FEATURE ARTICLE
Arnab Dutta et al.
The odyssey of cobaloximes for catalytic \( \text{H}_2 \) production and their recent revival with enzyme-inspired design
The odyssey of cobaloximes for catalytic H₂ production and their recent revival with enzyme-inspired design

Dependu Dolui, Shikha Khandelwal, Piyali Majumder and Arnab Dutta*

Cobaloxime complexes gained attention for their intrinsic ability of catalytic H₂ production despite their initial emergence as a vitamin B12 model. The simple, robust, and synthetically manoeuvrable cobaloxime core represents a model catalyst molecule for the investigation of optimal conditions for both photo- and electrocatalytic H₂ production catalytic assemblies. Cobaloxime is one of the rare catalysts that finds equal applications in the analysis of homogeneous and heterogeneous catalytic conditions. However, the poor aqueous solubility and long-term instability of cobaloximes have severely impeded their growth. Lately, interest in the cobaloxime-based catalysts has been resuscitated with the rational use of extended enzymatic features. This unique enzyme-inspired catalyst design strategy has instigated the formation of a new genre of cobaloxime molecules that exhibit enhanced photo- and electrocatalytic H₂ evolution with improved aqueous and air stability.

Introduction

The structural elucidation of vitamin B12 sprung a surprise in the bioinorganic community with the presence of a rare organometallic cobalt–carbon bond in biology. Vitamin B12 performs an array of metabolically vital chemical reactions such as methyl transfer, dehalogenation, and isomerization. Hence, the basic structure of vitamin B12 soon became the source of inspiration for developing several biomimetic model complexes...
for executing versatile industry-relevant chemical reactions, including alkene coupling, ring-opening metathesis, hydrogennation, and rearrangement. A stable organometallic cobalt complex, 5-deoxyadenosyl(5,6-dimethylbenzimidazolyl)-cobinamide (1), resides in the core of vitamin B12, where the equatorial corrin ring plays a crucial role in tuning its reactivity. The requirement of such a bulky and synthetically challenging tetradentate corrin ring can be avoided by innovative substitution with two molecules of bidentate dimethyl glyoximes while retaining the versatile edge of a Co–N₄ square planar core structure.

Schrauzer and Kohnle prepared one of the first examples of such square planar cobalt dimethylglyoxime complexes, where the axial coordination sites were occupied by cyanide and pyridine groups. Following up on this work, Wagner and Bernhauer replaced the axial cyanide group with a Grignard reagent to generate an air-stable cobalt-alkyl derivative, imitating the vitamin B12 coenzyme core. Later, the term “cobaloxime” was coined to describe the cobalt dimethylglyoxime [Co(DH)₂] moiety. The unique structure of these vitamin B12-inspired cobaloximes has instigated a series of attempts to probe their activity even as a functional model for the hydrogenase enzyme. The excellent reactivity of hydrogenases for H₂ production (2H⁺ + 2e⁻ → H₂) is attributed to the synchronized conglomeration of a redox-active metal cofactor, electron-transporting [FeS] cluster proteins, and proton-relaying polar amino acid side-chains. Among these, the redox-active metal core and closely lying polar functionalities (oximes) are already present in cobaloximes. Hence, an appropriate electron supplement (either from a photo- or potential-driven source) can activate the cobaloximes for the catalytic hydrogen evolution reaction (HER) (Fig. 1B).

This first proof of this “enzyme-inspired catalyst design” hypothesis was provided by Ziessel and co-workers, who observed photocatalytic H₂ production by cobaloximes in the presence of [Ru(bpy)₃]²⁺ and an organic amine as the photosensitizer and electron donor, respectively. Here, the Co(II) centre of cobaloximes readily coverts to Co(I) following the reductive quenching of photo-excited [Ru(bpy)₃]²⁺. Next, the subsequent protonation generates a highly reactive Co(III)-hydride intermediate, which ultimately decomposes to display H₂ production. The intrinsic O₂ tolerance of cobaloximes allowed the occurrence of this catalytic H₂ production even in aerobic conditions. Despite exhibiting such unique catalytic HER activity, cobaloximes failed to achieve prominence as HER catalysts. The intricate framework of natural metalloenzymes has always fascinated Arnab Dutta from the beginning. He had an opportunity to study those structural marvels of biology during his PhD with Dr Anne Jones, where he developed metallopetide-based candid models of hydrogenase (Arizona State University, 2012). In the next phase of his career, he mastered the finer details of enzyme-mimicry with Dr Wendy Shaw. This time, he generated versatile molecular catalysts, boasting minimal but essential enzymatic traits in their periphery (Pacific Northwest National Laboratory, 2015). As an independent researcher, he is trying to develop sustainable and all-weather ready catalysts that can boost the use of renewable energy. His quest to bring life into poorly active catalysts with the Midas touch of enzyme-derived features continues at IIT Bombay.
Photocatalytic HER activity by cobaloximes

The photocatalytic HER activity is typically driven by collaboration between three independent ingredients: (i) the photosensitizer (PS), (ii) the catalyst, and (iii) the sacrificial electron donor (ED). Here, our discussion will be limited to those systems where a cobaloxime derivative plays the catalytic role. Depending on the nature of the photosensitizer (PS), we have further fragmented our discussion into sections: (i) inorganic noble-metal-based PS, (ii) inorganic non-noble-metal based PS, (iii) organic PS, and (iv) nanomaterial-based PS. The robust nature, synthetic flexibility, and chemical property tunability of the cobaloxime core made it a popular choice for screening the photocatalytic efficiency of an array of photosensitizers under a wide chemical space.

