

Modular and Dynamic Functionalization of Polymeric Scaffolds

CLINTON R. SOUTH, CAROLINE BURD, AND MARCUS WECK*

School of Chemistry and Biochemistry, Georgia Institute of Technology, Atlanta, Georgia 30332-0400.

Received June 20, 2006

ABSTRACT

The design and synthesis of multifunctionalized, architecturally controlled polymers is a prerequisite for a variety of future applications of polymeric materials. On the basis of Nature's use of self-assembly in the creation of biomaterials, this Account describes concepts that were developed over the past 5 years that utilize noncovalent interactions such as hydrogen bonding, ionic interactions, electrostatic interactions, metal coordination, and π - π stacking in modification of copolymer side-chains to obtain multifunctional polymeric materials, induce polymer morphology changes, and influence bulk-polymer properties.

Introduction

In a perspective article last year current research in polymer chemistry was described as highly interdisciplinary with a large number of new research foci ranging from nanoscience to biorelated materials.¹ Challenges in polymer science have been changing dramatically over the past two decades, specifically in the ever-expanding field of polymer synthesis. In particular, three basic research efforts have fascinated the synthetic polymer chemist since the 1980s: (i) development of highly controlled and living polymerization methods, (ii) investigations into new catalysts that allow for full stereocontrol during polymerizations, and (iii) rapid synthesis of multifunctional copolymers. The first two research foci are still areas of intense investigation but have resulted already in a

Clinton South completed his B.S. degree in Chemistry in 2004 from The University of North Alabama. He is currently a third-year graduate student at Georgia Tech in Dr. Weck's group. Clint's research interests are supramolecular systems that can be manipulated noncovalently and applications of these systems in templated synthesis, materials, and surface science.

Caroline Burd earned her B.S. degree in Chemistry in 2002 from The University of Miami. She is currently a graduate student at Georgia Tech, working under the supervision of Dr. Weck. Her Ph.D. research focuses on noncovalent polymeric assemblies based on hydrogen bonding and metal coordination for the development of organized nanostructures.

Marcus Weck obtained his Diploma in Macromolecular Chemistry from the University of Mainz, working with Helmut Ringsdorf, and in 1998 his Ph.D. degree from the California Institute of Technology under the direction of Robert H. Grubbs. After a postdoctoral stay at Harvard University with George M. Whitesides, he joined the faculty at the Georgia Institute of Technology in 2000, where he is currently an Associate Professor. His research interests are in organic and polymer chemistry as well as materials science. The main focus of his group is on supported catalysis and the introduction of complexity through the use of multistep self-assembly to design and synthesize polymers, organized assemblies, and nanostructures.

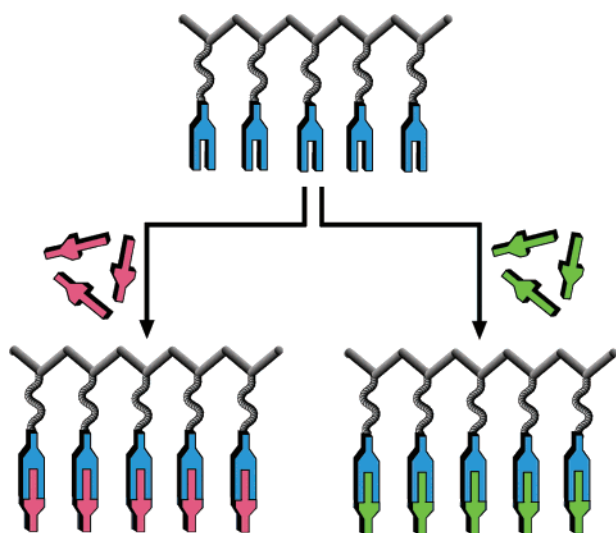
number of impressive accomplishments. Consider, for example, the developments in controlled polymerization methods. Twenty years ago the only widely useful living polymerization method was ionic polymerization.² Today, polymerization methods such as ring-opening metathesis polymerization (ROMP)³ and controlled radical polymerizations⁴ are standard methods in every polymer chemist's synthetic repertoire. Similar advances in the design and synthesis of stereospecific catalysts for a wide variety of polymerization methods have been accomplished. Ziegler–Natta polymerizations, for example, can be carried out in a highly stereoregular fashion using a wide variety of early, and more recently, late transition metals.⁵ Another example is the stereoregular ring-opening polymerization of lactides resulting in the formation of poly(lactic acid), an important biorenewal and biodegradable polymer for biomedical applications.⁶ In contrast, the third research focus, easy and rapid synthesis of multifunctional copolymers, is lacking behind.

The syntheses of highly functional polymers and copolymers are key for a wide variety of materials applications ranging from organic light-emitting diodes to drug-delivery vehicles and tissue engineering. Over the past century, polymer scientists have used covalent approaches to synthesize multifunctional polymers.² While highly successful, covalent chemistry is time consuming and often low yielding and does not allow for the employment of rapid prototyping and optimization methods. If Nature would have used covalent chemistry for the development of biopolymers such as DNA, RNA, and proteins, we might not have the high degree of sophistication on earth today that we take for granted. Nature uses other concepts in addition to covalent chemistry to 'screen' biopolymers for activity and optimize them. Nature's principles are based on a limited number of building blocks to achieve a high degree of complexity in materials and rely on *weak and reversible interactions* between building blocks to introduce function and diversity.⁷ Nature utilizes these noncovalent interactions to create vast libraries of biological materials in a simultaneous multistep self-assembly process that is reversible, selective, self-healing, and spontaneous. Over the past 20 years, polymer chemists have started to learn how to mimic Nature's use of noncovalent chemistry in polymer science, resulting in the foundation of supramolecular polymer science.

Supramolecular polymer chemistry started as an independent field in the 1980s mainly based on the work of Jean-Marie Lehn.⁸ Since then, a number of research groups have developed impressive strategies toward the synthesis, characterization, and use of supramolecular polymers. In general, the field can be divided into two categories: (i) main-chain supramolecular polymer science, i.e., the weak interaction(s) reside(s) in the polymer backbone, thereby noncovalently connecting monomer units, oligomers, and/or polymers, and (ii) side-chain supramolecular polymers, i.e., the noncovalent interac-

* To whom correspondence should be addressed. marcus.weck@chemistry.gatech.edu.

Scheme 1. Noncovalent Synthesis of Different Polymers from a Generic Polymer Backbone



tion(s) is(are) used to either functionalize and/or cross-link the covalent polymer backbone, thereby creating highly functionalized polymers with tailorable properties. This Account will concentrate on the second strategy, side-chain-functionalized supramolecular polymers, and describe current approaches to noncovalently side-chain-functionalized polymers with an emphasis on multifunctionalization.

Homofunctionalization via Side-Chain Self-Assembly

The self-assembly processes that govern Nature's complexity can be broken down into single types of noncovalent interactions working in unison to create complex structures. One example is the zinc finger, which consists of 30 amino acid residues forming two antiparallel β sheets and an α helix held together by a zinc ion. While the complicated morphology of a zinc finger might be hard to mimic with a synthetic polymer, the underlying principles governing structural biology can be utilized in synthetic polymer chemistry. Polymer scientists initially broke down Nature's complexity by using a single noncovalent interaction to functionalize polymeric receptors with small molecule substrates. This strategy allowed for the production of different types of homofunctional polymers from the same generic polymeric precursor (Scheme 1).

Homofunctionalization via Hydrogen Bonding

The majority of reports on the homofunctionalization of polymers utilize hydrogen bonding as the assembly mechanism.^{9,10} The versatility of hydrogen bonding in polymer functionalization is owed primarily to the responsiveness of these bonds. Hydrogen bonds can be manipulated with a variety of external stimuli, including temperature, solvent, and pH.⁹ While single hydrogen bonds are fairly weak (2–5 kcal/mol), arrays of multiple hydrogen bonds can be significantly stronger with as-

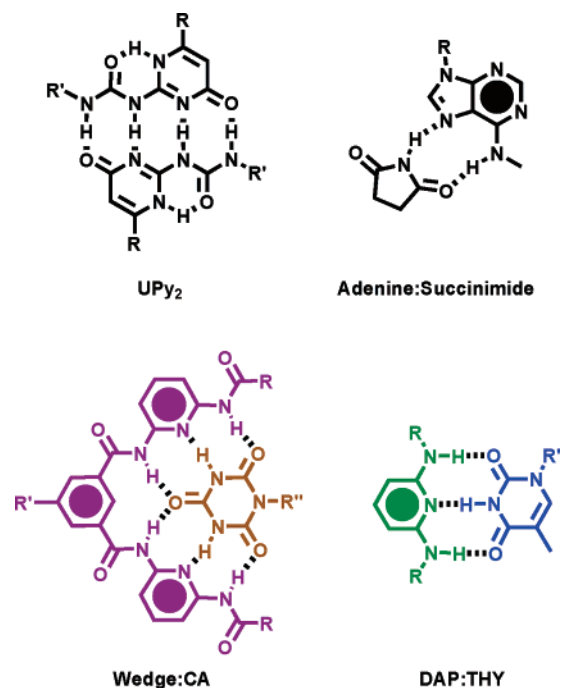


FIGURE 1. Complementary hydrogen-bonding pairs frequently used in supramolecular assemblies.

