# Reversible Side Chain Modification through Noncovalent Interactions. "Plug and Play" Polymers

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ABSTRACT: Polystyrene-based systems with varying donor−acceptor−donor (D−A−D) hydrogen bonding side chains were synthesized. Recognition interactions between these polymers and guest flavin **5** were studied through $^1$H NMR titration experiments. Using these systems, we have shown that the efficiency of recognition between the polymer and guest can be controlled through the choice of recognition element on the polymer by adjusting the balance between intra- and intermolecular interactions. The versatility of this "plug and play" strategy was readily extended to bulk materials. Using spin casting, we kinetically trapped these host−guest complexes in polystyrene films, resulting in highly efficient recognition processes, a key prerequisite for creation of supramolecular devices.

Inter- and intramolecular networks of noncovalent interactions are responsible for a wide array of phenomena in fields of biology and chemistry. Biological systems use specific patterns of complementary functionality to provide exquisite control over biopolymer recognition processes such as protein−protein and protein-polynucleic acid binding.[1] In Nature, these specific supramolecular interactions play many key roles, including stabilization of structure, information storage and transfer, catalysis, and self-assembly. Likewise, controlled application of noncovalent interactions provides an effective tool for fabrication of man-made systems, allowing the creation of higher order architecture required for devices and materials, as well as the dynamic properties required for efficient utilization of these attributes.[2,3]

In addition to the dynamic nature of supramolecular assembly, the modular nature of noncovalent interactions permits a divergent approach to polymer structure, allowing multiple systems to be assembled using a single backbone (Figure 1).[4] This versatility is further enhanced by the ability to control the supramolecular complexation through external chemical factors, including the matrix and the temperature.[5] We report here the creation of "plug and play" polymers that feature recognition elements designed to interact with specific guest molecules. Using these systems, the efficiency of interaction between the polymer and guest can be controlled through choice of recognition element. Additionally, we demonstrate the extension of this "plug and play" methodology to the creation of thin films, providing a new approach to materials development.

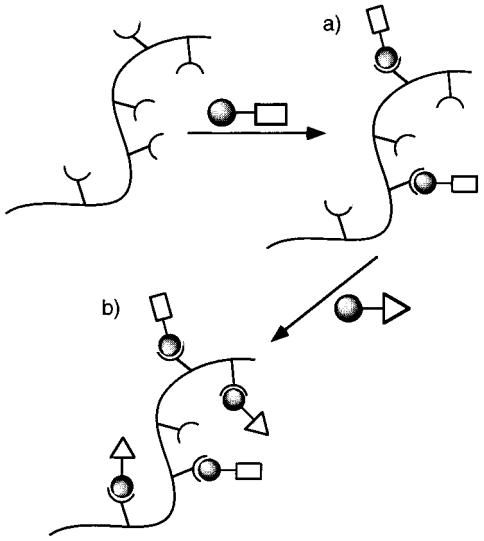


**Figure 1.** Schematic demonstration of noncovalent "plug and play" approach to polymer modification: (a) monofunctionalization; (b) polyfunctionalization.

## Section 1: Macromolecule−Target Recognition in Solution

In recent investigations, we synthesized diaminotriazine-functionalized polystyrene **1**, which provides a suitable scaffold for noncovalent functionalization through its side chain donor−acceptor−donor (D−A−D) hydrogen bonding units.[6] Polymer **1**[7] folds into a highly compact micelle-like structure in $CHCl_3$ as a result of intramolecular hydrogen bonding between the diaminotriazine moieties, as established by IR spectroscopy, gel permeation chromatography (GPC), and small-angle neutron scattering[8] (SANS). This compact macromolecular conformation results in inefficient complexation of guest molecules due to competition between polymer−guest and polymer−polymer interaction.[9]

To provide more efficiency in association, we have replaced diaminotriazine units with diacyldiaminopyridine sites. This recognition unit, while possessing the same D−A−D recognition motif as polymer **1**, would be expected to aggregate less strongly, a key requirement for limiting *intra*molecular binding. Polymer **3** was formed via reaction of the random copolymer of styrene and 4-chloromethylstyrene **9** with diacyldiaminopyridine derivative **6** (Scheme 1).

