Biomimetic in situ Regeneration of Cofactors NAD(P)+ and NAD(P)H Models Hantzsch Esters and Dihydrophenanthridine

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new tools

Abstract: Biomimetic recycling of the expensive cofactors NAD(P)H/NAD(P)+ and their models is a promising area in bio-inspired synthesis. This paper highlights the recent advances in the in situ regeneration of the oxidized cofactors NAD(P)+ through oxidation of cofactors NAD(P)H in the presence of an alcohol dehydrogenase by means of dioxygen and a synthetic Fe(III) porphyrin as a biomimetic NAD(P)H oxidase or flavin as catalyst, and biomimetic in situ regeneration of the expensive NAD(P)H models Hantzsch esters (HEH) and 9,10-dihydrophenanthridine (DHPD) by transition-metal and chiral Brønsted acid catalyzed relay asymmetric hydrogenation.

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Key words: biomimetic, regeneration, asymmetric hydrogenation, Hantzsch esters, dihydrophenanthridine
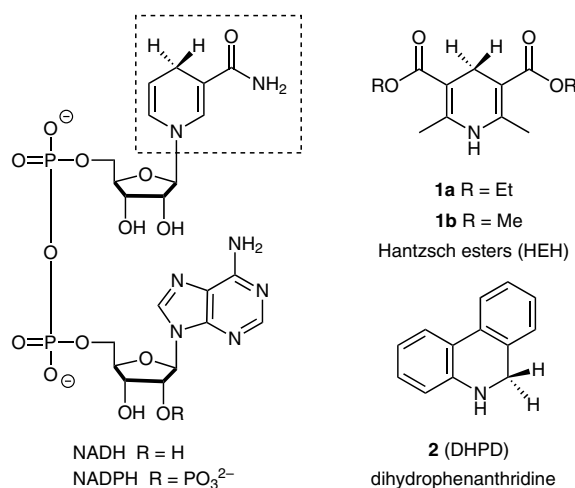

Figure 1 The structures of NAD(P)H and their models

1 Introduction

Dihydropyridines are bestowed with excellent reducing power which has been extensively used by the nature. Nicotinamide adenine dinucleotide (NADH), nicotinamide adenine dinucleotide phosphate (NADPH), and their oxidized forms NAD+ and NADP+ have been identified as the most important cofactors for the oxidoreduction in living systems.[1] Diverse 1,4-dihydropyridines have been developed for the reduction of various functionalities since their first synthesis by Hantzsch.[2,3] The well-known Hantzsch esters (HEH), 1,4-dihydropyridines **1**, are considered as the models (mimics) of cofactors NAD(P)H and have been utilized as the synthetic models to investigate the mechanism of NAD(P)H-dependent enzymes (Figure 1).[4] As organic reducing agents, Hantzsch esters **1** have recently been applied as promising biomimetic hydrogen source in transfer hydrogenation reactions[5–12] under organocatalytic conditions.[13–16] For bio-inspired organic synthesis, the development of readily available NAD(P)H/NAD(P)+ models is highly valuable, but remains a challenge.

NAD(P)H-dependent oxidoreduction can be used as valuable tools for the preparation of chiral compounds. However, in situ cofactor regeneration is required for the preparative applications because use of these cofactors in stoichiometric amounts is too expensive.[17] Usually, in situ regeneration of the cofactors undergoes in enzymatic redox reactions through biotransformations.[17,18] Since biomimetic catalysis has recently become more and more important in synthetic chemistry,[19–24] applicable recycling NAD(P)H and NAD(P)+ in situ through a biomimetic route is strongly desired. A variety of methods including photoirradiation[25,26] have been developed to regenerate NAD(P)H and NAD(P)+, and a biomimetic formate dehydrogenase was used for the regeneration of NAD(P)H from NAD(P)+ by oxidation of formic acid into carbon dioxide with a rhodium complex[27] or water-soluble HEH.[28] To date, only a few enzymes, such as NAD(P)H oxidases,[29] are synthetically suitable for the regeneration of cofactors NAD(P)+, and thus chemoenzymatic,[30] electrochemical,[31] and biomimetic[32] systems have been established for the same purpose. In this aspect, a green 'artificial' biomimetic water-producing NAD(P)H oxidase has been desirable as an alternative to oxidase-type enzymes in preparative synthesis (Scheme 1). Although Hantzsch esters have been extensively utilized as stoichiometric biomimetic reducing agents,[33] their in situ regeneration has seldom been paid attention.
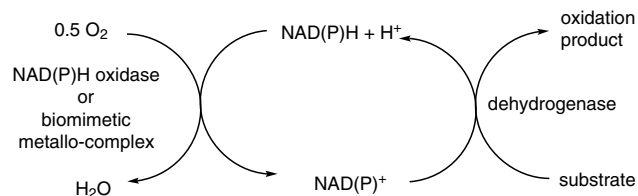
**Scheme 1** Concept of NAD(P)H oxidase catalyzed or biomimetic in situ cofactor regeneration of NAD(P)+

