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Synthesis and electrochemical behavior of clothespin-shaped bisflavin compounds

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Abstract

Clothespin-shaped bisflavin compounds **1** bearing doubly linked 3,3′:10,10′-methylene spacers exhibited significant enhancement of specific association with a variety of neutral aromatic compounds in DMF under electroreduction conditions. This specificity could be rationalized by the 'electric clip motion' of intermediate bis-anion radical species.

Keywords: Bisflavins; Electrochemistry; Molecular clips; Molecular recognition; Supramolecular chemistry

The electrochemical control of non-covalent interactions of molecules has been extensively studied not only for a variety of molecular devices, but also as forward-looking technologies for the creation of molecular machinery.[1] There have been many reports on electrochemical control of host–guest complexation of cationic and anionic species,[2] achieved by the functionalization of conventional host compounds with redox sensitive moieties including transition-metal complexes,[2a–c] quinones,[2d] and tetrathiafulvalenes.[2e] An alternative strategy has been to utilize the electrochemical enhancement of the H-bonding abilities of electron acceptor molecules. When redox-sensitive carbonyl compounds such as quinones,[3a] naphthalenediimide,[3b] and flavins[3c] were employed as H-bonding acceptors, their ability to bind various protic amino compounds increased under electroreduction conditions.

The use of clip- and tweezer-shaped molecules[4] is a powerful strategy for the creation of non-H-bonding molecular recognition systems, containing two cofacial aromatic blades combined with rigid or flexible spacers 7 Å apart. These have been employed as a key component of the systems used for general and specific binding to various aromatic guest compounds. Recently, we found that clothespin-shaped, binuclear palladium compounds bearing two cofacial *trans*-bis(salicylaldiminato)Pd blades underwent rapid, mutual, and consecutive associations when their stable solutions were briefly irradiated with ultrasound.[5] As part of our systematic studies on stimuli-responsive associations, we focused on the redox properties of flavins[6] bearing a common molecular structure. The chemical and electrochemical control of three stationary states of flavins, that is, their oxidized (Fl_{ox}), anion radical ($Fl^{\cdot -}$), and reduced (FlH_2) forms, has been investigated in the context of enzymatic functions[7] and catalytic molecular transformations.[8] The use of flavins for electrochemically controlled association was pioneered by Diederich, who employed flavin-containing macrocyclic compounds as electrochemically flexible cavitands.[9] Bending the planar flavin junction under electroreduction conditions enlarged the host cavities, inducing the association of naphthalene guests in the interior. In this Letter, we describe the synthesis and specific electrochemical association behavior of neutral, 3,3′:10,10′-doubly linked bisflavin molecules **1** (Scheme 1). The 'electric clip'-like motion of the clothespin-shaped, bis-anion radical species was rationalized by these experimental studies.

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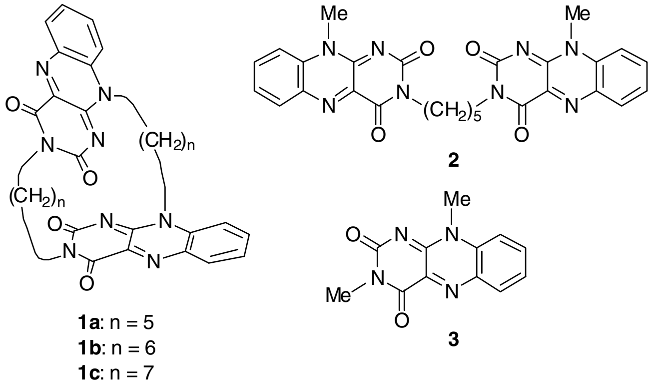


Scheme 1. Mono- and bisflavin compounds **1**–**3**.

