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Published on Web 10/28/2006

Chiral Translation and Cooperative Self-Assembly of Discrete Helical Structures Using Molecular Recognition Dyads

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Abstract: Complementary diaminopyridine (DAP) and flavin derivatives self-assemble into discrete helically stacked tetrads in hydrocarbon solvents. The self-assembled structure was demonstrated through induced circular dichroism using DAPs with chiral side-chains and flavin with achiral side-chains. Flavin derivatives with chiral side-chains were synthesized; cooperativity in the self-assembly was established through circular dichroism (CD) profiles and melting curves. It was found that placing stereocenters in both recognition units resulted in a strong bisignated profile and enhancement of complex stability, indicative of cooperative self-assembly.

Introduction

Molecular self-assembly presents access to ordered aggregates in materials science.[1] Extended self-assemblies provide three-dimensional networks, which have led to the development of materials for sensing,[2] optoelectronic devices,[3] transporting-channels,[4] gels,[5] and nanotube materials,[6] as well as highly versatile liquid crystalline materials.[7] Discrete self-assembly, in contrast, provides monodisperse and well-defined structures displaying useful properties.[8] Examples include molecular capsulation,[9] chiral amplification[10] and memory,[11] and selective

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10.1021/ja064554z CCC: $33.50

ionophores.[12] In many cases, the development of sophisticated self-assembled materials will require reliable methods to control the aggregation.

Chiral translation is ubiquitous in self-assembled materials and provides a tool for characterization of dynamic self-assembled structures. These self-assemblies generally feature helical structures consisting of racemic mixtures of right- and left-handed self-assembled structures. Installation of stereocenters into building blocks give rise to favored handedness of the aggregation, allowing us to modulate chiroptical properties, and thus three-dimensional structures of self-assemblies.[7f,13] Molecular capsulation featuring chiral cavities formed through chiral translation provides a platform for chiral discrimination of a targeted guest molecule,[9] offering novel methodologies for the creation of chiral sensors.[14] Thus, installment of stereocenters in building blocks generates a new strategy toward the control of chiral translation within self-assembled structures. The consequence of the interplay of chiral translation will create frustrated and cooperative systems, provided that the delicate interplay of stereocenters is substantial in the formation of self-assembled structures.

In previous studies, we[15] and others[16] have established specific molecular recognition through three-point hydrogen bonding using diaminopyridine (DAP) and flavin. The DAP−flavin dyad provides an effective platform for the demonstration of chiral translation: specific hydrogen bonding and long wavelength absorption of the flavin should enable us to detect chiral self-assembled structures. Herein, we report the design and characterization of discrete self-assembly of specific hydrogen-bonded dyads based on DAP and flavin (Figure 1a). These systems demonstrate (1) chiral translation to an achiral flavin from a chiral DAP due to the self-assembled structure and (2) the cooperative self-assembly system using chirality in both components of the DAP−flavin dyad. Chiral translation occurs through formation of a discrete tetramolecular complex, as established using light scattering. Induced CD (ICD) of the achiral flavin demonstrates the self-assembly of the complex in a helical sense. Finally, combination of chiral DAPs with the chiral flavin provides insight into the interplay of stereocenters and demonstrates the formation of cooperative and frustrated systems.

Results and Discussion

Synthesis. We prepared three DAP hosts (**1**, **1S**, and **1R**) and flavin guests (**2**, **2S**, and **3**) (Figure 1a) to provide a system for discrete self-assembly. Enantiomerically pure tails, (*S*) and (*R*)-citronellols, were installed in DAP **1S** and **1R**, respectively, to demonstrate chiral translation into the achiral flavin guest **2**, resulting in evidence for discrete self-assembled structures (Figure 1b). Flavin **2S** featuring (*S*)-citronellol was synthesized

