https://doi.org/10.1070/RCR4870

Amphiphilic multicomponent molecular brushes

Ivan V. Ivanov,[a] Tamara K. Meleshko,[a] Anna V. Kashina,[a] Alexander V. Yakimansky [a, b]

[a] *Institute of Macromolecular Compounds, Russian Academy of Sciences, Bolshoi prosp. 31, 199004 Saint Petersburg, Russian Federation*
[b] *Institute of Chemistry, Saint Petersburg State University, Universitetskii prosp. 26, 198504 Saint Petersburg, Peterhof, Russian Federation*

Multicomponent molecular brushes containing amphiphilic polymer moieties are promising objects of research of macromolecular chemistry. The development of stimulus-responsive systems sensitive to changes in environmental parameters, based on the molecular brushes, opens up new possibilities for their applications in medicine, biochemistry and microelectronics. The review presents the current understanding of the structures of main types of amphiphilic multicomponent brushes, depending on the chemical nature and type of coupling of the backbone and side chains. The approaches to the controlled synthesis of multicomponent molecular brushes of different architecture are analyzed. Self-assembly processes of multicomponent molecular brushes in selective solvents are considered.
The bibliography includes 259 references.

Contents

1. Introduction 1248
2. Amphiphilic copolymers 1250
3. Synthesis of molecular brushes 1250
4. Identification of the structures of multicomponent copolymers 1253
5. Amphiphilic multicomponent molecular brushes 1254
6. Self-assembly of amphiphilic multicomponent molecular brushes 1274
7. Application of multicomponent molecular brushes 1281
8. Conclusion 1285

1. Introduction

In recent years, attention of researchers has been attracted to systems responsive to changes in the environmental conditions. Among the most promising objects of study in this area are amphiphilic macromolecules, which contain functional groups with different affinities to polar and nonpolar solvents. Amphiphilic copolymers containing covalently attached hydrophilic and hydrophobic polymer blocks are prone to self-assembly in the presence of solvents selective to them.[1–3] The self-assembled structures are highly sensitive to external stimuli.[4–6] Changes in the physical parameters of the system (temperature, ionic strength, solvent quality, *etc.*) can promote either the formation or destruction of molecular (supramolecular) entities as a result of changes in intermolecular interactions and conformations of macromolecules.

The development of new controlled polymerization (living polymerization) techniques enabled the synthesis of numerous amphiphilic copolymers of different architecture such as linear block copolymers, polymer brushes, star-shaped polymers, hyperbranched polymers or dendrimers.[7–11] Among the indicated sorts of copolymers, molecular polymer brushes, a special class of graft copolymers with regularly grafted narrowly dispersed side chains, attract great interest because of their unique chemical and physical properties.[12–14] In comparison with linear copolymer analogues, molecular brushes have a more compact conformations of macromolecules in solutions and a greater number of chain ends bearing functional groups. Owing to their specific topology, they are readily soluble in a variety of solvents and have low intrinsic viscosity in solutions.

A large series of amphiphilic molecular brushes are those with different-type homopolymers as the backbone

I.V.Ivanov. Ph.D (Chemistry), Junior Researcher at the Laboratory of Polymer Nanomaterials and Compositions for Optical Media, IMC RAS.
Telephone: +7(812)328 – 7260, e-mail: gangspil@gmail.com
T.K.Meleshko. Ph.D (Chemistry), Senior Researcher at the same Laboratory.
Telephone: +7(812)328 – 7260, e-mail: meleshko@hq.macro.ru
A.V.Kashina. Junior Researcher at the same Laboratory.
Telephone: +7(812)328 – 7260, e-mail: kashina.anna@mail.ru
A.V.Yakimansky. Doctor of Chemical Sciences, Deputy Director for Science of the IMC RAS, Head of the Laboratory of Polymer Nanomaterials and Compositions for Optical Media, IMC RAS, Professor at the SPbU.
Telephone: +7(812)323 – 5025, e-mail: yak@hq.macro.ru
Current research interests of the authors: synthesis and chemical transformations of macromolecules of complex architecture, controlled radical polymerization, molecular brushes, amphiphilic copolymers.

Received 8 November 2018
Translation: Z.P.Svitanko

© 2019 Uspekhi Khimii, Russian Academy of Sciences and Turpion Ltd.

and side chains, which provide the copolymer with amphiphilic properties. However, in recent years, increasing attention has been paid to the synthesis and investigations of more complex brush structures that have more than two types of polymer blocks, often of different topologies, with different types of their coupling, which are called multicomponent brushes.[15,16] The introduction of chemically different blocks into side chains and the backbone endows these molecular brushes with additional structural variability and unique aggregation properties caused by incompatibility of their polymer components. Copolymers of this type belong to the group of smart materials capable of spontaneous self-assembly upon changes in the environmental properties and are promising for the use in electronics,[15,17–19] as templates for the synthesis of nanoparticles[20,21] and as targeted drug delivery systems.[16,22–25]

Several reviews published in the last decade[4,13,26–29] are devoted to general aspects and development of studies in the field of molecular brushes, which consider their structures, characteristic properties and methods of synthesis. Other reviews[30–34] address the properties and self-assembly of molecular brushes in solution and in the bulk and also their applications in various fields. The present review gives a systematic account of the current knowledge of multicomponent amphiphilic molecular brushes and describes the broad range of brushes of this type of different architecture synthesized to date. The attention is focused on approaches to the controlled synthesis of each type of amphiphilic brushes, since the preparation of molecular brushes that combine chemically incompatible blocks is faced with additional difficulties.

The following designations and abbreviations are used:

AFM — atomic force microscopy,

AIBN — azobis(isobutyronitrile),

AGET ATRP — activators generated by electron transfer ATRP,

ARGET ATRP — activators regenerated by electron transfer ATRP

ATRP — atom transfer radical polymerization,

a.u. — arbitrary units,

BA — butyl acrylate,

9-BBN — 9-borabicyclo[3.3.1]nonane,

Boc — *tert*-butoxycarbonyl,

bpy — 2,2′-bipyridine,

CMC — critical micelle concentration,

CP — controlled polymerization,

CRP — controlled radical polymerization,

CuAAC — Cu^{I}-catalyzed azide – alkyne cycloaddition,

$Đ$ — polydispersity index [the ratio of weight-average M_w and number-average (M_n) molecular weights],

DBU — 1,8-diazabicyclo[5.4.0]undec-7-ene,

DCC — *N*,*N*′-dicyclohexylcarbodiimide,

DMAP — 4-dimethylaminopyridine,

DMAEMA — *N*,*N*-dimethylaminoethyl methacrylate,

DLS — dynamic light scattering,

dNbpy — 4,4′-dinonyl-2,2′-bipyridine,

DOX — doxorubicin,

EC — ethylcellulose,

GMA — glycidyl methacrylate

HEMA — 2-hydroxyethyl methacrylate,

HEMA-TMS — 2-(trimethylsilyloxy)ethyl methacrylate,

Ip — isoprene,

LALLS — low-angle laser light scattering,

LCST — lower critical solution temperature,

MALLS — multi-angle laser light scattering,

MA — methacryloyl,

MAA — methacrylic acid,

MALDI MS — matrix assisted laser desorption – ionization mass spectrometry,

Me6TREN — tris(2-dimethylaminoethyl)amine,

MMA — methyl methacrylate,

MPEGA — methoxypolyethylene glycol acrylate,

MW — molecular weight,

MWD — molecular weight distribution,

NMP — nitroxide mediated polymerization,

NP — nanoparticle,

Oct — octyl,

ODA — octadecyl acrylate,

ODMA — octadecyl methacrylate,

OEGMA — oligo[(ethylene glycol) methacrylate],

PAA — polyacrylic acid,

PAIEMA — poly[2-(2-azidoisobutyryloxy)ethyl methacrylate],

PBA — poly(n-butyl acrylate),

PBIEMA — poly[2-(2-bromoisobutyryloxy)ethyl methacrylate],

PCL — polycaprolactone;

PDMAA — poly(*N*,*N*-dimethylacrylamide),

PDMAEMA — poly[2-(*N*,*N*-dimethylamino)ethyl methacrylate],

PDMS — polydimethylsiloxane,

PEDEGA — poly(ethoxydiethylene glycol acrylate),

PEG — poly(ethylene glycol),

PEGMA — poly(ethylene glycol methacrylate),

PEO — poly(ethylene oxide),

PEOMA — poly(ethylene oxide methacrylate),

PGMA — poly(glycidyl methacrylate),

PHEMA — poly(2-hydroxyethyl methacrylate),

PIp — polyisoprene,

PL — poly(L-lactide),

PMAA — polymethacrylic acid,

PMAPA — poly[2-(methacryloyloxy)ethyl pentynoate],

PMDETA — *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine,

PMMA — poly(methyl methacrylate),

PMPEGMA — poly(methoxypolyethylene glycol methacrylate),

P(MEO_2MA-co-OEGMA) — poly{2-[2-(methoxyethoxy)ethyl methacrylate]-co-oligoethylene glycol methacrylate},

PNIPAM — poly(*N*-isopropylacrylamide),

PNMEP — poly({*N*-[2-(methacryloyloxy)ethyl]pyrrolidone},

POEGA — poly(oligoethylene glycol arylate),

POEGMA — poly(oligoethylene glycol methacrylate),

PPEGMA — poly[poly(ethylene glycol) methyl ether monomethacrylate],

PSt — polystyrene,

PtBA — poly(*tert*-butyl acrylate),

PTEA — 2-phenyl-2-(2,2,6,6-tetramethylpiperidine-1-oxyl)ethyl acrylate,

PTMSPA — poly[3-(trimethoxysilyl)propyl acrylate],

PVP — poly(*N*-vinylpyrrolidone),

Py — pyridine,

Pyr —pyrene,

RAFT — reversible addition – fragmentation chain transfer,

ROMP — ring opening metathesis polymerization,
ROP — ring opening polymerization,
SAXS — small angle X-ray scattering,
SEC — size exclusion liquid chromatography,
SEM — scanning electron microscopy,
SFRP — stable free radical polymerization.
$Sn(Oct)_2$ — tin octanoate,
St — styrene,
tBA — *tert*-butyl acrylate,
tBMA — *tert*-butyl methacrylate,
TEM — transmission electron microscopy,
TEMPO — 2,2,6,6-tetramethylpiperidine-1-oxyl,
TMS — trimethylsilyl.

