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Aromatic Stacking Interactions in Flavin Model Systems

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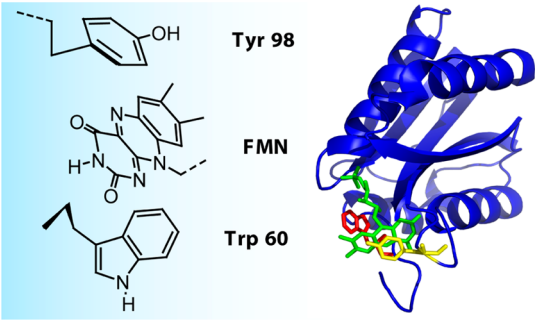
CONSPECTUS

Flavins feature multiple attributes that explain their widespread occurrence in nature, including photostability, reversible electrochemistry, and especially the tunability of their optical, electronic, and redox properties by supramolecular interactions and modification of their chemical structure. Flavins are important redox cofactors for enzymatic catalysis and are central to a wide variety of processes, including biosynthesis, electron transport, photosynthesis, and DNA repair. The wide range of processes catalyzed by flavins makes them promising leads for synthetic catalysts. Their properties are also relevant to organic electronic and optoelectronic devices, where they have the potential to serve as photoactive electron carriers, a very uncommon property in current photovoltaic systems.



In flavoenzymes, the flavin cofactor binds to the active site of the apoenzyme through noncovalent interactions. These interactions regulate cofactor recognition and tune the redox behavior of the flavin cofactor. In this Account, we describe the creation of host–guest systems based on small molecule, polymer, and nanoparticle scaffolds that explore the role of aromatic stacking on the redox properties of the flavin and provide insight into flavoenzyme function. We also describe the creation of synthetic flavin-based interlocked structures featuring aromatic stacking interactions, along with the use of aromatic stacking to direct self-assembly of flavin-based materials.

The interplay between redox events and aromatic stacking interactions seen in these synthetic models is important for fundamental understanding of biological systems including the flavoenzymes. The precise control of aromatic interactions and binding of flavins not only underpins their biological activity but gives them the potential to be developed into novel organic optoelectronic materials based on tuned synthetic flavin–receptor assemblies. In a broader context, the redox properties of the flavin provide a very concise tool for looking at the role of electronics in aromatic stacking, an issue of general importance in biological and supramolecular chemistry.

1. Introduction

The interplay between redox processes and molecular recognition is a central theme in many different biological systems.[1,2] Flavoenzymes are considered an important class of proteins due to their involvement in biological processes such as redox transformations, electron transfer, and signal transduction.[3] The flavin cofactors (e.g., riboflavin, FMN, or FAD; Figure 1) of flavoenzymes are usually bound to the active site of the apoenzyme via noncovalent interactions that modulate the redox properties of the flavin cofactor[2] and thus control the overall catalytic activity of the enzyme.[4]

Flavin model systems that replicate structural and functional aspects of flavoenzymes serve as model systems for probing the role of recognition events on redox processes. Clearly, construction of an artificial enzyme that effectively simulates the structure and reactivity of the prototype flavoenzyme requires a detailed understanding of how

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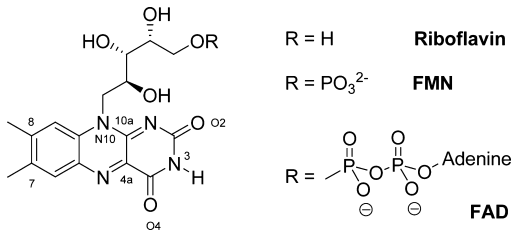


FIGURE 1. Structures of riboflavin, FMN, and FAD.

noncovalent interactions tune the properties of the flavin cofactor. This understanding can also be applied to man-made systems: the interdependence of redox events and molecular recognition is a fundamental aspect of redox enzymes including flavoenzymes and has been applied to the development of synthetic systems, molecular shuttles,[5] switches,[6] wires,[7] and logic gates.[8]

Aromatic stacking interactions[9] play a dual role in flavoenzyme function, providing efficient recognition of the flavin cofactor, and serving to modulate its reactivity.[10] This Account presents a summary of flavin model systems that probe the effect of aromatic stacking interactions on the redox behavior of flavin. The results of these studies provide insight into the role of aromatic stacking in flavoenzymes and provide new directions in the creation of flavin-based materials.

2. Aromatic Stacking in Solution

X-ray crystallographic studies indicate aromatic stacking interactions between aromatic side chain residues of flavoenzymes and the noncovalently bound flavin. For example, the FMN of the flavodoxin isolated from *Desulfovibrio vulgaris* is sandwiched between a tryptophan and a tyrosine.[11] These aromatic residues play an important role in modulating the redox properties of the flavin unit. However, it is difficult to decouple the many noncovalent interactions present in the flavoenzyme, making synthetic models effective tools for exploring the properties of these noncovalent interactions.

2.1. Hydrogen Bonding (H-Bonding) versus Aromatic Stacking. In initial model studies of the aromatic stacking in flavoenzymes, xanthene-based model systems (**1a**–**e**) were developed whereby a diaminotriazine (DAT) moiety orients the flavin over an aromatic surface through H-bonding interactions (Figure 2).[12] The modular receptor design allowed the aromatic surface to be varied parametrically while H-bonding interactions were kept constant, thereby allowing systematic probing of the effect of different aromatic moieties on flavin redox properties.

