The Convergence of Synthetic Organic and Polymer Chemistries

Craig J. Hawker[1]* and Karen L. Wooley[2]*

Several recent conceptual advances, which take advantage of the design criteria and practical techniques of molecular-level control in organic chemistry, allow preparation of well-defined polymers and nanostructured materials. Two trends are clear: the realization that synthesis of complex macromolecules poses major challenges and opportunities and the expectation that such materials will exhibit distinctive properties and functions. Polymer synthesis methods now being developed will yield well-defined synthetic macromolecules that are capable of mimicking many of the features of proteins (for example, three-dimensional folded structure) and other natural materials. These macromolecules have far-reaching potential for the study of molecular-level behavior at interfaces, in thin films, and in solution, while also enabling the development of encapsulation, drug-delivery, and nanoscale-patterning technologies.

By varying the three-dimensional (3D) structure and position of functional groups, synthetic organic chemists have developed the ability to accurately control, and in some cases predict, the physical properties of small molecules or their interactions with biological systems. Classic examples include the design of volatile esters in both nature and the fragrance industry, whose odors are directly related to molecular shape and size, and the discovery of numerous synthetic drugs. This general theme of property control through molecular design has found increasing attention and application in polymer science during recent years. Small changes in structure have been shown to have dramatic effects on the properties of polymers, and one need look no further than poly(ethylene) and poly(propylene) to observe these effects, with poly(propylene) having lower impact strength but superior working temperature and tensile strength compared with poly(ethylene). Increasing the sophistication of molecular design in polymers through the exploitation of organic chemistry concepts and tools is, therefore, a major direction of materials research with considerable potential for cross-fertilization between disciplines.

The most profound recent developments in polymer chemistry are based on this growing synergy between advanced organic chemistry and polymer synthesis. A driving force is the realization that many of the promising applications of nanotechnology rely on extending synthetic organic chemistry into the nanometer-length scale, especially as nanodevices are designed with increasing sophistication. There is also a desire to study fundamental aspects of polymer physics that require an exacting level of control over the structure of a polymer molecule to a degree that is associated traditionally with organic chemistry. Further developments in related fields, such as the synthesis of new catalysts, have also created new tools for making complex molecules. As a result, creative approaches using organic chemistry are required to control every facet of macromolecular structure and to enable functional groups to be introduced at defined locations.

Polymer Synthesis Is Different

Although the promise of accurately controlling chemical structure and functionality at the macromolecular level is considerable, it should be realized that it is not a simple process of transferring synthetic techniques directly from organic chemistry to polymer synthesis. Rather, because of the distinctive features of macromolecules compared with small molecules (e.g., number of functional groups, molecular weight distribution, and purification techniques), the elucidation of polymer synthesis protocols that proceed with structural fidelity and high levels of functional group compatibility is a grand challenge.

In general, polymerization is a multistage process involving an initiation or oligomerization step. Propagation, which follows, involves the successive addition of more monomers/oligomers to these initial activated species. Finally, a termination step halts chain growth to produce a stable polymer. Many traditional polymer syntheses are chaotic processes in which all stages of the polymerization operate concurrently and growing chains can merge with or branch off from one another. Recently, however, several polymerization systems have been developed that offer much better control. In a living radical polymerization (LRP), each molecule of catalyst promotes rapid initiation and then stabilizes the growing chain to prevent branching or termination. Thus, different types of monomer can be added to the reaction consecutively, leading to polymers with well-defined blocks that vary in structure and function.