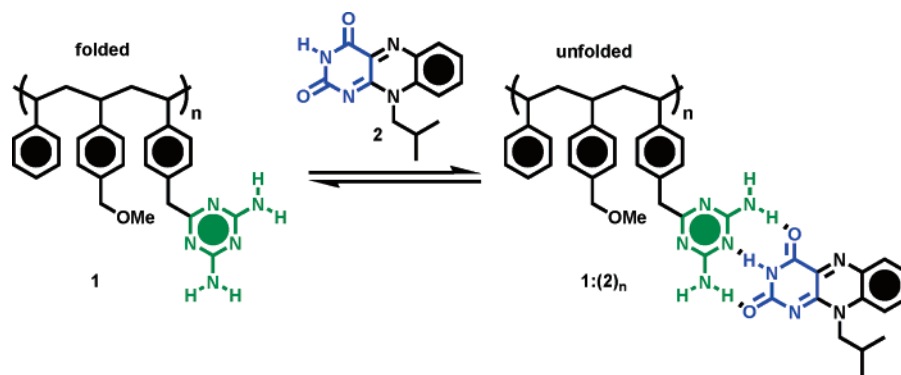
sociation constants approaching 10^9 M^{-1} (in nonpolar solvents) for some quadruple hydrogen-bonded structures (Figure 1).⁹

Self-complementary systems, such as ureidopyrimidone (UPy₂), are undesirable for polymer functionalization since they result in the uncontrolled cross-linking of polymers and not in the controlled functionalization of the materials.⁹ Therefore, researchers have focused their attention on non-self-complementary recognition pairs such as the diaminopyridine:thymine (DAP:THY) interaction, i.e., they have focused on hydrogen-bond arrays originating from functional groups that have a low tendency to self-dimerize in nonpolar solvents ($K_d < 50$ M^{-1}).⁹

Kato and Fréchet led the early work on the hydrogen-bonding-based functionalization of polymers to synthesize liquid crystalline materials.¹¹ While these studies are instrumental to the field, they have been reviewed extensively before¹¹ and the field has moved to more general functionalized systems ranging from nanomaterials to biomimetic materials.^{12,13}

Among the leading research groups working on side-chain supramolecular polymer functionalization is the group of Rotello. The majority of their contributions are based on the noncovalent functionalization of polymers with small molecules via hydrogen bonding. The Rotello group coined the phrase “plug and play” to describe this modular hydrogen-bonding functionalization strategy.¹⁵ The plug and play approach uses noncovalent synthesis to expand organic polymers into functional composite materials using a variety of small molecules for functionalization which can be used to influence bulk material properties.¹⁶ Among the first examples was the functionalization of a diaminotriazine-bearing poly(styrene) (1) with flavin (2) through a triple, non-self-complementary

Scheme 2. Hydrogen-Bonding Recognition between Diaminotriazine-Functionalized Copolymer and Flavin

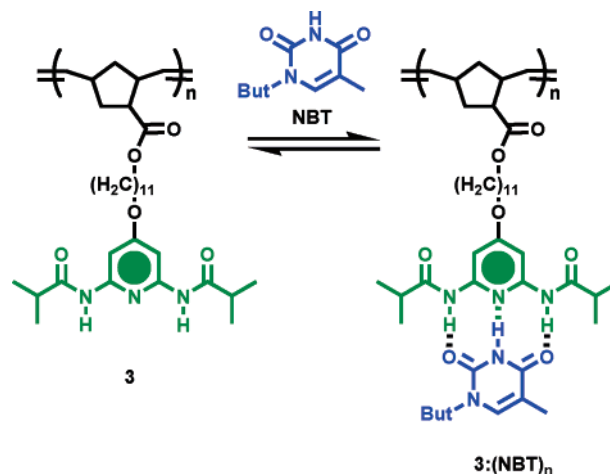


hydrogen-bond array (Scheme 2).¹⁴ In this case, the polymer morphology changed from a folded state (due to triazine dimerization) to a fully unfolded state ($1:(2)_n$) upon introduction of flavin. In addition, by using spin casting to kinetically trap host–guest complexes in poly(styrene) films, the Rotello group was able to demonstrate the recognition of guests in various polymeric host systems.¹⁵ This methodology was then expanded further by Rotello into nanoscience with the development of the “brick and mortar” strategy.¹⁷ For example, poly(styrene)s (mortar) functionalized with terminal thymine groups were hydrogen bonded to gold nanoparticles (bricks) containing complementary diaminopyridine receptors. These polymer–gold nanoparticle assemblies served then as the basis for the exploration of multivalency in recognition-induced polymersomes (RIPs).¹⁷

Similarly, the research efforts of our laboratory focused on rapidly optimizing materials via functional polymer libraries. Our objectives were 2-fold: (i) employment of a fully functional-group-tolerant and living polymerization method that results in highly controllable and well-defined polymers and (ii) use of a recognition unit that will allow for high-yielding functional-group attachment during the noncovalent functionalization steps. To achieve the first objective we employed ROMP, a living and fully functional-group-tolerant polymerization method.³ Objective two was met with the introduction of *N*-butylthymine (NBT) onto both diaminopyridine (3) and diaminotriazine polymeric receptors (Scheme 3).¹⁸ These diaminopyridine- (3) and diaminotriazine-functionalized polymers were then self-assembled with thymine-based molecules to create highly functionalized polymers ($3:(\text{NBT})_n$). The presence of the polymer did not significantly impact the association constant between the recognition partners, and it was possible to tune the polymer properties by adding small molecule substrates to the polymeric receptors.

While self-complementary hydrogen-bonding systems are undesirable for polymer functionalization, such systems can be used to influence polymer morphology. Using ROMP, the Sleiman group synthesized adenine-functionalized copolymers that are able to fold into cylindrical morphologies arising from the self-complementary of the adenine units.¹⁹ A similar self-complementary backbone was explored further with a series of triblock copolymers containing diacetoamidopyridine and its complementary

Scheme 3. Noncovalent Functionalization of Diaminopyridine-Based Polymers with Complementary Thymine Substrates



dicarboximide.²⁰ Sleiman reported that varying the triblock sequence and ratio resulted in different self-assembled architectures.²⁰

Side-Chain Functionalization via Metal Coordination

The second class of noncovalent interaction that has been employed in supramolecular polymer functionalization is metal coordination. Despite the extensive use of metal coordination in main-chain supramolecular polymers,²¹ its use for the functionalization of side-chain supramolecular polymers has been explored extensively only in the past 5 years. While hydrogen bonding is a relatively weak interaction, metal coordination is a significantly stronger binding interaction and yet can still be manipulated by external media, such as solvent and competitive coordinating ligands. An obvious place to start investigating the viability of polymerizable metal complexes and polymers functionalized through metal coordination are pyridyl-based systems, since a number of pyridine-based ligands are commercially available and many pyridine-based ligands can be structurally modified. Moreover, pyridyl-based complexes are prominent as actors in various materials including light-emitting materials and solar cells. Specifically, bipyridines (bpy) and terpyridines (trpy) are desirable since they can act as π acceptors to stabilize various metal oxidation states and are known to coordi-

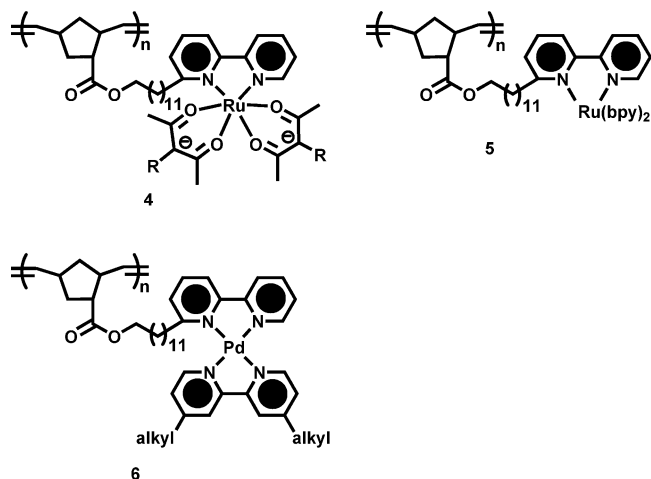


FIGURE 2. Bipyridine-containing polymers reported in the literature.

