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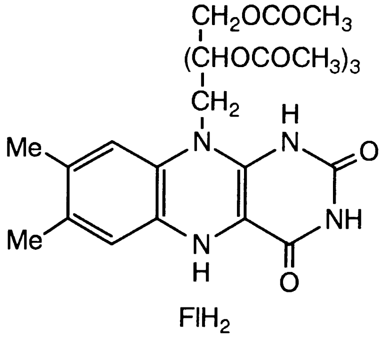
One-Electron and Two-Electron Redox Switch in the Reactions of 1,5-Dihydroflavin and Quinones Controlled by Acid and Base in Acetonitrile

Masashi ISHIKAWA, Yoshiharu MATSUDA, Kazuhiko YAMAMOTO,† and Shunichi FUKUZUMI††*
Department of Applied Chemistry and Chemical Engineering, Faculty of Engineering,
Yamaguchi University, Ube, Yamaguchi 755
†Laboratory of Organic Chemistry, Osaka Women's University, Sakai, Osaka 590
††Department of Applied Chemistry, Faculty of Engineering, Osaka University, Suita, Osaka 565

The acid-catalyzed reactions of 1,5-dihydroriboflavin-2',3',4',5'-tetraacetate (FlH_2) with quinones (Q) result in the one-electron oxidation of FlH_2 to $FlH_2^{+\bullet}$ and the two-electron reduction of Q to the hydroquinones (QH_2) in the presence of $HClO_4$ in acetonitrile. In the presence of Me_4NOH, the base-catalyzed reactions result in the two-electron oxidation of FlH_2 to Fl and the one-electron reduction of Q to $Q^{-\bullet}$.

In the biological redox systems, flavins and quinones are known to undergo both two-electron and one-electron redox reactions with obligate two-electron donors (*e.g.*, NADH) and obligate one-electron reagents (*e.g.*, iron-sulfur clusters and heme proteins), respectively.[1] Considerable efforts have so far been made to understand the mechanism of the redox switch between one- and two-electron redox systems of flavins and quinones.[2-7] However, most redox reactions of flavins and the two-electron reduced form (dihydroflavins) have so far been studied in protic media where two-electron redox chemistry predominates in both acidic and basic conditions.[4-6] We have recently reported unequivocal evidence that the reactions of 1,5-dihydroriboflavin-2',3',4',5'-tetraacetate (FlH_2) with quinones (Q) in an aprotic medium (acetonitrile) proceed *via* electron transfer from FlH_2 to Q, followed by proton and hydrogen transfer, resulting in the net two-electron reduction of Q to QH_2 and two-electron oxidation of FlH_2 to Fl.[8] We report herein that acid and base in acetonitrile (MeCN) can control the one- and two-electron redox switch in the reaction of 1,5-dihydroflavin and quinones.

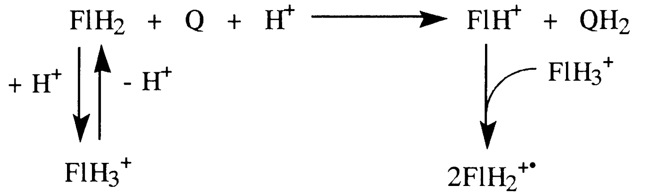
The FlH_2 was prepared by the reduction of riboflavin-2',3',4',5'-tetraacetate (Fl) by sodium dithionite according to the literature.[9] Upon mixing FlH_2 (1.0×10^{-4} mol dm^{-3}) and *p*-benzoquinone (Q; 5.0×10^{-5} mol dm^{-3}) in the presence of $HClO_4$ (1.5×10^{-2} mol dm^{-3}) in deaerated MeCN, the two-electron reduction of Q to hydroquinone (QH_2) occurs accompanied by the one-electron oxidation of FlH_2 to the radical cation ($FlH_2^{+\bullet}$). The stoichiometry was determined by the spectral titration as given by Eq. 1. The electronic spectrum of $FlH_2^{+\bullet}$ (λ_{max} = 504 nm) formed in the reaction of FlH_2 with *p*-benzoquinone is shown in Fig. 1.



