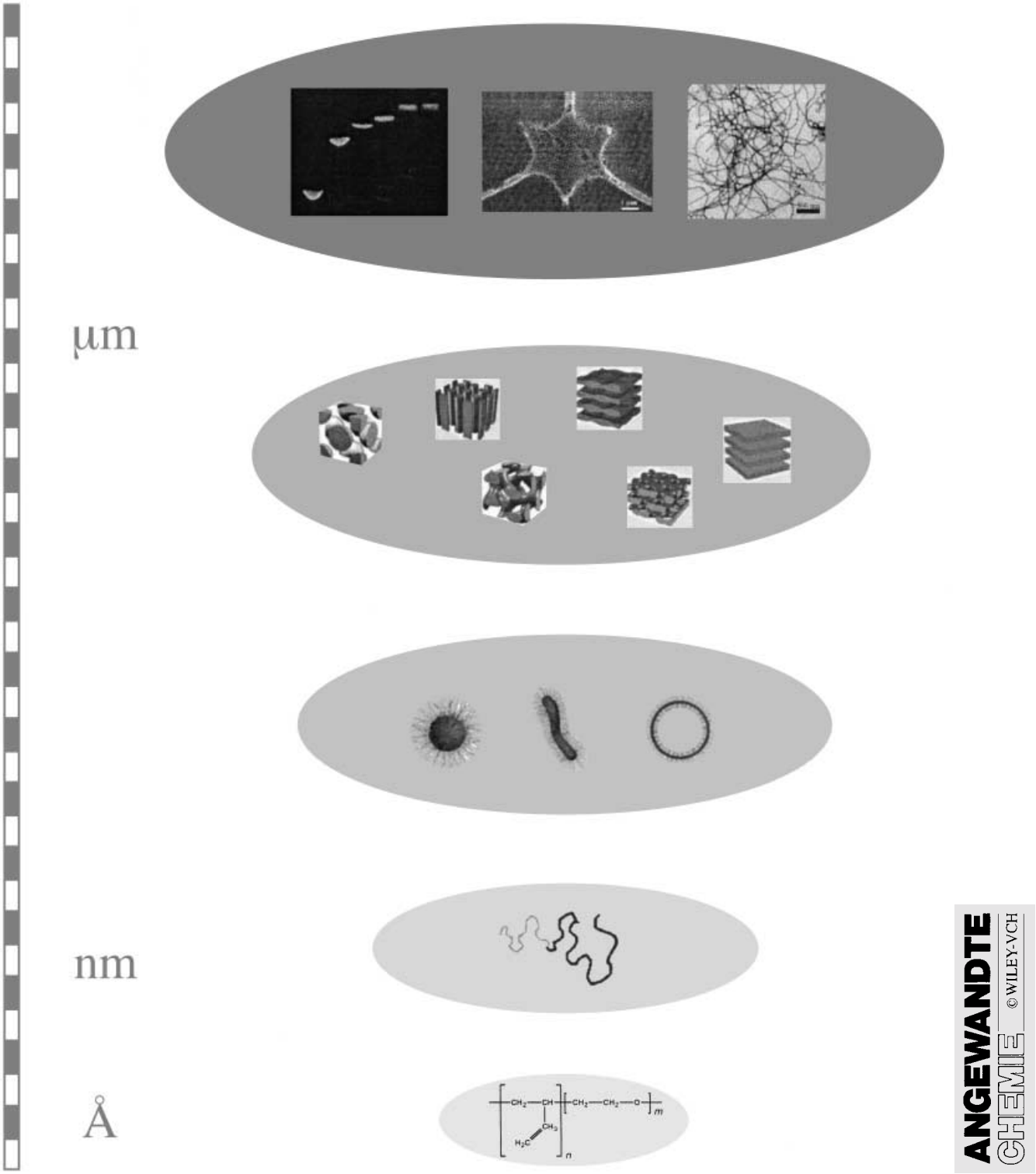
Functional structural hierarchies from self-organizing polymers



From Self-Organizing Polymers to Nanohybrid and Biomaterials

Stephan Förster* and Thomas Plantenberg

Block copolymers form a large number of superlattices with characteristic dimensions in the range of a few nanometers up to several micrometers by self-organization. The interplay of supramolecular physics and chemistry opens up new approaches to the production of inorganic, organic, and biological structures and to their integration into functional units. Possible applications in the fields of materials science and molecular biology are being investigated. Block copolymers find numerous applications from the production of inorganic nanoparticles (metals, semiconductors, magnets) and mesoporous materials up to take-up/release systems in chemo- and gene therapy.

Keywords: amphiphiles · hybrid materials · nanostructures · polymers · self-organization

1. Introduction

Today's materials science deals increasingly with nanostructures, that is, with structures of characteristic dimensions between 1 and 100 nm. This range is called the mesoscopic range as it is located between the microscopic range of atoms and molecules and the macroscopic range of solids. With lithography and etching processes, solid-state physics and electronics advance towards the field of nanostructures ("top-down" approach). A 1-GB chip, for example, is made with structures with a characteristic dimension of about 200 nm. Much smaller structures cannot be made with lithographic techniques because of the strong UV absorption of the coatings. Nature may serve as a model for the building-up of smaller structures. Here individual molecules are integrated into larger functional units and structural hierarchies by self-organization and the building-up of compartments ("bottom-up" approach). One of the great challenges facing physics, chemistry, and materials science today is to find a way to structure molecules so as to enable them to build functional superlattices by self-organization.

The aim of this review is to give a survey of the fundamental principles of self-organization recently developed, particularly in macromolecular chemistry, and applied to materials science. The close link between "supramolecular chemistry" and "supramolecular physics" is also shown. The compounds discussed are mostly molecules of simple chemical structure which, as a result of self-organization, can build up a wide variety of superstructures. A chemical functionalization can be achieved on every level of a structural hierarchy and results in functional materials in catalysis, electro-optics, high-performance ceramics as well as chemo- and gene therapy. Inorganic, organic, and biological materials can be integrated into functional systems. It is often necessary to bring together top-down and bottom-up strategies in order to realize structures with lengths ranging over several orders of magnitude.

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2. Self-Organization

Whereas technical systems are organized by technicians, many natural systems organize themselves by internal processes. Order by self-organization is a phenomenon which has fascinated scientists of many different fields of research.

A wide variety of phenomena are regarded as self-organization in the various scientific disciplines, and the definitions applied differ. The following selection is taken from the relevant literature:[1–3]

- Chemistry: Self-organization = well-defined structures result spontaneously from the components of a system by noncovalent forces (self-assembly), for example, in liquid crystals, micelles, oscillating reactions.
- Biology: Self-organization = a spontaneous building-up of complex structures which takes place under adequate environmental conditions solely on the basis of the respective molecular property, namely, without the effect of external factors, for example, protein folding, formation of lipid double layers, morphogenesis.

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- Physics: Self-organization = spontaneous formation of new three-dimensional and temporal structures in complex systems which results from the cooperative effect of partial systems, for example, ferromagnetism, superconductivity, convection cells.

Furthermore the different steps in the evolution of matter from the development of the universe up to the formation of biological macromolecules and to the origin of life are understood as a chain of fundamental processes of self-organization.

In spite of the diversity of the phenomena observed, there is a fundamental common feature. They share the fact that in the course of self-organization a system produces properties (for example, order) it did not have before. This development can be described by the theory of spontaneous symmetry breaking.[3] An isotropic homogeneous system has a high symmetry, that is, there are a lot of symmetry operations (for example, rotations, reflections) which transform the system in itself. When the system passes from an isotropic to an oriented state, symmetry elements get lost – -the symmetry is broken. Symmetry breaking is always followed by a new system property. This is shown by the equation of state of the system containing a new additional variable, the order parameter. The latter describes the degree of orientation or order of a system. The theory not only describes in general terms the fact that new properties develop, but moreover, explains what kind of properties emerge and how they develop.

In regard to materials science, we have to distinguish between equilibrium systems (for example, liquid crystals, lipid double layers, ferromagnetism) and nonequilibrium systems (for example, convection cells, oscillating reactions). In equilibrium systems symmetry breaking is associated with a phase transition, and in nonequilibrium systems with a dynamic instability. In systems far away from thermodynamic equilibrium, dynamic instabilities result in the formation of ordered, so-called dissipative structures. In the case of turbulence or convection, for example, the formation of regular convection cells (Bénard cells) or rotational vortices (Taylor vortices) is observed. Whereas equilibrium systems reach a stable state after phase transition, dissipative structures are instable and develop towards increasingly more complex and chaotic states. These are very fascinating and represent the object of many observations about morphogenesis and the origin of life. They are, however, not very suitable for materials structuring. Therefore they will not be dealt with in the following discussion.

2.1. Principles of Self-Organization

The transition from a disordered to an ordered state by spontaneous symmetry breaking can be described by an order parameter η which indicates the degree of order of the phase. From the definition, the order parameter is $\eta = 0$ in the disordered phase, it deviates from zero when symmetry breaking and the transition to the ordered phase take place, and reaches the value $\eta = 1$ in the ideal, ordered phase. This definition has proved to be useful for describing order processes in the field of condensed matter such as fluid crystals, ferromagnets, ferroelectrics, superconductors, and superfluids.

The transition from a disordered into an ordered phase takes place by changing thermodynamic or physical field strength. Such changes may be those of temperature and chemical potential (concentration, pH value, salt addition), of mechanical fields (pressure, shear, extension, ultrasonics), as well as of electric and magnetic fields. Systems which react to the change of field strength by a phase transition and hence by an abrupt change of a particular property, are called actuators. They play an important role in many pharmacological applications where active ingredients can be released purposefully by changing the salt concentration, pH value, temperature, or by applying ultrasound (see Section 5).

Stephan Förster studied chemistry at the University of Mainz and the University of Toronto (Canada). He completed his diploma and Ph.D. under the supervision of Prof. G. Wegner and Prof. M. Schmidt at the Max-Planck-Institute for Polymer Research, Mainz, Germany. He then went to the University of Minnesota, Minneapolis, USA, to work with Prof. F. S. Bates. In 1993, he joined the Max-Planck-Institute for Colloid and Interface Research in Teltow/Golm (Germany), where he led a project in Prof. M. Antonietti's group. In 1998 he was awarded the Dr. Hermann – Schnell prize by the Gesellschaft Deutscher Chemiker. In 1999 he completed his habilitation at the University of Potsdam (Germany) and took the chair of Physical Chemistry at the University of Hamburg.

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Thomas Plantenberg studied at the Universities of Köln and Potsdam (Germany). He completed his degree dissertation on polyelectrolytes under the supervision of Prof. J. Kötz at the University of Potsdam. He is presently completing his Ph.D. on polyelectrolyte micelles at the University of Hamburg in the group of Prof. Förster.

The ordered state is distinguished by the fact that individual molecules are located at restricted three-dimensional regions, for example, a lattice site in a crystal or the position in the three-dimensional structure of a protein. A localization is always accompanied by a decrease of the number of realizable states and hence a loss of entropy. Temperature plays always an important role in the case of phase transitions between different order states because of the contribution $T\Delta S$ to the free energy. Besides temperature, further external fields E may influence the degree of order and the phase transitions.

The field strength and temperature at which the phase transitions take place can be depicted schematically in phase diagrams (Figure 1). The critical temperature T_c above which

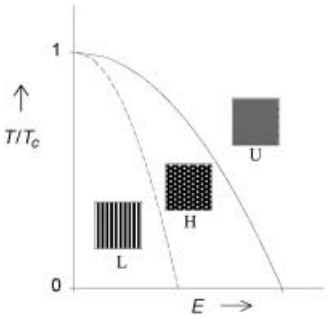


Figure 1. Transition from a disordered phase (U) to ordered phases (H, L) by variation of the temperature T and the external field E. T_c is the critical temperature above which ordered phases are not accessible. The transition $U \rightarrow H,L$ corresponds to a self-organization.

the system is disordered is indicated on the temperature axis. Phase transitions from the disordered phase (U) to different ordered phases (L, H) may take place below the critical temperature. These phase transitions are accompanied by a self-organization of the system. The stability range of the different phases can be taken from the phase diagram. Different ordered structures for one and the same material can be produced by varying the temperature and field strength. This variability has a favorable effect on the production and optimization of materials.

The phases L and H in Figure 1 are examples of systems with three-dimensionally modulated order parameters $\eta(x)$. In simple cases this can be described by a sine function $\eta(x) = \eta_0 \sin(2\pi x/d)$. η_0 represents the amplitude of the order parameter and d the periodic length, that is, the linear scale of this profile. The structures in Figure 1 were produced by a superposition of such sine functions.[4] Such an order parameter $\eta(x)$ describes the three-dimensional distribution of two states A and B in a binary state system. It can be a pair of spin states ($\uparrow\downarrow$, ferromagnetism), of electric polarization ($+-$, ferroelectricity), or of the three-dimensional distribution of molecules A and B in liquid crystalline systems.

Not only is the specific production of different modulated structures of interest, but also the variation of the linear scale d. In the mesoscopic range, namely, $1 < d < 100$ nm, materials properties such as band gap, catalytic activity, porosity, immune response, or endocytosis can decisively depend on this length scale. In simple systems as described below, this length scale can be controlled by the molecule size.

2.2. Molecular Prerequisites

In order to build up ordered structures it is indispensable that both long range repulsive and short range attractive forces exist at the same time (shown schematically in Figure 2). There are long-range repulsive interactions between the A and B regions. As a consequence of short-range attractive interactions (bond), however, both regions cannot move away from one another. When as many A/B pairs as possible but with as few A/B contacts as possible are to be distributed in space, it is advantageous to choose the configuration shown in Figure 2 for the A and B domains. Such a formation of ordered domains illustrates the principle of self-organization on the basis of attractive/repulsive pairs of forces.

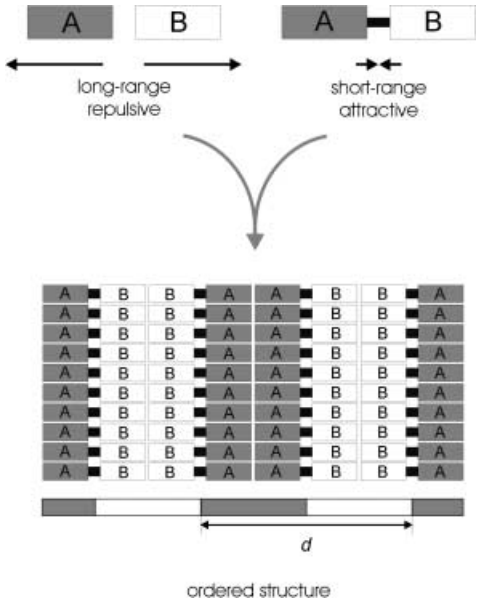


Figure 2. Illustration of long-range repulsive and short-range attractive forces leading to an ordered structure by self-organization (d is the periodic length of the structure).

Examples of such pairs of forces which are important for the formation of ordered materials are summarized in Table 1. Attractive interactions can be covalent bonds or the local conservation of electroneutrality. Repulsive interactions include the incompatibility of polymers, hydrophobic interac-

Table 1. Examples of pairs of forces which can lead to self-organization.

