Self-Sorting in Polymers

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ABSTRACT: Random and block copolymers containing two different classes of hydrogen-bonding side-chains have been prepared by ring-opening metathesis polymerization. The resulting copolymers can be viewed as "universal polymer backbones" based solely on two competitive hydrogen-bonding pairs. The hydrogen-bonding side chains containing thymine and cyanuric acid-based recognition motifs are shown to self-assemble with their complementary diamido pyridine and isophthalic wedge moieties, respectively, even in the presence of competitive recognition sites, i.e., selective functionalization of the copolymers can be accomplished via a one-step orthogonal self-assembly approach displaying self-sorting in a competitive environment. These results clearly demonstrate the concept of self-sorting in synthetic polymers and suggest the design of complex polymeric materials containing competitive noncovalent interactions.

Introduction

Self-sorting is the ability of objects such as molecules to find and self-assemble selectively with their corresponding recognition units. From complex systems, such as DNA replication and transcription, to simple phenomena, such as oil−water phase separation, self-sorting is evident throughout our daily lives. In synthetic systems, self-sorting based on hydrogen-bonding has been explored as a general phenomenon in low molecular weight organic molecules.[1] For example, Isaac and co-workers have shown that in the presence of complex mixtures self-sorting of small-molecule receptors via hydrogen-bonding still occurs regardless of potential competitive interactions.[1a] However, to date, the principle of self-sorting in polymeric and complex un-natural systems that can be viewed as simple synthetic analogue to biopolymers such as DNA has not been explored. While in polymer science many reports in the literature outline the use of pendant side-chain polymers based on multiple recognition units,[2] these examples however are in highly controlled systems without the presence of a competitive recognition unit. In this manuscript, we investigate the concept of self-sorting in polymers by employing norbornene copolymers composed of two different hydrogen-bonding side-chains. These hydrogen-bonding side-chains contain thymine and cyanuric acid-based recognition units that are able to self-assemble with diamido pyridine[3] and isophthalic wedge moieties,[4] respectively. We demonstrate that the principle of self-sorting can be translated to synthetic side-chain-functionalized polymers, i.e., copolymer side-chains self-assemble with their corresponding recognition unit in the presence of competitive recognition sites.

The concept of self-sorting in polymers is essential for replication and translation of genetic material. The Watson−Crick-type base pairs adenine−thymine, adenine−uracil, and guanine−cytosine are the three dominant sets of hydrogen-bonded dimers that nature offers. The specific interactions within these complementary pairs play a key role in the storage and decoding of genetic material. Recent research efforts have focused on the manipulation of the Watson−Crick base pairs of DNA[5] and employing them as a synthetic tool, using complementary DNA oligomers as a template to bring reactants together, thereby discovering new reactions.[6] Other investigations have utilized hydrogen-bonding moieties as enzyme mimics to induce catalytic activity.[7] In these examples, the inherent self-sorting of hydrogen-bonding receptors is key. The polymeric system presented herein follows this trend by relying on hydrogen-bonded dimers and a hydrogen-bonded enzyme mimic as recognition units.

The copolymers introduced herein can be viewed as a "universal polymer backbone"[2c] based solely on hydrogen-bonded recognition motifs that are able to self-assemble with their corresponding receptor molecule in the presence of competitive recognition units. The copolymers are based on two monomers that encompass three design elements: (1) norbornene as the polymerizable unit that propagates in a living fashion via ring-opening metathesis polymerization (ROMP),[10] (2) a spacer molecule to increase solubility and to decouple the polymer from the hydrogen-bonding recognition units, and (3) the recognition units themselves that are either thymine derivatives that can undergo three hydrogen bonds to self-assemble with diaminopyridines[3] or cyanuric acids that are able to self-assemble with isophthalic wedge type receptor via six hydrogen bonds (Chart 1).[4,9] These recognition units were chosen because of their structural similarity and thus their possibility to display competitive interactions during the self-assembly process.

Experimental Section

Materials. Unless otherwise noted, all commercially available reagents and solvents were used without further purification. Dueterated solvents were distilled over calcium hydride and stored in the dark. Anhydrous dichloromethane and THF were dried via passage through copper oxide and alumina columns under argon. Column chromatography was carried out on silica gel 60, 230 ± 400 mesh (Whatman). Gel-permeation chromatographies (GPC) were carried out on polymer solutions in THF at 30 °C (column combination: 2x

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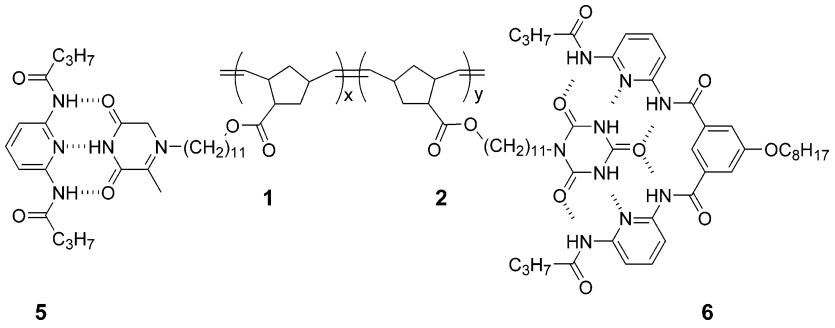
Chart 1. Fully Hydrogen-Bonded Copolymer and the Corresponding Recognition Units