Noble metal-based photosensitizer

As mentioned earlier, photocatalytic hydrogen production can be obtained by using these cobaloximes in the presence of a photosensitizer (PS) and a sacrificial electron donor. The majority of such early studies reported the utilization of expensive Ru/Pt/Ir-based photosensitizers for light-harvesting (Fig. 2 and Table 1). Due to the limited water solubility of typical cobaloximes, organic solvents remained the primary choice of medium for photocatalytic HER investigation. The photocatalytic activity is conventionally reported with the parameter turnover number (TON), where the amount of H₂ produced during the experiment is measured against the concentration of PS or cobaloxime catalyst. In one of the first examples, considerable photocatalytic H₂ production was observed for the [Co(DH)₂] complex in the presence of Cr⁶⁺ as an external reducing agent. Their success revived the research on oxygen-tolerant cobaloxime-based HER activity on both photocatalytic and electrocatalytic fronts. However, the limited catalytic efficiency, long-term aqueous instability, and loss of catalytic activity under acidic aqueous conditions have raised serious questions on the potential of these cobaloximes for large-scale applications. A similar roadblock was also observed for Ni-bis-(diphosphine)-based Dubois catalysts, which was resolved by the rational incorporation of extended features of enzyme architecture into their periphery of the Ni-core. Buoyed by this success of such unconventional enzyme-inspired catalyst design, researchers have also amended outer coordination sphere features around the cobaloxime core. This innovative track of catalyst design technique was the key to the formation of a new genre of cobaloxime catalysts that resuscitates the cobaloxime as a viable option for renewable energy research. The simple, robust, and synthetically maneuverable structure of the cobaloxime core has allowed researchers to optimize the combinations of ingredients for photocatalytic HER, analyze the catalytic pathways during the electrocatalytic H₂ evolution, and explore the effect of extended enzyme-inspired features, which are discussed in detail in the following sections.

![Fig. 2] Structures of various noble metal-based photosensitizers (7–11) used with cobaloxime derivatives, such as (6) for photocatalytic hydrogen evolution in homogeneous condition.
After 9 h of irradiation in DMF solution, [Co(DH)$_2$] displayed 150 TON (250 W, $\lambda > 400$ nm) in the presence of Re-based PS.$^{30}$ However, the use of such Re-based PS was futile as it exhibited significant degradation over time.$^{30}$ The substitution of the labile Br$^-$ with NCS$^-$ improved the stability of this Re-complex that resulted in better photocatalytic hydrogen production.$^{31}$ Castellano and co-workers developed a cyclometalated Ir-based photosensitizer (11), along with cobaloxime, for photocatalytic H$_2$ production in near neutral condition.$^{23}$

Continuing the search for a stable photocatalytic system, the axial pyridine ligand was used as a linker to covalently connect noble metal-based photosensitizers.$^{32-35}$ Fihri et al. prepared a supramolecular assembly, where a ruthenium-tris-di-imine PS was coupled to a cobaloxime core (12–13), Fig. 3) through the axial pyridine. This modification positively shifted the Co$^{II/III}$ reduction potential by $\sim 80$ mV, but it eventually slowed down in the longer run.$^{36}$ After 15 hours of irradiation ($\lambda > 350$ nm), a TON of 103 (measured vs. cobaloxime catalyst) was observed in the presence of 100 equivalents of Et$_3$N (electron donor) and Et$_3$NHBF$_4$ (proton source).$^{33}$

Sun and co-workers improvised this strategy to incorporate an amide linker at a variable length between the axial-pyridine and PS (14), Fig. 3). The presence of a methylene spacer between the linker and pyridine turned out to be a critical stabilizing factor, as it amplified the TON by $\sim 1.5$ times compared to the control complex during a 4 h irradiation (Xe lamp, 500 W, $\lambda > 400$ nm) in acetone. It is believed that this unconjugated methylene spacer possibly impedes the back electron transfer from the reduced metal to the PS to improve the overall photocatalytic efficiency.$^{34}$

The Ir-polypyridyl photosensitizer-based supramolecular PS–cobaloxime dyad (15) yielded a comparatively higher TON ($\sim 140$; after 8 h of irradiation in an acetone solvent with a Hg lamp [150 W, $\lambda > 380$ nm]).$^{32}$ Analogous heteroleptic Ru(II)-photosensitizer-bound cobaloxime assemblies (16–19), Fig. 3) were also developed to harvest the longer wavelengths due to their broad red-shifted emission.$^{37}$ However, they exhibited poor photocatalytic HER (4 h irradiation, TON: 9) that was attributed to the low quantum yield and short-lived excited states of those heteroleptic PS-catalyst dyads.$^{38}$ Further studies with such Ir-containing multi-component PS–cobaloxime assemblies (20), Fig. 4) revealed low efficiency, albeit a higher catalytic turnover with prolonged irradiation.$^{39,40}$ In a different approach, Mulfort and co-workers targeted the equatorial sites of the cobaloximes to append the light-harvesting Ru-PS component (21–22), Fig. 4). Through this transformation, they were even able to identify the key photosynthetic charge-separated intermediate (Co$^0$) for $\sim 26$ ps.$^{41}$

Most of the above-mentioned photocatalytic H$_2$ production reactions, containing a noble-metal-based PS and cobaloxime catalyst, suffered a setback when water was added to the reaction medium. Eisenberg and his team utilized a mixture of Pt-based PS [Pt(tpy)(C≡CPh)]ClO$_4$ (tpy$^+$ = 4′-p-tolylterpyridine) and cobaloxime derivative [ClCo(DH)$_2$(methylisonicotinate)] to demonstrate effective H$_2$ production even in a 3:2 acetonitrile:water mixture (200 W mercury xenon lamp, $\lambda > 410$ nm).$^{42}$

It can be summarized here that Ru- and Ir-based photosensitizers exhibited better photocatalytic HER in partnership
with the cobaloxime catalyst, and the reactivity improved significantly when both PS and catalyst modules were connected via covalent linker (Table 2).