2 Biomimetic in situ Regeneration of NAD(P)+

Recently, Gröger et al. reported a novel iron-catalysis protocol for the in situ regeneration of oxidized cofactor NAD(P)+ by means of activation and reduction of dioxygen with a synthetic metalloporphyrin, that is, Fe(III) complex **3** bearing a water-soluble, fourfold *meso*-tetrakis(4-sulfonatophenyl)porphyrin (TSPP) ligand (Scheme 2),[34] as a biomimetic NAD(P)H oxidase.[16] Here, cofactor NAD(P)H acted as the hydride donor (substrate) for the activation of molecular oxygen and thus reduced oxygen into water while simultaneously being recycled as a catalyst in the aqueous medium and was transformed into its oxidized form NAD(P)+. For the coupled biotransformation, enzymatic oxidation of D-glucose into D-gluconolactone in the presence of a glucose dehydrogenase was chosen. In the reaction, a catalytic amount of NAD(P)+ was required and transformed into its reduced form NAD(P)H. For the regeneration of NAD(P)+ through the oxidation of NAD(P)H, the activity of the regeneration catalyst with respect to the loading of **3** (in mg) ranged from 3.7–6.3 mg^{-1}, corresponding to TOF values of 0.06–0.11 s^{-1}. The synthetic and water-soluble iron(III) porphyrin **3** proved to be an artificial biomimetic NAD(P)H oxidase for the oxidation of cofactors NAD(P)H with molecular oxygen in an aqueous reaction medium, and
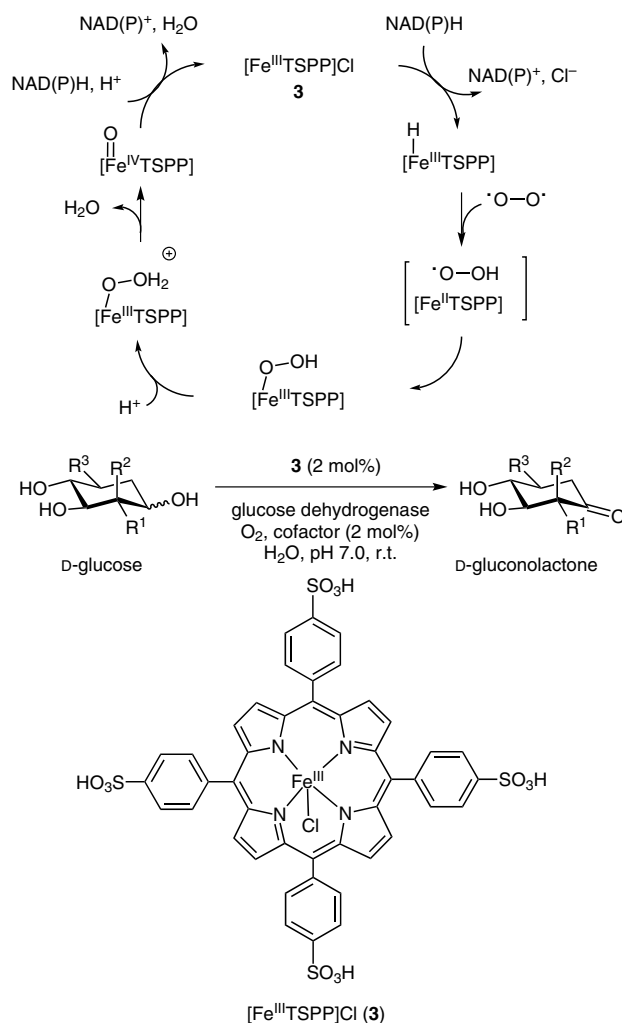
Scheme 2 Iron(III) porphyrin **3** catalyzed in situ cofactor regeneration of NAD(P)+

Biographical Sketches
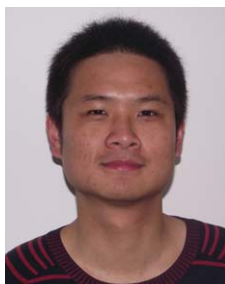
Wangming Du studied chemistry at the Central China Normal University and received his BSc in 2008. In September 2008, he came to Dalian Institute of Chemical Physics (DICP), Chinese Academy of Sciencesas (CAS) as a graduate student and joined Prof. Zhengkun Yu group to study for a PhD degree. His research project is focused on novel transition-metal-complex catalysts for transfer hydrogenation of ketones and relevant reactions.

