Journal of Molecular Modeling (2021) 27: 96
https://doi.org/10.1007/s00894-020-04650-8

ORIGINAL PAPER

The redox potential of flavin derivatives as a mediator in biosensors

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Received: 4 July 2020 / Accepted: 16 December 2020 / Published online: 28 February 2021

Abstract

The two-electron reduction potential for a set of 393 flavin derivatives is presented in this article. These derivatives are substituted flavin on carbon 6, 7, 8, and 9 by coinage transition metals (Cu, Ag, and Au) and conjugated double bond hydrocarbons; and both groups are examined with and without functional groups such as OH, Cl, CH_3, COOH, and NO_2. In order to show the validity of the results, the reduction potential of human life molecules, which have experimental values, such as flavin adenine dinucleotide (FAD) and riboflavin (vitamin B_2) is calculated. The experimental value for FAD is − 0.22 V, while the obtained theoretical value is − 0.21 V, and the corresponding values for riboflavin are − 0.18 and − 0.19 V, respectively. Theoretical calculations have been carried out by DFT procedure with a 6-31+G** basis set and BLYP *xc*-functional for coinage transition metals substitution, and MPW1PW9 *xc*-functionals for conjugated double bond hydrocarbon substitution. Both *xc*-functionals are chosen by the DFT calibration procedure.

Keywords Flavins · Reduction potential · Biosensor · Mediator · Density functional theory

Introduction

The effect of substitution on the property of chemical species is a type of research that can help to show how to change property of compounds with some different substituents. Such researches are related to the Hammett equations [1, 2], which is about changing acidity of benzoic acid with different substituents on benzene ring. There are many research articles about changing the aromaticity of the aromatic compounds, for instance nuclear independent chemical shift (NICS) research which is done by Schleyer and his co-workers [3, 4]. There are also some researches about changing the reduction potential of chemical compounds which is performed by Suresh and his co-workers [5–7]. The present research is about changing the reduction potential of flavin by different substituents; that flavin is an important species in life sciences.

Electron transfer is one of the main processes in nature that participate in many biological, physical, and chemical systems (both organic and inorganic) [8–10]. Mediators, one of the main parts of the biosensor, are electron transferring agents that enhance the speed of electron transfer between the electrode and other species such as biological compounds [11]. A proper mediator should be designed in such a way that it provides a more positive reduction potential for oxidative biocatalysts and more negative for reductive biocatalysts [11]. Therefore, for the fabrication of biosensor, it is of great interest to find a mediator that provides the most appropriate reduction potential.

The roadblock on the way to provide experimental conditions for measurement of reduction potential [12–14] is that it takes considerable time and cost for material synthesis and measurement of the redox potential of the desired molecules. Therefore, the experimental measurement of reduction potential seems rather disappointing. As a result, the quantum mechanical procedures have been applied to overcome experimental difficulties for the calculation of reduction potentials [15–29]. Therefore, this great opportunity motivated us to calculate the reduction potential of some substituted flavins with acceptable accuracy by performing quantum mechanical calculations.

Flavins are the most common derivatives of pteridine, formed by substituted 7-, 8-, and 10-isoalloxazine ring systems (Fig. 1). They are the central component of riboflavin (vitamin B_2), flavin mononucleotide (FMN), and flavin

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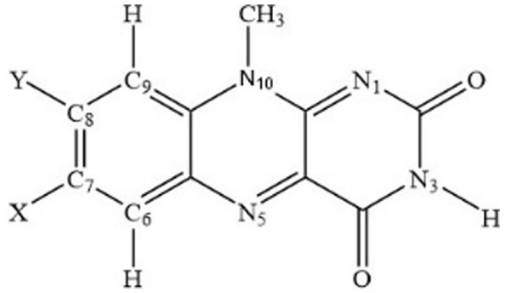

Fig. 1 The structure of the flavin molecule

adenine dinucleotide (FAD) cofactors [30]. Many dehydrogenations and hydroxylation reactions of FMN and FAD as a cofactor are linked to the isoalloxazine ring moiety. Therefore, its redox and acid-base properties have drawn considerable attention to realize [31, 32]. Flavins and its derivatives have been utilized as mediators to determine cholesterol [33], glucose [34], and fish freshness [35].

The effects of substitution on the electronic properties of flavins are the central issue in the experimental and theoretical studies in the literature. Rizzo and co-workers [36] have experimentally studied the substitution effect of 7 and/or 8 positions, on the reduction potential of flavins. Rotello and co-workers [32, 37–51] have considered the effect of the environment such as H bond and intermolecular interactions on the reduction potential of flavins by experimental means. Some theoretical studies are limited to investigate properties such as conformation, aromaticity, and electron spin density [21, 52–55]. Li and co-workers [23] investigated the reduction potential of 28 flavin derivatives theoretically for the first time. On the other hand, Truhlar and co-workers [56] have used M06-L DFT calculations to compute the energy of several substituted flavins in both gas and aqueous phases. Their computed values are consistent with experimental values with a mean unsigned error of only 42 mV [56].

The oxidation-reduction reaction is another important reaction in life sciences and biosensor research. The aim of this research is to show how to change the reduction potential of flavin by substitution on carbon 6, 7, 8, and 9. Therefore, three types of substitutions are considered that are organized as follows: In the "Two-electron reduction potential of life science molecules" section, the two-electron reduction potential of life science molecules that as illustrated in Fig. 2 are riboflavin (vitamin B_2), FMN, FAD, and NAD are calculated. The next section, "Two-electron reduction potential of coinage transition metals substituted flavins" section, is devoted to the studying of the effect of coinage transition metals (Cu, Ag, and Au) substitution alone and also with functional groups such as OH, Cl, CH_3, NO_2, and COOH on the reduction potential of flavin. Finally, in the last section, "Two-electron reduction potential of conjugated double bonds substituted flavins" section, the effects of conjugated double bond hydrocarbon substitution alone and also with OH and Cl functional groups on reduction potential are investigated. The trends of lowering or raising the reduction potential of flavin derivatives are investigated to realize which compounds are suitable to be used as a mediator for a particular measurement of interest.

Theoretical methods

The procedure to compute two-electron reduction potentials of compounds that belongs to one family is performed by using an isodesmic reaction. In this procedure, a compound with known experimental reduction potential is chosen as a reference molecule, and the reduction potential of a substituted compound is calculated through the reaction equation:

$$FH_2 + F' \rightarrow F + F'H_2 \quad (1)$$

where *F* here presents flavin molecule. Therefore, in this equation, the reference molecule is an unsubstituted flavin (FH_2) that is oxidized, and other substituted flavins (F′) are reduced. The theoretical reduction potential of substituted flavins can be obtained through:

$$E_{F'} - E_F = -\frac{\Delta G_{rxn}}{|Z|F} \quad (2)$$

where E_F is the experimental reduction potential of the unsubstituted flavins (reference molecule), $|z|$ is the number of electrons transferred (here equals two), *F* is the Faraday constant (96,485.338 $Cmol^{-1}$), and ΔG_{rxn} is the Gibbs free energy difference of products and reactants:

$$\Delta G_{rxn} = G_{products} - G_{reactants} \quad (3)$$

There is another way to calculate reduction potential in literature, which is used by Suresh and his co-workers by employing MSEP method [5–7]. Since we showed that our results have enough accuracy, we will continue to follow pervious way to obtain reduction potential in this research.