The discovery of simple and powerful approaches to polymerization reactions, which are not limited by the presence of additional functional groups and provide accurate molecular weights and narrow molecular weight distributions, allows nonspecialists access to well-defined materials, previously the domain of a select few. This issue has been addressed by the development of new chemistry and catalysts for LRPs and ring-opening metathesis polymerization (ROMP) (Fig. 1, Ai and Aii, respectively). Both polymerizations are characterized by a controlled-growth strategy, with LRP involving the addition of vinyl monomers (i.e., styrene) to growing polymers with a very reactive radical chain end. Control is afforded by the reversible capping of this radical chain end with a mediating molecule. In contrast, ROMP involves the ring opening of strained olefins (i.e., norbornene) by organometallic initiators and has benefited greatly by the design of faster, more efficient initiators that are highly selective for the ring-opening reaction and do not undergo unwanted side reactions with functional groups or impurities. These radical and ring-opening systems allow for a substantial degree of control over polymer topology and functional group incorporation through independent synthetic manipulation of the initiating moiety, the terminating unit, and the monomeric repeat units. The conditions for LRP and ROMP are considerably more user friendly (aqueous conditions and no monomer purification) than those employed for anionic polymerization (strictly water-free and oxygen-free with a high level of monomer purification), which is still the "gold standard" in polymer chain growth control. This fidelity allows for their wider adoption and exploitation. Moreover, the increased tolerance of functional groups for these new polymerization

[1]Materials Research Laboratory, Materials Department and Department of Chemistry, University of California, Santa Barbara, CA 93106, USA. [2]Center for Materials Innovation and Department of Chemistry, Washington University, Saint Louis, MO 63130, USA.

*To whom correspondence should be addressed. E-mail: hawker@mrl.ucsb.edu (C.J.H.); klwooley@artsci.wustl.edu (K.L.W.)

processes offers opportunities for combining different chemistries and the construction of macromolecules with a hierarchical arrangement of functional groups and branches.

Architecturally Defined Macromolecules

The basic importance of shape in defining the physical properties of macromolecules has been recognized in recent years, and the study of globular and rodlike materials has evolved in concert with synthetic procedures and advanced architectural designs. A major effort has been directed toward achieving accurate control over each parameter of composition and structure, including the chain ends and backbone segment lengths, as well as the overall macromolecular topology.

Traditionally, structural control could be gained by repetitive coupling reactions to produce macromolecules having accurate molecular sizes, compositions, and functional group placements (*1*). As an example, dendritic macromolecules, derived most often from condensation-based syntheses, have been recognized as adopting a synthetic protein-like structure, based on their monodisperse, globular 3D structures having diameters of a few nanometers. This feature, combined with the large number of chain-end functional groups, has led to their exploitation in a number of novel medicinal applications, for example, as an antiviral HIV drug (VivaGel) (*2*).

Although stepwise, condensation growth strategies and controlled addition chain polymerizations are often limited in the size to which the macromolecules can be constructed or the complexity of the resulting architectures, combinations of these two mechanisms have led to interesting new synthetic routes to distinctive macromolecular architectures. The application of multiple synthetic methods to construct complex macromolecules is most effective when a target structure is identified and then reverse engineered through a retrosynthetic analysis. For example, the tubular, dendronized polymers, important building blocks for nanotechnology, are difficult to prepare using traditional techniques involving the direct polymerization of a monomer carrying the large dendritic unit (*3*). In contrast, divergent and convergent chemistries have been developed to produce such structures by growth of the dendritic side groups or connection of preestablished dendritic units (Bi and Bii) on a prefabricated polymer backbone.

The stepwise, divergent growth of dendritic polyesters on linear poly(*p*-hydroxystyrene) by repetitive, generational coupling of benzylidene acetal- or isopropylidene ketal–protected 2,2-bis(hydroxymethyl)propionyl anhydride and acid-catalyzed cleavage of the protecting groups allowed for the preparation of dendronized polymers (*4*). Starting with poly(*p*-hydroxystyrene) of high molecular weight and narrow molecular weight distribution, the dendronization procedure maintained the narrow molecular weight distribution and chain length; however, the macromolecule underwent an expected but interesting transformation from a random coil (2.1 nm persistence length) to a rigid rod (12.2 nm persistence length) as the dendrimer generation number increased from 0 to 5. These materials represent one of the first examples of synthetic, molecular-based nano-objects that are nonspherical and have well-defined and controllable dimensions. Just as nature makes use of a variety of different building blocks to construct more sophisticated structures, the ability to make synthetic 3D shapes other than simple spheres or to combine different shapes holds enormous potential for understanding and optimizing the properties of <20-nm nano-objects. In addition, the effect of these structures on physical properties, such as increasing the strength or crack resistance of bulk materials, holds considerable promise.