Preliminary predictions of the structures of polymer **1** and polymer **3** were obtained through molecular dynamics calculations on model polymers, poly(styrene−*p*-(methyldiaminotriazine)styrene and poly(styrene−*p*-(methyl-2,6-dipropamidopyridine 4-oxide).[10] In vacuo molecular dynamics calculations predict a highly compact structure containing multiple intramolecular hy-

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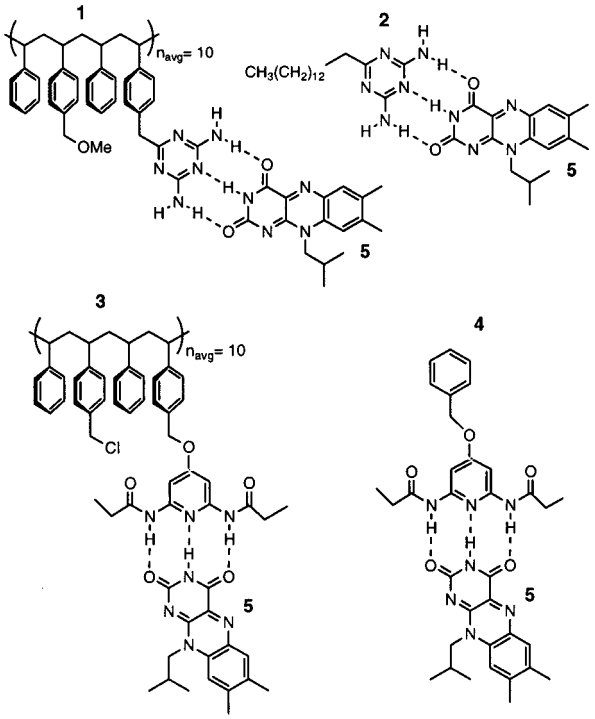
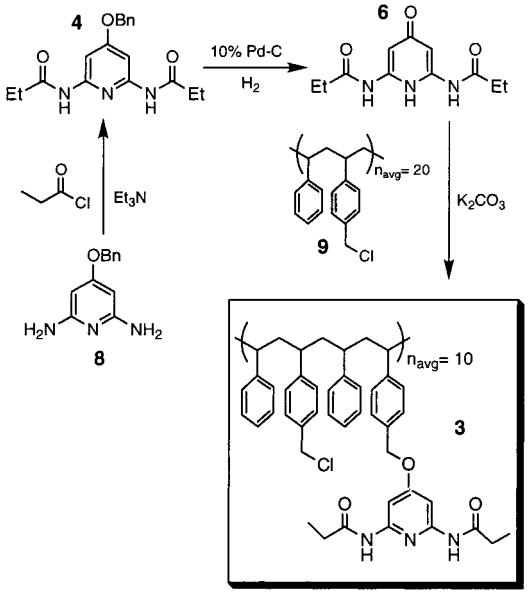



**Figure 2.** Complexation of polymer **1**, monomer **2**, polymer **3**, and monomer **4** with flavin **5**.

**Scheme 1. Synthesis of Diaminopyridine-Functionalized Polymer 3**




drogen bonds between triazine side chains for polymer **1**. This compact structure was quite robust, maintaining integrity at elevated temperatures. In further dynamics studies using a continuum solvent treatment, the compact structure was likewise retained. In contrast, the same calculations for diaminopyridine polymer **3** predict little intramolecular hydrogen bonding, resulting in a looser structure (Figure 3).

As mentioned above, implicit in the bimolecular recognition of *intra*molecularly associated polymer **1** is a decrease in the efficiency of *inter*molecular binding. This inefficiency arises from the requirement for polymer uncoiling prior to the recognition event. The decrease in binding efficiency was established through $^1$H NMR titration experiments. Polymer **1** binds flavin

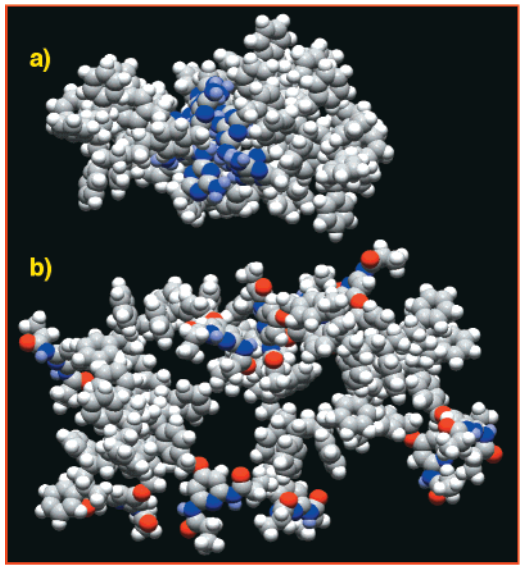



**Figure 3.** Structures sampled from dynamics runs (300 K, $CHCl_3$) for models of (a) polymer **1** and (b) polymer **3**. For these studies, atactic polymers featuring substituents at every fourth carbon were used as models.