### Non-noble metal-based photosensitizers

The low abundance and high expense of noble metals compelled the researchers to explore the possibility of employing non-noble metal-based photosensitizers for photocatalytic H₂ production with cobaloximes (Fig. 5 and 6). The presence of Mg-based chlorophylls and their active participation in the photo-harvesting process inspired the synthesis of magnesium (Mg)-based synthetic porphyrins. Following the similar synthetic methodology, zinc (Zn)-based porphyrin analogues were also prepared. Zinc porphyrins illustrated higher photocatalytic efficiency compared to the magnesium counterpart when they were appended with the cobaloxime via axial ligation (23), Fig. 5. This higher efficiency is attributed to the possible pre-coordination of trimethylamine (TEA) to the zinc porphyrin that facilitates inner sphere electron transfer (ET) from TEA to PS. In a follow-up study, an amide spacer was included in the linker that quenched the electron transfer rate, causing the irradiation to slow down the overall photocatalytic HER activity by this modified Zn-porphyrin–PS–cobaloxime assembly (24), Fig. 5. It is noteworthy that axial imidazole-linked cobaloximes display superior photocatalytic HER activity in comparison to axial pyridine-linked cobaloximes. Natali and co-workers developed in situ Al-porphyrin linked to the hydrogen-bridged cobaloximes (25), Fig. 5 through the pyridyl group, which exhibited limited photocatalytic HER [TON \text{max} = 352 \text{ vs. PS, } 175 \text{ W Xe-arc, } \lambda > 400 \text{ nm}]. In a parallel study, tin-based porphyrins (26–28), Fig. 6 were also probed for the role of PS under similar conditions. Interestingly, photocatalytic H₂ production was observed only in the presence of the water-insoluble tin-porphyrin derivative [SnTPyP(OH)₂] (28), Fig. 6, but not with the water-soluble tin-porphyrin chloride [SnTmPyP] (26), Fig. 6. Probst et al. reported a water-soluble Sn-porphyrin system (27), Fig. 6 that was active as a PS for photocatalytic H₂ production. However, its short-lived excited state reduced the overall catalytic efficiency. Later, several other zinc-porphyrin or corrole chromophores were screened with cobaloximes in aqueous or aqueous–organic solvent mixtures. In recent years, the earth-abundant copper-based [Cu(n)(dsbtmp)]⁺ (dsbtmp = 2,9-di(sec-butyl)-3,4,7,8-tetramethyl-1,10-phenanthroline) PS (29), Fig. 6) was also developed. This Cu(Ⅰ)-PS exhibited only moderate photocatalytic H₂ production in the presence of cobaloxime (TON ~ 35 vs. cobalt catalyst, \( \lambda_{\text{ex}} 450 \text{ nm} \)), although the photosensitizer retained activity over five days and six cycles of experiments under visible light. Analogously, tellurium (Te)-linked cobaloximes were also generated, but it showed negligible hydrogen evolution even in the presence of multiple light-harvesting components.

### Table 2

<table>
<thead>
<tr>
<th>Cbx–PS</th>
<th>ED</th>
<th>( \lambda_{\text{ex}} ) cut off (nm)</th>
<th>Irr. time</th>
<th>TON vs. PS</th>
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<td>(20)</td>
<td>TEOA⁺</td>
<td>595</td>
<td>18 h</td>
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**a** Cbx–PS: cobaloxime–photosensitizer conjugate. **b** ED: electron donor; solvents. **c** DMF. **d** Acetone. **e** Acetonitrile.
Table 3 Comparison of non-noble metal-based photosensitizer–cobaloxime assemblies

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>PS</th>
<th>λ&lt;sub&gt;ex&lt;/sub&gt; cut off (nm)</th>
<th>Irr. time (h)</th>
<th>TON vs. PS</th>
<th>Ref.</th>
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<td>((23), M = Zn)&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>400</td>
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<td>400</td>
<td>5</td>
<td>5</td>
<td>44</td>
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<tr>
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<td>26</td>
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<tr>
<td>[ClCo(DH₂COOH)]&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
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<tr>
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<td>(25)</td>
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<td>452</td>
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<td>48</td>
</tr>
<tr>
<td>(6)</td>
<td>(27)</td>
<td>390</td>
<td>20</td>
<td>20</td>
<td>48</td>
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Solvent/electron donor. <sup>a</sup> THF–H₂O (8:2)/TEA. <sup>b</sup> 1:1 CH₃CN–H₂O/TEOA. <sup>c</sup> 7:3 acetone–H₂O/ascorbic acid. <sup>d</sup> 1:1 CH₃CN–H₂O/DMT. <sup>e</sup> pH 8.5/TEOA.

Hence, it can be mentioned here that despite the evolution of a variety of non-noble metal-based photosensitizers, they were unable to match the excellent photo-driven cobaloxime-catalysed HER activity showcased by noble metal (especially Ru and Ir)-based PS assemblies (Table 3). However, the photobleaching of these inorganic photosensitizers under prolonged irradiation has cast serious doubts on their long-term applications.

**Organic photosensitizer**

The plausible role of organic dyes as a photosensitizer was also probed in detail in the pursuit of an artificial photosynthetic assembly. Various organic dye molecules containing diverse categories of functionalities, such as boron dipyrromethane (BODIPY),<sup>51</sup> Rose Bengal,<sup>54</sup> Rhodamine,<sup>55</sup> Acriflavin,<sup>56</sup> and Eosin,<sup>57</sup> represent the face of organic dye instigated photocatalytic HER research using cobaloxime derivatives as a diagnostic tool (Fig. 7). Analogous to their metal-based PS counterpart, the organic dye molecules were also utilized in two distinct formats for cobaloxime-derived photocatalytic HER: (i) untethered free organic dye PS and cobaloxime in solution, and (ii) covalently linked organic dye–cobaloxime dyads. We have reviewed the consistent growth in either of those approaches in the following sections.

**Untethered free organic dye as photosensitizer**

Xanthene-based dyes are one of the widely explored photoactive molecules, and were chosen for the initial photocatalytic studies to play the role of a PS. When the basic xanthene skeleton was mixed along with cobaloxime in solution, it failed to produce any H₂ under illumination. A close look into this failed experiment revealed that the excited state of the PS should be a long-lived one to support such a bimolecular photocatalytic reaction. The photophysical properties of xanthene molecules suggest that the lifetime of the photoexcited state can be prolonged by facilitating the intersystem crossing (ISC) process with the introduction of heavy atoms like halogens. With the use of Eosin and Rose Bengal (RB) as PS ((30), Fig. 7), the successful photocatalytic H₂ evolution validated that hypothesis.<sup>59</sup> Complex 6 exhibited TON = 900 (vs. catalyst, pH 7, 5% TEOA, 1:1 CH₃CN/H₂O, λ > 410 nm, 12 h irradiation, excess ligand) in the presence of Eosin-Y (EY<sup>2</sup>). However, this photocatalytic activity was hampered whether in acidic or basic medium.<sup>57</sup> The BF₂-bridged cobaloximes [Co<sup>II</sup>(DBF₂)]<sup>2</sup> exhibited better stability compared to the hydrogen-bonded cobaloximes when these xanthene derivatives were used as PS. The annulated cobaloxime [Co<sup>II</sup>(DBF₂)]<sup>2</sup> displayed a TON of 32 with maximum activity in basic medium (pH 10) in the presence of Rose Bengal PS (500 W Xe lamp, 5 h irradiation, 10% TEOA, λ > 400 nm).<sup>54</sup> The photo-activated proton movement in 6-bromo-2-napthol (31) was also employed for cobaloxime-generated photocatalytic H₂ production, which highlights the versatility of the cobaloxime core in screening different PS sources.<sup>60</sup> The photocatalytic HER activity was boosted when the O atom in the heterocycle of xanthine framework was replaced with heavier chalcogens S and Se.
Solvent/electron donor. a 2:1 CH$_3$CN–H$_2$O/TEOA. b 1:1 CH$_3$CN–H$_2$O/TEOA. c 3:1 DMF–H$_2$O/TEOA. d 3:2 CH$_3$CN–H$_2$O/TEOA.