Click Chemistry for Material Synthesis

To be applicable and useful in polymer synthesis, an organic reaction must proceed in high yield with little or no by-product. Both of these criteria are aptly fulfilled by the recent development of the click chemistry concept by Sharpless (*5*). Originally developed for use in organic synthesis and chemical biology, click chemistry encompasses any reaction that proceeds with complete specificity, 100% yield, and almost perfect fidelity in the presence of a wide variety of other functional groups. For example, Tirrell has recently demonstrated a reliable and site-specific method of labeling cell surfaces based on Cu-catalyzed [3+2π] cycloaddition chemistry that takes advantage of the benign reaction conditions and functional group tolerance (*6*).

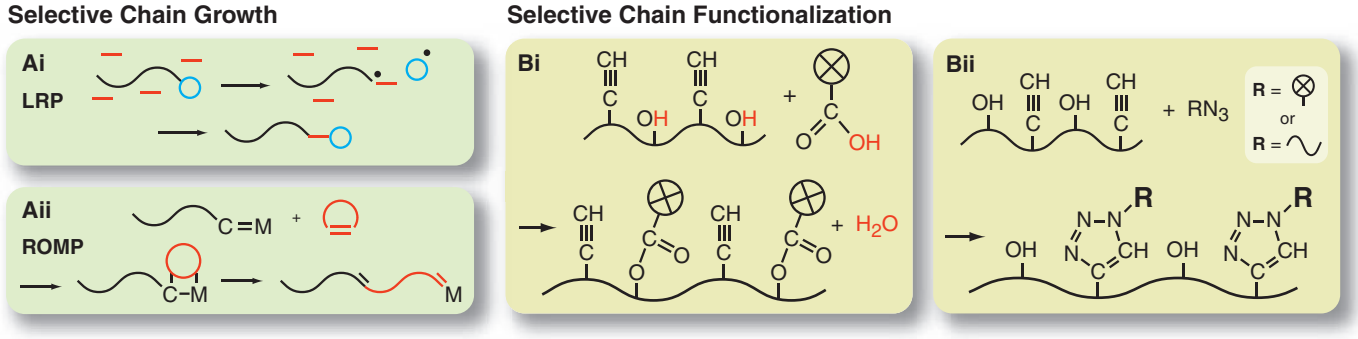

Fig. 1. (**A**) Strategies for selective chain growth. (**i**) In LRP, the growing polymer chain is stabilized by an end group that rapidly associates and dissociates for controlled addition of monomers. Different monomers can be added in batches to produce structurally distinct blocks in the polymer backbone. The end group is either a persistent radical or an atom such as a halogen that shuttles between the chain and a metal complex. (**ii**) In ROMP, a transition metal catalyst breaks open a cyclic alkene at the carbon double bond. The resulting complex then reacts with another cyclic alkene, and the process repeats to yield a chain of opened rings. Current catalysts are tolerant of a huge range of chemical groups adjacent to the double bond, so richly substituted monomers can be prepared and stitched together. (**B**) Strategies for elaborating preformed polymers. (**i**) Esterification is an efficient way to add large substituents to a polymer backbone. The backbone is prepared with pendant hydroxyl (OH) groups, which can be coupled to carbonyl (C=O) groups attached to dendrimers or other macromolecules. (**ii**) Click chemistry, or copper-catalyzed coupling of alkyne and azide groups, is another fast and high-yielding reaction to decorate a polymer backbone or to link two polymer chains together.

The promise of click chemistry toward materials synthesis has been demonstrated also by the complete modification of the side-chain functionalities of a linear polymer by reaction with a sterically bulky dendritic unit (*7*). The Cu(I)-catalyzed Huisgen [3+2π] dipolar cycloaddition reactions between the alkynyl repeat units of poly(vinyl acetylene) and the azido focal point unit of benzyl ether dendrimers were shown to occur with regiochemical control and quantitative conversion for dendrimers of generations 1 and 2 and with >98% conversion for the third-generation dendrimer (Fig. 1Bii). The efficiency of the click reactions, in comparison, for example, to esterification (Fig. 1Bi), allowed for macromolecule-macromolecule couplings to the extent that rigidified nano-objects were obtained.