Long-range repulsion	Short-range attraction	Examples
hydrophilic/hydrophobic incompatibility	covalent binding	micelles, lyotropic liquid crystals
	covalent binding	block copolymers
Coulombic repulsion	electroneutrality	ionic crystals
excluded volume	minimum space required	thermotropic liquid crystals
electric dipole field	electric dipole interaction	ferroelectric domains
magnetic field	magnetic dipole interaction	magnetic domains

tions, and the excluded volume of formanisotropic molecules. If there are several pairs of forces in the ordered structure of a system at the same time, these systems are called "frustrated" ones. They are characterized by a distinctive variety of ordered phases (polymorphism).

The formation of very similar, ordered structures (A and B domains) in such different materials as magnets, block copolymers, and liquid crystals (Figure 3),[5] is a clear sign of the universality of this principle of self-organization. The structures only differ in their periodic length d, which covers a range from 10 nm to 1 cm, hence seven orders of magnitude.

When the formation of ordered structures can be expected, as a result of an appropriate pair of forces, the question arises as to which kind and periodicity the superlattice will be. The

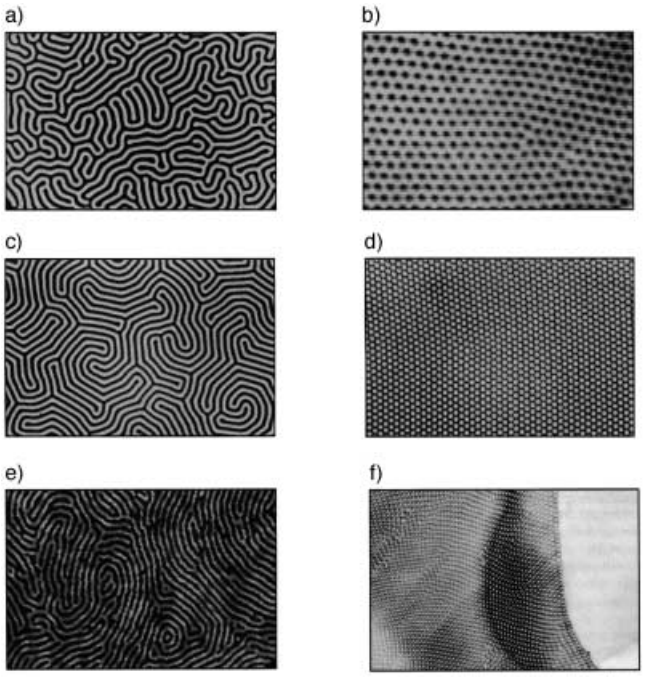


Figure 3. Lamellar (left) and hexagonal domains (right) in a ferrofluid with a) $d = 1$ cm, b) $d = 4$ μm, in a ferromagnetic film with c,d) $d = 10$ μm, and in a block copolymer superlattice with e) $d = 40$ nm, f) $d = 16$ nm. The examples give evidence of the universality of the order principles through pairs of forces. (From ref. [5].)

molecule subject to the interaction of the pair of forces, will join other molecules in such a way that domains and interfaces are formed which reflect the shape of the molecule. Figure 4 uses the example of Figure 2 once more. The A and B domains are separated from each other by an interface (dotted line). Planar interfaces are formed preferably because of the stretched shape of an A/B pair, and hence stripe or lamellar domains result. The periodic length d of the superlattice results from the size of the A and B domains.

When the B domain is smaller than the A domain, there will be curved interfaces. The bend can be characterized by the curvature radius R (Figure 4). It is not readily apparent with curved interfaces what will be the topology of the domains of the superlattice. By means of differential geometry it is, however, possible to predict the topologies and symmetries of the superlattices from the given curvature and

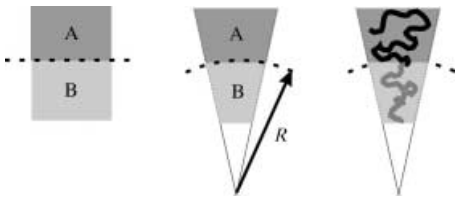


Figure 4. Local geometry and the curvature of domains and interfaces. The kind of superlattice depends on the volume ratio $f = V_A/V_B$ of the domains and on the curvature radius R of the interface. For a planar interface $R = \infty$. The application of this model to block copolymers is shown at the right hand side.

domain size. These do not only contain the classical superlattices of spheres, cylinders, and lamellae, but also complicated minimal surfaces such as G (gyroid), P (plumbers nightmare), or D surfaces (double diamond). These ones consist of bicontinuous, branched domains of cubic symmetry. As a consequence of their bicontinuous structure, they are of interest as materials for separation processes.

The free energy of a superlattice can be calculated by means of self-consistent mean field theory. The superlattice with the lowest energy conforms to the equilibrium structure, the stability range of which can be represented in a phase diagram (Figure 5).[6] The product χN is plotted on the ordinate. N is the total degree of polymerization of the block copolymer

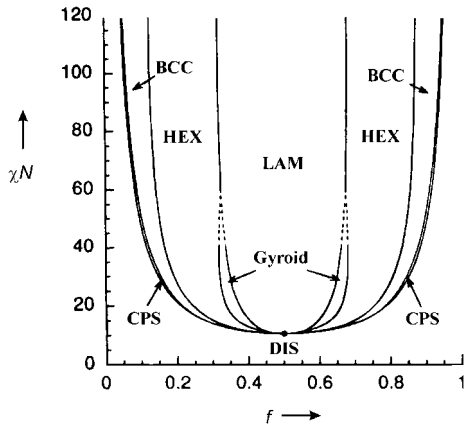


Figure 5. Theoretical phase diagram of block copolymers. Various ordered superlattices can be obtained by variation of the block lengths (f-axis) and the temperature (χN-axis; see the legend to Figure 13 for an explanation of the abbreviations). (From ref. [6].)

which results from the sum of the degrees of polymerization of the different blocks, namely, $N = N_A + N_B$. χ is the Flory–Huggins interaction parameter which indicates the strength of the repulsive interaction between both polymer blocks. The value of χ decreases with increasing temperature according to $\chi \sim 1/T$. Therefore this phase diagram seems to be turned upside down compared to the schematic phase diagram in Figure 1. f is the block length ratio ($f = N_A/N$) and, as a geometric factor, decides on the symmetry of the superlattice. By making use of such a phase diagram it is possible to purposefully produce different superlattices by varying the block lengths.

3. Block Copolymers

Macromolecules are particularly well suited for implementing physical, chemical, and biological functions at the same time. Nature demonstrates this with innumerable examples of biopolymers. Polymers permit the length scales to be greatly varied, the superstructure to be controlled, and specific functions to be performed. The simplest primary structure which permits these functions to be carried out are AB block copolymers. The last few years have seen considerable progress in the development of methods to synthesize block polymers, some of them applicable on an industrial scale.

3.1. Synthesis

3.1.1. Living Polymerization Techniques

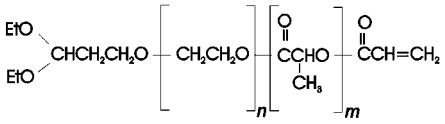
During the last decade more and more advanced techniques of "living" or controlled polymerization to prepare block copolymers have become available. It has become possible to prepare block copolymers of various architectures, solubility, and functionality.[7] Architectures comprise diblock, triblock, and multiblock copolymers arranged linearly as stars or grafts. The solubilities vary from polar solvents such as water to media with very low cohesion energies such as silicon oil or fluorinated solvents. Control of functionality has become important, motivated by the necessity to stabilize metallic, semiconductor, ceramic, or biological systems.

The different synthetic routes to block copolymers comprise living anionic, living cationic, and living radical polymerization. Combining different polymerization techniques provides a larger variety of block copolymers.[8] This is done by attaching functional groups which start the polymerization of the next polymer block (macroinitiators). Figure 6 shows the schematic structure of a block copolymer obtained by sequential living polymerization. The chain ends α and ω may be functional groups either for molecular binding or for the fixation of superlattices.

There are a large number of published strategies for preparing block copolymers by living anionic polymerization.[9] Recent years have seen the development of new methods for living cationic[10] and living radical polymerization[11] (for example, RAFT technique[12–15]). New monomers have become accessible for controlled polymerization, which has given rise to the preparation of new classes of amphiphilic or functional polymers. The lower reactivity of the living chain ends enables polymerization to be accomplished with less technical effort (inert gas, high vacuum, rigorous exclusion of air and humidity). Therefore, these polymerization techniques are of considerable interest from a technical point of view. The preparation of block copolymers by means of controlled radical polymerization in aqueous emulsions is currently being investigated. Some block copolymers such as the well-known Pluronic (BASF Wyandotte) and Kraton (Shell) block copolymers, which serve as emulsifiers or as thermoplastic elastomers, are already being prepared on an industrial scale. Table 2 gives a survey of common living polymerization methods together with corresponding monomers.

α-[A]$_n$-[B]$_m$-ω

1



2

Figure 6. Schematic structure (**1**) and example (**2**) of a functionalized AB block copolymer. **2** is a biocompatible poly(ethylene oxide-*b*-D/L-lactide) with an acetal (α) and a methacryloyl end group (ω). The aldehyde group obtained after hydrolysis at the α position is used for the binding of proteins. ω is a polymerizable group for the covalent fixation of superlattices.

Table 2. Common living polymerization techniques.

Reactive group	Polymerization technique	Monomers
anion	anionic polymerization[a]	styrenes, vinylpyridines, methacrylates, acrylates, butadiene, isoprene, *N*-carboxyanhydrides (amino acids)
	ring opening[b]	epoxides, siloxanes
	GTP[c]	methacrylates, acrylates
	ROMP[d]	norbornenes
cation	cationic polymerization	vinyl ether, isobutylene
	ring opening	oxazoline
radical	nitroxide polymerization	styrene
	organometals	acrylates
	ATRP[e]	styrenes, methacrylates, acrylates, acrylonitriles
	RAFT[f]	methacrylates, styrene, acrylates

[a] Industrial products: kraton, solprene. [b] Industrial product: pluronics. [c] Group transfer polymerization. [d] Ring-opening metathesis polymerization. [e] Atom transfer radical polymerization. [f] Reversible addition–fragmentation chain transfer polymerization.

Living polymerization techniques have made it possible to prepare polymers with exact predetermined degrees of polymerization and low polydispersities. The degree of polymerization N of the polymer blocks depends on the molar ratio of initiator I to monomer A and B in the reaction medium: $N_A = [A]/[I]$ and $N_B = [B]/[I]$. The polydispersities are mostly in the range $M_w/M_n < 1.1$, which corresponds to a relative standard deviation in the degree of polymerization of less than 30%.

3.1.2. Polymer-Analogue Reactions

Block copolymers can be further modified by subsequent chemical reaction. The two most important demands on a polymer-analogue reaction are to maintain the block copolymer architecture and to achieve a selective reaction, which should be as complete as possible. To reach the first goal, the reaction conditions must be such that the chains will neither be degraded nor cross-linked. To reach the second goal, reactive and selective reagents are necessary to allow the reaction to be determined by their molar ratio. This is

important because polymers are often hard to purify after such reactions. A number of polymer-analogue reactions have so far been carried out with block copolymers. These comprise hydrogenation,[16–19] epoxidation[20] with subsequent ring opening by nucleophiles[20] and acid chlorides,[20] hydroboration/oxidation[21–24] with subsequent esterification of the OH group,[21, 22] quaternization,[25] hydrolysis of *tert*-butylmethacrylates,[26] sulfonation,[27, 28] fluorocarbene addition,[29] and the reaction of olefinic double bonds with *N*-chlorosulfonyl isocyanate for the preparation of blood-compatible heparin analogues.[30] By means of polymer-analogue reactions the polymer blocks are transformed into blocks of desired solubility, flexibility, and chemical functionality. The solubility of polymer blocks may extend over a range from very polar up to very nonpolar solvents (see Table 3).

3.1.3. Heterophase Polymerization

The outstanding feature of living or controlled polymerizations is their ability to provide more complex polymer architectures. By controlling growth kinetics it has become possible to obtain well-defined polymer structures by means of heterophase polymerization. The mostly spherical particles with diameters from 10 nm to 10 μm are polymerized in microemulsions,[31, 32] miniemulsions,[33, 34] or conventional macroemulsions.[35] A variety of latex particles made of polystyrene, polyvinyl chloride, polybutadiene, or melamine formaldehyde resins can be produced with very narrow particle size distribution ($\sigma < 10\,\%$). In the presence of repulsive/attractive force pairs these polymer particles can form superstructures which are important, for example, for the production of photonic crystals or for paint-film formation. Hydrolysis and polycondensation of inorganic silica esters enable monodisperse spherical silica particles (Stöber silica) to be prepared.[36, 37]

3.2. Structures of Self-Organization

In the following section the self-organization of block copolymers will be described with the help of some examples. They are divided into dilute solutions (micelles, cylindrical micelles, vesicles), lyotropic phases of higher concentration, and bulk phases, each of them being well-suited for the preparation of interesting materials.

3.2.1. Micelles

Surfactants as well as block copolymers form micelles[38–43] in dilute solutions. As a consequence of the chemical structure of the blocks, block copolymers form micelles not only in polar solutions, such as water, but also in very nonpolar media, such as fluorinated hydrocarbons or supercritical CO_2 (see Table 3). The well-defined micelles have a core consisting of the insoluble A blocks and a shell or corona of the soluble B blocks (Figure 7).

Micelle formation is a simple and well-known example of the self-assembly of polymers. The block copolymers self-assemble to a micelle with defined size and shape. The size of the micelle depends on the length of the polymer blocks. Figure 8 shows the systematic correlation between the aggregation number Z (the number of block copolymers in a micelle) and the degree of polymerization of the insoluble block, N_A.[44] The experimental results can be described by a scaling law (1),

$$Z = Z_0 N_A^{\alpha} N_B^{-\beta} \quad (1)$$

where $\alpha = 2$ and $\beta = 0.8$. Z_0 depends mainly on the enthalpy of mixing between the insoluble polymer block A and the solvent. Scaling laws with fractional exponents such as 0.8 can often be found in polymer systems. Equation (1) describes the formation of micelles for diblock,[44, 45] triblock,[45] graft,[46] and heteroarm star copolymers,[47, 48] as well as for low molecular cationic, anionic, and non-ionic surfactants, that is over a range of three orders of magnitude in block length N. This proves the universality of such self-assembly mechanisms. The value of Z_0 is tabulated for many block copolymers, and for many systems $Z_0 \approx 1$, which allows the aggregation numbers to be estimated from the degrees of polymerization of the blocks. Thus the aggregation number and the size of the micelles can directly be set through the degrees of polymerization of the blocks. This possibility is of relevance to the preparation of nanocolloids, of porous ceramics, and to drug-delivery systems.