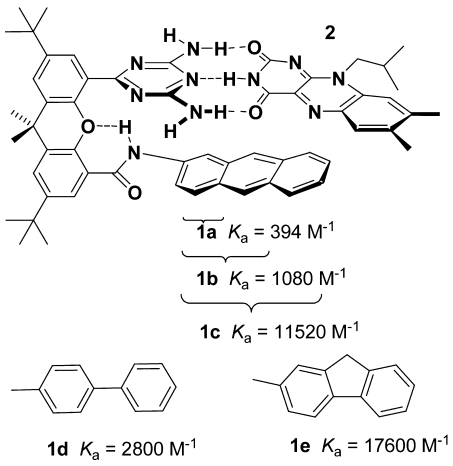


FIGURE 2. Schematic representation of flavin binding to xanthene receptors **1a**–**e**.

Stacking interactions between the receptors **1a**–**e** and flavin **2** in nonpolar solvents (CH_2Cl_2 and $CDCl_3$, chosen for their electrochemical and NMR properties, respectively) were verified using fluorescence quenching experiments. While little quenching of the fluorescence of **2** was observed for the phenyl system **1a**, near complete quenching occurred with anthracenyl system **1c**. Further evidence for aromatic stacking interactions between these receptors and the flavin unit was observed using ^{1}H NMR titration experiments. A substantial increase in binding energy and association constant (K_a) was observed for those receptors offering maximum π-overlap with the flavin moiety. For example, there was a significant 2.1 kcal/mol difference in the binding efficiency of the flavin derivative **2** with **1a** ($K_a = 394\ M^{-1}$) compared with **1e** ($K_a = 17600\ M^{-1}$). Cyclic voltammetry measurements performed on the flavin alone and in the presence of receptors **1a**–**e** revealed an increasingly negative reduction potential for the flavin unit as the extent of π-orbital overlap increases in the host–guest complexes, with receptor **1e** generating a −91 mV shift in the reduction potential of the flavin unit relative to receptor **1a** where no aromatic overlap occurs. Thus, electrochemical data demonstrate that host–guest complexation is more favorable when the flavin is in its oxidized state than when it is reduced to its radical anion state, presumably due to less favorable electrostatic interactions with reduced flavin.

The redox "turn-off" of aromatic stacking was used to create a solution-phase device. Receptor **1c** was used to fabricate a three-component molecular switch with compound **3** (diamidopyridine) and related naphthalimide **4** (Figure 3).[13] In this study, the differing roles that H-bonding and π-stacking interactions play in the stabilization of the

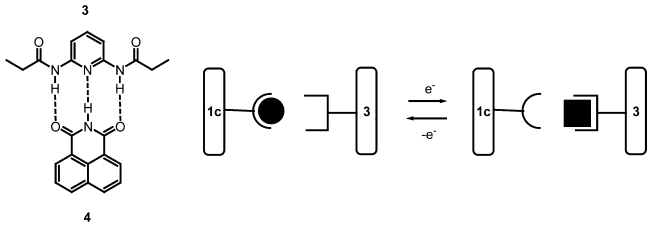
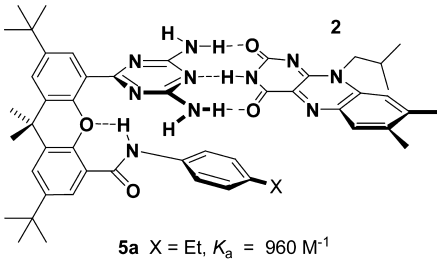


FIGURE 3. Structures of receptors **3** and **4** and a schematic representation of the three-component switch formed with **1c**.

radical anion state of **4** were exploited to fabricate a two-pole, three-component switch. Previous work revealed that H-bonding interactions stabilize[14] and aromatic stacking destabilizes complexes with the flavin radical anion. Both receptors **3** and **1c** were shown to form three-point hydrogen bond interactions with the imide **4**. However, receptor **1c**, due to the additional aromatic stacking interactions, forms a 10-fold stronger complex with compound **4** than **3** forms. ^{1}H NMR spectroscopy revealed that the addition of compound **4** to a binary mixture of **1c** and **3** in $CDCl_3$ resulted in complexation with **1c** only. Simultaneous electrochemistry and EPR (SEEPR) measurements showed that the reduced state, $\mathbf{4}^{\bullet-}$, has a significantly stronger binding preference to receptor **3** than to **1c** in an equimolar mixture of the three species. Therefore, the electrochemical conversion of **4** to $\mathbf{4}^{\bullet-}$ results in the disruption of complex $\mathbf{1c}\cdot\mathbf{4}$ due to the onset of unfavorable electrostatic interactions between the radical anion state of **4** and the electron-rich anthracene moiety and the formation of a new complex, $\mathbf{3}\cdot\mathbf{4}^{\bullet-}$, due to more favorable redox-controlled H-bonding interactions.

2.2. The Donor Atom$-\pi$ Interaction. A frequently encountered motif in the crystal structures of flavoenzymes is the positioning of an electron-rich moiety (e.g., hydroxyl moieties of tyrosine residues, protein carbonyl oxygen atoms, and disulfides) adjacent to the electron-deficient flavin nucleus.[11] DFT calculations undertaken on flavin **2** and its radical anion form $\mathbf{2}^{\bullet-}$ suggested that **2** possesses significant positive electrostatic potential adjacent to the C(4a)−C(10a) ring junction that should interact favorably with appropriately positioned electron-rich donor atoms.[15] Conversely, $\mathbf{2}^{\bullet-}$ has significant negative potentials in this region and as a consequence would not interact significantly with donor atoms. It was postulated that the loss of favorable interactions on going from **2** to $\mathbf{2}^{\bullet-}$ would result in significant negative perturbation of the flavin reduction potential. Experimental demonstration of this effect was obtained using xanthene-based receptors **5a**−**d** (Figure 4).[16] Other interactions (e.g., H-bonding) were kept constant to determine the specific role played by each donor substituent.



5a X = Et, K_a = 960 M^{-1}

5b X = F, K_a = 2900 M^{-1}

5c X = OMe, K_a = 2200 M^{-1}

5d X = SMe, K_a = 4800 M^{-1}

FIGURE 4. Receptors for probing donor atom$-\pi$ interactions.