nate a variety of metals. We and others have explored the polymerization behavior of various norbornene-based transition-metal complexes containing bpy monomers that can be polymerized via ROMP.^{22,23} Norbornene-based monomers containing (tris-bpy)ruthenium(II) (**5**), (bis-bpy)palladium(II) (**6**), and heterolytic ruthenium complexes (**4**) (Figure 2) were synthesized and polymerized. Similarly, Ru(II) tris-bpy block copolymers synthesized by Sleiman were found to self-assemble in acetonitrile/toluene solutions into micellar aggregates with luminescent properties similar to the monomeric analogues.²²

While ROMP has been highly successful in producing well-defined polymers containing pyridyl-based metal complexes, other polymerization methods have also been investigated. Tew and Schubert demonstrated the controlled radical polymerization of trpy-containing monomers to yield trpy-functionalized poly(styrene) and poly(acrylate) copolymers. Postpolymerization modification via metal coordination of the copolymers proved to be a versatile route to polymers functionalized with metal complexes.^{24–27}

Pincer-type complexes containing platinum-group metals have also become versatile tools in supramolecular science.²⁸ Van Koten and others used pincer complexes as supramolecular synthons for a variety of applications in supramolecular chemistry and catalysis.²⁸ Covalent tethering of pincer complexes to polymers can give rise to versatile and responsive materials via simple noncovalent functionalization. In 2002, we reported the first side-chain pincer-functionalized polymer (**7**) that could be functionalized easily and quantitatively with pyridines (**9**) and nitriles (**10**), resulting in formation of fully soluble and highly functionalized metal-coordination polymers (**8**: (**9**)_n and **8**:(**10**)_n) (Scheme 4).²⁹

While we and others have shown that rapid functionalization of polymers can be accomplished via side-chain self-assembly by either hydrogen bonding or metal coordination, our ultimate goal lies in extending these techniques to incorporate multiple functionalities for highly complex materials. However, a reoccurring problem we encountered in using poly(norbornene)s as scaffolds for noncovalent polymer functionalization was an inability

to control the polymerization rate of endo/exo norbornene mixtures. To overcome this problem, we employed isomerically pure *exo*-norbornene esters as monomers. We not only obtained efficient and controlled polymerizations of all functionalized monomers but also were able to polymerize norbornenes containing Pd(II) pincer complexes and/or diaminopyridine groups in a living fashion.³⁰ This was an important step in advancing our methodology into more complicated systems and enabled full architectural control in the next generation of noncovalently functionalized polymers.

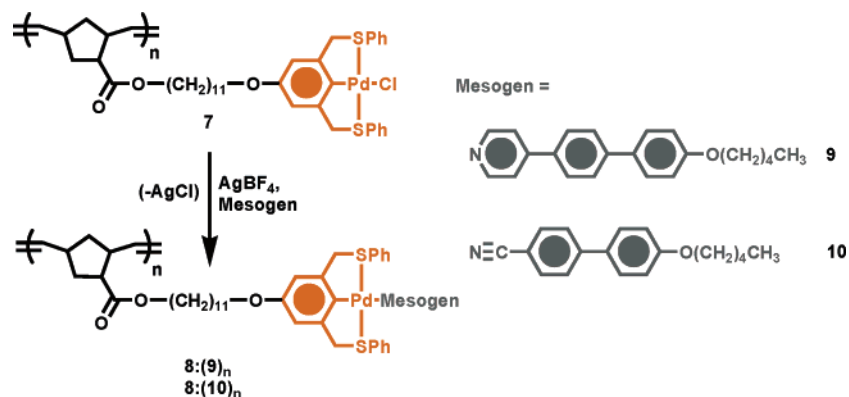
Multifunctionalization via Side-Chain Self-Assembly

In the previous section we outlined some examples where scientists have used noncovalent interactions to produce homofunctional polymers. One remaining challenge is the development of *abiotic* systems with nonbiological functions that rival Nature's complexity.⁸ An important problem in polymer chemistry is one that Nature probably encountered a long time ago: production of multifunctional polymeric architectures with narrow polydispersities. Years of research have been devoted to create functional-group-tolerant catalysts and living polymerization techniques. However, such covalent approaches often fall short of natural analogues that utilize noncovalent interactions. Therefore, we and others began to envision noncovalent multifunctionalization strategies as simple alternatives to covalent approaches toward multifunctional polymers.

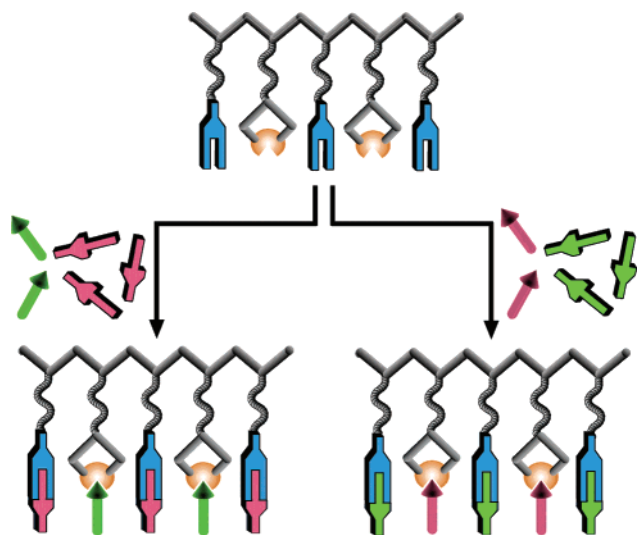
A number of groups have taken advantage of multiple types of noncovalent interactions to produce supramolecular structures based on both natural and non-natural recognition motifs. Metal coordination in concert with hydrogen bonding has been used to synthesize dendrimers³¹ and supramolecular polymers.³² Both hydrogen-bonding and ionic interactions have been used in the synthesis of thermotropic liquid crystals,³³ self-organizing polymeric materials,³⁴ interwoven supramolecular arrays,³⁵ electrochemical switchable dyes,³⁶ molecular elevators,³⁷ and functionalized surfaces.³⁸

While these are examples of supramolecular structures formed through multiple types of noncovalent interactions, use of different types of interactions on the side-chains and in the main-chains of polymers was not demonstrated when we started investigating this strategy 6 years ago.¹³ This was surprising given that noncovalently functionalized copolymers can potentially minimize many of the problems associated with traditional covalent copolymer synthesis.³⁹ For instance, multiple functionalities can be introduced noncovalently onto a copolymer with few side reactions. Side reactions that might occur can be corrected since the multifunctionalized polymer has the ability to "self-heal". We envisaged a strategy that would allow for functionalization of a single polymer backbone bearing noncovalent receptors with different types of substrate motifs (Scheme 5), thereby creating fully functionalized copolymers fast and efficiently.

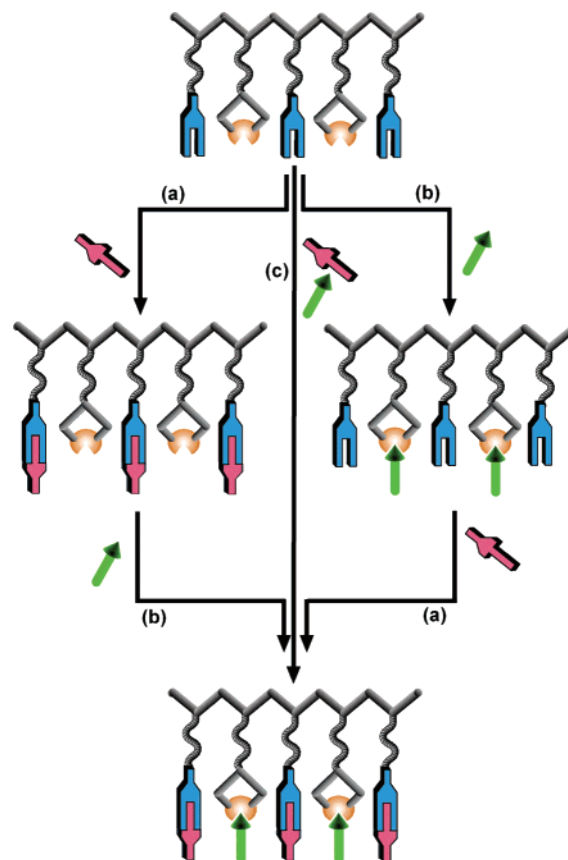
Scheme 4. Formation of Polymeric Liquid Crystals through the Noncovalent Functionalization of Pincer-Containing Homopolymers



Scheme 5. Noncovalent Approach to Different Copolymers from a Generic Polymer Backbone



In our laboratories the use of multiple noncovalent interactions to functionalize a single polymer backbone has proven to be an exciting new route to densely functionalized random and block copolymers as well as terpolymers. In a series of reports,^{13,40–47} we were able to functionalize polymers bearing two or three complementary noncovalent receptors and/or hosts with their corresponding substrates and/or guests. We examined in detail different strategies for obtaining densely functionalized polymers, including the use of (i) two different hydrogen-bonding motifs, (ii) both weak and strong hydrogen-bonding motifs in concert with metal coordination, and (iii) ionic interactions combined with metal coordination and/or hydrogen bonding. Our goal in all of these endeavors was to develop a generalized route to highly functional polymers. Of foremost concern was the orthogonality of the functionalization sequence. Keeping this in mind, we designed and synthesized several polymeric scaffolds that can accommodate a variety of noncovalent functionalities that interact very little, if any, with neighboring groups. This allowed us to modify the order of the postpolymerization functionalization steps as well as achieve a rapid, one-pot functionalization in many cases (Scheme 6).

