by considering absorption, distribution, metabolism, and excretion of the molecule/s. Finally, the optimized molecule/s should be scaled-up for further drug development process and efficacy testing.

In the area of bio-marker studies related to PM, antibodies used as molecular probes have now been replaced by 'aptamers' which are single-stranded synthetic oligonucleotides composed of DNA or RNA, with a length of 20-100 nucleotides. These aptamers are promising molecules with binding affinity to a variety of targets such as metal ions, small molecules, proteins, and intact cells. Aptamers are produced by an *in-vitro* selection process called 'Systematic Evolution of Ligands by Exponential Enrichment (SELEX)' depending on chemical artistry. They are chemically synthesized and can be designed to conjugate with other molecules such as bioaffinity molecules, chemical linkers and nanomaterials. Thus, aptamers are used as indispensable molecular tools for biomarker studies.

In summary, PM is becoming promising field in medicine which improves the precision of medications based on personal variations of patients due to the diversity of their genetic make-up. Chemistry, especially medicinal chemistry plays a significant role in PM to enhance its efficacy by proposing and synthesizing drug molecules based on computational approaches in drug development programs. Moreover, chemical synthesis of different molecular probes solely based on chemical artistry has improved the efficacy on bio-marker based studies in drug development. Likewise chemistry in collaboration with modern molecular techniques is ever moving the field of medicine forward, especially with the novel approaches like PM, speed of which is also getting enhanced day by day on as a result of the promising researches in the field of medicinal chemistry.

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Photochemical Water Reduction by Organic Hydrides

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Increasing concerns on anthropogenic climate change, skyrocketing global energy needs, and depletion of fossil fuels have made the discovery of alternative carbon-neutral and sustainable energy sources, one of the most urgent challenges in the scientific community. Among many renewable energy sources, solar energy stands out as the most promising candidate since it is the highest exploitable resource, delivering more energy in one hour to the earth surface than the amount of energy that we consume worldwide in an entire year. However, its nature of diurnal variation, intermittence, and unequal distribution requires efficient and cost-effective capture, conversion, and storage. Molecular fuels produced from solar energy input represent an promising approach to meet this goal, due to the high energy density that can be stored within chemical bonds. As such, hydrogen generated from solar-driven water splitting has been widely considered as an attractive option; the sole product of hydrogen combustion is water, rendering a carbon-neutral energy cycle, and the substrate water is by far the most abundant chemical on earth. However, water splitting involves the transfer of multiple electrons and protons ($2H_2O \rightarrow O_2 + 4H^+ + 4e$ and $2H^+ + 2e \rightarrow H_2$), hence catalysts are needed to make it energetically feasible.

The molecular hydrogen-evolving catalysts are more diverse than the corresponding water-oxidation systems, due to the fact that proton reduction involves a relatively simple, two-electron transfer step. For this reason, molecular hydrogen-evolving electrocatalysts can be directly coupled with a light-absorbing chromophore to achieve the photocatalytic process. The electrocatalysts that are currently explored fall into several major categories: (i) bimetallic Ni-Fe and Fe-Fe based catalysts inspired by natural hydrogenases; (ii) monometallic Co, Ni and Mo based catalysts, which generally evolve H_2 *via* Co(III) or Mo(IV) hydride species generated by the reaction of protons with electrogenerated Co(I) or Mo(II) intermediate. Some of
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these electrocatalysts were used to design photocatalytic systems by mixing in or covalently linking the chromophores in the presence of sacrificial electron donors such as amines or ascorbic acid. The chromophores frequently utilized for this work exhibit strong absorption in the visible range and long-lived excited states, and are either transition metal complexes (such as Ru, Ir, and Pt based chromophores), or organic dyes (such as Eosin Y and Rose Bengal).

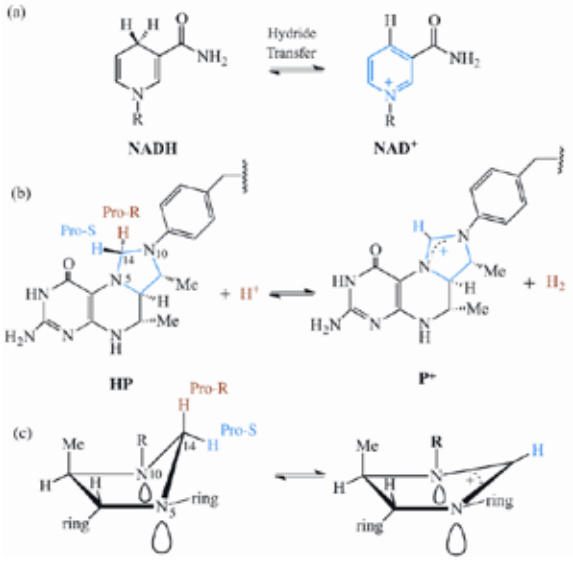
The major drawback of these multicomponent photocatalysts is that they require two consecutive photoinduced electron transfer steps, each of which can undergo unproductive charge recombination or undesired chemical reactions. Thus, photocatalytic systems with fewer components are desirable for efficient photocatalytic H_2 generation. An interesting approach towards single-component catalysts is investigated by the D G Nocera's team, who study bimetallic photocatalysts that split hydrogen-halides ($2HX \rightarrow H_2 + X_2$) in two separate photochemical events.

The complexity of the chromophore-catalyst multicomponent systems could be reduced if the chromophore is made of an organic hydride that photochemically undergoes heterolytic C-H bond scission and reduces protons. ($R\text{-}H + H^+ + h\nu \rightarrow R^+ + H_2$). In such an approach, the excitation event can be directly coupled with the hydrogen-forming step, and the generation of reactive intermediates can be avoided if the photoreduction can be achieved in a concerted fashion. The oxidized R^+ formed in the photochemical event can be chemically or electrochemically reduced back to R-H.