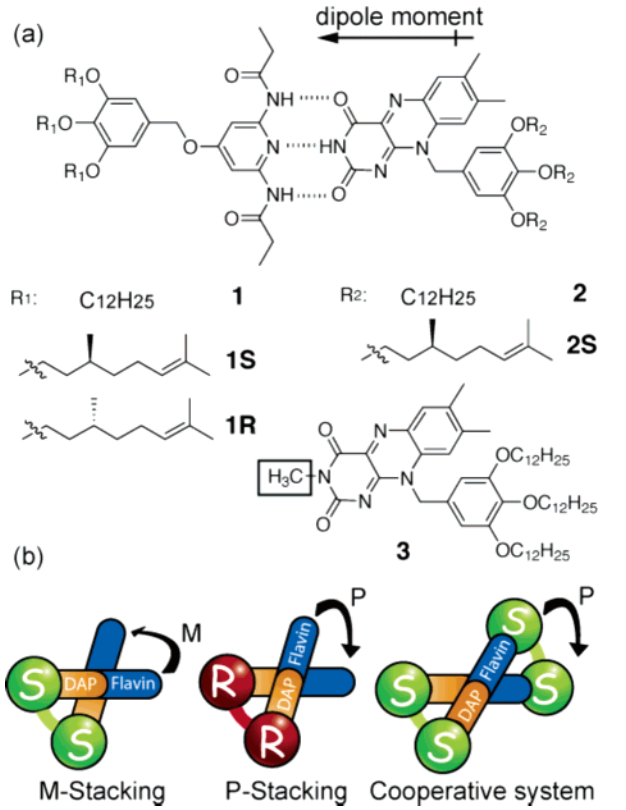

Figure 1. (a) Molecular structures of specific hydrogen-bonding dyad based on diaminopyridine−flavin. (b) Illustrative representation of right-handed (*P*) and left-handed (*M*) stacking structures for the complexes (**1S**−**2**, **1R**−**2**, and **1S**−**2S**); achiral flavin **2** can be CD active due to the formation of self-assembled structure based on biased helical stacking of dyads, and the **1S**−**2S** system provides the cooperative self-assembly.

to demonstrate cooperative assembly in combination with **1S-R**. *N*-Methyl flavin **3** was employed to provide a non-hydrogen-bonding control.

Chiral Translation in Self-Assembled Structures. Binding affinity between **1** and **2** through specific hydrogen bonding was quantified using ^{1}H NMR titration in $CDCl_3$, resulting in an association constant (K_a) of 1050 M^{-1} at 23 °C. CD spectra of achiral flavin **2** with **1S** and **1R** were recorded in a variety of solvents to probe ICD[17] in DAP−flavin systems. No significant Cotton effect was observed in solvents such as toluene and halomethanes (CH_2Cl_2 and $CHCl_3$), where DAP−flavin hydrogen bonding occurs. This lack of ICD indicates that formation of the DAP−flavin dyad does not result in efficient translation of chirality. In contrast, strong ICD was observed in less polar hydrocarbon solvents such as hexanes, cyclohexanes, and dodecane, indicative of the formation of helical self-assembled structures. As expected from the self-assembled nature of these systems, significant temperature dependence of ICD was observed. A 1:1 mixture of DAP **1S** and flavin **2** (**1S**−**2**) showed induced Cotton effect in the range of −10 to 20 °C °C (Figure 2), whereas at elevated temperatures (30−50 °C) the Cotton effect completely disappeared. This dependence was completely thermally reversible (Figure 2a). The consistency and lack of hysteresis of the two curves obtained upon heating and cooling cycles reflect the reversible formation of discrete

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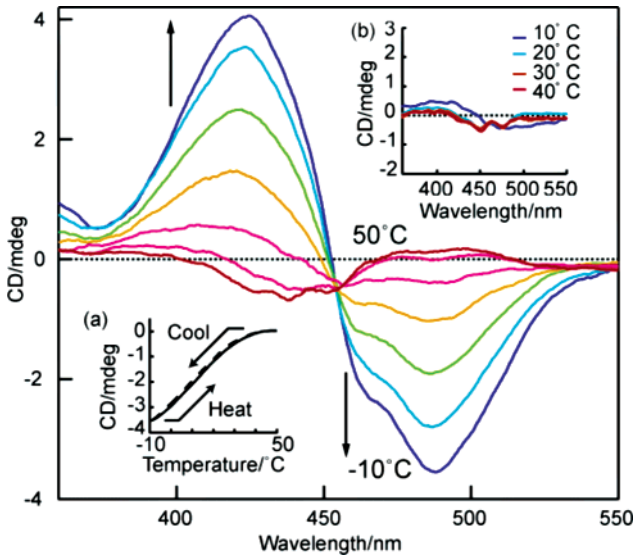