Covalently linked organic dye–cobaloxime dyad

In an attempt to improve the long-term stability and raise the photocatalytic efficiency, the organic dyes were covalently anchored with cobaloxime to generate a series of organic PS-catalyst assemblies (Fig. 8 and Table 5). First, BODIPY dyes were tethered to the axial position of [Co(DH$_2$)$_2$] through the meso-positioned pyridyl group ((36–38), Fig. 8). Even with the variation of the electron-donating and -withdrawing substituents on the BODIPY motif, these adducts demonstrated poor reactivity. However, the inclusion of heavy atoms like halides was able to enhance the photocatalytic H$_2$ production to reach a TON of 85 (5 h Irr., 4:1 CH$_3$CN/H$_2$O, p H 8.5). The efficiency of such light-activated HER improved further with the inclusion of thienyl functionality to the BODIPY–cobaloxime dyad. Despite this initial success, the instability of these adducts in aqueous blended solvents continued to impede their durability. The reactive Co–N(pyril) bond is believed to be the primary reason for the instability of the BODIPY–cobaloxime adducts, especially under irradiation.

The activity was improved slightly when the triphenylamine-vinylthiophene-pyridine chain ((39), Fig. 8) was used as a donor–π-linker–acceptor triad. Following the footsteps of BODIPY, Eisenberg et al. linked amido-fluorescein to the axial position of cobaloxime ((40), Fig. 8). This amido-fluorescein–cobaloxime adduct exhibited approximately three-fold improvement in photocatalytic HER activity compared to the untethered components under analogous reaction conditions. The Wasielski group developed a rational model of a donor-linker–acceptor-[Co(DBF)$_2$] cobaloxime assembly framework, without the presence of any heavy atom, to improve the transfer of the photocatalyzed electron. In this strategy, they synthetized...
a molecule containing perylene, xylene and pyridyl-substituted 1,8-naphthalimide as a donor, bridge and acceptor, respectively, along with a [Co(DBF₃)₂]cobaloxime core to achieve moderate photocatalytic HER activity (41–42), Fig. 8). In a recent study, our group simplified the donor–linker–acceptor chain by using a pyridinyl derivative of a stilbene motif (43), Fig. 8). Although this [ClCo(DH₂)₂pyridyl-stillbene] adduct was able to exhibit photocatalytic H₂ evolution even under natural sunlight, the overall photocatalytic efficiency and long-term aqueous stability remained poor.

**Nanomaterial-based photosensitizer**

An ideal photocatalytic assembly should exhibit the following properties to fulfill the demands of harsh practical applications: (i) the PS component should be stable under prolonged irradiation in aerobic conditions, (ii) the catalyst module should be able to produce H₂ from the ubiquitous source of protons, i.e., water. Hence, the generation of a robust photocatalytic assembly, operational in pure aqueous media, remains the final frontier for their practical applications. As mentioned in the earlier sections, the rational utilization of the cobaloxime motif allowed the scientists to screen an array of photosensitizers, ranging from inorganic to organic dye molecules, in the pursuit of an optimized photocatalytic H₂ production assembly. Although some of those dye molecules exhibited considerable H₂ evolution in tandem with cobaloxime, the overall effectiveness of such combinations (in either tethered or untethered forms), especially in the presence of water, were low due to the long-term instability of the dye molecules. In this scenario, the semiconductor materials emerged as a possible solution for this conundrum owing to their robust photophysical properties, where it can play the role of a charge mediator between PS and catalyst, while stabilizing the dye molecules under photocatalytic conditions.

Reisner et al. employed the resilient TiO₂ nanoparticle (TiO₂ nP) as a mediator for immobilizing both cobaloxime [ClCo(DH₃)₂(pyridyl-4-hydrophosphonate)] (CoP) and [Ru(bpy)₂(bpy-phosphonate)]³⁺ (RuP) PS via phosphonate–TiO₂ binding. The CoP–TiO₂ nP–RuP combination exhibited significant photocatalytic H₂ production [400 mmol H₂ h⁻¹ (g TiO₂)⁻¹] in neutral aqueous conditions (pH 7, in the presence of TEOA) (Fig. 9A). Here, the conduction band of the TiO₂ nP was believed to facilitate the fast movement of charge carriers from RuP to the CoP motif. Despite expanding the reactivity in pure aqueous solution, the photocatalytic H₂ evolution by this assembly slows down after 2 hours, and completely ceases after 8 hours under continuous irradiation.

