https://doi.org/10.1595/205651323X16686913816837 *Johnson Matthey Technol. Rev.*, 2023, **67**, (4), 452–454

JOHNSON MATTHEY
TECHNOLOGY REVIEW
technology.matthey.com

In the Lab

Heterogeneous Catalysis Mediated Interconversion between NAD(P)$^+$ and NAD(P)H Accompanied by Consumption and Generation of Hydrogen

***Johnson Matthey Technology Review* features laboratory research**

NON-PEER REVIEWED FEATURE

Received 16th November 2022; Online 17th November 2022

Xiaodong Wang is a Senior Lecturer in Chemical Engineering at Lancaster University, UK. Prior to this, he was a Lecturer in Chemical Engineering at the University of Aberdeen, UK, Postdoctoral Research Associate at Heriot-Watt University, UK, where he also obtained his PhD (2014). He completed both MSc and BEng studies at Tianjin University, China. 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), The Royal Society, UK Catalysis Hub and industry.

About the Researcher

- **Name:** Xiaodong Wang
- **Position:** Senior Lecturer in Chemical Engineering
- **Department:** School of Engineering
- **University:** Lancaster University
- **Address:** Engineering Building, Lancaster
- **Postcode:** LA1 4YW
- **Country:** UK
- **Email:** xiaodong.wang@lancaster.ac.uk

About the Research

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 (for example, supported metals) in enzymatic transformations *via* cofactor regeneration (1, 2), 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, 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)$^+$. NAD(P)H must be regenerated (i.e. NAD(P)$^+$ reduction to

NAD(P)H) *in situ* to make the entire process viable (**Figure 1(a)**). Similarly, enzymatic oxidation reactions depend on the stoichiometric use of $NAD(P)^+$ 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 $NAD(P)^+$, namely regeneration, is essential (**Figure 1(c)**). 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 scale-up, decreasing cost and energy demand (3).

The first example of hydrogen-driven NAD(P)H regeneration (Equation (i)) employing heterogeneous catalysts was reported in 2016 (1).

$$NAD(P)^+ + H_2 \rightarrow NAD(P)H + H^+ \quad \text{(i)}$$

A platinum-on-alumina catalyst was systematically examined in the hydrogenation of NAD^+. It was established that high hydrogen pressure (1 atm to 9 atm), pH (pH 4.0 to pH 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 platinum-on-alumina catalyst can also be enhanced by a hydrogen pretreatment at 350°C, which generated more metallic platinum active sites. The solid catalyst-promoted *in situ* regeneration system is compatible with enzymatic propanal reduction to propanol using alcohol dehydrogenase. Subsequently, it was shown that NADH production from NAD^+ hydrogenation was also feasible (with various degrees of success) over a few other supported metal systems. These include alumina-supported gold, rhodium, ruthenium, palladium and nickel, as well as platinum supported on iron(II,III) oxide, silica, carbon and magnesia (3–5).

Until mid-2021, publications were exclusively from the Wang group. It was extremely difficult to understand the reaction mechanism and optimise catalysts. The particular challenges of this topic became apparent: i.e. rigorous experimental examination of $NAD(P)^+$ conversion, product distribution (i.e. isomers, dimers; it is not always selective) and carbon and material balance. Inaccurate and often misleading results have unfortunately been reported in the literature for nonenzymatic regeneration approaches (6, 7). A novel analytical method combining ultraviolet-visible spectroscopy and enzymatic assays was thus