Figure 2. Variable-temperature CD spectra of **1S**−**2** in *n*-hexane (total concentration: 4×10^{-4} M, −10 to 50 °C, 10 mm path). Inset (a) shows the reversibility of the Cotton effect at 490 nm upon temperature control between −10 and 50 °C. Arrows indicate changes upon decreasing temperature. Inset (b) shows variable-temperature CD spectra of DAP **1S** and *N*-methyl flavin **3** in cyclohexane (total concentration: 4×10^{-4} M, 10−40 °C, 10 mm path).

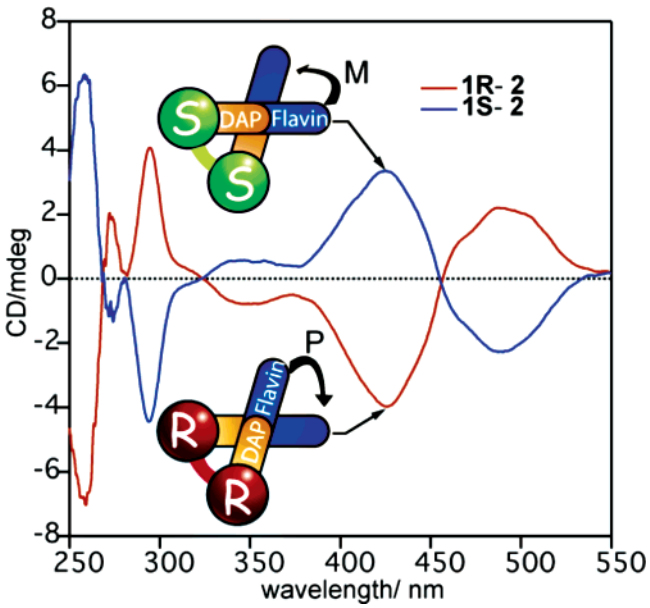

Figure 3. CD spectra of **1S**−**2** and **1R**−**2** recorded at −10 °C in *n*-hexanes (total concentration: 3×10^{-4} M, 10 mm path); mirror-image Cotton effects were observed for **1S**−**2** and **1R**−**2**.

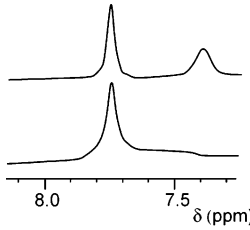

Figure 4. ^{1}H NMR spectra of **1S** (top) and **1S**−**2** (bottom) recorded at 25 °C in *n*-hexane-d_{14} (total concentration: 1×10^{-3} M). DAP amide peak (7.38 ppm) completely disappeared, and DAP aromatic peak (7.74 ppm) was broadened upon mixing with flavin **2**. Flavin peaks for aromatic core protons were significantly broadened due to the aggregation of flavins inside of the self-assembled structure.

self-assembled structures. A 1:1 mixture of DAP **1S** and *N*-methyl flavin **3** (**1S**−**3**) in cyclohexane[18] displayed no Cotton effect even at reduced temperatures (Figure 2b), whereas substantial ICD was observed with the DAP **1S** and flavin **2** in the same solvent.[19] This contrasting behavior demonstrates the requirement for three-point hydrogen bonding in the chiral translation process.