American Polymer Standards 10 μm particle size, linear mixed bed packing, flow rate 1 mL min^{-1}) with a Waters 1525 binary pump coupled to a Waters 2414 refractive index detector. Calibrations are based on poly(styrene) standards. NMR spectra were recorded on a Varian Mercury 300 spectrometer (^{1}H, 300 MHz; ^{13}C, 75 MHz). Chemical shifts are reported in ppm on the δ scale relative to the solvent signal. Electrospray ionization (ESI) mass spectra were obtained on a Micromass Quattro LC spectrometer and fast atom bombardment (FAB) mass spectra on a VG Instruments 70SE spectrometer. Elemental analyses were performed by Atlantic Microlabs, Norcross, GA. Monomer **2**[4c] and recognition units **5**[3e] and **6**[4c,f] were prepared as previously reported.

***exo*-Bicyclo[2.2.1]hept-5-ene-2-carboxylic acid-11-(3-methyl-4,6-trioxo-[1,5]diazinan-1-yl)-undecyl Ester (1).** To a stirred solution of **4** (4.0 g, 10.8 mmol)[4c] and thymine (108 mmol) in DMSO (100 mL), K_2CO_3 (3.0 g, 22 mmol) was added. The reaction mixture was allowed to stir at room temperature for 60 h, poured into a solution of $NaHSO_3$(aq) (500 mL), extracted with a 1:1 mixture of diethyl ether/dichloromethane, and dried over magnesium sulfate. The solvent was removed by rotary evaporation, and the residue was purified by passage over silica (1:1 mixture EtOAc/hexanes). After drying on high vacuum, **1** was obtained as a white solid in 53% yield. ^{1}H NMR (300 MHz $CDCl_3$): δ = 9.33 (br s, 1H, NH), 6.96 (br s, 1H), 6.10 (m, 2H, CH=CH), 4.07 (t, 2H, J = 6.7 Hz, CH_2O), 3.88 (t, 2H, J = 7.5 Hz, CH_2N), 3.03 (m,1H), 2.91 (m, 1H), 2.22 (m, 1H), 1.91 (m, 1H), 1.90 (s, 3H), 1.69−1.49 (m, 5H), 1.41−1.24 (m, 16H). ^{13}C NMR (75 MHz $CDCl_3$): δ = 176.3, 164.5, 151.1, 140.6, 138.2, 135.9, 111.2, 64.9, 48.9, 46.9, 46.7, 43.5, 41.9, 30.64, 29.8, 29.5, 29.4, 29.0, 26.8, 26.3, 12.7. MS (EI): *m/z* (%) = 416.26601 (M^+, 416.26751 calcd.). Anal. Calcd for $C_{24}H_{36}N_2O_4$: C, 69.10; H, 8.64; N, 6.70. Found: C, 68.75; H, 8.83; N, 6.64.

Polymerizations. To a 0.2 M stirred solution of monomer in THF, 0.006 mmol of ruthenium catalyst was added. The mixture was stirred at room temperature, and the reaction progress was monitored by ^{1}H NMR until completion. After complete conversion, two drops of ethyl vinyl ether were added to terminate the reaction. The polymers were purified by precipitation into hexanes.

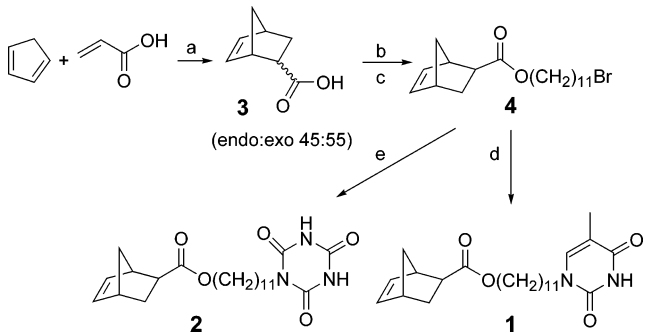
Polymer 1. ^{1}H NMR (300 MHz, 15:85 dioxane-d_6:$CDCl_3$): δ = 9.8 (br s, 1H, NH), 6.90 (br s, 1H), 5.4−5.1 (m, 2H), 3.90 (br m, 2H), 3.60 (t, 2H, J = 5.5 Hz, CH_2N), 2.7−2.3 (br m, 5 H), 2.2−0.5 (br m, 23 H).