Prof. Zhengkun Yu obtained his PhD degree at Dalian Institute of Chemical Physics (DICP), CAS in July of 1995. From October 1995 to January 2003 he worked as a post-doctoral fellow and research associate in the labs of Prof. Rudolf Aumann (University of Münster, Germany), Prof. John G. Verkade (Iowa State University, USA), Prof. Chuck Winter (Wayne State University, USA), and in the Japan Corporation of Science and Technology (Tokyo, Japan). He returned to DICP as a 'Hundred Talents Program of CAS' professor in February 2003. His current research interests are focused on novel organometallic complex catalysts and catalytic C–X bond activation.

also highly suitable for the cofactor regeneration of other oxidative reactions. For example, cyclooctanol was oxidized to the corresponding ketone in a phosphate buffer in 93% yield by means of 2 mol% of **3** as catalyst in the presence of 2 mol% cofactor and an alcohol dehydrogenase. Considering the catalytic efficiency and ready availability of **3**, this biomimetic recycling of cofactors NAD(P)$^+$ in water can be regarded as an alternative to enzymetic cofactor regeneration with an NAD(P)H oxidase.

A photocatalytic regeneration approach for NAD(P)$^+$ was also documented.[26] By simple irradiation with visible light, the NAD(P)H oxidation was performed by using a catalytic amount of flavin **4** under aerobic conditions. Combined with alcohol dehydrogenases (ADH), photoenzymatic oxidation schemes were obtained allowing for selective, oxygen-driven oxidation of primary and secondary alcohols (Scheme 3). The simplicity and practical applicability of this oxidation approach can be demonstrated in the oxidative lactonization of 1,4- and 1,5-diols, exhibiting total turnover numbers of 170 and 340 for the nicotinamide cofactor and the flavin catalyst under nonoptimized conditions, respectively.
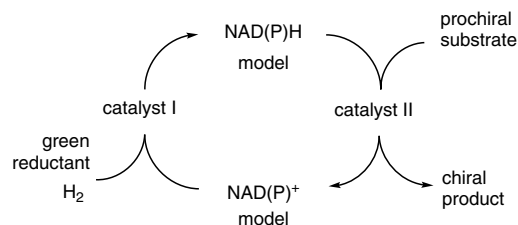
3   Biomimetic in situ Regeneration of Hantzsch Esters (HEH)

Hantzsch esters **1** are also expensive as stoichiometric biomimetic reducing agents.[15] However, developing a biomimetic asymmetric hydrogenation system that simultaneously involves an asymmetric reduction process for the in situ regeneration of Hantzsch esters still remains a challenge in the field of NAD(P)H mimics.[35] Hydrogen gas has been used as the most efficient reductant to produce bioactive compounds by transition-metal-catalyzed asymmetric hydrogenation.[36–39] Thus, biomimetic asymmetric hydrogenation employing hydrogen as the reductant is highly desired for the in situ regeneration of NAD(P)H models, that is, Hantzsch esters **1**, from their oxidized forms Hanztsch pyridines of type **6** (Scheme 4 and Scheme 5).

In 2011, Zhou et al. found that [Ru(p-cymene)I$_2$]$_2$ could catalyze the reduction of Hantzsch pyridine **6** to Hantzsch
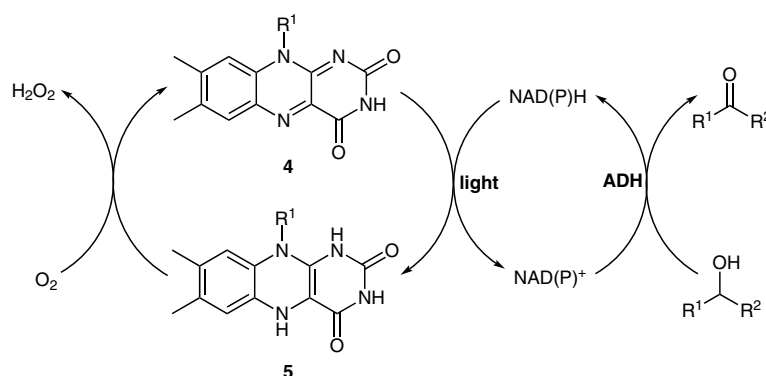
Scheme 4 Biomimetic in situ cofactor model regeneration (catalyst I for regeneration; catalyst II for production)