^{1}H NMR and fluorescence titrations in nonpolar solvents ($CDCl_3$ and CH_2Cl_2) revealed that the presence of a donor atom resulted in a substantial increase in association constant for the complex compared with control receptor **5a**. Thiomethyl-functionalized receptor **5d** displayed the most significant increase in association constant, which was attributed to size and polarizability of the sulfur atom. Cyclic voltammetry experiments indicated that receptors with appropriately located donor atoms gave rise to significantly more negative shifts in half-wave potentials than control receptors. Thus, the generation of the flavin radical anion species greatly reduces the favorable donor atom$-\pi$ interactions featured in the complexes prior to reduction.

2.3. Redox Stabilization versus Aromatic Stacking. In the aforementioned examples, the DAT moiety was used to provide H-bonding to the imide moiety of the flavin. However, this unit provides less stabilization of the flavin radical anion state than the diamidopyridine (DAP) moiety. To assess the interplay of H-bonding and aromatic stacking, a new class of receptors (**6a**−**c**) were synthesized that featured the DAP moiety to allow comparison with the analogously functionalized DAT-based receptors (Figure 5).[17] The association constants for receptors **6a**−**c** displayed the same trends as their DAT-based brethren **1c**, **5d**, and **1a**, respectively. However, the magnitude of the observed changes were approximately two thirds as strong.

With host−guest complexation verified, cyclic voltammetry was used to show that receptors **6a**−**c** displayed significant binding enhancement relative to DAT analogs when the flavin was in its radical anion state. When the flavin is in its neutral state, all noncovalent interactions promote binding to the receptors. However, upon reducing the flavin to its electron-rich radical anion state, π-stacking interactions become less favorable, and recognition is

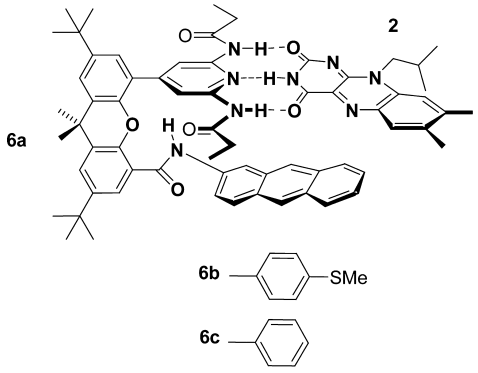
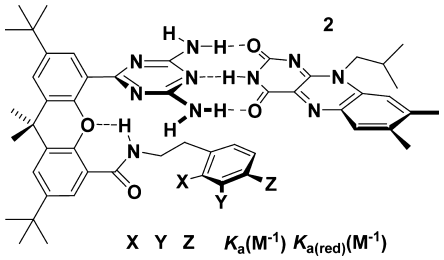


FIGURE 5. Receptors for probing the interplay of aromatic stacking and H-bonding.



	X	Y	Z	$K_a(M^{-1})$	$K_{a(red)}(M^{-1})$
7a	H	H	H	920	1839
7b	F	H	H	690	966
7c	H	F	H	1270	2761
7d	H	H	F	1920	3330

FIGURE 6. Receptors for exploring dipolar effects on aromatic stacking.

therefore dominated by H-bonding interactions. In this study, the DAP unit of receptors **6a**–**c** allowed significant enhancement of binding to the flavin radical anion that outweighed the concomitant onset of repulsion between the flavin radical anion and the π-system.

In a related study, xanthene model systems **7a**–**d** were prepared to study interactions of dipole-containing aromatic moieties with flavin **2** in its neutral and reduced states (Figure 6).[18] In particular, this receptor design allowed direct control of the orientation of polar aromatic groups in relation to the flavin nucleus. *Ab initio* calculations performed on the complexes (neutral and reduced) predicted that when the flavin was in its neutral state, the stability of the complexes increased on going from the *ortho* to the *para* functionalized aromatic system. Upon reduction of the flavin unit, similar trends were predicted with pronounced repulsion observed in the dyad $\mathbf{2}_{(red)}\cdot\mathbf{7b}$ resulting in lateral motion of the phenyl ring of **7b** to a nonbinding position. The loss of aromatic stacking was also observed for the receptors **7c** and **7d**; however, the *para*- substituted receptor complex gained stability through edge-to-face interactions.

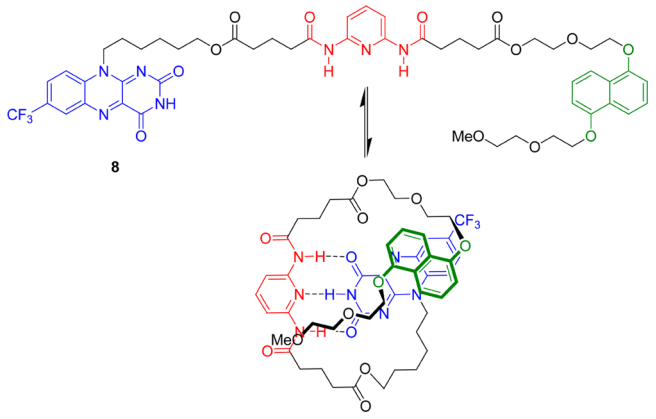


FIGURE 7. Structure of **8** and its proposed intramolecular complexation.

Association constants confirmed the predicted increase in binding efficiency on going from the *ortho*- to *para*-functionalized receptors for the neutral flavin. Cyclic voltammetry measurements were used to determine the association constants for the reduced flavins, which displayed the same geometry dependency for fluorine substitution.