2. Amphiphilic copolymers

Amphiphilic copolymers possess specific properties, most important of which is self-assembly in the bulk, in solution or on the surface. This ensures not only a prominent place for them in theoretical studies, but also a broad range of possible application areas such as materials science, biomedicine and environment protection, in particular, drug delivery, solubilization, catalysis, modification of coatings and synthesis of artificial nanoparticles (NPs). Studies of self-assembly of amphiphilic copolymers in solvents selective to these copolymers revealed numerous structures of different morphology, including spheres, cylinders, rods, vesicles, tubes, toroids, discs, *etc.*[35–37] Furthermore, polymer-based systems form thermodynamically more stable structures than low-molecular-weight surfactants. The critical micelle concentration (CMC) of polymer-based systems is normally 10^{-6}–10^{-7} mol litre^{-1}, whereas in the case of low-molecular-weight surfactants, this value is about 10^{-3}–10^{-4} mol litre^{-1} (Ref. 38). The supramolecular structures of amphiphilic copolymers are also kinetically more stable, because their dissociation to single macromolecules is retarded.[39]

Until recently, most studies in this area have addressed linear amphiphilic block copolymers. In recent years, studies of amphiphilic copolymers of more complex architectures have also been actively developed. Examples of these structures are polymer brushes, which represent assemblies of polymer chains attached to a surface or a linear macromolecule (molecular brushes).[40] Molecular brushes (called also bottle-brushes, molecular bottle-brushes and cylindrical polymer brushes) are graft copolymers with regularly grafted narrowly dispersed side chains.[13]

The active development of synthetic routes to molecular polymer brushes became possible owing to the latest achievements in the so-called controlled (living) polymerization (CP). If the length of the backbone is much greater than the length of side chains, then with a sufficiently dense grafting of side chains, the macromolecule has an elongated cylindrical shape because of the steric repulsion between the grafted side chains. Therefore, these polymer brushes are often called cylindrical.[13,40] If the backbone and side chain lengths are comparable or if the grafting density of side chains is moderate, the macromolecule can assume different conformations, in particular, spherical one.[13] The unique spatial structure of molecular brushes and the possibility of targeted control of their size (from tens to hundreds of nanometres) make them especially attractive as molecular building blocks for the fabrication of nanostructured materials. By controlling the backbone and side chain lengths, grafting density and the chemical nature and architecture of components, the properties of molecular brushes can be varied over a wider range than the properties of linear block copolymers. All these parameters are determined by the method and conditions of synthesis of molecular brushes.

3. Synthesis of molecular brushes

Most often, molecular brushes are synthesized *via* one of the three approaches (Fig. 1) called 'grafting through',[41,42] 'grafting onto'[43–45] and 'grafting from'.[46–48]

Within the framework of each approach, several polymerization methods can be used, *e.g.*, traditional (free radical) polymerization and controlled radical polymerization (CRP); anionic and cationic polymerization; ring opening polymerization (ROP) and ring opening metathesis polymerization (ROMP). Each approach and polymerization method has both certain advantages for molecular design and limitations regarding the synthesis. The choice and combination of these approaches and polymerization methods make it possible to vary parameters of the resulting molecular brushes, including the grafting density, chemical composition, size, morphology, uniformity and lengths and distribution of the backbone and side chains.

The 'grafting through' approach (see Fig. 1) comprises homo- or copolymerization of macromonomers. This approach may give molecular brushes with 100% grafting density of side chains, that is, brushes containing one covalently bonded side chain per repeating unit of the backbone. Within the framework of this method, it is

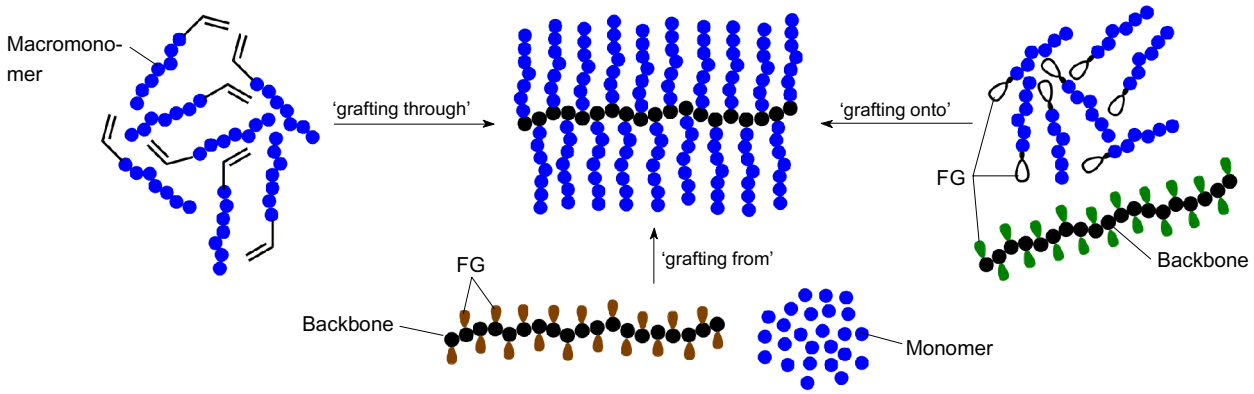


Figure 1. Approaches to the synthesis of molecular brushes. FG are functional groups.

possible to completely characterize the side chains before polymerization, as they are prepared in advance prior to the backbone formation stage. However, high viscosity of the reaction medium even at low conversions may prevent the synthesis of polymeric brushes with a high degree of polymerization of the backbone. This is especially pronounced when heavy and bulky macromonomers are used. An additional obstacle related to the use of the 'grafting through' approach is the need for a labour-consuming purification procedure such as fractionation or dialysis to remove the unreacted macromonomers. Nevertheless, this route towards molecular brushes has been used more and more often in recent years.

According to the 'grafting onto' approach to the synthesis of molecular brushes (see Fig. 1), the backbone with side functional groups and polymer precursors of side chains with terminal functional groups are obtained separately. Grafting of the side chains onto the backbone is performed *via* a polymer analogous coupling reaction involving the functional groups of the backbone and side chains. An advantage of this approach is that both the backbone and side chains are formed separately, *i.e.*, they can be synthesized by methods appropriate for the particular monomers. Thus, this method makes it possible to use a broad range of monomers and to specify the degree of polymerization and chemical nature of the molecular brushes thus formed. Grafting of pre-synthesized side chains onto the backbone allows full characterization of the components before the synthesis of a molecular brush.

The grafting density of the obtained molecular brushes is affected by a number of factors including the binding efficiency, the length and chemical structure of side chains and the ratio of side chain precursors to backbone functional groups. The grafting density of molecular brushes prepared in this way is most often moderate because of increasing steric hindrance caused by the already grafted side chains, which limit the diffusion of side chain precursors towards the active sites of the backbone.[40] The low grafting efficiency, in turn, leads to labour-consuming purification of the resulting brushes. The key requirements for the preparation of molecular brushes with high grafting density are the use of side chain precursors with highly reactive terminal groups and a large excess of side chains over the backbone functional groups. For example, high conversion was attained by using the high-performance Cu^{I}-catalyzed azide – alkyne cycloaddition (CuAAC) reaction (click reaction).[44, 49]

According to the 'grafting from' approach (see Fig. 1), the backbone with side functional groups (most often OH groups) is the first to be prepared.[6, 50, 51] After that, modification of functional groups is conducted in some cases. For example, esterification with 2-bromoisobutyroyl bromide introduces α-bromo-substituted ester groups in order to generate a specified number of initiating sites. The backbone may be represented by a polymer chain with appropriate functional groups, which can be subsequently modified into initiating sites. After preparation of the backbone, which is a multicentre macroinitiator, grafting of side chains from the initiating groups along the backbone is carried out, as a rule, by CP methods.

Unlike the two approaches described above, in this case side chains are 'grafted from' the backbone *via* successive addition steps of small monomer molecules to the active sites, which ensures the uniformity of molecular brushes and allows for the control over the composition and length of side chains during polymerization. In addition, it is possible to obtain molecular brushes with a high degree of polymerization. The brushes obtained by the 'grafting from' technique are formed as the only polymeric reaction product and can be easily purified using relatively simple methods such as reprecipitation. The disadvantages of this approach include more sophisticated control over the grafting density and analysis of side chains requiring their preliminary careful cleavage from the backbone.[52 – 54]

Since the discovery, the 'grafting from' method has proven to be most efficient for the synthesis of well-defined molecular brushes. A combination of the 'grafting from' strategy with living polymerization[26, 46, 55] provides a low current concentration of the growing radicals, which minimizes chain termination. This is a crucial factor for the synthesis of molecular brushes, as chain termination deactivates the initiating sites.

By living polymerization is meant a polymerization process deprived of irreversible chain termination and chain transfer steps.[56 – 59] The main features of living polymerization are the following: (i) the number of growing chains is maintained constant during the process, which leads to linear first-order kinetics; (ii) the number-average molecular weight (MW) of the polymer product depends linearly on the monomer conversion; (iii) the polymer product has a narrow molecular weight distribution (MWD); (iv) the isolated polymerization products are macroinitiators themselves; hence addition of a fresh portion of the monomer induces further polymerization and an increase in the molecular weight.[56, 59 – 63]

For a long time, the living regime of polymerization was achievable only in anionic polymerization reactions. Until recently, the use of living anionic polymerization in the syntheses of molecular brushes was mainly reduced to obtaining the brush backbone functionalized for the subsequent grafting of side chains. The backbone obtained in this way usually had a low polydispersity index ($Đ \leqslant 1.20$) typical of living anionic polymerization. The side chains were grafted *via* the 'grafting onto' or 'grafting from' strategy.

However, the extensive practical use of the living anionic polymerization, is hampered by the rather narrow range of appropriate monomers, the necessity of using reagents and solvents of a high degree of purity and drying and by low temperature. The need for the development of more convenient procedures for this type of polymerization brought about the discovery and upgrading of CRP technique,[64] which is applicable to a wide range of monomers, proceeds at more 'convenient' temperatures and is little sensitive to the presence of impurities, including water.

From the mechanistic standpoint, the CRP differs from the classical free radical polymerization by the presence of reversible deactivation step of the growing macroradicals, or reversible inhibition,[65, 66] that is, conversion of the macroradicals to dormant chains, which can be reactivated by a thermal, photochemical and/or chemical stimuli. Depending on the mechanism of conversion of chains from the reactive to dormant state, CRP processes are subdivided into three types,[67, 68] which are based on

— reversible dissociation – recombination processes involving stable radicals (stable free radical polymerization; SFRP), which are most often mediated by nitroxides (nitroxide mediated polymerization; NMP); in Russian publica-

tions, this group of methods is often called reversible inhibition;

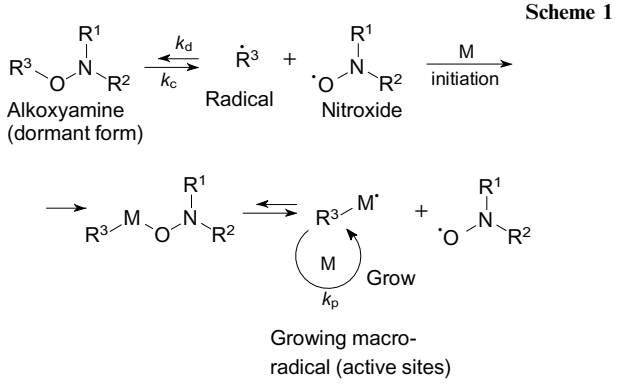
— reversible halogen atom transfer to a transition metal complex (atom transfer radical polymerization; ATRP).

— degenerate transfer (DT), or reversible addition fragmentation chain transfer (RAFT).

Hundreds of thousand publications are devoted to the CRP syntheses of a variety of copolymers. The use of these methods to obtain molecular brushes is covered in reviews.[26,28] A brief description of CRP methods is presented below.

The first implemented CRP process involved nitroxides such as TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl) or its analogues, which were used together with conventional radical initiators.[65,69–74] One of the most efficient procedures of NMP[71] is polymerization in the presence of unimolecular initiator systems, *e.g.*, alkoxyamines (Scheme 1).[65,73] Such systems were named 'iniferters', by the word derived from the names of radical polymerization steps: INItiation, transFER and TERmination. On heating, alkoxyamines are split into two radicals, one functioning as an initiator of polymerization, while the other one (nitroxide) reversibly inhibiting the growing macroradicals.

