Encouraging developments in the field of photocatalysis in last decades, biomolecules namely flavins have been observed to act as a catalyst in several photoredox-catalysed synthetic methodologies. Due to its excellent redox window and good chemical stability, this promising photoactive biological molecule has emerged as a powerful and attractive metal-free organophotocatalyst. This review highlights the design, properties, biosynthesis and application of flavin photoredox catalysts and is expected to contribute to a great extent towards the advancement and development of synthetic methodologies.

1. Introduction

In recent years, both academia and industry\textsuperscript{1-10} have attracted extensive interest in the context of green and sustainable chemistry due to the development of clean, economical and efficient chemical processes. Over the last decade, visible light photocatalysis has evolved into a widely used method in organic syntheses as it is the most sustainable reaction inducer and has been increasingly used as a powerful strategy to promote numerous synthetic transformations in organic chemistry\textsuperscript{11} as it is a safe, renewable, and inexpensive source of chemical energy. Solar energy (visible light) has great prospects in developing sustainable and eco-friendly protocols and can be used in organic synthesis\textsuperscript{12} because it is clean, easy to handle and an unlimited energy source. The conversion of solar energy into chemical energy for chemical transformations,\textsuperscript{13,14} has fascinated some researchers, who have incorporated an excellent tactic for the implementation of photoredox catalysts to commence single electron transfer (SET) processes.\textsuperscript{15,16} In organic synthesis, the visible light photoredox catalysis has received considerable attention owing to the ready availability, non-toxicity and ease-of-handling.\textsuperscript{17} In the last few decades, several metal-free organic dyes, such as eosin Y, rose bengal, Nile red, fluorescein, rhodamine B and perylene, have been applied as inexpensive and environmentally benign preferable alternatives to Ru(II) and Ir(II) complexes in visible-light promoted organic transformations involving SET.\textsuperscript{18,19} These organic dyes can serve as a superior alternative to transition metal photoredox catalysts, and have great potential for application in visible-light mediated organic synthesis.\textsuperscript{20} In spite of these facts, the general synthetic utility of organic dyes is still rather limited due to relatively few catalyst options.

Vishal Srivastava is working as Assistant Professor, Department of Chemistry, C. M. P. College, (Constituent P. G. College of Central University of Allahabad) Prayagraj, India. He has completed Graduation (B.Sc.), Post-Graduation (M.Sc.) in Organic Chemistry and Doctoral Degree (D.Phil.) from Department of Chemistry, University of Allahabad, India. His current research work involves the designing of novel biologically active photoredox catalysed synthetic organic compounds.

Pravin K. Singh is working as Assistant Professor, Department of Chemistry, C. M. P. College, Allahabad, India (Constituent P. G. College of Central University of Allahabad). Dr Singh is actively engaged in advanced research work for the development of environmentally benign, new synthetic routes for various bioactive heterocyclic compounds. He has completed his B.Sc., M.Sc., Doctorate (D.Phil.) and Post-Doctorate (D.Sc.) from the University of Allahabad, India.
The application of inexpensive organic dyes has received increasing attention since some chromophores allow access to unique chemical reactivity. Their use has been restrained due to far more limited availability of their spectroscopic, kinetic, and electrochemical data in comparison to the transition-metal catalysts and for most organic dyes the reactive triplet state is not characterized by charge separation. Furthermore, not all of these dyes can engage in both oxidative and reductive quenching, as well as due to its poor recyclability these organic dyes have limited widespread application.

Flavin catalysis is recognized as an attractive approach for designing green and sustainable transformations. Recently, one of the most widespread examples of dye-based photoredox catalysts is vitamin B₂, riboflavin (RF) and its derivatives, which have received remarkable attention as unique redox organocatalysts that promote numerous catalytic oxidations. Flavin derivatives (FLs), serving as the building blocks of redox-active coenzymes, are the reaction sites of numerous thermal and photoinduced processes and are tolerant to the variation of redox potentials. Riboflavin and its derivatives exhibit some advantages: among others, they can have maximum absorption in the blue region of the visible light spectrum with high molar absorption coefficients. These photocatalysts are easily accessible, providing a versatile and green method for numerous organic chemical reactions. (-)-Riboflavin (vitamin B₂) is a highly versatile organocatalyst for a variety of transformations due to its inherent energy transfer (ET) and single electron transfer (SET) modes that can be activated upon irradiation. Therefore, it is highly desirable to design new organic photocatalysts with broad redox capabilities. Thus, in modern organic synthesis, flavins exhibit a superior performance in comparison to other photocatalysts due to their better photostability, which will ultimately bring about the future development trend of organic photocatalysts.