Click chemistry has also been used as a highly efficient reaction to couple two distinct linear polymers to make block copolymers, a

notoriously difficult synthetic challenge because of the reduced reactivity that occurs between polymeric chain ends (*8*). Linear homopolymers of methyl methacrylate and styrene, for which α-alkynyl or ω-azido functionalities were incorporated from an alkynyl-functionalized initiator or from chain-end modification, were found to undergo high-yielding Cu(I)-catalyzed dipolar cycloaddition reactions to produce block copolymers. This is a particularly elegant example, because it illustrates chemical control over the polymer backbone composition and structure as well as the chain-end functionalities. The approach was also demonstrated for monoalkynyl or monoazido poly(ethylene oxide) and for telechelic azido-terminated polystyrene, offering a general and efficient method by which to conduct chemoselective ligation of well-defined polymers (of any architecture) bearing distinctive terminal or side-chain functionalities (*9*).

The quantitative yields for these click reactions overcame one of the central difficulties in translating organic chemistry to the preparation of polymeric systems, as even high yields (i.e., >95%) can lead to decreased purity and poor molecular level control when large numbers of reactions are performed on a single macromolecule. Hawker and Sharpless have exploited the fidelity of the click chemistry during an accelerated dendrimer synthesis. Their synthetic route avoided numerous time-consuming purification steps as a result of complete chain-end functionalization of the acetylene-terminated dendrimer. For example, reaction with the azidothymidine derivative has no need for protection/deprotection strategies or large excesses of reagents, and represented an ~99.9% yield over 12 to 48 coupling reactions (Fig. 2) (*10*). In a similar vein, Matyjaszewski prepared well-defined homopolymers and copolymers of acrylonitrile by atom transfer radical polymerization, which were further modified using a click reaction with sodium azide and zinc chloride to yield polymeric materials having 5-vinyltetrazole side-chain units (*9*). The widespread use and availability of poly(acrylonitrile)-based materials makes this a simple and attractive route to functionalized materials derived from a commodity polymer.

Discrete Molecular Objects by Diels-Alder Chemistry

In considering highly efficient reactions that can be used to construct polymeric materials, the broad scope and simplicity of operation for Diels-Alder chemistry makes it one of the most powerful synthetic methods and one that is accessible to specialists and nonspecialists. The Diels-Alder reaction consists of the cycloaddition of a conjugated diene to a dienophile, typically an alkene or alkyne, with the driving force of the reaction being the formation of new σ bonds, which are energetically more stable than the π bonds.

This efficiency overcomes one of the key challenges in synthetic organic chemistry—the preparation and isolation of complex molecules with functionalities in specific spatial orientations. Control over the spatial orientation of functional groups becomes increasingly difficult with increasing molecular size, as conformational degrees of freedom and dynamics increase. However, a recent report by Müllen exploits the efficiency of Diels-Alder chemistry to construct poly(phenylene)-based molecular objects of increasing size and sophistication and with distinctive physical properties between regioisomers, which allows for their separation (*11*). This report is also of importance as the first route to the preparation of desymmetrized poly(phenylene) objects by a two-step approach, each involving Diels-Alder cycloaddition reactions and the extrusion of carbon monoxide. In the first step, substoichiometric ratios of reagents were used to generate a monosubstituted desymmetrized core as a mixture of two regioisomers. It was not until subsequent reactions upon the remaining three alkynyl sites with various cyclopentadienones and growth of the full, shape-persistent structure that topological isolation of surface functional groups was achieved. The chain ends then occupied different environments, permitting chromatographic separation of the regioisomers. This discovery has been followed by the selective placement of peptides in specific locations within a 3D macromolecular framework, bringing the spatial refinement of small organic molecules to macromolecular systems (*12*).