Nomenclature

In the case of coinage transition coinage metals substitution on flavin, "Two-electron reduction potential of life science molecules" section, metal or M represents in general Cu, Ag, or Au, and G represents functional groups (OH, CH_3, Cl, COOH, NO_2). For instance, 8-OH-6-Cu-Flavin means OH connects to carbon atom 8 of flavin, and Cu connects to carbon atom 6 of flavin.

For conjugated double bond hydrocarbon substituted flavin, "Two-electron reduction potential of coinage transition metals substituted flavins" section, from now on, H represents

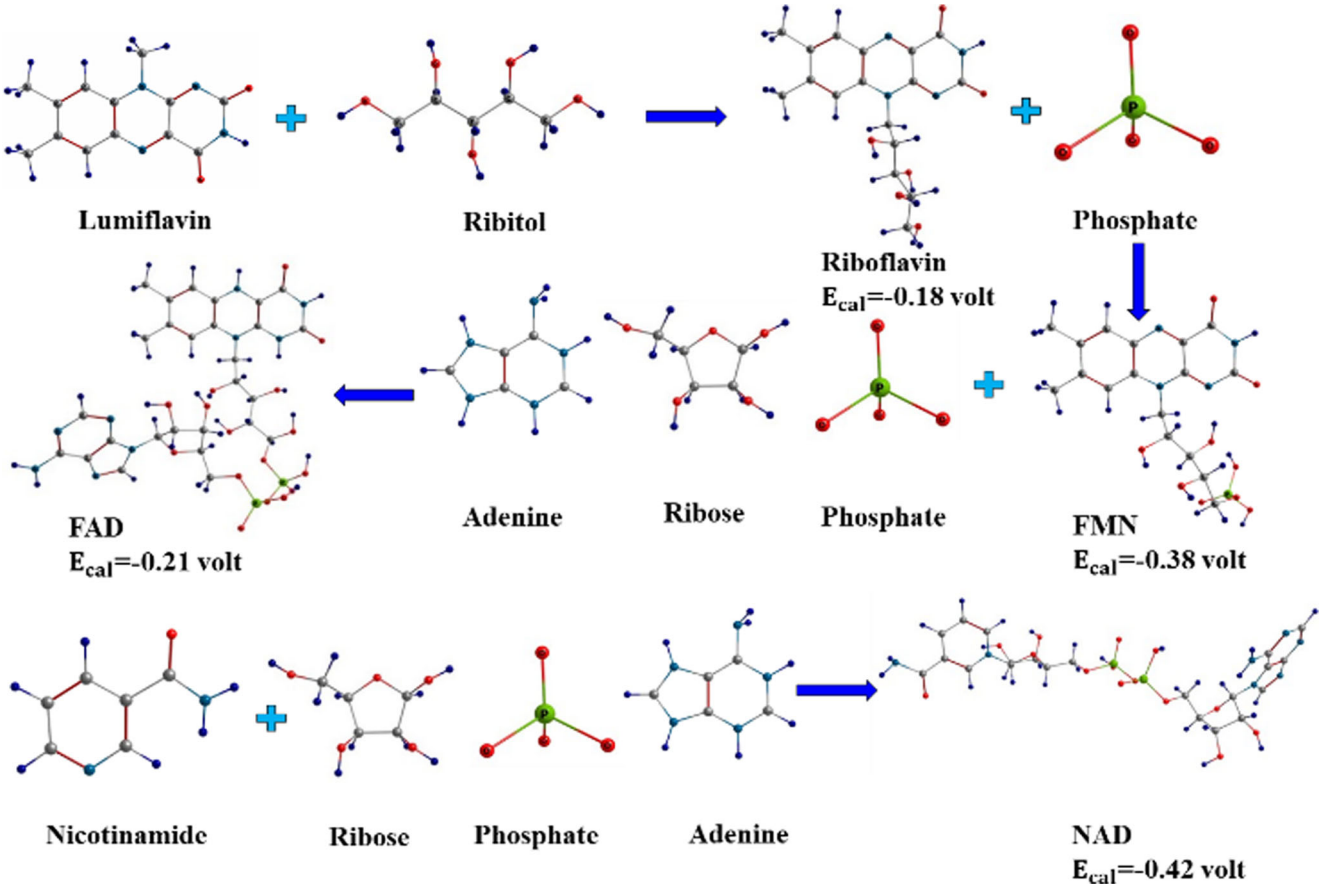

Fig. 2 Structure of riboflavin, FMN, FAD, and NAD

generally hydrocarbons such as butadiene, hexatriene, or benzene, and G stands for functional group substitutions such as –OH and –Cl. Therefore, i-H-Flavin represents the connection of these hydrocarbons (butadiene, hexatriene, or benzene) to i carbon atom of flavin. Another example, i-H-j-G-Flavin, represents that combination of hydrocarbons and functional groups connects to i carbon atom and j carbon atom of flavin as substitutions, respectively. In the case of benzene derivative, for instance, 6-(meta-G-Ben)-Flavin means G has a connection with benzene in a position of meta with respect to carbon 6 of flavin. Another example is 6-(ortho para-G-Ben)-Flavin which means that two G functional groups are on benzene which are in ortho and para positions with respect to carbon 6 of flavin.

Results and discussion

In this paper, density functional theory (DFT) calibration was applied to select an appropriate exchange-correlation functional (*xc*-functional) for calculations of two-electron reduction potential. There are many xc-functionals that are available in DFT method. To find suitable *xc*-functional with minimum and acceptable error with experimentally known of reduction potential, we have to examine several *xc*-functionals. We call this procedure "DFT calibration" which will be shown in the following.

DFT calibration

Unfortunately, no experimental data was found for the reduction potential of coinage transition metals or hydrocarbon-double bond substituted flavins. Therefore, DFT calibration has been done for life science molecules such as riboflavin and FAD, since their experimental values are available. As represented in Table 1, to select appropriate functional, we have calculated the reduction potential of riboflavin and FAD using the B3LYP, BLYP, B1B95, M06L, and MPW1PW91 functional.

As reported in Table 1, for the life science molecules, the calculated two-electron reduction potential obtained using MPW1PW91 functional is in reasonable agreement with the experimental value. As mentioned in the previous paragraph, due to the unavailability of experimental data for coinage transition metals substituted flavins, two-electron reduction potential calculations were performed using BLYP *xc*-functional. BLYP functional is reported as an appropriate *xc*-functional for TM containing compounds by Truhlar and co-

Table 1 Two-electron reduction potential values and average unsigned error for DFT calibration of riboflavin and FAD with B1B95, B3LYP, BLYP, M06L, and MPW1PW91 functional and 6-31+G** basis set. (units in volt)

Functional	E_{cal} (v) Riboflavin	% Error	E_{cal} (v) FAD	% Error
B1B95	−0.158	17.06	–	–
B3LYP	−0.159	16.11	−0.171	22.06
BLYP	−0.161	15.53	−0.173	21.57
M06L	−0.146	23.37	−0.177	19.39
MPW1PW91	−0.181	7.92	−0.213	3.18
E_{exp} (v)	−0.19		−0.22	

workers and also our research group calculations [57–59]. We applied MPW1PW91 *xc*-functional also for conjugated double bond flavin derivatives. Therefore, MPW1PW91 and BLYP functional with 6-31+G** basis set which is embedded in Gaussian 09 program [60] were selected for geometry optimization in this study. We have used "6-31+G** + LANL2DZ" mixed basis set just for metals. All geometry optimizations have passed frequency calculations to obtain a real stationary point and Gibbs free energies.