Scheme 1

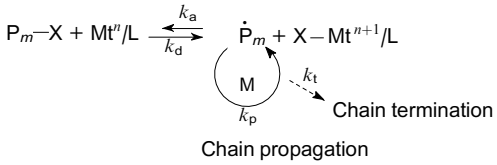


k_c is recombination rate constant, k_d is dissociation rate constant, k_p is propagation rate constant, M is monomer

The NMP method is quite tolerant to the presence of contaminants and the final polymers require no additional purification to remove the catalyst. Polymerization of this type can be used for controlled synthesis of linear block copolymers and is particularly suitable for polymerization of styrene (St) derivatives. Some nitroxides provide good controllability for polymerization of, at the best, acrylates, but control over the polymerization of methacrylates is quite problematic.[71] Currently, polymerization mediated by stable radicals is mainly used to graft polymer chains onto various surfaces, including nanoparticles, nanocrystals and nanofibres. This type of surface modification may improve the physicochemical properties (wettability, adhesion, catalytic or biological activity, *etc.*).[75–77] This CRP method is seldom used to obtain branched copolymers of complex architecture.

The method used most often for the macromolecular design of copolymers of different architecture is the ATRP method discovered by Matyjaszewski[78] and Sawamoto.[79] The ATRP mechanism is based on reversible transfer of a halogen atom to a transition metal complex containing a metal in a lower oxidation state (Scheme 2), where P_m-X is

Scheme 2



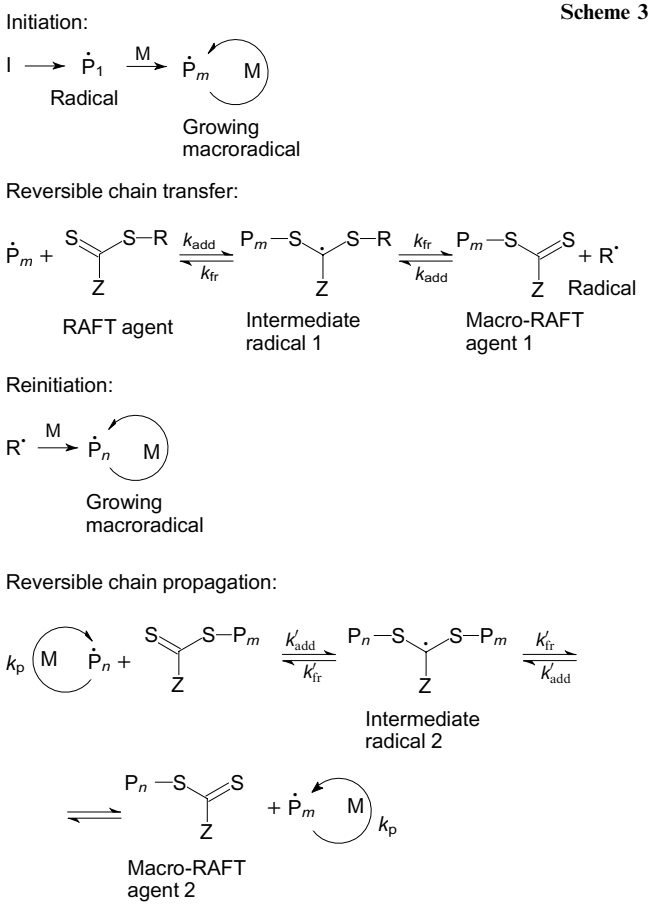
the polymerization initiator and a dormant polymer chain, X is a halogen atom (Cl or Br), Mt^n/L is a complex of a lower oxidation state transition metal halide with ligand L (activator), $X-Mt^{n+1}/L$ is a metal halide complex containing the same metal in a higher oxidation state (deactivator). Polymerization is initiated *via* a redox reaction of alkyl halide P_m-X with the complex Mt^n/L to give the initiating radical $P^{\bullet}$. The subsequent chain propagation includes reversible termination upon the reaction between the chain propagating radical and the complex $X-Mt^{n+1}/L$, which is accompanied by halogen atom X transfer from the complex to the macroradical.

The above described method is applicable to many sorts of monomers (except for unprotected acids). Many initiators are commercially available, including multifunctional and hybrid systems, and polymerization can be carried out over a broad temperature range. One more ATRP-related problem is the necessity to remove oxygen as fully as possible from the reaction medium and to purify the polymer product from transition metals. The strive towards overcoming these difficulties led to the development of a number of new ATRP procedures, according to which an air-stable higher oxidation state transition metal complex is added to the initial reaction mixture. In this case, the catalytic complex of a transition metal in a lower oxidation state needed for ATRP to proceed is formed *in situ* upon reduction of the deactivator. Copolymers of branched topology can be prepared using methods such as AGET ATRP (that is, activators generated by electron transfer ATRP) and ARGET ATRP (activators regenerated by electron transfer ATRP).[28]

In recent years, increasing attention has been attracted by the RAFT polymerization method in which control over polymerization is attained by adding reversible addition–fragmentation chain transfer (RAFT) agents, in particular, organosulfur compounds of the general formula RSC(=S)Z (R and Z are chemically different alkyl and aryl substituents).[68,80–82] The steady chain propagation is provided by fast chain transfer between reactive radical species as a result of fragmentation of stable radicals formed upon addition of growing macroradicals to the RAFT agent (Scheme 3).

The advantages of RAFT polymerization include the possibility to conduct the reaction over a wide temperature range using monomers of various types, including unprotected carboxylic acids.[81] Most of the known dithioesters are effective in the polymerization of styrene and acrylates; for methacrylic monomers, their number is markedly lower. The RAFT method is unsuitable for polymerization of monomers containing primary and secondary amines, which may induce decomposition of dithioesters under conditions of polymerization. Furthermore, the use of RAFT polymerization is limited by commercial unavailability of many RAFT agents and the necessity to remove the dithioester terminal groups from the final product, as

Scheme 3



I is initiator, M is monomer, k_{add} and k'_{add} are addition rate constants, k_{fr} and k'_{fr} are fragmentation rate constants, k_p is propagation rate constant

these groups can endow the polymer with undesirable colour and odour and also toxicity.

The brief description of CRP types should be supplemented by ring opening polymerization techniques, ROP and ROMP, which are also often used for macromolecular design of branched copolymers.

In the case of cyclic monomers (cyclic esters, lactams, lactones and cyclic siloxanes), ROP is an efficient method for introducing carbochain and heterochain blocks, *e.g.*, linear aliphatic polyether or polysiloxane blocks, into a copolymer.[83] A large number of catalytic systems for ROP have been reported in the literature. Tin [84] and aluminium [85] based compounds are the most active and best studied catalysts for the introduction of polyester blocks. Tin octanoate $Sn(Oct)_2$ is the most popular catalyst for ROP, since it is readily soluble in both the monomer and the polymer block and since high monomer conversions are rapidly reached with this catalyst.

The living polymerization criteria are also met for the ROMP method,[18, 86–89] which is gaining increasing popularity and is suitable for controlled synthesis of molecular brushes containing double bonds in the molecules.[18, 88, 89] Often, a multicentre macroinitiator (brush backbone) is prepared using ROMP; and then side chains are 'grafted from' the backbone using ROP [90, 91] or CRP by the NMP,[92] RAFT [93] or ATRP mechanism.[18, 50, 94–97] It was shown [18] that ROMP allows successful polymerization of monomers containing a bromoester group, which serves as the ATRP-initiating group in the next step. One more way of using ROMP consists in the initial synthesis of macromonomers with terminal norbornene groups, for example, by the RAFT polymerization process.[98–100] After that, molecular brushes are synthesized [101, 102] by the 'grafting through' approach using the ROMP process.

The above examples illustrate the active use of CP processes for the synthesis of multicomponent molecular brushes, often based on monomers that are polymerized by fundamentally different mechanisms. The implementation of these methods requires the addition of initiators that may initially contain several types of functional groups able to initiate each of the mentioned processes either simultaneously or successively;[103, 104] alternatively, a functional group initiating polymerization of the next monomer should be introduced at either the initiation or termination step during polymerization of the first monomer.[105] Examples of combining various polymerization methods will be given below in the Sections devoted to different types of multicomponent molecular brushes.

4. Identification of the structures of multicomponent copolymers

Development of the synthesis of multicomponent copolymers requires their comprehensive characterization, including the determination of chemical composition and architecture of chains and the MW and MWD of both the whole copolymer and separate blocks. With increasing complexity of structure and architecture of the copolymers, the accurate determination of their molecular characteristics becomes more and more important; otherwise, neither optimization of synthesis nor practical use of the copolymers are possible. The determination of the mentioned structural parameters can be used not only to prove the copolymer structure, but also to elucidate the influence of the molecular parameters of single blocks on the copolymer properties.

The structural and molecular parameters of copolymers are determined, most often, from the data of high performance liquid chromatography (HPLC) and spectral methods, generally, ^{1}H NMR spectroscopy. The latter is mainly used to confirm the chemical composition of the copolymer; however, the molecular weight (MW) can also be calculated using the quantitative data on the contents of terminal groups. However, the MW values found by this method are not very reliable, as determination of the type and number of terminal groups is often complicated by their low concentration in the sample. Furthermore, using the NMR method, it is impossible to unambiguously decide whether a product is an individual polymer or a mixture of a copolymer and a linear homopolymer. In this respect, liquid chromatography provides more information, including not only the MW, but also the MWD of the obtained polymers and also the presence or absence of homopolymer impurity.

Among HPLC techniques based on different separation mechanisms, most popular is size exclusion liquid chromatography (SEC) in which the macromolecules are separated according to their hydrodynamic volume. As compared with classical methods for studying the molecular characteristics of macromolecules, such as light scattering or osmotic and hydrodynamic methods, an indisputable advantage of SEC is the possibility of fast measurements.[106–108] Under

thoroughly selected conditions, conventional SEC measurements using only concentration detection give reliable quantitative data on the molecular characteristics of linear homopolymers provided that the system has been calibrated against polymer standards that have a hydrodynamic volume similar to that of the polymer to be analyzed and if their MW are also similar. However, in this way, it is impossible to correctly determine the molecular characteristics of copolymers with more complex composition and architecture, since the hydrodynamic volume is dictated by not only the molecular weight, but also copolymer chemical composition, chain rigidity and macromolecular architecture. Therefore, in recent years new advanced multiple detection methods have found increasing use.

For correct determination of the MW of copolymers with a complex architecture by means of SEC, a popular approach is the simultaneous use of a concentration (usually refractive index) detector and a detector sensitive to the MW value (MW detector).[109] The response of these relatively new detectors depends on not only the concentration, but also on the polymer molecular weight. Currently, two types of MW-sensitive detectors are mainly used, namely light-scattering (LSD) and viscosity (VD) detectors. The first type includes detectors that record the low-angle laser light scattering (LALLS)[107, 108] or multi-angle laser light scattering (MALLS),[110, 111] while the second type includes differential viscometers[112, 113] and single and dual capillary viscometers.[112, 114] Connection of one or two such detectors to a concentration detector provides information on not only molecular weight and MWD, but also on the architecture of the macromolecule. One more type of MW-sensitive detectors used in SEC are those utilizing Fourier transform NMR method and matrix assisted laser desorption – ionization mass spectrometry (MALDI MS).[115, 116] For example Toy *et al.*[117] used this method to analyze the products of RAFT polymerization of methyl acrylate. Ma *et al.*[118] determined the absolute M_n values for a series of molecular brushes with targeted variation of the grafting density of polystyrene (PSt) side chains by tetra-detection using a combination of refractive index, spectrophotometric and viscosity detectors with a two-angle light scattering detector.