Supramolecular Chemistry

The use of noncovalent interactions and supramolecular assembly is a recurring theme in

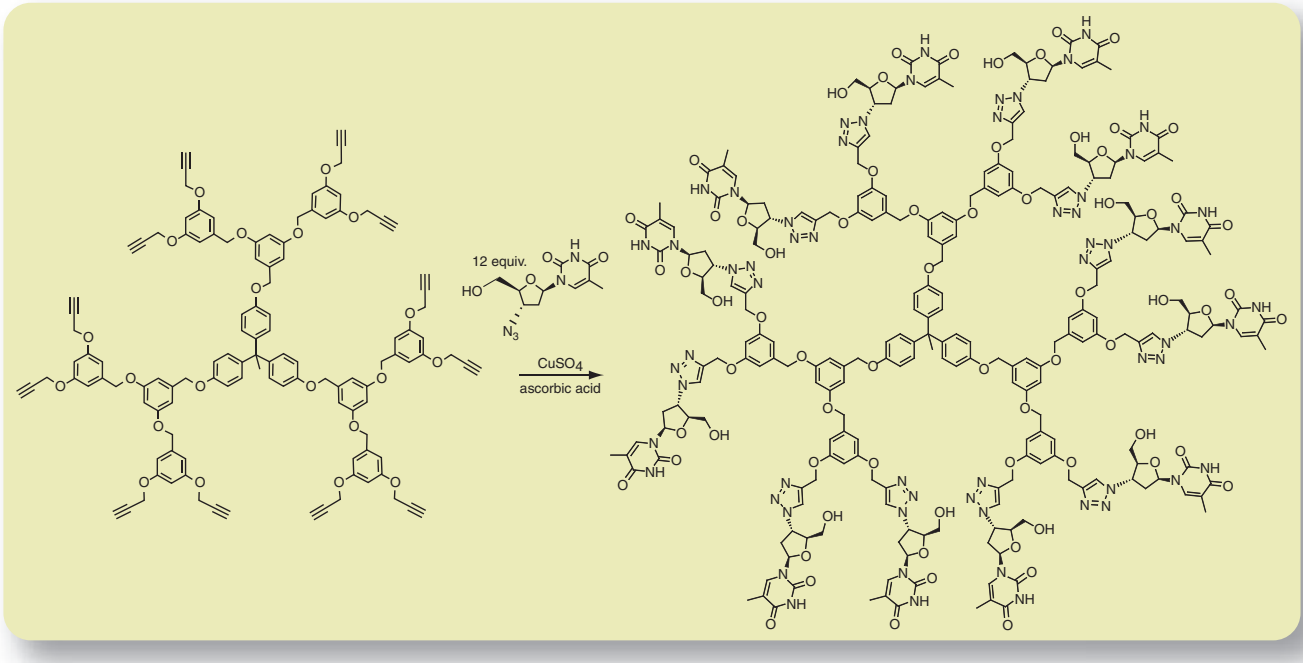

Fig. 2. Preparation of dendritic macromolecules terminated with 3′-azido-3′-deoxythymidine groups using aqueous click chemistry, illustrated with second-generation, dodeca-functionalized derivative.

many natural systems, where its full exploitation is enabled by accurate placements of functional subunits at specific points within macromolecular building blocks such as peptide chains, oligosaccharides, or nucleic acid sequences. Nature exploits both intramolecular and intermolecular assembly in the construction of many functional systems, and this combination of intra/intermolecular assembly has only recently been addressed synthetically. Foldamers have emerged as elegant oligomeric structures that take advantage of the synthetic advances in preparing well-defined materials described above. In particular, synthetic control over the backbone structure and side-group presentation allows for 3D macromolecular designs with defined conformational states of the backbone and side-chain units similar to those found in biological materials such as proteins (*13*). These structural elements guide the intramolecular coiling and intermolecular stacking of the linear segments, through a combination of intramolecular interactions and solvent-directed supramolecular assembly, to afford interesting programmed 3D structures.

