Synthesis and Recognition Properties of Polymers Containing Embedded Binding Sites

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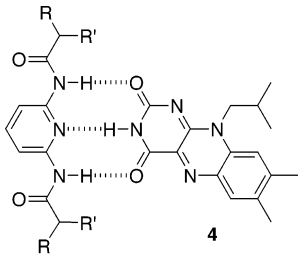
ABSTRACT: We report the synthesis and guest affinities of polymers featuring a single recognition site in the middle of the polymer chain. These polymers were synthesized from difunctional initiators based on the 2,6-diacyldiaminopyridine moiety. Binding efficiencies were experimentally determined using a complementary fluorescent guest, N(10)-isopropyl flavin. The effect of polymer length on recognition was explored by the synthesis of 5 PMMA samples ranging from 4K to 25K. Over this range binding constants increased almost 2-fold, from 282 to 522 M^{-1}. Variable temperature fluorescence of bound samples shows a 15% difference in release between polymer samples and model compounds.

Introduction

Control of macromolecular structure and function through specific noncovalent interactions is central to a wide variety of applications in bio- and nanotechnology.[1−12] Systems studied include soluble polymers,[3,13−17] bulk solids,[18−23] and thin films.[24,25] In recent studies, the incorporation of specific recognition elements has been used to generate a diverse array of architectures in solution and the solid state.[9,10,13,26] In these studies, recognition elements have been employed to transform common polymer backbones (acrylates, styrenics) into drug delivery systems,[27] liquid crystals,[26,28,29] highly ordered nanostructures,[3,8,17,30−39] vesicles,[40] and organogels.[41]

Embedding a recognition element within a polymer chain can potentially provide biologically inspired catalysts and delivery systems. This information is difficult to assess with random copolymers due to the heterogeneity of binding sites, a feature that arises from the synthetic methodologies typically employed. To examine the effects of polymer chains on host−guest affinity, we have designed polymers that have a single recognition element at the center of the polymer chain. These polymers were synthesized by living/controlled polymerizations. The effect of the binding site buried in the middle of the three-dimensional polymeric globule can then be quantified by the comparison of binding constants (K_a) obtained from the polymers to that of monomeric model compounds.

For our studies, we used diacyl diaminopyridines (DAP) **1** and **2** as hosts, with the complementary three-point hydrogen-bonding partner, N(10)-isopropyl flavin (**4**), as guest (Figure 1). The use of flavin **4** allows for quantification of the K_a via fluorescence titrations.[42,43] Here, we report the synthesis of well-defined polymers containing a single recognition unit, and the corresponding thermodynamic characterization of the host−guest chemistry.



1 R=CH_3, R'=H
2 R=CH_3, R'=CH_3
3 R= Polymers **7**-**13**

Figure 1. Structure of host−guest dyads used in this study, 2,6-diacyldiaminopyridine-based systems (**1**−**3**) and N(10)-isopropyl flavin (**4**). **3** stands for polymers **7**−**13**, polymer blocks on both sides of the diaminopyridine moiety.

Experimental Section

General. All reagents were purchased from Aldrich. 2,6-Diaminopyridine (98%), triethylamine (99.5%), bromopropionyl bromide (97%), anisole (99.7%), copper(I) bromide (99.999%), 4,4′-dinonyl-2,2′-bipyridyl (DNBP, 97%), *N*,*N*,*N*′,*N*′,*N*″-pentamethyldiethylenetriamine (PMDETA, 99%), 4-pentenoic acid (97%), oxalyl chloride (99+%), 0.5 M solution of 9-borabicyclo-[3.3.1]nonane (BBN) in tetrahydrofuran (THF), 4-(dimethylamino)pyridine (99%), and DL-lactide were used as received. Solvents were purchased from VWR. All reactions were carried out under argon using oven-dried glassware. All polymerizations and water/air-sensitive manipulations were carried out using standard Schlenk techniques in a dry argon atmosphere. THF was distilled from sodium/benzophenone ketyl. Dichloromethane was distilled from calcium hydride. Methyl methacrylate (MMA, 99%) was vacuum-distilled from calcium hydride prior to use. *tert*-Butyl acrylate (*t*BA, 98%) was extracted three times with 5% aqueous solution of NaOH and washed with distilled water. After stirring over calcium chloride overnight, the monomer was vacuum-distilled prior to use. All compounds were stored in the dark and under refrigeration to avoid photodegradation or thermal degradation. NMR spectra were recorded using a Bruker 200 MHz spectrometer. Elemental analyses were performed by the Microanalytical Lab at the University of Massachusetts, Amherst. Compounds **1**, **2**, and **4** were synthesized according to literature procedures.[44]

