

Carving Out Niches for Nanostructures: Implementation and Interplay of Building Blocks, Methods, and Tools

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The number and diversity of techniques to create well-defined polymeric architectures has set the foundation to reinvent macromolecular chemistry's tenor. This development offers the chance to build refined structures with multifaceted, cross-disciplinary applications. We discuss a few advances in the design and development of selected nanoobjects with far-reaching potential. Herein, well-defined building blocks and introduced methods to establish three-dimensional architectures will be presented. Sequential attachment strategies and tools taken from biological chemistries achieve new levels of specificity.

Manuscript received: 13 July 2006.

Final version: 22 August 2006.

Introduction

Rich chemistries for the modification and design of macromolecules allow us to create polymeric building blocks, combine and modify them in ways to carve out niches, and to mimic the sophistication and diversity of biological materials. In general, we find a few main directions for the implementation of novel techniques, leading to highly specialized nanostructures. Several concepts for applications in biological systems, such as delivery scaffolds mimicking encapsulation, release, and recognition strategies, are taken from cells, viruses, and bacteria. Thereby structural fidelity, compatible with bioconjugation, is a focus in the design of the polymer topology. The importance of imaging and efficacy testing of drug carriers has opened up a new area for polymeric architectures, meeting the high demand and requirements for precise preclinical evaluation. As a result, encapsulation of imaging reagents or chromophores, especially in three dimensions, also vitalized the investigation of electronic properties through site isolation effects of electroactive entities in well-defined nanoobjects.

We will examine several highlights of the most active and trend-setting areas, underlining the fundamentals, tools and techniques, and various levels of modification for turning a simple polymer into a specialized product.

Linear Building Blocks

Biological systems such as proteins, three-dimensional macromolecules derived from linear polypeptides, are perfect examples to demonstrate the influence of the building block in both their assembly and their final implementation. The importance of the chemical and physical nature of linear

building blocks has given advanced polymer chemistries a basis to reach similar sophistication in structure and design.

Well-controlled linear polymers with a variety of functional groups can be prepared with living free radical polymerization (LFRP) procedures such as atom-transfer radical polymerization (ATRP),^[1] nitroxide-mediated polymerization (NMP),^[2,3] and reversible addition–fragmentation transfer polymerization (RAFT).^[4] While all of these methods create non-degradable vinyl backbones, the individual polarity and functionality can be controlled by the nature of the participating acrylate and methacrylate derivatives, respectively. Whereas in the last decade the focus of living polymerization techniques has been the investigation of mechanisms, it is now directed more towards their evaluation to establish concepts for forming polymers with multiple functionalities and cross-disciplinary applications.

Included functionalities are the key to achieve different levels of macromolecular utilization, and two main classes can be distinguished. The first group allows the attachment of moieties in a mild and orthogonal approach, thereby enabling sequential attachment strategies for entities which determines the ultimate application. Popular functionalities are derived from monomers such as *N,N*-acryloxysuccinimide,^[5,6] *N,N*-acrylaminoacids acids,^[7–9] epoxides,^[10–12] and acetylene,^[13,14] which have shown high fidelity in esterification, amination, and 'click reactions',^[15] among others. The second group of embedded functionalities provokes a conformational change of the linear polymeric precursors and locks the linear polymer into a three-dimensional conformation via covalent^[16] or reversible bonds, such as hydrogen bonds^[17–19] or disulfide bridges,^[20] and leads to helical or collapsed structures. In this vein, linear random copolymers can be programmed through the smart

selection of monomer units that offer functionalization concepts derived from nature to achieve materials with their own niche.

In the past, di- and tri-block copolymers with hydrophilic and hydrophobic characteristics have been prepared with great finesse with the intention of forming discrete architectures with interesting morphologies and patterning abilities. While block copolymers in general require a more rigid synthesis regime and the choice of monomers is limited, ATRP and RAFT polymerization methods^[21–24] in particular have been shown to be very effective in creating symmetrical AB, ABA, and amphiphilic ABC type block copolymers. The functionalities in block copolymers can be extended by the sequential addition of crosslinking units and entities for molecular imprinting. These modified block copolymers are poised to react to a variety of physicochemical stimuli and assemble into vesicles,^[25] micelles,^[26,27] reversed micelles,^[28,29] and layers.^[30,31] These rather labile but very precise structures are preserved by units that crosslink, either of a permanent or reversible nature,^[32–35] and will be discussed in the second part of this review.

Other linear structures which continue to gain importance as building blocks, are conjugated and metallic polymers.^[36] Their semiconducting and luminescent properties have been the stimulus for the development of ‘plastic’ optoelectronic devices,^[37,38] sophisticated electronic circuits,^[39] and chemical sensors.^[40,41] However, despite advantageous characteristics for device fabrication and a large number of photophysical studies conducted, the nature of inter-chain excited states in polymers such as poly(*para*-phenylene vinylene) remain controversial.^[42] Often, strong electronic couplings between the delocalized portions of the polymer’s backbone give rise to detrimental emission quenching and low quantum yields.^[43] Furthermore, the tendency of conjugated backbones to aggregate in solution leads both to rendering the material insoluble and the appearance of a new absorption band in films of these materials that is red-shifted relative to that in solution. Several strategies to discourage these interactions include the introduction of solubilizing bulky hydrophobic or hydrophilic substituents or additives^[44] (Fig. 1), as well as site isolation using branched, dendritic,^[45] and linear polymer side chains.^[46–48] The improvement in luminescence in such materials is usually offset by poorer charge transport and remains a key challenge in the optimization of electroluminescent devices. On the other hand, fluorescence spectroscopy has become an increasingly powerful tool to trace individual molecules in living systems or targeted drug delivery vectors in conjunction with imaging and localization of specific tissues. Thereby linear, conjugated polymeric backbones such as poly(*para*-phenylene ethynylene) substituted with branched poly(ethylene oxide) side chains lead to non-ionic, non-protic amphiphilic derivatives that display both respectable solubility and exceptionally high fluorescence quantum yields in water.^[49,50] These are promising sensory materials for biologically relevant analytes. Apart from the spectral properties of a fluorescent probe in aqueous media, chemical stability with respect to the cell metabolism and low toxicity are

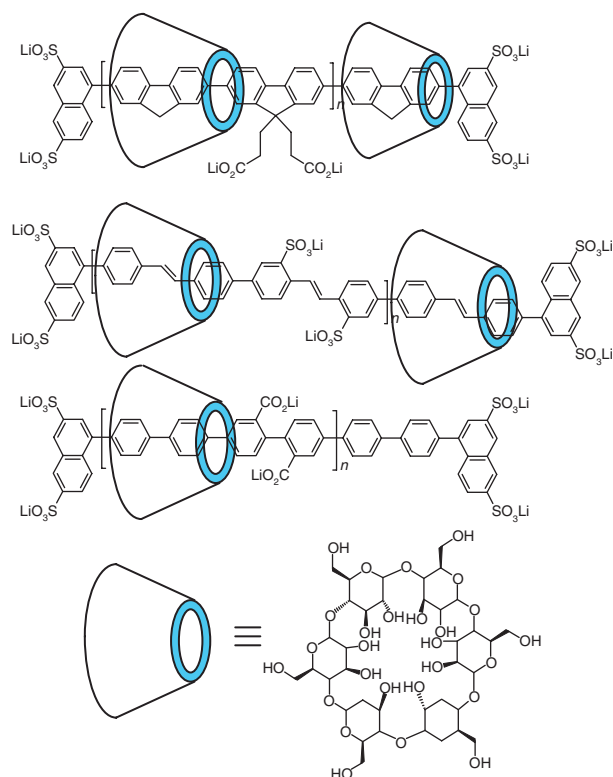


Fig. 1. Cyclodextrin-threaded conjugated polyrotaxanes.^[44]

crucial criteria for meaningful experiments *in vivo*. In contrast to conventional fluorescent dyes, conjugated polymers show improved photostability and enable sophisticated photophysical investigations.