2.4. Intramolecular H-Bonding and π-Stacking Interactions. So far we have been discussing intermolecular interactions of the flavins in solution. Intramolecular interactions can also occur, as seen in flavin-containing compound **8** featuring the H-bonding DAP moiety and an electron-rich naphthalene unit designed to undergo intramolecular self-assembly through H-bonding[19] and π-stacking interactions (Figure 7).[20] ^{1}H NMR spectroscopy performed in $CDCl_3$ revealed significant downfield shifts of the imide hydrogen of the flavin moiety, indicating H-bonding interactions between the flavin and the DAP. This interaction was also corroborated through cyclic voltammetry experiments, with a positive shift in half-wave potential of the flavin following stabilization of the radical anion through H-bonding. Furthermore, upfield shifts in the aromatic signals suggested that face-to-face stacking interactions occur simultaneously between the flavin and the naphthalene units. Nuclear Overhauser effect spectroscopy (NOESY) indicated intramolecular complexation via the presence of long-range couplings between the flavin moiety and the naphthalene unit.

2.5. Combined Metal-Augmented π-Stacking and H-Bonding Interactions. The binding of DAP-functionalized porphyrins **9a**,**b**[21] (Figure 8) to flavin **2** through a combination of π-stacking and H-bonding interactions was investigated.[22] ^{1}H NMR titration data for both porphyrin receptors revealed significant downfield (imide) and upfield (aromatic) shifts, suggesting simultaneous H-bonding and π-stacking interactions. Interestingly, the presence of the coordinated

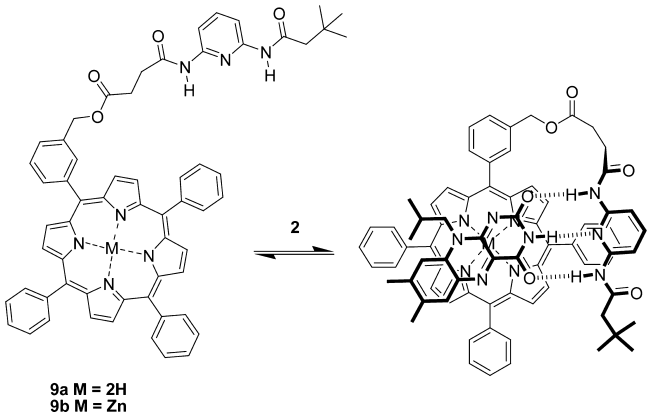


FIGURE 8. Structures of porphyrin receptors **9a**,**b** and their proposed complexes with flavin **2**.

Zn atom resulted in a significant lowering of the association constant (**9a**·**2** $K_a = 2400\ M^{-1}$, **9b**·**2** $K_a = 1500\ M^{-1}$). Cyclic voltammetry measurements revealed a larger positive shift in half-wave potential for the addition of receptor **9b** to a solution of **2** compared with **9a**, presumably due to the presence of the Zn atom destabilizing aromatic stacking interactions. In both cases, the shift in redox potential was less than that observed for the DAP systems that do not contain porphyrin moieties (e.g., **3**); further enforcing the destabilizing effect of aromatic stacking interactions with reduced flavins.

2.6. Interlocked Structures. Flavin-incorporating rotaxane **10**[23] and catenane **11**[24] have been synthesized in attempts to create new flavin-based molecular machines (Figure 9), where aromatic stacking potentially could be one of the interactions used to drive their mechanical behavior.[25] These mechanically interlocked structures feature a *p*-xylylene-based wheel as one of the components. X-ray crystallography has shown that this macrocycle preferentially resides over the succinamide moiety of the flavin-containing portion of the interlocked structure in the solid state. This is largely a consequence of H-bonding interactions between the amide groups of the smaller macrocycle and carbonyl moieties of the succinamide group of the flavin-based component.[26] ^{1}H NMR spectra recorded in $CDCl_3$ indicated that the *p*-xylylene-based macrocycle also resides over this portion of the flavin-containing component in solution, because significant upfield shifts of the succinamide methylene protons were observed that are presumably due to CH$-\pi$ interactions. However, when spectra of **11** were recorded in more polar solvents (e.g., DMSO-d_6), the smaller macrocycle was shown to reside over the alkyl chain adjacent to the N(10) of the flavin moiety. Interestingly, the X-ray structure of **11** provided evidence for intercatenane

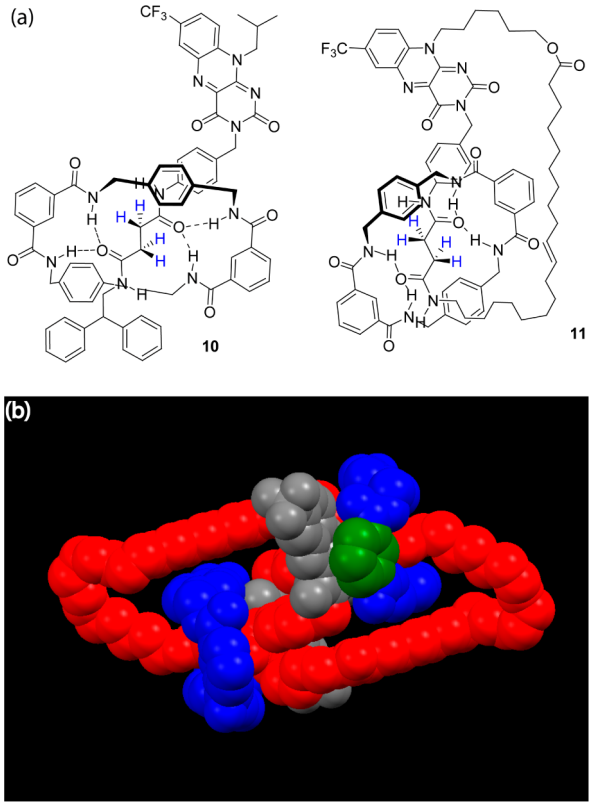


FIGURE 9. (a) Structures of rotaxane **10** and catenane **11** (succinamide methylene hydrogens highlighted in blue). (b) X-ray crystal structure of **11** showing the packing for two catenane units (flavin-based macrocycle highlighted in red and xylylene-based macrocycle highlighted in blue, and the flavin and isophthaloyl units participating in π-stacking interactions highlighted in gray and green, respectively).