ester **1a** by hydrogen gas, suggesting a possibility to in situ regenerate Hantzsch esters under biomimetic reduction conditions.[35] Through coupling with chiral phosphoric acid (*S*)-**7a** promoted the asymmetric transfer hydrogenation of benzoxazinone **8a** by Hantzsch ester **1a**, in situ regeneration of the Hantzsch ester was successfully realized (Scheme 5). Substrate **8a**, [Ru(p-cymene)I$_2$]$_2$ (1.25 mol%), (*S*)-**7a** (2 mol%), a catalytic amount of Hantzsch ester **1a** (10 mol%), and H$_2$ (70 atm) were employed to establish the catalytic system in THF–CH$_2$Cl$_2$ (v/v, 1:3) at 50 °C. Over a period of 48 hours, up to 98% yields and 99% ee were obtained for the desired products dihydrobenzoxazinones **9a** regardless of the electronic properties of the aryl substituents in **8a**. It is noteworthy that the catalytic efficiency of such a catalytic system is identical to that of a pure organocatalytic process which consumed a stoichiometric amount of Hantzsch ester **1a**.[40] It is proposed that chiral phosphoric acid (*S*)-**7a** catalyzes the asymmetric transfer hydrogenation of benzoxazinones **8a** with Hantzsch ester **1a** first, affording the desired reduction product **9a** and **6**. Hantzsch pyridine **6** then undergoes a Ru(II)-catalyzed hydrogenation to regenerate **1a** for the next catalytic cycle. Because of $k_2 > k_3$, formation of **9a** in a racemic manner was inhibited.

4   Biomimetic in situ Regeneration of Dihydrophenanthridine (DHPD)

Very recently, in a fashion similar to the in situ regeneration of Hantzsch ester **1a**,[35] Zhou et al. developed a new and readily regenerable NAD(P)H model, 9,10-dihydrophenanthridine (DHPD, **2**), for biomimetic asymmetric

Scheme 3 Flavin **4** mediated in situ cofactor regeneration of NAD(P)$^+$

Scheme 5 Biomimetic asymmetric hydrogenation of benzoxazinones **8a** using a catalytic amount of Hantzsch ester **1a**

hydrogenation of imines and N-heteroaromatic compounds.[41] Thus, [Ru(*p*-cymene)I$_2$]$_2$ (0.5–1.0 mol%), a Brønsted acid (*S*)-**7** (1–5 mol%), and phenanthridine (**10**, 10 mol%) were utilized to construct the catalytic system (Scheme 6). Because hydrogen gas (3–34 atm) was used as the terminal reductant under mild conditions, the substrate scope could be extended from benzoxazinones **8a** to benzoxazines **8b**, quinoxalines **8c**, and quinolines **8d** with excellent activities. Excellent enantioselectivities (85–97% ee) were also obtained for the desired products **9**. As illustrated in Scheme 6, the proposed mechanism suggests that phenanthridine (**10**) is hydrogenated to DHPD (**2**) first under the Ru(II) catalysis, Brønsted acid (*S*)-**7** then promotes the transfer hydrogenation of **8** with DHPD to form the desired product **9** and phenanthridine (**10**) for the next catalytic cycle. It should be noted that much milder conditions were required as compared with the biomometic asymmetric hydrogenation at 70 atm of hydrogen gas using a catalytic amount of Hantzsch ester **1a**.[35] The excellent enantioselectivities are attributed to the fact that the major reaction rate k_2 is faster than that of the undesired reaction k_3 leading to the racemic products.

5   Future Perspective

In summary, biomimetic recycling of cofactors NAD(P)+ by Fe(III) porphyrin or flavin-catalyzed oxidation or dehydrogenation of NAD(P)H in the presence of dioxygen and coupling with dehydrogenation of alcohols can be regarded as an alternative to enzymatic cofactor regeneration with NAD(P)H oxidases. The NAD(P)H models Hantzsch esters (HEH) and 9,10-dihydrophenanthridine (DHPD) can be in situ regenerated as biomimetic hydrogen sources by means of transition-metal/Brønsted acid catalyzed relay asymmetric hydrogenation. These biomi-

metic recycling systems have exhibited promising potentials to develop efficient catalytic procedures for the in situ regeneration of cofactors and their models for the preparative applications.

7a Ar^2 = 9-phenanthryl
7b Ar^2 = Ph
7c Ar^2 = 9-phenanthryl [H8]
7d Ar^2 = Ph [H8]
7e Ar^2 = 2-MeC$_6$H$_4$
7f Ar^2 = 9-anthryl

Scheme 6 Biomimetic asymmetric hydrogenation of **8** using a catalytic amount of phenanthridine (**10**)

Acknowledgment

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