In order to elucidate the structural parameters, including the grafting density, branched copolymers are disassembled into homopolymer components. For this purpose, grafted chains are cleaved from copolymers by selective hydrolysis,[74, 119, 120] and then molecular characteristics for the isolated linear homopolymers are determined. These results, in combination with the monomer conversion values found from gravimetric data, ^{1}H NMR spectra or gas chromatography are used to determine the grafting density. Meanwhile, examples of less labour-consuming well-posed determination of these parameters by the combined use of the results of fast methods (multiple detector SEC and ^{1}H NMR spectroscopy) have been reported.[118]

The absolute value of the number-average molecular weight (M_n) of molecular brushes can be determined by combining atomic force microscopy (AFM) and Langmuir – Blodgett (LB) methods.[121] This approach is based on the visualization of single macromolecules and can serve for quantitative analysis of dimensions (contour length of molecules, distances between molecules and monolayer thickness) and for estimation of the conformation of absorbed macromolecular brushes. The LB method provides the monolayer mass density, *i.e.*, the mass per unit area, while AFM visualization of single molecules makes it possible to calculate the molecular density, *i.e.*, the number of molecules per unit area. From the ratio of mass density to molecular density, it is possible to calculate M_n. Apart from calculation of M_n, combining AFM and LB methods can be used to characterize the MWD of the visualized molecules.[121] In view of the facts that side chains are evenly distributed along the backbone and the MW is proportional to the contour length of the molecules, the length distribution of macromolecules is actually equivalent to the MWD. It was shown that for macromolecular brushes, the molecular weight characteristics found by combining AFM and LB methods are in good agreement with the absolute values determined on the basis of MALLS data and static light scattering.[53, 121, 122]

Besides, AFM visualization of molecules can be used to estimate the contribution of termination reactions, which are inevitable at high monomer conversions, to polymerization.[123, 124]

5. Amphiphilic multicomponent molecular brushes

The amphiphilic multicomponent molecular brushes can be conventionally subdivided into several types depending on the chemical nature and distribution of side chains (Fig. 2).

The introduction of blocks possessing particular properties, such as hydrophilicity (hydrophobicity), thermal sensitivity, pH sensitivity, crystallizability and so on, into molecular brushes may endow the copolymer with these properties depending on copolymer structural parameters, and thus provide the possibility to control these properties by varying structural parameters. The use of different-type blocks may impart new interesting properties to molecular brushes. Examples of preparation of these types of multicomponent molecular brushes illustrating the

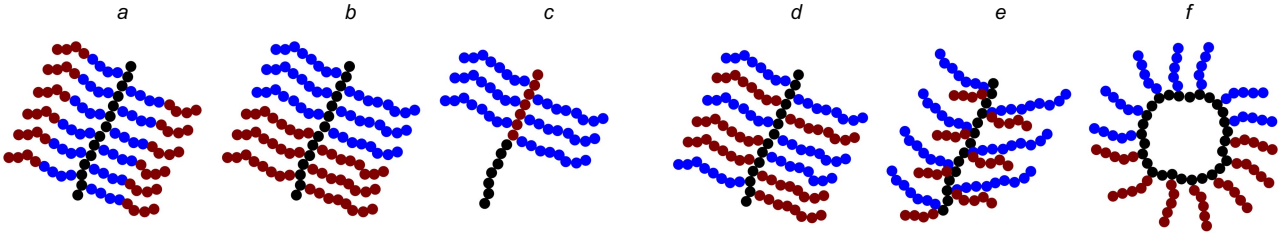
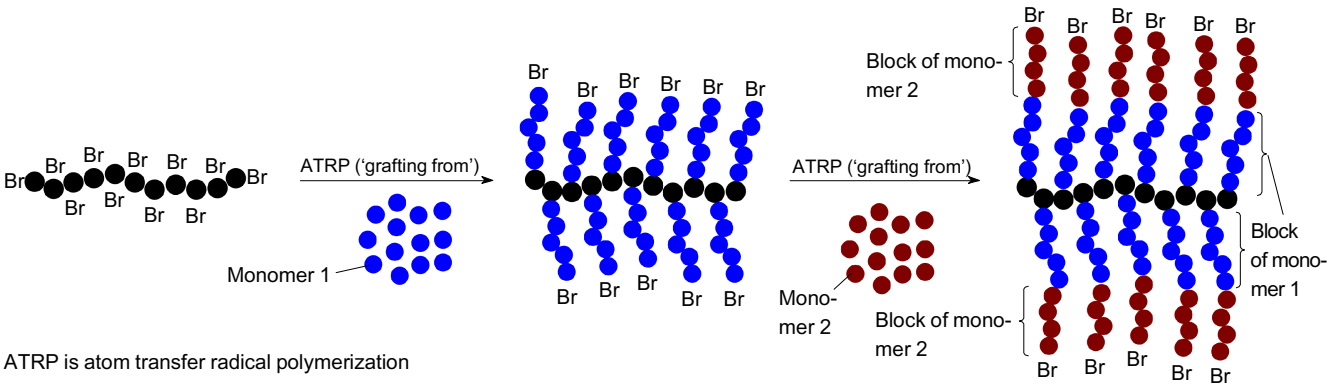


Figure 2. Molecular brushes with block copolymer side chains (*a*), AB, ABA or ABC type block copolymer brushes (*b*), tadpole type block graft (*c*), heterograft (*d*), asymmetric (*e*) and cyclic (*f*) brushes.

Scheme 4



ATRP is atom transfer radical polymerization

modern synthetic strategies and their possible combinations are presented below.

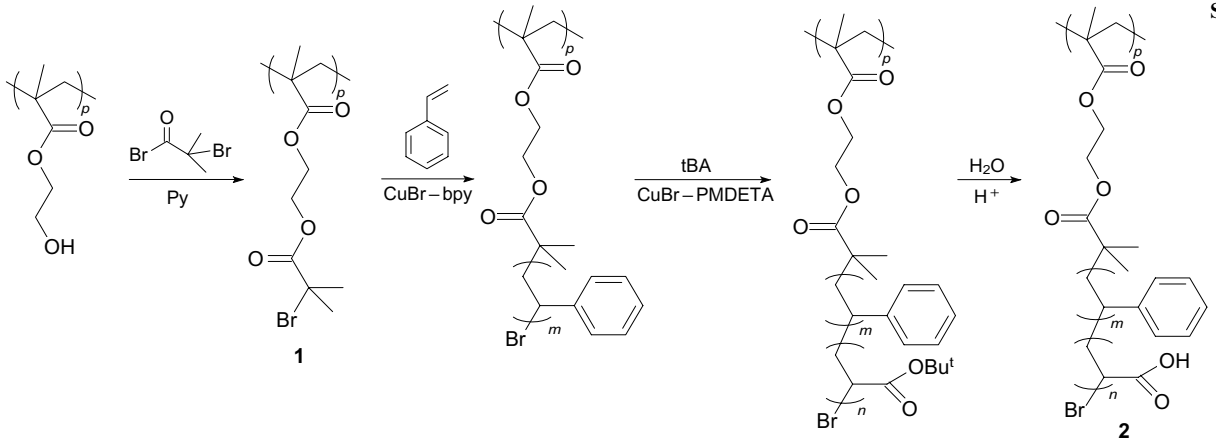
5.1. Molecular brushes with block copolymer side chains

In recent years, increasing attention has been attracted by copolymer systems in which the side chains grafted to the backbone consist of di- or triblock copolymers. The unique nano-sized molecular structure of these multicomponent molecular brushes makes them applicable for the design of promising nanomaterials. In the case of diblock copolymer side chains, the brushes are usually called core – shell brushes, while those with triblock chains are called core – shell – corona brushes. Two major methods for the preparation of molecular brushes with block copolymer side chains are described in the literature: (i) copolymerization of diblock macromonomers ('grafting through' approach)[125–127] (ii) successive polymerization of two different monomers with multifunctional macroinitiators ('grafting from' approach).[48, 55, 92, 93, 128, 129] The 'grafting from' approach is preferable for the synthesis of this type of brushes, since this makes it possible to control the degree of polymerization and the composition of side chains. According to this approach, first, brushes with homopolymer side chains, containing living functional groups that are able to initiate polymerization, are prepared by CRP methods. These homopolymer brushes are used as branched multicentre macroinitiators for the introduction of various additional blocks into the side chains (Scheme 4).

This approach was first described independently by Matyjaszewski and co-workers[47] and Müller and co-workers[55] In the former study,[47] molecular brushes with diblock copolymers containing PSt and poly(n-butyl acrylate) (PBA) blocks as side chains were obtained by ATRP. The synthesis of these brushes consisted of the initial preparation of graft copolymer with PSt or PBA side chains on poly[2-(2-bromopropionyloxy)ethyl methacrylate] as the a multicentre macroinitiator. The brushes with block copolymer side chains were prepared by polymerization (chain extension) of butyl acrylate (BA) or St, respectively, in which the copolymer synthesized in the first stage served as a branched multicentre macroinitiator. Müller and co-workers[55] used a virtually identical method (Scheme 5): by anionic polymerization, they prepared a well-defined multicentre macroinitiator, poly[2-(2-bromoisobutyryloxy)ethyl methacrylate] (PBIEMA, **1**), and then grafted block copolymer side chains by two-stage ATRP of *tert*-butyl acrylate (tBA) (or St) and St (or tBA). Hydrolysis of the PtBA block to hydrophilic polyacrylic acid (PAA) gave molecular brushes PBIEMA-graft-(PSt-block-PAA) **2** with amphiphilic block copolymer side chains.