Licheng Sun and team designed an organic dye-sensitized photoelectrochemical (PEC) cell that can perform water splitting under neutral aqueous (pH 7) conditions using visible light. This PEC cell consisted of two parts: (i) photoanode (for water splitting), and (ii) photocathode (for hydrogen generation). A cobalt catalyst Co₁[Co(DBF₃)₂(H₂O)₂] was directly connected to the semiconductor-based photocathode (p-type NiO) surface with phosphoric acid linker along with an organic dye P₁, which acted as a photosensitizer (Fig. 9B). This photocathode produced a decent amount of hydrogen upon irradiation. However, scaling up such NiO film is an issue, which prevented a higher amount of catalyst and dye loading for improved H₂ production. The poor charge carrier property of the NiO surface also negates their

<table>
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<tr>
<th>Catalyst–PS conjugates</th>
<th>Solvent</th>
<th>ED*</th>
<th>λₑₓ cut off (nm)</th>
<th>Irr. time</th>
<th>TON vs. PS</th>
<th>Ref.</th>
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Electrocatalytic HER activity by cobaloximes

As mentioned earlier, cobaloxime can act as a functional model for the hydrogenase enzyme, where the electron-transporting [Fe₃S₄] clusters can be mimicked by an electrode surface (Fig. 1B). The catalytic efficiency of the cobaloxime derivatives can be monitored as a function of the applied potential on the electrode surface (i.e., the energy of the electron) and the resultant catalytic current (that is directly proportional to the catalytic rate). Utilizing the unique structure of the cobaloxime core, researchers have probed the effect of electron-donating/-withdrawing substituents present in the primary coordination sphere and the influence of peripheral proton network via electrochemistry experiments. Such electrocatalytic studies have been performed on cobaloxime molecules in two different conditions: homogeneous and heterogeneous. In homogeneous conditions, the catalytic molecule and substrate (H⁺ in the case of H₂ production) remain in the solution phase, and it interacts with the solid electrode surface in its electrochemical double layer. On the other hand, the catalyst is immobilized on the electrode surface during the heterogeneous study, while only the substrate stays in the solvent phase. In the following sections, the results from either set of experiments have been analyzed. It is worth mentioning that analogous nickel dimethylglyoximato complexes exhibited moderate HER activity in organic solvents, while they degraded into nanoparticles in aqueous solution under a reducing potential.

Homogeneous electrocatalytic HER

Instability of the basic [Co(DH₂)₃] framework led to the development of an air- and moisture-stable N-axial pyridine cobaloxime system. [ClCo(DH₂)₃(py)] typically displays a reversible (Co II/I) and an irreversible (Co III/II) redox reduction feature in dry organic media. Irreversible Co III is related to the loss of an axial ligand in the Co²⁺ state. The addition of an acid (Et₄NHCl⁻) in the solution transforms the reversible Co II signal into an irreversible one, and the reductive current continues to increase with an increasing amount of acid. Complementary bulk electrolysis (i.e., chronocoulometry) and gas chromatography experiments identified the enhanced reductive response as catalytic hydrogen generation. Complex (6) exhibited 85–100% faradaic efficiency (FE) during this electrocatalytic HER during the 2.5 h of bulk electrolysis in dichloromethane (graphite electrode, −0.9 V vs. Ag/AgCl). The initial modifications to the cobaloxime core were executed on the equatorial motif. The substitution of the methyl groups of the dimethylglyoximato moiety with phenyl groups not only reduced the catalytic HER response, but also increased the overpotential requirement (the difference between the applied potential and standard reduction potential for H₂ evolution at the experimental conditions; η = E_app - E_H⁺/₂H⁻ / 0.591). Interestingly, the overpotential requirement value was lowered when the hydrogen-bonded oxime network was replaced by the BF₂ groups in [(CH₃CN)₂Co(BF₂)₃] (−0.28 V vs. SCE in CH₃CN).
However, this difluoroboryl annulated complex demonstrated reduced HER activity, and it required the presence of a stronger acid for electrocatalytic H₂ production.⁹⁴ As the axial halide ligands are labile in nature, especially in the reduced oxidation states of cobalt, the axial pyridine gained more attention for axial ligand modification. A series of diverse functionalities (such as amine, alcohol, ester, carboxylic acid, thiol, phosphate, alkyl, halide) have been introduced in the axial pyridyl motif to generate a library of axial-pyridine modified cobaloximes (Fig. 10). Reisner and co-workers have developed an electro-chemical method, known as “Electrochemical Molecular Catalyst Screening” or EMOCs, for studying the electrocatalytic behaviour of such in situ generated pyridyl cobaloximes prior to their actual synthesis. This EMOCs method turns out to be a user-friendly screening method for comparing the axial ligand effect on the HER activity of cobaloxime core in analogous conditions.⁹⁵ The detailed electrochemical results from these studies revealed a unique structure-function relationship for the axial-pyridine modified cobaloximes. The electron-donating substituents improved the electrocatalytic rate for the cobaloximes, but at the expense of the catalytic efficiency (overpotential also increases). In contrast, the electrocatalytic H₂ production rate was reduced in the presence of an electron-withdrawing group in the axial pyridine, while making it an efficient catalyst (overpotential also decreases). Inclusion of the phosphate derivative in the axial ligand further improves the oxygen-tolerance of the cobaloxime core. However, it exhibited an acute CO poisoning effect.⁹⁶,⁹⁷ The bimolecular cobaloximes, containing an equatorial octamethylene unit, were also prepared via the equatorial BF₃ groups as the bridging ligand. However, no significant enhancement in the electrocatalytic performance was noticed in comparison to the mononuclear cobaloxime.⁸⁸

All of the cobaloxime derivatives discussed so far in this section were screened in an organic solvent due to their poor aqueous solubility. Zhang et al. introduced a glucose-functionalized pyridine motif to the cobaloximes to improve the water solubility. This modification produced water-soluble cobaloximes that operated under a neutral aqueous medium. However, they lost their catalytic properties as the acidity of the solution increased (pH ≤ 3).⁹⁸ This loss of activity under acidic conditions is attributed to the cleavage of the oxime-derived hydrogen-bonding network, which acts as the primary protonation site during the electrocatalytic cycle. Hence, the activity of cobaloximes, even in acidic conditions, can be revived with the inclusion of an alternative protonation site. The introduction of an enzyme-inspired outer coordination sphere around the cobaloxime core allowed the presence of such a secondary protonation site that will be discussed in detail in a following section.⁹⁹