Mirroring Cotton effects were observed upon self-assemblies of **1S**−**2** and **1R**−**2** (Figure 3). Given that the sign of coupling and the direction of dipole moments are established, the coupling in the flavin visible region allows the determination of the chirality of stacking using semiempirical methods.[20] In general, CD spectra featuring bisignate Cotton effects showing positive features at longer wavelength and negative ones at shorter wavelength indicate that the chirality of the dipole moments is right-handed, so-called "positive chirality". In the DAP−flavin assembly, UV absorption at 450 nm results exclusively from $\pi-\pi^*$ transition across the flavin ring with the directionality shown in Figure 1a.[21] This absorption showed bisignated Cotton effects centered at 450 nm in CD; negative (negative first and positive second) and positive (likewise positive first and negative second) chiralities were observed for **1S**−**2** and **1R**−**2**, respectively. The negative chirality induced by the (*S*)-configuration in the peripheral chains corresponds to a left-handed stacking, and the positive chirality induced by the (*R*)-configuration indicates a right-handed stacking in the self-assembled structures (Figure 1b).

With ICD demonstrated in the DAP−flavin system, we focused on determining the structure of the DAP−flavin assembly. Variable-temperature UV experiments were performed to demonstrate interactions between dyads. Absorption at 450 nm showed a 4 nm hypochromic effect upon decrease of temperature (50 to 20 °C), indicative of solvophobic $\pi-\pi$ stacking.[19] Further structural insight was obtained using ^{1}H NMR in *n*-hexanes-d_{14} (Figure 4). Addition of flavin **2** to DAP **1S** resulted in the disappearance of the DAP amide peak, and peak broadening and upfield shift of the aromatic protons of DAP branching group. Significantly, resonances arising from flavin **2** were extremely broad. The observed line-broadening and upfield shifts were typical for self-assembled structures resulting from close contact of aromatics and restricted mobility of flavins in the self-assembled structures.[3c,4a,22] The upfield shifts in DAP support the stacked structures of self-assemblies. Given that the loss of mobility increases the relaxation time in NMR, resulting in line-broadening or even disappearance of the peaks for flavins, we can conclude that flavins are stacked in the self-assembled structures with low mobility. The contrasting behavior of the DAP and flavin resonances is indicative of

(18) Cyclohexane was required for the mixture of **1S** and **3** due to the solubility in *n*-hexanes.
(19) See Supporting Information.
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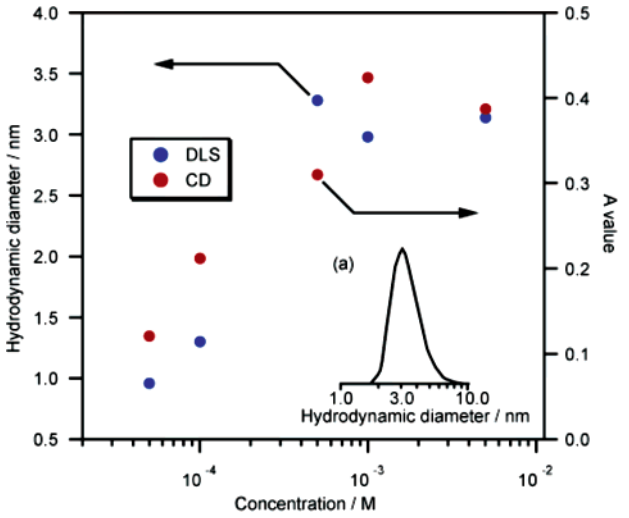

Figure 5. Variable-concentration DLS and CD experiments of **1S**−**2**, recorded at 20 °C (DLS (blue), CD (red), total concentration: 5×10^{-5} to 5×10^{-3} M). Inset (a) is the DLS result at 5×10^{-3} M showing essentially monodisperse assembly.

a complex where flavins are stacked atop one another, where the stacking is more rigid than the stacking of the DAPs atop each other.