A series of bisflavin compounds **1**, in which two neutral flavins were doubly connected by flexible methylene spacers at the 3- and 10-positions (**a**: $n = 5$; **b**: $n = 6$; **c**: $n = 7$), was prepared by the reaction of the corresponding 10,10′-linked bisflavin[8e] with 1,ω-diiodoalkanes in the presence of K_2CO_3 in DMF. These compounds were characterized by ^{1}H, ^{13}C NMR, IR, and high resolution mass spectra.[10] The clothespin-shaped structure of **1a** shown in Figure 1 was unequivocally established by single crystal X-ray diffraction.[11] Fast flipping between the *syn* and *anti* forms of **1a** at room temperature was confirmed using ^{1}H NMR spectroscopy, which showed two broad signals of $N(10)CH_aH_b$ at 4.14 and 5.43 ppm in DMF below their coalescence temperature of 243 K. Activation parameters $\Delta H^\ddagger$ and $\Delta S^\ddagger$ of the averaged flipping motions were determined to be $79 \pm 2\ \text{J mol}^{-1}$ and $151 \pm 10\ \text{J mol}^{-1}\ \text{K}^{-1}$ from Eyring relationship of the flipping rates ($R^2 = 0.991$) estimated by the line-shape method. Inertness in self- association was confirmed in a series of flavin compounds **1**–**3**, based on the concentration independence of all ^{1}H NMR chemical shifts at 298 K in $CDCl_3$. However, a slight low-field shift was observed especially in the H(8) protons ($\Delta = -0.032$ and -0.040 ppm) of **1a** and **3**, when a similar analysis was carried out in DMF-d_7 in the presence of 2-cyanonaphthalene (**4**), showing a weak stacking association of these flavin compounds with electron-deficient aromatic compounds. The equilibrium constants for the association with 2-cyanonaphthalene (**4**) under non-electrochemical conditions were determined to be $2.8\ M^{-1}$ and $3.8\ M^{-1}$ for **1a** and **3**, respectively, by NMR titration experiments in DMF-d_7.

The electrochemical properties of these cyclic bisflavins were examined in UV–vis spectroelectrochemical experiments. As shown in Figure 2, the time-dependent absorbance spectra of a solution of **1a** in DMF during electrolysis under constant potential exhibited hyper- and hypochromic changes at 375 and 445 nm, respectively, with sharp isosbestic points at 390 and 485 nm. Since the absorption maxima at 375 and 478 nm were characteristic of flavin radical anions,[9,12] this profile with clear isosbestic points showed that single radical anion species were formed exclusively during the whole electrolysis process. A reversible single redox wave in the cyclic voltammogram (Fig. 3a) also showed the formation of a sole species under electroreduction conditions. The number of electrons transferred to **1a** under similar conditions was determined to be 1.6 per molecule of **1a** based on the application of Faraday's Law to the coulometric data.[13] These results clearly indicated that bisflavin **1a** underwent two-electron transfer to afford the bis-radical anion species $\mathbf{1a}^{2(\cdot-)}$ without the formation of one electron-reduced species stabilized by the intramolecular donor–acceptor interaction Fl_{ox}–$Fl^{\cdot-}$.

Cyclic voltammetry of **1a** in DMF exhibited a cathodic shift of $E_{1/2}$ (+0.020 V) upon the addition of excess 2-cyanonaphthalene (**4**, 15 equiv), as shown in Figure 3b. Similar shifts were observed with **1a** in the presence of other neutral guest molecules such as 2,3-dicyanonaphthalene (**5**), phthalonitrile (**6**), and naphthalene (**7**) (Table 1). The ratios of association constants under electrochemical and

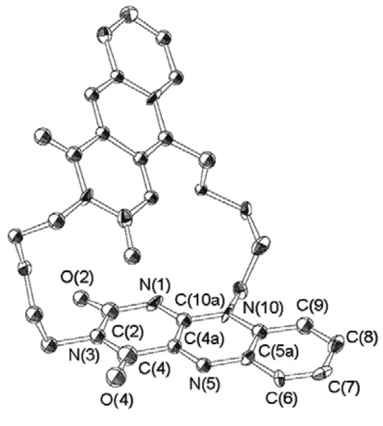


Fig. 1. Molecular structure of **1a**. Thermal ellipsoids are shown at 50% probability level. Selected bond angles (°): N(1)–C(10a), 1.307(3); O(2)–C(2), 1.221(3); O(4)–C(4), 1.219(3), N(5)–C(4a), 1.298(3); N(10)–C(10a)–N(1)–C(2), 177.7(4); C(6)–C(5a)–N(5)–C(4a), 178.6(9).