Copolymer 1:2. ^{1}H NMR (300 MHz, 15:85 dioxane-d_6: $CDCl_3$): δ = 10.0 (br s, 2H, NH), 9.8 (br s, 1H, NH), 6.90 (br s, 2H), 5.4−5.1 (m, 4H), 3.90 (br m, 4H), 3.60 (t, 4H, J = 6.4 Hz, CH_2N), 2.7−2.3 (br m, 10 H), 2.2−0.5 (br m, 46 H).

Self-Assembly. To a 0.04 M solution (15:85 dioxane: chloroform) of polymer, 2.8 equiv of recognition unit (either **5**, **6**, or both) dissolved in 0.5 mL of 15:85 dioxane:chloroform were added dropwise.

Titration Studies. Association constants were measured by NMR titration of a 0.2 M solution (15:85 dioxane:chloroform) of the receptor molecules with a 0.04 M solution (based on recognition units) of the corresponding polymer, where the molarity is based on the number of recognition units. The chemical shifts of the imide protons on either the thymine or the cyanuric acid moieties were monitored by ^{1}H NMR. The NMR data was evaluated using the computer program ChemEquili.[11]

Scheme 1. Synthesis of Monomers 1 and 2[a]



[a] Key: (a) 180 °C, reflux 8 h, 70%; (b) 1. NaOH, H_2O, 2. KI, I_2, H_2O 44%; (c) DCC/DMAP, Br $(CH_2)_{11}$OH, 50 °C, 82%; (d) thymine, K_2CO_3, DMSO, room temperature, 53%; and (e) cyanuric acid, K_2CO_3, DMSO, room temperature, 36%.

Results and Discussion.

Monomer Synthesis. The monomers were synthesized as outlined in Scheme 1. Isomerically pure *exo*-norbornene carboxylic acid was synthesized from the endo:exo mixture by iodolactonaization using established literature procedures.[8] The *exo*-norbornene carboxylic acid was then functionalized with 11-bromoundecanol using DCC/DMAP to yield the corresponding norbornene bromide **4**.[9] Monomers **1** and **2** were formed in one step by reacting **4** with an excess of either thymine or cyanuric acid, respectively. Dibutylamido pyridine **5** was synthesized in one step from the acylation of diamino pyridine (recrystallized from chloroform) using butyl chloride. The octyl-ether isopthalic wedge receptor **6** was synthesized in close analogy to literature procedures[4c,f] after functionalizing the phenolic hydroxyl of dimethyl 5-hydroxy isopthalate with 1-bromo-octane via a Williamson ether synthesis.

Polymer Synthesis and Living Characterization. All monomers were subjected to ROMP using Grubbs' first-generation catalyst.[10] The polymerizations were carried out in 0.2 M solutions of deuterated tetrahydrofuran at room temperature with monomer-to-catalyst ratios of 20:1−120:1. All polymerizations were monitored via ^{1}H NMR. A 50:1 monomer-to-catalyst ratio of **2** polymerizes within less than five minutes, while the ROMP of **1** (50:1 monomer-to-catalyst ratio) is complete within an hour. Figure 1 shows the kinetic data for the ROMP of **1** (the detailed polymerization behavior of **2** has been reported before[4c]). All polymers were purified and isolated by repeated precipitations into hexanes. The polymers were characterized by GPC, and the

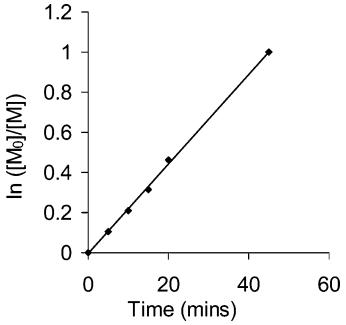


Figure 1. Kinetic data for the ROMP of **1**.

Table 1. Polymer Characterization Data for Polymers 1 and 2

	[M]:[I]	M_n (10^{-3})	M_w (10^{-3})	PDI
poly-**1**	20	12.0	15.0	1.23
	40	20.0	29.5	1.46
	60	26.8	42.2	1.57
	80	33.2	55.2	1.66
	120	46.7	63.1	1.35
poly-**2**	20	12.1	14.6	1.20
	40	21.2	29.1	1.26
	60	30.9	42.3	1.37
	80	44.7	66.5	1.49
	120	66.1	108	1.64

obtained molecular weights and polydispersities are displayed in Table 1.

For both monomers we explored the living nature of the polymerization by investigating whether the stoichiometry was decisive in the resultant polymers. A linear relationship between M_n and the monomer-to-catalyst ratios was found in both cases (Figure 2A). To further characterize the living nature of the monomers, we carried out homoblock copolymerizations in two steps. A 20:1 [M]:[I] ratio of the desired monomer (**1** or **2**) was polymerized to completion and allowed to sit for 1 h. Subsequently, 100 equiv of additional monomer were added. As shown in Figure 2B, a dramatic increase in the molecular weight of **1** was observed for the polymer after the addition of additional monomer. These results in conjunction with the stoichiometric experiments clearly prove the living nature of **1**. While this dramatic increase during the block copolymerization experiment did not occur for polymers based on **2**, polymerization of **2** still displays a linear relationship between M_n and monomer-to-catalyst ratios. This data suggests but does not prove unequivocally the living nature of the ROMP of **2**.