Block copolymers containing conjugated rod blocks together with nonconjugated coil blocks have been investigated to produce ordered microphase-separated morphologies^[51] that can be controlled to be a sphere,^[52] cylinder,^[53] lamellae,^[52,54–56] or bicontinuous phase depending on the length, macroscopic shape, and the ratio of each block.^[57] Procedures including LFRP have been studied initially from macroinitiators (PPV-TEMPO) with polystyrene grown from the TEMPO functionality as the flexible block (TEMPO: 2,2,6,6-tetramethyl-1-piperidinoxy; PPV: poly(*para*-phenylene vinylene)).^[58,59] From the same strategy di- and triblock copolymers containing poly(alkylthiophene) or fluorene moieties were prepared through ATRP^[60] or NMP of styrene at the end-functional group of the poly(alkylthiophene) or fluorene block, respectively. The resulting microphase morphology ranges from honeycomb^[59] to well-defined nanowires with a 30–40 nm lateral spacing that is equivalent to the fully extended block length.^[61] Other microporous structures originate, for example, from micelle formations of poly(phenylquinoline)-*block*-poly(styrene).^[62]

Implementation of Building Blocks and Assembly of Three-Dimensional Nanostructures

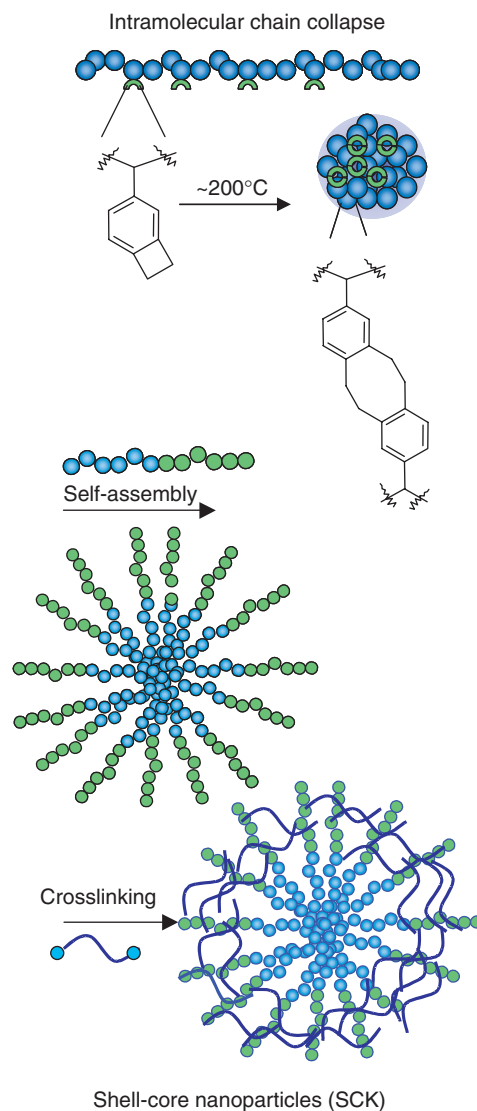
The second part of this review focusses on the successful implementation of the linear building blocks to form three-dimensional architectures, and we will give evidence

of successful strategies to build nanostructures from the bottom-up. It will be obvious that the key criteria in this assembly process must be:

- The precise selection of the linear building blocks based upon their constitution and functionality.
- The selection of synthetic tools and conditions to arrange the linear building blocks into a three-dimensional conformation. This will be accomplished partly either through incorporated permanent or reversible crosslinking units, or through entities known to respond to physicochemical stimulus in the form of intra- and inter-chain hydrogen bond formation, yielding bioinspired architectures corresponding to proteins or vesicles. On the other hand, other synthetic tools can drive the assembly, such as adding crosslinking units to linear copolymers and block polymers derived from LFRP procedures. These polymers will be joined together randomly and will form, depending on the nature of the crosslinker, degradable or non-degradable star polymer architectures, crosslinked nano-objects, or micelles. Furthermore, linear building blocks can be attached or grafted to three-dimensional features engaged in the polymerization process as macroinitiators. The core can include features of biological nature, for example proteins, or artificial structures, such as organic hyperbranched cores or metallic particles.
- Enabling sequential attachments of units in a top-down approach which will define the technological niche and fine-tune its properties toward the end application. This key criterion addresses the ability to modify functionalities or conjugate other building blocks to the assembled nanostructure and emphasizes the necessity of integrated multifunctional units for sequential attachment of relevant moieties. Hence, a careful assessment of the targeted utilization leads to precisely planned incorporation of tailored functionalities in the backbones of polymeric building blocks with previously described facets. Orthogonal protecting groups and conjugation conditions chosen to be compatible with functionalities and already previously conjugated units are a key concern to create specialized structures. Excellent review articles^[63,64] cover the increasing influence of organic chemistries into polymer chemistries and feature examples of polymeric materials such as macromolecules from intramolecular chain collapse processes and crosslinked micelles from tailored block copolymers (Scheme 1). We will focus in our review on recent reports of implementation strategies with nanovectors for imaging or detection and bioinspired nanostructures with multifunctional features and applications in the life sciences.

Nanovectors for Imaging and Detection

The increasing significance of the early detection of cancer, for example by means of precancerous and malignant lesions in biological fluids, provides means to bio-nanotechnological approaches.^[65] Highly fluorescent nanoparticles, such as inorganic semiconducting quantum dots,^[66,67] quantum



Scheme 1. Nanoparticle formation via intramolecular chain collapse^[16] and covalent crosslinking of micelles.^[34]

dot-doped silica colloids, dye-doped silica colloids,^[68,69] and dye-doped latex spheres,^[70] possess high brightness and show improved photostability to conventional fluorescent dyes.^[71] The utilization of such nanoparticles in ultrasensitive assays and live cell imaging^[65] is primarily dependent on their capacity for subsequent conjugation and thereby nanoparticle assembly. Whereas dye-loaded silica particles are previously well studied, the encapsulation of π -conjugated polymers is largely unexplored. Recently, conjugated polymer loaded silica particles were described as a successor over dye-loaded particles.^[72,73] These beads are more than 30 nm larger and contain limited dye-loading concentration due to self-quenching. The silica shell, encapsulating the conjugating polymer, reduces the rate of photooxidation and improves the photostability and extinction coefficients so that adequate quantum yields, comparable to those of quantum dots, are observed.^[74] However, nanoparticles which display site isolation of individual linear conjugated polymers remain largely unexplored and will be important subjects of future investigation. In particular, entirely organic structures are desirable,

mainly due to the possibility of engaging multiple functionalities and implementing other versatile building blocks as described above.