Supramolecular assembly of well-defined macromolecular subunits can also lead to the preparation of functional nanoscopic objects based on intermolecular interactions alone. In the simplest forms, for example, fibrillar or core-shell micellar and vesicular assemblies have been related to extracellular matrix materials, lipoproteins, and virus particles (*14*–*16*). Recent work has included the synthesis and use of porphyrin-functionalized initiators for LRP of styrene. The resulting amphiphilic polymers underwent multimolecular supramolecular assembly in tetrahydrofuran/water to afford structures that differed depending on the hydrophilic balance of the porphyrin head group relative to the apolar polystyrene chain segment (*17*). The zinc metalloporphyrin was of particular interest because of the ability to exchange metal ions, altering the physical properties and the energy transfer and catalytic properties. Additionally, polymers having the longest apolar polystyrene chain segment aggregated into nanoscale spherical micelles when water was added to a tetrahydrofuran solution of the amphiphile, whereas the fraction having a polystyrene chain segment of comparable radius of gyration as the porphyrin head group assembled into microscopic hollow spherical vesicles. This ingenious example of functional group incorporation and its effect on self-assembly by Nolte (*17*) also demonstrates the power and enabling capability of new polymerization techniques such as LRP. The ability of LRP to tune the PS chain length while tolerating a wide variety of functional groups, which permits numerous well-defined materials to be easily prepared, provides the foundation for these structure-property studies. Using traditional anionic procedures to prepare a similar range of materials is structurally restrictive and not synthetically practical.

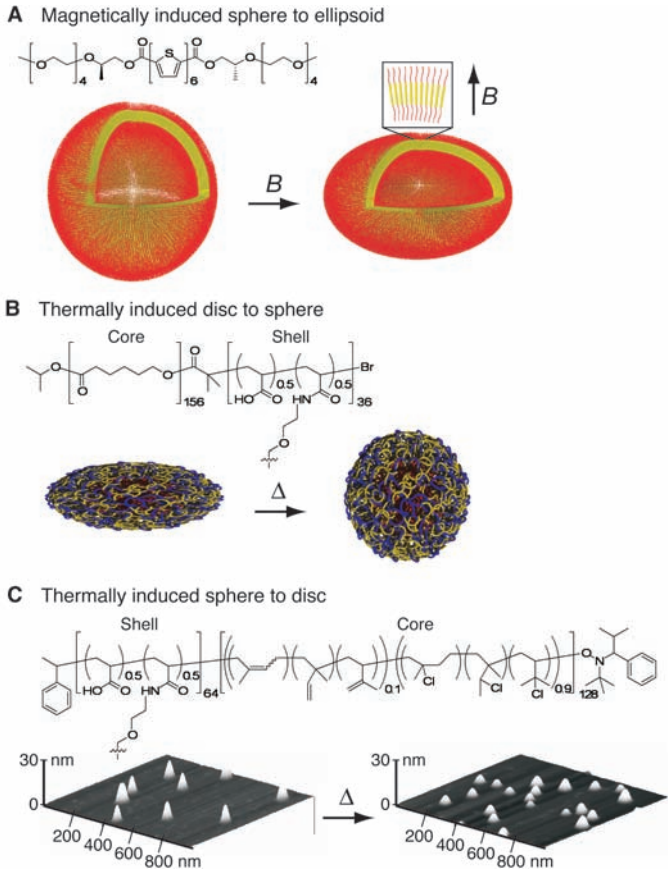

Fig. 3. The physical shaping of nanostructures derived from the supramolecular assembly of amphiphilic linear block copolymers. (**A**) Application of an external magnetic field to assemblies having hexameric thiophene core components. (**B** and **C**) The application of heat to shell cross-linked nanoparticles having (B) crystalline or (C) glassy core domains.

Shapeable Molecular Objects

Shaping of prefabricated polymeric assemblies is a process that is being developed as a new methodology for the preparation of distinctive nanostructures, a similar concept to the foldamers but on a much larger size scale. As described above, the large number of functional groups along a polymeric backbone can lead to difficulties during synthesis; however, their presence can be advantageously used during self-assembly to facilitate and enhance phase separation. By the use of retrosynthetic analysis, traditionally associated with small-molecule syntheses, high levels of control over the structure of monodisperse oligomers and polymer molecules have recently been achieved. This increased level of structural perfection also facilitates the development of an understanding of the rules that govern the assembly of block copolymers and the fundamental polymer physics aspects.