$\pi-\pi$ stacking interactions between the flavin and isophthaloyldiamide moieties of adjacent catenane units.

3. π-Stacking Interactions in Sol–Gel and Liquid Crystalline Systems

Complex matrices provide capabilities in terms of model system design not available in solution models while also potentially providing functional materials. To these ends, the recognition and catalysis of the flavin unit was examined within silicate sol–gels where the silicate matrix simultaneously replicated the 2-fold role of isolation and preorganization performed by the protein scaffolding.[27,28] Interestingly, the recognition was greatly enhanced in the sol–gel system compared with the solution phase. Flavin-containing sols were prepared by addition of dilute acid and tetraethyl orthosilicate (TEOS) to an aqueous solution of flavin mononucleotide (FMN; Figure 10).[27] The aromatic stacking interactions were probed by fluorescence emission spectroscopy of the flavin unit. Similar to solution models,[12] increasing quantities of receptor **12a** resulted in

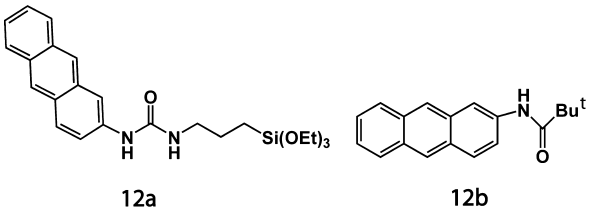
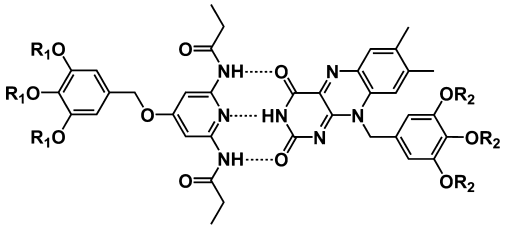


FIGURE 10. Structures of anthracene derivative **12a** and acylated aminoanthracene **12b**.



Dyad	R_1	R_2
13a	$C_{12}H_{25}$	$C_{12}H_{25}$
13b		
13c		$C_{12}H_{25}$
13d	$C_{12}H_{25}$	
13e		

FIGURE 11. Structures of DAP–flavin dyads **13a**–**e** used to form LCs.

decreased flavin fluorescence due to the aromatic stacking between the electron-rich anthracene and the electron-poor flavin. The higher association constant for a FMN–receptor **12a** sol–gel complex ($\sim 200 \pm 50\ M^{-1}$) compared with flavin **2**–acylated aminoanthracene **12b** complex ($<3\ M^{-1}$) in ethanol demonstrated the active role of the silicate matrix in recognition enhancement in the sol–gel systems.

Noncovalent interactions such as aromatic stacking[29] and H-bonding[30] have been used to develop supramolecular liquid crystal (LC) systems. Due to their ability to generate ordered aggregates[31] using H-bonding and π-stacking interactions, DAP–flavin dyads (**13a**–**e**; Figure 11) were synthesized to provide LC systems.[32]

Apart from liquid crystalline systems, aromatic stacking interactions have also been used to assemble nanostructured materials.[33,34] In these assembly strategies, the direction of the dipole–dipole attractions between molecules is critical to control the preferential growth of nanostructures.[35] The control of nanostructure morphology in a flavin derivative was obtained through synergistic aromatic stacking and H-bonding.[36] Self-assembly of ABFL resulted in multimillimeter length nanowires through a combination of H-bonding and aromatic stacking interactions (Figure 12). However, non-H-bonding analog, methylated ABFL (MABFL) generated

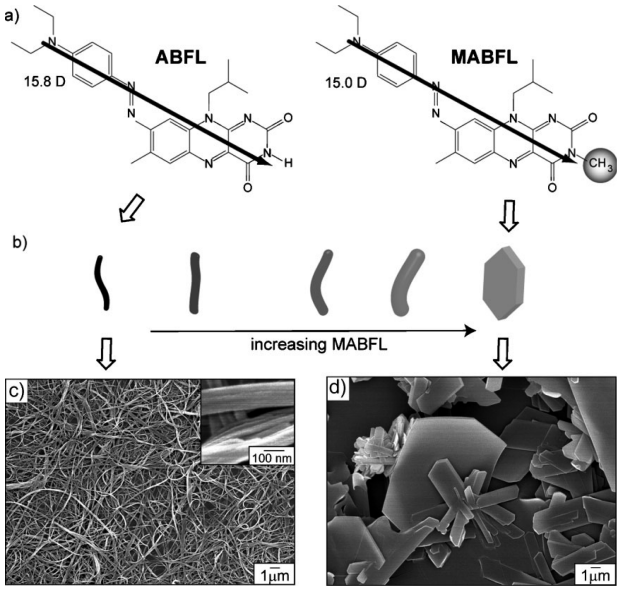


FIGURE 12. (a) Structures of ABFL and MABFL with predicted dipole moments. (b) Schematic depiction of the control of aspect ratio through doping of ABFL with MABFL. SEM micrographs of assemblies formed with (c) ABFL and (d) MABFL. Reprinted with permission from ref 36. Copyright 2008 John Wiley & Sons.

micrometer-sized hexagonal platelets. Incorporation of MABFL into ABFL solutions provided efficient control over nanowire length and diameter due to competitive disruption of the H-bonding within the nanowires.