An important issue with the DAP−flavin assembly is whether discrete assemblies or extended aggregates are formed. The size of self-assembled structures was determined using variable-concentration dynamic light scattering (DLS). An increase in the hydrodynamic diameter was observed with increasing total concentration, reaching a limiting value of 3.2 nm. In the range of 5×10^{-4} to 5×10^{-3} M, DLS profiles showed narrow monomodal distributions (over 90% is in the range of 2−5 nm) (Figure 5a). The limiting value accompanied with the narrow monomodal distribution in the concentration-dependent DLS demonstrates the formation of discrete self-assembly rather than extended self-assembly. This profile was strongly correlated with the concentration-normalized induced Cotton effect (Figure 5). No detectable aggregation was observed with DLS in solvents that do not induce ICD such as CH_2Cl_2 and toluene.

Because of the broadening within the NMR and lack of crystallinity of the complexes, direct determination of the structure of the complex was not possible. From the CD data (vide supra), we could conclude that dyad formation was required for transduction based on the lack of ICD when using *N*-methyl flavin **3**. Moreover, on the basis of the lack of ICD in halogenated solvents where nonaggregating dyads were formed, we could conclude that more than one dyad was required in the assembly. NMR provides further information on the structure. From the selective broadening of the flavin in the complex, we can infer that the flavins are stacked atop each other. Finally, DLS provides an approximate diameter for the complex of 3.2 nm.

To provide a possible structure for the assembly, Monte Carlo conformation analysis using Amber* force field[23] was used to provide structures based on the above experimental observations. We found that two dyads stacked one upon the other provided a structure with an average diameter of 3.4 nm, in excellent

(23) Macro Model v.7.0: Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440−467.

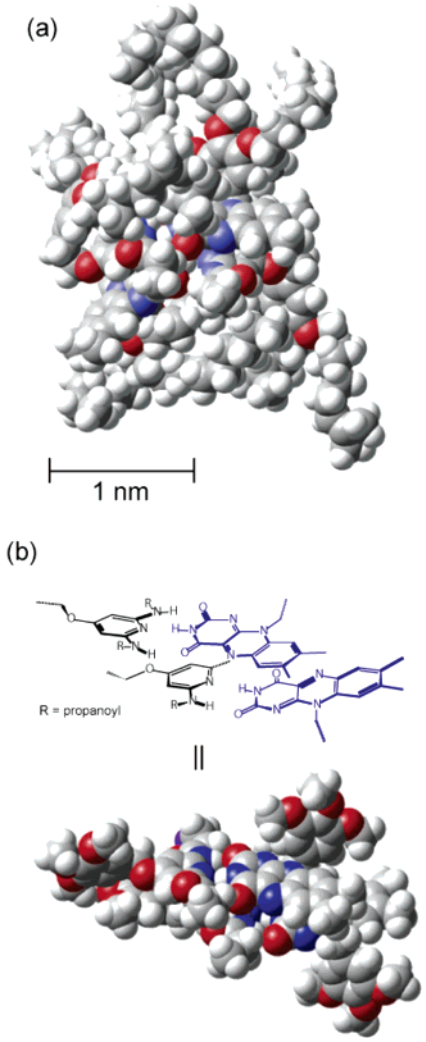

Figure 6. (a) Energy-minimized models of self-assembled dyad-dimer. Surrounding aliphatic tails preclude further aromatic stacking within the dyad-dimer structure. (b) Aromatic core of tetramolecular structure (*trans*-flavin over flavin arrangement is shown, and side-chains are omitted for clarification).

agreement with the 3.2 nm obtained using DLS results (Figure 6a). From these simulations, it was clear that the aliphatic tails surrounding aromatic cores prevented further stacking within the dyad-dimer structure, preventing extended aggregation. These results were consistent with the discrete structures that were observed experimentally (Figure 6). Modeling also provided further insight into the arrangement of specific hydrogen-bonding units in the self-assembled structure. Given that the ^{1}H NMR spectrum of the DAP **1S** and flavin **2** assembly indicated flavin−flavin stacking, two possible arrangements were considered: *trans*- and *cis*-arrangements relative to the direction of side-chains on the flavin−flavin stacked system.[19] The *trans*-flavin over flavin complex shown in Figure 6 was found to be 2.7 kcal/mol (11.4 kJ/mol) more stable than the *cis*, indicating that the *trans* structure is the most likely one found in solution.