**Heterogeneous electrocatalytic HER**

The cobaloxime motif was immobilized on variable electro-active surfaces in an attempt to improve its electrocatalytic performance compared to the homogeneous conditions. Reisner and co-workers led the research in this front and developed a cobaloxime-meso-ITO film (via phosphonate group) on an ITO electrode, which exhibited H₂ production at a moderate overpotential. However, the cobaloxime bound on this mesoporous electrode degraded over time.¹⁰⁰ They improved the stability of the surface-bound cobaloxime by using multiwall carbon nanotube (mw-CNT) material. Multiple cobaloxime molecules containing pyrene tails were anchored on the mw-CNT surface through π–π interactions.¹⁰¹ Artero et al. further improvised this approach and prepared a nano-hybrid of mw-CNT and cobaloxime using a self-assembled polymeric amphiphile. This amphiphile contained diacetylene (DA) as a hydrophobic tail and a pyridine (pyr) moiety as the polar head, which was directly coordinated to the cobaloxime core (Fig. 11A). A glassy carbon electrode surface was modified with this cobaloxime–CNT hybrid that exhibited 110–120 turnovers for electrocatalytic HER in a neutral aqueous medium. However, this surface-modified catalyst suffered from degradation after 30 min under electrolytic conditions as the unstable cobaloxime leached out from the CNT surface.¹⁰²

Moore and co-workers studied the photoelectrocatalytic behaviour of a cobaloxime catalyst grafted on a p-type gallium phosphide (100) semiconductor via polyvinylpyridine (PVP) ligands. This assembly was active for photocatalytic HER activity, which was sensed via electrochemistry.¹⁰³ They developed the next generation of such modified electrodes by immobilizing cobaloximes on the nanostructured indium tin oxide (nano-ITO) surface via in-built polyvinylpyridine (PVP) ligands (Fig. 11B). This nano-ITO was employed as a working...
electrode for the hydrogen evolution reaction in phosphate buffer (pH 7). This heterogeneous assembly displayed a hydrogen production rate of 3 µL min⁻¹ cm⁻² with a relatively lower faradaic efficiency of 50 ± 3%. The calculated TOF for this electrocatalytic HER was 1200 ± 200 h⁻¹ per cobalt centre, which is orders of magnitude lower in contrast to analogous cobaloximes in homogeneous conditions. Recently, the Artero group was also able to achieve electrocatalytic HER activity by using a modified electrode containing CuFeO₂ semiconductor–TiO₂-cobaloxime layers.

Ott and co-workers immobilized a cobaloxime derivative on a metal–organic framework (MOF), and studied its electrochemical behaviour in acetate buffer (pH 4). This catalyst consisted of a 3D MFO UU-100 Co and cobaloxime catalyst with carboxylates as the anchoring groups (Fig. 12). This cobaloxime-grafted MOF generated hydrogen with a faradaic efficiency of 79%, with an average TOF of 1171 h⁻¹. The overall TON of 20 875 was obtained for this catalyst after 18 h of electrocatalysis. The MOF backbone ensured that the cobaloxime motif could be active in a 3D structure, while the robust nature of MOF provided the acid-stability. The porous structure of the catalyst-modified MOF also allowed access to the internally buried catalytic side, while instigating a facile diffusion of the electrolyte and substrates during electrocatalysis. However, the poor charge transfer properties and non-conducting nature of MOF have raised questions on its long-term implementation.

Thus, the homogeneous electrocatalytic experiments with cobaloxime derivatives provided us with a deep insight into the structural and electronic factors that regulate their electrocatalytic behaviour. However, the overall catalytic performance (both catalytic rate and overpotential) was inferior compared to the state of the art Ni-bis-(di-phosphine)-based Dubois catalysts. On the other hand, cobaloximes were immobilized on different solid surfaces, including carbon nanotubes, semiconductor nanomaterials, and metal organic frameworks. Although these heterogeneous materials replicated the electrocatalytic HER activity of cobaloximes in heterogeneous conditions, they were unable to improve its long-term durability and catalytic efficiency under practical conditions.

The limited success with the current approaches towards cobaloxime-promoted photocatalytic and electrocatalytic HER activities for extensive industrial-scale usage necessitated a new direction in this research area. The successful evolution of Dubois catalysts indicates that the unconventional enzyme-inspired catalyst design strategy can be a way forward to invigorate the basic cobaloxime core in the first place. In the next step, the improvised cobaloxime derivatives can be investigated for efficient and robust photocatalytic and electrocatalytic H₂ evolution under the most practical conditions.

**Enzyme-inspired modifications of cobaloximes**

Naturally evolved hydrogenase enzyme has been known to play a critical role in H₂-based metabolism in various life forms for millions of years. All of the different variants of this enzyme contain naturally abundant Fe and Ni in its active site (referred to as [FeFe]- and [NiFe]-hydrogenase). They catalyze H₂ production from water at a rapid rate, while maintaining a low overpotential requirement. All of these features have prompted the hydrogenase active site as a popular choice for the development of biomimetic model complexes for artificial hydrogenases. Interestingly, most of the active site models fail to imitate the enzymatic reactivity under practical conditions, which led to the hypothesis that the presence of the protein scaffold around the active site has a significant role in attaining the catalytic excellence. Consequently, several research groups have extended their bio-mimetic design beyond the active site to the secondary and outer coordination sphere features.

The HER activity by the cobaloxime core is sensitive to its surrounding environment. Hence, it was rationally combined with variable supramolecular scaffolds (proteins/polymers) to probe the effect of secondary and outer coordination sphere features on the cobaloxime-derived HER activity.

A research group led by Utschig and Tiede inserted a cobaloxime motif [Co(DH)₂(pyr)Cl, (6)] with a natural Photosystem-I (PSI) protein to fabricate a PSI-cobaloxime hybrid (Fig. 13A). This hybrid construct was active for photocatalytic H₂ production in a neutral aqueous solution in the presence of an electron mediator cytochrome c6. This particular construct was able to produce 170 mol H₂ per mol of PSI per min that is equivalent to the 50% catalytic rate of an analogous PSI–Pt nanoparticle system, while it outperformed the PSI–hydrogenase hybrid. Later, they simplified their construct and removed the bulky PSI protein. In this new assembly, they utilized an electron-transporting ferredoxin (Fd) protein to bridge a synthetic photosensitizer [Ru(bpy)₂²⁺] with the catalytic cobaloxime core [Co(DBF₃)₂] (Fig. 13B). This [Ru(bpy)₂²⁺]–Fd–[Co(DBF₃)₂]...
hybrid exhibited the production of 60 mol H₂ per mol of [Ru(bpy)₃²⁺] per hour in a neutral aqueous solution upon photo-irradiation, which was improved by ~3 times in the presence of the axial pyridine bound cobaloxime. In a follow-up study, another [Ru(bpy)₃²⁺]-Fd-[Co(DBF₂)₂] biohybrid was prepared by replacing the Fd protein with a flavodoxin (Fld) scaffold, which afforded HER activity via a different pathway.