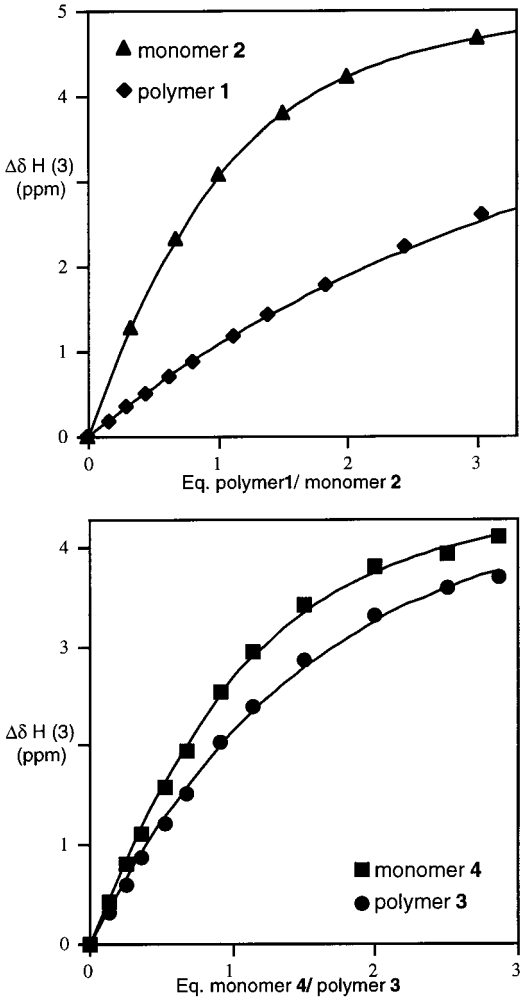



**Figure 4.** Chemical shift changes flavin **5** H(3) upon addition of monomer **2**/polymer **1** and monomer **4**/polymer **3**.

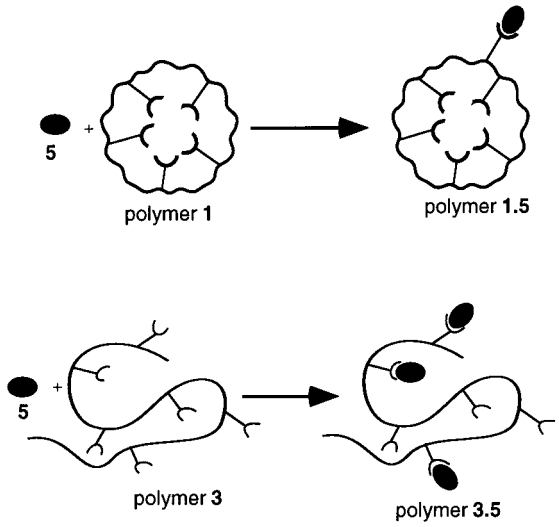
**5** (Figure 2) with an association constant ($K_a$) of 36 $M^{-1}$ in ($CDCl_3$),[11] more than an order of magnitude less than monomer **2** with the same recognition element (476 $M^{-1}$) (Figure 4).[12]

**Table 1. Association Constants ($M^{-1}$) for Flavin 5 with Corresponding Guests in Different Matrixes[14]**

| host | $K_a(CDCl_3)$,[a] $M^{-1}$ | $K_a$(PS),[b] $M^{-1}$ |
|---|---|---|
| monomer **2** | 476 | 53 |
| polymer **1** | 36 | 450 |
| monomer **4** | 520 | 3200 |
| polymer **3** | 220 | 5600 |

[a] All $^1$H NMR titrations were performed at 23 °C.[15] [b] Reported $K_a$'s for polystyrene films are apparent values obtained by fluorescence titrations.[16]

**Scheme 2. Schematic Demonstration of the Recognition Behavior of Polymers 1 and 3 with Flavin 5**




Complexation of polymer **3** and monomer **4** with flavin **5** (Figure 4) was likewise quantified through $^1$H NMR titration experiments. A $K_a$ of 220 $M^{-1}$ was obtained for polymer **3**−flavin **5** complex formation in $CDCl_3$, only slightly less than the 520 $M^{-1}$ observed for monomer **4** with flavin **5** (Table 1). This demonstrates that the recognition ability of polymer **3** is much enhanced compared to polymer **1**. Since the monomeric units **2** and **4** utilizing these two different recognition elements have essentially identical $K_a$'s with flavin **5**, this difference in recognition efficiency arises from their different *intra*molecular association behaviors: the enhanced intermolecular binding constant for polymer **3** is a direct result of less competitive *intra*molecular association (Scheme 2).[13]