Calculation of two-electron reduction potential for substituted flavins

The reduction potential of 393 flavins with substitutions of coinage transition metal and conjugated double bond hydrocarbons are calculated in this research. All obtained results of two-electron reduction potential are useful for specific experimental works, whether the percentage of reduction is low or high, or whether the percentage of shifting reduction potential with respect to the reduction potential of unsubstituted flavin is positive or negative. Although we attempt to find some types of trends to predict the future of some substitutions on flavin, we notice certain substitutions in different positions of flavin, showing quite a different reduction potential. For instance, for compound 7-Cl-8-OH-6-Cu-Flavin, the reduction potential is − 0.518 V (30.8% decreasing with respect to unsubstituted flavin), whereas the reduction potential for compound 6-OH-9-Cl-8-Cu-Flavin is − 0.179 V (% decreasing is − 3.1). Therefore, the prediction of the reduction potential of substituted flavin is quite impossible.

Two-electron reduction potential of life science molecules

At first, our study devotes on the calculation of two-electron reduction potential of life science molecules, which are, as illustrated in Fig. 2, riboflavin (vitamin B_2), FMN, FAD, and NAD. The results of calculated two-electron reduction potential using MPW1PW91 functional and 6-31+G** basis set have been presented in Table 2. These results have been compared with available experimental results [61] that show good resemblance. It is found that by adding ribitol group and also diphosphate, ribose, and adenine groups to flavin, leading to riboflavin and FAD, the reduction potential has increased toward the reference molecule, but adding ribitol and phosphate group to flavin, leading to FMN, has decreased the reduction potential toward the reference molecule.

The calculated two-electron reduction potential of NAD is − 0.42 V that rather agrees with the available experimental value (− 0.31 V) [62]. From these values for reduction potential, it can be concluded that by adding adenine, phosphate, and ribose group to niacinamide, the reduction potential has decreased toward the reduction potential of reference molecule (− 0.38 V) [62].

It has been shown that riboflavin is stronger oxidizing agents than FAD, FMN, and NAD, and FMN and FAD is the stronger oxidizing agent than NAD. Our results are in agreement with experimental data and what happened in nature. Qualitatively in nature, NADH is oxidized and FAD is reduced.

Two-electron reduction potential of coinage transition metals substituted flavins

In this part, the effects of coinage transition metals (Cu, Ag, and Au) substitution alone and also with some functional groups such as OH, CH_3, Cl, NO_2, and COOH on the two-electron reduction potential of flavin are studied. The results of compounds that show significant changes in reduction potential in comparison with unsubstituted flavin (− 0.21 V) are presented in Tables 3 and 4. The further results of the calculated two-electron reduction potential of all coinage metals substituted flavins are presented in Tables S1-S11 and Figs. S1-S11. In general, substitution with coinage transition metals decreases the reduction potential (more negative values in comparison with the experimental value of reduction potential of unsubstituted flavin − 0.21 V).

Homo and mixed, mono, and multi metals substituted flavins

The results of some significant reduction potential of pure

Table 2 Two-electron reduction potential value of riboflavin, FMN, and FAD with MPW1PW91 functional and 6-31+g** basis set (units in volts)

Molecule	E_{cal} (V)	E_{exp} (V) [61]	% Decreasing toward ref molecule
Riboflavin	−0.18	−0.19	7.92
FMN	−0.38		−12.4
FAD	−0.21	−0.22	4.68

The reduction potential of the reference molecule (lumiflavin): − 0.26 V [36]

Table 3 The calculated reduction potential of homo, mono, and multi-metals and mixed metals substituted flavins at BLYP level of theory and "6-31+G** + LANL2DZ" mixed basis set (units in volts)

Number	Species	Type	Reduction potential	% Decreasing	Tables	Figures
1	6-Ag-Flavin	Mono-metal	−0.440	23.0	Table S1	Fig. S1
2	6-Cu-Flavin	Mono-metal	−0.457	24.7	Table S1	Fig. S1
3	8-Au-Flavin	Mono-metal	−0.384	17.4	Table S1	Fig. S1
4	6,7-di-Ag-Flavin	Di-metal	−0.468	25.8	Table S2	Fig. S2
5	6,7-di-Cu-Flavin	Di-metal	−0.480	27.0	Table S2	Fig. S2
6	6,7,8-tri-Ag-Flavin	Tri-metal	−0.490	28.0	Table S3	Fig. S3
7	6,7,8,9-tetra-Cu-Flavin	Tetra-metal	−0.463	25.3	Table S3	Fig S3
8	6-Cu-7-Ag-Flavin	Di-metal	−0.481	27.1	Table S4	Fig. S4
9	6,7,8,9-tetra-Ag-Flavin	Tetra-metal	−0.413	20.3	Table S3	Fig. S3

coinage transition metals and mixed coinage transition metals (Cu, Ag, and Au) substitution of flavin in comparison with the reduction potential of unsubstituted flavin (− 0.21 V) are collected in Table 3. Tables S1-S4 and Figs. S1-S4 present more results of pure metal and mixed metals substituted flavin. The best result for mono-metal substitution is for 6-Cu-Flavin, compound 2, with a reduction potential of − 0.457 V and a 24.7% decrease. The best result for di-metal substitution belongs to 6,7-di-Cu-Flavin, compound 5, with a reduction potential of − 0.480 V and a 27.0% decrease in reduction potential in comparison to unsubstituted flavin. The best result of three metals substitution is for 6,7,8-tri-Ag-Flavin, compound 6, which is − 0.490 V with a 28.0% decrease. When we try with mixed di-metal substitution, the promotion of reduction potential is always being high, and the best reduction potential, − 0.481 V, for compound 8 was obtained, while the reduction potential of four metals substituted flavin, compound 7, does not show a significant decrease in comparison with the results of the best multi-metals substituted flavin.

We would like to show again the unpredictability of the reduction potential. The results of calculated reduction potentials for one to four Ag substituted flavins in Table 3 are −

Table 4 The results of reduction potential of metal mixed with functional groups substituted flavins at BLYP level of theory and "6-31+G** + LANL2DZ" mixed basis set (units in volts)