In general the non-toxic feature of polymeric nanoparticles offers advantages over traditional quantum dot in vivo imaging and early detection of invasive cell types or plaques, tumours, and necroses. Furthermore, co-registration of tissues with different imaging modalities can give complementary information that improves disease diagnostics. In addition to the optical methods, medical diagnostic imaging procedures currently in use are based on nuclear medicine (γ -ray scintigraphy), positron emission tomography, and magnetic resonance imaging techniques.^[75] The quantity of reporter compound to be accumulated in the area of interest strongly varies between these imaging techniques. Monomolecular gadolinium-based multimodal imaging reagents, for example, must incorporate multiple paramagnetic gadolinium chelates per moiety to compensate for the relative low sensitivity of the magnetic resonance methods. In order to reach the required local concentration of contrast reagents of paramagnetic complexes, macromolecular architectures ranging from micelles,^[76–79] dendrimers,^[80] linear polymers,^[81,82] to proteins^[81,83] are being investigated. Hereby, the macromolecular architectures can influence the relaxivity of the paramagnetic complexes to a high degree and are capable of reducing the concentration of the reporter compound necessary. Mixed micellar aggregates with gadolinium diethylene triamine pentaacetate (DPTA) complexes as end-functionalities and crosslinked micelles ('shell-crosslinked knedels', SCK) with incorporated 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid units have been shown to be promising candidates.^[79] These examples emphasize the advantages of building blocks that can be arranged into nanosized objects addressing the needs of multimodal imaging reagents. However, the inherent problems with large molecules, including low diffusion rate into diseased tissue and rapid uptake by the liver, will have to be solved by smaller and densely packed systems or fine-tuned degradable materials.

The coexistence of fluorophores and metal particles in nanostructures for imaging applications and detection assays may find its counterpart in nanoparticles for electronic applications in optoelectronic devices. It has been long known that lanthanide emission can be sensitized via the 'antenna effect' by using complexes with ligands that absorb in the UV-visible region.^[84,85] Recently, it has been shown that this effect can be extended to conjugated polymer systems by blending the lanthanide complex into a luminescent host.^[86] However, as noted by several authors,^[87,88] phase segregation becomes problematic when constructing efficient thin film optoelectronic devices. Some efforts have now been centered on directly connecting the inorganic components to the conjugated polymer ligands.^[89] These novel nanostructures have provided evidence of enhanced energy transfer between the conjugated polymer and in this case quantum dot components, resulting in dramatically different photoluminescence spectra relative to blended films accompanied by a suppression of blinking.^[90]

Bioinspired Nanostructures with Multifunctional Features for Further Utilization

Tubular and globular three-dimensional structural motifs are constructed from of one or multiple linear building blocks. Novel synthetic architectures, inspired to a great extent by biological structures, are governed through non-covalent interactions such as hydrogen bonding and π - π or arene-arene interactions. The resulting structures are strongly dependent on the strength of the non-covalent interaction between the incorporated monomer units and their individual location in the polymer backbone.^[91–93] The tailoring of monomeric units to control and define a dominant direction of the interactions between chains to govern a specific macromolecular architecture give initial design rules for their construction. For example, telechelic polymers possessing ureidopyrimidione end groups form very stable supramolecular linear polymers, in solution as well in bulk. The quadrupole hydrogen-bond has high association constants and results in polymers and networks with mechanical properties strongly dependent on temperature, giving rise to polyolefins with thermoelastic properties.^[94,95] The reversible nature of the hydrogen bonds is an attractive feature for the development of self-healing materials that can reassemble to the thermodynamically most favorable state. Other hydrogen-bonding interactions of complementary diaminopyridine (DAP) and thymine (Thy) functionalized polymers in nonpolar media results in the formation of giant vesicular polymersomes (Fig. 2).^[96] Discrete microspheres with an average diameter of 10 μm are observed with self-complementary DAP-containing polymers and can be transformed into vesicles via addition of a polymer functionalized with another complementary recognition partner such as thymine. Arene-arene interactions are exploited in linear amphiphilic self-assembled polythiophenes. It was found that the stability of the assemblies is related to the π -conjugation length and right-handed helices are formed in septithiophenes.^[97–99] In this vein, related tubular structures have been constructed with amphiphilic hexabenzocoronenes via columnar phase ordering of the disk-shaped hexabenzocoronene.^[100,101] These architectures are discussed in applications as organic nanowires, and the self-assembly behavior provides the means for any putative utilization of these systems.^[101] In general, these examples demonstrate the organization of supramolecular structures through thoughtful selection of functional groups implementing non-covalent interactions.

Other attractive approaches to form tubular structures include the stiffening of linear polymers by grafting bulky groups onto the linear backbone.^[102,103] In a novel strategy, the bulky side groups such as dendrons are grown in an iterative, divergent approach and they lead to an increase in molecular weight in an order of a magnitude.^[104] In contrast to linear polymers, where functional groups are limited by the monomer, the number of peripheral moieties can be increased exponentially. In this way, specific functionalities or conjugated groups could be protected on the interior of the tubular layered nanovectors and the outer functionalities engaged in

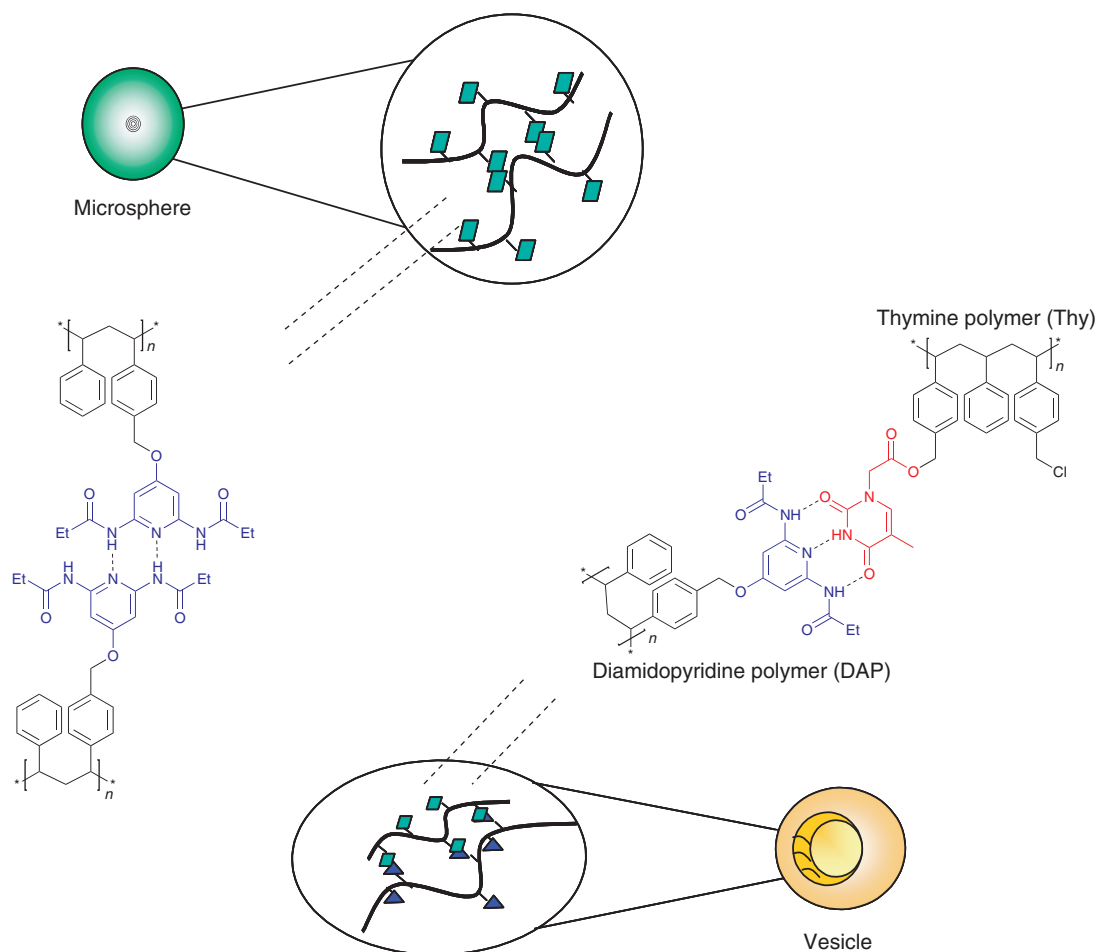


Fig. 2. Reversible morphology control using noncovalent interactions.^[96]