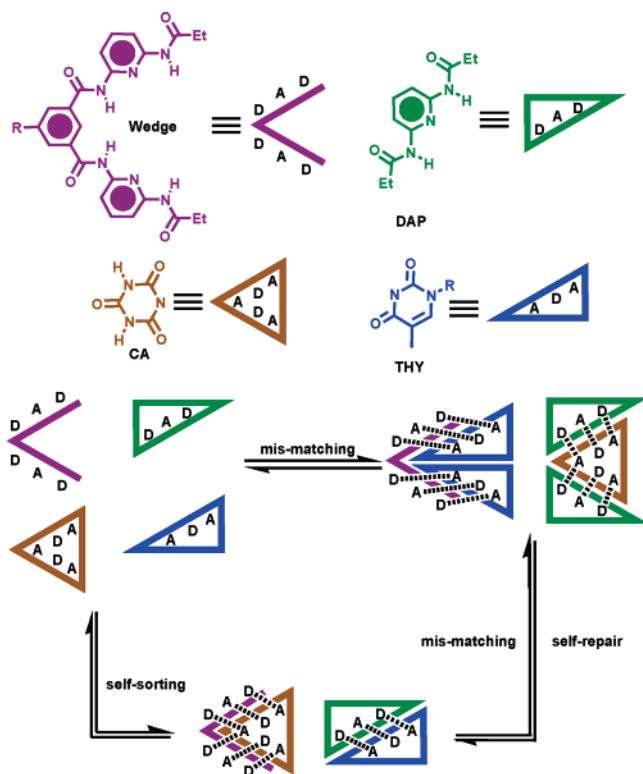
Scheme 6. Generalized Orthogonal Route to Multifunctional Polymers^a

^a Addition of substrate with (a) recognition type I; (b) recognition type II; (c) one-pot addition of both substrates.

Polymer Multifunctionalization via Self-Sorting

First, we examined the possibility of using different hydrogen-bonding recognition processes to functionalize copolymers using the same *type* of interaction through a process known as “self-sorting” (molecules that specifically associate with themselves: *narcissistic molecules*⁴⁸ or other molecules: *social molecules*⁴⁹ through noncovalent interactions in the presence of other competitive noncovalent forces are referred to as “self-sorting” molecules). Hallmark examples of hydrogen-bonding “self-sorters” are the biopolymers DNA and RNA that are able to match base pairs with very few mistakes along a polymeric backbone,

Scheme 7. Self-Sorting, Mismatching, and Self-Repair in Triple DAD–ADA and Sextuple DAD–ADA Hydrogen-Bond Arrays



despite the presence of competing nonspecific hydrogen-bonding interactions. Isaacs and co-workers found that many molecular systems are capable of “self-sorting”.⁵⁰ On the basis of the incredible fidelity of small molecule “self-sorters” and biomacromolecular “self-sorters” like DNA and RNA, we decided to investigate unnatural, polymeric “self-sorters”. The “self-sorting” processes we chose to study along polymer backbones were the association between thymine (THY) and diaminopyridine (DAP) through DAD-ADA triple hydrogen-bond arrays and association between cyanuric acid (CA) and isophthalic wedge-type receptors (Wedge) through DAD-ADA sextuple hydrogen-bond arrays (Scheme 7).

A potential challenge for achieving “self-sorting” in polymer solutions is overcoming competitive interactions beyond those that exist in dilute small molecule solutions because of a high *local* concentration of competitive noncovalent interactions along a polymer chain. Despite this obstacle, we found that in both block and random copolymers (**11**) bearing competitive hydrogen-bonding receptors “self-sorting” can be achieved, i.e., two competitive recognition pairs along a polymer backbone are able to recognize each other with high fidelity (Scheme 8).⁴³

In addition to the observation of “self-sorting” in supramolecular polymers, we also investigated the possibility of using two competitive hydrogen-bonding interactions to achieve stepwise site-specific polymer multifunctionalization. We studied the addition of diaminopyridine (DAP) to a random copolymer (**11**) containing both cyanuric acid and thymine receptors. While the thymine is the target receptor for DAP, cyanuric acid is also able to hydrogen bond with DAP via a triple hydrogen-

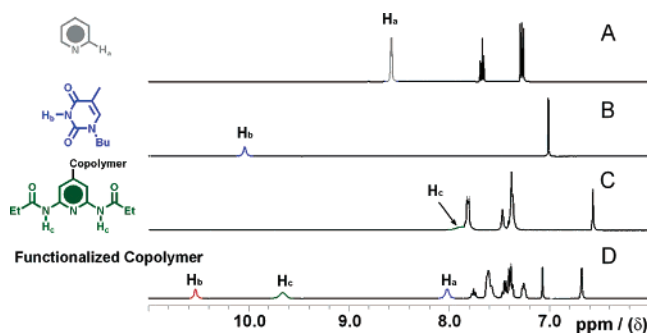


FIGURE 3. Stacked plot of a partial ^1H NMR spectrum (400 MHz, 298 K, CD_2Cl_2) used to characterize the copolymer functionalization: (A) Pyr, (B) NBT, (C) **12**, and (D) fully functionalized $\mathbf{12}:(\text{Pyr})_m(\text{NBT})_n$.

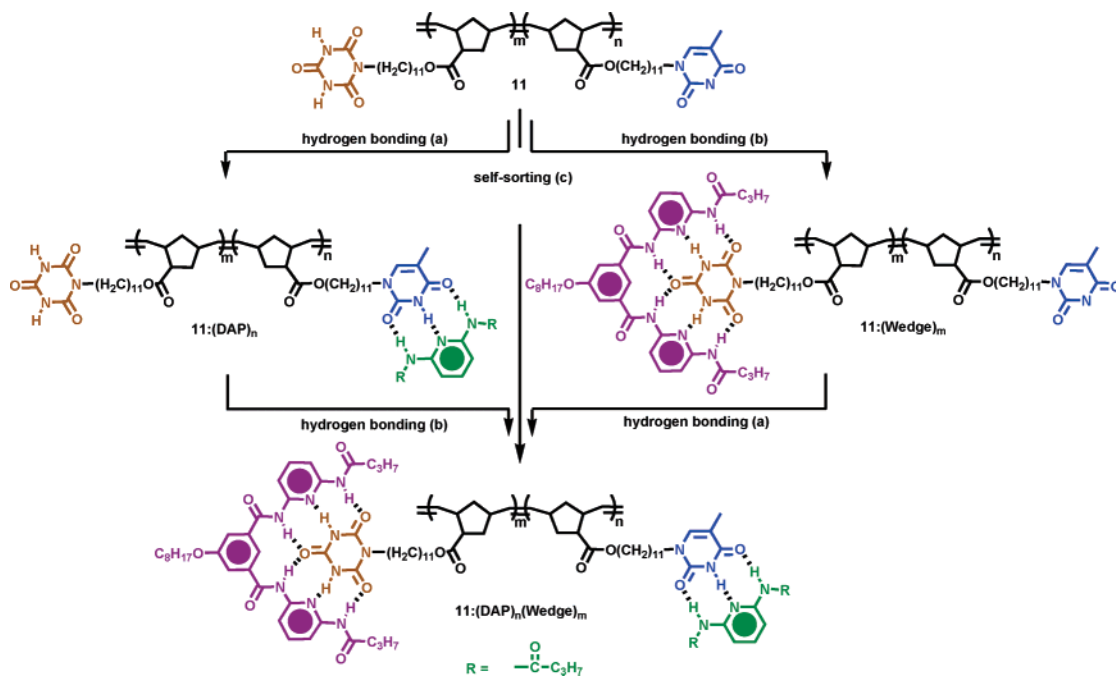
bond-based interaction, thereby competing with the thymine receptors. Using ^1H NMR spectroscopic titration experiments we established that DAP and the cyanuric acid receptors are indeed interacting with each other through a mismatch that could be relieved upon addition of Wedge to the mixture, resulting in the fully functional copolymer (**11**): $(\text{DAP})_n(\text{Wedge})_m$.

Our unnatural polymeric “self-sorters” behave similarly to biomacromolecular analogues such as DNA or RNA. Despite the presence of very high local concentrations of competitive hydrogen-bonding actors along the polymer backbones, we observed that highly specific hydrogen-bonding interactions prevail over nonspecific mismatches. Clearly, polymeric “self-sorting” functions as an efficient means for obtaining multifunctional polymers at the very least and serves as an interesting example of how tools used by Nature can potentially be translated to synthetic systems.