After establishing the living nature of the ROMP of **1** and **2**, we synthesized AB block copolymers starting with monomer **1** followed by **2**. A 50:1 [M]:[I] ratio of **1** was polymerized to completion. Subsequently, 50 equiv of **2** were added and allowed polymerize to completion. Random copolymers were synthesized by polymerizing an equimolar solution of **1** and **2** (50 equiv each) to completion. Both copolymers were characterized by GPC and ^{1}H NMR. Polymers were found to have molecular weights between 1 and 7.0×10^4 vs poly(styrene) standards, with polydispersities ranging from 1.2 to 1.6 (Table 1).

Self-Assembly. The pendant functional groups of our polymers have been shown throughout the literature to exhibit well-defined self-assembly behavior with their corresponding recognition units, diamino pyridine for **1** and isophthalic wedge for **2**.[3,4] To address the question whether self-sorting occurs on polymers, i.e., if hydrogen-bonded recognition units on polymers containing two hydrogen-bonded moieties are able to find their complementary recognition units in the presence of each other, we carried out self-assembly studies in 15:85 dioxane:chloroform solutions. First we investigated the self-assembly of small molecules onto the monomers and the homopolymers of **1** and **2** by carrying out NMR titration experiments of the monomers and the individual homopolymers thereby establishing the hydrogen-bonding properties and measuring the association constants of **5** onto **1** and **6** onto **2** *without* the presence of competitive moieties. All association constants were determined by titration of the corresponding recognition unit (**5** or **6**) into a chloroform/dioxane solution of the polymer (**1** and **2**) and following the shift of the polymeric imide signals by ^{1}H NMR (Figures 3 and 4 and Table 2). The association constants of the self-assembly steps of **5** onto **1** and **6** onto **2** were measured to be 1.0×10^2 and 3.0×10^2 M^{-1}, respectively. These association constants are very similar to the association constants between the monomers and their corresponding units suggesting that the bond strengths between the receptor units along the polymer and their small molecule recognition units are comparable to the bond strength of their monomeric analogues. It is important to note that these constants were measured in the presence of a competitive solvent (mixture of dioxane:chloroform), thereby reducing the association constant to reported values in the literature that were obtained in pure halogenated solvents.[3,4] However, the use of this mixed solvent system was necessary to tailor the solubility of both homopolymers and copolymers throughout all self-assembly experiments thereby allowing us to compare all data.

To prove if the concept of self-sorting in synthetic polymers is possible, we carried out titration experiments on both block and random copolymers containing 50:50 mixtures of **1** and **2** using both recognition units in a one pot procedure (Figures 5 and 6). Figure 6 shows the amide region (10.5−13.5 ppm) of the ^{1}H NMR spectra of the homopolymers self-assembled with 2.8 equiv of their corresponding units in a mixture of 15:85 dioxane-d_8:$CDCl_3$ followed by both the block and random copolymers assembled with 2.8 equiv of both complementary units. The figure clearly shows that the signals observed for the homopolymers (spectra A and B) are a superposition with those observed for the copolymers (spectra C and D). This superposition is evident that self-sorting of these mixed solutions does occur, i.e., each individual recognition unit finds its receptor molecule in the copolymer mixtures with the same fidelity as in the homopolymer solutions. We also determined the binding constants of both side-chain recognition units on the random and block copolymers. The association constants were measured to be 1.0×10^2 and 3.2×10^2 M^{-1} for the random copolymer and 6.0×10^1 and 2.5×10^2 M^{-1} for the block copolymer. These numbers are strikingly similar to their noncompetitive homopolymer analogs which were measured to be 1.0×10^2 and 3.0×10^2 M^{-1}. It is important to note that the association constants for the random and block copolymers are the same within the error range of the measurements. Combining these results on the association constants measurements with the titration and NMR data clearly demonstrates that, by simply selecting competitive recognition units that have well-defined self-assembly motifs in equimolar concentrations, it is