recognition and targeting. The same strategy of forming a distinct periphery and providing protected inner cores can be observed in research efforts in the utilization of globular three-dimensional nanostructures as drug delivery systems or novel electro-optic materials.^[105–113] In particular, the last decade has been very innovative in the creation of a variety of synthetic bioinspired three-dimensional nanostructures derived from viral^[114–116] and cellular models.^[117,118] One of the most prominent systems are self-assembled micelles and crosslinked micelles (SCK) which have been studied extensively.^[34] The crosslinking of self-assembled, well-defined block copolymers preserves the micellar structures of 20–200 nm in size and opens up the possibility of multiple top-down manipulation strategies.^[34] Recent advances in LFRP processes and the implementation of ‘click chemistry’ in polymer science allows the preparation of linear building blocks with an extended number of functionalities and enable efficient and sequential conjugation of bioactive compounds.^[119] The interplay of architectural features and incorporated functionalities will give the opportunity to specifically modify sub-locations in three-dimensional architectures.

Bioinspired protein architectures can be prepared from linear polymers through the intra-molecular chain collapse

process. It has been found that a highly efficient crosslinking chemistry is crucial for the successful formation of collapsed nanoparticles via intra-molecular chain collapse to give nanoparticle of ~4–10 nm in size.^[16] The crosslinking mechanism is based on the thermal activation of *ortho*-chinodimethane precursors, which form cycloaddition products maintaining the nanoparticle architecture derived from one linear polymer. The copolymerization with various degrees of crosslinking opens up the possibility of obtaining particles with adjustable porosity and density.^[16,120,121] High temperatures required during the collapse process have so far limited the use of a broader range of functional copolymers and block copolymers. Thus the further development of low-temperature crosslinkers would enhance the implementation of these materials in drug delivery and novel electro-optic systems with site-isolated electroactive reagents.

Another technique to utilize linear polymers derived from LFRP processes is the star formation, in which a small molecule crosslinker drives the assembly on the living, dormant, chain end of the polymer.^[122–124] The ideal ratio of each critical parameter such as crosslinker, solvent, and linear polymer was precisely investigated with polymers derived from NMP techniques and combinatorial methods.^[125,126] So far, water-soluble star polymers from vinyl polymers are more

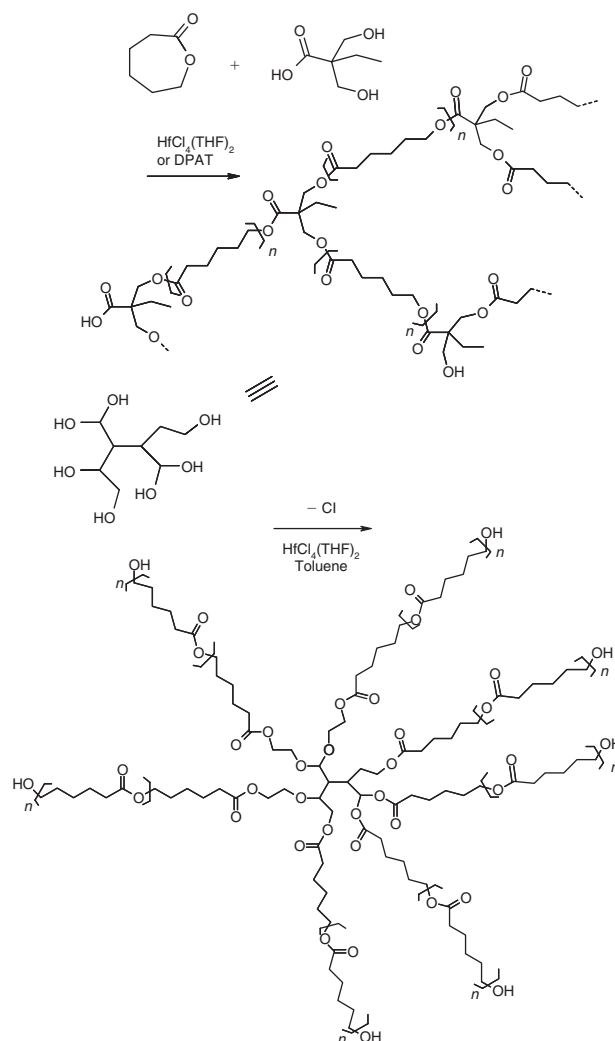
difficult to obtain and recent interests in biological materials have intensified the research efforts to find methods to create hydrophilic and degradable nanoscopic architectures.^[127–129] Future applications of these core–shell structures will be directed through syntheses involving sophisticated divinyl crosslinking compounds with incorporated functionalities, interesting physicochemical and electro-optical features, as well as the nature of the linear polymers involved.^[130–134] In particular, the macromolecular architecture promotes the enhancement of local proton relaxation processes of the water molecules in the presence of a contrast reagent. The investigation of these structures in providing longer circulation times will lead to bimodal imaging reagents with the potential for active targeting.

Degradable polymeric star architectures for biological applications with larger cores^[135] are being synthesized stepwise from hyperbranched polymers using ring opening polymerization methods and function as macroinitiators (Scheme 2).^[136] Degradable linear polymers can be grown directly with ring opening polymerization or using LFRP procedures after an initiator is conjugated to three-dimensional cores of up to 150 kDa. In a similar fashion, natural proteins like albumin and lysozyme have been used as three-dimensional macroinitiators to form protein–polymer conjugates.^[137] This approach involves the modification of the protein with initiation sites, and the polymerization takes place at specific domains to form well-defined nanostructures. Controlled growth of the polymer at site-specific domains reflects on the biological properties and ensures that the protein's bioactivity stays intact and biorecognition sites are available. It has been shown that ATRP and RAFT methods proved to be especially successful in governing controlled polymerization compatible with biological structures.^[138]

Chemical strategies to further fine-tune the targeted application are programmed through the degree and nature of the introduced functional groups. Thereby, for the attachment of biological groups such as targeting units, including various formulations to target $\alpha_v\beta_3$ integrin^[139,140] and translocation domains,^[141] reaction conditions have to be mild and orthogonal to the other groups in the macromolecule.^[6] In this way, small molecules, such as sugars and folic acid, linear polymers, and dendrons can further specify the function of the nanostructure. The presented strategies open up diverse possibilities to precisely integrate entities into sublocations of macromolecules and will advance the intended exploitation of microenvironments in properties of materials.

Conclusions

These research facets presented emphasize the role of recent accomplishments in polymer science in the realization of multiplex macromolecules. We are aware that the creativity in this area is vivid and that we left out other interesting approaches that could not be covered entirely in this short review. However, less-stringent limitations in the syntheses, aiming for even higher degrees of accuracy and functional versatility in the building blocks, will be the defining features for future breakthroughs in areas such



Scheme 2. Synthesis of hyperbranched copolyesters by combined ring-opening polymerization/polycondensation.^[136]

as bio-nanotechnology procedures. At this time, imaging and recognition devices including the development of technologies for biomarkers and targeted delivery of multiple therapeutic reagents are two of the most challenging and exciting areas in macromolecular research.