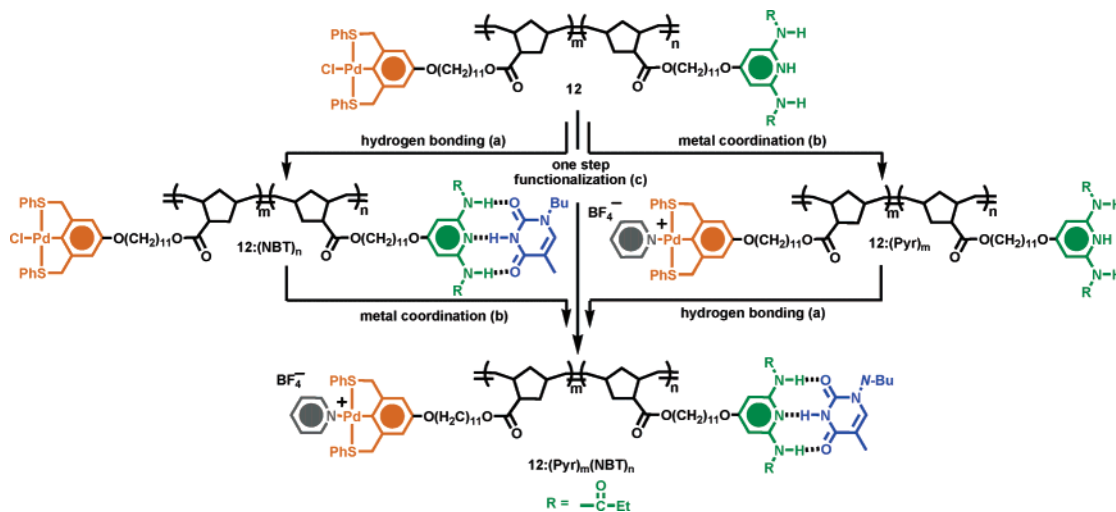
Polymer Multifunctionalization via Metal Coordination and Hydrogen Bonding

We hypothesized that a more modular polymer functionalization strategy could be realized through the use of two unique types of molecular recognition that would not interfere with each other, such as metal coordination and hydrogen bonding. We demonstrated that random copolymers (**12**) bearing side-chains with Pd(II) pincer complexes and diaminopyridine receptors could be functionalized with pyridines (Pyr) (through metal coordination) and thymines (NBT) (through DAD-ADA hydrogen-bond arrays) by both stepwise and one-step, orthogonal synthetic strategies (Scheme 9).⁴¹

This multicomponent functionalization strategy was found to be efficient, and fully functionalized random copolymers could be easily obtained. Most importantly, characterization of the functionalized polymers proved facile. The lack of interference between the two functionalized side-chains could be established by ^1H and ^{13}C NMR spectroscopy experiments. Figure 3 shows an example of a ^1H NMR spectroscopic characterization of the one-pot functionalization strategy. The α -pyridyl signals display a marked upfield shift upon coordination, and the imide proton signal originating from the thymine substrate

Scheme 8. Stepwise and One-Pot ("self-sorting") Functionalization of Copolymers^a

^a Reagents: (a) diaminopyridine (DAP); (b) isophthalic wedge (Wedge); (c) DAP and Wedge, one pot.

Scheme 9. Stepwise and One-Step Orthogonal Functionalization of Copolymers through Metal Coordination and Hydrogen Bonding^a

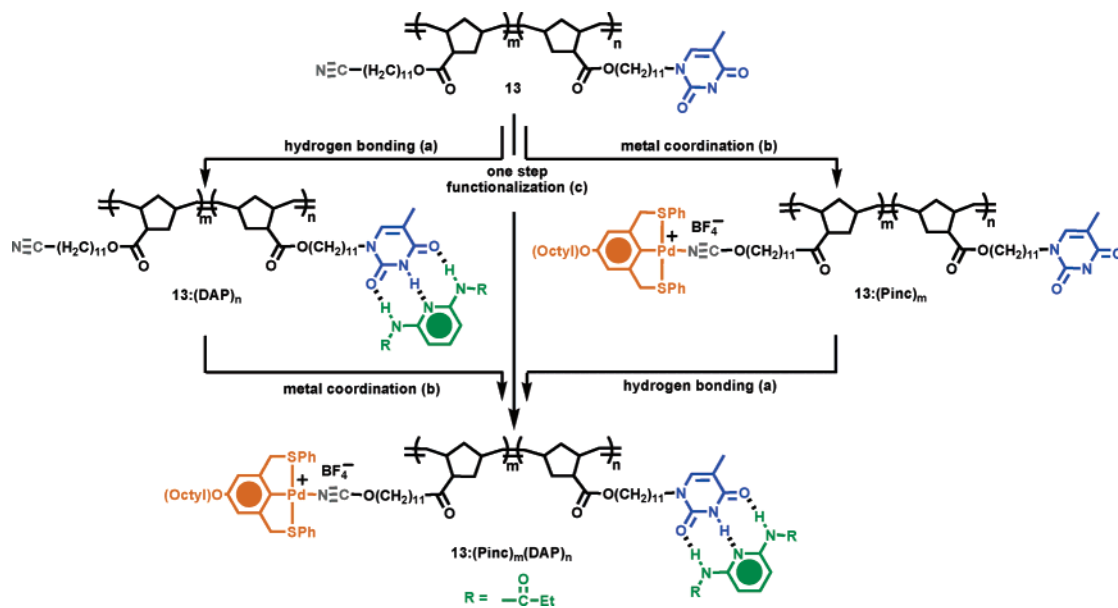
^a Reagents: (a) *N*-butylthymine (NBT); (b) pyridine (Pyr), AgBF₄; (c) *N*-butylthymine (NBT), pyridine (Pyr), AgBF₄, one step.

displays a characteristic downfield shift upon hydrogen bonding to the diaminopyridine receptor.

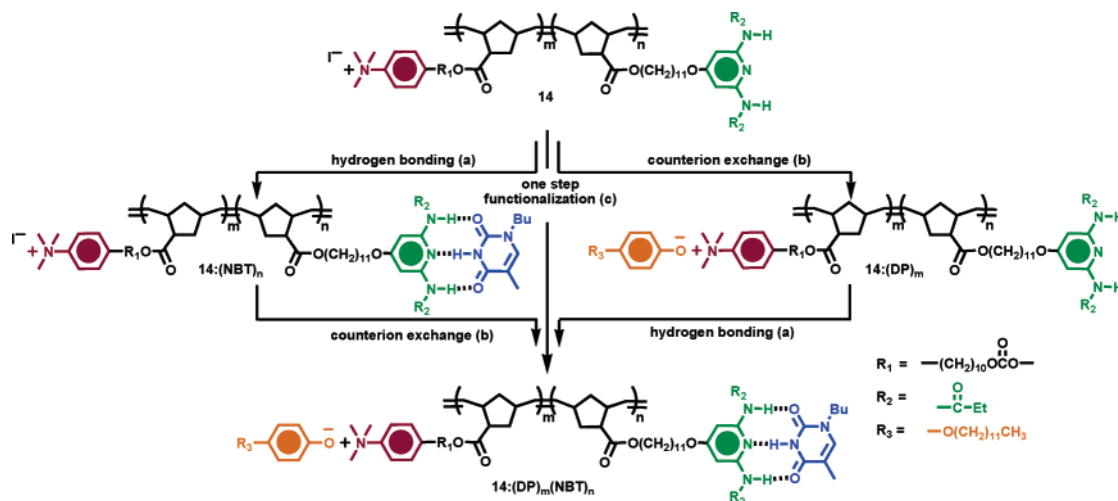
The orthogonality of combining pincer-type metal coordination and hydrogen bonding was tested through an examination of the association constants between receptors and substrates. We found that association constants (K_a s) for the hydrogen-bonding event between diaminopyridine receptors (**12**, **12**:(Pyr)_{*m*}) and thymine substrates (NBT) to be approximately 500 M⁻¹ (in CH₂-Cl₂) regardless of whether or not pyridines (Pyr) were assembled onto pincer complexes. Likewise, the assembly of the hydrogen-bonding units did not affect subsequent metal coordination steps. In contrast to our previous "self-sorting" experiments, the use of metal coordination and hydrogen bonding provides an efficient platform for

obtaining polymers with functional groups that can be manipulated independently by external stimuli.

Afterward, we extended the orthogonal multifunctionalization strategy from random to block copolymers.⁴⁶ We found that in the case of a thymine-functionalized block copolymer receptor (**13**) association constants for formation of ADA-DAD hydrogen-bond arrays between the thymine receptor and DAP substrate were slightly lower than those observed for polymeric diaminopyridine receptors (**12**) functionalized with THY substrates which can be attributed to the greater degree of self-association of the thymine receptor versus the diaminopyridine receptor. However, the independence of the two recognition events remained intact, and an orthogonal functionalization (Scheme 10) could be achieved just as in the previous

Scheme 10. Block Copolymer Functionalization through Metal Coordination and Hydrogen Bonding^a

^a Reagents: (a) DAP; (b) pincer complex (Pinc); (c) DAP, Pinc, one pot.