Number	Species	Type	Reduction potential	% Decreasing	Figures
1	8-OH-6-Cu-Flavin	Mono-metal-mono-G	−0.533	32.3	Fig. S5
2	8-CH_3-6-Cu-Flavin	Mono-metal-mono-G	−0.459	24.9	Fig. S5
3	7,8-di-OH-6-Cu-Flavin	Di-G-mono-metal	−0.579	36.9	Fig. S6
4	7,8-di-CH_3-6-Cu-Flavin	Di-G-mono-metal	−0.494	28.4	Fig. S6
5	7,8,9-tri-OH-6-Cu-Flavin	Tri-G-mono-metal	−0.498	28.8	Fig.S7
6	6,7,8-tri-CH_3-9-Cu-Flavin	Tri-G-mono-metal	−0.421	21.1	Fig. S7
7	6,7-di-Cu-8-OH-Flavin	Di-metal-mono-G	−0.546	33.6	Fig S8
8	6,7-di-Cu-8-CH_3-Flavin	Di-metal-mono-G	−0.484	27.4	Fig. S8
9	7-CH_3-8-OH-6-Cu-Flavin	Di-G-mono-metal	−0.547	33.7	Fig. S9
10	7-Cl-8-OH-6-Cu-Flavin	Di-G-mono-metal	−0.518	30.8	Fig. S9
11	6,9-di-Cu-7,8-di-CH_3-Flavin	Di-metal-di-G	−0.450	24.0	Fig. S10
12	7,9-di-Cu-6,8-di-OH-Flavin	Di-metal-di-G	−0.678	46.8	Fig. S10
13	6,7,8-tri-Ag-9-OH-Flavin	Tri-metal-mono-G	−0.202	17.8	–
14	6,7,9-tri-Cu-8-OH-Flavin	Tri-metal-mono-G	−0.561	35.1	Fig. S11
15	6,8,9-tri-Cu-7-CH_3-Flavin	Tri-metal-mono-G	−0.490	28.0	Fig. S11
16	6-OH-9-CH_3-8-Cu-Flavin	Di-G mono-metal	−0.181	−2.90	Fig. S9
17	6-OH-9-Cl-8-Cu-Flavin	Di-G mono-metal	−0.179	−3.1	Fig. S9
18	6-NO_2-8-Cu-Flavin	Mono-G mono-metal	−0.160	−5.0	Fig. S5
19	9-COOH-7-Cu-Flavin	Mono-G mono-metal	−0.193	−1.7	Fig. S5
20	6-COOH-8-Cu-Flavin	Mono-G mono-metal	−0.441	23.1	Fig. S5
21	7-NO_2-8-Cu-Flavin	Mono-G mono-metal	−0.344	13.4	Fig. S5

0.440, − 0.468, − 0.490 and − 0.413 V, respectively. The trend of reduction potentials is descending for one Ag to three Ag substitutions, but not for four Ag substitutions, which goes up.

As presented in Fig. 3, compared to the reduced form, the double bond is lengthened and the single bond is shortened in the oxidized form. This observation shows that the π-electron is more delocalized in the oxidized form.

Metal mixed with functional groups substituted flavins In this section, the changes in the reduction potential of flavins upon the substitution of coinage transition metals mixed with functional groups are investigated. The considered functional groups are OH, Cl, CH_3, NO_2, and COOH which as presented in Table 4 usually promote the reduction potential significantly. As shown in Tables 4, S5, and S9, the calculated reduction potentials for coinage transition metals with functional groups substituted flavins show that Cl-substituted flavins behave quite differently; promotion of reduction potential depends on the position of substitution on flavin (Tables S5 and S9). For instance, the reduction potential of 7-Cl-8-OH-6-Cu-Flavin, compound 10, is − 0.518 V (% decreasing 30.8), while reduction potential for 6-OH-9-Cl-8-Cu-Flavin, compound 17, is − 0.179 V (% increasing − 0.31). Table 4 shows that the promotion of reduction potential occurs in compound numbers (1), (3), (4), (5), (7), (8), (9), (10), (11), (12), (14), (15), and (20) when they have OH substitution on flavin. So, OH substitution is maybe an important substitution to promote two-electron reduction potential.

Figure 4 presented the optimized structure of compound numbers (1), (3), (5), (7), (9), (10), (12), and (14). In these compounds, the bond length of the oxidized form double bond is longer than the reduced form, and for the single bond, the reduced form bond length is longer.

It would be interesting to see whether functional group substitution can itself cause such promotion in reduction potential or not. The results in Table 5, which are only functional group substitution, clearly show that the substitution of the functional group alone cannot promote the reduction potential of flavin significantly. As shown in Table 5, NO_2 and COOH functional groups make the two-electron reduction potential of flavin toward more positive voltage. Hence, functional groups must be combined with coinage transition metals to gain considerable promotion in reduction potential such as − 0.678 V for compound 12 in Table 4.

Two-electron reduction potential of conjugated double bonds substituted flavins

For conjugated double bonds substituted flavins, the two-electron reduction potential was calculated to analyze the effect of double bond hydrocarbons such as butadiene, hexatriene, and benzene substitution alone,

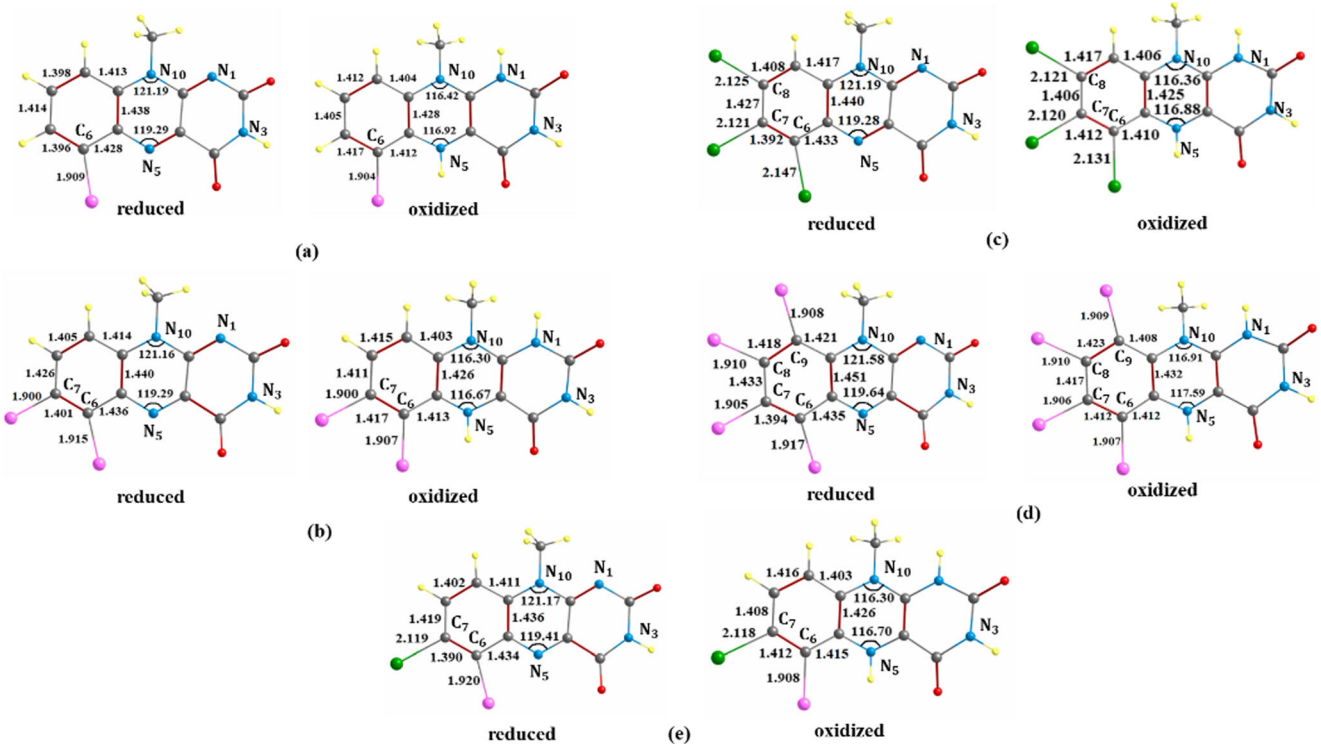

Fig. 3 The optimized structure of oxidized and reduced form of (**a**) 6-Cu-Flavin, (**b**) 6,7-di-Cu-Flavin, (**c**) 6,7,8-tri-Ag-Flavin, (**d**) 6,7,8,9-tetra-Cu-Flavin, and (**e**) 6-Cu-7-Ag-Flavin at BLYP level of theory and "6-31+G** + LANL2DZ" mixed basis set. Atom color code: carbon (gray), nitrogen (blue), oxygen (red), hydrogen (yellow), copper (pink), and silver (green) (double bonds are shown with red color)