Recently, flavin and its derivatives have been found to be ingenious photocatalysts for various reactions (Fig. 1) and emerged as outstanding organic photoredox catalysts for diverse synthetic organic transformations. As this is a robust emerging field, a summary of flavins for organic transformation is highly appreciable. In continuation of our study on photocatalysed organic syntheses, in this study, the recent trends in using flavins as a visible light photocatalyst in organic synthesis are reviewed.

2. Biosynthesis of riboflavin

The biosynthesis of riboflavin was investigated by Bachner et al. in 2000. One riboflavin molecule requires one molecule of GTP and two molecules of ribulose 5-phosphate as substrates (Scheme 1). Most commercial riboflavin is currently produced or was produced earlier via microbial synthesis using specially selected strains of bacteria and fungi.

3. Flavin-related compounds in photocatalysis

Besides flavin related compounds that have also been applied in photoredox catalysis, some of them are naturally occurring, while few compounds are semi-synthetic (Fig. 2).
4. Photochemistry of flavin

Three redox states: oxidized, one-electron reduced (as semi-quinone) or reduced by two electrons, exhibited by flavins, and each of these redox states has three different protonation states (Scheme 2). Substitution, noncovalent interactions such as hydrogen bonds, and nature of the surrounding protein affect the redox properties, absorption and reactivity of flavins. From electrochemical studies, in water and in protic organic solvents, the redox properties, absorption and reactivity of flavins (Scheme 2). Substitution, noncovalent interactions such as hydrogen bonds, and nature of the surrounding protein affect the redox properties, absorption and reactivity of flavins. From electrochemical studies, in water and in protic organic solvents, the redox properties, absorption and reactivity of flavins.

5. Synthetic applications of flavin

5.1. Cyclization of thiobenzanilides

Schmidt et al.\textsuperscript{51} reported an efficient photochemical approach for the cyclisation of thiobenzanilides. They performed visible light irradiated synthesis of benzothiazoles from thiobenzanilides using riboflavin as a photocatalyst and potassium peroxodisulfate as a sacrificial oxidizing agent up to 97% yield (Scheme 4).

A plausible mechanism is shown in Scheme 5. Upon the photogeneration of singlet and/or triplet excited states of RFTA, thiobenzanilides can act as a quencher by an electron-transfer reaction, giving rise to the corresponding thiobenzanilide radical cation (1\textsuperscript{+}) along with the radical anion RFTA\textsuperscript{−}. Notably, the riboflavin moiety can also act as a base (pK\textsubscript{a} of [RFTA-H\textsuperscript{−}] = 8.3), assisting the deprotonation of 1\textsuperscript{+}. The deprotonation of the thiobenzanilide radical cation 1\textsuperscript{+} gives the sulfur radical, which undergoes cyclization and further rearomatization by any oxidant species affording 2-substituted benzothiazoles 2. Peroxodisulfate is necessary to close the catalytic cycle and return RFTA to its ground state.

5.2. Direct cyclization

The photocatalytic synthesis of benzo-3,4-coumarins 4 directly from biaryl carboxylic acids 3 without the need for substrate prefuctionalization was investigated by Gilmour et al.\textsuperscript{52} (Scheme 6). This disconnection relies on the oxidation...
The competence of photoactivated (−)-riboavin to generate the heterocyclic core via photoinduced single electron transfer. They proposed that singlet state electron transfer from benzoic acid to excited state (−)-riboavin \([E^*(3RF^*/RF^+) = 1.46 \text{ V vs. SCE}]\) is operational (Scheme 7).

The catalytic cycle is likely initiated by the protonation of (−)-riboavin (RF) with the strong absorption of the protonated (−)-riboavin (Scheme 7, RFH⁺) occurring at \(\lambda_{\text{max}} = 402 \text{ nm}\). Subsequent single electron transfer from the carboxylate anion (3a) to RFH⁺ yields the protonated flavin radical (RFH⁺) and the carboxy radical (3b), which can undergo rapid cyclization to intermediate 3c. Final oxidation and rearomatization of 3c with RFH⁺ in a hydrogen atom transfer or SET/deprotonation reaction releases the desired product. The reduced (−)-riboavin (RFH₂) can, in turn, be reoxidized by molecular oxygen as well as the oxidation of benzoic acid.