While photohydrides are yet to be discovered, the ground-state organic analogs are abundant in nature. For example, the most common hydride source in biological systems is the reduced form of nicotine-adenine dinucleotide (NADH), which acts to reduce carbonyl groups, carbon-dioxide and other substrates. The hydride release from NADH is driven by the aromatic stabilization of the oxidized product, NAD^+ (Scheme 1a). The mechanistic studies of model systems have demonstrated that, depending on the type of the transition state, the overall hydride ion can be transferred either in a single concerted step or by one of the stepwise processes, such as electron-hydrogen atom or electron-proton-electron transfer steps.

Another important example of a biological organic hydride donor can be found in a hydrogenase called methylenetetrahydromethanopterin dehydrogenase(MD). Unlike well-studied metal-containing [NiFe], [FeFe] and [Fe] hydrogenases the active cofactor of MD is an organic, pterin-derived hydride HP, which performs a hydride transfer reaction to generate molecular hydrogen and the corresponding iminium ion P^+ (Scheme 1b).

It is interesting to note some structural similarities of NADH and HP: both compounds are nitrogen containing cyclic derivatives that, upon hydride transfer, generate stable iminium cations that delocalize the positive charge through the conjugated or aromatic framework. In the case of HP, the hydride transfer is facilitated by an additional mechanism: the lone pairs of nitrogen atoms 5 and 10 are in hyperconjugation with the antibonding σ* orbital of the anti-periplanar C14-H bond, which significantly weakens this bond and facilitates the hydride transfer (Scheme 1c).



Scheme 1. Ground-state natural hydride donors. (a) Hydride release from NADH forming aromatized NAD^+ (b) Reaction catalyzed by MD to form N5,N10 methylenetetrahydromethanopterin cation (P^+) and H2 from N5,N10 methenyltetrahydromethanopterin (HP) and H^+. (c) Hyperconjugation effect which weakens the pro-R C14-H bond leading to the hydride release.

The design of photochemical analogs of NADH and HP requires the extension of their π conjugation, to assure that the excited states can be generated using visible photons. One of the simplest NADH mimics that exhibits extended π conjugation is the acridine derivative Ph-AcrH (Figure 1: the triplet state is shown). The ground-state hydride release from this and related compounds has been documented and extensively studied by Fukuzumi. The absorption maximum of PhAcrH appears at 287 nm, which is not the desired spectral range for solar fuel applications, but this model system enables the initial thermodynamic and kinetic analysis of the photoinduced hydride transfer and potential for the proton reduction ($PhAcrH + H^+ + h\nu \rightarrow PhAcr^+ + H_2$).

An important aspect of acridine framework is that its derivatives exhibit a tendency to convert to the aromatic iminium cation ($Ph\text{-}Acr^+$) upon photoexcitation. For example, the hydroxylated analog (PhAcrOH) and the corresponding methoxy derivative (PhAcrOMe) undergo efficient photochemical release of HO- and MeO- groups in protic solvents. It is interesting to note that the photoin-

duced heterolysis does not occur in aprotic solvation, indicating that the solvent-induced hydroxide/methoxide ion stabilization is required for this reaction.

Photochemistry of the model photohydride, PhAcrH, is similar to that of PhAcrOH.

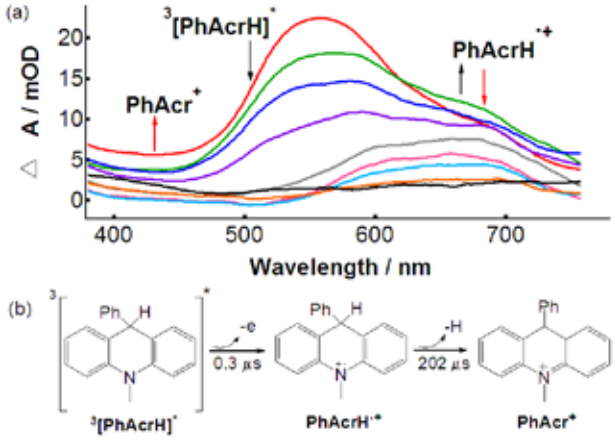


Figure 1. Photochemical hydride release from PhAcrH. (a) Nanosecond transient absorption spectra of PhAcrH in ACN and pH 0.65 H2O mixture (V:V=1:1). (b) Proposed mechanistic scheme for stepwise hydride release.

For example, irradiation of PhAcrH in acidic medium generates the corresponding iminium ion PhAcr$^+$ due to the associated hydride transfer to the solvent mixture. The yield of H_2 is low, (2.5 %). Even though the electron-hydrogen atom transfer mechanism eventually leads to an overall hydride transfer process, the stepwise mechanisms are not energetically desirable. For example, photoinduced electron transfer from PhAcrH to aqueous protons requires ~80 kcal/mol of energy, and such process can be driven only by UV photons, while the direct concerted hydride transfer could be achieved by visible photons if one designs the organic hydride with appropriate absorption characteristics. For this reason, it is desirable to find systems in which the concerted hydride release mechanism predominates over other competing mechanisms.

There are certain approaches that could be taken to achieve this concerted mechanism. One such approach towards improved photohydrides is to increase the thermodynamic driving force for the excited-state hydride transfer process (ΔG^* for the reaction: R-H + H^+ + hυ → R^+ + H_2). Even though thermodynamic arguments alone do not assure that the photochemical reaction will take place, the likelihood of the process is expected to rise with increasingly negative ΔG^* values. This concept along with other scenarios need to be thoroughly evaluated in order to produce effective photohydrides.

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