Instrumentation. Absolute and/or relative molecular weights of the polymers were determined by gel permeation chromatography (GPC) with a Polymer Laboratories (PL) LC 1120 pump, a Waters R403 differential refractometer detector, and three PL gel columns (particle size = 50 μm, pore size = mixed D and 50 Å) with THF as an eluent at 1 mL/min at

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room temperature. The system was calibrated with poly(methyl methacrylate) (PMMA) and polystyrene (PS) standards. Fluorescence spectroscopy was performed on a Shimadzu RF-5301PC spectrofluorophotometer.

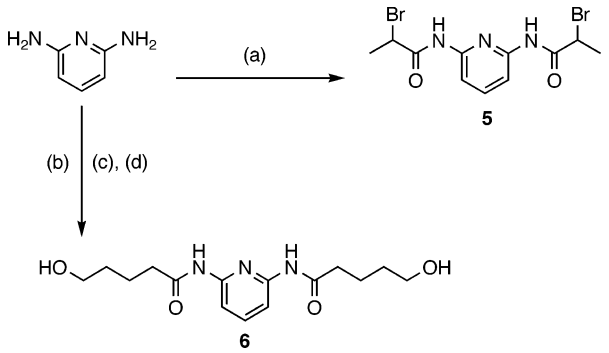
Synthesis of 5. To a solution of 2,6-diaminopyridine (1.0 g, 9.2 mmol) and triethylamine (2.83 mL, 20.0 mmol, 2.2 equiv) in dichloromethane (150 mL) was slowly added 2-bromopropionyl bromide (1.92 mL, 20.0 mmol). The solution was stirred for 12 h, the solvent removed in vacuo, and the resulting red solid dissolved in ethyl acetate (100 mL) and successively extracted with brine (100 mL), saturated sodium bicarbonate (100 mL), and 0.1 M HCl (75 mL). The organic layer was collected and dried using $MgSO_4$, and the residue was purified by flash column chromatography on silica (1:1 hexanes:ethyl acetate). The resulting white solid was vacuum-dried overnight. Yield 1.68 g, 83%; mp 128−129 °C. ^{1}H NMR ($CDCl_3$): δ = 8.42 (s, NH, 2 H), 7.96 (d, 3,5-PyH, 2 H, 7.9 Hz), 7.76 (t, 4-PyH, 1 H, 8.0 Hz), 4.53 (q, Br−CH−, 2 H, 6.9 Hz), 1.93 (d, −CH3, 6 H, 6.9 Hz). $C_{11}H_{13}N_3O_2Br_2$ (379.05) Calcd: C, 34.86; H, 3.46; N, 11.09. Found: C, 34.62; H, 3.46; N, 10.91.

General Procedure of the Atom-Transfer Radical Polymerization (ATRP) of PMMA Initiated by 5. A heat-dried, nitrogen-purged 10 mL Schlenk tube was charged with freshly distilled MMA, anisole (50 wt %), copper(I) bromide, and 9,9′-dinonyl-2,2′-bipyridine. The dark red solution was degassed by a freeze−pump−thaw technique three times, backfilled with argon, and then sealed via a Teflon stopcock. It was then heated with stirring at 90 °C. The resulting green solution was then dissolved in THF (15 mL) and precipitated into hexanes (100 mL), filtered, and dried in vacuo. The green solid was then dissolved in ethyl acetate (100 mL) and washed with aqueous ammonia (10 wt %) (2 × 50 mL) and brine (1 × 50 mL). The organic layer was collected and dried over $MgSO_4$, and the solvent was removed by rotary evaporation.