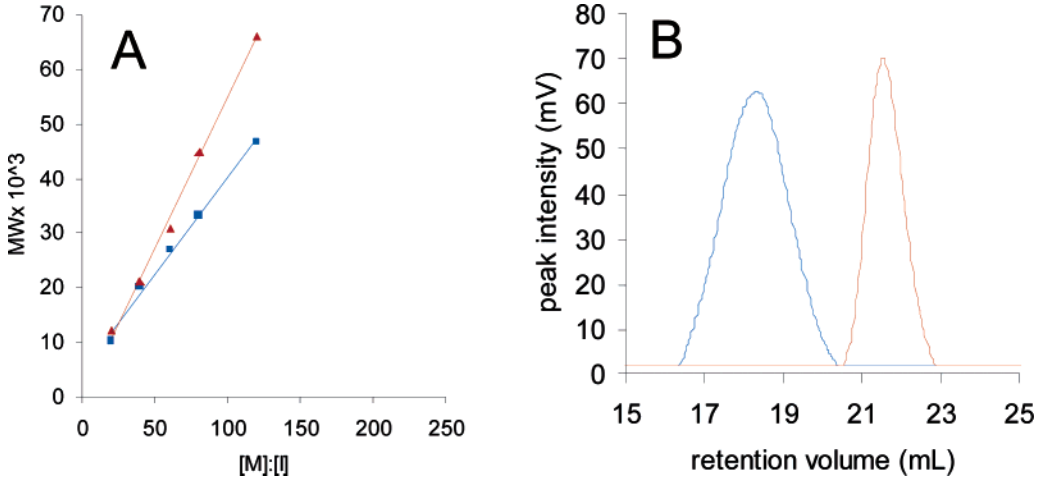


Figure 2. (A) Characterization of the living character of the ROMP of monomers **1** and **2**: (■) stoichiometric polymerization of **1**, (▲) stoichiometric polymerization of **2**. (B) GPC traces of polymers prepared using monomer **1**. (blue) Polymer after complete conversion ([M]:[I] = 20:1, $M_w = 1.5 \times 10^4$, $M_n = 1.2 \times 10^4$, polydispersity index (PDI) = 1.23). (red) Same polymer after standing for 0.5 h followed by polymerization of 100 equiv ([M2]:[M1] = 100:1, [M]:[I] = 20:1, $M_w = 1.1 \times 10^5$, $M_n = 7.2 \times 10^4$, PDI = 1.78) of additional monomer.

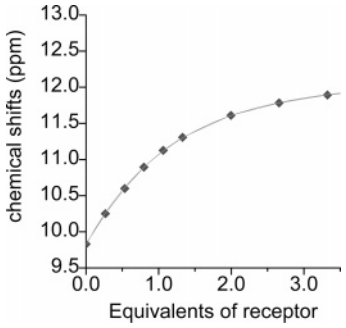


Figure 3. Chemical shifts of the imide protons of poly-**1** (◆) as a function of the equivalents of **5**.

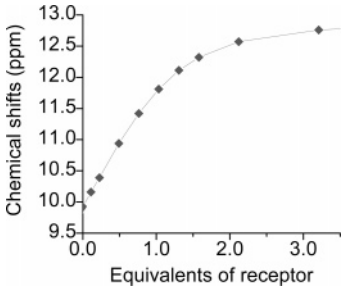


Figure 4. Chemical shifts of the imide protons of poly-**2** (◆) as a function of the equivalents of **6**.

Table 2. Association Constants Determined by ^{1}H NMR Data[11]

	K_a [M^{-1}]
Association Constants of **1:5**	
monomer **1:5**	1.0×10^2 (±4)
poly-**1:5**	1.0×10^2 (±5)
50:50 block copoly. **1:2:5**	8.0×10^1 (±8)
50:50 random copoly. **1:2:5**	1.0×10^2 (±10)
Association Constants of **2:6**	
monomer **2:6**	3.0×10^2 (±52)
poly-**2:6**	3.0×10^2 (±60)
50:50 block copoly. **1:2:6**	2.5×10^2 (±108)
50:50 random copoly. **1:2:6**	3.2×10^2 (±134)

possible to translate the concept of self-sorting into synthetic polymer chemistry.

With the previous result clearly demonstrating the principle of self-sorting on random and block copolymers, the question arises whether individual recognition units along the copolymers can be addressed by their complementary receptors in the presence of a second competitive recognition unit. To address this question, we investigated the copolymers by measuring the association constants using only one recognition unit at a time, i.e., single self-assembly experiments in the presence of a competitive receptor (Figure 7). The binding constants were determined by a stepwise titration of the single recognition unit into a copolymer solution. The dynamic equilibrium of the hydrogen bonds is responsible for competition when a single-side chain's pairing nature is left unsatisfied. Because of the competitive nature of the monomers (when there is only one complementary receptor available for hydrogen-bond-