## Section 2: Engineering Macromolecule−Target Interactions in Thin Films

Polymer matrix isolation is an effective technique for the immobilization and isolation of molecules,[17] providing access to materials, devices, and sensors.[18] Utilization of this methodology in the isolation of host−guest complexes is limited by issues of aggregation and competition. Creation of matrices using nonpolar polymers can cause aggregation and concomitant phase separation of polar host−guest complexes. On the contrary, matrix formation from polar polymers creates a competitive environment, disrupting the desired interactions such as hydrogen bonding.

Recently, we reported the kinetic isolation of host monomer **2**-flavin **5** complexes in a highly nonpolar polystyrene film matrix (Table 1).[19] The polymer-doped films were prepared by spin-casting[20] from solutions of 1.75% w/w polystyrene ($M_n$ = 1.1 × $10^5$, PDI = 2.3)

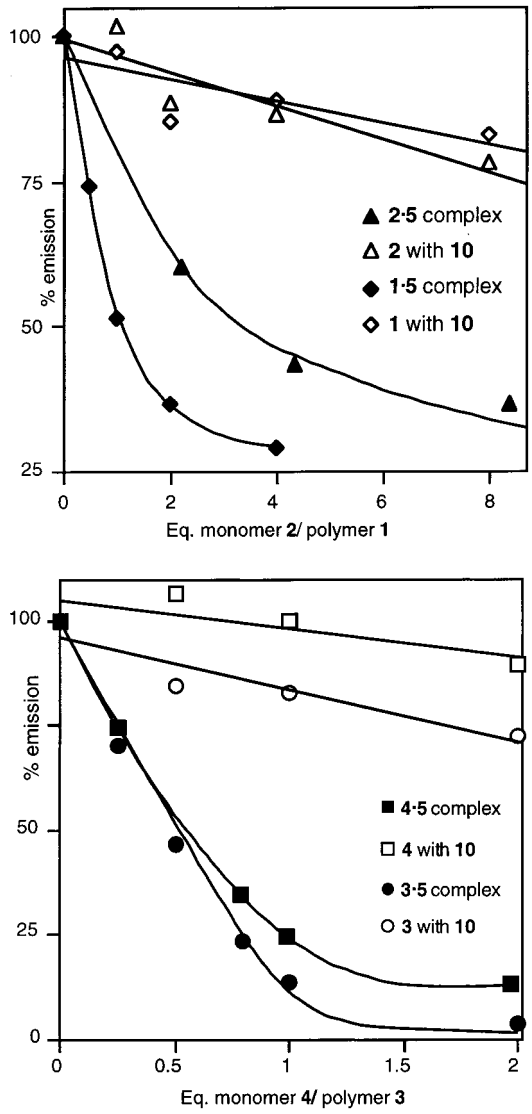



**Figure 5.** Fluorescence emission changes of flavin **5** and *N*(3)-methylflavin **10** upon addition of monomer **2**/polymer **1** and monomer **4**/polymer **3**. The lines for the control studies (monomer **2**/polymer **1** and monomer **4**/polymer **3** with *N*-methylflavin **10**) are least-squares curve fits to the data, and are meant only to lead the eye. The curve fits for the other studies represent best fits to the 1:1 binding isotherm.

containing flavin **5** and monomer **2** in $CHCl_3$ on $SiO_2$ surfaces The optical transparency of these films allowed direct observations of flavin **5** fluorescence behavior. Titration studies revealed marked decreases in fluorescence of flavin **5** with increasing concentrations of receptor **2**, reaching a limiting value. An apparent association constant of 53 $M^{-1}$ was estimated by fitting the fluorescence spectroscopy data to a (1:1) binding isotherm (Figure 5). This value is considerably lower than the $K_a$ of 476 $M^{-1}$ which was obtained for the same host−guest complex formation in $CHCl_3$, despite the noncompetitive nature of the polystyrene matrix. This inefficiency can be ascribed to competitive aggregation of the triazine moieties, analogous to the behavior observed for triazine-functionalized polymer **1**.