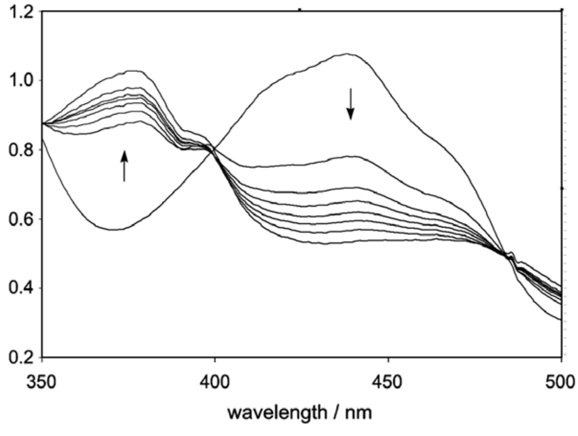


Fig. 2. Time-dependent UV–vis spectra of a 0.66 mM solution of **1a** in DMF under electroreduction conditions (0.1 M TBAP, applied potential −1.2 V vs Ag/AgCl). Data acquisition was continued until saturation of the absorbance change (0–1050 s, 150 s intervals).

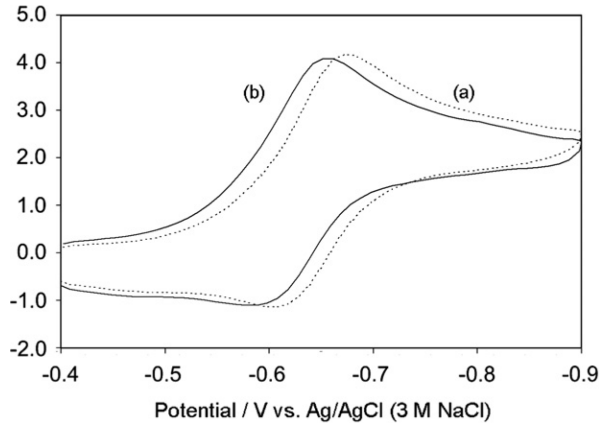


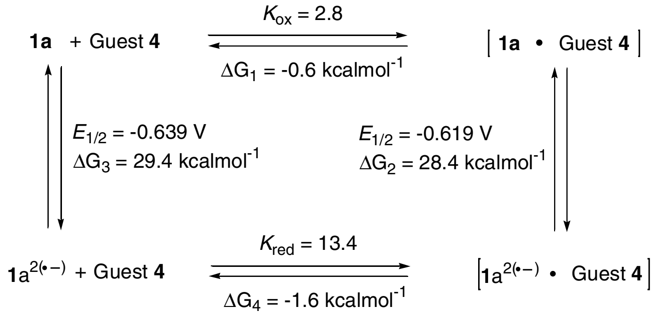
Fig. 3. CV traces of a 0.4 mM solution of **1a** in DMF, recorded in the absence (a) and in the presence (b) of **4** (6 mM) (0.1 M TBAP, sweep rate = 0.1 V s^{-1}).