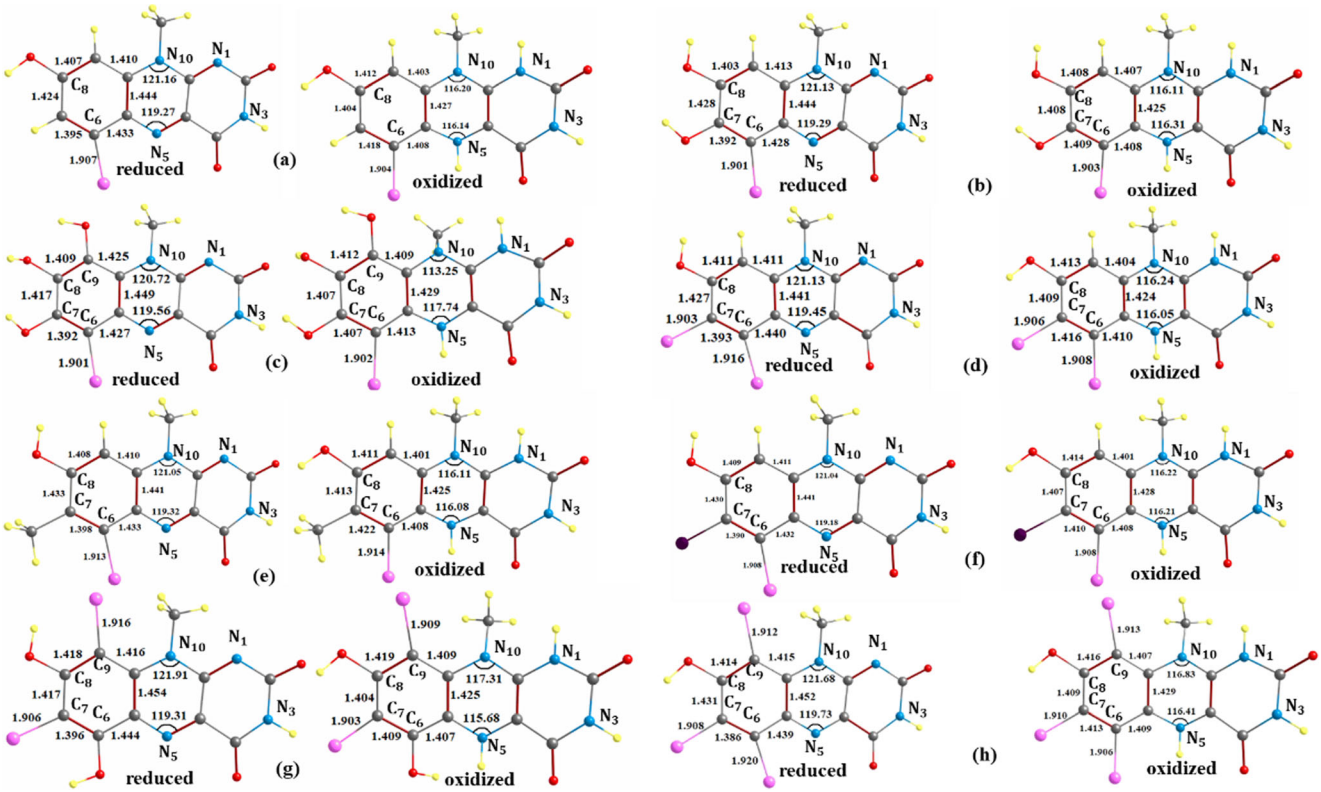

Fig. 4 The optimized structure of oxidized and reduced form of (**a**) 8-OH-6-Cu-Flavin, (**b**) 7,8-di-OH-6-Cu-Flavin, (**c**) 7,8,9-tri-OH-6-Cu-Flavin, (**d**) 6,7-di-Cu-8-OH-Flavin, (**e**) 7-CH_3–8-OH-6-Cu-Flavin, (**f**) 7-Cl-8-OH-6-Cu-Flavin, (**g**) 7,9-di-Cu-6,8-di-OH-Flavin, and (**h**) 6,7,9-tri-Cu-8-OH-Flavin at BLYP level of theory and "6-31+G** + LANL2DZ" mixed basis set. Atom color code: carbon (gray), nitrogen (blue), oxygen (red), hydrogen (yellow), chloride (purple), copper (pink), and silver (green) (double bonds are shown with red color)

and also mixed with functional groups such as OH, Cl, CH_3, and O (ketone or aldehyde) on the reduction potential of flavin. Three hydrocarbons are presented by But for butadiene, Hex for hexatriene, and Ben for benzene. The carbon number 6, 7, 8, or 9 of flavin contact with mentioned hydrocarbons.

Table 5 The effect of functional group substitution on the reduction potential of flavin at BLYP/6-31+G** level of theory (units in volts)

Number	Species	Type	Reduction potential	% Decreasing
1	6,8-OH-Flavin	Di functional group	−0.241	3.1
2	6-OH-Flavin	Mono functional group	−0.175	−3.5
3	7-OH-Flavin	Mono functional group	−0.195	−1.5
4	8-OH-Flavin	Mono functional group	−0.279	6.9
5	9-OH-Flavin	Mono functional group	−0.133	−7.7
6	6-CH_3-Flavin	Mono functional group	−0.237	2.7
7	7-CH_3-Flavin	Mono functional group	−0.221	1.1
8	8-CH_3-Flavin	Mono functional group	−0.238	2.8
9	9-CH_3-Flavin	Mono functional group	−0.076	−13.4
10	6-Cl-Flavin	Mono functional group	−0.139	−7.1
11	7-Cl-Flavin	Mono functional group	−0.184	−2.6
12	8-Cl-Flavin	Mono functional group	−0.205	−0.5
13	9-Cl-Flavin	Mono functional group	−0.048	−16.2
14	6-COOH-Falvin	Mono functional group	0.003	−21.3
15	7-COOH-Flavin	Mono functional group	−0.176	−3.4
16	8-COOH-Flavin	Mono functional group	−0.125	−8.5
17	9-COOH-Flavin	Mono functional group	−0.086	−12.4
18	6-NO_2-Flavin	Mono functional group	0.055	−26.5
19	7-NO_2-Flavin	Mono functional group	−0.132	−7.8
20	8-NO_2-Flavin	Mono functional group	−0.062	−14.8
21	9-NO_2-Flavin	Mono functional group	−0.052	−15.8

Table 6 Two-electron reduction potential value of mono hydrocarbons substituted flavins at MPW1PW91/6-31+G** level of theory (units in volts)

Number	Molecule	But	% Decreasing	Hex	% Decreasing	Ben	% Decreasing
1	6-H-Flavin	−0.220	1.00	−0.227	1.70	−0.189	−2.10
2	7-H-Flavin	−0.223	1.30	−0.260	5.00	−0.206	−0.40
3	8-H-Flavin	−0.212	0.200	−0.256	4.60	−0.216	0.60
4	9-H-Flavin	−0.064	−14.60	−0.062	−14.8	−0.087	−12.3