To provide more efficient recognition in the thin film system, we explored the interaction of diaminopyridine **4** with flavin **5** (Table 1). Using conditions identical to those used for the above thin film titrations, we observed an apparent $K_a$ of 3200 $M^{-1}$, ~60 fold more than that for triazine functionalized monomer **2**. This demon-

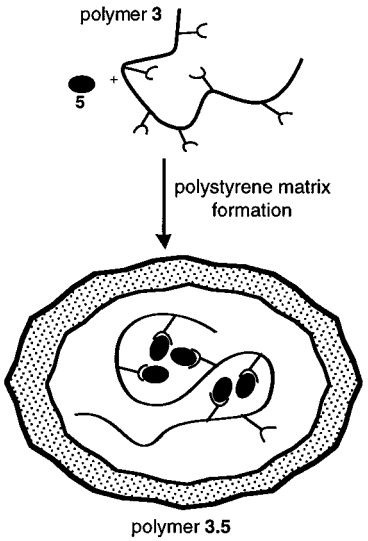



**Figure 6.** Schematic illustration of polymer **3**−flavin **5** polyvalent complexation in polystyrene matrix.

strates that the inefficient binding of **5** observed with triazine **2** arises from preferential aggregation of the triazine during the formation of the nonpolar polymer matrix.

The comparison of complexation data between polymers **1** and **3** and flavin **5** was equally striking (Figure 5). For the triazine polymer **1**−flavin **5** complex there was ~13 fold in the $K_a$ ($K_a$ = 450 $M^{-1}$), relative to that observed in $CDCl_3$ solution studies ($K_a$ = 36 $M^{-1}$). Such an increase can be attributed to less competitive nature of polystyrene matrix compared to relatively polar $CDCl_3$ environment. Likewise, diaminopyridine polymer **3** binds flavin **5** with an association constant of 5600 $M^{-1}$, corresponding to a ~25 fold increase compared to that observed in $CDCl_3$ ($K_a$ = 220 $M^{-1}$).

Comparison of the binding efficiencies of the monomeric hosts **2** and **4** with their polymeric counterparts **1** and **3** provides further insight into recognition within the polystyrene matrix (Figure 5). The significantly higher affinities observed with the polymeric system are indicative of the creation of nanoenvironments within the polymer hosts featuring preferential binding properties. This is analogous to the binding processes seen in biopolymers,[21] which are driven by solvophobicity of host and guest molecules. (Figure 6).

Control experiments utilizing *N*(3)-methylflavin **10**, a molecule not capable of complementary binding through hydrogen bonding**,** in place of flavin **5** did not demonstrate any measurable complexation with either diaminotriazine- (**1**, **2**) or diaminopyridine-based (**3**, **4**) polymers or monomers. (Figure 7).

## Conclusion

In summary, we have synthesized polystyrene-based polymers grafted with recognition units. These polymers are quite soluble in many organic solvents including chloroform, and bind reversibly to small molecule guests in solution, providing a methodology for the creation of diverse materials and devices. Guest recognition in these systems can be controlled through engineering of intramolecular association tendencies: increased intrachain interactions reduce guest binding.

The versatility of the "plug and play" strategy can be readily extended to bulk materials. Using spin casting to kinetically trap host−guest complexes in polystyrene

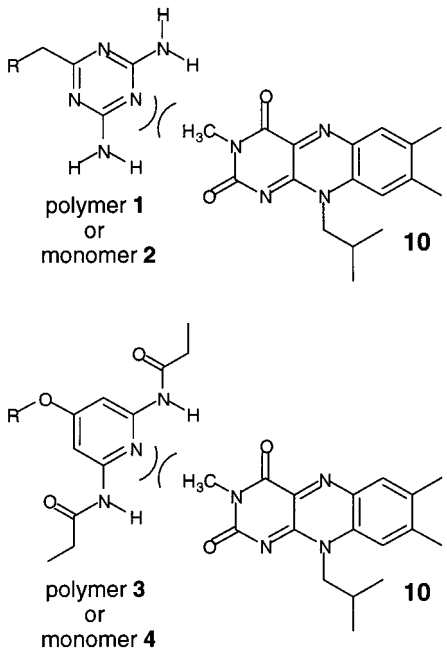



**Figure 7.** *N*(3)-Methylflavin **10** with guests **1**, **2**, **3**, and **4**.

films, we were able to demonstrate highly efficient recognition of guests using both monomeric and polymeric host systems. Applications of these "plug and play" polymers in both solutions and solids to applied areas of chemistry varying from delivery systems to sensors are currently under investigation, and will be reported in due course.

