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\*\*\*\*\*Accepted Manuscript\*\*\*\*\*

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It will be published in the **October 2023** issue of the *Johnson Matthey Technology Review*

Please visit the website <https://technology.matthey.com/> for Open Access to the article and the full issue once published

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<<https://doi.org/10.1595/205651323X16686913816837>>

<First page number: TBC>

## **In the Lab: Heterogeneous Catalysis Mediated Interconversion between NAD(P)<sup>+</sup> and NAD(P)H Accompanied by Consumption and Generation of Hydrogen**

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<Article history>

NON-PEER REVIEWED FEATURE

Received 16th November 2022; Online 17th November 2022

<End of article history>

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Dr. Wang is a Senior Lecturer in Chemical Engineering at Lancaster University. Prior to this, he was a Lecturer in Chemical Engineering at the University of Aberdeen, Postdoctoral Research Associate at Heriot-Watt University, where he also obtained his PhD (2014). He completed both MSc and BEng studies at Tianjin University. Wang has been the author of over 50 peer-reviewed publications, an editorial board member of *Chinese Chemical Letters* and his research has mainly been funded by the Engineering and Physical Sciences Research Council (EPSRC),

Royal Society, UK Catalysis Hub and industry. Wang's research interest ranges from reaction engineering, green energy and materials to chemicals, where heterogeneous catalysis is the core discipline. His recent work has focused on the innovative use of heterogeneous catalysts (e.g., supported metals) in enzymatic transformations via cofactor regeneration,<sup>1,2</sup> paving the way to a potential new regeneration technology.

Biotechnology has been widely used in the chemical and pharmaceutical industries, where synthesis using enzymes plays a significant role. Oxidoreductases, as one of the largest classes of enzymes (~25% of all enzymes), are essential for enzymatic redox reactions that in turn are key steps in the manufacture of products ranging from specialty to commodity chemicals. Enzymatic reduction typically requires the stoichiometric consumption of an expensive cofactor, NAD(P)H (the reduced form of nicotinamide adenine dinucleotide), which acts as a hydride/electron donor and is oxidised to its oxidised form, i.e., NAD(P)<sup>+</sup>. NAD(P)H must be regenerated (i.e., NAD(P)<sup>+</sup> reduction to NAD(P)H) *in situ* to make the entire process viable (Figure 1a). Similarly, enzymatic oxidation reactions depend on the stoichiometric use of NAD(P)<sup>+</sup>, as a hydride/electron acceptor, which is reduced to NAD(P)H. Due to the high cost, *in situ* oxidation of NAD(P)H back to NAD(P)<sup>+</sup>, namely regeneration, is a must (Figure 1c). The Wang group has been the first team to establish the utilisation of heterogeneous catalysis in such regeneration reactions accompanied by the consumption and generation of molecular hydrogen. A heterogeneous catalyst is preferred over other regeneration methods because it is easy for downstream separation, catalyst recycling/reuse and scaling up, decreasing cost and energy demand.<sup>3</sup>

## The Research

### **H<sub>2</sub>-Driven NAD(P)H Regeneration ( $\text{NAD(P)}^+ + \text{H}_2 \rightarrow \text{NAD(P)H} + \text{H}^+$ )**

The first example of H<sub>2</sub>-driven NAD(P)H regeneration employing heterogeneous catalysts was reported in 2016.<sup>1</sup> A Pt/Al<sub>2</sub>O<sub>3</sub> catalyst was systematically examined in the hydrogenation of NAD<sup>+</sup>. It was established that high H<sub>2</sub> pressure (1 to 9 atm), pH (4.0 to 9.9) and a modest temperature (37 °C in the range of 20-60 °C) were beneficial for the regeneration of NAD(P)H. The activity of the Pt/Al<sub>2</sub>O<sub>3</sub> catalyst can also be enhanced by a H<sub>2</sub> pre-treatment at 350 °C, which generated more metallic Pt active sites. The solid catalyst promoted in situ regeneration system has been compatible with enzymatic propanal reduction to propanol using alcohol dehydrogenase. Subsequently, it was shown that NADH production from NAD<sup>+</sup> hydrogenation was also feasible (with various degrees of success) over a few other supported metal systems. These include Al<sub>2</sub>O<sub>3</sub>-supported Au, Rh, Ru, and Pd and Ni, as well as Pt supported on Fe<sub>3</sub>O<sub>4</sub>, SiO<sub>2</sub>, carbon and MgO.<sup>3,4,5</sup>