FlH_2

$$2FlH_2 + Q + 2H^+ \longrightarrow 2FlH_2^{+\bullet} + QH_2 \qquad (1)$$

The $FlH_2^{+\bullet}$ thus formed was very stable and no apparent decay was observed in 7 days. In the presence of slight excess $HClO_4$, FlH_2 is protonated to FlH_3^+ in MeCN as shown in Fig. 1. The reducing ability of FlH_3^+ is decreased significantly as compared to FlH_2, judging from the more positive one-electron oxidation potential of FlH_3^+ than that of FlH_2.10) Thus, the unprotonated FlH_2 that is in equilibrium with FlH_3^+ may reduce Q to QH_2, accompanied by the oxidation of FlH_2 to FlH^+ (Scheme 1). It is well known that FlH^+ is readily converted to $FlH_2^{+\bullet}$ by the facile comproportionation reaction with FlH_3^+ in the presence of $HClO_4$ in MeCN (Scheme 1).2,3,11)



Scheme 1.

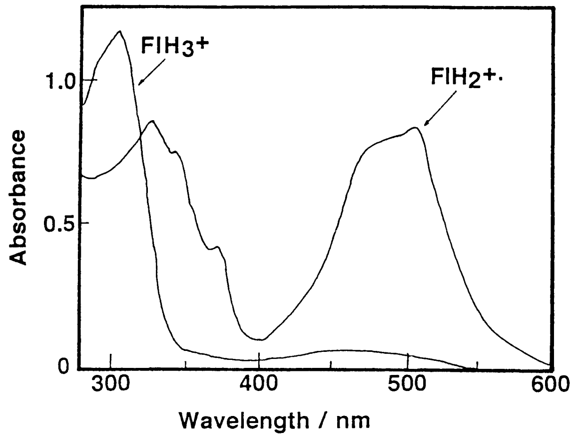


Fig. 1. Electronic spectra observed before and after the addition of *p*-benzoquinone (5.0×10^{-5} mol dm^{-3}) to FlH_2 (1.0×10^{-4} mol dm^{-3}) in the presence of $HClO_4$ (1.5×10^{-2} mol dm^{-3}) in MeCN at 298 K.

The net reaction in Scheme 1 gives the overall stoichiometry of Eq. 1, where the rate-determining step may be the reaction of FlH_2 with Q. In such a case, the rate of formation of $FlH_2^{+\bullet}$ should obey the second-order kinetics under the experimental conditions that the ratio of initial concentrations of FlH_2 to Q is 2 ($[FlH_2]_0/[Q]_0 = 2$), as given by Eq. 2, where t is reaction time, and $[FlH_2^{+\bullet}]$ and $[FlH_2^{+\bullet}]_\infty$ are the concentration at the reaction time t and the final concentration of $FlH_2^{+\bullet}$, respectively.

$$k_{obsd}\,t = 1/([FlH_2^{+\bullet}]_\infty - [FlH_2^{+\bullet}]) - 1/[FlH_2^{+\bullet}]_\infty \qquad (2)$$

The kinetic formulation of Eq. 2 was confirmed by measuring the rate of formation of $FlH_2^{+\bullet}$ with use of a stopped-flow spectrophotometer. The k_{obsd} values were approximately constant with an increase in $[HClO_4]$ as reported for the acid-catalyzed reduction of Q by 10-methyl-9,10-dihydroacridine ($AcrH_2$),12) since the increase in the reactivity of FlH_2 toward Q with an increase in $[HClO_4]$ may be canceled by the deactivation of FlH_2 due the protonation (Scheme 1). The k_{obsd} values for various quinones in the presence of $HClO_4$ are listed in Table 1, together with the k_{obsd} values in the absence of $HClO_4$.8) The k_{obsd} values in the absence of $HClO_4$ increase with an increase in the E^0_{red} values,13) indicating the significant contribution of the electron transfer process from FlH_2 to Q in the rate-determining step for the overall two-electron reduction of Q.8) The k_{obsd} values in the presence of $HClO_4$ are larger than those in its absence, indicating the efficient acid catalysis on the reduction of Q. However, the difference in the k_{obsd} values decreases with an increase in the E^0_{red} value, since the k_{obsd} values in the presence of $HClO_4$ are rather constant except for anthraquinone. Such constant reactivities of various quinones may be ascribed to the canceling effect such that the stronger oxidant is less activated by acid as reported for the acid-catalyzed electron transfer reduction of Q14) as well as the acid-catalyzed reduction of Q by $AcrH_2$.12)

In the presence of a base, tetramethylammonium hydroxide (Me_4NOH), in deaerated MeCN, the

Table 1. Observed Second-Order Rate Constants k_{obsd} for the Oxidation of FlH_2 by Q in MeCN at 298 K and the One-Electron Reduction Potentials (E^0_{red}) of Q in MeCN