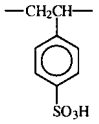
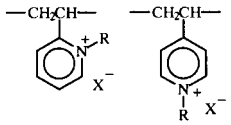
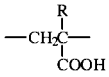
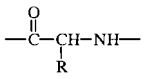
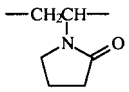
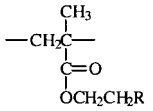
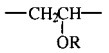
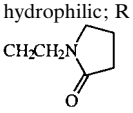
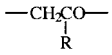
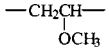
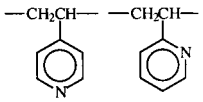
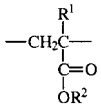
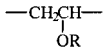
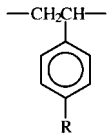
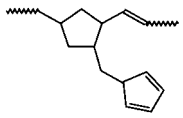
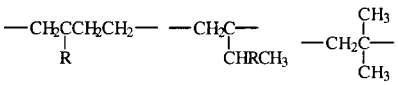
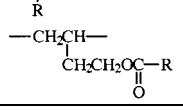
The compartmentization of micelles into a core/shell structure can be well observed in the electron micrograph in Figure 9a.[49] The micelles have a total diameter of 30 nm, with the core diameter being 10 nm.

In some cases the block lengths can also affect the shape of the micelles. Block copolymers with large soluble B blocks, that is, with small curvature radii R (Figure 4) form spherical micelles preferably, whereas cylindrical micelles or vesicles result from smaller soluble blocks, that is, with greater curvature radii. Cylindrical micelles,for example, of poly(butadiene-*b*-ethylenoxide (PB-PEO; Figure 9b) may have lengths of several micrometers.[50] Block copolymer vesicles were observed with diameters from 100 nm up to several micrometers. Polymer vesicles (polymersomes) are mechanically and thermodynamically much more stable[51, 52] than the well investigated lipid vesicles, and are well suited for the encapsulation and the release of substances. Figure 9c shows vesicles of poly(2-vinylpyridine-*b*-ethylene oxide) (P2VP-PEO) with diameters of more than 10 μm (giant vesicles) into which, for example, fluorescent dyes can be encapsulated.[53]

3.2.2. Lyotropic Phases

Higher concentrations of the block copolymers induce lyotropic liquid crystalline phases. Their range of stability can strongly depend on temperature. In aqueous solutions poly(ethylene oxide) (PEO) is usually the soluble block. A temperature increase reduces the solubility of the PEO block, which can result in phase transitions into disordered phases. Most of the current knowledge on lyotropic phase behavior of block copolymers was obtained from studies of poly(ethylene oxide-*b*-propylene oxide-*b*-ethylene oxide) (PEO-PPO-PEO;

Table 3. Solubilities and functionalities of important polymer blocks, arranged according to polarity.

S block	Structure	Remarks
poly(styrene sulfonic acid) (PSS)		strong polyelectrolyte, very hydrophilic (hygroscopic); also Na, K salts; ion exchanger
poly(*N*-alkylvinylpyridinium halogenide) (PQ2VP, PQ4VP)		strong polyelectrolyte, very hydrophilic (hygroscopic); R = H, Me, Et, Bz; X = Br, I
poly((meth)acrylic acid) (PMAc, PAAc)		polyelectrolyte, hydrophilic; R = H, Me; also Na salts; ionic bond, biomineralization
poly(amino acids) (PAs)		R = $(CH_2)_4NH_2$ (lysine); R = CH_2COOH (aspartic acid), CH_2CH_2COOH (glutamic acid); drug delivery, biocompatible, biodegradable, biomineralization
poly(*N*-vinylpyrrolidone) (PVP)		hydrophilic
poly(hydroxyethyl methacrylate) (PHEMA)		hydrophilic; R = OH, NMe_2
poly(vinyl ether) (PVEE)		hydrophilic; R = CH_2CH_2OH, $(CH_2CH_2O)_3CH_3$, 
poly(ethylene oxide), poly(propylene oxide) (PEO, PPO)		amphiphilic; R = H, Me; PEO hydrophilic at $T < 80\,^{\circ}C$; PPO hydrophilic at $T < 20\,^{\circ}C$; biocompatible
poly(vinyl methyl ether) (PVME)		amphiphilic; hydrophilic at $T < 70\,^{\circ}C$
poly(ethyleneimine) (PEI)		soluble in hot water (branched also soluble in cold water), synthesis by saponification of poly(2-ethyl-2-oxazoline), papermaking production, gene transfection
poly(4-vinylpyridine), poly(2-vinylpyridine) (P4VP, P2VP)		polar, hydrophobic, ligand, acid–base reactions
polyglycolide, polylactide (PLac, PGly)		R = H (PGly), R = CH_3 (PLac); hydrophobic, biocompatible, biodegradable
poly(methyl)acrylate (PMMA)		hydrophobic; R^1 = H, Me; R^2 = Me, *n*Bu
poly(vinyl butyl ether) (PVBE)		hydrophobic; R = *i*Bu
polystyrene (PS)		hydrophobic; R = H, *t*Bu, $CH(SiMe_3)_2$
poly(cyclopentadienylmethylnorbornene) (PCp)		hydrophobic; coordination of transition metals through metallocene complexes
polyethylenpropylene, poly(ethylethylene), poly(isobutylene) (PEP, PEE, PIB)		hydrophobic; R = H, Me
polysiloxane (PDMS)		very hydrophobic (silicone oil); R = Me (biocompatible), Et, Ph; gas separation, low-energy surfaces
partially fluorinated polymers (PF)		very hydrophobic; soluble in freon, CO_2; R = C_4F_9, C_8F_{17}; gas separation, low-energy surfaces, emulsion polymerization in CO_2

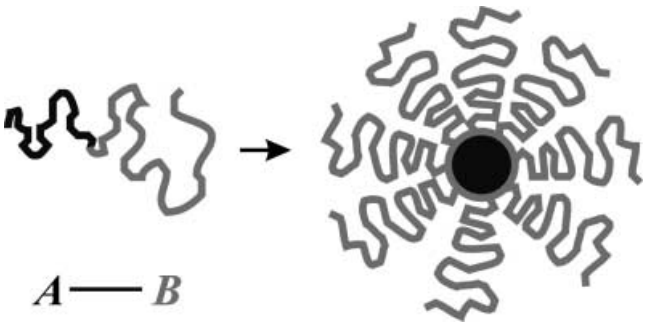


Figure 7. Formation of a micelle (aggregation number $Z = 8$) of AB block copolymers as the simplest form of self-organization.

pluronics).[54] The phase diagrams of block copolymers with shorter chains, in particular, resemble those of low molecular surfactants.

Figure 10 shows electron micrographs of lyotropic block copolymer phases of poly(butadiene-*b*-ethylene oxide) (PB-PEO) in water. The dark regions are the hydrophobic PB domains. There are cubic phases of spherical micelles on a *bcc* lattice, hexagonally arranged cylindrical micelles, and lamellar phases. The periodic length is between 30 and 100 nm and can be controlled by the water content. Homogeneously oriented domains have a dimension of up to several micrometers. Lyotropic phases can be applied to the preparation of porous materials (Section 4.4) while cubic micellar phases are also used in gel electrophoresis to separate proteins and oligonucleotides (Section 5.2). For optimization purposes it is possible to control the morphology and the periodic length through block lengths and polymer concentration.

3.2.3. Bulk Phases

Block copolymers in a microphase-separated state are also present in bulk. A variety of copolymer morphologies such as lamellae (LAM), hexagonally ordered cylinders (HEX), arrays of spherical microdomains (BCC, FCC), modulated (MLAM) and perforated layers (PLAM), ordered bicontinuous structures such as the gyroid, as well as the related inverse structures have been documented. The morphology mainly depends on the relative block length. If, for example, both blocks are of identical length, lamellar structures are formed. The stability ranges of the different structures can be represented in a phase diagram as shown in Figure 11 for the system poly(styrene-*b*-isoprene) (PS-PI).[55, 56] The experimentally determined phase diagram is equivalent to the theoretically calculated diagram (Figure 5). This proves the efficiency of theoretical approaches.

The periodic length scale of the superlattice can be adjusted over the whole mesoscopic range (from a few up to several hundred nanometers) by varying the degree of polymerization. Figure 12 shows with the example of PB-PEO how the long period d is connected with the degree of polymer-

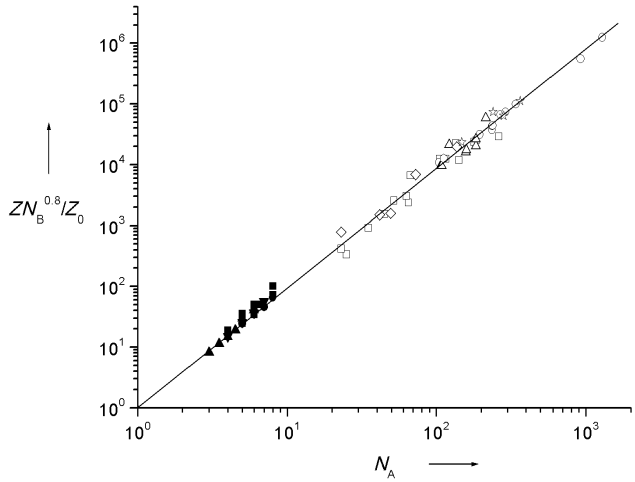


Figure 8. Aggregation numbers Z as a function of the degree of polymerization N_A of the insoluble block. ○,□: diblock copolymers (PS-P4VP, PS-PMAc), △: triblock copolymers (PMAc-PS-PMAc), ▽: graft copolymers (PSMSA-g-PEO), ☆: heteroarm star polymers (PS-P2VP), ◇: heteroarm star polymers (PS-PAAc), ●: nonionic surfactants (C_xE_y), ■: cationic surfactants ($RNMe_3Br$), ▲, ▼: anionic surfactants ($ROSO_3Na$, RSO_3Na). (From ref. [44].)

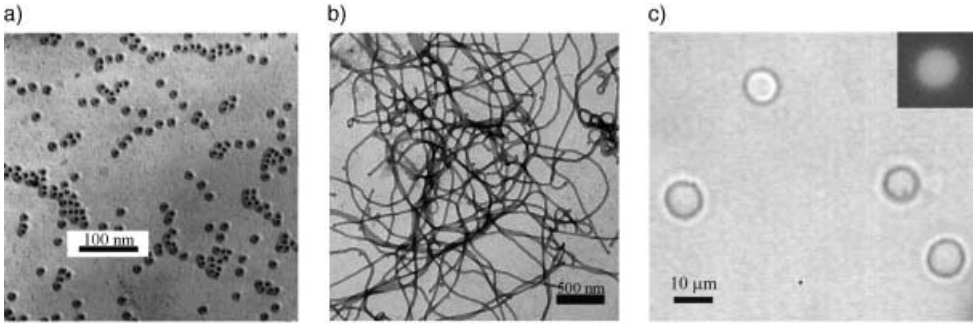


Figure 9. Electron micrographs (a, b) and optical micrographs (c) of the three most frequent forms of self-organization of block copolymers: a) spherical micelles (PS-PI/DMF),[49] b) cylindrical micelles (PB-PEO/water),[50] and c) vesicles (P2VP-PEO/water).[53] Figure c shows top right a single vesicle in which the solution of a fluorescent dye was encapsulated.

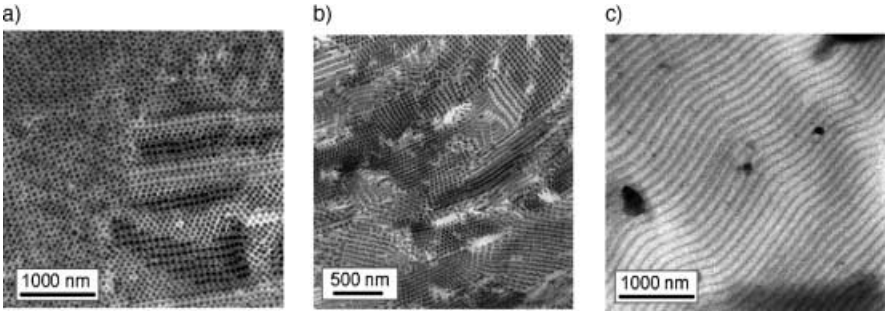


Figure 10. Electron micrographs of a cubic (a), hexagonal (b), and lamellar (c) superlattice of block copolymers in lyotropic liquid crystalline phases. The structure of the lyotropic phases was fixed by γ irradiation.[50, 95]

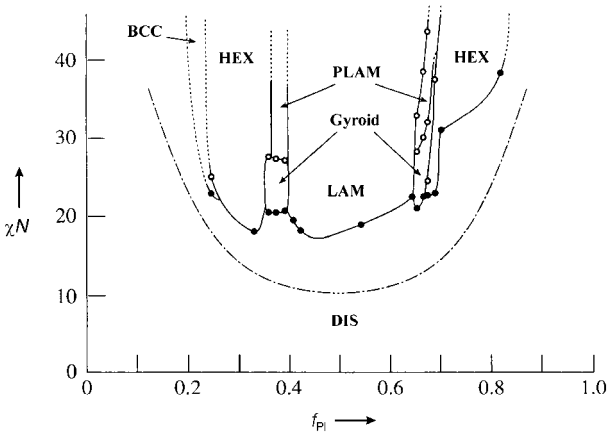


Figure 11. Experimentally determined phase diagram of PS-PI.[55, 56] The individual superlattices can be specifically prepared by adjusting the volume ratio f_{PI} of the block copolymers, the total degree of polymerization N, and the temperature ($\chi \sim 1/T$). The structures of the individual phases are depicted in Figure 13.

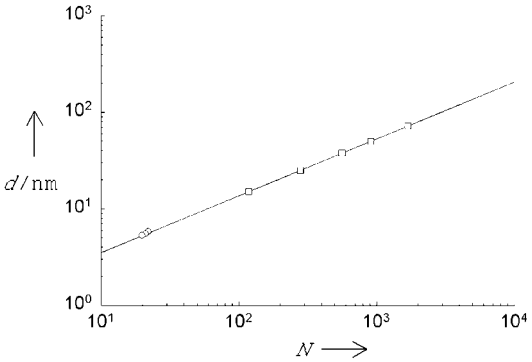


Figure 12. Long period d as a function of the degree of polymerization N of PB-PEO (□) and nonionic surfactants (○).[50] The periodic length of the nanostructure can be specifically adjusted over the whole mesoscopic range (1 – 100 nm) by the degree of polymerization.

ization N. The data points at the lower end of the length scale result from short-chain non-ionic surfactants. This shows the universal behavior of surfactants and amphiphilic block copolymers. In accordance with theoretical predictions, the behavior can be described by a scaling law $d = d_0 N^{2/3}$ ($d_0 =$ 0.9 nm) over three orders of magnitude of N. This allows a superlattice of tailor-made size to be chosen from the degree of polymerization of the macromolecule.

The broad variety of self-organizing structures of surfactants and block copolymers is shown in Figure 13. Particulate structures such as spherical and cylindrical micelles as well as vesicles form in dilute solution. Spherical micelles with cubic packing (FCC, BCC), hexagonally packed cylindrical micelles (HEX), and lamellar phases (LAM) form in the solid state, in lyotropic phases, as well as in ternary systems. Besides there are modulated and perforated layer phases as well as cubic bicontinuous structures such as the gyroid.[57] By using the phase diagrams one can specifically adjust the morphology of these structures through the choice of block lengths and polymer concentration. Thus, it is possible to prepare tailor-made nanostructured materials.

3.3. Structural Hierarchies

A single self-organization step is often not sufficient to realize functional systems. We are taught from natural processes that several hierarchies of self-organization are often needed. For example, collagen, a connective tissue protein, consists of helices which form a triple helix. It is this structure that results in the special mechanical properties of collagen. As depicted in Figure 14, several hierarchy levels can also be distinguished for block copolymers, their characteristic lengths ranging from 1 nm up to 1 μm.