The reduction potential of the reference molecule (unsubstituted flavin): − 0.21 V

The results of conjugate double bond hydrocarbon substitutions on flavin are presented in Tables 6, 7, 8, and Table S12. There are two general points in this case: (a) They show that they cannot change the

Table 7 Mixed substitution of hydrocarbons and functional groups on flavin at MPW1PW91/6-31+G** level of theory (units in volts)

Number	Species	OH	% Decreasing	Cl	% Decreasing
Butadiene					
1	6-But-7-G-Flavin	−0.028	−18.2	−0.036	−17.4
2	6-But-8-G-Flavin	−0.205	−0.5	−0.13	−8.0
3	6-But-9-G-Flavin	0.034	−24.4	0.103	−31.3
4	7-But-6-G-Flavin	−0.355	14.5	−0.095	−11.5
5	7-But-8-G-Flavin	−0.299	8.9	−0.186	−2.4
6	7-But-9-G-Flavin	−0.118	−9.2	−0.032	−17.8
7	8-But-6-G-Flavin	−0.175	−3.5	−0.149	−6.1
8	8-But-7-G-Flavin	−0.211	0.1	−0.175	−3.5
9	8-But-9-G-Flavin	−0.104	−10.6	−0.026	−18.4
10	9-But-6-G-Flavin	−0.02	−19.0	0.012	−22.2
11	9-But-7-G-Flavin	−0.035	−17.5	−0.037	−17.3
12	9-But-8-G-Flavin	−0.133	−7.7	−0.202	−0.8
Hexatriene					
1	6-Hex-7-G-Flavin	−0.032	−17.8	−0.033	−17.7
2	6-Hex-8-G-Flavin	−0.161	−4.9	−0.080	−13.0
3	6-Hex-9-G-Flavin	0.021	−23.1	0.091	−30.1
4	7-Hex-6-G-Flavin	−0.399	18.9	−0.133	−7.7
5	7-Hex-8-G-Flavin	−0.333	12.3	−0.271	6.1
6	7-Hex-9-G-Flavin	−0.163	−4.7	−0.055	−15.5
7	8-Hex-6-G-Flavin	−0.22	1.0	−0.159	−5.1
8	8-Hex-7-G-Flavin	−0.251	4.1	−0.222	1.2
9	8-Hex-9-G-Flavin	−0.146	−6.4	−0.075	−13.5
10	9-Hex-6-G-Flavin	−0.061	−14.9	−0.030	−18.0
11	9-Hex-7-G-Flavin	−0.097	−11.3	−0.077	−13.3
12	9-Hex-8-G-Flavin	−0.168	−4.2	−0.114	−9.6
Benzene					
1	6-(Meta-G-Ben)-Flavin	−0.191	−1.9	−0.197	−1.3
2	6-(Ortho para-G-Ben)-Flavin	−0.192	−1.8	−0.186	−2.4
3	7-(Meta-G-Ben)-Flavin	−0.209	−0.1	−0.184	−2.6
4	7-(Ortho para-G-Ben)-Flavin	−0.240	3.0	−0.177	−3.3
5	8-(Meta-G-Ben)-Flavin	−0.215	0.5	−0.185	−2.5
6	8-(Ortho para-G-Ben)-Flavin	−0.239	2.9	−0.197	−1.3
7	9-(Meta-G-Ben)-Flavin	−0.096	−11.4	−0.083	−12.7
8	9-(Ortho para-G-Ben)-Flavin	−0.141	−6.9	−0.096	−11.4

The carbon of hydrocarbons connect with flavin is terminal atom (carbon atom number one)

Table 8 Two-electron reduction potential value of mono functional group substituted butadiene at MPW1PW91/6-31+G** level of theory (units in volts)

Number	Molecule	OH	% Decreasing	Cl	% Decreasing	O	% Decreasing
1	6-(1-G-But)-Flavin	−0.142	−6.8	−0.147	−6.3	−0.071	−13.9
2	6-(2-G-But)-Flavin	−0.292	8.2	−0.242	3.2	−0.294	8.4
3	6-(3-G-But)-Flavin	−0.232	2.2	−0.232	2.2	−0.235	2.5
4	6-(4-G-But)-Flavin	−0.284	7.4	−0.246	3.6	−0.238	2.8
5	7-(1-G-But)-Flavin	−0.205	−0.5	−0.186	−2.4	−0.198	−1.2
6	7-(2-G-But)-Flavin	−0.228	1.8	−0.205	−0.5	−0.216	0.6
7	7-(3-G-But)-Flavin	−0.202	−0.8	−0.191	−1.9	−0.172	−3.8
8	7-(4-G-But)-Flavin	−0.217	0.7	−0.197	−1.3	−0.192	−1.8
9	8-(1-G-But)-Flavin	−0.189	−2.1	−0.188	−2.2	−0.115	−9.5
10	8-(2-G-But)-Flavin	−0.232	2.2	−0.191	−1.9	−0.229	1.9
11	8-(3-G-But)-Flavin	−0.215	0.5	−0.207	−0.3	−0.151	−5.9
12	8-(4-G-But)-Flavin	−0.241	3.1	−0.202	−0.8	−0.206	−0.4
13	9-(1-G-But)-Flavin	−0.101	−10.9	−0.082	−12.8	−0.083	−12.7
14	9-(2-G-But)-Flavin	−0.136	−7.4	−0.118	−9.2	−0.038	−17.2
15	9-(3-G-But)-Flavin	−0.105	−10.5	−0.095	−11.5	−0.076	−13.4
16	9-(4-G-But)-Flavin	−0.111	−9.9	−0.095	−11.5	−0.052	−15.8

The reduction potential of the reference molecule (unsubstituted flavin): − 0.21 V

reduction potential of flavin toward the very high negative voltage comparable to coinage transition metal substitutions, neither themselves nor when they mix with a functional group. (b) The second point is the unpredictability of voltage for different substitutions, which we discuss further.