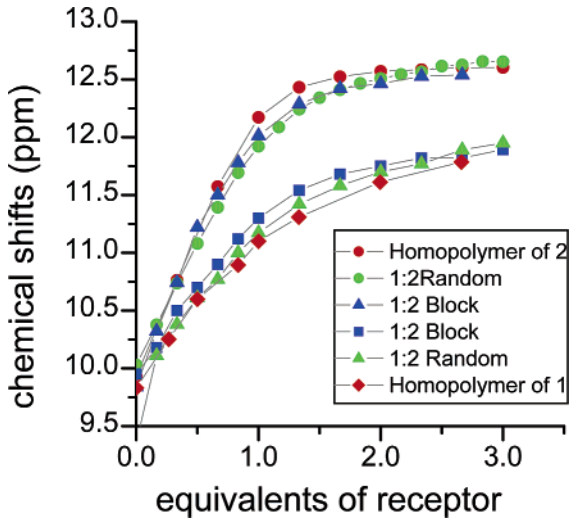


Figure 5. Self-sorting on polymers: NMR titration curve of the addition of equimolar solutions of both recognition units at once: (red circle) shift of the imide protons of the cyanuric acid moieties of a cyanuric acid based homopolymers, (green circle) shift of the imide protons of the cyanuric acids of a 50:50 **1:2**-random copolymer, (blue triangle) shift of the imide protons of the cyanuric acids of a 50:50 **1:2**-block copolymer, (blue square) shift of the imide protons of the thymines of a 50:50 **1:2**-block copolymer, (green triangle) shift of the imide protons of the thymines of a 50:50 **1:2**-random copolymer, and (red rhombus) shift of the imide protons of the thymine moieties of thymine homopolymers.

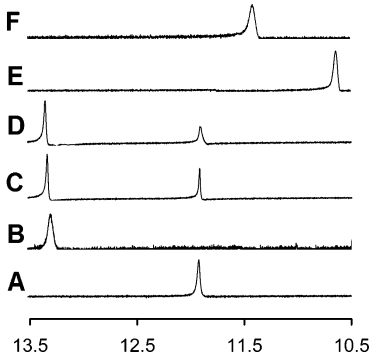


Figure 6. Self-sorting on polymers. Amide region of the ^{1}H NMR of the polymers after the addition of 2.8 equiv of recognition units (A) homopolymer (50 repeating units) of **1** after the addition of 2.8 equiv of **5**, (B) homopolymer (50 repeating units) of **2** after the addition of 2.8 equiv of **6**, (C) random copolymer of **1** and **2** after the addition of 2.8 equiv of both **5** and **6**, (D) block copolymer of **1** and **2** after the addition of 2.8 equiv of both **5** and **6**, (E) homopolymer (50 repeating units) of **2** after the addition of 2.8 equiv of **5**, and (F) homopolymer (50 repeating units) of **1** after the addition of 2.8 equiv of **6**.

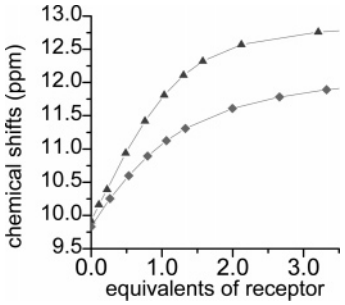


Figure 7. Chemical shifts of a 50:50 **1:2** random copolymer stepwise titration with only one recognition unit at a time: (▲) shift of the imide protons of the cyanuric acid moieties with **6**; (◆) shift of the imide protons of the thymine moieties with **5** on the copolymer.

ing), the association constants of the copolymers are slightly decreased. The stronger interaction of **2:6** shows less of a decrease from a K_a of 3.0×10^2 M^{-1} for the homopolymer to 2.5×10^2 M^{-1} for the copolymer systems, as opposed to that of the weaker interaction of **1:5** from 1.0×10^2 M^{-1} to 6.0×10^1 M^{-1}. This result demonstrates that (a) competitive interactions take place along the copolymer backbones and (b) by employing recognition units with stronger association constants (such as **2:6**) any interference from competitive moieties can be minimized.

Finally, we investigated if the hydrogen-bonding and self-sorting processes are truly dynamic processes. If the notion of a truly dynamic process holds, a stepwise self-assembly experiment onto the copolymers with both receptor molecules should yield fully self-sorted copolymers. Therefore, we carried out self-assembly experiments on the random and block 50:50 copolymers in a stepwise fashion using first one receptor (12 equiv) followed by the second one and vice versa. Figures 8 and 9 show the results of these experiments. In both cases, the titration curves of the first self-assembly step clearly showed the expected shifts of the imide protons of the targeted side-chain recognition unit along the copolymers. However, the nontargeted recognition unit also displayed some degree of hydrogen-bonding, which is evident by the slow shifting of the imide protons of the nontargeted side-chain recognition unit. Nevertheless,

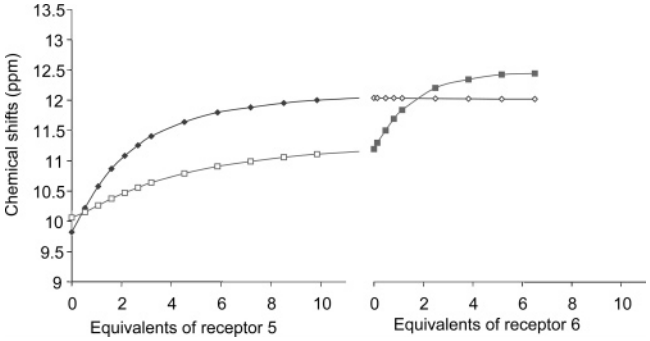


Figure 8. Chemical shifts of a 50:50 **1:2** random copolymer stepwise titration (first addition of **5** followed by the addition of **6**): (◆) thymine imide proton shift associated with **5**, (◇) thymine imide proton shift associated with **6** after full assembly of **5** (equivalents are for a combination of **5** and **6**), (□) cyanuric acid imide proton shifts associated with the addition of **5**, followed by the addition of **6** (■).