These first publications are exclusively (till mid-2021) from the Wang group and have disclosed, after finding it was extremely difficult to understand the reaction mechanism and optimise catalysts, a particular challenge of this topic, i.e., rigorous experimental examination of NAD(P)<sup>+</sup> conversion, product distribution (i.e., isomers, dimers; it's not always selective) and carbon/material balance. Inaccurate and often misleading results have unfortunately been reported in the literature for nonenzymatic regeneration approaches.<sup>6,7</sup> A novel analytical method combining UV-vis spectroscopy and enzymatic assays was thus developed.<sup>8</sup> It has since contributed significantly, allowing the unequivocal determination of the species

(Figure 1b) involved in such systems. It was then possible to understand the role of catalyst surface charge in controlling activity<sup>4</sup> and to obtain the most selective heterogeneous catalyst (i.e., PtSn alloy on a silica carrier) that achieved a 90% selectivity to 1,4-NADH (at full conversion).<sup>9</sup> The exceptional selectivity can be attributed to Sn disturbing the Pt ensemble, altering the mode of NAD<sup>+</sup> adsorption and directing the reduction to the 1,4-position of the nicotinamide ring. It is expected that exclusive 1,4-NAD(P)H selectivity becomes achievable in the future and heterogeneous catalytic regeneration can contribute to NAD(P)H dependant bio-reductive transformations.

#### **Proton-driven NAD(P)<sup>+</sup> Regeneration (NAD(P)H + H<sup>+</sup> → NAD(P)<sup>+</sup> + H<sub>2</sub>)**

The Wang group has recently been interested in the reverse reaction of the above discussion, namely NAD(P)<sup>+</sup> regeneration. As mentioned previously, this is essential for NAD(P)<sup>+</sup> dependant enzymatic oxidation/dehydrogenation. Being able to employ H<sup>+</sup> as an oxidant allows the regeneration process to produce molecular H<sub>2</sub>. This becomes particularly interesting and promising when the regeneration method is coupled *in situ* with enzymatic oxidative reactions. It should however be flagged that NAD(P)<sup>+</sup> regeneration has been studied to a much lesser extent than its counterpart. A breakthrough here would be very beneficial. The focus of Wang's work is again on the development of heterogeneous catalysts for such applications.

A series of activated carbon-supported Pt catalysts with different surface functional groups (e.g., quinone-type carbonyls, carboxylic acids, anhydrides, lactones, phenols, phenolic groups) were active and selective for the NAD(P)H to NAD(P)<sup>+</sup> conversion, releasing a stoichiometric amount of H<sub>2</sub>.<sup>2</sup> The reaction was favoured at a low pH (10 to 4). The Pt/C catalyst with the highest degree of electron

donation from carbon (an overall effect from all functional groups) generated the highest TOF ( $\sim 580 \text{ h}^{-1}$ ): a result of electron-rich Pt-promoted electron transfer to protons. A tandem catalytic system involving enzymatic alcohol/diol oxidations and in situ Pt/C catalysed  $\text{NAD}^+$  regeneration was also proven feasible.

The results from both directions of the reaction catalysed by heterogeneous catalysts have shown great potential for integrating with enzymatic redox transformations, such as  $\text{CO}_2$  reduction, chiral synthesis and  $\text{H}_2$  production. It is hoped that those coupling/tandem catalytic systems can ultimately contribute to decarbonisation, carbon neutrality and net zero.

### Acknowledgements

Dr. Wang thanks all his PhD students and postdoctoral research associates/assistants as well as his collaborators for their contributions. This line of research has been developed with financial support from the EPSRC (EP/V048635/1 and EP/X018172/1), UK Catalysis Hub (via EP/R026645/1 and EP/K014706/2), Royal Society (ICA\R1\180317, IES\R3\170162, IE150611, and RG150001), British Council Newton Fund and Carnegie Trust for the Universities of Scotland (70265).

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Fig. 1. Schematic showing heterogeneous catalysis mediated interconversion between  $\text{NAD(P)}^+$  and  $\text{NAD(P)H}$  accompanied by consumption and generation of hydrogen: (a) enzymatic reduction with concurrent  $\text{H}_2$ -driven  $\text{NAD(P)H}$  regeneration; (b) selectivity challenge in  $\text{NAD(P)}^+$  hydrogenation and (c) enzymatic dehydrogenation with concurrent proton-driven  $\text{NAD(P)}^+$  regeneration and  $\text{H}_2$  production.