As discussed earlier, the inclusion of pyridine or imidazole axial ligands can positively influence the catalytic H₂ production by cobaloxime-based complexes. On the other hand, biology has widely employed the imidazole side chain from the histidine residue for anchoring metal cofactors, especially in hemoproteins. Following this lead, Artero et al. have rationally inserted two different variants of cobaloxime motifs (hydrogen-bonded [Co(DH)₂] and difluoroboryl annulated [Co(DBF₂)₂]) into the heme-binding pocket of apo-Sperm-whale myoglobin (SwMb) (Fig. 14A). These synthetic metalloproteins displayed photocatalytic activity for HER, although at a considerably reduced efficiency (TON ~ 3–4, calculated vs. [catalyst] in the presence of [Ru(bpy)₃²⁺]PS) compared to the corresponding free cobaloximes. This drop in the catalytic activity was attributed to the strained flexibility experienced by the histidine-ligated cobaloxime in the heme-binding cavity, which in turn terminated the competitive binuclear pathway for H₂ production (Fig. 14B). In a follow-up study, they tuned the reactivity of the cobaloxime-bound biohydrs by altering the heme-binding pocket. For this purpose, the cobaloxime cores were installed in the heme-binding cavity of two strains of heme oxygenase proteins: rat heme oxygenase 1 (HO1) and Corynebacterium diphteriae heme oxygenase (HmuO). The resultant synthetic metalloproteins demonstrated an increase of ~3 times in the photocatalytic HER activity (TON ~ 6.3–15.3, calculated vs. [catalyst] in the presence of deazaflavin PS) compared to either free or SwMb-supported cobaloxime [Co(DH)₂]₁₂¹

Kato and Yagi explored cyclodextrins (cyclic oligosaccharides of glucose) as an alternative for protein structures to induce a supramolecular effect on the reactivity of cobaloximes. For this purpose, they have designed a 1:1 adduct between the sulfonated-cobaloxime [Co(dmgH₂)₂(pyridine-4-sulfonate)Cl] and β- and γ-cyclodextrin via host–guest interaction (Fig. 15A). Among them, only the γ-cyclodextrin bound cobaloxime exhibited a ~10% increase in photocatalytic HER activity in the presence of...
the Eosin-Y photosensitizer in aqueous solution (TON ~ 47, calculated vs. [catalyst] in the presence of Eosin-Y PS). The best-fitted insertion of the sulfonate group into the cyclodextrin cavity occurred in the case of γ-cyclodextrin, presumably due to the optimal size-matching. During the formation of this host-guest adduct, the core Co-N₄ motif of cobaloxime approached within the hydrogen-bonding distance with the hydroxyl groups present in the rim of the cyclodextrin (Fig. 15B). The dynamic proton exchange interaction between those groups possibly played a crucial role to induce the kinetic effect on the cobaloxime HER activity.98

Interestingly, the increment in the catalytic HER activity for these biohybrid constructs was either inconsequential (or even negative) compared to the free cobaloxime analogues. This observation suggested that the inclusion of cobaloxime inside the robust supramolecular structure may severely restrict the fluxionality of the cobaloxime motif to affect the overall reaction rate. A significant increase in the catalytic H₂ evolution was noticed only for a few constructs where the correctly oriented hydrogen-bonding interactions induced facile H⁺ movement. The results from these earlier studies indicate “a minimally constrained cobaloxime motif containing a peripheral proton relay” possibly holds the key for generating the second generation of enzyme-inspired cobaloxime-based H₂ production catalysts. Following this queue, a series of four cobaloxime complexes were created, where only the para-position of the axially coordinated pyridine ligand was altered, around an otherwise identical cobaloxime core [Co(dmgH)₂(pyridine-derivative)Cl]. Variable combinations of the secondary amine (–NH–), carboxylic acid group (–COOH), and phenolic (–Ph–OH) groups were utilized to fabricate one, two, and three-component proton relays in the cobaloxime periphery (Fig. 16).99 The effect of the incorporation of the minimal (but essential) outer coordination sphere features was imminent as these cobaloxime derivatives were found to be active for electrocatalytic H₂ evolution in 100% aqueous solution. The three-component H⁺-relay containing [ClCo(DH)₄⁺(pyridine–methylene–tyrosine)] recorded the fastest TOF for HER (~8830 s⁻¹, pH 7) among these complexes, which is a ~10-fold increase in the catalytic rate compared to the original [ClCo(DH)₂(pyridine)]. The catalytic rate for H₂ evolution for these complexes followed the following trend with varying pyridine substituents, tyrosine > tyramine ≈ phenylalanine > tyramine, to establish a direct connection between the extent of the outer coordination sphere feature and catalytic rate. This hypothesis was further supported by the two-dimensional Nuclear Overhauser effect spectroscopy (NOESY) NMR experiment, where a dynamic proton exchange among those peripheral basic groups, the oxime hydrogen-bonded network, and the solvent water molecules were observed. Typically, the cobaloxime motif becomes inactive for homogeneous H₂ production with increasing acidity of the solution (pH ≤ 5.0). The disruption of the oxime-derived hydrogen-bonding network, which acts as the protonation site during HER catalysis, is believed to be the prime reason for this behaviour. However, the outer coordination sphere functionalities present in the cobaloxime derivatives provides an alternate protonation spot, even in the acidic condition, to allow homogeneous H₂ production by those complexes even at pH 3–5. This particular aspect highlights that the incorporation of enzyme-inspired features can even impact the overall stability of the complexes. However, the effect of this distant protic groups is inferior in comparison to the closely lying oxime network, which is reflected by a contrasting change in the HER catalytic rate with a decrease in pH for all of those cobaloximes (Fig. 16).99

