co-workers demonstrate the requirement of dioxygen during aldehyde cleavage by the enzyme, and with $^{18}O_2$ only the formate product is labeled with ^{18}O (but not when run using solvent).[9] The proposed mechanistic pathway (Scheme 3) involves: 1) O_2 addition to the reduced cofactor **A** to generate a di-iron(III)peroxo species **B**, 2) metal-bound peroxide attacks the substrate carbonyl group to form a peroxyhemiacetal-di-iron(III) species **C**, 3) reductive cleavage of the O–O bond generates a *gem*-diolyl radical (**D**) which is on its way to initiate a radical scission of the C–CHO bond, 4) a metal-bound formate and an alkyl radical result in **E**, and this radical is ready to abstract a hydrogen atom from the cofactor, 5) finally, alkane or alkene formation (**F**) with a subsequent two-electron reduction of the oxidized bimetallic center regenerate the reduced bimetallic center **A**, the O_2-reactive form. The alkyl radical generated in **E** can form alkanes without formation of the diiron tyrosyl radical



Scheme 3. Proposed mode of action for cyanobacterial aldehyde decarbonylase.[9b]

cofactor, thus indicating that deformylation proceeds through a mechanism different from ribonucleotide reductase. Interestingly, continuous presence of O_2 and the reducing system throughout the whole catalytic cycle are required.

In conclusion, biological systems oxygenate aldehydes, without oxidizing them to generate formate and alkanes or alkenes. Synthetic deformylation reactions primarily rely on rapid oxidative addition into the C(O)–H bond and subsequent rate-determining extrusion of CO. Selective conversion of carbohydrates into fuel-grade alkanes may thus be an attractive alternative to the existing expensive hydrogenation methodologies.

Received: June 7, 2011
Revised: September 21, 2011
Published online: October 24, 2011

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