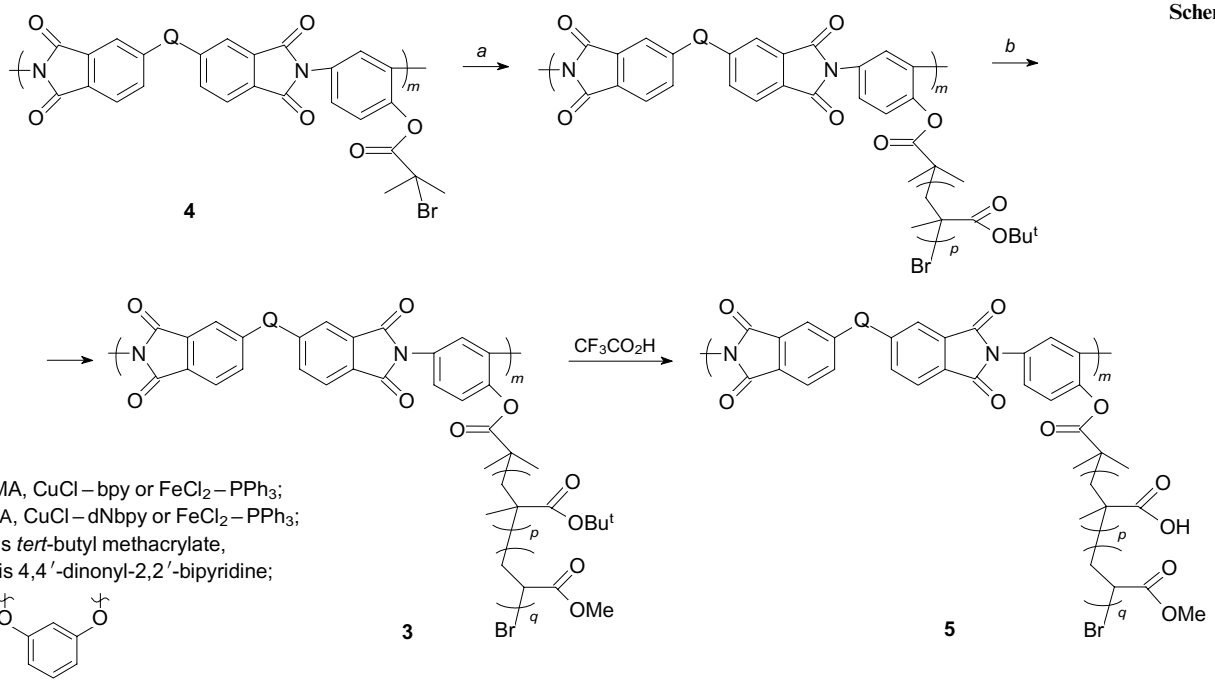
Subsequently many research groups employed a similar approach to prepare molecular brushes with a variety of block copolymer side chains. Meleshko *et al.*[130] used various ATRP procedures to synthesize multicomponent brushes with the hydrophobic polyheteroarylene polyimide (PI) backbone and amphiphilic diblock copolymer side chains with the polymethacrylic acid-block-poly(methyl

Scheme 5



PMDETA is *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine, bpy is 2,2′-bipyridine, tBA is *tert*-butyl acrylate

Scheme 6

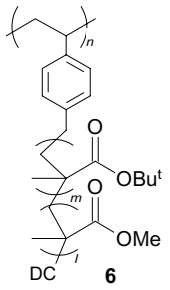


(*a*) TBMA, CuCl – bpy or $FeCl_2 - PPh_3$;
(*b*) MMA, CuCl – dNbpy or $FeCl_2 - PPh_3$;
TBMA is *tert*-butyl methacrylate,
dNbpy is 4,4′-dinonyl-2,2′-bipyridine;

Q =

methacrylate) (PMAA-block-PMMA) structure **3** (Scheme 6). They were prepared by successive polymerization of *tert*-butyl methacrylate (tBMA) and methyl methacrylate (MMA) on a PI-multicentre initiator **4** and graft copolyimide PI-graft-PTBMA **5**, respectively, followed by acid hydrolysis of tBMA units in side chains. Conditions of synthesis suitable for targeted control of the length, polydispersity and grafting density of PMAA and PMMA blocks in the side chains of multicomponent brushes were established. According to the results of dynamic light scattering (DLS) and transmission electron microscopy (TEM), molecular brushes of this type containing highly chemically different components in the molecules form micelle-like nanostructures of virtually equal sizes in ethanol solution.

Structure 6



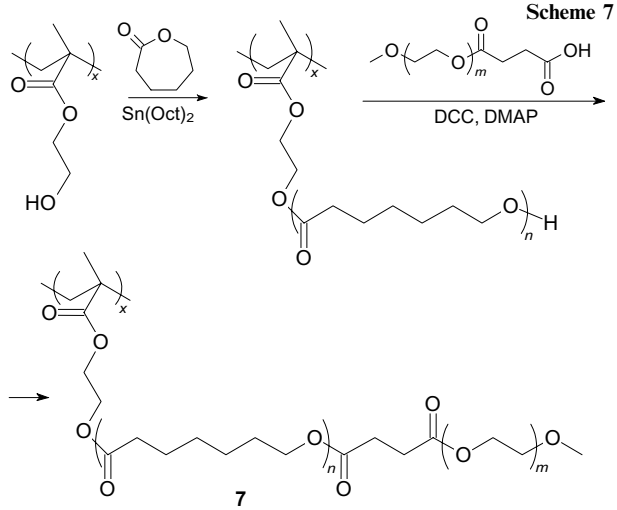
DC is diethyldithiocarbamate

6

Ishizu and Kakinuma [131] synthesized molecular brushes PSt-graft-(PtBMA-block-PMMA) **6** using successive photoinitiated ATRP of tBA and MMA monomers with poly(vinylbenzyl-*N*,*N*-diethyldithiocarbamate) as the initiator.

Along with ATRP, other CP processes are also used to prepare molecular brushes with block copolymer side chains. For example, a combination of ATRP, ROP and coupling reactions was utilized for the synthesis of brushes **7** with a poly(2-hydroxyethyl methacrylate) (PHEMA) backbone and polycaprolactone-block-polyethylene oxide (PCL-block-PEO) side chains (Scheme 7).[132] In aqueous solutions, brushes **7** were found to form micelles and to have a twice lower CMC than the linear PCL-block-PEO diblock copolymers with the structure similar to that of the grafted side chains of the brushes. This attests to higher stability of molecular brush-based micelles.

Scheme 7



7

DCC is *N*,*N*′-dicyclohexylcarbodiimide,
DMAP is 4-dimethylaminopyridine

Apart from numerous molecular brushes with diblock copolymer side chains, core – shell – corona type brushes with triblock copolymer side chains were prepared. For this purpose, different monomers were successively polymerized. For example, the backbone was obtained by anionic polymerization, while the block copolymer side

chains were fabricated by ATRP or ROP.[20, 132 – 134] Müller *et al.*[133] synthesized brushes with triblock copolymer side chains in the following order: PtBA (core), poly[3-(trimethoxysilyl)propyl acrylate] (PTMSPA) (shell) and poly(oligoethylene glycol methacrylate) (POEGMA) (corona) by ATRP of appropriate monomers.

A combination of CRP and ROMP methods for the preparation of molecular brushes with multiblock copolymer side chains has been reported. Wooley and co-workers[92] utilized a combination of NMP and ROMP. By ROMP carried out in the presence of Grubbs catalyst, inimer **8**, containing alkoxyamine (NMP initiator) and norbornene (ROMP monomer) functional groups in the molecule, initiator **9** with NMP-initiating groups was prepared. Molecular brushes **10** with amphiphilic side chains were obtained using the 'grafting from' approach *via* nitroxide-mediated polymerization of isoprene (Ip) and tBA followed by hydrolysis of the PtBA block (Scheme 8).

A different approach to combination of ROMP and CRP as a RAFT version has been reported.[135] First, a linear triblock macromonomer **11** terminated with a norbornene group was synthesized by RAFT polymerization. Then brush **12** with triblock side chains was synthesized using 'grafting through' strategy by ROMP (Scheme 9).

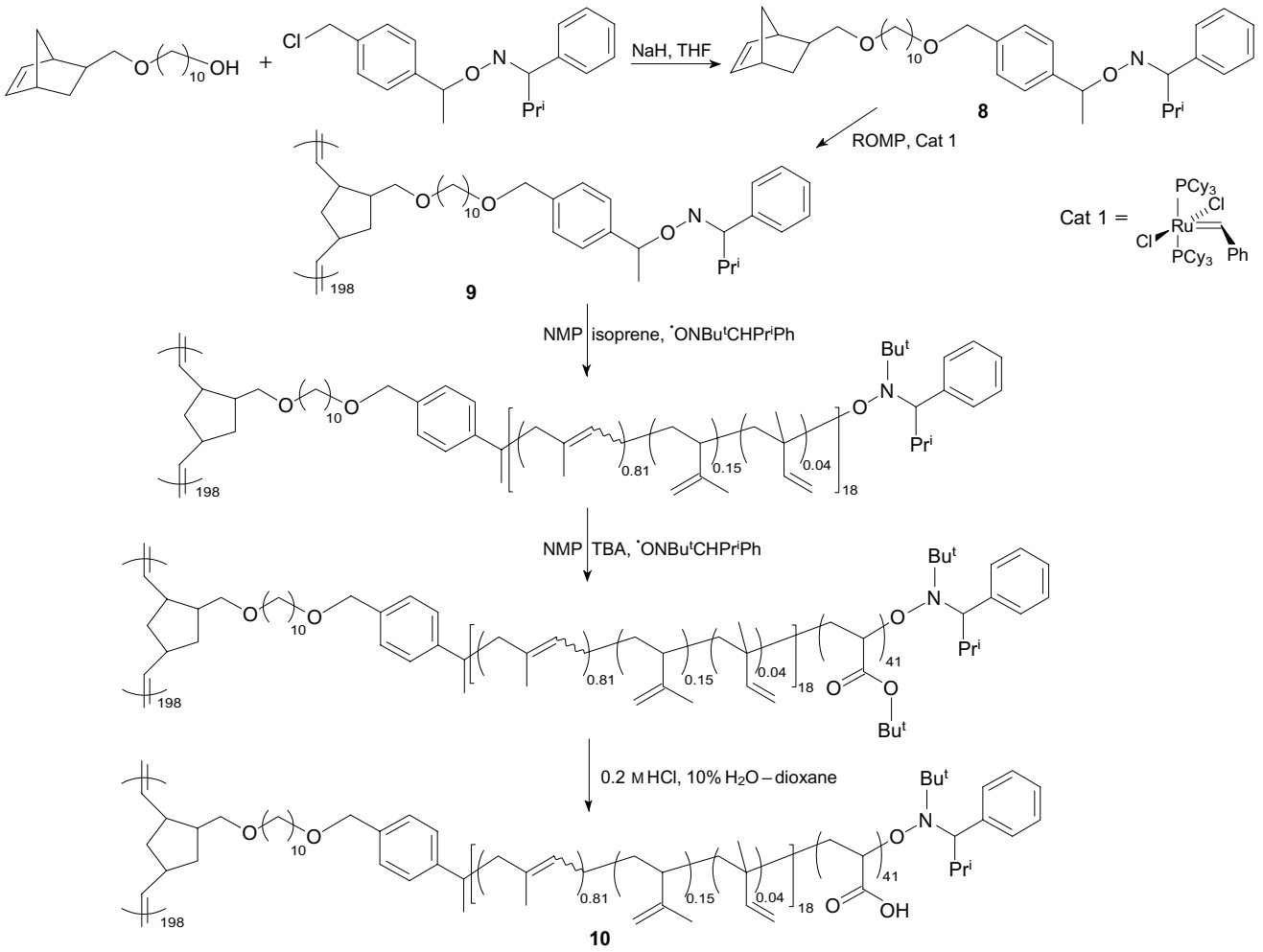
5.2. AB, ABA and ABC type block copolymer molecular brushes

Amphiphilic block copolymer molecular brushes consist of two or more densely grafted brushes with hydrophilic or hydrophobic side chains covalently attached to each other. Brushes of this type are prepared, most often, using a combination of 'grafting through' and 'grafting from' approaches. The synthesis includes the preparation of block copolymer backbone ('grafting through') bearing functional groups and the subsequent 'grafting-from' of side chains. This is done *via* various CP techniques such as ROMP, ATRP and RAFT.[13, 136 – 139] For example, Ishizu *et al.*[140] used this approach for the synthesis of amphiphilic block copolymer molecular brushes **13** with PEO and PHEMA side chains in each block (Scheme 10).