References

- [1] J. S. Wang, K. Matyjaszewski, *J. Am. Chem. Soc.* **1995**, *117*, 5614. doi:10.1021/JA00125A035
- [2] D. Benoit, V. Chaplinski, R. Braslau, C. J. Hawker, *J. Am. Chem. Soc.* **1999**, *121*, 3904. doi:10.1021/JA984013C
- [3] C. J. Hawker, A. W. Bosman, E. Harth, *Chem. Rev.* **2001**, *101*, 3661. doi:10.1021/CR990119U
- [4] J. Chiefari, Y. K. Chong, F. Ercole, J. Krstina, J. Jeffery, T. P. T. Le, R. T. A. Mayadunne, G. F. Meijs, C. L. Moad, G. Moad, E. Rizzardo, S. H. Thang, *Macromolecules* **1998**, *31*, 5559. doi:10.1021/MA9804951
- [5] R. Shunmugam, G. N. Tew, *J. Polym. Sci. Part A Polym. Chem.* **2005**, *43*, 5831. doi:10.1002/POLA.21102
- [6] M. Malkoch, R. J. Thibault, E. Drockenmüller, M. Messerschmidt, B. Voit, T. P. Russell, C. J. Hawker, *J. Am. Chem. Soc.* **2005**, *127*, 14942. doi:10.1021/JA0549751

- [7] R. G. Ezell, I. Gorman, B. Lokitz, N. Ayres, C. L. McCormick, *J. Polym. Sci. Part A Polym. Chem.* **2006**, *44*, 3125. doi:10.1002/POLA.21408
- [8] H. Mori, H. Iwaya, A. Nagai, T. Endo, *Chem. Commun.* **2005**, 4872. doi:10.1039/B509212D
- [9] H. Mori, K. Sutoh, T. Endo, *Macromolecules* **2005**, *38*, 9055. doi:10.1021/MA0509558
- [10] I. Kroutilova, L. Matejka, A. Sikora, K. Soucek, L. Stas, *J. Appl. Polym. Sci.* **2006**, *99*, 3669. doi:10.1002/APP.22548
- [11] A. Nebioglu, M. D. Soucek, *JCT Res.* **2006**, *3*, 61.
- [12] M. D. Soucek, H. Ni, *J. Coat. Techn.* **2002**, *74*, 125.
- [13] P. Wu, M. Malkoch, J. N. Hunt, R. Vestberg, E. Kaltgrad, M. G. Finn, V. V. Fokin, K. B. Sharpless, C. J. Hawker, *Chem. Commun.* **2005**, 5775. doi:10.1039/B512021G
- [14] B. Helms, J. L. Mynar, C. J. Hawker, J. M. J. Frechet, *J. Am. Chem. Soc.* **2004**, *126*, 15020. doi:10.1021/JA044744E
- [15] M. Malkoch, K. Schleicher, E. Drockenmuller, C. J. Hawker, T. P. Russell, P. Wu, V. V. Fokin, *Macromolecules* **2005**, *38*, 3663. doi:10.1021/MA047657F
- [16] E. Harth, B. Van Horn, V. Y. Lee, D. S. Germack, C. P. Gonzales, R. D. Miller, C. J. Hawker, *J. Am. Chem. Soc.* **2002**, *124*, 8653. doi:10.1021/JA026208X
- [17] J. van Herrikhuyzen, P. Jonkheijm, A. P. H. J. Schenning, E. W. Meijer, *Org. Biomol. Chem.* **2006**, *4*, 1539. doi:10.1039/B517993A
- [18] R. W. Sinkeldam, M. H. C. J. van Houtem, G. Koeckelberghs, J. A. J. M. Vekemans, E. W. Meijer, *Org. Lett.* **2006**, *8*, 383. doi:10.1021/OL0524757
- [19] G. B. W. L. Ligthart, H. Ohkawa, R. P. Sijbesma, E. W. Meijer, *J. Am. Chem. Soc.* **2005**, *127*, 810. doi:10.1021/JA043555T
- [20] Y. T. Li, B. S. Lokitz, S. P. Armes, C. L. McCormick, *Macromolecules* **2006**, *39*, 2726. doi:10.1021/MA0604035
- [21] L. Barner, C. Barner-Kowollik, T. P. Davis, M. H. Stenzel, *Aust. J. Chem.* **2004**, *57*, 19. doi:10.1071/CH03232
- [22] J. F. Quinn, R. P. Chaplin, T. P. Davis, *J. Polym. Sci. Part A Polym. Chem.* **2002**, *40*, 2956.
- [23] H. Mori, S. Nakano, T. Endo, *Macromolecules* **2005**, *38*, 8192. doi:10.1021/MA050918G
- [24] A. J. Convertine, B. S. Lokitz, Y. Vasileva, L. J. Myrick, C. W. Scales, A. B. Lowe, C. L. McCormick, *Macromolecules* **2006**, *39*, 1724. doi:10.1021/MA0523419
- [25] U. Borchert, U. Lipprandt, M. Bilanz, A. Kimpfler, A. Rank, R. Peschka-Süss, R. Schubert, P. Lindner, S. Förster, *Langmuir* **2006**, *22*, 5843. doi:10.1021/LA060227T
- [26] J. Q. Jiang, X. Tong, D. Morris, Y. Zhao, *Macromolecules* **2006**, *39*, 4633. doi:10.1021/MA060142Z
- [27] M. Licciardi, G. Giammona, J. Z. Du, S. P. Armes, Y. Q. Tang, A. L. Lewis, *Polymer* **2006**, *47*, 2946. doi:10.1016/J.POLYMER.2006.03.014
- [28] G. S. Kwon, M. L. Forrest, *Drug Dev. Res.* **2006**, *67*, 15. doi:10.1002/DDR.20063
- [29] C. F. van Nostrum, D. Neradovic, O. Soga, W. E. Hennink, in *Polymeric Drug Delivery Vol. I: Particulate Drug Carriers, ACS Symp. Ser. 923* (Ed. S. Svenson) **2006**, p. 40 (American Chemical Society: Washington, DC).
- [30] D. H. Kim, K. H. A. Lau, J. W. F. Robertson, O. J. Lee, U. Jeong, J. I. Lee, C. J. Hawker, T. P. Russell, J. K. Kim, W. Knoll, *Adv. Mater.* **2005**, *17*, 2442. doi:10.1002/ADMA.200500170
- [31] I. Luzinov, V. V. Tsukruk, *Macromolecules* **2002**, *35*, 5963. doi:10.1021/MA0205818