Polymerization of *t*BuA with ATRP (Polymer 13). A heat-dried, nitrogen-purged 10 mL Schlenk tube was charged with freshly distilled *t*BuA (3.5 mL, 24 mmol), **5** (64 mg, 0.17 mmol), CuBr (24 mg, 0.17 mmol), and PMDETA (36 μL, 0.17 mmol). The green solution was degassed by a freeze−pump−thaw procedure three times, backfilled with argon, and then sealed via a Teflon stopcock and placed in a 60 °C oil bath for 3 h. The solution was then dissolved in THF (10 mL) and precipitated into a mixed solvent (H_2O:MeOH 1:1 v:v, 50 mL), filtered, and dried in vacuo to give a white polymer (0.56 g, 16%). $M_n = 4.7 \times 10^3$, $M_n/M_w = 1.27$ (PMMA standards).

***N,N′*-(5-Hydroxylpentanoyl)-2,6-diaminopyridine (6).** Initiator **6** was synthesized through a three-step reaction sequence from 2,6-diaminopyridine. To a solution of 4-pentenoic acid (2.0 g, 20 mmol) and oxalyl chloride (2.0 mL, 2.2 mmol) in dry CH_2Cl_2 (150 mL) was added one drop of DMF. After stirring for 2 h, the mixture was added dropwise to a solution of 2,6-diaminopyridine (1.1 g, 10 mmol) and triethylamine (3.1 mL, 22 mmol) in dry CH_2Cl_2 (100 mL) under an argon atmosphere. After stirring overnight at room temperature, the mixture was washed with brine (100 mL), the organic fractions were collected and dried with $MgSO_4$, and the solvent was removed by rotary evaporation. The crude product was purified by flash column chromatography on silica gel with hexane/EtOAc (1:1 v:v) to give a white solid (1.1 g, 40%). This product was sufficiently pure for the subsequent reaction and was used without further purification. A 0.5 mol L^{-1} solution of 9-BBN in THF (16 mL) was added dropwise to a solution of dipentenoyl-2,6-diaminopyridine (0.54 g, 2.0 mmol) in dry THF (4 mL) at room temperature. After stirring for 1 h at room temperature H_2O (5 mL) was added dropwise, followed by 3 M NaOH (10 mL). 30% H_2O_2 solution (10 mL) was added carefully to maintain the reaction temperature stay between 30 and 50 °C. The precipitate was filtered, and the filtrate was evaporated and purified with flash chromatography on silica gel with CH_2Cl_2/MeOH (95:5 v:v) to give a white solid (**2**, 0.27 g, 43%); mp 125−6 °C. ^{1}H NMR (*d*-DMSO): δ = 10.0 (s, NH, 2H), 7.72 (s, PyH, 3H), 4.44 (s, OH, 2H), 3.42 (m, $-CH_2-OH$, 4H), 2.41 (t, $-CO-CH_2-$, 4H, 7.2 Hz), 1.70−1.35 (m, $-CH_2-$, 8 H). $C_{15}H_{23}N_3O_4$ (309.36) Calcd: C, 58.24; H, 7.49; N, 13.58%. Found: C, 58.26; H, 7.42; N, 13.38%.

Scheme 1. Synthesis of Bis-Initiators for ATRP (5) and Lactide ROP (6) Containing a Central Moiety Capable of Molecular Recognition[a]



[a] (a) 2-Bromopropionyl bromide (2 equiv), NEt_3 (2.2 equiv), CH_2Cl_2; (b) 4-pentenoyl chloride (2 equiv), NEt_3 (2.2 equiv), CH_2Cl_2; (c) 9-BBN (4 equiv), THF; (d) NaOH, H_2O_2.

Polymerization of DL-Lactide with ROP (Polymer 12). *N,N′*-(Dimethylamino)pyridine (DMAP, 0.28 g, 23 mmol), **6** (18 mg, 0.58 mmol), DL-lactide (0.50 g, 35 mmol), and dry dichloromethane (2.5 mL) were added to a dry tube equipped with a Teflon stopcock. The mixture was degassed via a repeated freeze−pump−thaw cycle (3×). The polymerization tube was placed in the oil bath at 35 °C. The mixture was added to cold methanol (50 mL) to quench the polymerization. The precipitate was filtered and dried in vacuo to give a white polymer (0.42 g, 82%). $M_n = 7.5 \times 10^3$, $M_n/M_w = 1.34$ (PS standards).