A similar procedure combining ATRP (AGET ATRP version) and ROP was used to obtain block type molecular brushes — poly(L-lactide)-block-poly(methoxypolyethylene glycol methacrylate) (PL-block-PMPEGMA) **14** with a controlled molecular weight and narrow MWD (Scheme 11).[141]

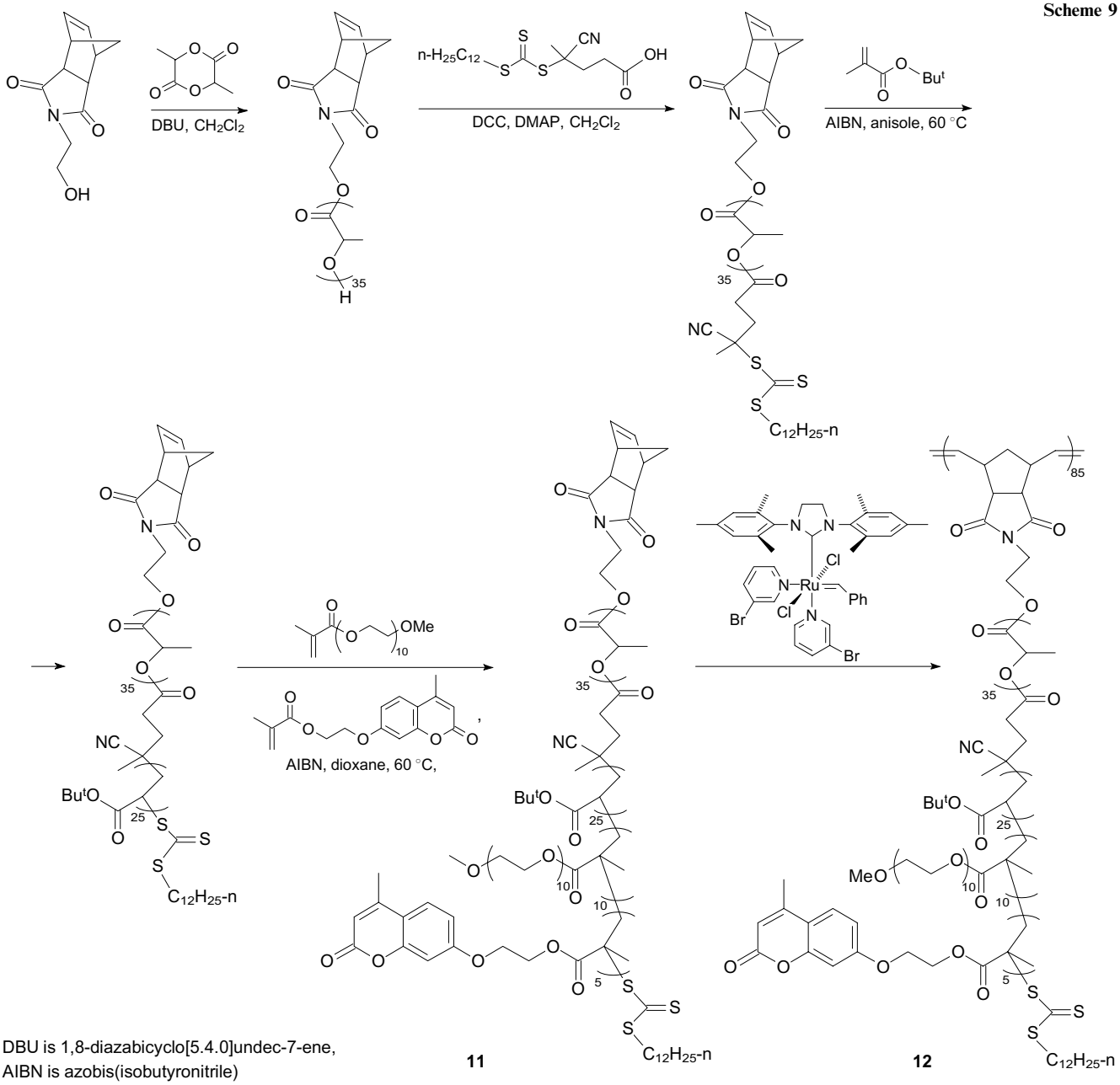
The possibility of combining 'grafting through' and 'grafting from' approaches for the synthesis of molecular brushes was extended by Zehm *et al.*,[142] who synthesized

Scheme 8



ROMP is ring opening metathesis polymerization, NMP is nitroxide mediated polymerization, Cy is cyclohexyl

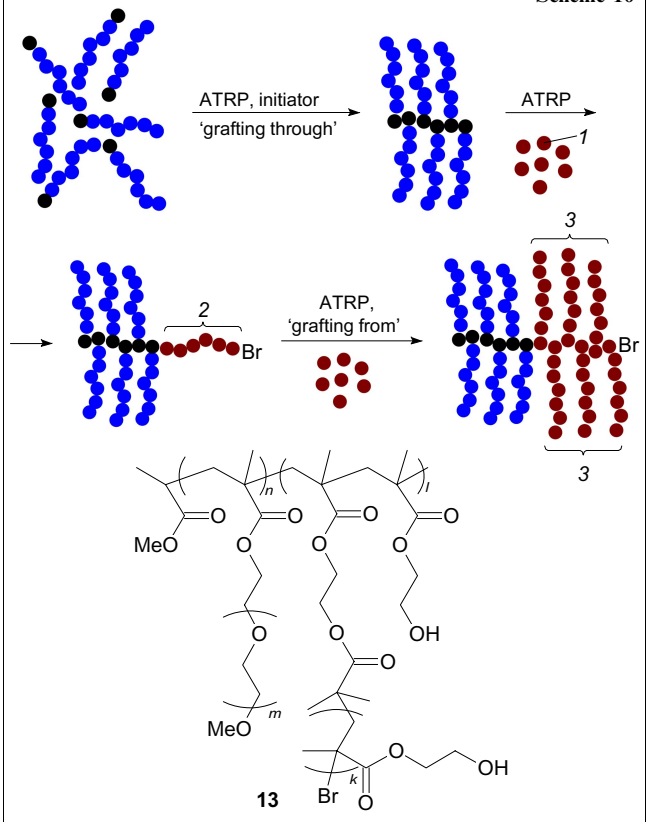
Scheme 9



amphiphilic diblock copolymer brushes and symmetric triblock copolymer brushes by RAFT polymerization and NMP. The hydrophilic block contained PEO side chains, while the hydrophobic block had PSt side chains. According to this method, inimer **15** — 2-phenyl-2-(2,2,6,6-tetramethylpiperidine-1-oxyl)ethyl acrylate (PTEA) — was prepared by the RAFT polymerization. Depending on the RAFT agent used (monofunctional or bifunctional trithiocarbonate), RAFT copolymerization of the hydrophilic macromonomer, methoxy(polyethylene glycol acrylate) (MPEGA, **16**), and inimer **15** gave amphiphilic diblock or triblock copolymers. The subsequent preparation of diblock and triblock copolymer brushes **17** by NMP ('grafting from') was accomplished *via* polymerization of styrene from the alkoxyamine moieties of the PTEA backbone. The synthetic procedure was simplified by using inimer **15**, which eliminated the necessity of further modification of the backbone for introducing initiater groups for NMP (Scheme 12).

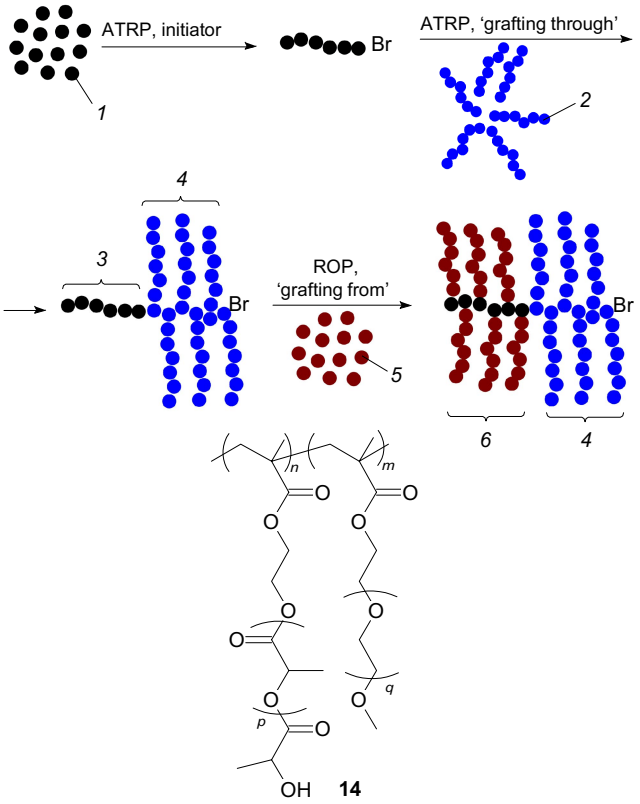
Zhao and co-workers [143] reported a new efficient one-step synthetic route to diblock copolymer brushes bearing PSt and PEO side chains, (PBIEMA-graft-PSt)-block-(PAIEMA-graft-PEO) **18**, with well-defined structure. The method includes the initial synthesis of linear diblock precursor **19** — poly(2-bromoisobutyryloxyethyl methacrylate)-block-poly[2-(2-azidoisobutyryloxy)ethyl methacrylate] (PBIEMA-block-PAIEMA) — in which one block contains terminal 2-bromoisobutyrate initiating groups and the other one contains terminal azide groups. Owing to this structure of the diblock initiator, the authors were able to simultaneously carry out grafting of PSt side chains to the PBIEMA block *via* the ATRP procedure and attachment of polyethylene glycol methyl ether with terminal alkynyl groups to the PAIEMA block by a one-pot click reaction, which considerably simpli-

Scheme 10



(*1*) Monomer, (*2*) chain of the monomer, (*3*) blocks of the monomer

Scheme 11



(*1*) Monomer 1, (*2*) macromonomer, (*3*) monomer 1 chain, (*4*) macromonomer blocks, (*5*) monomer 2, (*6*) monomer 2 blocks