Cooperative Self-Assembly. Chiral flavin **2S** was synthesized to further understand the effect of side tails on chiral translation. Considering the stereocenters of the side-chains in the dyad, three unique systems were explored: **1**−**2S**, **1S**−**2S**, and **1R**−**2S**. The **1**−**2S** in contrast to **1S**−**2** complex has the stereocenter on the flavin, revealing the effect of stereocenter location on

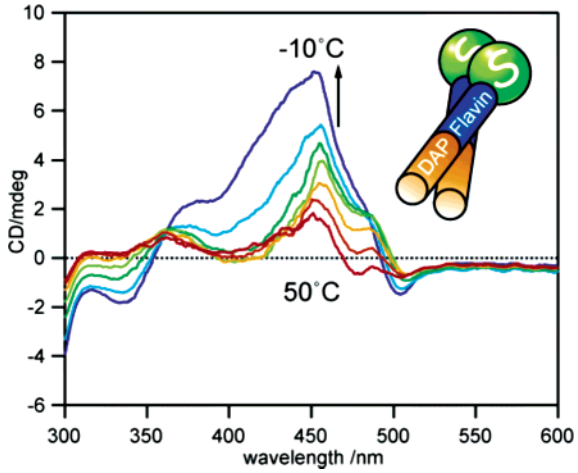

Figure 7. CD spectra of **1**−**2S** recorded in the range of −10 to 50 °C in *n*-hexanes (total concentration: 6×10^{-4} M, 10 mm path). The arrow indicates changes upon decreasing temperature.

the self-assembly. CD spectra of **1**−**2S** were recorded in hexanes and CH_2Cl_2. As expected, the **1**−**2S** complex also provided chiroptical properties associated with flavin due to the formation of the self-assembled structures; **1**−**2S** showed a temperature-dependent Cotton effect in hexanes (Figure 7), and no Cotton effect was observed in CH_2Cl_2 in the given temperature range. The relatively complicated signature observed in hexanes (Figure 7) is in contrast to that observed in the **1S**−**2** and **1R**−**2** systems (Figures 2 and 3). This difference clearly shows the effect of location of the stereocenters on chiral translation; chiral flavin **2S** provides remote control of self-assembly distinct from that of chiral DAPs (**1S** and **1R**). This discrepancy is presumably due to the distance from assembly center and heterogeneity of hydrogen-bonding units.

As demonstrated in Figures 2, 3, and 7, stereocenters on the side-chains on each recognition unit provide differing self-assembly properties. To determine if there is cooperativity based on the interplay of side-chain chirality in the recognition process, hybridized self-assemblies (**1R**−**2S** and **1S**−**2S**) were prepared in hexanes and CD spectra were recorded. The **1R**−**2S** system that has (*R*)-citronellols on DAP and (*S*)-citronellols on flavin showed weak Cotton effects indicative of frustrated self-assembly for **1R**−**2S** (Figure 8). In sharp contrast, the **1S**−**2S** system that has (*S*)-citronellols in both recognition units showed a strong bisignate Cotton effect indicative of cooperative process (Figure 9). Ellipticity at 458 nm for three systems (**1S**−**2S**, **1**−**2S**, and **1R**−**2S**) was recorded in the temperature range of −10 to 60 °C to provide preliminary insight of cooperative and frustrated translations (Figure 10). From melting curves, it was clear that the stability of **1S**−**2S** was greatly improved in comparison to other systems (**1**−**2S** and **1R**−**2S**). A sigmoidal curve was observed for **1S**−**2S**, and simple slopes were observed for **1**−**2S** and **1R**−**2S** in the given temperature range. The observed sigmoidal curve evidently supports the cooperative self-assembly for **1S**−**2S**, resulting in the stabilization of the structures.