Scheme 11. Copolymer Functionalization through Ion Exchange and Hydrogen Bonding^a

^a Reagents: (a) NBT; (b) sodium dodecyloxyphenate (SDP); (c) NBT and SDP.

study. Therefore, we concluded that both block and random copolymers are excellent candidates for obtaining multifunctional polymers through a combination of metal coordination and hydrogen bonding.

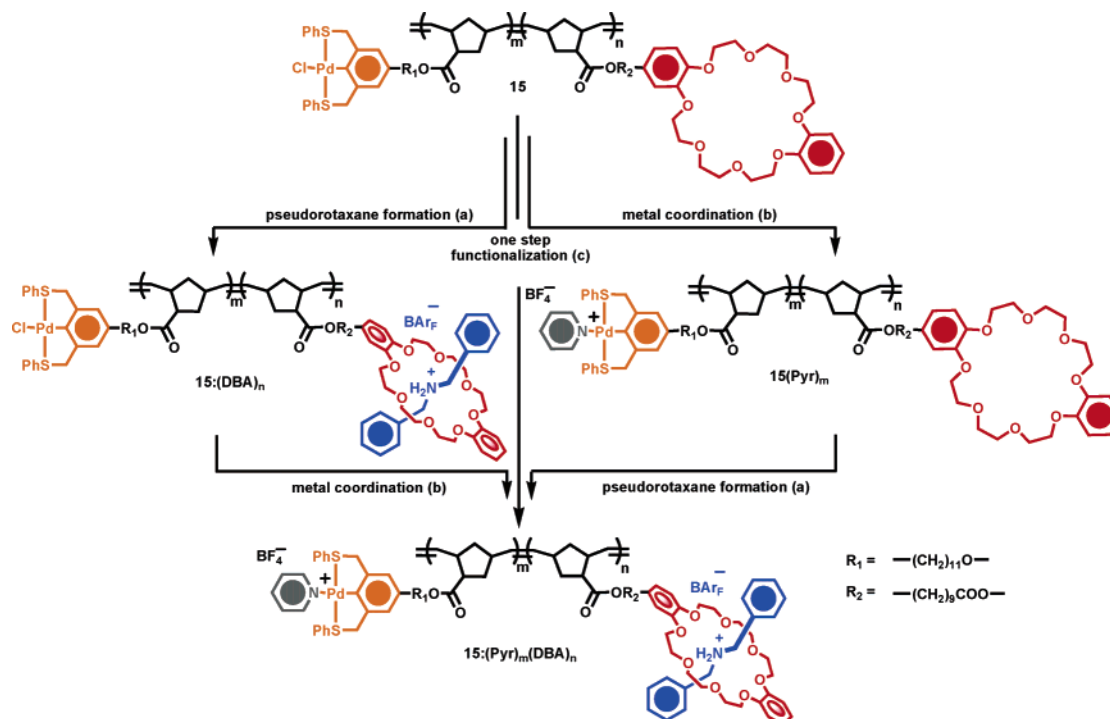
Polymer Multifunctionalization via Hydrogen-Bonding and Ionic Interactions

We reasoned that other types of interactions such as Coulombic forces could also be used in our orthogonal multifunctionalization strategy. Our hypothesis was that the combination of hydrogen-bonding and ionic interactions would be an interesting new route to bifunctional ionomers. We found that bifunctional ionomers based on diaminopyridine and thymine recognition partners and ammonium salts could be synthesized through stepwise or one-step orthogonal strategies (Scheme 11).⁴⁷ Most importantly, the presence of the ionic complex does not interfere with the hydrogen-bonding strength of the DAP:

THY pair and the hydrogen-bonding interactions do not impede ion exchange. These results demonstrate that noncovalent synthetic strategies based on two recognition events are not limited to metal coordination and hydrogen bonding.

Polymer Multifunctionalization via Metal Coordination and Pseudorotaxane Formation

Our initial noncovalent, orthogonal polymer functionalization strategies relied either on metal coordination or Coulombic interactions with a high association constant (K_a) and a hydrogen-bonding process with a lower K_a or on two hydrogen-bonding recognition events. While these combinations are certainly suitable for some applications, such as cross-linked materials,⁴² other applications require *two* strong interactions in order to truly rival a covalently functionalized copolymer analogue. Thus, we developed such a system by combining the Pd(II) pincer-type metal

Scheme 12. Noncovalent Polymer Functionalization through Metal Coordination and Pseudorotaxane Formation^a

^a Reagents: (a) DBA-BAr_F; (b) AgBF₄, Pyr (–AgCl); (c) DBA-BAr_F, AgBF₄, Pyr (–AgCl).

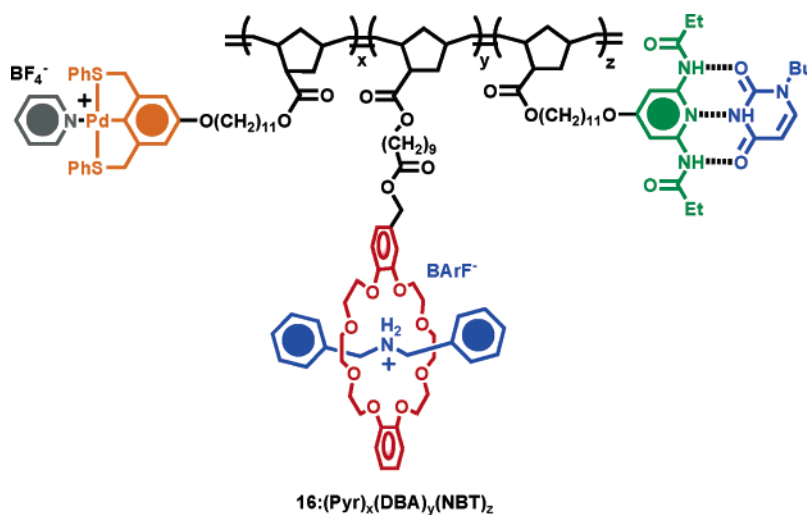
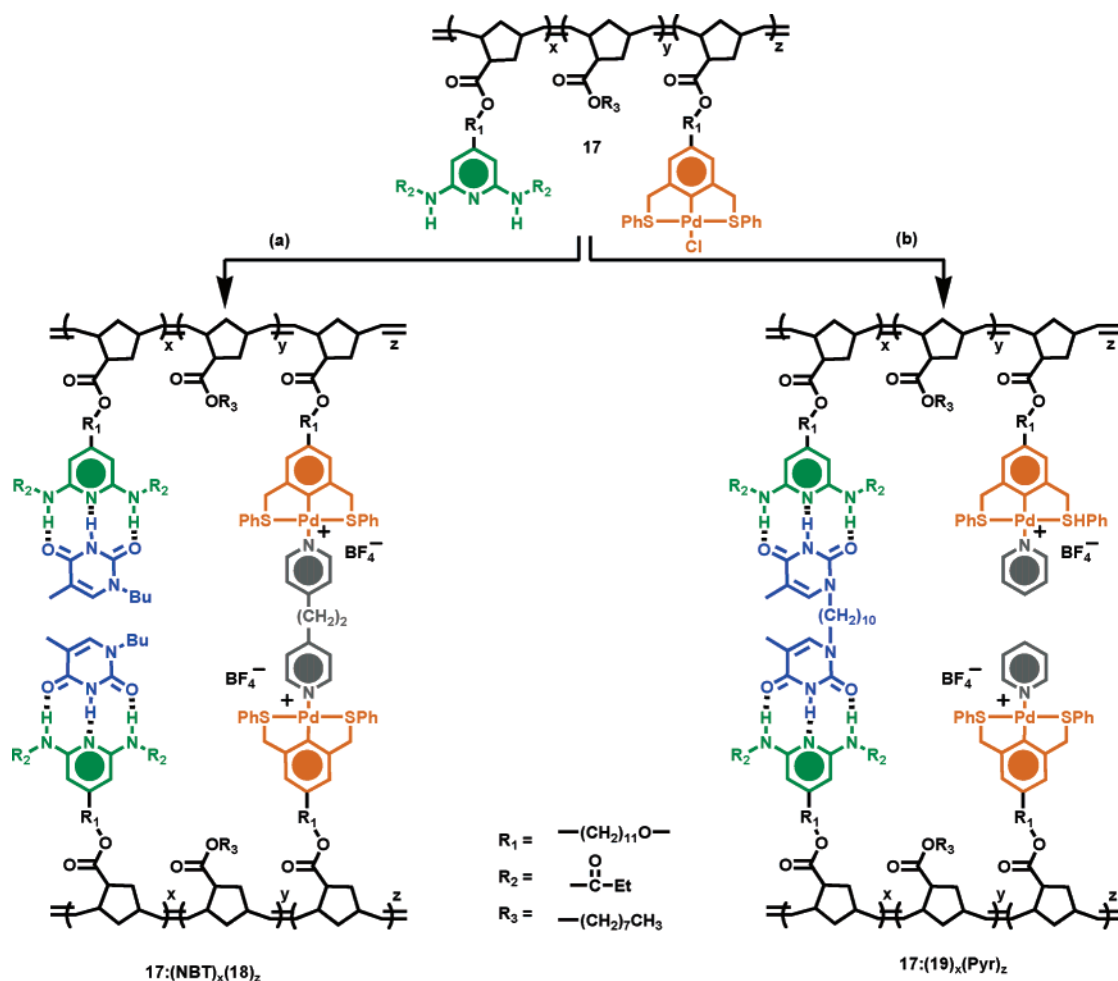