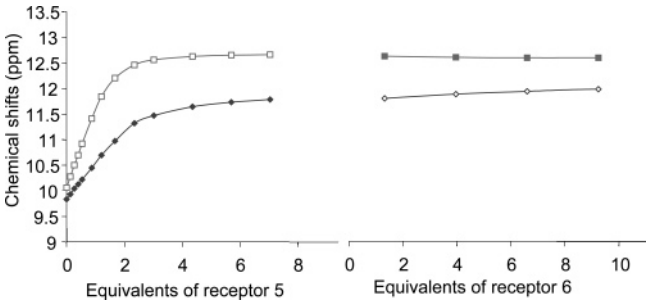


Figure 9. Chemical shifts of a 50:50 **1:2** random copolymer stepwise titration, (first addition of **6** followed by the addition of **5**): (◆) thymine imide proton shift associated with **6**, (◇) thymine imide proton shift associated with **5** after full assembly of **6** (equivalents are for a combination of **5** and **6**), (□) cyanuric acid imide proton shifts associated with the addition of **6**, followed by the addition of **5** (■).

when carrying out the second self-assembly titration, these weak nonspecific hydrogen-bonding interactions between the first receptor unit and its noncomplementary copolymer side-chain give way to a specific hydrogen-bonding interaction between the second receptor and its targeted recognition unit as evident by the strong and selective titration curve. Furthermore, *NO* shifts of the imide protons of the first targeted self-assembly pair are observed, i.e., in Figures 8 and 9, the imide signals corresponding to **1** and **2**, respectively, do not change or increase further; however the signals associated with **2** or **1** show a subsequent increase. The final placements of each of the imide signals of both **1** and **2** in Figures 8 and 9 are an exact superposition of the full titration of both of their corresponding homopolymers. Therefore, while the binding constants in a competitive environment (only one recognition unit) are decreased, when the competition is removed through the addition of a second recognition unit, self-sorting is again observed.

Conclusion

We have clearly demonstrated that self-sorting can be translated to synthetic side-chain-functionalized polymers and occurs even in the presence of highly competitive recognition units. This was shown by designing, synthesizing (via ROMP), and self-assembling copolymers containing both cyanuric and thymine acid-based moieties with their corresponding recognition units. The resulting copolymers can be viewed as "universal polymer backbones" based solely on two

competitive hydrogen-bonding recognition motifs. Selective functionalization of the resultant copolymers was accomplished via a one-step orthogonal self-assembly displaying self-sorting in a competitive environment. This methodology, that can be viewed on a very primitive level as a synthetic DNA analogue, has the potential to create a variety of complex, rapidly functionalizable materials for use in areas such as material science, drug delivery, and biomimetic chemistry.

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References and Notes

(1) (a) Wu, A.; Isaacs, L. *J. Am. Chem. Soc.* **2003**, *125*, 4831−4835. (b) Mukhopadhyay, P.; Wu, A.; Isaacs, L. *J. Org. Chem.* **2004**, *69*, 6157−6164. (c) Corbin, P. S.; Lawless, L. J.; Li, Z.; Yuguo, M.; Witmer, M. J.; Zimmerman, S. C. *Proc. Natl. Acad. Sci. U. S.A.* **2002**, *99*, 5099−5104. (d) Cai, M.; Shi, X.; Sidorov, V.; Fabris, D.; Lam, Y.-F.; Davis, J. T. *Tetrahedron* **2002**, *58*, 661−671. (e) Jolliffe, K. A.; Timmerman, P.; Reinhoudt, D. N. *Angew. Chem., Int. Ed.* **1999**, *38*, 933−937. (f) Ma, Y.; Kolotuchin, S. V.; Zimmerman, S. C. *J. Am. Chem. Soc.* **2002**, *124*, 13757−13769. (g) Wu, A.; Chakraborty, A.; Fettinger, J. C.; Flowers, R. A., II.; Isaacs, L. *Angew. Chem., Int. Ed.* **2002**, *41*, 4028−4031.

(2) (a)Valkama, S.; Lehtonen, O.; Lappalainen, K.; Kosonen, H.; Castro, P.; Repo, T.; Torkkeli, M.; Serimaa, M.; Brinke, G. T.; Leskelä, M.; Ikkala, O. *Macromol. Rapid Commun.* **2003**, *24*, 556−560. (b) Bazzi, H. S.; Bouffard, J.; Sleiman, H. F. *Macromolecules* **2003**, *36*, 7899−7902. (c) Pollino, J. M.; Stubbs, L. P.; Weck, M. *J. Am. Chem. Soc.* **2004**, *126*, 563−567. (d) Ruokolainen, J.; Makinen, M.; Torkkeli, M.; Makela, T.; Serimaa, R.; ten Brinke, G. *Science* **1998**, 280, 557−560. (e) van Ekenstein, G. A.; Polushkin, E.; Nijland, H.; Ikkala, O.; ten Brinke, G. *Macromolecules* **2003**, *36*, 3684−3688.