Next, the effect of such neighbouring basic groups on the cobaloxime motif was studied on the [Co(DH)₄(imidazole-derivative)Cl] platform, with an alternating axially ligated imidazole scaffold (Fig. 17).68 The presence of multiple protic functionalities and their spatial orientation tunes the HER activity of these complexes. As expected, the natural amino acid histidine (which contains an imidazole side chain along with carboxylic acid and primary amine groups)-bound cobaloxime exhibited the highest kinetic rate (TOF ~ 4500 s⁻¹) for electrolytic H₂ production in a neutral aqueous solution. These complexes were probed even in the photocatalytic conditions to monitor the effect of the outer coordination sphere features

![Fig. 16](image1.png)

(A) The basic structures of the [ClCo(dmgH)₂(pyridine-derivative)] complexes, along with the number of basic components present in their corresponding outer coordination sphere (OCS): (from left to right) only pyridine (Py), zero component; pyridine–methylene–benzylamine (Py–Brz), one component (–NH): pyridine–methylene–tyramine (Py–Tyr), two components (–NH and –Ph–OH): pyridine–methylene–phenylalanine (Py–Phel), two components (–NH and –COOH); pyridine–methylene–tyrosine (Py–Tyr), three components (–NH, –COOH, and –Ph–OH). (B) The experimentally tabulated electrocatalytic H₂ evolution reaction rate (TOF) variation for each complex in aqueous solution (pH 3.0–7.0). These figures were adapted from ref. 99.

![Fig. 17](image2.png)

(A) The basic structures of the [ClCo(DH)₄(imidazole-derivative)] complexes along with the number of basic components present in their corresponding outer coordination sphere (OCS): (from left to right) only imidazole (Im), one component (imidazole –NH–); imidazole–2-acetic acid (Im–2-AA), one component (–COOH); imidazole–4-acetic acid (Im–4-AA), two components (imidazole–NH– and –COOH); histidine (His), three components (imidazole–NH–, –COOH, and –NH₂). (B) The comparative TON (measured vs. photosensitizer) for photocatalytic H₂ evolution for Im (black bar) and His (cyan bar) in 1:1 water/acetonitrile, and His in 100% water (blue bar). (C) A schematic diagram of His activity in 100% water in the presence of Eosin-Y as a photosensitizer. These figures were adapted from ref. 68.
beyond the standard electrochemical settings. In the presence of the Eosin-Y dye, the overall photocatalytic \( \text{H}_2 \) production by \([\text{Co(DH)}_2(\text{histidine})\text{Cl}]\) was enhanced by 1.7 times (TON ~ 250, calculated vs. [catalyst] in the presence of Eosin-Y PS), compared to the rudimentary \([\text{Co(DH)}_2(\text{imidazole})\text{Cl}]\) in 1:1 water/acetoneitrile media, to underline the impact of the additional protic groups appended from the imidazole. Again, the facile proton dynamics among these peripheral groups, along with the oxime and solvent water molecules, are believed to be the prime reason for this amplified HER performance. The presence of these enzyme-stimulated outer coordination sphere features even allowed us to obtain the first generation of fully water-soluble \([\text{ClCo(DH)}_2(\text{imidazole-derivative})]\) complexes. This unique trait allowed us to achieve the first natural sunlight-irradiated photocatalytic \( \text{H}_2 \)-producing cobaloxime complex that is active in an aerobic, neutral (pH 7.0) aqueous solution (TON ~ 1000, calculated vs. [catalyst] in the presence of Eosin-Y PS).\(^8\) Hence, this enzyme-inspired complex represents an ideal candidate for investigating solar-driven \( \text{H}_2 \) production from water under the most practical circumstances.

Conclusions

Although cobaloxime was developed as a structural model for vitamin B12, it has recently gained more attention due to its catalytic properties for \( \text{H}_2 \) evolution reactions. The structural flexibility of this cobaloxime framework enabled the generation of a myriad of compounds with varying physiochemical electronic and solubility properties. The HER activity of the cobaloxime derivatives across a wide variety of conditions has established it as a diagnostic tool for optimizing photosensitizers for photocatalytic \( \text{H}_2 \) production. The display of better HER activity by the covalently-linked cobaloxime–photosensitizer adduct compared to independent segments established the significance of the directly coordinated photocatalytic assemblies for photo-driven \( \text{H}_2 \) production reactions. Later, the electrochemical investigation of cobaloximes provided insight into the intricacy of the structure–function relationship at the molecular level. Again, the versatility of the cobaloxime core shines as a critical element for probing its HER activity in both aqueous and non-aqueous solvent media. Despite all these advantages, the acid-instability of the primary coordination sphere-bound oxime motifs has narrowed the active HER catalytic space of cobaloximes to near-neutral conditions. Additionally, the poor \( \text{H}^+ \) movement around the core has limited the HER activity of cobaloximes to moderate compared to contemporary first-row transition metal-based catalysts. As a result, the cobaloxime-based HER research faced a lag period.

The architectural blueprint of metalloenzymes suggested that the inclusion of enzymatic hallmarks, such as an artificial proton relay, can influence the HER activity by cobaloxime. The simple yet robust nature of the cobaloxime core provided ample opportunity to either include cobaloxime into an already existing protein pocket, or rationally design a multi-component proton relay with precisely positioned peripheral functionalities around the core. This bio-mimetic catalyst design strategy has evolved a new genre of widely stable cobaloxime complexes that can photo-/electro-chemically produce \( \text{H}_2 \) at an unprecedented rate. Hence, the cobaloxime core is utilized as a model indicator for a broad spectrum of catalytic \( \text{H}_2 \) production functionalities, including optimizing the photocatalytic assembly, probing the electro-catalytic conditions, and exploring the effects of the peripheral enzyme-inspired features. In this review, we have covered the revival of the cobaloxime motif in the pursuit of a durable, efficient, and user-friendly \( \text{H}_2 \)-producing catalyst, a key ingredient for the development of the \( \text{H}_2 \)-based renewable energy infrastructure.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

The authors would like to thank the support provided by the Indian Institute of Technology Gandhinagar (IITGN) and Indian Institute of Technology Bombay (IITB). D. D. would like to thank the support of the DST-Inspire fellowship provided by the Department of Science and Technology (DST), India (DST/INSPIRE Fellowship/2017/IF170385). A. D. acknowledges the Ramanujan Fellowship (SB/S2/RJN-112/2015). P. M. would like to thank DST-SERB national post-doctoral fellowship (PDF/2018/000837).

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