Results and Discussion

Synthesis. We used initiators **5** and **6** (Scheme 1) capable of initiating living/controlled polymerizations to provide polymers with a single recognition element embedded within the backbone. Soluble polymers containing one recognition unit were synthesized from bifunctionalized DAP-based initiators (**5** and **6**) using well-defined living/controlled polymerization methodologies, either atom-transfer radical polymerization (ATRP) (using **5**) or (*N,N*-dimethylamino)pyridine-catalyzed living ring-opening polymerization (ROP) (using **6**) (Scheme 2).[45] The use of controlled polymerization methodologies allowed for control over molecular weight and provided polymer samples with low polydispersities. Polymers initiated by **5** and **6** were readily prepared according to Scheme 2. Poly(methyl methacrylate) (PMMA) and poly(*tert*-butyl acrylate) (P*t*BA) were polymerized using a CuBr-controlled ATRP methodology and resulted in polymers of predictable molecular weight and expected polydispersities (1.23−1.27) for a secondary initiator.[46] Poly(DL-lactide) was synthesized at 35 °C in methylene chloride using a procedure adapted from a recently reported DMAP-catalyzed living ring-opening polymerization methodology.[45]

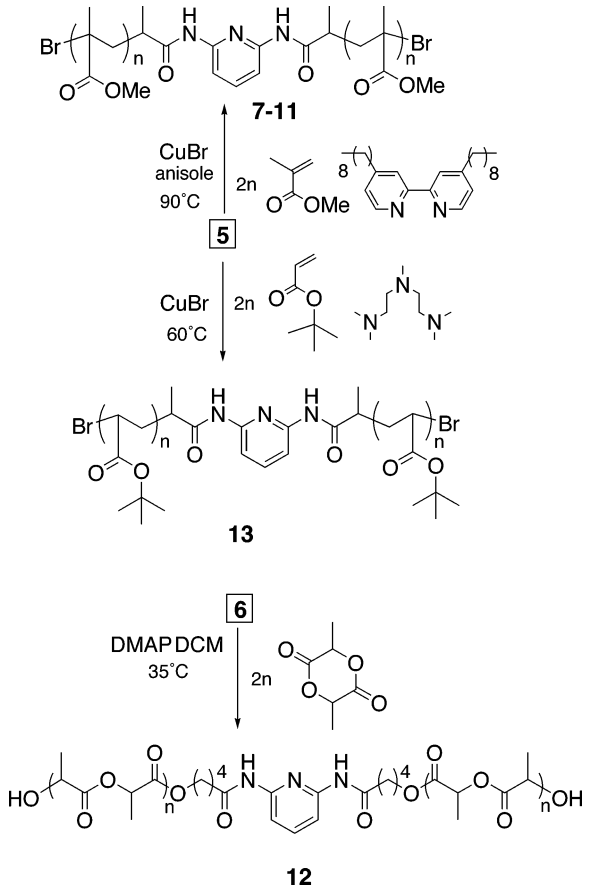
Thermodynamic Characterization of Polymer−Flavin Complexes. The affinity of the polymeric hosts for flavin **4** was experimentally quantified via fluorescence titration in chloroform. Flavin **4** has characteristic emission peak at 515 nm in chloroform that is strongly quenched upon binding to diaminopyridine derivatives, allowing the quantification of host−guest binding.[42,43,47] As expected, addition of all of the polymers (except PtBuA) to flavin solutions strongly quenched flavin fluorescence. To eliminate the possibility that the polymer chains were responsible for this quenching, PMMA samples without the DAP moiety were added to a chloroform solution containing flavin **4**. As expected, no change in fluorescence was observed, showing that

Table 1. Polymerization Conditions for the Synthesis of Polymers 7−11

polymer	**5** (mmol)	MMA (mmol)	anisole (mL)	CuBr (mmol)	DNDP (mmol)	time (h)	M_n[a]	M_w/M_n[a]
7	0.29	13.2	1.24	0.15	0.29	6	4 000	1.23
8	0.15	13.2	1.24	0.07	0.15	12	8 100	1.23
9	0.15	26.4	2.48	0.07	0.15	23	15 000	1.26
10	0.16	34.5	3.24	0.08	0.16	30	20 000	1.28
11	0.16	41.4	3.88	0.08	0.16	36	25 000	1.25

[a] Detemined by GPC calibrated with PMMA standards.