The monomers defining the chemical functionality are on the smallest length scale. Several polymerization processes lead to the formation of block copolymers. Their block lengths and block length ratios define a local length scale and a local symmetry. The long-range repulsion and the short-range attraction result in microphase separation, for example, the formation of a micelle. This is the stage in which micro-compartments and interfaces form with typical length scales between 10 – 100 nm. The volume fraction of the microphases and the local geometry of the interface result in different superlattices forming, with the degree of order and the orientation being determined by application of macroscopic fields.

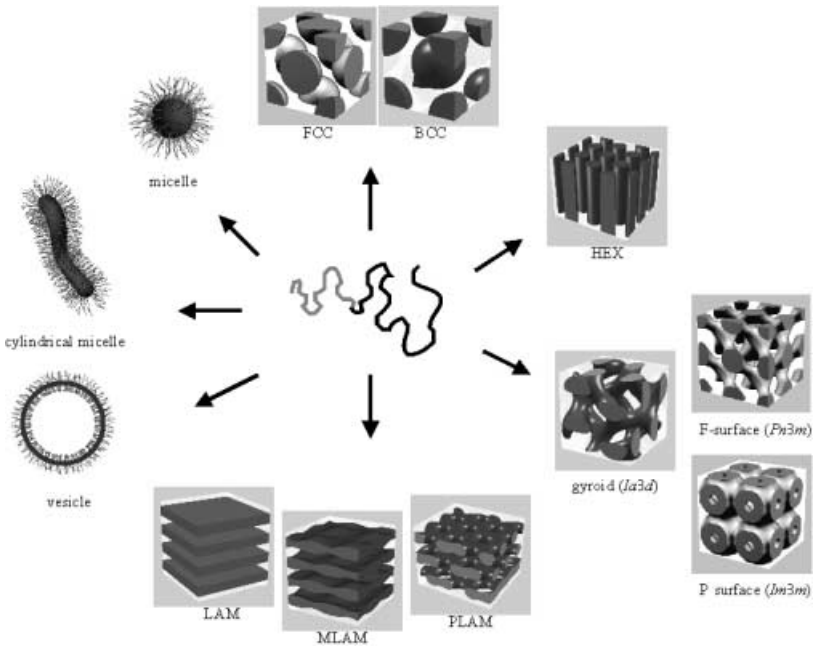


Figure 13. Self-organization structures of block copolymers and surfactants: spherical micelles, cylindrical micelles, vesicles, *fcc*- and *bcc*-packed spheres (FCC, BCC), hexagonally packed cylinders (HEX), various minimal surfaces (gyroid, F surface, P surface), simple lamellae (LAM), as well as modulated and perforated lamellae (MLAM, PLAM).

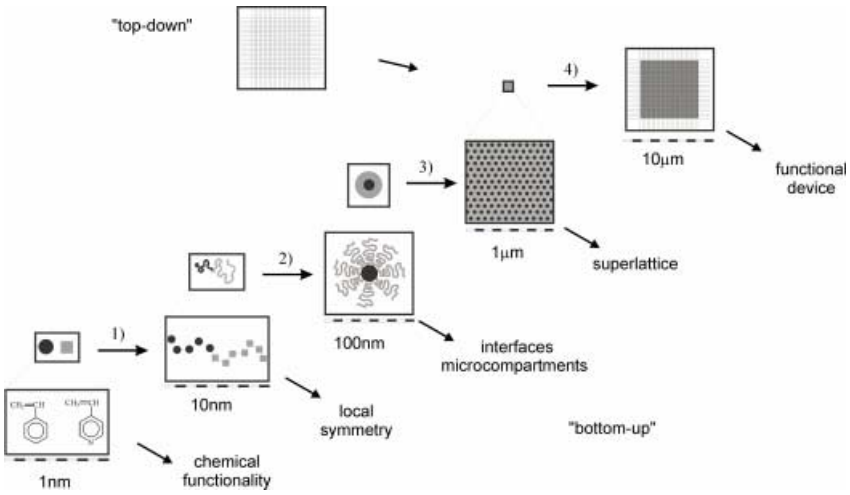


Figure 14. Various structure hierarchies in block copolymer systems. More complex functional systems can be realized by combining bottom-up and top-down strategies.

One advantage of using block copolymers is the high degree of structure control that can be achieved at every stage of the hierarchy:

1) Living polymerization is successfully used to specifically prepare block lengths N_A and N_B (Section 3.1).
2) The aggregation number and thus the size of the micelle (Figure 8) or the lamellar long period (Figure 12) are directly controlled by the block lengths.
3) Depending on the volume fraction of the block copolymer, there is formation of well-defined superlattices in lyotropic phases or in the solid phase, the stability range of which has been documented in phase diagrams (Figure 11).
4) External mechanical or electric fields can result in a macroscopic orientation of the superlattices. By this means it is possible to specifically prepare structured materials on a scale of 1 nm to 1 μm.

The stepwise synthesis of ordered structures with the help of self-organization processes is called bottom-up strategy. In contrast to these there are top-down strategies which prepare nanostructures using, for example, lithographic techniques. These methods permit the synthesis of preset addressable structures with a high degree of structure control. As a result of the strong UV absorption of the polymer masks there is a natural limit at about 100 nm for lithographic methods which does not allow the structural elements to be down-sized deep into the submicrometer range. Recently, techniques have been developed which fall below this limit by using scanning microscopy methods.[58, 59] To get more complex functional systems, bottom-up and top-down strategies can be integrated (see Figure 14). The superlattice is generated in a lithographically produced structure. This helps to avoid the considerable number of defects which often occur in self-organized systems on length scales above 100 nm.

The combination of different principles of self-organization (see Table 1) enables more complicated structural hierarchies to be synthesized. Block copolymers can, for example, be linked to low molecular weight liquid crystals through covalent bonds, ionic interactions, or hydrogen bonds. Thus, the binding of surfactants to poly(styrene-*b*-4-vinylpyridine) (PS-P4VP) leads to superlattices as shown in Figure 15a. Block copolymer cylinders consist of lamellar surfactants.[60] The lamellar surfactants have a period length of 3 nm while the block copolymer cylinders have a diameter of 30 nm. Extending binary AB systems to ternary ABC systems can result in the formation of complicated superlattices. Highly complex structures such as the "knitting pattern" in Figure 15b found by Stadler and co-workers, form in the presence of ABC triblock copolymers.[61]

3.4. Compartmentalization

The building of compartments is an important organizational principle in nature. Many metabolic processes become effective only because of the existence of

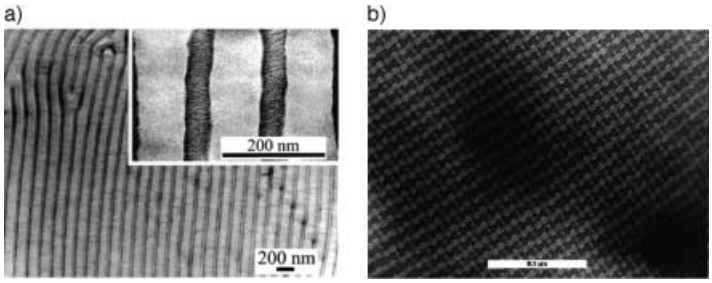


Figure 15. Complex and hierarchic superlattices of AB block copolymer/surfactant systems (a)[60] and ABC triblock copolymers (b, "knitting pattern").[61]

compartments. For example, energy-liberating processes for the production of ATP, such as the oxidation of fatty acids, the citrate cycle, and phosphorylation, take place in special compartments (mitochondria), whereas processes such as fatty acid synthesis and glycolysis are located in the surrounding cytosol. The microphase separation of block copolymers or surfactants can be regarded as a kind of formation of compartments.

In processes of self-organization as well as in the building up of compartments it is possible to distinguish between disperse and continuous compartments or microdomains. A further domain in polymer systems is that of the micelle shells which can be functionalized. These domains are schematically shown in Figure 16.

The micelle cores are appropriate for the solubilization and the storage of substances. The shells are provided with receptors facilitating a specific transport to, for example, tumor cells to deliver pharmaceutically active agents. Low molecular weight as well as high molecular weight substances such as polypeptides and polynucleotides can be stored and transported in different domains. This is of special importance in gene and drug delivery.

The continuous matrix is used mostly because of its permeability and its mechanical stability. The permeability together with the partition equilibrium with the hydrophobic domain are the principles of separation when using lyotropic

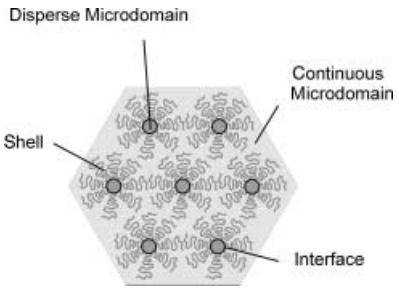


Figure 16. Different compartments in polymer systems which can be used for various functions such as transport, storage, addressing, and chemical reaction.

phases in chromatography. The mechanical stability plays an important role with respect to the properties of thermoplastic elastomers and high-impact materials.

Table 4 summarizes previous work on the utilization of polymer compartments such as micelle cores, micelle shells, and matrices. The materials used cover a wide range: from organic drugs and dyes to inorganic materials up to biopolymers and plastics. This wide variety is also evident in the different applications. In order to purposefully place functional groups in the outer shell, the chain end of the soluble polymer block should be chemically activated (Figure 6). This can be achieved through special initiating and terminating reactions during living polymerization.

3.5. Solubilization and Adhesion

For utilization purposes, it is necessary to "fill" the compartment, that is, to solubilize particular substances. This is mainly done by using secondary valence forces. These comprise the classical mechanisms of physi- and chemisorption:

- cohesion energy density, solubility, for example, toluene/polybutadiene;
- acid–base interaction, for example, $HAuCl_4$/poly(vinylpyridine), ZnO/polymethacrylic acid;
- complex formation, for example, Au/thiols, Pd/polybutadiene;
- hydrogen bridges, for example, SiOH/polyethylene oxide.

These interactions can be used to stabilize the interfaces between polymers and inorganic materials. The adhesion of both materials acts as the "glue" which holds the supramolecular structures together.

If solubilization takes place mainly through differences in the cohesion energy density, this can be explained by a simple thermodynamic description from which one can derive a scaling law $\phi_{max} \sim \chi^{-b}$ for the solubilization capacity ϕ_{max}. ϕ_{max} is the maximum quantity of solubilized substance per block copolymer, χ the Flory–Huggins interaction parameter, and b a positive empiric constant. Cohesion energy densities and their relative χ values have been tabulated in standard works. Nagarajan et al. found this relation when they investigated the solubilization of aliphatic and aromatic hydrocarbons,[62] alcohols, ethylene esters, ketones, and aldehydes, all of which are typical components of food flavoring.[63]

For many applications not only does the solubilization capacity play a decisive role, but also the selectivity does, that is, the accumulation of particular substances from mixtures. The lower entropy of mixing in polymers results in a higher selectivity than can be expected for low molecular weight surfactant systems. Investigations focused on the selectivity in

Table 4. Use of polymeric compartments.

Materials, substance	Solubilization	Storage	Transport	Release	Chemical reaction	Application, function
micelle cores						
dyes	×	×				de-inking
odorous substances		×		×		perfumes
drugs	×	×		×		drug delivery chemotherapy
proteins	×	×	×	×		drug targeting
DNA	×	×	×	×		gene therapy
inorganic precursors	×				×	nanoparticle synthesis, biomineralization
noble metals	×	×			×	catalysis
semiconductors	×	×				electroluminescence, UV protection, cell marking
enzymes	×	×			×	mitochondrium
elastomer						high-impact and tear-resistant plastics
micelle shells						
polymer block						solubility
PEO			×			stealth particles
heparin			×			anticoagulant
enzymes					×	catalyst support
RGD sequence			×			detection
IgG			×			endogenic vectors
polyelectrolyte						ion exchange
dye						labeling
ligand		×				heavy metal binding
matrix						
inorganic sols					×	mesoporous ceramics
proteins		×				gel electrophoresis
polynucleotides		×				gel electrophoresis
polymers	×	×	×			gel permeation chromatography
gases		×				gas separation
elastomer						rubber, hydrogel

the solubilization of orange oil components,[64] polycyclic aromatic hydrocarbons,[65] benzene,[66] xylene,[67, 68] and fluorescent probes.[69] All these experiments show that very large solubilization capacities and high selectivities can be achieved through the use of block copolymer micelles. The fourfold difference between the solubilization of benzene and hexane in a low molecular weight surfactant (SDS) is much less compared to the 20- to 40-fold difference in block copolymers.[62]

Block copolymers are also able to solubilize or adhere to inorganic materials. This feature is of special relevance for the controlled synthesis of inorganic colloids and the controlled assembly of hybrid materials. The incorporation of inorganic materials into polymeric domains can be achieved through ligands. These ligands are also able to stabilize the contact surface between metals and inorganic materials. The ligands should be chosen based on Pearson's hard and soft acid and base (HSAB) principle. In the HSAB sense, most metals are soft and acidic and are therefore well-stabilized by soft bases, such as thiols and phosphanes, known as "capping agents" from the synthesis of small metal clusters. Many semiconductors and metal oxides are fairly soft and most of them are bases, therefore, fairly soft acidic ligands such as alcohols, phosphates, and carboxylates provide good stabilization effects.[70] The stabilization of inorganic polyacids, which are of relevance as intermediates in sol/gel processes, can proceed through formation of hydrogen bridges (for example, with polyethylene oxide). The solubilization of polymers[71, 72] and biopolymers[73] is partly achieved through Coulombic interactions.

The specific interface in materials with nanodomains is very large, therefore, it is essential to stabilize it sufficiently in order to achieve stable hybrid systems. The interface per volume is given by $A_V = D\phi/R$ where D is the dimensionality of the domains ($D = 3$ for spheres, $D = 2$ for cylinders, $D = 1$ for lamellae), ϕ is the volume fraction of the nanodomains, and R is the radius (or half diameter) of the domain. Thus, a material with spherical domains of 1 nm diameter at a volume fraction of 50% ($\phi = 0.5$) has an interface of 3000 $m^2 cm^{-3}$ interface(!), which is nearly the size of a football field that has to be stabilized. The following example of the adhesion between natural rubber and brass-plated steel for the steel cord tyre application is an illustration of such a concept. There is only poor adhesion between natural rubber and steel because of their difference in hardness (in the HSAB sense). Interestingly, brass-plated steel was found to bind much more effectively to natural rubber. Sulfur (the cross-linking or vulcanizing agent) actually also functions as a chemical adhesive between natural rubber and brass to form the Cu_xS/ZnS interphases.[74] Alkyl sulfides are soft bases which preferably bind to soft acids such as Cu. The binding of rubber to metallic cord fibers in this manner is responsible for the performance of the present generation of tyres. This is a good example of the challenges one has to overcome when constructing stable nanohybrid materials.