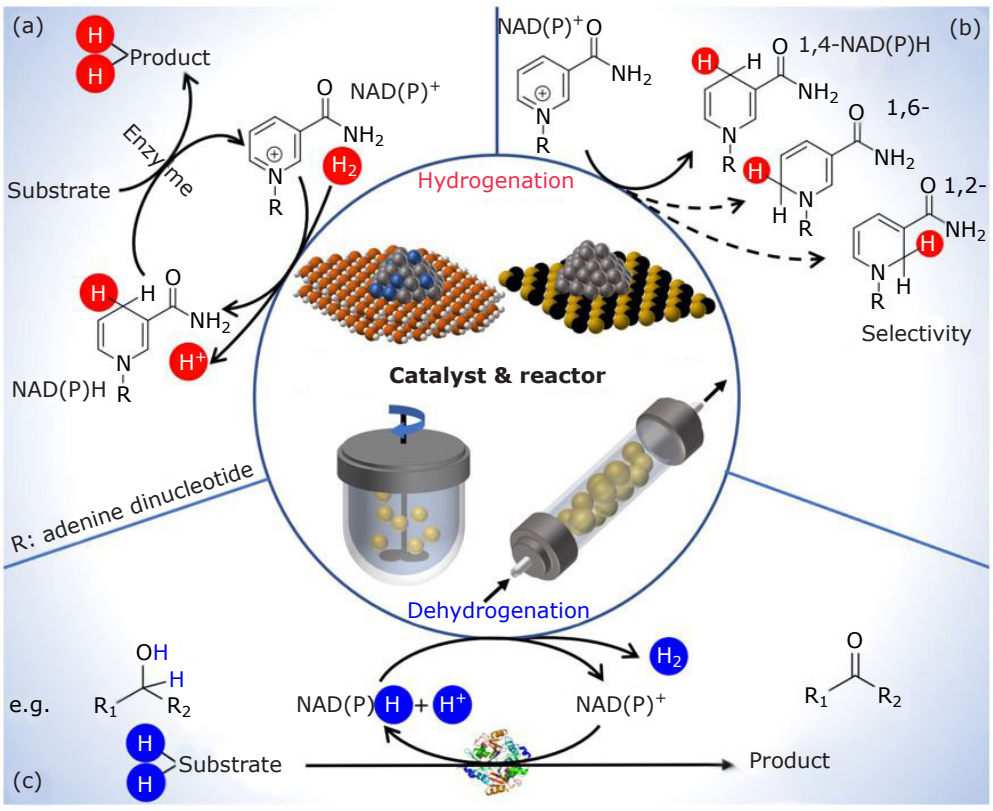

Fig. 1. Schematic showing heterogeneous catalysis mediated interconversion between $NAD(P)^+$ and NAD(P)H accompanied by consumption and generation of hydrogen: (a) enzymatic reduction with concurrent H_2-driven NAD(P)H regeneration; (b) selectivity challenge in $NAD(P)^+$ hydrogenation; and (c) enzymatic dehydrogenation with concurrent proton-driven $NAD(P)^+$ regeneration and H_2 production

developed (8). It has since contributed significantly, allowing the unequivocal determination of the species (**Figure 1(b)**) involved in such systems. It was then possible to understand the role of catalyst surface charge in controlling activity (4) and to obtain the most selective heterogeneous catalyst, i.e. platinum-tin alloy on a silica carrier that achieved a 90% selectivity to 1,4-NADH at full conversion (9). The exceptional selectivity can be attributed to tin disturbing the platinum ensemble, altering the mode of NAD^+ 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 will become achievable in the future and heterogeneous catalytic regeneration can contribute to NAD(P)H-dependent bio-reductive transformations.

The Wang group has recently been interested in the reverse reaction of the above discussion, namely proton-driven $NAD(P)^+$ regeneration (Equation (ii)).

$$NAD(P)H + H^+ \rightarrow NAD(P)^+ + H_2 \quad \text{(ii)}$$

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

A series of activated carbon-supported platinum catalysts with different surface functional groups such as quinone-type carbonyls, carboxylic acids, anhydrides, lactones, phenols and phenolic groups were active and selective for the NAD(P)H to $NAD(P)^+$ conversion, releasing a stoichiometric amount of hydrogen (2). The reaction was favoured at low pH (pH 10 to pH 4). The platinum-on-carbon catalyst with the highest degree of electron donation from carbon (an overall effect from all functional groups) generated the highest turnover frequency of ~580 h^{-1}: a result of electron-rich platinum-promoted electron transfer to protons. A tandem catalytic system involving enzymatic alcohol/diol oxidations and *in situ* platinum-on-carbon-catalysed 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 CO_2 reduction, chiral synthesis and hydrogen production. It is hoped that these coupling and tandem catalytic systems can ultimately contribute to decarbonisation, carbon neutrality and net zero.

Acknowledgements

Xiaodong Wang thanks all his PhD students and postdoctoral research associates and 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), The Royal Society (ICA\R1\180317, IES\R3\170162, IE150611 and RG150001), British Council Newton Fund and Carnegie Trust for the Universities of Scotland (70265).

References

1. X. Wang, H. H. P. Yiu, *ACS Catal.*, 2016, **6**, (3), 1880
2. J. W. H. Burnett, H. Chen, J. Li, Y. Li, S. Huang, J. Shi, A. J. McCue, R. F. Howe, S. D. Minteer, X. Wang, *ACS Appl. Mater. Interfaces*, 2022, **14**, (18), 20943
3. X. Wang, T. Saba, H. H. P. Yiu, R. F. Howe, J. A. Anderson, J. Shi, *Chem*, 2017, **2**, (5), 621
4. T. Saba, J. Li, J. W. H. Burnett, R. F. Howe, P. N. Kechagiopoulos, X. Wang, *ACS Catal.*, 2021, **11**, (1), 283
5. T. Saba, J. W. H. Burnett, J. Li, X. Wang, J. A. Anderson, P. N. Kechagiopoulos, X. Wang, *Catal. Today*, 2020, **339**, 281
6. W. Jones, J. W. H. Burnett, J. Shi, R. F. Howe, X. Wang, *Joule*, 2020, **4**, (10), 2055
7. J. W. H. Burnett, R. F. Howe, X. Wang, *Trends Chem.*, 2020, **2**, (6), 488
8. T. Saba, J. W. H. Burnett, J. Li, P. N. Kechagiopoulos, X. Wang, *Chem. Commun.*, 2020, **56**, (8), 1231
9. J. W. H. Burnett, J. Li, A. J. McCue, P. N. Kechagiopoulos, R. F. Howe, X. Wang, *Green Chem.*, 2022, **24**, (4), 1451