Q	E^0_{red} V *vs.* SCE	k_{obsd} / $dm^3\ mol^{-1}\ s^{-1}$ in the presence of None[b]	$HClO_4$ (9.7×10^{-4} mol dm^{-3})	Me_4NOH (1.0×10^{-3} mol dm^{-3})
Anthraquinone	-0.94	8.3×10^{-2}	1.8×10^3	1.1×10^3
Vitamin K_1	-0.86	8.7[c]	3.4×10^4	6.3×10^4
Tetramethyl-*p*-benzoquinone	-0.84[a]	3.4	5.3×10^4	4.5×10^4
Trimethyl-*p*-benzoquinone	-0.75[a]	5.7×10	6.8×10^4	8.6×10^5
Methyl-*p*-benzoquinone	-0.58[a]	2.3×10^3	6.7×10^4	d)
p-Benzoquinone	-0.50[a]	1.1×10^4	6.3×10^4	d)

a) Taken from Ref. 13. b) Taken from Ref. 8 unless otherwise noted. c) This study. d) Too fast to be determined accurately.

stoichiometry of Eq. 1 is reversed: the one-electron reduction of Q to semiquinone radical anions ($Q^{-\bullet}$) occurs accompanied by the two-electron oxidation of FlH_2 to Fl. The spectral titration in the presence of equivalent amount of OH^- to FlH_2 revealed the stoichiometry as given by Eq. 3, where one-third of Q is reduced to QH_2. The spectral change according to the stoichiometry in Eq. 3 is shown in Fig. 2. The addition of equivalent amount of OH^- to FlH_2 results in the facile deprotonation of FlH_2 to FlH^- as also shown in Fig. 2. When the ratio of OH^- to FlH_2 is larger than 2, only one-electron reduction of Q is observed (Eq. 4). Such a change in the stoichiometry depending on the amount of OH^- can be well explained by Scheme 2. The FlH^- formed by the deprotonation of FlH_2 with OH^- reacts with Q to yield Fl and Q^{2-} in the presence of excess OH^-. The Q^{2-} is converted to $Q^{-\bullet}$ by the comproportionation reaction with Q, resulting in the net one-electron reduction of Q. In the presence of equivalent amount of OH^- to FlH_2, no OH^- is left to deprotonate QH^- and the QH^- is converted to (1/2)QH_2 and $Q^{-\bullet}$ by the reaction with Q.[13]

$$FlH_2 + (3/2)\,Q + OH^- \longrightarrow Fl + Q^{-\bullet} + (1/2)QH_2 + H_2O \qquad (3)$$

The rate of formation of Fl was determined under the experimental conditions that $[Q]_0$, $[OH^-]_0$ >> $[FlH_2]_0$ (3.3×10^{-5} mol dm^{-3}) with use of a

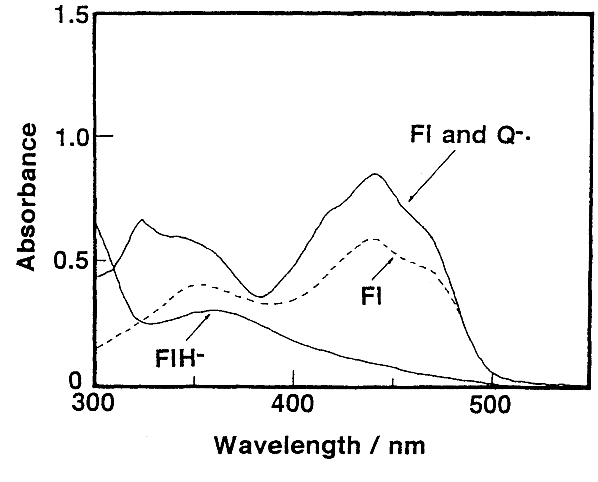
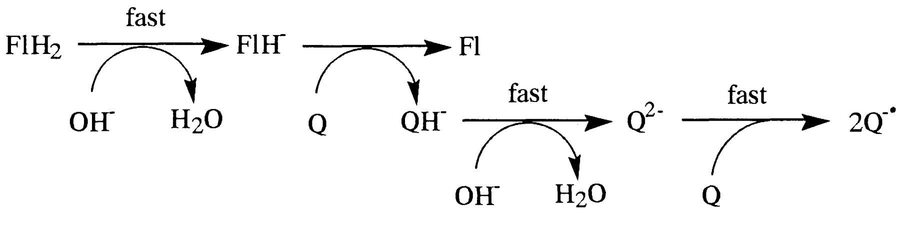