| Compound                        | \(\lambda_1^a\) (nm) | \(\lambda_2^a\) (nm) | \(\lambda_F^b\) (nm) | \(\Phi_F^c\) | \(\tau_F^d\) | \(E^{0e}\) (V) |
|---------------------------------|----------------------|----------------------|----------------------|--------------|--------------|----------------|
| Riboflavin tetraacetate         | 440                  | 343                  | 505                  | 0.37         | 6.8 ns       | −1.18 (−1.87)  |
| Lumiflavin                      | 443                  | 342                  | 533                  | 0.16         | 7.7 ns       | −0.761         |
| 5-Deazariboflavin               | 399                  | 329                  | 457                  | 0.11         | 4.03 ns      |               |
| Lumichrome                      | 380                  | 334                  | 437                  | 0.028        | 0.64 ns      | −1.3           |
| 5EtFl⁺ClO₄⁻                    | 557                  | 414                  | 661                  | —            | 590 ps       | 0.306 (−0.389) |
| 5EtFlOH                        | 348                  | —                    | 496                  | 0.0003       | 500 fs       | —              |

\(\lambda_1\) and \(\lambda_2\) are the positions of the two lowest energy bands in the absorption spectra. \(\lambda_F\) is the maximum of the fluorescence emission spectrum. \(\Phi_F\) is the fluorescence quantum yield. \(\tau_F\) is the fluorescence lifetime. \(E^{0e}\) is the reversible redox potentials (Fl/Fl⁺ and Fl⁻/Fl⁺ in the brackets) measured by CV using SCE as standard electrode.}

**Scheme 3** General mechanisms of flavin catalysis.

**Scheme 4** Visible light-mediated cyclisation of thiobenzanilides.

**Scheme 5** A plausible mechanism for the cyclisation of thiobenzanilides via visible light photocatalysis.

**Scheme 6** Direct, photocatalytic synthesis of benzocoumarins via (−)-riboflavin-mediated electron transfer.

**Scheme 7** A plausible mechanism for the direct, photocatalytic synthesis of benzocoumarins.
intermediate 3c and RFH’ by molecular oxygen cannot be ignored.

5.3. Decarboxylative cyanation of aliphatic carboxylic acids

Gomez et al.54 reported the decarboxylative cyanation of aliphatic carboxylic acids at room temperature. Riboflavin tetraacetate promotes the visible light-irradiated oxidation of carboxylic acids. After decarboxylation, the generated radicals are trapped by TsCN, yielding the desired nitriles without any further additive, in a redox-neutral process (Scheme 8). This protocol can be adapted to flow conditions.

Mechanistically, they anticipated that, upon irradiation with visible light ($\lambda_{max} \approx 450$ nm) and after rapid intersystem crossing, the long-lived triplet-excited state of flavin would be oxidant enough ($E_{red} = +1.50$ V vs. SCE) to undergo the single-electron oxidation of aliphatic carboxylates [$E_{red}$ from +1.0 V to +1.50 V vs. SCE]. Importantly, the flavin moiety can also act as a base, favoring the protonation of carboxylic acid prior to its single-electron oxidation, or in a proton-coupled electron transfer (PCET). After the rapid decarboxylation of the aliphatic acyl oxyl radical, the generated radical is intercepted by Ts-CN, affording the desired nitrile and p-toluenesulfonyl radical (Ts’). The latter radical could be reduced by the hydroxyl radical, regenerating the photocatalyst and producing TsH after protonation, in a redox-neutral process. Alternatively, the p-toluenesulfonyl radical could abstract a hydrogen atom (HAT) from FH’ to turn over the photocatalyst (Scheme 9).

5.4. Aerobic oxidation of benzylic C–H bonds

Pasau and co-workers55 reported a continuous mesofluidic process for benzylic C–H oxidation with moderate to good yields using a flavin photocatalyst upon visible-light irradiation and an iron additive [Fe(ClO$_4$)$_2$] via the incorporation of singlet oxygen ($^1$O$_2$) for the direct formation of oxidized C=O or CH-OH compounds (Scheme 10).

A plausible mechanism is shown in Scheme 11. Upon irradiation, photocatalyst (RFT), is excited to its triplet state (RFT$^*$) and can undergo consecutive electron reduction and protonation, leading concomitantly to the formation of RFTH$_2$ and the radical (R’, 8a). At this stage, the $^1$O$_2$ singlet will react with the radical species to generate the peroxy-radical (ROO’, 8b) intermediate, affording the ketone or alcohol precursor of the desired products. $^1$O$_2$ will then oxidize the intermediate RFTH$_2$ in order to regenerate the catalyst and form the H$_2$O$_2$ side product. Finally, hydrogen peroxide is reduced to O$_2$ and H$_2$O in the presence of an iron additive.