4. π-Stacking Nanoparticle Surfaces

Nanoparticles can serve as hosts to study multivalent recognition processes.[37] In these systems, the recognition elements on the colloid surface can be controlled during and after particle formation, providing a method for the divergent fabrication of multivalent surfaces.[38] Mixed monolayer protected gold clusters (MMPC) were developed to be capable of multivalent recognition with flavin.[37] MMPC **14a** was functionalized with both H-bonding (DAP) and aromatic stacking (pyrene) elements while MMPC **14b** was functionalized with only H-bonding moieties (Figure 13). The association constant of MMPC **14a**–flavin **2** was nearly twice that of MMPC **14b**–flavin, **2** indicating multivalent interactions further promoted the recognition.

MMPC–flavin binding was used to template preorganized binding sites on the nanoparticle surface. MMPC **14c** (Figure 13), a trifunctional system with H-bonding and aromatic stacking recognition elements diluted into an octanethiol supporting monolayer was prepared.[39] Chemical shifts of flavin **2** protons in the presence of **14c** were monitored as a function of time. The N(3)H flavin chemical shift in the MMPC **14c**–flavin **2** complex moved smoothly

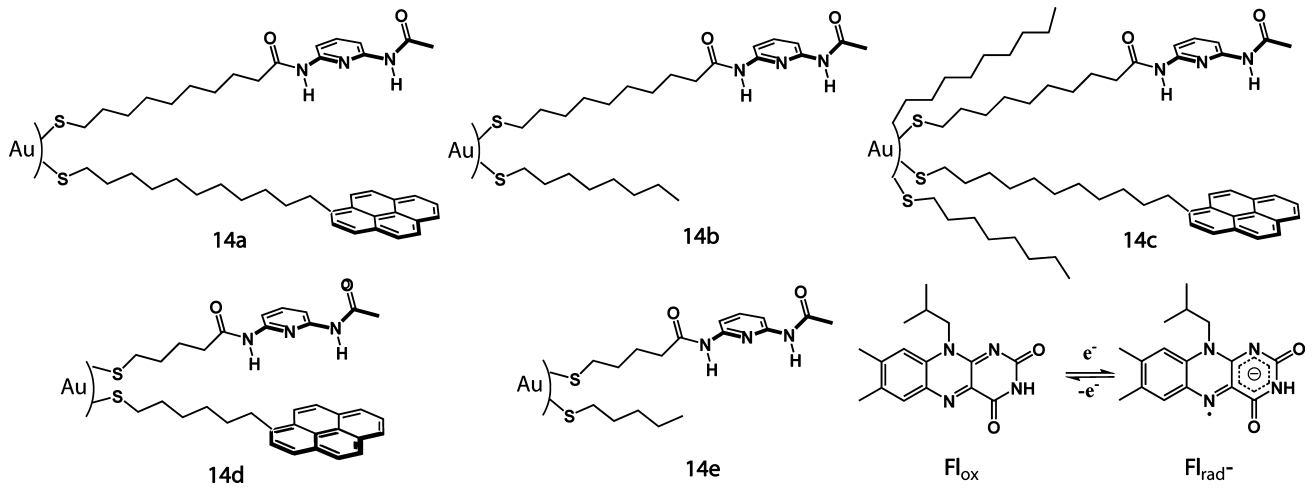


FIGURE 13. Structures of MMPCs **14a**–**e**, Fl_{ox}, and Fl_{rad-} used in this study.

downfield over 24 h, directly correlated to an increase in colloid–flavin recognition. As expected, there was a concomitant upfield shift of the aromatic protons of flavin **2**, indicative of the enhanced aromatic stacking provided by binding site optimization.

Because the monolayer coatings of MMPCs are radial in nature, the monolayer preorganization decreases with increasing distance from the nanoparticle core.[40] The radial structure of MMPC monolayers was used to tune multivalent recognition of flavin.[41] To quantify the radial effect, MMPCs **14a**–**e** were prepared (MMPCs **14d** and **14e**; Figure 13). NMR titration of flavin **2** with MMPCs **14d** and **14e** showed that bifunctional MMPC **14d** bound more strongly than the corresponding monofunctional MMPC **14e** due to π-stacking interactions between flavin **2** and the pyrene side chains. A clear radial effect was observed for the MMPCs **14a** and **14d** when complexed with flavin **2** (Fl_{ox}). The shorter chain MMPC **14d** showed much stronger enhancement in recognition compared with the MMPC **14a**. However, for reduced flavin (Fl_{rad-}), a reverse radial effect was observed. The binding affinity of MMPC **14d** was found to be 7 times lower than that of MMPC **14a**. The decrease in binding was attributed to the unfavorable aromatic stacking interactions between the electron-rich Fl_{rad-} and the electron-rich pyrene units.

5. π-Stacking Interactions with Macromolecular Scaffolds

Peptides provide scaffolds for exploring flavin stacking interactions. A 12-residue β-hairpin peptide **15** (Ac-Arg-Trp-Val-Lys-Val-Asn-Gly-Orn-Trp-Ile-Lys-Gln-NH_2) was synthesized that bound to FMN strongly in water (Figure 14) with stacking provided by the tryptophan residues and lysine

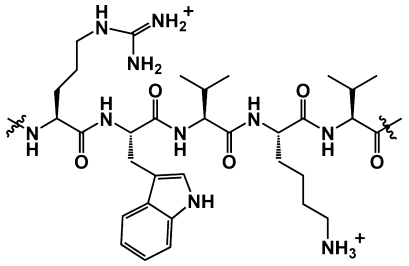


FIGURE 14. Structure of a section of peptide **15** (-Arg-Trp-Val-Lys-Val-).

residues providing electrostatic interactions with the FMN phosphate group. This model demonstrated many of the same features as those observed in the flavoproteins, including modulation of the flavin redox potential.[42] Significantly, these interactions were studied in water, providing a realistic model for protein-mediated flavin interactions.