- [32] D. Zschech, D. H. Kim, A. P. Milenin, S. Hopfe, R. Scholz, P. Göring, R. Hillebrand, S. Senz, C. J. Hawker, T. P. Russell, M. Steinhart, U. Gösele, *Nanotechnology* **2006**, *17*, 2122. doi:10.1088/0957-4484/17/9/008
- [33] R. C. Hayward, B. F. Chmelka, E. J. Kramer, *Adv. Mater.* **2005**, *17*, 2591. doi:10.1002/ADMA.200500334
- [34] K. L. Wooley, *J. Polym. Sci. Part A Polym. Chem.* **2000**, *38*, 1397. doi:10.1002/(SICI)1099-0518(20000501)38:9<1397::AID-POLA1>3.0.CO;2-N
- [35] E. Drockenmuller, L. Y. T. Li, D. Y. Ryu, E. Harth, T. P. Russell, H. C. Kim, C. J. Hawker, *J. Polym. Sci. Part A Polym. Chem.* **2005**, *43*, 1028. doi:10.1002/POLA.20553
- [36] A. J. Heeger, *J. Phys. Chem. B* **2001**, *105*, 8475. doi:10.1021/JP011611W
- [37] T. M. Brown, R. H. Friend, I. S. Millard, D. J. Lacey, J. H. Burroughes, F. Cacialli, *Appl. Phys. Lett.* **2001**, *79*, 174. doi:10.1063/1.1383800
- [38] R. E. Martin, F. Geneste, R. Riehn, B. S. Chuah, F. Cacialli, A. B. Holmes, R. H. Friend, *Synth. Met.* **2001**, *119*, 43. doi:10.1016/S0379-6779(00)01507-1
- [39] K. Petritsch, R. H. Friend, A. Lux, G. Rozenberg, S. C. Moratti, A. B. Holmes, *Synth. Met.* **1999**, *102*, 1776. doi:10.1016/S0379-6779(98)01035-2
- [40] L. H. Chen, D. W. McBranch, H. L. Wang, R. Helgeson, F. Wudl, D. G. Whitten, *Proc. Natl. Acad. Sci. USA* **1999**, *96*, 12287. doi:10.1073/PNAS.96.22.12287
- [41] G. Yu, J. Wang, J. McElvain, A. J. Heeger, *Adv. Mater.* **1998**, *10*, 1431. doi:10.1002/(SICI)1521-4095(199812)10:17<1431::AID-ADMA1431>3.0.CO;2-4
- [42] K. Becker, J. M. Lupton, J. Feldmann, B. S. Nehls, F. Galbrecht, D. Q. Gao, U. Scherf, *Adv. Funct. Mater.* **2006**, *16*, 364. doi:10.1002/ADFM.200500550
- [43] T. Q. Nguyen, V. Doan, B. J. Schwartz, *J. Chem. Phys.* **1999**, *110*, 4068. doi:10.1063/1.478288
- [44] F. Cacialli, J. S. Wilson, J. J. Michels, C. Daniel, C. Silva, R. H. Friend, N. Severin, P. Samori, J. P. Rabe, M. J. O'Connell, P. N. Taylor, H. L. Anderson, *Nat. Mater.* **2002**, *1*, 160. doi:10.1038/NMAT750
- [45] Z. S. Bo, C. M. Zhang, N. Severin, J. P. Rabe, A. D. Schluter, *Macromolecules* **2000**, *33*, 2688. doi:10.1021/MA991287R
- [46] P. R. L. Malenfant, J. M. J. Frechet, *Macromolecules* **2000**, *33*, 3634. doi:10.1021/MA000003W
- [47] E. E. Sheina, S. M. Khersonsky, E. G. Jones, R. D. McCullough, *Chem. Mater.* **2005**, *17*, 3317. doi:10.1021/CM050083O
- [48] D. Marsitzky, R. Vestberg, P. Blainey, B. T. Tang, C. J. Hawker, K. R. Carter, *J. Am. Chem. Soc.* **2001**, *123*, 6965. doi:10.1021/JA010020G
- [49] A. Khan, S. Hecht, *J. Polym. Sci. Part A Polym. Chem.* **2006**, *44*, 1619. doi:10.1002/POLA.21238
- [50] A. Khan, S. Muller, S. Hecht, *Chem. Commun.* **2005**, 584. doi:10.1039/B413616K
- [51] C. J. Hawker, T. P. Russell, *MRS Bull.* **2005**, *30*, 952.
- [52] N. Sota, N. Sakamoto, K. Saijo, T. Hashimoto, *Polymer* **2006**, *47*, 3636. doi:10.1016/J.POLYMER.2006.03.017
- [53] J. K. Hobbs, R. A. Register, *Macromolecules* **2006**, *39*, 703. doi:10.1021/MA051402O
- [54] T. Heiser, G. Adamopoulos, M. Brinkmann, U. Giovanella, S. Ould-Saad, C. Brochon, K. van de Wetering, G. Hadziioannou, *Thin Solid Films* **2006**, *511*, 219. doi:10.1016/J.TSF.2005.12.134
- [55] B. Schmaltz, M. Brinkmann, C. Mathis, *Macromolecules* **2004**, *37*, 9056. doi:10.1021/MA048421E
- [56] M. E. Mackay, *CR Chimie* **2003**, *6*, 747. doi:10.1016/J.CRCI.2003.05.003
- [57] H. Xiang, K. Shin, T. Kim, S. I. Moon, T. J. McCarthy, T. P. Russell, *Macromolecules* **2005**, *38*, 1055. doi:10.1021/MA0476036
- [58] B. de Boer, U. Stalmach, H. Nijland, G. Hadziioannou, *Adv. Mater.* **2000**, *12*, 1581. doi:10.1002/1521-4095(200011)12:21<1581::AID-ADMA1581>3.0.CO;2-R
- [59] G. Widawski, M. Rawiso, B. Francois, *Nature* **1994**, *369*, 387. doi:10.1038/369387A0
- [60] M. C. Iovu, M. Jeffries-El, E. E. Sheina, J. R. Cooper, R. D. McCullough, *Polymer* **2005**, *46*, 8582. doi:10.1016/J.POLYMER.2005.05.035
- [61] R. Bjørnholm, T. Hassenkamy, D. R. Greve, R. D. McCullough, M. Jayaraman, S. M. Savoy, C. E. Jones, J. T. McDevitt, *Adv.*