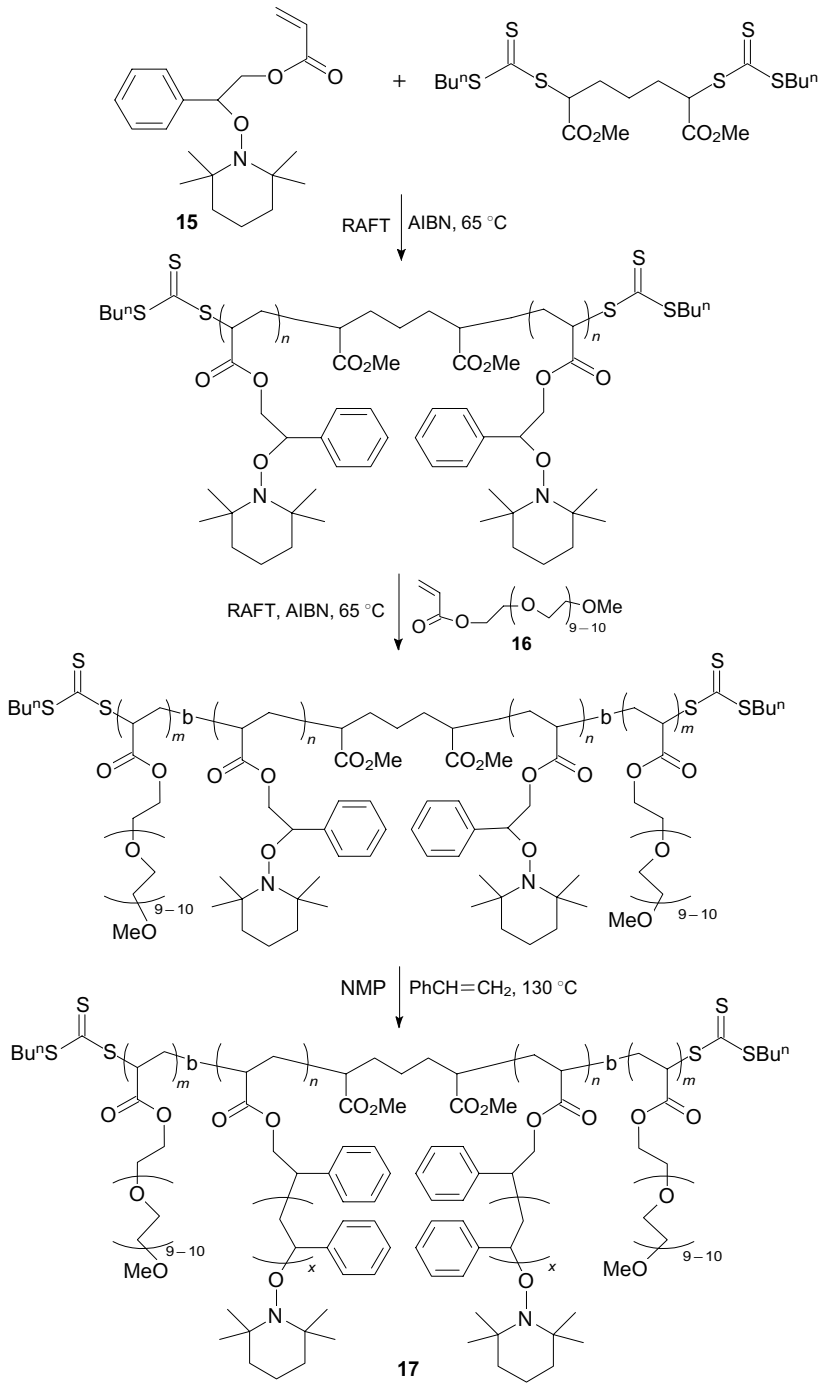
fied the procedure of preparation of these brushes (Scheme 13).

The chemical structure of compounds **18** and **19** was confirmed by NMR spectroscopy. According to ^{1}H NMR data, the degree of conversion for the azide alkyl addition was about 70% and the average degree of polymerization of PSt chains was about 60. The ^{1}H NMR data were also used to calculate the molecular weight of diblock copolymer brush **18**. The resulting values were compared with the MW values found by SEC (refractive index detector). Although according to SEC data, all brush samples had a low polydispersity index ($Đ$ = 1.13 – 1.19), the MW values determined from spectral data were much higher than those obtained by SEC using polystyrene standards. The authors explained this result by more compact conformation of the brushes and, hence, a smaller hydrodynamic radius compared to the linear standard.

A conceptually similar one-step approach was used by Wang *et al.*,[144] who prepared AB (**20**) and ABA (**21**) type amphiphilic block copolymer molecular brushes with PL and poly(*N*-vinylpyrrolidone) (PVP) side chains using the 'grafting from' strategy by successive ROP and RAFT polymerization without isolation and purification of the intermediate compound (Scheme 14). The reaction was initiated by block copolymers containing dithiocarbamate and hydroxyl initiating groups. Poly[2-(2-bromopropanoyl)oxyethyl methacrylate] was chosen as the first block for the introduction of chain transfer agents, while polyhydroxypropyl methacrylate served as the second block for the introduction of ROP-initiating hydroxyl groups. For the preparation of these copolymer brushes, grafting of PCL side chains was carried out in the first stage, while in the second stage, RAFT polymerization was performed without purification of the intermediate product. A series of block copolymer brushes **20** and **21** with different ratios between the blocks was prepared. The chemical composition and MW of the products were determined by ^{1}H NMR spectroscopy and SEC (refractive index detector). Although in SEC analysis of the products of each stage, the authors thoroughly selected the eluent, elution conditions and calibration standards, the obtained MW values did not seem to be reliable, as evidenced by the pronounced difference between these values and the MW values calculated from conversions derived from ^{1}H NMR data. According to SEC data, polymerization products were contaminated by linear homopolymers, which was attributed to possible chain transfer to the monomers. Atomic force microscopy visualization of single molecules demonstrated that, depending on structural parameters, the macromolecules of the resulting block copolymer brushes had a 'dumbbell', 'brush-coil' or 'Janus rod' morphology.

Recently, a similar technique including successive grafting of different-type side chains was used [145] to synthesize AB diblock copolymer molecular brushes **22** with PSt and PL side chains of different length. First, polyfunctional macroinitiator **23** (backbone) — poly[2-(2-bromoisobutyryloxy)ethyl methacrylate]-block-poly[2-(trimethylsilyloxy)-ethyl methacrylate] {PBIEMA-block- [P(HEMA-TMS)]} — was obtained by successive RAFT polymerization of the corresponding monomers. After removal of the trimethyl-

Scheme 12



silyl (TMS) protection in compound **23**, the 'grafting from' approach was applied for successive polymerization of L-lactide (ROP) and St (ATRP) with variation of the length of PSt side chains (Scheme 15).

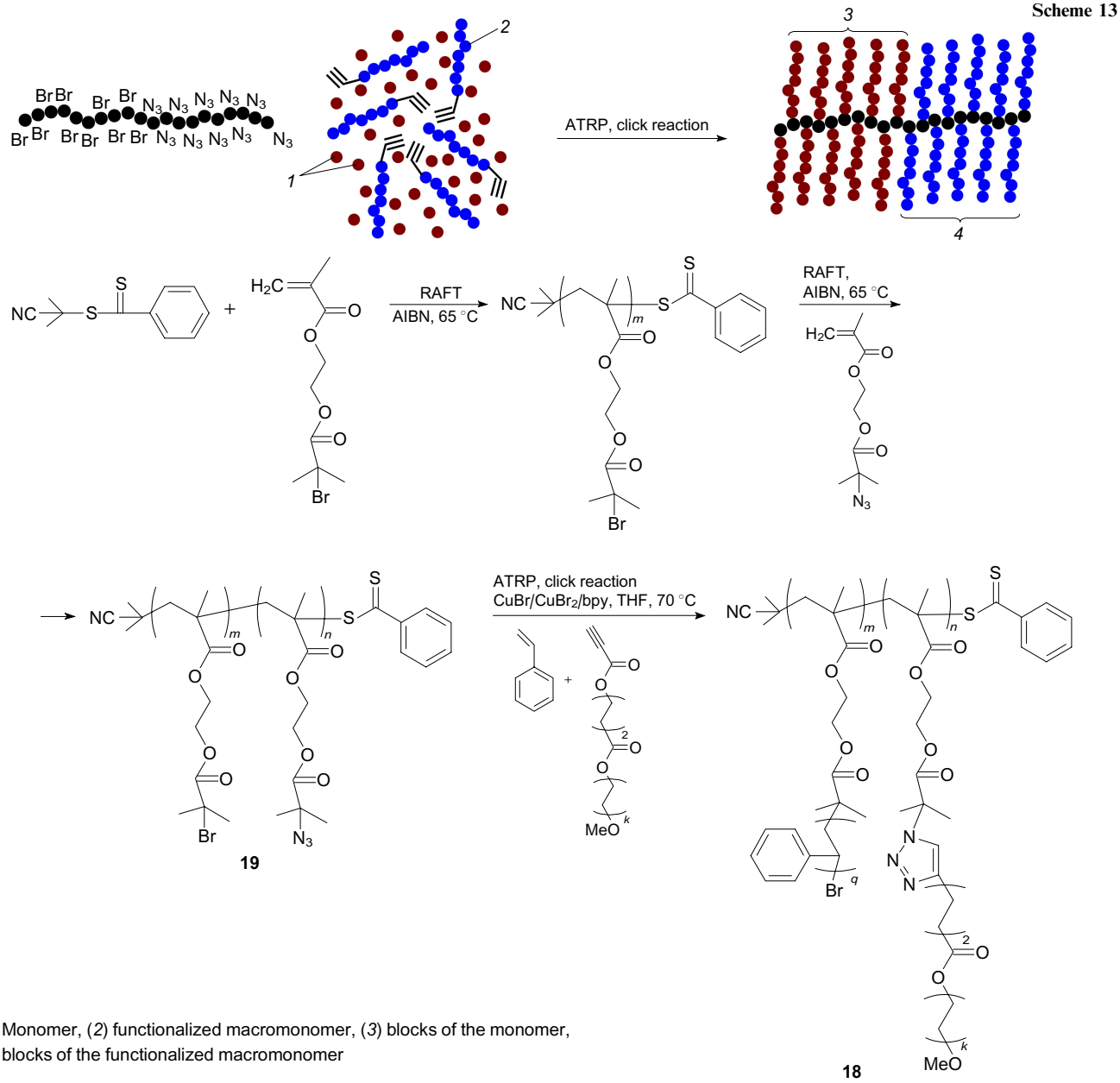
Lately, ROMP has been actively used to synthesize multicomponent brushes. For example, 'grafting through' polymerization of norbornene-terminated macromonomers has been proposed [100] for the synthesis of amphiphilic ABC triblock copolymer brushes **24** and **25** with cyclopentane moieties in the backbone. The initial macromonomers were prepared by ROP and RAFT methods using norbornene alcohol to initiate polymerization of D,L-lactide and norbornene-terminated dithioesters as RAFT agents, respectively. According to SEC data, both macromonomers and block copolymer brushes had a narrow unimodal MWD. The polydispersity indices $Đ$ were 1.06 – 1.16 for the former and 1.16 – 1.26 for the latter.

A study of self-assembly processes for brushes **24** and **25** demonstrated that, depending on the ratio of hydrophilic to hydrophobic brush blocks in the copolymer, they form, in aqueous media, micellar nanostructures or vesicles with an average diameter of approximately 30 nm or 270 nm, respectively.