Interfacial energies are also fundamentally related to properties of material in the area of bioadhesion. Materials with an interfacial tension γ between 20 and 30 $N m^{-1}$ bind very weakly to the surface of cell tissue. This has to be taken into account when adapting the surface of implants in a way to avoid the occurrence of blood clots and thrombosis. Polymers such as polydimethylsiloxane ($\gamma = 22 N m^{-2}$) and polyisobutylene ($\gamma = 30 N m^{-2}$) are well suited for surface modification of materials.

3.6. Structure Fixation

It is often necessary to add substance, to initiate chemical reactions, and to change temperature and concentration for self-organized structures to be used. These changes may result in a destabilization of the structure. Chemical and physical cross-linking can, however, stabilize the superlattices. It is possible to cross-link the disperse phase (micelle core, micelle shell), the continuous phase (matrix, matrix + shell), or both phases (Figure 17).

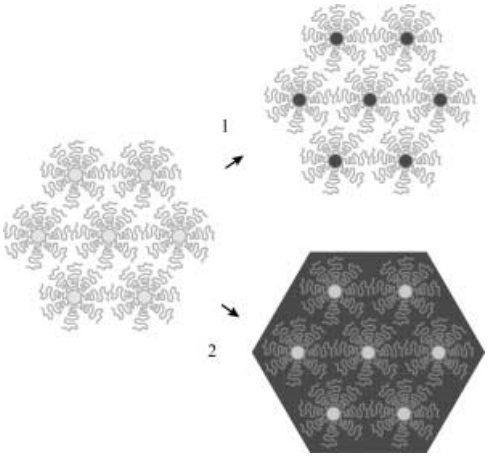


Figure 17. Structure stabilization in polymer systems by fixation of the micelle cores (1) or the micelle shells (2).

The increase of the molecular weight resulting from cross-linking is in many cases sufficient to initiate phase transitions into other superlattices. This represents a problem mainly with superlattices of low molecular weight surfactants. Only in very few cases was it possible to stabilize lyotropic phases by using cross-linkable low molecular weight surfactants.[75, 76] Polymer superlattices are thermodynamically more stable and are, thus, easier to stabilize. An overview of the most common cross-linking reactions is given in Table 5.[50, 77–95]

A simple fixation of lyotropic polymer phases is achieved by means of γ irradiation.[50, 95] Cross-linking by γ irradiation is possible when the rate of depolymerization is lower than that of cross-linking. If this condition, which is prerequisite for both blocks in the case of block copolymers, is met this method is a very efficient one for combining high cross-linking efficiency with high penetration depth and minimum change of the thermodynamic state. It is, for example, well suited for fixation of the superlattices of lyotropic phases so that the obtained gels can be swollen or dried whilst maintaining their structure. The electron microscopy investigation of the lyotropic phases in Figure 10 were obtained from thin layers of the dried gels obtained by this method.

After fixation, well-defined stable superlattices are obtained which can undergo further chemical change and

Table 5. Fixation of supramolecular structures.

Cross-linking	Reaction	Example
photochemical	[2+2] cycloaddition	anthracene, cinnamic acid, diacetylene[77–80]
	radical recombination	photoinitiator, e.g. irgacure
chemical	polycondensation	epoxy resin,[81, 82] polyester[87]
	sol/gel process	silicic acid
	quaternization	1,4-dibromobutane, *p*-dibromoxylylene[83–85]
thermal	radical recombination	redox initiator, e.g. Ce^{4+}[86, 87] fragmentation, e.g. AIBN, dibenzoyl peroxide[88–92]
radiochemical		^{60}Co[50, 95]
secondary valence bond	H-bonds	cytosine/guanine
	ligands	chelates
	Coulombic	simplex formation[93, 94]
physical	supercooling, freezing	cooling below glass transition temperature ("frozen micelles"), fast crystallization

functionalization. The functionalization of molecular surfaces is an important aspect, as is the case with dendrimers and fullerenes. Various structures can be classified according to their curvature radii (Figure 18). Plane surfaces have a curvature radius approaching infinity.

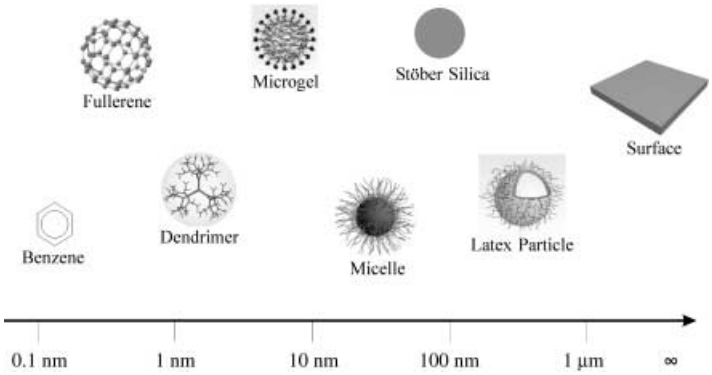


Figure 18. Particles with defined topology and surface ordered according to the curvature radii *R* of their surfaces. The surfaces can be functionalized through specific chemical reactions.

Whereas many supramolecular systems are synthesized stepwise from smaller molecules (dendrimers, macrocycles), a number of larger molecular systems are formed by self-organization or by specific control of growth kinetics. This applies for fullerenes as well as for micelles or latex particles. It is often much easier to synthesize larger molecular structures by using physicochemical concepts than by a stepwise chemical synthesis. Many procedures taking place on an industrial scale have long made use of such concepts. The "price" to pay for the use of these physicochemical concepts is a certain size distribution of the self-organized structures. However, the relative standard deviation is in many cases only a few percent. Fractionation methods allow this value to be further decreased, so that in some cases only one species, for example, in the case of C_{60} fullerenes, is obtained.

4. Inorganic Nanohybrid Materials

Nanostructures represent the transition from atom to solid. Their special optical, electronic, magnetic, and chemical properties are the result of size quantization effects as well as of the high number of surface atoms and the subsequent special surface states. These properties favor nanostructures to be applied in the areas of signal transmission, data and energy storage, as well as catalysis.

An important goal of materials science is the controlled and specific synthesis of well-defined nanostructures comprising nanoparticles as well as nano- and mesoporous materials. It is essential to obtain particles or pores with uniform diameters and shapes and, for the purpose of particular applications, to arrange and embed them in a superstructure.

In order to produce inorganic nanoparticles the materials are either mechanically crushed in a conventional manner or synthesized from precursor compounds by controlling the crystal growth kinetics. For the production of ferrofluids, for example, it is necessary to pulverize magnetite particles to a diameter of < 100 nm in a ball mill for one week! Appropriate ligands have to be added to stabilize the extremely large specific surface. The same applies to controlled growth kinetics. It has become possible to produce nanometer-sized uniform metal or semiconductor particles of some materials.

Nanoparticles can also be synthesized in the microcompartments of self-organized systems. This possibility offers the advantage of restricting the size growth of the particles to a definite diameter and preventing the particles from aggregating into larger sizes. If the microcompartments are arranged on a superlattice this kind of synthesis results in the nanoparticles also becoming integrated into the lattice. This situation gives rise to the formation of nanostructured inorganic/polymer hybrid materials. The extremely large inorganic/polymer interface can be stabilized by binding appropriate ligands to the polymer blocks.

Figure 19 is a schematic diagram of how nanocolloids can be prepared in polymers. The synthesis is similar to that in usual reaction flasks. The starting material is introduced into a compartment of appropriate size by solubilization (1). With adequate sorption provided, the material is distributed into the compartment by simple stirring, impregnation, or swelling. The next step is the chemical conversion to the desired material (2). For this purpose an additional reagent has in some cases to be added, a sufficient permeability being necessary which is directly connected with the solubilization and the diffusivity of the matrix. Both factors are prerequisite for an optimized synthesis. Gaseous reagents are often used for high diffusivities; these can quickly diffuse into the compartment. Alternatively the compartment material itself can be used as a reagent.[96]

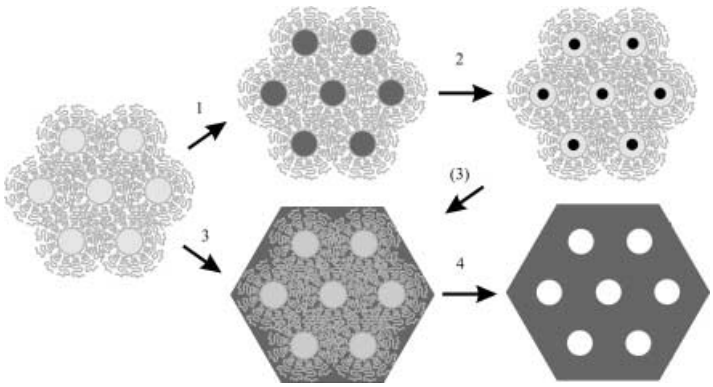


Figure 19. Synthetic scheme for the preparation of nanostructured hybrid materials. Nanoparticles (by steps 1 and 2) and mesoporous structures (by steps 3 and 4) can be synthesized. Steps 1 to 4 lead to pore structures with embedded nanoparticles.

After chemical reaction has taken place, small inorganic primary particles are formed which are homogeneously distributed in the microdomain. Depending on the strength of the ligands, the primary particles can be stabilized at this stage or they can further grow inside the microdomain. The size of the resulting inorganic particles depends on the conditions of nucleation and growth (concentration, size of domain, viscosity of the matrix, stabilization of the interface). Thus, nano-sized single crystals of uniform size can be prepared in the microdomains under appropriate conditions. The particle size can exactly be adjusted through the quantity of inorganic precursor material per microdomain. For many applications, for example, electrooptics, or catalysis, the material can remain in the compartment or in the matrix.

Figure 19 also shows how the continuous domain can be used for the preparation of porous structures. A sol/gel process leads to a continuous inorganic network in the matrix (3). After removing the block copolymer by extraction or calcination, one obtains the porous material. The shape and the diameter of the pores correspond to the hydrophobic microdomains of the polymer phase. Nanocolloids embedded in the pore structure can be obtained by following steps 3 and 4 after 1 and 2.

4.1. Metal Hybrids

Small metal clusters represent the transition from metal atom to solid state. The cluster size decides on the optical, electronic, and chemical properties of the metal. Thus the standard potential of the silver atom $(Ag)_1$ increases through *n*-atomic silver clusters $(Ag)_n$ up to solids $(Ag)_\infty$ from -1.8 to $+0.8$ V. Collective oscillations of the electrons lead to plasmon resonances which in the case of metal clusters belonging to group Ib (Cu, Ag, Au) cause strong absorptions in the optical range ($400\text{ nm} < \lambda_{max} < 600\text{ nm}$). As the refractive index takes on high values near a strong absorption band, such systems are being investigated for applications in nonlinear optics. Most of the atoms of small metal clusters are surface atoms. Special surface states combined with the large specific surface area lead to extraordinary catalytic properties.

To prepare metal clusters in polymer matrices (polymer/metal hybrids), the interface between both materials has to be stabilized sufficiently. According to the HSAB concept, metals are mostly soft acids and it should, therefore, be possible to stabilize them well with soft bases. Thus, polymer blocks functionalized with N, S, or P ligands are applied. Unstable metal complexes with hard bases (chlorides, acetates) serve as precursor materials which, by complexing with the softer ligands, can be solubilized into the polymer compartments. The complexation between the precursor and the ligand must not be too strong otherwise there will be no further reaction to the elementary metal.

Figure 20 shows electron microscopic images of micelles of poly(styrene-*b*-4-vinylpyridine) (PS-P4VP). For the preparation of Au nanocolloids, $HAuCl_4$ was solubilized as the precursor into the P4VP micelle core. After reaction with a strong reducing agent ($LiAlH_4$) has taken place, small primary

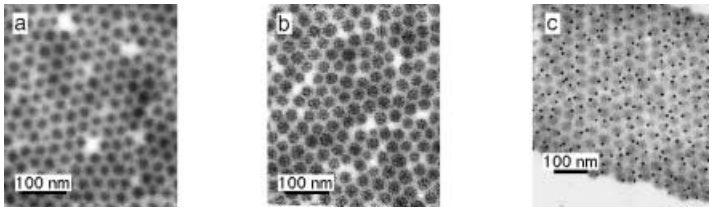


Figure 20. Preparation of gold nanocolloids in micellar block copolymer systems.[104] a) Micelles loaded with the precursor ($HAuCl_4$), b) Au nanocolloids after fast reduction, c) Au nanocolloids after slow reduction.

Au particles with a diameter of about 1 nm develop in the micelle core. One single crystal with a diameter of 3 nm arises per micelle core upon slow reduction with Et_3SiH as a reducing agent. The micelle shells prevent further growth to colloidal aggregates.[104] A number of metal colloids such as Au,[97–107] Ag,[97, 98, 106] Pd,[98, 106, 108–111] Pt,[98, 107, 108, 110, 112] Cu,[98] Ni,[98] Pb,[98] Rh,[106, 112] and Co[113] can be prepared in this way.

Co clusters with a diameter below 20 nm consist of a magnetic single domain (Weiss region). Solutions of such clusters are called magnetic liquids or ferrofluids. They show superparamagnetic behavior. Ferrofluids are being investigated with regard to their suitability as sealing liquids and magnetic inks for printers as well as for medical applications (artificial muscles, tumor diagnostics, and cancer therapy). The clusters, being fixed in a matrix, keep the direction of magnetization and store magnetic information.

The giant magnetoresistance (GMR) in magnetic nanodomains discovered in 1988 represents an example of how fast nanomaterials find acceptance in technical applications. It was possible to develop very sensitive sensors for magnetic fields which were integrated into read/write heads for magnetic storage systems. Meanwhile, these systems have completely replaced the former conventional ones. New magnetic storage systems (MRAMS) with storage densities of 10 GB per chip and access times below 10 ns are being developed based on the GMR effect.

Of special significance are the catalytic properties of small metal clusters. At their surface, such clusters have a large number of atoms with a low coordination number to which substrates bind. Catalytic hydrogenation, hydrosilylation,

hydration, and the Heck reaction are being studied. Moreover, metal clusters are of importance with regard to redox and electron-transfer processes such as the photochemical decomposition of water (fuel cells) and photocatalytic hydrogenation.

The outstanding features of metal clusters prepared in block copolymer micelles[114] are their high catalytic activity combined with high stability. Such micellar catalyst systems can be recovered after reaction by precipitation or ultrafiltration. In some cases high stability has been observed. Cyclohexadiene, for example, is selectively hydrogenated by Pd colloids only to cyclooctene.[102]

Special attention has been focused on studies carried out on the Heck reaction. This reaction is of great interest in preparative organic and macromolecular chemistry, for example, in the synthesis of luminescing poly-*p*-phenylenevinylenes (PPVs). Figure 21 shows the percentage of reaction for

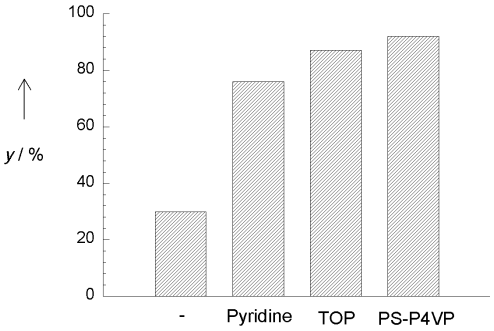


Figure 21. Percentage of reaction *y* of the Heck reaction with Pd without ligand and for different ligand systems.[114] The catalyst embedded in the micelles shows the highest reaction at considerably better stabilizing. TOP = tri-*o*-tolylphosphane.

different ligand systems in the coupling of bromacetophenone and styrene to the stilbene product. Without stabilizing ligands the activity remains low, and after some time "palladium black" is observed. This is avoided by using stabilizing ligands. Pd clusters embedded in block copolymer micelles show the highest activities. A proof of the good stabilization are the high turnover numbers (70000 mol product per mol catalyst) which are clearly higher than those of other systems investigated.