Scheme 2. Synthesis of Polymers Based on 5 and 6



the quenching we observed resulted directly from the DAP−flavin **4** recognition process.

Efficient binding of **4** was obtained using both the PLA and the PMMA polymers (Figure 2 and Table 2). PtBuA has a lower affinity for flavin **4**, presumably arising from the steric hindrance of the bulky side chains; a similar trend is observed in the comparison of K_as between the model compounds **1** and **2** and previously reported results.[44] These results indicate that the efficiency of this noncovalent interaction was dependent on the polymer chain covalently attached to the recognition unit and that the polymer chains surprisingly have a *favorable* effect on the recognition process.

Preliminary insight into the temperature dependence of host−guest interactions was obtained through variable temperature release experiments. For these studies, 99%-bound solutions of **1**:**4** (model compound of low molecular weight), **7**:**4** (PMMA), and **12**:**4** (PLA) in chloroform were prepared, and fluorescence was measured as a function of temperature. As the temperature was increased, the observed fluorescence intensity increased, indicating a decrease in the concentration of bound species (Figure 3). More binding efficiency for **1**:**4** is lost with increasing temperature than for any of the polymer samples. These results are also consistent with

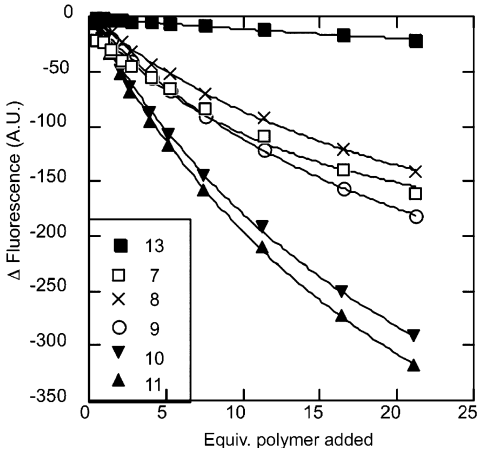


Figure 2. Fluorescence emission changes for flavin (**4**) upon addition of **7**−**11** and **13** at room temperature. Excitation = 465 nm, emission = 511 nm. Concentration of **4** = 1×10^{-4} M, equivalents guest refers to the diaminopyridine recognition element.

Table 2. Binding Constants Determined by Fluorescence Titration

compound/ polymer	$M_n \times 10^3$	M_w/M_n	K_a (M^{-1})	ΔG (kcal/mol)
1			540[c]	−3.68
2			190[c]	−3.07
7 (PMMA)	4.0[a]	1.23	282 ± 8	−3.30 ± 0.02
8 (PMMA)	8.1[a]	1.23	311 ± 9	−3.36 ± 0.03
9 (PMMA)	15.0[a]	1.23	365 ± 7	−3.45 ± 0.01
10 (PMMA)	20.0[a]	1.28	411 ± 7	−3.52 ± 0.01
11 (PMMA)	25.5[a]	1.25	522 ± 20	−3.66 ± 0.02
12 (PLA)	7.5[b]	1.39	352 ± 20	−3.47 ± 0.03
13 (P*t*BuA)	4.7[b]	1.27	56 ± 26	−2.3 ± 0.4

[a] GPC (PMMA standards). [b] GPC (PS standards). [c] Reference 44.

previous results reported by Rotello using random copolymers.[48]