Advances in synthetic organic polymer chemistry have recently allowed a magnetically induced spherical to ellipsoidal transition, predicted theoretically for three decades, to be confirmed experimentally for nanoscale vesicles comprising an ABA bola-amphiphile based on the oligio(thiophene) derivative, 2,5‴″-(*R*-2-methyl-3,6,9,12,15-pentaoxahexadecyl ester)sexithiophene prepared by a multistep organic reaction sequence (*18*). As observed by increasing birefringence, the hollow spheres became increasingly oblate with increasing magnetic field. This shaping process was promoted by the differing degrees of torque exerted by the external magnetic field on each of the molecular subunits within the different regions of the spherical vesicular assemblies (polar versus equatorial regions) due to the large anisotropy in the diamagnetic susceptibility imparted by the six thiophene repeat units (Fig. 3A).

The thermally induced shaping of nanoscale block copolymer micelle assemblies by the chemical transformation of polymer chains within their corona or core domains is also an example of the importance of controlling functional group reactivity and protecting group strategies. The synthesis and reaction of these structures is highly reliant on protection/deprotection strategies borrowed directly from organic chemistry. A multitude of structures can, thereby, be prepared and shaped in solution and upon substrates, mediated by the thermal properties of the core domains. For crystalline core chain segments of poly(ε-caprolactone), the lamellar crystalline phase exerts a disc-shaped morphology to each nanoscale object, which collapses to a sphere upon heating above the melt-transition temperature (*19*) (Fig. 3B). The disc-shaped nanostructure was reestablished upon cooling to induce recrystallization of the core material. Alternatively, a sphere to disc transition was induced thermally upon adsorption from

solution onto a flat substrate (mica or graphite) for core-shell nanoparticles containing polyisoprene core materials (*20*) (Fig. 3C).

The programmed assembly of structurally and compositionally detailed block copolymers has also been studied while in contact with various substrates, which, with subsequent physical and chemical manipulation, has led to important technological developments. The physical adsorption of amphiphilic copolymers upon CdSe/ZnS core-shell quantum dots has been followed by covalent cross-linking to establish robust water-soluble quantum dots, which are of interest for a number of biological and medical applications (*21*, *22*). Remaining carboxylic acid residues allow for conjugation of targeting ligands, for example, whereas the cross-linked polymer shell provides for a stable barrier layer between the quantum dot and the surrounding medium (*23*). Physical isolation of gold nanoparticles has been accomplished similarly, by the physical encapsulation of dodecanethiol-functionalized Au nanoparticles within mixtures of polystyrene-*b*-poly(acrylic acid) and poly(methyl acrylate)-*b*-poly(acrylic acid) (*24*). Dodecanethiol functionalization of the Au nanoparticles allowed for hydrophobic physisorption of the amphiphilic block copolymer to produce the aqueous-phase dispersible encapsulated materials. These studies confirm the need to control the nature of the block copolymer and the interfaces with which contact will be made to achieve the desired nanoscale conformational and directional alignment of the polymer chains as they adsorb onto the substrate. Moreover, these examples illustrate that the reversible intermolecular interactions that drive the assembly process thermodynamically can be supplemented by covalent linkages to capture and stabilize the desired morphologies.

Hybrid Synthetic-Biological Macromolecules

The challenge of combining biopolymers with synthetic macromolecules represents an interesting and powerful opportunity for merging the distinctive properties of each class of material (i.e., programmed assembly of biomolecules and synthetic versatility of synthetic polymers) while at the same time overcoming specific limitations (i.e., decreased stability of biopolymers and poor structural control of synthetic systems) (*25*). In fact, synthetic polymer-protein hybrids (*26*) are already used to increase the circulation time of medicinally relevant proteins, such as Filgrastim, by the covalent attachment of poly(ethylene glycol). Recent work has substantially increased both the complexity of the synthetic polymers and the sophistication of the organic coupling chemistry employed, while at the same time strategies have been developed for the conjugation of these systems to specific points along the backbone of each macromolecule.