- Mater.* **1999**, *11*, 1218. doi:10.1002/(SICI)1521-4095(199910)11:14<1218::AID-ADMA1218>3.0.CO;2-G
- [62] X. L. Chen, S. A. Jenekhe, *Langmuir* **1999**, *15*, 8007. doi:10.1021/LA9810253
- [63] C. J. Hawker, K. L. Wooley, *Science* **2005**, *309*, 1200. doi:10.1126/SCIENCE.1109778
- [64] K. L. Wooley, C. J. Hawker, *Funct. Molec. Nanostruct.* **2005**, *245*, 287.
- [65] R. Weissleder, *Science* **2006**, *312*, 1168. doi:10.1126/SCIENCE.1125949
- [66] A. P. Alivisatos, *Cytometry A* **2004**, *59A*, 29.
- [67] P. Alivisatos, *Nat. Biotechnol.* **2004**, *22*, 47. doi:10.1038/NBT927
- [68] H. Ow, D. R. Larson, M. Srivastava, B. A. Baird, W. W. Webb, U. Wiesner, *Nano Lett.* **2005**, *5*, 113. doi:10.1021/NL0482478
- [69] L. Wang, C. Y. Yang, W. H. Tan, *Nano Lett.* **2005**, *5*, 37. doi:10.1021/NL048417G
- [70] L. A. Kolodny, D. M. Willard, L. L. Carillo, M. W. Nelson, A. Van Orden, *Anal. Chem.* **2001**, *73*, 1959. doi:10.1021/AC001472Z
- [71] S. Santra, B. Liesenfeld, C. Bertolino, D. Dutta, Z. H. Cao, W. H. Tan, B. M. Moudgil, R. A. Mericle, *J. Lumin.* **2006**, *117*, 75. doi:10.1016/J.JLUMIN.2005.04.008
- [72] M. Lal, L. Levy, K. S. Kim, G. S. He, X. Wang, Y. H. Min, S. Pakatchi, P. N. Prasad, *Chem. Mater.* **2000**, *12*, 2632. doi:10.1021/CM000178K
- [73] A. Burns, P. Sengupta, T. Zedayko, B. Baird, U. Wiesner, *Small* **2006**, *2*, 723. doi:10.1002/SMLL.200600017
- [74] C. F. Wu, C. Szymanski, J. McNeill, *Langmuir* **2006**, *22*, 2956. doi:10.1021/LA060188L
- [75] R. Weissleder, U. Mahmood, *Radiology* **2001**, *219*, 316.
- [76] P. L. Anelli, L. Lattuada, V. Lorusso, M. Schneider, H. Tournier, F. Uggeri, *Magn. Reson. Mater. Phys. Biol. Med.* **2001**, *12*, 114. doi:10.1016/S1352-8661(01)00107-7
- [77] V. P. Torchilin, *Adv. Drug Deliv. Rev.* **2002**, *54*, 235. doi:10.1016/S0169-409X(02)00019-4
- [78] J. P. Andre, E. Toth, H. Fischer, A. Seelig, H. R. Macke, A. E. Merbach, *Chem. Eur. J.* **1999**, *5*, 2977. doi:10.1002/(SICI)1521-3765(19991001)5:10<2977::AID-CHEM2977>3.0.CO;2-T
- [79] J. L. Turner, D. P. J. Pan, R. Plummer, Z. Y. Chen, A. K. Whittaker, K. L. Wooley, *Adv. Funct. Mater.* **2005**, *15*, 1248. doi:10.1002/ADFM.200500005
- [80] E. C. Wiener, M. W. Brechbiel, H. Brothers, R. L. Magin, O. A. Gansow, D. A. Tomalia, P. C. Lauterbur, *Magn. Reson. Med.* **1994**, *31*, 1.
- [81] S. Liu, D. S. Edwards, *Chem. Rev.* **1999**, *99*, 2235. doi:10.1021/CR980436L
- [82] Z. R. Lu, X. H. Wang, D. L. Parker, K. C. Goodrich, H. R. Buswell, *Bioconjug. Chem.* **2003**, *14*, 715. doi:10.1021/BC0340464
- [83] U. Schmiedl, M. E. Moseley, R. Sievers, M. D. Ogan, W. M. Chew, H. Engeseth, W. E. Finkbeiner, M. J. Lipton, R. C. Brasch, *Invest. Radiol.* **1987**, *22*, 713.
- [84] R. A. Negres, X. Gong, J. C. Ostrowski, G. C. Bazan, D. Moses, A. J. Heeger, *Phys. Rev. B* **2003**, *68*, 115209. doi:10.1103/PHYSREVB.68.115209
- [85] N. R. Evans, L. S. Devi, C. S. K. Mak, S. E. Watkins, S. I. Pascu, A. Köhler, R. H. Friend, C. K. Williams, A. B. Holmes, *J. Am. Chem. Soc.* **2006**, *128*, 6647. doi:10.1021/JA0584267
- [86] M. D. McGehee, T. Bergstedt, C. Zhang, A. P. Saab, M. B. O'Regan, G. C. Bazan, V. I. Srdanov, A. J. Heeger, *Adv. Mater.* **1999**, *11*, 1349. doi:10.1002/(SICI)1521-4095(199911)11:16<1349::AID-ADMA1349>3.0.CO;2-W
- [87] C. R. McNeill, H. Frohne, J. L. Holdsworth, P. C. Dastoor, *Synth. Met.* **2004**, *147*, 101. doi:10.1016/J.SYNTHMET.2004.06.042
- [88] P. Taranekar, X. W. Fan, R. Advincula, *Langmuir* **2002**, *18*, 7943. doi:10.1021/LA025517Y
- [89] Y. You, S. H. Kim, H. K. Jung, S. Y. Park, *Macromolecules* **2006**, *39*, 349. doi:10.1021/MA052015T
- [90] M. Y. Odoi, N. I. Hammer, K. Sill, T. Emrick, M. D. Barnes, *J. Am. Chem. Soc.* **2006**, *128*, 3506. doi:10.1021/JA058429J
- [91] L. Brunsveld, E. W. Meijer, R. B. Prince, J. S. Moore, *J. Am. Chem. Soc.* **2001**, *123*, 7978. doi:10.1021/JA010751G
- [92] P. van der Schoot, M. A. J. Michels, L. Brunsveld, R. P. Sijbesma, A. Ramzi, *Langmuir* **2000**, *16*, 10076. doi:10.1021/LA000794V
- [93] L. Brunsveld, B. J. B. Folmer, E. W. Meijer, R. P. Sijbesma, *Chem. Rev.* **2001**, *101*, 4071. doi:10.1021/CR990125Q
- [94] L. R. Rieth, R. F. Eaton, G. W. Coates, *Angew. Chem. Int. Ed.* **2001**, *40*, 2153. doi:10.1002/1521-3773(20010601)40:11<2153::AID-ANIE2153>3.0.CO;2-W
- [95] H. M. Keizer, R. van Kessel, R. P. Sijbesma, E. W. Meijer, *Polymer* **2003**, *44*, 5505. doi:10.1016/S0032-3861(03)00631-1
- [96] O. Uzun, A. Sanyal, H. Nakade, R. J. Thibault, V. M. Rotello, *J. Am. Chem. Soc.* **2004**, *126*, 14773. doi:10.1021/JA047643P
- [97] O. Henze, W. J. Feast, F. Gardebien, P. Jonkheijm, R. Lazzaroni, P. Leclère, E. W. Meijer, A. P. H. J. Schenning, *J. Am. Chem. Soc.* **2006**, *128*, 5923. doi:10.1021/JA0607234
- [98] A. F. M. Kilbinger, A. P. H. J. Schenning, F. Goldoni, W. J. Feast, E. W. Meijer, *J. Am. Chem. Soc.* **2000**, *122*, 1820. doi:10.1021/JA994231L
- [99] A. P. H. J. Schenning, A. F. M. Kilbinger, F. Biscarini, M. Cavallini, H. J. Cooper, P. J. Derrick, W. J. Feast, R. Lazzaroni, Ph. Leclère, L. A. McDonell, E. W. Meijer, S. C. J. Meskers, *J. Am. Chem. Soc.* **2002**, *124*, 1269. doi:10.1021/JA0113403
- [100] W. Jin, T. Fukushima, A. Kosaka, M. Niki, N. Ishii, T. Aida, *J. Am. Chem. Soc.* **2005**, *127*, 8284. doi:10.1021/JA051859P
- [101] J. P. Hill, W. S. Jin, A. Kosaka, T. Fukushima, H. Ichihara, T. Shimomura, K. Ito, T. Hashizume, N. Ishii, T. Aida, *Science* **2004**, *304*, 1481. doi:10.1126/SCIENCE.1097789
- [102] L. J. Shu, T. Schafer, A. D. Schluter, *Macromolecules* **2000**, *33*, 4321. doi:10.1021/MA000124W
- [103] C. Bottcher, B. Schade, C. Ecker, J. P. Rabe, L. J. Shu, A. D. Schluter, *Chem. Eur. J.* **2005**, *11*, 2923. doi:10.1002/CHEM.200401145
- [104] J. L. Mynar, T. L. Choi, M. Yoshida, V. Kim, C. J. Hawker, J. M. J. Frechet, *Chem. Commun.* **2005**, 5169. doi:10.1039/B509398H
- [105] P. T. Hammond, *Adv. Mater.* **2004**, *16*, 1271. doi:10.1002/ADMA.200400760
- [106] R. V. Ulijn, *J. Mater. Chem.* **2006**, *16*, 2217. doi:10.1039/B601776M
- [107] D. A. Groneberg, M. Giersig, T. Welte, U. Pison, *Curr. Drug Targets* **2006**, *7*, 643. doi:10.2174/138945006777435245
- [108] I. Bertholon, H. Hommel, D. Labarre, C. Vauthier, *Langmuir* **2006**, *22*, 5485. doi:10.1021/LA060570Y
- [109] W. H. Moos, S. Barry, *Drug Dev. Res.* **2006**, *67*, 1. doi:10.1002/DDR.20061
- [110] C. J. Sunderland, M. Steiert, J. E. Talmadge, A. M. Derfus, S. E. Barry, *Drug Dev. Res.* **2006**, *67*, 70. doi:10.1002/DDR.20069
- [111] K. J. Longmuir, R. T. Robertson, S. M. Haynes, J. L. Baratta, A. J. Waring, *Pharm. Res.* **2006**, *23*, 759. doi:10.1007/S11095-006-9609-X
- [112] D. H. Geho, C. D. Jones, E. F. Petricoin, L. A. Liotta, *Curr. Opin. Chem. Biol.* **2006**, *10*, 56. doi:10.1016/J.CBPA.2006.01.003
- [113] N. G. Portney, M. Ozkan, *Anal. Bioanal. Chem.* **2006**, *384*, 620. doi:10.1007/S00216-005-0247-7
- [114] F. Ahmed, P. J. Photos, D. E. Discher, *Drug Dev. Res.* **2006**, *67*, 4. doi:10.1002/DDR.20062
- [115] L. K. Pattenden, A. P. J. Middelberg, M. Niebert, D. I. Lipin, *Trends Biotechnol.* **2005**, *23*, 523. doi:10.1016/J.TIBTECH.2005.07.011
- [116] R. L. Garcea, L. Gissmann, *Curr. Opin. Biotechnol.* **2004**, *15*, 513. doi:10.1016/J.COPBIO.2004.10.002
- [117] R. Duncan, H. Ringsdorf, R. Satchi-Fainaro, *Adv. Polym. Sci.* **2006**, *192*, 1.