The titration of peptide **15** with the FMN demonstrated an upfield shift of the flavin aromatic ring protons as well as H-5 protons of tryptophan residues in the NMR spectra, suggesting substantial π-stacking interactions between tryptophan side chains and FMN. In addition, quenching of the FMN fluorescence upon titration with peptide **15** also denoted a strong interaction ($K_a = 2200\ M^{-1}$) between FMN and peptide **15** in water, with weaker binding ($K_a = 350\ M^{-1}$) observed with riboflavin due to the absence of electrostatic interactions. Square wave voltammetry measurements showed a shift of the FMN reduction potentials to more negative values with increasing peptide concentration, confirming the influence of aromatic interactions on the reduction potential of flavin.

Polymeric scaffolds have been used to observe the multivalent recognition of flavin derivatives.[43] Copolymers **16a** and **16b** were functionalized with DAP and anthracene moieties, respectively. Reaction of the monofunctionalized

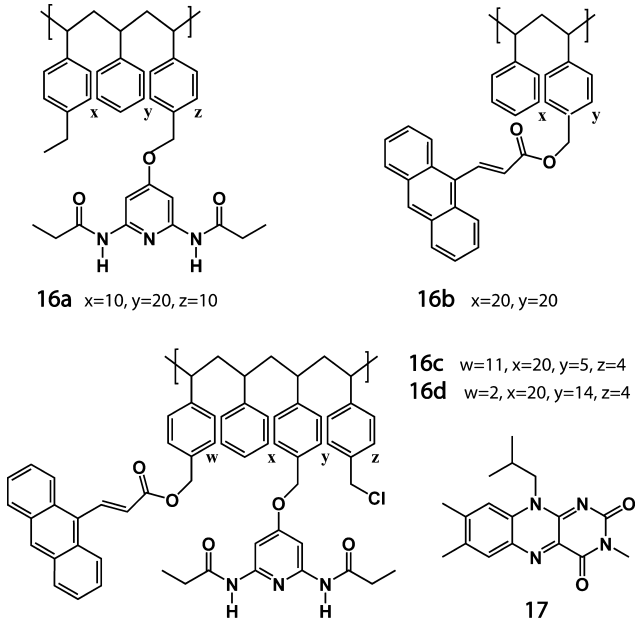


FIGURE 15. Structures of polymers **16a**–**d** and *N*-methyl flavin **17**.

polymers provided multi-functionalized polymers **16c** and **16d** (Figure 15). Fluorescence titration of the flavin **2** with the DAP-functionalized polymer **16a** showed strong interactions (K_a = 300 M^{-1}), while *N*-methyl flavin **17** showed almost no quenching ($K_a \approx 10\ M^{-1}$). However, titrations of both flavins **2** and **17** in the presence of the anthracene-functionalized polymer **16b** showed similar quenching behavior. Upon addition of increasing concentration of **16b**, the fluorescence of flavins **2** and **17** was quenched with both systems exhibiting a $K_a = 500\ M^{-1}$. The fluorescence behavior of flavin **2** and **17** with polymer **16a** and **16b** demonstrated that while hydrogen bonding is critical for quenching the fluorescence, the non-specific π interactions also provide favorable contribution to the total binding. Similar recognition behavior was demonstrated in fluorescence titrations of polyfunctional polymers **16c** and **16d** with flavin **2**. The increased anthracene concentration in polymer **16c** (K_a = 1050 M^{-1}) gave rise to a ~5-fold increase in binding efficiency of flavin **2** in comparison to polymer **16d** ($K_a = 250\ M^{-1}$).

Dendritic scaffolds have been reported to encapsulate flavin derivatives and tune their electrochemical behavior.[44] Dendrons functionalized with the DAP unit (**20a**–**c**) were utilized to encapsulate monomeric and polymeric flavins **18** and **19,** respectively (Figure 16a). Fluorescence titration of both flavins **18** and **19** with DAP dendrons showed quenching of the flavin fluorescence. However, the quenching was significantly higher in the polymeric flavin **19** (K_a = 550–700 M^{-1}) compared with the monomeric flavin **18**

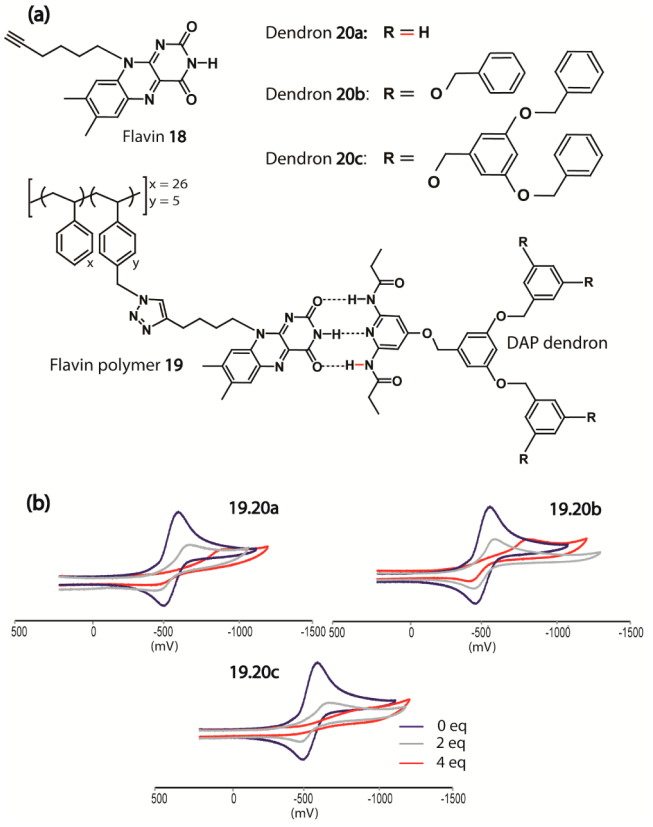


FIGURE 16. (a) Structures of alkyne-functionalized flavin **18** and flavin polymer **19** exhibiting specific three-point H-bonding interactions with complementary dendrons **20a**–**c**. (b) Cyclic voltammetry traces of polymeric flavin **19** exhibiting different flavin redox behaviors in the presence of DAP dendrons **20a**–**c**. Reproduced with permission from ref 44. Copyright 2010 The Royal Society of Chemistry.