Interestingly, swapping achiral tails to (*S*)-citronellyl tails on flavin unit promotes dramatic chiroptical switching in the cooperative self-assembly (Figure 11). The observed bisiganted Cotton effects for **1S**−**2** and **1S**−**2S** are almost mirror-image, providing evidence for opposite sense of stacking: (*M*)-stacking for **1S**−**2** and (*P*)-stacking for **1S**−**2S**. Considering that the

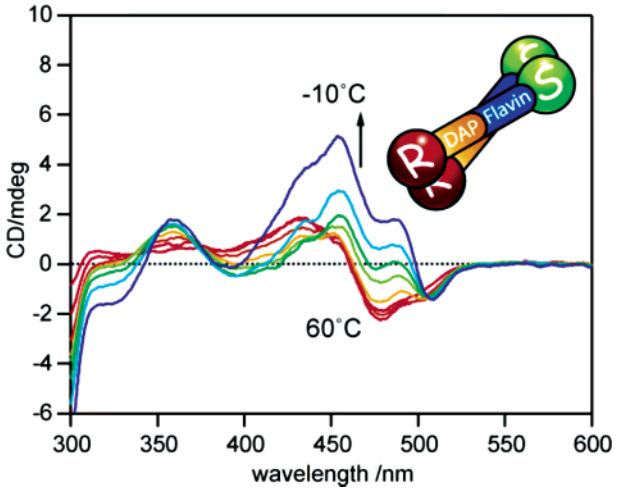

Figure 8. CD spectra of **1R**−**2S** recorded in the range of −10 to 60 °C in *n*-hexanes (total concentration: 6×10^{-4} M, 10 mm path). The arrow indicates changes upon decreasing temperature.

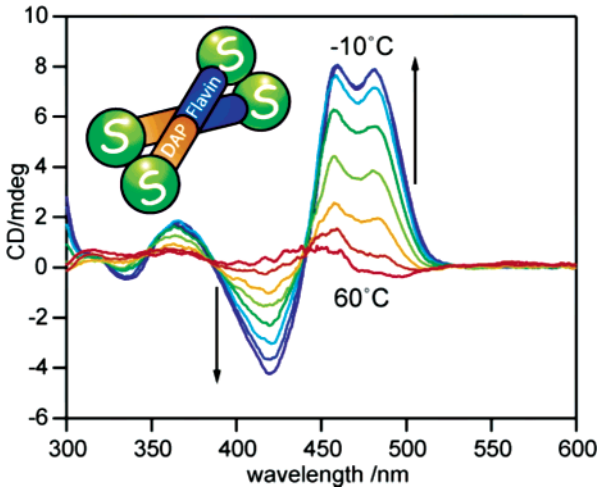

Figure 9. CD spectra of **1S**−**2S** recorded in the range of −10 to 60 °C in *n*-hexanes (total concentration: 6×10^{-4} M, 10 mm path). Arrows indicate changes upon decreasing temperature.

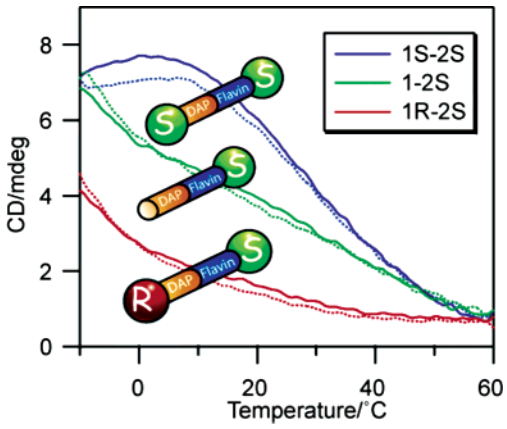

Figure 10. Melting curves for **1**−**2S**, **1S**−**2S**, and **1R**−**2S** recorded in the range of −10 to 60 °C in *n*-hexanes (total concentration: 6×10^{-4} M, 10 mm path). Ellipticity at 458 nm was monitored. Solid lines present heating profiles, and dotted lines present cooling profiles.