(3) (a) Lehn, J.-M. *Supramolecular Chemistry*; Wiley-VCH: Weinheim, 1995. (b) Thilbault, R. J.; Hotchkiss, P. J.; Gray, M.; Rotello, V. M. *J. Am. Chem. Soc.* **2003**, *125*, 11249−11252. (c) Ilhan, F.; Gray, M.; Rotello, V. M. *Macromolecules* **2001**, *34*, 2597−2601. (d) Carroll, J. B.; Waddon, A. J.; Nakade, H.; Rotello, V. M. *Macromolecules* **2003**, *36*, 6289−6291. (e) Stubbs, L. P.; Weck, M. *Chem.−Eur. J.* **2003**, 9, 992−999. (f) Pranata, J.; Wierschke, S. G.; Jorgenson, W. L. *J. Am. Chem. Soc.* **1991**, *113*, 2810−2819. (g) Murray, T. J.; Zimmerman, S. C. *J. Am. Chem. Soc.* **1992**, *114*, 4010−4011. (h) Jorgenson, W. L.; Pranata, J. *J. Am. Chem.* Soc. **1990**, *112*, 2008−2010. (i) Kyogoku, Y.; Lord, R. C.; Rich, A. *Proc. Natl. Acad. Sci. U.S.A.* **1967**, *57*, 250−257. (j) Beijer, F. H.; Sijbesma, R. P.; Vekemans, J. A.; Meijer, E. W.; Koojman, H.; Spek, A. *J. Org. Chem.* **1996**, *61*, 6371−6380. (k) 26. Dewey, V. C.; Kidder, G. W. *J. Med. Chem.* **1968**, *11*, 126−129.

(4) (a) Berl, V.; Schmutz, M.; Krische, M. J.; Khoury, R. G.; Lehn, J.-M. *Chem.−Eur. J.* **2002**, *8*, 1227−1244. (b) Binder, W. H.; Kunz, M. J.; Kluger, C.; Hayn, G.; Saf, R. *Macromolecules* **2004**, *37*, 1749−1759. (c) Pollino, J. M.; Nair, K. P.; Stubbs, L. P.; Adams, J.; Weck, M. *Tetrahedron* **2004**, *60*, 7205−7215. (d) Chang, S. K.; Hamilton, A. D. *J. Am. Chem. Soc.* **1988**, *110*, 1318−1319. (e) Chang, S. K.; Van Engen, D.; Fan, E.; Hamilton, A. D. *J. Am. Chem. Soc.* **1991**, *113*, 7640−7645. (f) Berl, V.; Krische, M. J.; Huc, I.; Lehn, J.-M.; Schmutz, M. *Chem.−Eur. J.* **2000**, *6*, 1938−1947. (h) Loeb, S. J.; Shimizu, G. K. H. *J. Chem. Soc., Chem. Commun.* **1993**, 1395. (i) Binder, W. H.; Kluger, C. *Macromolecules* **2004**, *37*, 9321−9330.

(5) Kool, E. T. *Chem. Rev.* **1997**, *97*, 1473−1487.

(6) Gartner, Z. J.; Kanan, M. W.; Liu, D. R. *J. Am. Chem. Soc.* **2002**, *124*, 10304−10306. (b) Calderone, C. T.; Puckett, J. W.; Gartner, Z. J.; Liu, D. R. *Angew. Chem., Int. Ed.* **2002**, *41*, 4104−4108. (c) Kanan, M. W.; Rozenman, M. M.; Sakurai, K.; Snyder, T. M.; Liu, D. R. *Nature* **2004**, *431*, 545−549.

(7) (a) Tecilla, P.; Jubian, V.; Hamilton, A. D. *Tetrahedron* **1995**, *51*, 435−438. (b) Valenta, J. N.; Dixon, R. P.; Hamilton, A. D.; Weber, S. G. *Anal. Chem.* **1994**, *66*, 2397−2403. (c) Tecilla, P.; Chang, S. K.; Hamilton, A. D. *J. Am. Chem. Soc.* **1990**, *112*, 9586−9590.

(8) (a) Manning, D. D.; Strong, L. E.; Hu, X.; Beck, P. J.; Kiessling, L. L. *Tetrahedron* **1997**, *53*, 11937−11952. (b) Ver Nooy, C. D.; Rondestvedt, C. S. *J. Am. Chem. Soc.* **1955**, *77*, 3583−3586. (c) Roberts, J. D.; Trumbull, E. R.; Bennett, W.; Armstrong, R. *J. Am. Chem. Soc.* **1950**, *72*, 3116−3124.

(9) Pollino, J. M.; Weck, M. *Synthesis* **2002**, 1277−1285.

(10) *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, 2003.

(11) Solov'ev, V. *ChemEquili 6.1* **1996**−**1998**.

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