FIGURE 4. Noncovalently functionalized terpolymer.

complex with the interaction between dialkylammonium ions and crown ether macrocycles. Specifically, we introduced the well-known pseudorotaxane formed between dibenzo[24]-crown-8 and dibenzylammonium ions onto a block copolymer backbone that also housed a Pd(II) pincer complex.⁴⁴ Again, we found that this new approach is a highly versatile polymer functionalization strategy in which polymer backbones could be functionalized with pyridines and/or dibenzylammonium ions site-specifically (Scheme 12). Most importantly, we found strong association constants ($K_a > 10^9 \text{ M}^{-1}$ for metal coordination and $K_a \approx 10^5 \text{ M}^{-1}$ for pseudorotaxane formation in CH_2Cl_2) for both recognition processes and proved that both recognition pairs are independent of one another.

Noncovalent Terpolymer Functionalization

Having demonstrated that a new, more complicated type of interaction can be used to functionalize block copolymers, we expanded this system to functionalize terpolymers (Figure 4).⁴⁵ For this study, we used metal coordination, pseudorotaxane formation, and hydrogen-bonding arrays. A stepwise functionalization strategy was used to reach the fully functional terpolymer **16**. We investigated the K_a values for the formation of each receptor:guest complex in CH_2Cl_2 . In the case of pincer complexation, we found the K_a to be greater than 10^9 M^{-1} . Association constants for pseudorotaxane formation were approximately 10^5 M^{-1} , while association constants for the weaker interaction between diaminopyridine receptors and thym-

Scheme 13. Noncovalent Synthetic Approach to Functionalized, Cross-Linked Polymers^a

^a Reagents: (a) NBT, AgBF₄, **18**; (b) **19**, AgBF₄, Pyr.

ine substrates were found to be approximately 10^3 M^{-1} . In this study, we also investigated the effect of recognition unit density along the polymer backbone and found no correlation between recognition unit density and bond strength. The results of this study demonstrate that (i) a noncovalent synthetic strategy can be successfully applied to polymers bearing more than two functionalities and (ii) the relative functional unit density can be varied without a decrease in binding affinities between receptor and substrate, potentially allowing for production and optimization of a catalog of tailorable materials.

Cross-Linking

The possibility of obtaining functional materials using our noncovalent functionalization strategies is key for the success of this methodology.⁴² Our first goal was to produce both densely cross-linked and densely functionalized polymers using exclusively noncovalent side-chain interactions (Scheme 13). One advantage of combining both metal coordination and hydrogen-bonding containing materials is that the dynamics of each interaction can be co-opted individually or in concert with the other to obtain a variety of polymers responsive to a catalog of external stimuli, including temperature, pH, solvent,

polymer concentration, and competitive metal-coordinating ligands. For example, when hydrogen bonding is used to cross-link polymers and pincer-type metal coordination to functionalize the side-chains of the resulting cross-linked arrays, it is possible to break up the cross-links thermally and yet maintain the integrity of the metal complex. On the other hand, when metal coordination is used to cross-link polymers and hydrogen bonding for the functionalization, the cross-links can be reversed by the addition of PPh₃, which coordinates stronger to the Pd(II) pincer complex than pyridine.

Polymer multifunctionalization can often be difficult to achieve with traditional covalent synthetic strategies due to incompatibilities between functional groups and polymerization methods, interferences among functional groups, and differences in comonomer reactivity ratios. Over the past 5 years we have shown that a viable solution to these three common problems is employment of noncovalent synthetic strategies to produce multifunctional polymers. Using this approach, multifunctional polymers can be easily obtained with the use of hydrogen-bonding self-sorters, copolymer receptors bearing hydrogen-bonding and metal coordination recognition units or ionic complexes, and copolymer receptors bearing hy-

drogen-bonding and pseudorotaxane recognition units. Moreover, these synthetic strategies not only are limited to two recognition types but can be extended to higher orders of functionalization. Finally, we have proven that these approaches can be applied to materials chemistry by fabricating highly responsive and densely functionalized cross-linked polymers.

Conclusion and Outlook

In this Account we described strategies for obtaining densely functionalized polymers through noncovalent synthetic strategies. Noncovalent interactions such as hydrogen bonding, ionic interactions, metal coordination, electrostatic interactions, and π - π stacking can be used individually or in concert with one another to obtain homofunctionalized or multiply functionalized polymers. These noncovalent synthetic strategies can be advantageous over covalent analogues for several reasons: (i) noncovalently functionalized polymers have the ability to self-heal due to the reversibility of noncovalent bonds, (ii) a generic polymer backbone can be used to obtain a library of fully functionalized polymers, (iii) several different types of noncovalent interactions are orthogonal to one another, while many covalent modifications are not, and (iv) such polymers are highly responsive to external stimuli. Aside from simply adding functionality to a polymer, this approach also allows for the tuning of bulk properties such as morphology or the degree of cross-linking. The research efforts described in this Account clearly demonstrate the potential of noncovalently functionalized polymers and have certainly laid the ground work for future endeavors in this area. The real test will be the synthesis of materials for specific applications and examination of the materials performance in devices. A few examples have already emerged with good results. Our future research emphasis will follow this trend by examining the influence of noncovalent functionalities on bulk-polymer properties and test noncovalently functionalized materials in applications.

We gratefully acknowledge the support and enthusiasm of former and current group members, collaborators, and colleagues. Financial support has been provided by the National Science Foundation (ChE-0239385) and the Office of Naval Research (MURI, Award No. N00014-03-1-0793.). M.W. gratefully acknowledges a 3M Untenured Faculty Award, a DuPont Young Professor Award, an Alfred P. Sloan Fellowship, and a Camille Dreyfus Teacher/Scholar Award.