4.2. Semiconductor Hybrids

Reducing the diameter of semiconductor particles to a few nanometers results in a change of their electronic properties. Confinement to the nanometer range is possible in one, two, and three dimensions, that is, in the form of quantum wells, quantum wires, and quantum dots. These quantum structures serve as control and storage elements which can be switched with one single electron (or its spin), which enables very high computing speeds to be achieved.

Reducing semiconductor nanoparticles to the nanometer scale results among other things in:

1) an increase of the band gap by several eV (size quantization effect), which leads to a blue shift of the absorption and of the photo- and electroluminescence;
2) an increased energy of photogenerated electrons which is utilized, for example, in photovoltaics, and
3) an increase in the optical absorption coefficient which is significant for applications related to UV protection.

Normally semiconductor structures are prepared by means of top-down technologies such as photolithography or molecular beam epitaxy. Recently bottom-up methods have been successfully studied. By using self-organization processes and by controlling growth kinetics these methods can be used to prepare quantum dots and nanoparticles in high quality. Monodisperse nanoparticles of CdS, CdSe, CdTe, InP, and InAs, which are able to organize in superlattices, have been prepared. It is furthermore possible to synthesize semiconductor nanoparticles in the superlattices of block copolymers.[104] Semiconductor clusters of CdS,[115–117] ZnS,[116, 118, 119] PbS,[116, 120] ZnF,[119] CuS,[116] CoS,[116] FeS,[116] and ZnO[121] are mostly generated by sulfidic precipitation with H_2S.

Size control is an important goal when preparing semiconductor nanoparticles. This can be achieved by varying the size of the block copolymer domains. In smaller domains we observe smaller semiconductor particles which, as a result of the size quantization effect, have absorption edges or smaller wavelengths. Figure 22 shows this blue shift of the absorption band with decreasing particle size of CdS clusters. A CdS solid has an absorption edge at $\lambda = 480$ nm. Small CdS nanoparticles have an absorption edge shifted below 400 nm. These particles were synthesized in polymethacrylic acid domains of poly(styrene-*b*-methacrylic acid) (PS-PMAc).

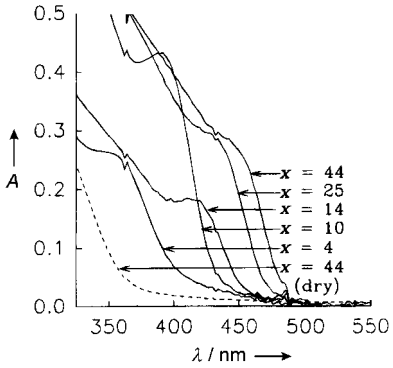
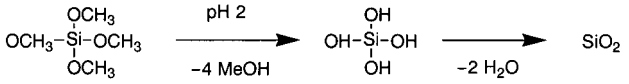


Figure 22. Blue shift of the absorption edge of CdS with decreasing particle size (size quantization effect).[115] The particle size was adjusted by the degree of polymerization *x* of the polymethacrylic acid block.

Semiconductor particles with tunable optical properties are well-suited for applications in optoelectronics and communication technology wherewith higher transfer frequencies and a more efficient use of the optical spectrum larger band widths for data transfer can be achieved. Quantum dots have recently been used as fluorescent labels for biological tagging experiments in diagnostics and for visualizing molecular processes in living cells.[122, 123] TiO_2 particles with diameters of 10 – 30 nm have been studied with regard to their application in photovoltaics (Graetzel cells) or as photocatalysts for the photooxidation of waste water contaminations.[124]

4.3. Glasses, Ceramics, and Biominerals

Nanostructured inorganic materials and inorganic/polymer hybrids are known for their good mechanical and thermal properties. They are often harder and less fragile than the same material without inner structuring. Nature provides innumerable examples of inorganic/polymer composites such as bones, teeth, and shells. Such hybrid materials can be prepared by means of controlled crystallization, by sol/gel processes in microcompartments, or by mixing polymers with layer silicates. In sol/gel processes a hydrolysis and subsequent condensation of inorganic precursor materials take place, as a result of which amorphous inorganic materials originate, for example, upon preparing silica by hydrolysis of tetramethyleneorthosilicate and subsequent condensation (Scheme 1).



Scheme 1.

When carried out in nanostructured polymer matrices, this reaction leads to mechanically stable silica/polymer hybrid materials. The polymer matrix can be removed by means of calcination and the pure minerals are obtained. Nanometer-sized glass or ceramic particles originate, depending on the topology of the microstructure. Wiesner and co-workers succeeded in preparing spherical, cylindrical, and pellet-shaped silica particles from hybrid materials.[125]

Mineral/polymer composites are prepared in nature by crystallization in the presence of particular proteins (biomineralization). It has not yet been possible to elucidate the function of these proteins in detail. It is, however, possible to simulate many of these functions with block copolymers.[126] For this purpose various systems such as $CaCO_3$,[127–129] $Ca(HPO_4)$,[130] ZnO,[131] and $BaSO_4$[132, 133] have been investigated. The crystallization depends on the binding polymer block, such that $CaCO_3$, for example, can crystallize as calcite, vaterite, or aragonite. The formation of spheres, hollow spheres, dumbbells, or fibers was observed depending on the conditions of crystallization.[126] The way block copolymers operate in the case of controlled biomimetic mineralization is based on their specific adhesion to particular crystal growth surfaces as well as on a steric stabilization of the microcrystals originating.

Polymer nanocomposites are being investigated with regard to their application as substitutes for metals in the motor industry, for the reinforcement of polymer fibers and tyres, as scratch-resistant and inflammable coatings, and as biocompatible materials for prosthetic use.

4.4. Porous Inorganic Structures

Porous materials can be distinguished according to their pore size as microporous ($d < 2$ nm), mesoporous ($2 \leq d < 50$ nm), and macroporous ($d \geq 50$ nm; Figure 23). Zeolites belong to the most important microporous inorganic materials. These are crystalline alumosilicates with a framework structure consisting of cavities and channel systems of defined size and shape. The pore diameter depends on type of zeolite and is between 0.4 – 1.5 nm. As a consequence of this structure, zeolites have particular properties, such as the ability to exchange ions and to reversibly desorb water. These properties are made use of when employing zeolites as ion exchangers and molecular sieves. Above all zeolites are applied as catalysts, and in the area of petrochemistry alone (ZSM-5, zeolite Y) there is an annual turnover of more than US$ 30 billion. The catalytic properties of the zeolites result from Brønsted acid centers at the inner surface and from the electrostatic field inside the cavities and the channels.

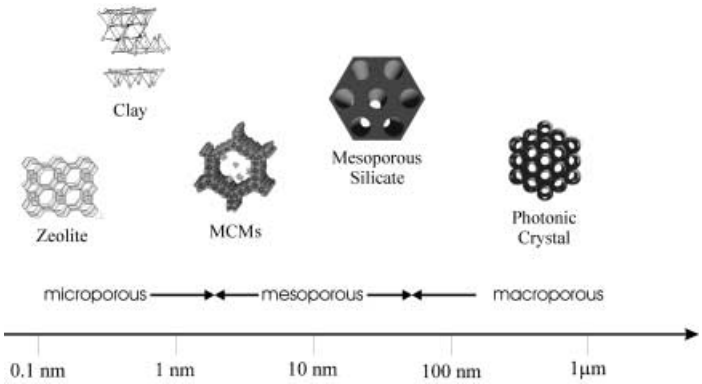


Figure 23. Typical length scales of three-dimensional porous structures.

Mesoporous materials with pore diameters of more than 2 nm were developed by Mobil Co. in 1992 and were called MCM materials. They are amorphous silicates or alumosilicates with pore sizes between 1.6 and 10 nm. This larger pore size represents a considerable advantage over zeolites because much bigger molecules can be received and made to react.

Similar to some zeolite syntheses, short-chain surfactants are used to synthesize MCMs. In aqueous solutions these surfactants form micellar phases, where the dissolved silicate species is made to condensate. In this way amorphous silicate walls, about 1-nm thick, originate between the micelles. Lyotropic, lamellar, hexagonal, and cubic phases develop, depending on the concentration of the surfactant, which leads to varying silicate structures. Materials with free pore systems are obtained after thermal removal of the surfactant by calcination.

Lyotropic phases of block copolymers are well-suited for the preparation of mesoporous inorganic materials with still bigger pore diameters. Pore diameters and a wall thickness of more than 50 nm lead to mechanically stable monolithic materials. According to the structure of the lyotropic phases, porous cubic, hexagonal, and lamellar structures can be prepared (Figure 24).[95, 134] By means of the sol/gel process it is possible to prepare mesoporous SiO_2,[135–146] TiO_2,[146, 147] NiO_2,[147] ZrO_2,[147] Al_2O_3,[147] Nb_2O_5,[147] Ta_2O_5,[147] WO_3,[147] HfO_2,[147] SnO_2,[147] as well as mixed oxides such as $SiAlO_{3.5}$,[147] $SiTiO_4$,[147] $ZrTiO_4$,[147] Al_2TiO_5,[147] and ZrW_2O_8.[147] The porous inorganic material is obtained after removing the polymer by calcination. The size and shape of the pores are predetermined by the hydrophobic domains in the lyotropic phase.

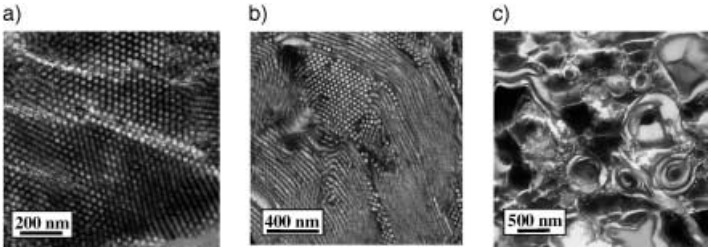


Figure 24. Silicates with a) spherical pores of cubic order, b) hexagonally ordered cylindrical pores, and c) lamellar pores prepared from lyotropic phases of block copolymers.[95, 134]

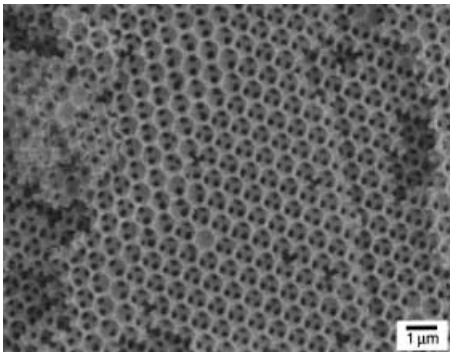


Figure 25. Photonic crystal synthesized from polystyrene latices by a sol/gel procedure.[149]

Studies are currently being carried out on a large number of applications for mesoporous structures, for example,

- as sorbents for the removal of heavy metals from sewage and of gaseous contaminations from natural gas,
- as hydrogen and methane reservoirs for fuel cells,
- as catalysts and catalyst supports,
- as transparent thermal insulating layers,
- for the storage and controlled delivery of plant nutrients (fertilizers, water).

Intensive investigations are currently being performed on how to vary the chemical composition of the silicates, to coat the surface, to vary the pore size, and to fix catalysts at the surface.[148]

Macroporous materials with pore diameters of more than 50 nm which can be generated with the aid of polymer latex particles are being investigated with regard to their applicability as photonic crystals. The periodic length of the crystal structure must be in the range of some 100 nm in order to prepare a photonic crystal working in the region of wavelengths of visible light. Monodisperse polymer latices are used which organize spontaneously under high concentrations to form cubic superlattices. An inorganic matrix can be prepared in the interspaces filled with water by means of the sol/gel process. A porous inorganic structure is obtained after removal of the latex particles by calcination (Figure 25).[149] The shape and size of the pores and the pore distances correspond to those of the latex particles in the self-assembled superlattice. Materials with high dielectric constant (TiO_2, semiconductors, metals, chalcogenide glasses) are used as the matrix. The size of the photonic band gap can be adjusted by the periodic length and the dielectric constant of the matrix. Superlattices with photonic band gaps are only transparent for particular regions of wavelength and are used for low-loss guiding and switching of optical signals.

The following example shows how the bottom-up and top-down strategies can be combined for the generation of functional structure hierarchies (Section 3.3). Periodic structures (triangles linked by bridges) with a periodic length of $d_1 = 15$ µm are produced by microcontact printing (Figure 26). The bridges and triangles consist of porous SiO_2 with pore sizes of $d_2 = 500$ nm (achieved by the templating of latex particles) and of $d_3 = 2$ nm (lyotropic block copolymer phase).[150] Microscopy images of these three structural levels are depicted in Figure 26. Such porous silicate structures have a low refractive index ($n \approx 1.15$) and can be loaded with laser dyes. They are currently being studied as wave guides for lasers in integrated optical systems.[151]

5. Biomaterials

The organization and functionalization of molecules on several size scales is one of the key properties of biological systems. Many of these functions can be imitated by using self-organized structures, with the material properties of the polymers playing an important role. Only 10 to 20 different polymers are currently used as biomaterials. Most of them were initially not developed for clinical purposes, but were chosen according to trial-and-error procedures. A lot of them cause long-term side effects and complications when used in medical applications. The future generation of polymer biomaterials will be systematically developed and shall offer a broad spectrum of specific applications and functions with the highest possible safety.

There is a wide variety of functional polymers able to adopt functions such as encapsulation, stealth, cell adhesion, and cell

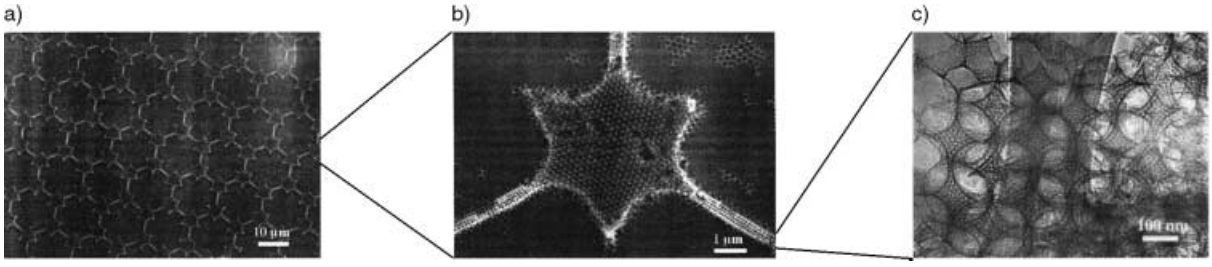


Figure 26. Electron micrographs of a structure hierarchy over three organization levels[150] prepared with the aid of microcontact printing and self-assembly: a) microcontact sample ($d = 15$ µm), b) macroporous structure ($d = 200$ nm), c) mesoporous structure ($d = 2$ nm).

recognition as well as different actuator functions (Figure 27, Table 6). Polymers must be biocompatible. This feature is influenced predominantly by the polymer surface. Polymers with hydrophilic surfaces are often well-suited and so are those with an inert surface, that is, which have a surface tension of $\gamma < 30\ \mathrm{N\,m^{-1}}$ (teflon, polysiloxan, polyisobutylene). Hydrophilic, noninteracting materials cannot be recognized by living systems (stealth systems) and therefore have low cytotoxicity. It is often advantageous to introduce functional groups into the polymer chain in order to bind bioactive molecules such as peptides, oligosaccharides, and antibodies.