## Experimental Section

All chemicals were reagent grade, and were used without further purification. All $^1H$ NMR spectra were recorded using $CDCl_3$ as solvent on a Bruker 200 MHz spectrometer. IR spectra for polymers were recorded using $CHCl_3$ as solvent and KBr pellets for all other systems on a MIDAC 1200 FTIR spectrometer. Melting points presented are uncorrected.

**4-Oxybenzyl-2,6-dipropamidopyridine (4).** A suspension of 4-oxybenzyl-2,6-diaminopyridine, **8**,[22] (2.0 g, 9.3 mmol) and triethylamine (2.6 mL, 18.6 mmol) in dry $CH_2Cl_2$ (250 mL) was stirred at room temperature under an argon atmosphere. To this was added propionyl chloride (1.6 mL, 18.6 mmol) in dry $CH_2Cl_2$ (150 mL) dropwise, and the mixture was stirred for 3 h. The resulting solution was then extracted with water (2 × 100 mL) and brine (1 × 50 mL). Concentration in vacuo, followed by chromatography ($SiO_2$, Hex/EtOAc (2:1)) provided 2.7 g (89%) of the title compound as a cream-colored solid, mp = 105−107 °C.

**2,6-Dipropamidopyrid-4-one (6).** 4-Oxybenzyl-2,6-dipropylamidopyridine, **4**, (0.80 g, 2.44 mmol) was stirred in the presence of 10% palladium on carbon (1 wt eq) in 2 mL of methanol for 3 h under a hydrogen atmosphere. The suspension was filtered and the filtrate was evaporated to dryness in vacuo to obtain 480 mg (83%) of the title compound, mp = 142−144 °C.

**Polymer (3).** A solution of polymer **9** (0.2 g, 0.755 mmol equiv of Cl), the diacylated diaminopyridine derivative **6** (0.088 g, 0.37 mmol), potassium carbonate (0.052 g, 0.38 mmol), and 3.5 mL of DMF was stirred at 65 °C for 16 h under an argon atmosphere. The resulting solution was concentrated in vacuo and the polymer product was precipitated by addition of water. The cream-colored solid product (0.25 g) was collected by filtration and washed with water. The $^1H$ NMR of this product indicates 50% conversion of the chloromethylstyrene into its diacyl diaminopyrdine derivative.

**Polystyrene Film Preparation and Fluorescence Measurements.** Films were spin-cast at 4500 rpm onto 22 mm

square $SiO_2$ slides, using 300 $\mu$L of polystyrene/flavin **5** and host solution in $CHCl_3$. Prior to coating, the slides were sonicated for 10 min sequentially in 1,1;2,2-tetrachloroethane, acetone, and 2-propanol. The slides were then dried for 2 h at 120 °C and allowed to cool to ambient temperature in a $CaSO_4$ desiccator. After casting, films were dried in vacuo for 16 h prior to spectroscopic observations.

Fluorescence measurements were performed using a machined slide holder. The slides were vertically set, with the polymer coated surface 60° to the excitation beam. (excitation: 445 nm, emission: 525 nm).

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**Supporting Information Available:** Text and figures showing $^1$H NMR and IR information for polymer **3** and monomer **4** (NMR). This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) The $K_a$'s used in this paper for polymer **1** and **3** refer to the association constant per recognition unit.

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(14) The error in reported $K_a$'s for monomer **2** and **4** complexation with **5** are less than 20%. However, since polymers do not exactly follow a 1:1 recognition process, the absolute errors for their complexation with flavin **5** cannot be calculated.

(15) The data were fitted to the following equation to provide $K_a$s.:

$$\delta_{obs} = \delta_H + \frac{(\delta_{HG} - \delta_H)\left(\left([H_t] + [G_t] + \frac{1}{K_a}\right) - \left(\left([H_t] + [G_t] + \frac{1}{K_a}\right)^2 - 4[H_t][G_t]\right)^{1/2}\right)}{2[H_t]}$$

where the experimentally determined parameters are as follows: $[G_t]$ and $[H_t]$, the total guest and host concentrations, respectively, $\delta_{obs}$ the observed shift, and $\delta_H$, the shift of the host in the absence of guest. Parameters determined through fitting are $K_a$, the host−guest association constant, and $\delta_{HG}$, the chemical shift of the host−guest complex.

(16) The same formula in ref 15 was used to obtain apparent $K_a$ values for the fluorescence titrations of the polymer films. The concentrations for host and guest used are the resulting concentrations in the dried polymer film.

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