References

- Lovinger, A. J. Nano-, Bio-, Multi-, Inter-, ... Polymer Research in an Era of Prefixes. *J. Macromol. Sci., Part C: Polym. Rev.* **2005**, *45*, 195–199.
- Odian, G. *Principles of Polymerization*; John Wiley & Sons: New York, 1991.
- Handbook of Metathesis*; Wiley-VCH: Weinheim, 2003.
- Fischer, H. The Persistent Radical Effect: A Principle for Selective Radical Reactions and Living Radical Polymerizations. *Chem. Rev.* **2001**, *101*, 3581–3610.
- Coates, G. W. Precise Control of Polyolefin Stereochemistry Using Single-Site Metal Catalysts. *Chem. Rev.* **2000**, *100*, 1223–1252.
- Dechy-Cabaret, O.; Martin-Vaca, B.; Bourissou, D. Controlled Ring-Opening Polymerization of Lactide and Glycolide. *Chem. Rev.* **2004**, *104*, 6147–6176.
- Philp, D.; Stoddart, J. F. Self-Assembly in Natural and Unnatural Systems. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1154–1196.
- Lehn, J.-M. Toward Complex Matter: Supramolecular Chemistry and Self-Organization. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 4763–4768.
- Brunsveld, L.; Folmer, B. J. B.; Meijer, E. W.; Sijbesma, R. P. Supramolecular Polymers. *Chem. Rev.* **2001**, *101*, 4071–4098.
- Farnik, D.; Kluger, C.; Kunz, M. J.; Machl, D.; Petraru, L.; Binder, W. H. Synthesis and Self Assembly of Hydrogen-Bonded Supramolecular Polymers. *Macromol. Symp.* **2004**, *217*, 247–266.
- Kato, T.; Mizoshita, N.; Kishimoto, K. Functional Liquid-Crystalline Assemblies: Self-Organized Soft Materials. *Angew. Chem., Int. Ed.* **2006**, *45*, 38–68.
- Gohy, J.-F.; Lohmeijer, B. G. G.; Schubert, U. S. From Supramolecular Block Copolymers to Advanced Nano-Objects. *Chem. Eur. J.* **2003**, *9*, 3472–3479.
- Pollino, J. M.; Weck, M. Non-Covalent Side-Chain Polymers: Design Principles, Functionalization Strategies, and Perspectives. *Chem. Soc. Rev.* **2005**, *34*, 193–207.
- Deans, R.; Ilhan, F.; Rotello, V. M. Recognition-Mediated Unfolding of a Self-Assembled Polymeric Globule. *Macromolecules* **1999**, *32*, 4956–4960.
- Ilhan, F.; Gray, M.; Rotello, V. M. Reversible Side Chain Modification Through Noncovalent Interaction. "Plug and Play" Polymers. *Macromolecules* **2001**, *34*, 2597–2601.
- Carroll, J. B.; Waddon, A. J.; Nakade, H.; Rotello, V. M. "Plug and Play" Polymers. Thermal and X-ray Characterizations on Noncovalently Grafted Polyhedral Oligomeric Silsesquioxane (POSS)-Polystyrene Nanocomposites. *Macromolecules* **2003**, *36*, 6289–6291.
- Shenhar, R.; Rotello, V. M. Nanoparticles: Scaffolds and Building Blocks. *Acc. Chem. Res.* **2003**, *36*, 549–561.
- Stubbs, L. P.; Weck, M. A Polymeric Scaffold for the Self-Assembly of Receptors Through Hydrogen Bonding. *Chem. Eur. J.* **2003**, *9*, 992–999.
- Bazzi, H. S.; Sleiman, H. F. Adenine-Containing Block Copolymers via Ring-Opening Metathesis Polymerization: Synthesis and Self-Assembly into Rod Morphologies. *Macromolecules* **2002**, *35*, 9617–9620.
- Bazzi, H. S.; Bouffard, J.; Sleiman, H. F. Self-Complementary ABC Triblock Copolymers via Ring-Opening Metathesis Polymerization. *Macromolecules* **2003**, *36*, 7899–7902.
- Lohmeijer, B. G. G.; Schubert, U. S. Playing LEGO with Macromolecules: Design, Synthesis, and Self-Organization with Metal Complexes. *J. Polym. Sci., Part A: Polym. Chem.* **2003**, *41*, 1413–1427.
- Chen, B.; Sleiman, H. F. Ruthenium Bipyridine-Containing Polymers and Block Copolymers via Ring-Opening Metathesis Polymerization. *Macromolecules* **2004**, *37*, 5866–5872.
- Carlise, J. R.; Weck, M. Side-Chain Functionalized Polymers Containing Bipyridine Coordination Sites: Polymerization and Metal Coordination Studies. *J. Polym. Sci., Part A: Polym. Chem.* **2004**, *42*, 2973–2984.
- Aamer, K. A.; Tew, G. N. Synthesis of Terpyridine-Containing Polymers with Blocky Architecture. *Macromolecules* **2004**, *37*, 1990–1993.
- Tew, G. N.; Aamer, K. A.; Shunmugam, R. Incorporation of Terpyridine into the Side Chain of Copolymers to Create Multifunctional Materials. *Polymer* **2005**, *46*, 8440–8447.
- Shunmugam, R.; Tew, G. N. Efficient Route to Well-Characterized Homo, Block, and Statistical Polymers Containing Terpyridine in the Side Chain. *J. Polym. Sci., Part A: Polym. Chem.* **2005**, *43*, 5831–5843.
- Gohy, J.-F.; Hofmeier, H.; Alexeev, A.; Schubert, U. S. Aqueous Micelles from Supramolecular Graft Copolymers. *Macromol. Chem. Phys.* **2003**, *204*, 1524–1530.
- Albrecht, M.; van Koten, G. Platinum Group Organometallics Based on "Pincer" Complexes: Sensors, Switches, and Catalysts. *Angew. Chem., Int. Ed.* **2001**, *40*, 3750–3781.
- Pollino, J. M.; Weck, M. Supramolecular Side-Chain Functionalized Polymers: Synthesis and Self-Assembly Behavior of Polynorbornenes Bearing Pd^{II} SCS Pincer Complexes. *Synthesis* **2002**, 1277–1285.
- Pollino, J. M.; Stubbs, L. P.; Weck, M. Living ROMP of Exo-Norbornene Esters Possessing Pd(II) SCS Pincer Complexes or Diaminopyridines. *Macromolecules* **2003**, *36*, 2230–2234.
- Huck, W. T. S.; Hulst, R.; Timmerman, P.; van Veggel, F. C. J. M.; Reinhoudt, D. N. Noncovalent Synthesis of Nanostructures: Combining Coordination Chemistry and Hydrogen Bonding. *Angew. Chem., Int. Ed.* **1997**, *36*, 1006–1008.
- Hofmeier, H.; El-ghayoury, A.; Schenning, A. P. H. J.; Schubert, U. S. New Supramolecular Polymers Containing both Terpyridine Metal Complexes and Quadruple Hydrogen Bonding Units. *Chem. Commun.* **2004**, 318–319.

- (33) Bazuin, C. G.; Brodin, C. Thermotropic Liquid Crystalline Complexes of Hydrogen-Bonded Poly(pyridylpyridinium dodecyl methacrylate) Bromide and Octylphenol. *Macromolecules* **2004**, *37*, 9366–9372.
- (34) Ruokolainen, J.; Mäkinen, R.; Torkkeli, M.; Mäkelä, T.; Serimaa, R.; TenBrinke, G.; Ikkala, O. Switching Supramolecular Polymeric Materials with Multiple Length Scales. *Science* **1998**, *280*, 557–560.
- (35) Fyfe, M. C. T.; Stoddart, J. F. Interwoven Supramolecular Arrays via the Noncovalent Polymerization of Pseudorotaxanes. *Coord. Chem. Rev.* **1999**, *183*, 139–155.
- (36) Deng, W.-Q.; Flood, A. H.; Stoddart, J. F.; Goddard, W. A., III An Electrochemical Color-Switchable RGB Dye: Tristable [2]Catenane. *J. Am. Chem. Soc.* **2005**, *127*, 15994–15995.
- (37) Badjic, J. D.; Ronconi, C. M.; Stoddart, J. F.; Balzani, V.; Silvi, S.; Credi, A. Operating Molecular Elevators. *J. Am. Chem. Soc.* **2006**, *128*, 1489–1499.
- (38) Xu, H.; Hong, R.; Lu, T.; Uzun, O.; Rotello, V. Recognition-Directed Orthogonal Self-Assembly of Polymers and Nanoparticles on Patterned Surfaces. *J. Am. Chem. Soc.* **2006**, *128*, 3162–3163.
- (39) Odian, G. *Principles of Polymerization*, 4th ed.; Wiley-Interscience: Hoboken, 2004.
- (40) Gerhardt, W.; Crne, M.; Weck, M. Multifunctionalization of Synthetic Polymer Systems via Self-Assembly. *Chem. Eur. J.* **2004**, *10*, 6212–6221.
- (41) Pollino, J. M.; Stubbs, L. P.; Weck, M. One-Step Multi-Functionalization of Random Copolymers via Self-Assembly. *J. Am. Chem. Soc.* **2004**, *126*, 563–567.
- (42) Pollino, J. M.; Nair, K. P.; Stubbs, L. P.; Adams, J.; Weck, M. Cross-linked and Functionalized 'Universal Polymer Backbones' via Simple, Rapid, and Orthogonal Multi-site Self-assembly. *Tetrahedron* **2004**, *60*, 7205–7215.
- (43) Burd, C.; Weck, M. Self-sorting in Polymers. *Macromolecules* **2005**, *38*, 7225–7230.
- (44) South, C. R.; Higley, M. N.; Leung, K. C.-F.; Lanari, D.; Nelson, A.; Grubbs, R. H.; Stoddart, F. F.; Weck, M. Self-Assembly With Block Copolymers Using SCS Pd(II) Pincer Metal Coordination and Pseudorotaxane Formation. *Chem. Eur. J.* **2006**, *12*, 3789–3797.
- (45) South, C. R.; Leung, K. C.-F.; Lanari, D.; Stoddart, J. F.; Weck, M. Noncovalent Side-Chain Functionalization of Terpolymers. *Macromolecules* **2006**, *39*, 3738–3744.
- (46) Nair, K. P.; Pollino, J. M.; Weck, M. Non-Covalently Functionalized Block Copolymers Possessing Both, Hydrogen-Bonding and Metal-Coordination Centers. *Macromolecules* **2006**, *39*, 940–949.
- (47) Nair, K. P.; Weck, M. Noncovalently Functionalized Poly(norbornene)s Possessing both Hydrogen Bonding and Coulombic Interactions. Submitted for publication.
- (48) Taylor, P. N.; Anderson, H. L. Cooperative Self-Assembly of Double-Strand Conjugated Porphyrin Ladders. *J. Am. Chem. Soc.* **1999**, *121*, 11538–11545.
- (49) Shivanyuk, A.; Rebek, J., Jr. Social Isomers in Encapsulation Complexes. *J. Am. Chem. Soc.* **2002**, *124*, 12074–12075.
- (50) Wu, A.; Isaacs, L. Self-Sorting: The Exception or the Rule? *J. Am. Chem. Soc.* **2003**, *125*, 4831–4835.

AR0500160