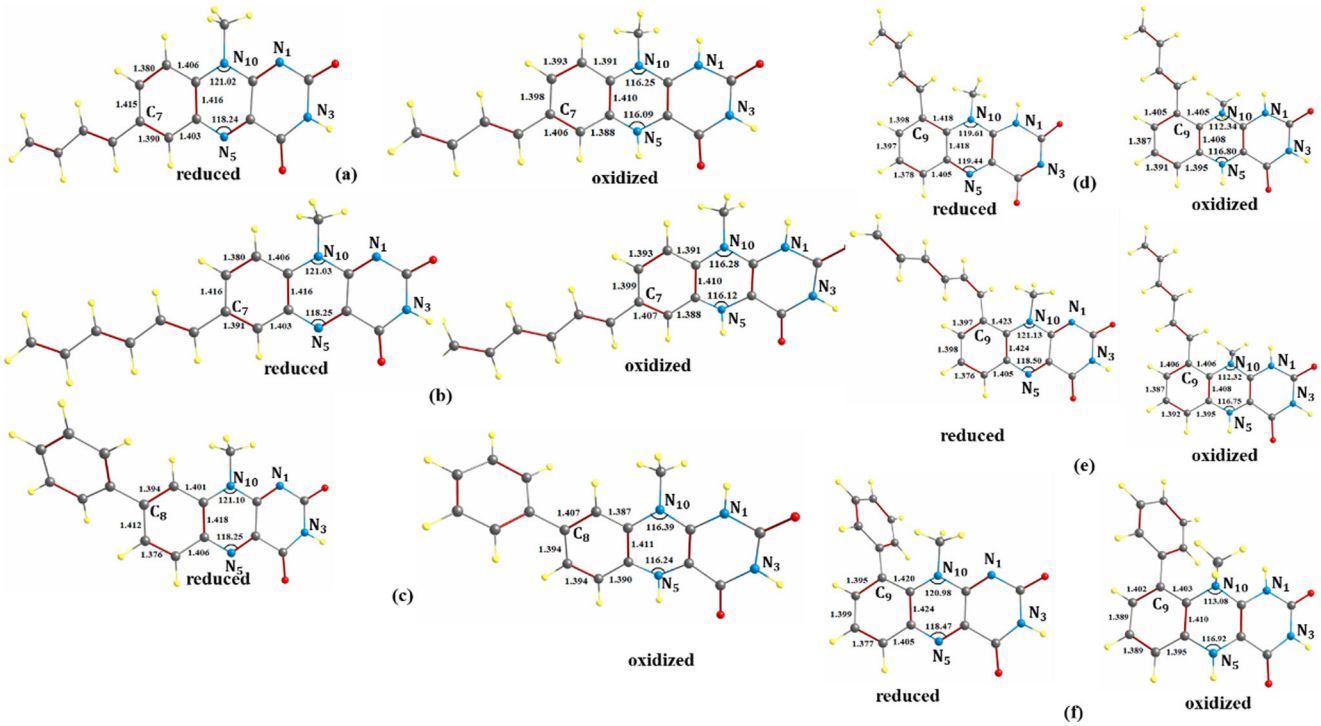

Fig. 5 The optimized structure of oxidized and reduced form of (**a**) 7-But-Flavin, (**b**) 7-Hex-Flavin, (**c**) 8-Ben-Flavin, (**d**) 9-But-Flavin, (**e**) 9-Hex-Flavin, and (**f**) 9-Ben-Flavin at MPW1PW91 level of theory and 6-31+G** basis set. Atom color code: carbon (gray), nitrogen (blue), oxygen (red), chloride (purple), and hydrogen (yellow) (double bonds are shown with red color)

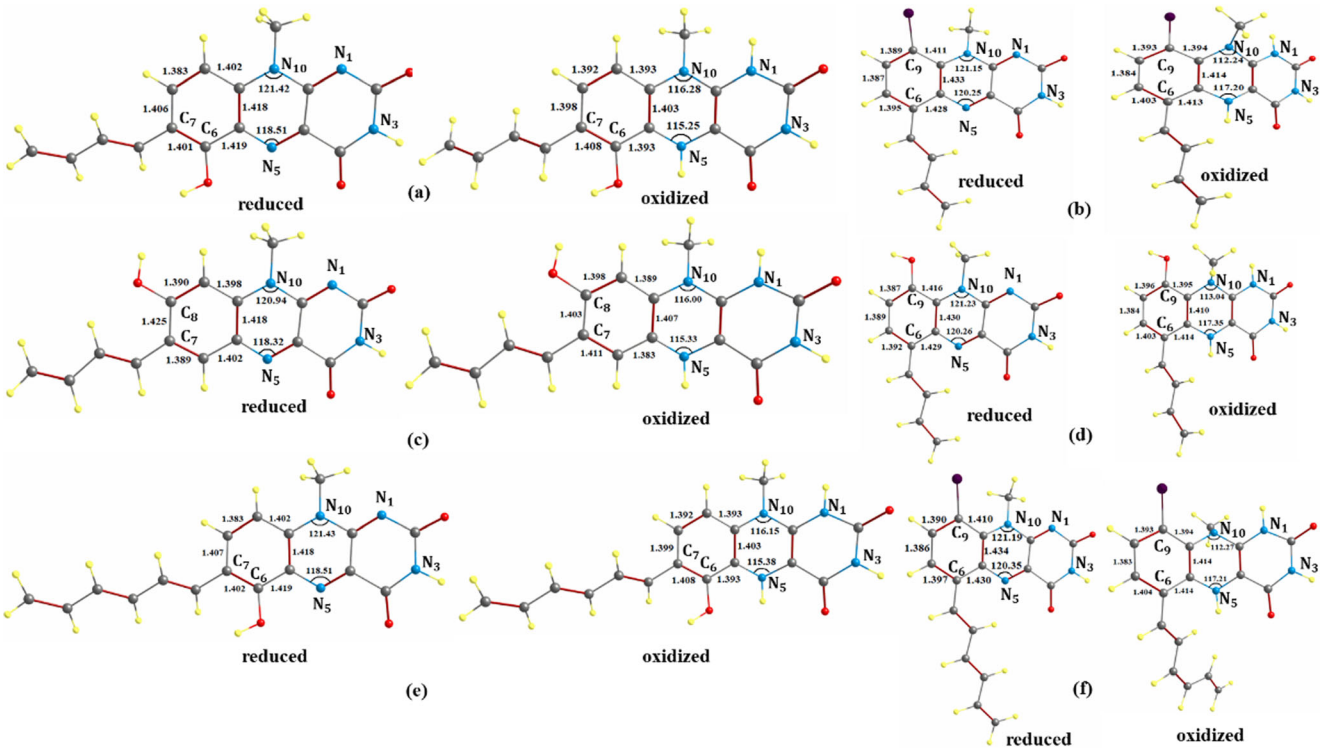

Fig. 6 The optimized structure of oxidized and reduced form of representative set for (**a**) 7-But-6-OH-Flavin, (**b**) 6-But-9-Cl-Flavin, (**c**) 7-But-8-OH-Flavin, (**d**) 6-But-9-OH-Flavin, (**e**) 7-Hex-6-OH-Flavin, and (**f**) 6-Hex-9-Cl-Flavin at MPW1PW91 level of theory and "6-31+G** basis set. Atom color code: carbon (gray), nitrogen (blue), oxygen (red), and hydrogen (yellow) (double bonds are shown with red color)

Mono hydrocarbon substituted flavins The computed two-electron reduction potentials of mono conjugated double bond hydrocarbons substituted flavins are presented in Table 6. The unpredictability of the results is clear in Table 6, as shown substitutions of But and Hex on positions 6, 7, and 8 of flavin are quite different than on position 9; they do not follow the same trend as substitutions on positions 6, 7, and 8 of flavin. The reduction potentials of But and Hex substitution at positions 6, 7, and 8 of flavin go toward more negative potential in comparison with unsubstituted flavin (− 0.21 V) while on position 9 are toward the positive voltage. Benzene substitutions on positions 6, 7, 8, and 9 of flavin are quite different from aliphatic conjugated double bond hydrocarbons, because the benzene ring has actually an aromatic character.

The optimized structure of hydrocarbon substituted flavin with the lowest two-electron reduction potential (a, b, and c) and with the highest two-electron reduction potential (d, e, and f) are presented in Fig. 5. For both cases, the bond length of the oxidized form double bond is longer than the reduced form, and for the single bond, the oxidized form single bond is shorter.