(K_a = 400 M^{-1}). The enhanced binding affinity was attributed to the cooperative noncovalent interactions including H-bonding and aromatic stacking within the polymeric–dendritic supramolecular complex.

The redox behavior of the monomeric flavin **18** showed fully reversible electrochemical behavior in the presence of the DAP dendrons consistent with previous flavin model systems.[45] However, the polymer flavin **19** exhibited distinctly different electrochemical kinetics with increasing generations of the DAP dendrons. The peak current was found to be significantly smaller and broader for each corresponding dendrimer generation, indicating a decrease in rate of electron transfer as a function of the dendrimer size (Figure 16b). The broadening of the peak and the decrease in the current indicated the isolation of appended flavins from outside interfering species.

Dendron architectures[46] have been used to generate synthetic flavoenzymes providing biomimetic environments.[47] In the dendritic architecture, the catalytic center

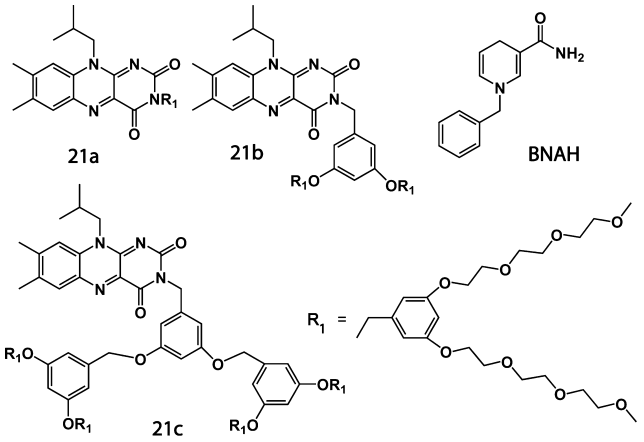


FIGURE 17. Structures of the flavin dendrons (**21a**–**c**) and BNAH.

(the flavin residue) was introduced at the focal point of the dendron to provide a substrate-accessible biomimetic hydrophobic pocket around the active site (Figure 17). Fluorescence of the flavin dendrons (**21a**–**c**) was significantly quenched due to aromatic interactions between the flavin and the aromatic units of the dendron. The catalytic activity of the flavin dendrons was also investigated using the aerobic oxidation of BNAH by riboflavin and the flavin dendrons. Relative to riboflavin, a significant increase in catalytic reaction rate was observed in the flavin dendrons that further increased with increasing dendron generations. This acceleration was attributed to the aromatic stacking interactions between the aryl moieties of the dendrons and the reduced form of BNAH.

6. Conclusions

We have developed flavin model systems where synthetic receptors interact with flavin via noncovalent interactions, providing insight into flavoenzyme function. The properties of flavins are also relevant to organic electronic and optoelectronic devices. In particular, while many organic semiconductors are capable of hole transport, electron-transporting materials are much rarer. The electron-deficient nature of flavins makes them candidates for electron-transporting materials for devices such as organic light-emitting diodes, organic field effect transistors, and organic solar cells. These roles would mirror the electron transferases used as electron carriers in photoinduced electron transfer.[48] Flavins are attractive candidates because of their photostability, their reversible electrochemistry, and the scope for tuning their optical, electronic, and redox properties by synthetic manipulation.[49] The ability to tune aromatic-interactions and energy levels is very desirable, and as shown in this Account, can be achieved in many ways. Hence the precise control of aromatic interactions and binding of flavins not only underpins their biological activity but gives them the potential to be developed into novel organic optoelectronic materials.

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Vikas Nandwana received his Ph.D. in Materials Science and Engineering at the University of Texas at Arlington under the guidance of Professor J. Ping Liu. Currently, he is a postdoctoral researcher at the University of Massachusetts at Amherst in Professor Vincent M. Rotello's research group. His research interests include synthesis of semiconducting and magnetic nanoparticles and hybrid photovoltaics.

Ifor Samuel received his Ph.D. at the University of Cambridge, working at the Cavendish Laboratory on optical spectroscopy of organic semiconductors. He was a Research Fellow at Christ's College, Cambridge, and performed postdoctoral work at CNET-France Telecom in Paris. His current position is Professor of Physics and Director of the Organic Semiconductor Centre at the University of St Andrews in Scotland. He is a Fellow of the Royal Society of Edinburgh, the Institute of Physics, and the Royal Society of Chemistry. His current work focuses on the development of organic semiconductors, including their photophysics and device applications.

Graeme Cooke received his Ph.D. from the Department of Chemistry at the University of Durham in 1992 under the guidance of Professor Martin Bryce. Following postdoctoral work at Arizona State University (1992) and the University of East Anglia (1994), he obtained faculty positions at Teesside University (1996), University of Northumbria (1997), and Heriot-Watt University (2000). In 2005, he joined the School of Chemistry at the University of Glasgow and is currently Professor of Physical Organic Chemistry and codirector of the Glasgow Centre for Physical Organic Chemistry. His current research interests include functional polymers and micelles, biomimetic chemistry, organic photovoltaics, and the application of redox umpolung in synthetic, supramolecular, and materials chemistry.

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FOOTNOTES

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The authors declare no competing financial interest.

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