Fig. 2. Electronic spectra observed before and after the addition of *p*-benzoquinone (7.5×10^{-4} mol dm^{-3}) to FlH_2 (5.0×10^{-4} mol dm^{-3}) in the presence of Me_4NOH (5.0×10^{-4} mol dm^{-3}) in MeCN at 298 K.

$$\mathrm{FlH_2} + 2\mathrm{Q} + 2\mathrm{OH^-} \longrightarrow \mathrm{Fl} + 2\mathrm{Q^{-\bullet}} + 2\mathrm{H_2O} \qquad (4)$$



Scheme 2.

stopped-flow spectrophotometer, obeying the first-order dependence on [$\mathrm{FlH_2}$] and [Q]. The observed second-order rate constants (k_{obsd}) were approximately constant with an increase in [$\mathrm{Me_4NOH}$], and the k_{obsd} values are also listed in Table 1. The k_{obsd} value in the presence of $\mathrm{Me_4NOH}$ increases with an increase in the E^0_{red} value in parallel with that in its absence. The approximately 10^4 times larger k_{obsd} values in the presence of $\mathrm{Me_4NOH}$ than those in its absence (Table 1) may be ascribed to the stronger electron-donating ability of $\mathrm{FlH^-}$ as compared to $\mathrm{FlH_2}$ (the one-electron oxidation potentials of $\mathrm{FlH_2}$ and $\mathrm{FlH^-}$ are -0.21 V and -0.36 V *vs.* NHE in $\mathrm{H_2O}$, respectively).[10)]

In conclusion, acid and base catalyze efficiently the redox reactions of $\mathrm{FlH_2}$ and quinones in MeCN, and control the one- and two-electron redox switch.

References

1) C. Walsh, *Acc. Chem. Res.*, **13**, 148 (1980); T. C. Bruice, *ibid.*, **13**, 256 (1980).
2) S. Fukuzumi and T. Tanaka, "Photoinduced Electron Transfer," ed by M. A. Fox and M. Chanon, Elsevier, Amsterdam (1988), Part C, Chap. 11; P. F. Heelis, *Chem. Soc. Rev.*, **11**, 15 (1982).
3) S. Fukuzumi, "Advances in Electron Transfer Chemistry," ed by P. S. Mariano, JAI Press, Greenwich (1992), Vol. 2, pp. 67-175.
4) T. C. Bruice and Y. Yano, *J. Am. Chem. Soc.*, **97**, 5263 (1975); R. F. Williams and T. C. Bruice, *ibid.*, **98**, 7752 (1976); T. C. Bruice and J. P. Taulane, *ibid.*, **98**, 7769 (1976); R. F. Williams, S. Shinkai, and T. C. Bruice, *ibid.*, **99**, 921 (1977).
5) G. Dryhurst, K. M. Kadish, F. Scheller, and R. Renneberg, "Biological Electrochemistry," Academic Press, New York (1982), Vol. 1.
6) C. Eberlein and T. C. Bruice, *J. Am. Chem. Soc.*, **105**, 6685 (1983).
7) M. J. Gibian and A. L. Baumstark, *J. Org. Chem.*, **36**, 1389 (1971); Y. Yano, T. Sakaguchi, and M. Nakazato, *J. Chem. Soc., Perkin Trans. 2*, **1984**, 595.
8) M. Ishikawa, K. Yamamoto, and S. Fukuzumi, *J. Chem. Soc., Chem. Commun.*, **1992**, 1008.
9) C. G. van Schagen and F. Müller, *Helv. Chim. Acta*, **61**, 3139 (1978).
10) O. S. Ksenzhek and S. A. Petrova, *Bioelectrochem. Bioenerg.*, **11**, 105 (1983).
11) K. Ishikawa, S. Fukuzumi, T. Goto, and T. Tanaka, *J. Am. Chem. Soc.*, **112**, 1577 (1990).
12) M. Ishikawa and S. Fukuzumi, *J. Chem. Soc., Faraday Trans.*, **86**, 3531 (1990).
13) S. Fukuzumi, N. Nishizawa, and T. Tanaka, *J. Org. Chem.*, **49**, 3571 (1984).
14) S. Fukuzumi, K. Ishikawa, K. Hironaka, and T. Tanaka, *J. Chem. Soc., Perkin Trans. 2*, **1987**, 751.

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