5.5. Nitration of protected anilines

König et al.56 investigated the nitration of protected anilines with riboflavin tetraacetate (RFTA) upon visible light irradiation. In this protocol, sodium nitrite serves as the NO$_3$ source in the visible-light-driven room temperature reaction. Numerous nitro anilines are obtained in moderate to good yields without the addition of acid or stoichiometric oxidation agents. The catalytic cycle is closed by aerial oxygen as the terminal oxidant (Scheme 12).

After excitation, photocatalyst (RFTA) oxidizes the aniline derivative 10 via the loss of a proton can occur.69,70 The radical species nitrogen dioxide is formed via different pathways and is able to react with 10a.51,63 After rearomatization, the desired para- and ortho-regioisomeric substituted products 11 are obtained (Scheme 13).

5.6. E $\rightarrow$ Z isomerization of polarized alkenes (olefins)

Mettnerich et al.53,54 reported the first highly $Z$-selective isomerization 13 of polarized alkenes 12, catalysed by riboflavin under visible light irradiation. This study was inspired by the susceptibility of crystalline ($\lambda$)-riboflavin in the eyes of vertebrates to invert the intrinsic directionality of retinal isomerization. They demonstrated broad substrate scope (up to 99 : 1 $Z: E$) along with the evidence of mechanistic dichotomy via both singlet and triplet energy transfer mechanisms (Scheme 14). The simple $E \rightarrow Z$ isomerization of activated dienes, based
on the β-ionyl motif intrinsic to retinal, is also reported by Gilmour et al. by using inexpensive (−)-riboflavin (vitamin B2) under irradiation at 402 nm.

5.7. Chemoselective synthesis of unsymmetrical disulfides

Iida et al. have developed the chemoselective synthesis of unsymmetrical disulfides using the oxidative heterocoupling reaction of two different thiols. The riboflavin-based catalyst successfully promoted the formation of the phototropin-like flavin–thiol adduct under visible light irradiation, the mild reactivity of adduct, played a crucial role in the chemoselective cross-coupling. This green oxidative transformation is driven by visible light due to the photo and redox-organocatalysis of flavin, and molecular oxygen under mild metal-free conditions (Scheme 15).

6. Cooperative catalysis

Cooperative catalysis is applicable when two catalysts and two catalytic cycles work in concert to generate a single new bond in organic transformations. Being a stable photocatalyst, flavin is also applied as a cooperative catalyst in combination with other organocatalyst and flavin–amine hybrid to carry out aerobic oxidations as well as oxyamination reactions.

6.1. Aerobic oxidation of unactivated benzylic substrates

Cibulka et al. reported a system with ethylene-bridged flavinium salt (combining flavin photocatalysis and organocatalysis), which catalyzes the aerobic oxidation of tolenes and benzyl alcohols with high oxidation potential (Eox > +2.5 V vs. SCE) to give the corresponding benzoic acids under visible light irradiation (Scheme 17). This is caused by the high oxidizing power of excited (E(2b*) = +2.67 V vs. SCE) involved in photooxidation and by the accompanying dark organocatalytic oxygenation provided by the in situ formed flavin hydroperoxide (Scheme 16).

6.2. Peptide bridged flavin–amine hybrid

Imada et al. reported a peptide-bridged flavin–amine hybrid that can catalyze the α-oxyamination of aldehydes with
TEMPO 22 under weak blue light irradiation to achieve an extremely high quantum yield of reaction ($\Phi = 0.80$). The flavin ring system and a secondary amine have been integrated through a short peptide linker with the aim of using photons as efficiently as possible in the photoredox/enamine dual catalysis (Scheme 18).

7. Conclusions

Flavins and their derivatives can serve as a green and versatile catalyst to carry out several organic transformations. In the last few years, few flavin catalysed chemical reactions were reported that clearly indicate that properties and possible synthetic applications of flavins and their derivatives are still in their preliminary stage, which needs to be further explored to realize its full potential. The photostability of the flavin catalyst must be enhanced. For the application of the oxidised form of the flavin catalyst with higher substrate concentration and substrate binding sites, the ISC rate to triplet state after excitation must be enhanced and further exploration is needed to use the reduced form of flavin in organic transformations. In summary, flavins and their derivatives have been used as simple, economical and metal-free photocatalysts for organic transformation recently, with a view of exploring new routes for the development of a novel visible light-induced organic synthesis and it will explore a new era for the biomaterial-based photoredox synthesis.

Conflicts of interest

There are no conflicts to declare.

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