Molecular weight effects on the affinity of polymer hosts with flavin **4** were examined using PMMA polymers **7**−**11** systems using samples of molecular weight 4K, 8K, 15K, 20K, and 25K.[49,51] The K_as could then be compared with reference monomers **1** and the α-branched monomer **2** that is sterically similar to the polymeric hosts.[44] The results demonstrate a monotonic increase in the binding constant with increased molecular weight (Table 2). For the shortest polymer chain (**7**$_{4K}$), the obtained binding constant is slightly higher than that of the **2**:**4** complex (280 M^{-1} vs 190 M^{-1}). As the molecular weight of the sample increased the K_a determined for each sample increased, ultimately reaching a value more than twice that of the model compound **2** and close to the value of the less hindered host **1**. It is known that in a solvent such as ethyl acetate, a good hydrogen-bond acceptor, the values for the binding constant would be extremely low, below, or near the lower limits that can be measured by our fluorescence

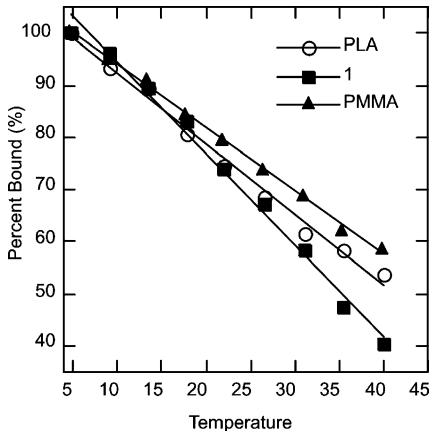


Figure 3. Percent release data for 99% bound (at 5 °C) complexes of polymers (**7** and **12**) and monomer **1** with flavin guest **4** as a function of temperature in $CHCl_3$.

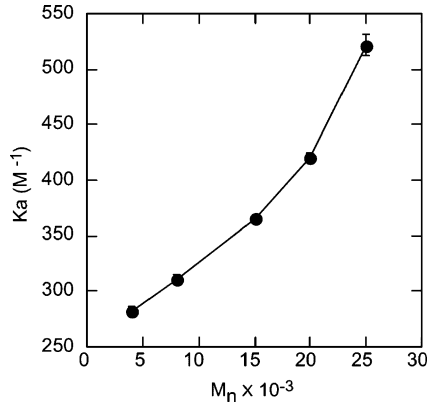


Figure 4. Plot of number-average molecular weight of PMMA samples **7**−**11** vs their observed binding constant with **4**.

technique.[42,43] Likewise, very low values for K_a should be expected in a "pure" PMMA environment, whose polarity is known to be very close to that of ethyl acetate.[50] The much larger values observed in our experiments indicate, as expected, that the local environment in the polymer is not PMMA-like and reflects the presence of $CHCl_3$ molecules in the random coil. The increase in binding efficiency observed as a function of increase in molecular weight (M_n) (Figure 4) suggests that the local environment of the binding site within the polymer coil is progressively less competitive for hydrogen bonding than that of chloroform, a weak hydrogen bond donor. This trend is compatible with well-established theories of polymer solution. It is known in particular that the average concentration of monomer units inside the volume enclosed by a radius of the polymer chain coil decreases with increasing molecular weight.[51] This implies that for longer polymer chains the local chloroform concentration around the center of mass where the binding event occurs is higher, leading to a better environment for hydrogen bonding and larger values for K_a. The exact nature of the local environment is currently being investigated and will be reported in due course.

Overall, PMMA samples **7**−**11** had a moderate change in K_a between the values of model **1** and **2**, showing that **7**−**11** have unfavorable steric hindrance competing with a favorable "polymeric" effect arising from the polymer chain, resulting in an overall increase in affinity with increasing polymer length.

Conclusions

We have designed, synthesized, and characterized polymers containing a single recognition element embedded in the middle of the polymer backbone. An enhancement of binding affinity was observed for PMMA and PLA polymer backbones, indicating the polymer chains covalently attached to the recognition unit cause a change in the local binding environment. Binding affinity of **7**−**11** was ranged between those of **1** and **2**. The molecular weight dependence of binding affinity of **7**−**11** arises from the difference of the average solvent concentration inside the volume enclosed by the polymer chain. Further studies focused on determining the origins of this enhancement as well as applications of these systems in catalysis and delivery applications are currently underway.

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