Mixed substitution of hydrocarbons and functional groups on flavins As shown in Table 7 and Figs. S13-S14, almost the majority of reduction potentials of mixed substitution of hydrocarbons and functional groups on flavin in that table go toward a positive direction. The maximum decrease of reduction potential is − 0.399 V for 7-Hex-6-G-Flavin, compound 4; greater voltage than this potential is never obtained. However, these results show that the changes in reduction potential of OH substitution are more significant than Cl. The voltage changes in this type of substitution are quite different from those in Table 4 when mixed coinage transition metals and functional group substitution are applied to flavin.

The optimized structures for the representative set of mixed substitution of hydrocarbons and functional groups on flavins are shown in Fig. 6. The comparison between the bond length of double and single bond in oxidized and reduced form displays that these bonds are lengthen and shorten in the oxidized form, respectively.

Mixed functional groups with hydrocarbon on flavin when functional groups (OH, Cl, and ketone O) substituted on hydrocarbon The calculated reduction potentials of this part are given in Table 8, Table S12, and Figs. S15-S17. These results are the same as Table 7 going toward the positive sign and some toward the negative sign with respect to the unsubstituted flavin reduction potential (− 0.21 V). The optimized structures for the representative set are displayed in Fig. 7. As shown in Fig. 7, in the reduced form of 6-(2-O-But)-Flavin, the oxygen atom interacted with N_5, and in the oxidized form, the oxygen atom interacted with the hydrogen

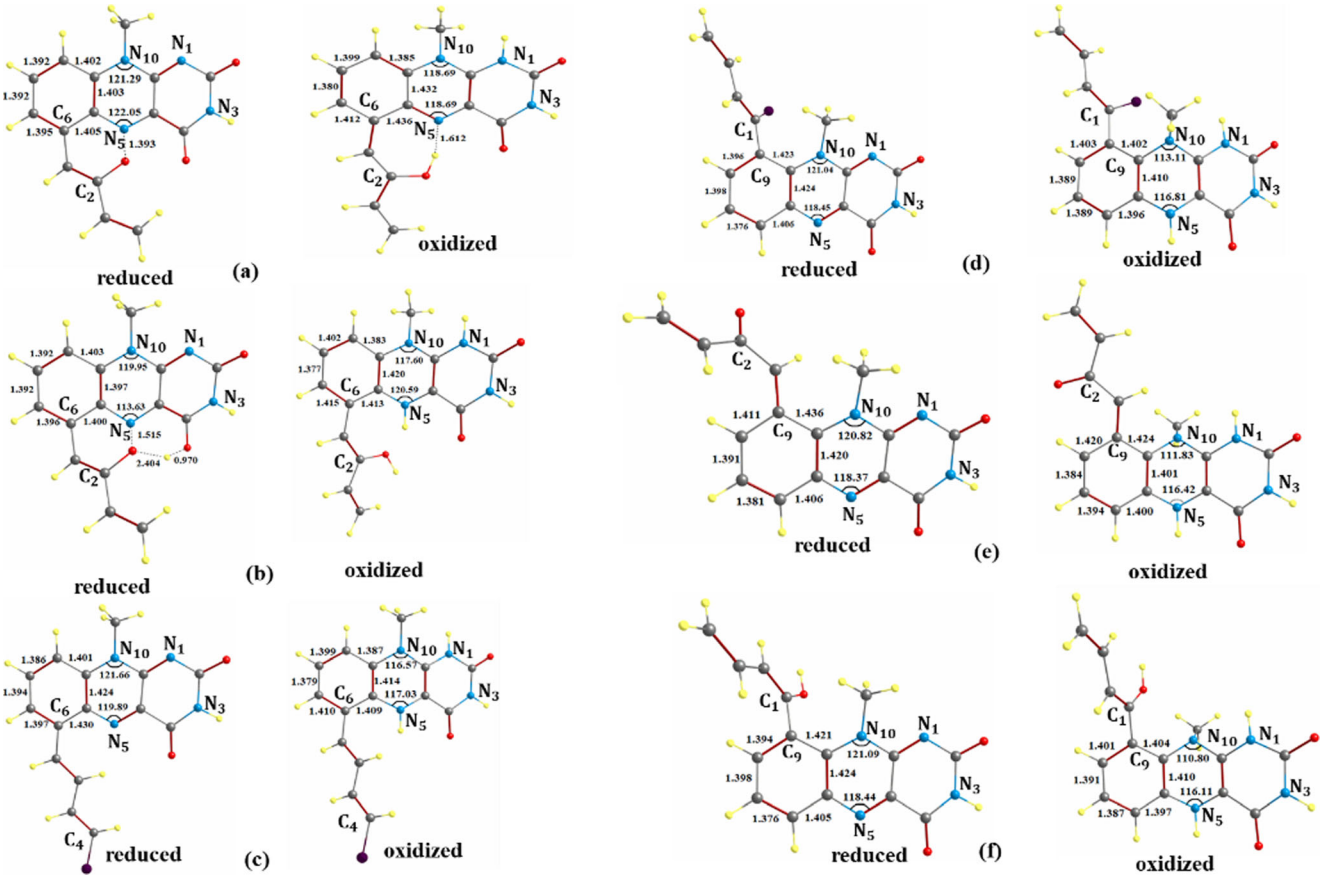

Fig. 7 The optimized structure of oxidized and reduced of (**a**) 6-(2-O-But)-Flavin, (**b**) 6-(2-OH-But)-Flavin, (**c**) 6-(4-Cl-But)-Flavin, (**d**) 9-(1-Cl-But)-Flavin, (**e**) 9-(2-O-But)-Flavin, and (**f**) 9-(1-OH-But)-flavin at MPW1PW91 level of theory and "6-31+G** basis set. Atom color code: carbon (gray), nitrogen (blue), oxygen (red), chloride (purple), and hydrogen (yellow) (double bonds are shown with red color)

atom of N_5. In the reduced form of the 6-(2-OH-But)-Flavin, the hydrogen atom of substituted OH interacted with the oxygen, and the oxygen atom of substituted OH interacted with N_3.

Conclusions

In this research, we have calculated the two-electron reduction potential of 393 flavin derivatives. To this end, the accuracy of some recommended DFT functionals was evaluated for FAD and riboflavin as a life science molecule. Finally, BLYP and MPW1PW91 functionals were selected for coinage transition metals and double bond hydrocarbon substituted flavins, respectively.

The results of the reduction potential of human life compounds such as FAD and riboflavin with a low percentage of error encourage us to work on flavin derivatives. The results of coinage transition metal substitution (alone and with functional groups) on flavin show usually high changes (such as − 0.678 V) of reduction potential toward negative voltage with respect to the experimental value of unsubstituted flavin, − 0.21 V. The changes in the reduction potential of conjugated double bond hydrocarbon substitution (alone and combined with functional groups) on flavin are not usually high (maximum − 0.399 V) and usually go toward positive voltage and sometime go toward negative voltage. Therefore, our results showed that anticipating the effect of substitution on reduction potential is impossible and no relationship is found between lowering or decreasing reduction potential and the type of substitution.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00894-020-04650-8.

Authors' contributions A.H. Pakiari designed the project. M. Salarhaji, T. Abdollahi, and M. Safapour performed the theoretical calculations and analyzed the data. A.H. Pakiari and M. Salarhaji wrote the paper.

Data availability N/A

Code availability N/A

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

Ethics approval N/A

Consent to participate N/A

Consent for publication N/A

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