This increase in sophistication is perhaps best exemplified by the development of polymer-DNA hybrids by Mirkin and Nguyen (*27*, *28*). In the original studies, hydroxymethyldiphenylacetylene-functionalized poly(norbornene) was prepared by ROMP, followed by phosphoamidite coupling with preformed oligonucleotides. Although synthetically interesting, the promise of these hybrid systems was not realized until the complexity of the synthetic polymer backbone was increased by the incorporation of redox active elements into a multiblock architecture. The living nature of the ROMP process coupled with recent breakthroughs in the design of Ru initiators allowed low polydispersity, controlled molecular weight ferrocenyl- and dibromoferrocenyl-substituted poly(norbornene) blocks to be integrated into the hybrid DNA structure. These triblock systems exhibited high DNA duplex stability and unusually sharp melting transitions with electrochemically distinct signals for the ferrocenyl derivatives, allowing single base-pair mismatches to be detected on the basis of triblock composition.

The development of solid-phase techniques for the synthesis of organic and biological molecules has been instrumental in allowing the coupling between biological and synthetic macromolecules to evolve from random coupling along the polymeric backbone to specific attachment at predetermined sites. Initial work (*29*) demonstrated the efficiency achieved in biosynthetic hybrid syntheses by sequential growth of peptide fragments from a solid-phase support using standard chemistry followed by initiator attachment and growth of the synthetic polymer through LRP techniques (*30–32*). Conversely, the preformed synthetic macromolecule can be attached to (or grown from) the solid support and peptide fragments extended from the appropriate functional groups along the backbone or at the chain terminus of the synthetic system. This approach has been developed for the preparation of amphiphilic diblock and triblock copolymers of hydrophilic peptide sequences and hydrophobic polystyrene chain segments (*33*). By skillfully manipulating the structure of the initial synthetic system, Stupp has recently demonstrated the design of "reverse" peptide amphiphiles, constructed by coupling at the C terminus instead of the traditional and synthetically easier N terminus (*15*). Having free N termini and opposite peptide polarities, these reversed structures permit a wider array of 3D assemblies to be prepared with improved properties by coassembly with the complementary structures having free C termini. For example, nanofibers containing β sheets prepared by mixing traditional and "reverse" hybrids exhibited improved stability when compared with each parent material.

Polysaccharides represent the third main class of biomacromolecular components, and their coupling strategies involve many organic reactions developed for small-molecule oligosaccharides. A particularly interesting development from Haddleton's laboratory used oligosaccharide-functionalized initiators for LRP to place the saccharide moiety at the synthetic polymer-chain terminus (*34*). This was then extended to placement at the terminus of the hydrophilic chain segment of amphiphilic block copolymers to decorate block copolymer micelles (*35*) and cross-linked nanoparticles (*36*) with biologically active sugar residues. Well-defined nanostructures bearing surface accessible and bioavailable ligands are of interest as polyvalent containment devices for carrying imaging labels and therapeutics to selective tissues for development broadly in medical applications (*30*, *37*).

Challenges for Polymer Design

In many cases, specific applications are driving areas of research. For targeted drug delivery and/or diagnostic agents, precisely defined macromolecules and nanoscale objects are needed and will require multiple functional groups for drug payload, cell targeting, delivery, and tracking. Other diverse fields, such as microelectronics, where the drive is to develop <50-nm feature sizes, require polymers with accurate control over their length, dispersity, and functionality not only for traditional photolithography but also for alternative nanopatterning techniques. An excellent example is the enabling influence of functionalized block and random copolymers, prepared by LRP, on self-assembling block copolymer template strategies (*38–41*). This synergy and molecular-level focus will be matched by a closer connection between nanotechnology and organic/polymer chemistry. The controlled manipulation of nanoscale objects and patterns by predictable changes in polymer structure is a potent concept that is only beginning to be exploited.

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10.1126/science.1109778