- [118] Y. Kaneda, Y. Tabata, *Cancer Sci.* **2006**, *97*, 348. doi:10.1111/J.1349-7006.2006.00189.X
- [119] M. J. Joralemon, R. K. O'Reilly, C. J. Hawker, K. L. Wooley, *J. Am. Chem. Soc.* **2005**, *127*, 16892. doi:10.1021/JA053919X
- [120] M. E. Mackay, T. T. Dao, A. Tuteja, D. L. Ho, B. Van Horn, H. C. Kim, C. J. Hawker, *Nat. Mater.* **2003**, *2*, 762. doi:10.1038/NMAT999
- [121] A. Tuteja, M. E. Mackay, C. J. Hawker, B. Van Horn, *Macromolecules* **2005**, *38*, 8000. doi:10.1021/MA050974H
- [122] M. Stenzel-Rosenbaum, T. P. Davis, V. Chen, A. G. Fane, *J. Polym. Sci. Part A Polym. Chem.* **2001**, *39*, 2777. doi:10.1002/POLA.1256
- [123] H. J. Lee, K. Lee, S. N. Lee, *J. Polym. Sci. Part A Polym. Chem.* **2006**, *44*, 2579. doi:10.1002/POLA.21356
- [124] Y. Miura, A. Narumi, S. Matsuya, T. Satoh, Q. Duan, H. Kaga, T. Kakuchi, *J. Polym. Sci. Part A Polym. Chem.* **2005**, *43*, 4271. doi:10.1002/POLA.20837
- [125] A. W. Bosman, A. Heumann, G. Klaerner, D. Benoit, J. M. J. Frechet, C. J. Hawker, *J. Am. Chem. Soc.* **2001**, *123*, 6461. doi:10.1021/JA010405Z
- [126] A. W. Bosman, R. Vestberg, A. Heumann, J. M. J. Frechet, C. J. Hawker, *J. Am. Chem. Soc.* **2003**, *125*, 715. doi:10.1021/JA028392S
- [127] M. H. Stenzel, T. P. Davis, C. Barner-Kowollik, *Chem. Commun.* **2004**, 1546. doi:10.1039/B404763J
- [128] E. Themistou, C. S. Patrickios, *Macromolecules* **2006**, *39*, 73. doi:10.1021/MA0513416
- [129] K. A. Boduch-Lee, T. Chapman, S. E. Petricca, K. G. Marra, P. Kumta, *Macromolecules* **2004**, *37*, 8959. doi:10.1021/MA0493630
- [130] A. J. Limer, A. K. Rullay, V. San Miguel, C. Peinado, S. Keely, E. Fitzpatrick, S. D. Carrington, D. Brayden, D. M. Haddleton, *React. Funct. Polym.* **2006**, *66*, 51. doi:10.1016/J.REACTFUNCTPOLYM.2005.07.024
- [131] T. Ooya, J. Lee, K. Park, *J. Control. Release* **2003**, *93*, 121. doi:10.1016/J.JCONREL.2003.07.001
- [132] L. Kilian, Z. H. Wang, T. E. Long, *J. Polym. Sci. Part A Polym. Chem.* **2003**, *41*, 3083. doi:10.1002/POLA.10885
- [133] K. Kanki, T. Masuda, *Macromolecules* **2003**, *36*, 1500. doi:10.1021/MA021368E
- [134] P. Banerjee, R. Weissleder, A. Bogdanov, *Bioconjug. Chem.* **2006**, *17*, 125. doi:10.1021/BC050083E
- [135] O. Altintas, I. Yilmaz, G. Hizal, U. Tunica, *J. Polym. Sci. Part A Polym. Chem.* **2006**, *44*, 3242. doi:10.1002/POLA.21432
- [136] M. Smet, C. Gottschalk, S. Skaria, H. Frey, *Macromol. Chem. Phys.* **2005**, *206*, 2421. doi:10.1002/MACP.200500397
- [137] D. Bontempo, H. D. Maynard, *J. Am. Chem. Soc.* **2005**, *127*, 6508. doi:10.1021/JA042230+
- [138] K. L. Heredia, D. Bontempo, T. Ly, J. T. Byers, S. Halstenberg, H. D. Maynard, *J. Am. Chem. Soc.* **2005**, *127*, 16955. doi:10.1021/JA054482W
- [139] D. A. Sipkins, D. A. Cheres, M. R. Kazemi, L. M. Nevin, M. D. Bednarski, K. C. P. Li, *Nat. Med.* **1998**, *4*, 623. doi:10.1038/NM0598-623
- [140] S. A. Anderson, R. K. Rader, W. F. Westlin, C. Null, D. Jackson, G. M. Lanza, S. A. Wickline, J. J. Kotyk, *Magn. Reson. Med.* **2000**, *44*, 433. doi:10.1002/1522-2594(200009)44:3<433::AID-MRM14>3.0.CO;2-9
- [141] J. M. de la Fuente, C. C. Berry, *Bioconjug. Chem.* **2005**, *16*, 1176. doi:10.1021/BC050033+