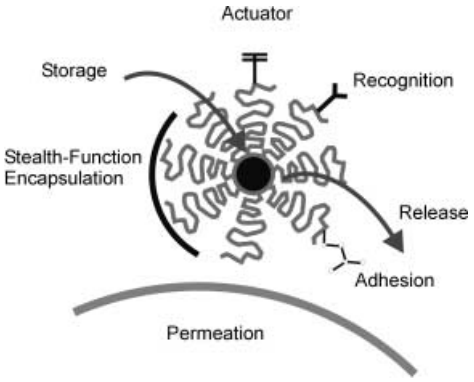


Figure 27. Schematic diagram of biological functions which can be executed by self-organized polymeric structures.

Several of these polymer materials can be integrated into block copolymers. The spontaneous self-assembly leads to functional compartment structures such as micelles, vesicles, and gels which have been tested in many clinical investigations with promising results. They can be applied in prosthetics (artificial intervertebral disks, bone cement), diagnostics (gel electrophoresis), therapeutics (chemotherapy, gene therapy), and sustained drug release.

5.1. Implants

There are three biological prerequisites for implants:

1) the mechanical properties such as elasticity and toughness must correspond to those of the tissue to be replaced,
2) the implant must not be encapsulated by fibrous tissue, and
3) a binding continuous surface should develop between the implant and surrounding tissue.

The mechanical demands on the implants may vary considerably. Intervertebral disks are recognised for their high elasticity whereas bone cement has to be very hard. Implants can well be adapted to the tissue to be replaced by using microstructured copolymer systems. Telechelic prepolymers such as polyisobutylene (PIB) star polymers with chain-end functionality are preferably used. The material separates into microphases upon growth of the second polymer block. The resulting microstructure corresponds to that of microphase-separated block copolymers, but without having the defined order of the microdomains.

Upon injection of PIB stars with cyanoacrylate end groups at the place of the intervertebral disk to be substituted, the polymerization of the terminal groups is spontaneously initiated by the ambient humidity as is the case with superglue. As a result an elastic PIB matrix chemically and physically cross-linked by the cyanoacrylate microdomains originates, which can replace fractured intervertebral disks.[152] Broken hip joints are repaired using bone cement out of PIB stars with methyl methacrylate (MMA) end groups. In the application, MMA is added and polymerized and a PMMA matrix cross-linked with PIB microdomains is obtained. The outstanding feature of PMMA (plexiglass) is its hardness. The elastic PIB microdomains make the material less brittle by dissipating mechanical tension (high-impact PMMA).[153–155]

Biocompatibility of the surface is one of the prerequisites of a successful implantation. Microstructured polymers and gels offer a lot of advantages. PIB stars end-functionalized with 2-hydroxy(methyl methacrylate) (HEMA) or with *N*,*N*-dimethylacrylamide (DMA) lead to microstructured amphiphilic networks on polymerization with additional monomer (HEMA, DMA). The microstructure resembles that of lyotropic block copolymer phases with domain sizes of 2 to 5 nm, yet without defined domain order ("salt-and-pepper" morphology).[156–158]

Elastic implants out of PIB-PHEMA and PIB-PDMA show low protein absorption because of their hydrophilic surface. Figure 28 depicts the protein absorption from blood plasma compared with conventional materials such as glass, polyethylene (PE), and polydimethylsiloxane (PDMS).[159] Above all, the low values of fibrinogene adsorption prove the good blood compatibility of such materials. Fibrin adsorption should be low so as to avoid the blocking of capillaries, which often have diameters of only few millimeters. Biodegradable components can also be incorporated into amphiphilic gels, for example, in materials made out of PEO-PPO-PEO/PLac[160, 161] or PI-PLac,[162] which can also be used as biodegradable flexible fibers.

Table 6. Functional principles of polymeric biomaterials.

Function	Action principle	Example
stealth	hydrophilicity	PEO, polyacrylic acid, polysaccharide, poly(vinyl alcohol), PVP
chemically inert	$\gamma < 30\ \mathrm{N\,m^{-2}}$	PDMS, teflon, PIB, PU
biodegradable	hydrolytically or enzymatically degradable polyester	PGly, PLac, PA
cell adhesion		adhesive glycoproteins, fibronectin
cell detection	vectors	immunoglobulins (IgG), RGD sequence
cell permeation	membrane compatibility	PEO, lipids
salt actuator	polyelectrolytes	PAAc, poly-L-Lysine
temperature actuator	phase separation	PPO, PNIPAM
pressure actuator	phase transition through ultrasound	metastable micelles
glucose actuator	complex formation	tetraphenylene boronic acid

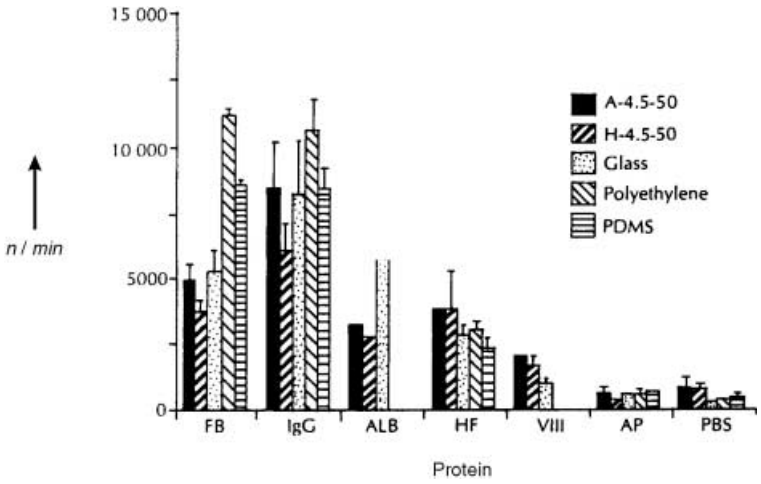


Figure 28. Protein absorption of amphiphilic gels (A, H) compared with conventional materials (glass, PE, PDMS).[159] FB: fibrinogen, IgG: immunoglobulin G, ALB: albumin, HF: Hageman factor, VIII: Willebrand factor, AP: alphatetoprotein, PBS: phosphate-buffered salt solution (control experiment). The low values of the fibrinogen adsorption (FB) indicate good blood compatibility.

5.2. Gel Electrophoresis

Gel electrophoresis is one of the most important analytical methods of molecular biology. In most cases, polyacrylamide gels are used as stationary phase. Efficient separation media for the analysis of biopolymers are intensively being developed. The planned classification of acrylamide into a special poison category throughout the European Community requires an urgent search for alternative separation media. In principle, the chromatographic separation of a substance mixture results from enthalpic and entropic interactions with a stationary phase. When lyotropic phases of amphiphilic block copolymers are used as the stationary phase, the substances enter an enthalpic distribution equilibrium between the micelle shells and the eluant. Since the hydrophobic domains of lyotropic block copolymer phases are rather large, it is possible to solubilize biopolymers such as polypeptides and polynucleotides. Distribution equilibria between dextrane solutions and lyotropic PEO-PPO-PEO phases (P105, F68) have been thoroughly investigated. Dextranes are water-soluble polysaccharides which are applied in chromatography as column materials or blood plasma expanders. Hydrophilic proteins such as lysozyme, bovine serum albumin, and cytochrome C remain in the aqueous phase whereas hydrophobic membrane proteins such as bacteriorhodopsin and gramicidin D accumulate almost completely in the hydrophobic PPO phase.[163, 164] Slightly hydrophobic substances such as tryptophane and phenylalanine oligopeptides and cytochrome b(5) are distributed, depending on salt concentration and temperature, in both phases.[165]

This variable accumulation or partitioning of biomolecules in lyotropic block copolymer phases can be made use of in capillary gel electrophoresis (CGE). Detailed studies on this matter have been carried out with PEO-PPO-EO (F127) which forms cubic liquid crystalline gel phases at a concentration of 18–30% and a temperature of 20–30 °C (Figure 10). Chu and co-workers[166, 167] carried out a detailed structural analysis with light, X-ray, and neutron diffraction of F127 in buffer solution as used for DNA separation. A temperature decrease to less than 5 °C leads to a reversible gel/sol transition to solutions of low viscosity which are easy to fill into the CGE capillaries, thus offering advantages for technical applications. The separation of various nucleic acids, oligonucleotides, DNA fragments, and of plasmid DNA have been described.[168]

The separation can be optimized to produce the best possible results by varying the polymer concentration and the temperature. Conditions such as those necessary for DNA sequence analysis or oligonucleotide therapy can be achieved (Figure 29). Single nucleotides in dT(12–18) and dT(19–24) standards are separated with baseline separation within eight minutes.[169] The block copolymer gel does not only operate as the separating phase but also as a coating which suppresses the electroosmotic flux at the inner wall of the quartz capillary. The advantage of block copolymer gels becomes evident in their high selectivity and solubility, the fact that it

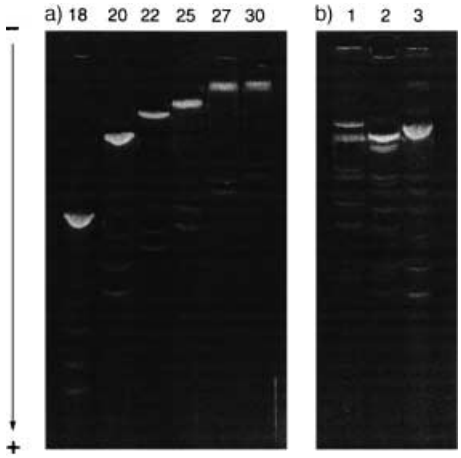


Figure 29. Electrophoretic separation of double-stranded DNA fragments in a lyotropic block copolymer phase.[171] a) $N \times 123$ bp DNA in 18, 20, …, and 30% solution. b) DNA restriction fragments.

is possible to exchange the stationary phase (in contrast to the cross-linked hydrogels), and the convenient column handling. High reproducibilities of the elctrophoretic migration times (<2%)[170] allow miniaturization and automation of CGE.[171]

One problem still remains unsolved, namely, elution in media which break hydrogen bonds, for example, in concentrated urea/formaldehyde solutions. These are used to separate the two complementary DNA strands. The solubility of the block copolymers differs so strongly in these media that it is often not possible to maintain the structure of the superlattice. The latter may, however, be stabilized by methods as described in Section 3.6.

5.3. Drug Delivery

Currently research is increasingly being done in the field of drug delivery and drug targeting on a molecular level. Fresh

impetus is given in particular by the progress made in biotechnology and immunology supplying new classes of highly effective therapeutics such as polypeptides, oligonucleotides, and genes. For these high molecular weight active agents new delivery and targeting mechanisms have to be developed. At the same time the discovery of monoclonal antibodies and an increased knowledge of cellular receptors led to new approaches in this field. To transport an active agent specifically to the target at the right moment and over a predetermined period of time is the goal for scientists.

Macromolecules offer a wide variety of possibilities as specific transportation systems in biology and medicine. They allow a large number of functions in a molecule to be combined. Small molecules cannot cope with such a number of functions.[172] One problem when using high molecular weight active ingredients is proteolytic decomposition, for example, upon oral administration, and in low permeation through cellular membranes. For this reason such substances have mostly to be administered parenterally, that is, intravenously, subcutaneously, or intramuscularly. Their tissue specificity is first confined to the cells of the reticuloendothelial system (RES) which recognizes them as foreign microparticles and transports them to the liver and spleen. Their biodistribution can, however, be regulated by surface modification, for example, by introducing PEO (stealth systems) or monoclonal antibodies (site-specific targeting). The proteolytic decomposition can be suppressed by encapsulation, for example, in liposomes, polymers, or polysaccharides. By this means, the residence time, bioavailablity, and permeability of polymeric active agents can be increased.

After the polymers have been transported to the place of their target, the active agent is released. This takes place either by depolymerization or by splitting the active component from the polymer, by a swelling of the polymer and resulting release of the active ingredient, or by effusion of the active agent. For control purposes an actuator function may be of use which triggers the release of the active agent depending on local conditions such as salt concentration, temperature, and pH value. Amphiphilic polymers and their association structures are of increasing interest as carriers of active ingredients.[173] An example of such a carrier system is shown in Figure 27.

5.3.1. Micellar Systems

Block copolymer micelles are being investigated in many research groups as carriers of hydrophobic active agents and genes. Their core/shell structure resembles that of lipoproteins and viruses. The micelle shell causes the interaction with proteins and cells. These interactions decide on the biodistribution of the active component. Endogenic ligands with target function can be bound at the end of the chain of the outer polymer block. Such "intelligent" carriers are able to select their targets. The binding and release of the active agent are, however, determined by the polymer block in the micelle core. Various studies provide evidence of a long residence time of block copolymer micelles in blood proving the applicability of block copolymer nanoparticles as carriers

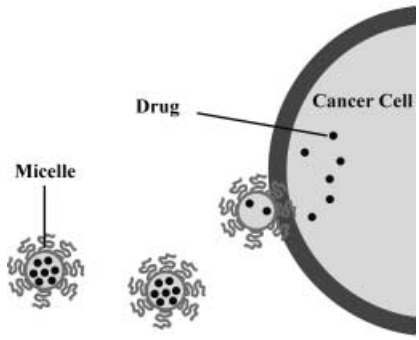


Figure 30. Chemotherapy with block copolymer micelles transporting drugs into the tumor cell.

for the specific transport of active components (site-specific drug delivery; Figure 30).[174]

The idea of using block copolymer micelles as carriers of active agents results from studies carried out by Ringsdorf and co-workers in 1984[175] who investigated micelles of poly(L-lysine-*b*-ethylene oxide)(PLys-PEO).[176] The active components can be bound with labile peptide bonds. Protease, which occurs in increased concentration in many tumor types, is able to break this bond. Later Kataoka and co-workers were able to prove with a similar system, poly(asparaginic acid-*b*-ethylene oxide (PAsp-PEO),[177] that anticancer drugs can physically be solubilized in the micelle core. Such polypeptide PEO block copolymers are very well suited as carriers of active components. PAsp solubilizes large quantities of drugs and, being a polypeptide, is biodegradable. PEO is water soluble, chemically stable under physiological conditions, and reduces the antigenic effect of the block copolymer/agent conjugate. Ligands with target function can be bound to the OH end groups of the PEO block.[178–181]

In water the PAsp-PEO block copolymer micelles have a diameter of approximately 60 nm. As a result of this size, neither renal filtration nor uptake by the RES occurs. Hence the micelles circulate in the blood stream for a long time. The low critical concentration of micelle formation (cmc) means that block copolymers generate micelles even when highly diluted in blood. The low concentration of unimers are excreted by the kidneys. As an example the loading of PAsp-PEO with doxorubicin (DOX) and the corresponding anticarcinogenic effect were systematically investigated.[177, 180–185] In a few cases it was possible to completely remove subcutaneous tumors of mice through the increased doses with this kind of chemotherapy (Figure 31).[186] For many kinds of tumors the specific transport to the tumor cells can be accomplished through the increased vascular permeability of diseased tissue.