1S−**2** system has the (*S*)-citronellyl tails on DAP **1S** and **1S**−**2S** has the (*S*)-citronellol tails on both DAP and flavin for the chiral translation, the switching was triggered by conferring the same configuration of (*S*)-citronellyl tails on the recognition

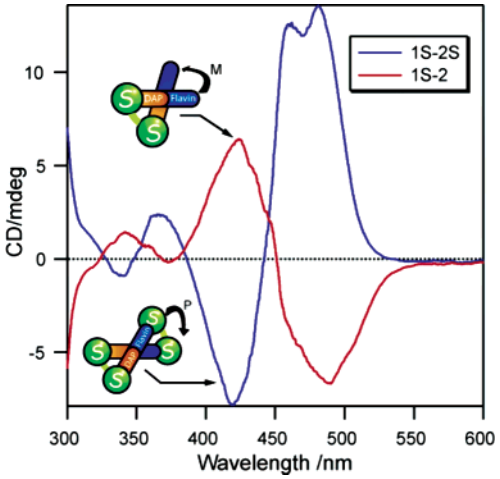

Figure 11. CD spectra of **1S**−**2S** and **1S**−**2** recorded at −10 °C in *n*-hexanes (total concentration: 7×10^{-4} M, 10 mm path).

dyads. The results clearly suggest that the location and combination of chiral tails dictate chiroptical property and cooperativity in the DAP−flavin self-assembly.

Given that **1S**−**2S** provides the cooperative translation, we focused on chiral amplification effects in the DAP−flavin self-assembly, the "Sergeants and Soldiers" effect.[24] This effect demonstrates the ability of chiral building blocks to guide the achiral components in effect of the helicity induced by chiral blocks, apparent in dynamic helical polymers[25] and self-assemblies.[7c,26] Observation of this phenomena would reflect the control of achiral unit **2** by chiral unit **2S** in the self-assembled structures. To provide preliminary insight of this effect, hybridized experiments of **1S**−**2** and **1S**−**2S** solutions were performed at a fixed total concentration of flavin (**2** and **2S**), and chiroptical responses at 425 nm were monitored. Figure 12 shows chiroptical response as a function of the mole fraction of **2S**. The distinctive nonlinear behavior at 425 nm indicates that flavin **2S** can direct achiral **2** to follow the preorganized helical structures in a "Sergeants and Soldiers" fashion; a dyad with 80% of the chiral building block **2S** provides essentially the same chiroptical property as a dyad prepared with 100% of the chiral building block.

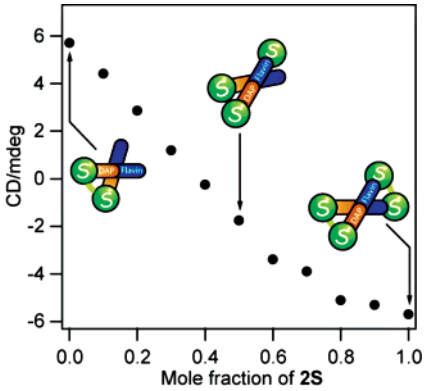

Figure 12. CD response changes in variable mole fraction of **2S** in the mixture of **1S**−**2** and **1S**−**2S**.

Conclusions

We demonstrated the chiral translation in a DAP−flavin self-assembled structure using ICD. Specific three-point hydrogen bonding triggers the formation of a tetrameric complex that exhibits chiral translation. The combination of the same stereocenters on both recognition units provides cooperative self-assembly resulting in improvement of stability and efficient chiroptical switching. The observed location and cooperative effects provide new directions of molecular design for self-assembly. Ongoing studies are focused on bulk and surface properties of the discrete self-assembly as well as the electronic control of the properties.

Acknowledgment. This research was supported by the NSF [CHE-0518487] and MRSEC (DMR 0213695). G.C. thanks EPSRC. We acknowledge Cambridge Isotope Laboratories, Inc. for the donation of a series of deuterated solvents. B.J.J. acknowledges the NSF [DUE-044852] for an IGERT fellowship, and R.R.A. thanks the NIH for a CBI fellowship (T32 GM008515).

Supporting Information Available: Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

JA064554Z

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