Table 1
Electrochemical data and ratios of binding constants for **1a** with neutral guest molecules **4**–**7**

Guest	$E_{1/2}$[a] (V)	$\Delta E_{1/2}$ (V)	K_{red}/K_{ox}
None	−0.639	—	—
4	−0.619	+0.020	4.8
5	−0.604	+0.035	15
6	−0.625	+0.014	2.9
7	−0.624	+0.015	3.2

[a] Half-wave potential of **1a** obtained at 298 K in DMF with guest molecules (0.1 M TBAP).

non-electrochemical conditions, K_{red}/K_{ox}, were estimated to be 4.8 (**1a·4**), 15 (**1a·5**), 2.9 (**1a·6**) and 3.2 (**1a·7**) from the equation $(nF/RT)(\Delta E_{1/2}) = \ln(K_{red}/K_{ox})$, which has been used in various redox-switchable association systems.[14] The K_{red} value for the association of **1a** with **4** was calculated to be 13.4 M^{-1} based on the value for K_{ox} (2.8 M^{-1}) estimated from the aforementioned ^1H NMR analysis. The thermodynamic relationships for the switching association of **1a** with **4** are shown in Scheme 2. Cyclic bisflavin **1b** ($n = 6$) also underwent a positive shift of 0.021 V upon the addition of excess **4**, while no change was observed in the half-wave potentials of other flavin compounds such as bisflavin **2** and monoflavin **3.**



Scheme 2. Thermodynamic cycle for the redox-switched association of **1a** with **4**.

The specific electrochemical association behaviors observed for **1** meant that this phenomenon required two flavin blades with two spacers of appropriate position and length. Given the fact that bisflavin **1a** afforded the corresponding bis-radical anion species exclusively under electroreduction conditions, it was entirely reasonable to conclude that this redox-responsive association proceeded via clipping of planar guest molecules between the two anion radical blades due to strong donor–acceptor interactions. Molecular modeling of **1a** showed that the two methylene spacers enabled reliable and smooth opening and closing of the two flavin blades with a minimum of structural deviation. Also, bisflavin **1a** was able to adopt a conformation including a 7 Å cavity for the complexation of guest compounds with minimal steric congestion when the two blades were parallel. These structural features of **1** led to the at-present rare phenomenon of redox-controlled association. Efforts are currently underway to create new, efficient electric molecular clips based on the redox properties of flavin moieties.

Acknowledgment

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.02.122.

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10. *Selected characterization data for* **1a**: IR (KBr) 1669 (C=O, s), 1557 (s), 1273 (s), 775 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.62–1.63 (m, 4H), 1.68–1.73 (m, 4H), 1.93 (tt, $J = 7.8$, 7.8 Hz, 4H), 3.70 (t, $J = 6.0$ Hz, 4H, N(3)CH_2), 4.73 (br, 4H, N(10)CH_2), 7.64 (ddd, $J = 8.2$, 7.2, 1.1 Hz, 2H, H(7)), 7.65 (br dd, $J = 8.8$ Hz, 2H, H(9)), 7.91 (ddd, $J = 8.8$, 7.2, 1.5 Hz, 2H, H(8)), 8.35 (ddd, $J = 8.2$, 1.5, 0.4 Hz, 2H, H(6)); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 23.5, 26.9, 27.9, 41.1, 114.9, 126.0, 132.5, 133.6, 135.0, 135.9, 137.6, 149.2, 159.6, 161.5; HRMS (FAB) calcd for $C_{30}H_{28}O_4N_8$ [M+H^{+}] 565.2312, found 565.2233.
11. Crystallographic data for **1a**·$CHCl_3$: $C_{31}H_{29}Cl_3N_8O_4$, $M = 683.97$, orthorhombic, $a = 7.908(3)$, $b = 14.055(6)$, $c = 27.430(1)$ Å, $U = 3049.61(2)$ Å^3, $T = 120$ K, space group $P2_12_12_1$ (no. 19), $Z = 4$, $D_{\text{calcd}} = 1.490\ \text{g cm}^{-3}$, $\mu(\text{Mo K}\alpha) = 0.354\ \text{mm}^{-1}$, 57,439 reflections collected, 6913 unique [$R(\text{int}) = 0.1439$] which were used in all calculations, final $R_1 = 0.0548$ and $wR_2 = 0.0693$ for all data. CCDC 667070 contains the supplementary crystallographic data. This data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.
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