PEO-PPO-PEO micelles as conjugates with anthracyclin antibiotics (doxorubicin, Ruboxyl, EPI) have also been applied in chemotherapy with the result that life expectancy increased by more than 150% and the growth of the tumor was inhibited by more than 90%. Some conjugates caused the tumors to completely disappear.[187] In these cases especially, the influence of ultrasound increased the absorption of the active agent by the tumor cells. Encapsulation and subsequent focused sonication of micelle conjugates represent an addi-

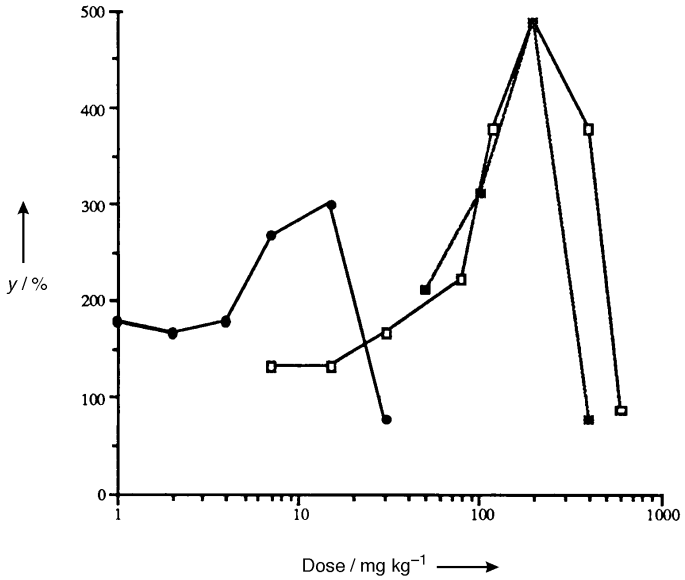


Figure 31. Increase of life expectancy y after chemotherapy with block copolymer micelles:[186] ● = DOX, □ = PEO-PAsp/DOX 4–17, ■ = PEO-PAsp/DOX 5–80. The block copolymer conjugates can be administered at higher doses thus achieving a higher antitumor effect. Doxorubicin (DOX) was used. $y = 100$ corresponds to life expectancy without chemotherapy.

tional way of gentle transport of active agents and specific release in tumors.[188, 189]

The high activity of PEO/agent conjugates is closely connected with their special transport behavior through biological barriers. PEO influences the microviscosity and permeability of cell membranes.[190] This is the result of a special property of PEO: at a high degree of hydration in aqueous media PEO is hydrophilic, while at a low degree of hydration in hydrophobic environment it is, however, hydrophobic. Thus, PEO can dehydrate at hydrophobic surfaces and can be transported into or through these boundary surfaces. The penetration and accumulation of PEO in hydrophobic lipid layers was proved by X-ray reflection studies.[191]

5.3.2. Multidrug Resistance

The development of a multidrug resistance (MDR) represents a considerable problem in the successful treatment of cancer by chemotherapy. Although many types of cancer recede in the beginning, recurrence often occurs and is accompanied by a resistance against a wide variety of structurally different drugs. An overexpression of the MDR1 gene which encodes the plasma membrane protein P-gp (P glycoprotein) is mainly responsible for this situation. This transport protein transports drugs out of the tumor cell thus causing the resistance against these cytotoxins. A short application of usual chemotherapeutics already often leads to a quick increase in the gene expression.

In order to avoid this, active agents are being developed which block P-gp, thus guaranteeing an accumulation of the drugs in the cancerous cell. PEO-PPO-PEO micelles have proved to be surprisingly efficient. By using PEO-PPO-PEO/daunorubicin conjugates, already resistant cancer cells showed a dramatic increase (by a factor of 700) in the daunorubcin activity ("hypersensitization"). The ID_{50} dose of 25 μg mL^{-1} of free daunorubicin was decreased to 0.16 μg mL^{-1} for block copolymer/conjugated daunorubicin. An increase of activity by a factor of 20–1000 caused by the block copolymer was also observed with other drugs such as doxorubicin, epirubicin, vinblastin, and mitomycin C. This procedure in combination with chemotherapeutic drugs could well be used to overcome MDR.[192–194]

5.3.3. Blood–Brain Barrier

The blood–brain barrier hinders detrimental substances from penetrating the extremely sensitive brain. The permeability of the capillary wall is selectively decreased for many substances, especially for electrically charged molecules. This effect corresponds to other blood–tissue barriers of the organism (for example, blood–liver, blood–placenta), but it is more effective. The function of the blood–brain barrier is to protect the central nervous system against detrimental chemical influences as well as to maintain a high concentration of the substances important for the metabolism of the central nervous system, such as glutamic acids, K^+, and phosphate.

In vitro experiments showed that nonionic block copolymers such as PEO-PPO-PEO proved to be surprisingly effective with regard to the transport of active agents through the blood–brain barrier. Monolayers of brain capillary endothelial cells served as a model system. In the presence of block copolymers a much more effective transport and the accumulation of the fluorescence marker rhodamin 123 into the cells were observed. The investigations made it evident that the increased effectiveness has also to be attributed to an inhibition of the P-gp protein and to a more effective transport via micelles or vesicles through the cell membrane.[195] Increased transport and accumulation have also been observed in regard to the penetration of intestinal epithelium cells.[196]

5.3.4. Lyotropic Phases as Drug Reservoirs and Actuators

Lyotropic phases (gels) can also be used as delivery systems. They are either directly administrated, as in the case with antibiotics,[197] rheumatics,[198] or insulin,[199] or they are dispersed as microparticles. The latter, with a diameter of approximately 5 μm, are frequently produced by means of a w/o/o emulsion/solution extraction technique. Adsorption capacity and release profiles have been studied in detail for some systems. Up to 40% ovalbumin, for example, can be adsorbed in microparticles of a PEO-PPO-PEO/PLGA conjugate. With a release capacity of up to 3 μg mg^{-1} per day, linear release profiles are observed in vivo over a period of 25 days.[200] The release of insulin[201] as well as of vaccine formulations from microparticles[202] are also being investigated.

In regard to controlled release, there is a wide variety of applications of gels and microparticles which react to environmental conditions such as temperature, salt concentration, or pH value (actuators; Table 7). Sensitivity to these factors can be achieved by conjugation with other polymers or by the use of special ligands. As an example, the PEO-PPO-PEO/

Table 7. Biological functionalization of block copolymer micelles and microparticles.

Particle	Core block	Shell	Active ingredient	Remarks
micelles	PPO, PLys, PAsp, PLac	PEO	DOX, ruboxyl, EPI, daunorubicin	HL-60 cancer cells, subcutaneous cancer cells
	PPO	PEO	daunorubicin, DOX, EPI, vinblastin, mitocytin	multidrug resistance
	PPO	PEO	rhodamine	blood–brain barrier
	PAsp	PEO	fluorescein	permeation into endothelial cells
simplex micelles	P4VPEtBr	PEO	plasmide DNA	gene transfection
	polyspermine	PEO	oligonucleotide	herpes virus inhibition
	PAsp	PEO	lysozyme	
microparticle/gels	PEI	PEO	plasmid DNA	gene transfection
	PPO	PEO	antibiotics	wound treatment
	PPO	PEO	diclofenac	antirheumatic treatment
	PIB	PHEMA		
	PU/PPO	PEO		
	PLac/PGly/PPO	PEO	ovalbumin	
	PAAc/PPO	PEO	steroid hormone	
		PEO	insulin	glycemia
	polyurethane/PPO	PEO		
	plasmide DNA/lipid/PPO	PEO		gene transfection
	PPO	PEO		phagocyte resistance, radiodiagnostic, imaging, bone marrow, spleen, lymph nodes

polyacrylic acid conjugates can easily be obtained by spontaneous complex formation through the generation of hydrogen bonds and hydrophobic interactions.[203, 204] They have a pH value, salt concentration, and temperature-actuator effect. By specific variation of these parameters it is possible to shrink, swell, or dissolve the gels.[205, 206] Proteins, steroid hormones, and insulin, for example, have been conjugated with these gels and purposefully released.[207] Glyco-responsive systems can be obtained through the binding of phenylboronic acid, which forms covalent complexes with polyols such as glucose.[208] When the local glucose concentration decreases glucose is released out of the microparticles so as to maintain the complexation equilibrium. Model conjugates of PEO-PPO-PEO/polyacrylic acid/concanavalin for a glucose-responsive insulin release are being developed.[209].

5.4.1. Gene Therapy

The results of the international humane genome project, which has meanwhile been concluded, holds out the prospect that it will be possible to cure diseases through the use of genetic engineering and therapy. There is a wide therapeutic potential for gene therapy; more than 4000 human genetic diseases are known and practically every illness is fundamentally affected by genetic factors.

In gene therapy genes are introduced into the cells to replace a lacking or defective gene or to block a faulty one. Genetically modified viruses (retroviruses) are used in which the gene sequence for multiplying has been taken out and replaced by foreign DNA. They integrate their genome as a part of their lifecycle into the genetic material of the host cell (transfection). The disadvantages of genetic therapy with retroviruses are a high antigen reaction, the risk of recombination with wild-type viruses, and cell damage caused by viral vectors.

Therefore, scientists are searching for synthetic, nonviral gene-transfer systems using plasmide DNA which can be produced on an industrial scale by means of modern fermentation technology. Plasmids are small, circular extrachromosomal DNA molecules which are able to replicate independently in a host cell. Accumulation and transport of plasmid DNA can take place with the aid of cationic particles. As a result of electrostatic attraction, the latter form stable complexes with the negatively charged plasmid DNA. Liposomes from positively charged lipids are used for complex formation. The use of polycations also leads to the spontaneous formation of stable polyelectrolyte complexes (simplexes). Soluble simplexes prepared from plasmid DNA with different polycations exhibited increased plasmid penetration in cells. This is a new approach to effective transfection of genetic materials in vivo.[210]

The unsatisfactory low solubility of simplexes can be improved considerably by using polycation-PEO-block copolymers. Studies carried out with simplexes made from PMAc-PEO and poly-4-vinyl-*N*-ethylpyridinium bromide (P4VPEtBr) showed that water-soluble stoichiometric complexes are formed which have a well-defined micellar structure with a core of the simplexes surrounded by a PEO shell. The micelles dissolve upon addition of salt (Figure 32).[211–213] To address particular cell types, the micelle can be conjugated with a ligand which is recognized and absorbed only by cells with the corresponding receptor. This was, for example, achieved by the covalent binding of a glycoprotein with exposed galactose residues to a poly-L-lysine which complexes negatively charged DNA.

Studies of the therapeutic effect were, for example, carried out with polyspermine-PEO block copolymers which spontaneously form water-soluble complexes with oligonucleotides.[214] A DNA segment which inhibits the reproduction of the herpes simplex virus 1 served as the oligonucleotide. Titration after 22 and 39 hours after the infection showed that the complex inhibits the reproduction of the virus to below the detection limit. The free oligonucleotide had only a short-term effect.[215] Absorption of plasmid DNA and cell transfection can be further increased when PEO-PPO-PEO block copolymers which modify the membrane properties are added at the same time.[216, 217]

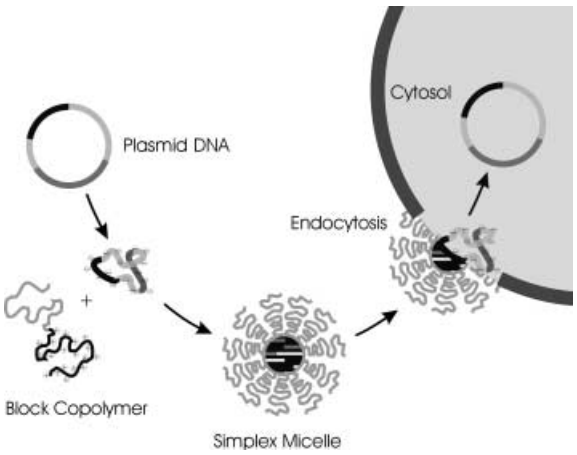


Figure 32. Encapsulation and transport of plasmide DNS in micelles. After transport into the cell the DNA is released as a result of the high local ionic concentration.

6. Conclusion and Outlook

Self-organizing systems offer a wide variety of methods for structuring and functionalizing materials on the nano- and mesoscopic length scale. A large number of superlattices can be realized with the help of quite simple molecules. Of special interest in this respect are macromolecules: their fundamental mechanisms of self-organization and their good material properties are known and it is possible to implement several functions on one macromolecule. This process leads to many approaches for the preparation of novel inorganic materials and of materials with biological function. These concepts can in many cases be transferred to polymers, such as graft copolymers and latices, which can more easily be prepared on a technical scale. This opens up ways for an economic scale-up of the synthesis.

In some cases it has already become possible to synthesize structure hierarchies. In nature hierarchical structures are the basis of the spacial and temporal organization of the chemical processes in a cell. The formation of the secondary structure $\leftrightarrow$ tertiary structure $\leftrightarrow$ quaternary structure of proteins which all are predetermined by the primary structure or—in the case of muscles—the hierarchy of actin/myosin filament $\leftrightarrow$ myofibril $\leftrightarrow$ muscular fiber may serve as examples for this. Only the simultaneous coordination of all structure units leads to muscle contraction. It will still take quite a lot of time until the structural and dynamic organization in polymeric systems will be mastered in a similarly perfect way. Until now results of controlled coordination have been achieved best with actuators. In many cases it will not be either a bottom-up or top-down strategy, but the integration of both procedures which will lead to functional structures.

In the years to come the question of how to address self-organized systems will become more and more important. This involves, for example, the control of transmission and storage of electrical and magnetic signals in self-organized architectures. The transmission and storage of information in neurons proves that in nature this is in principle possible. The processing of information takes place through complicated structure hierarchies, for example, neurotransmitter $\leftrightarrow$ synapse $\leftrightarrow$ axon $\leftrightarrow$ neurone network. The binding of such self-organized information structures to the outside world through a defined interface represents a problem which is being dealt with in quite another connection: Some research teams are working on the binding of neurons to transistors and external circuits.[218, 219] Approaches to the development of self-organized information structures, such as signal transmission and storage in brains, represent a challenge as well as a fount of inspiration.

The potential of applied technology resulting from the investigation of nano- and mesoscale materials is beyond controversy. In 2000 the US President originated the National Nanotechnology Initiative with an investment volume of more than US$ 500 million. There are similar activities in Japan and in Europe.[220] In all cases, the necessary training of scientists in interdisciplinary fields of chemistry, physics, biology, medicine, and materials research is promoted. Multidisciplinarity is a characteristic feature of this kind of research. It has become evident that new routes at junctions of traditional specific fields can be very promising, as they often represent the starting point for novel and unconventional approaches.

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[220] See, for example, webpage of the Bundesministeriums für Bildung und Forschung (www.nanonet.de), *Virtual Journal of Nanoscale Science & Technology* (www.vjnano.org), *Nanostructure Science and Technology* (www.itri.loyola.edu/nano).