5.3. Tadpole-shaped block – graft molecular brushes

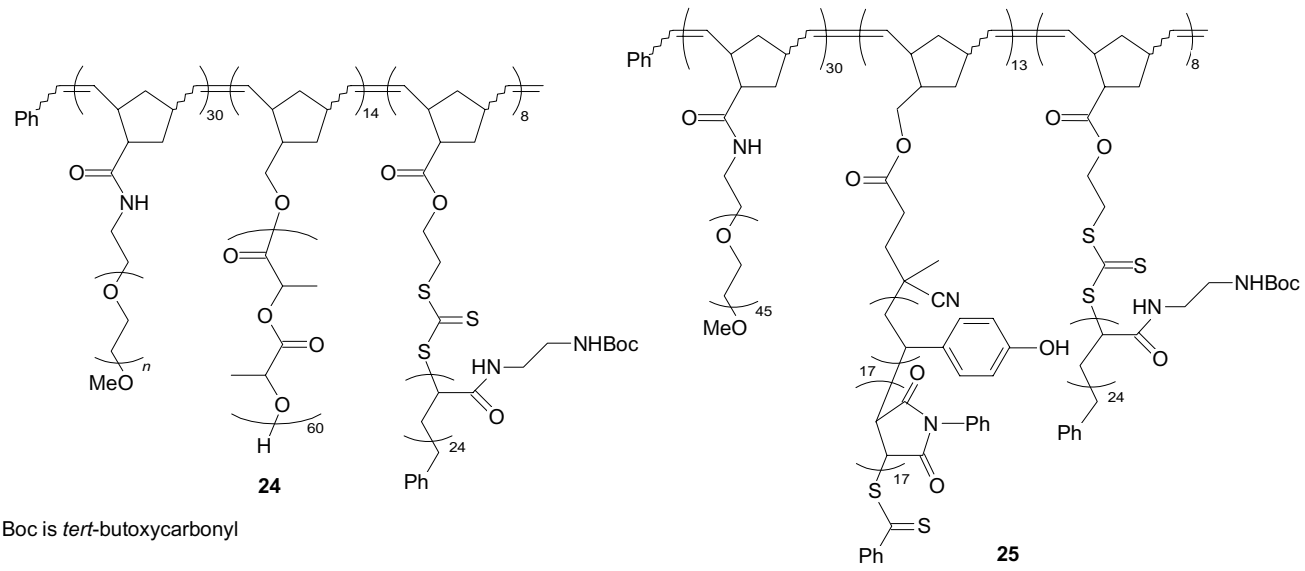
Using linear polymers as mono- and bifunctional macroinitiators for polymerization, it is possible to obtain block – graft copolymers described as A-block-(B-graft-C)

Scheme 13



(*1*) Monomer, (*2*) functionalized macromonomer, (*3*) blocks of the monomer, (*4*) blocks of the functionalized macromonomer

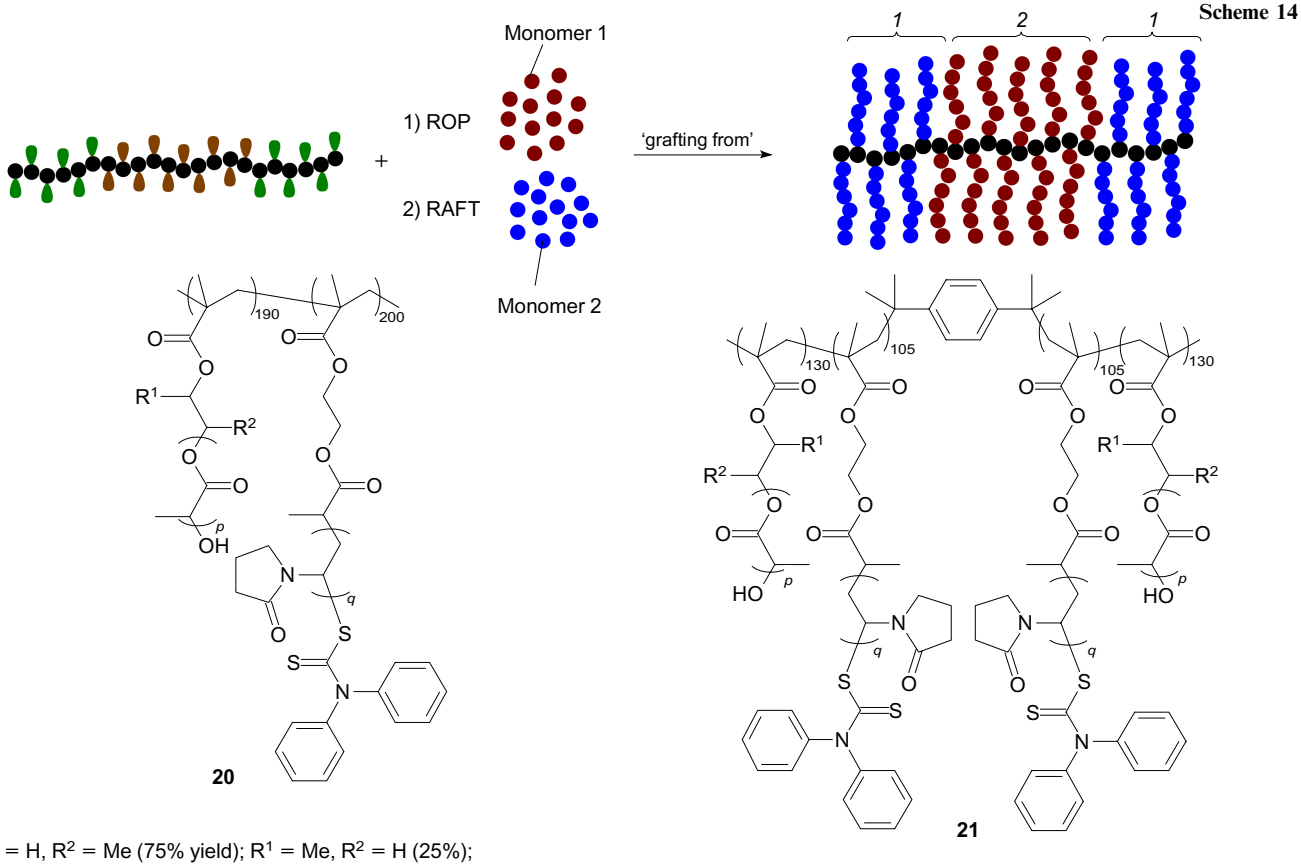
Structures 24, 25



24 **25**

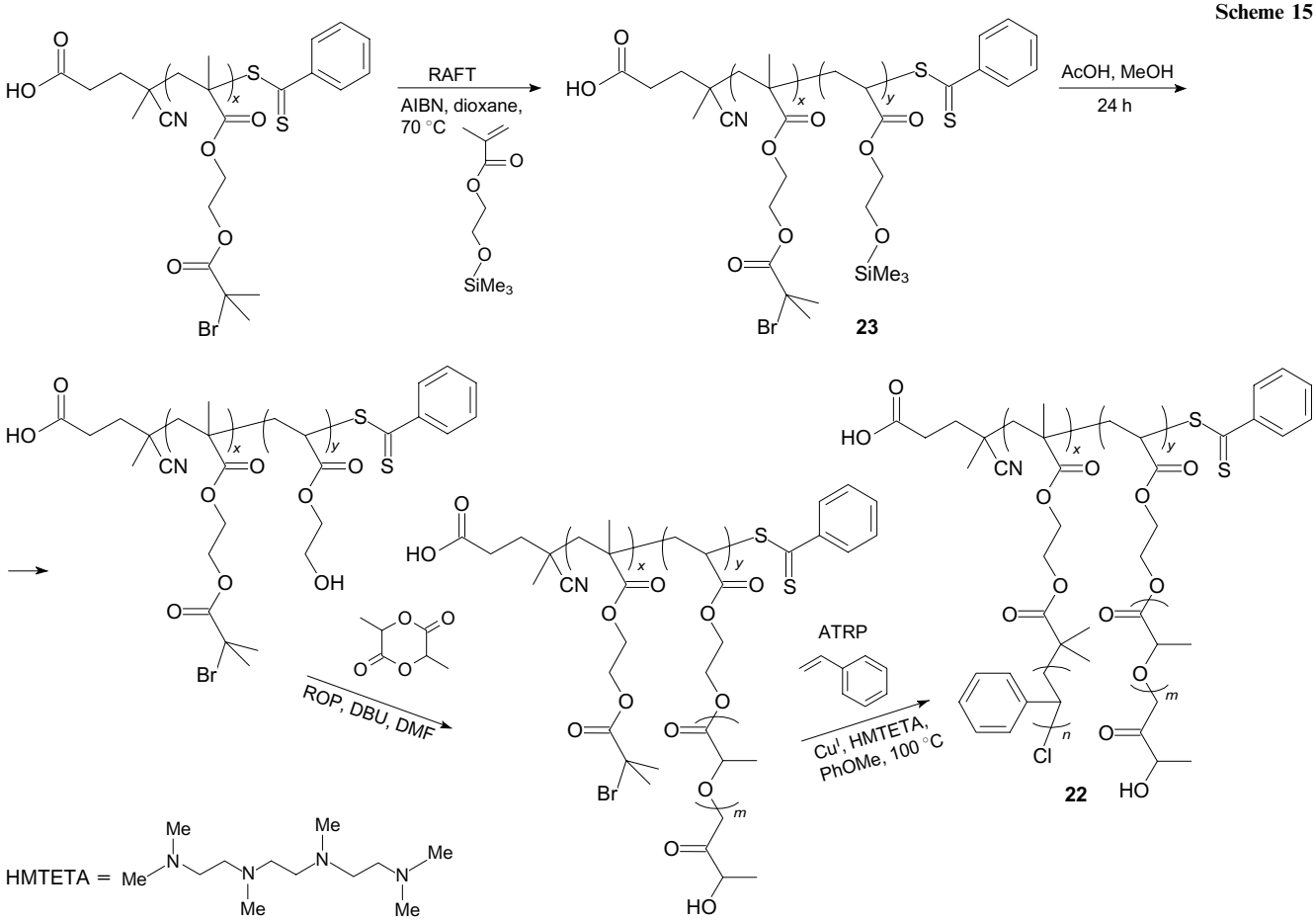
Boc is *tert*-butoxycarbonyl

Scheme 14



R^1 = H, R^2 = Me (75% yield); R^1 = Me, R^2 = H (25%);
ROP is ring opening polymerization; (*1*) monomer 2 blocks, (*2*) monomer 1 blocks

Scheme 15

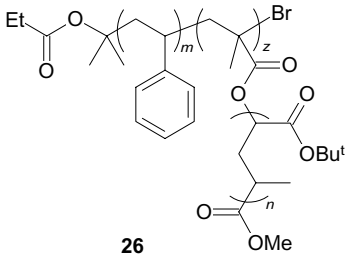


and (B-graft-C)-block-A-block-(B-graft-C) with mixed linear-and-brush topology. Examples of such copolymers are tadpod-shaped amphiphilic brushes, that is, block copolymers consisting of a molecular brush block with hydrophilic side chains and a helical hydrophobic block.

Using the 'grafting through' approach, Matyjaszewski and co-workers[146] prepared amphiphilic block-graft brushes, in which a macromolecular brush with PAA side chains was covalently attached to a linear PSt block. For this purpose, the hydrophilic methacryloyl-terminated PtBA macromonomer and the monofunctional PSt macroinitiator (M_n = 18 000 g mol^{-1}, $Đ$ = 1.09) as the first linear block were separately prepared by ATRP. Then a brush block with PtBA side chains was attached to the latter by ATRP of macromonomers. Hydrolysis of PtBA units gave amphiphilic block-graft brush **26** with PAA side chains. The chemical structure of the products of each stage was identified and the degree of hydrolysis was determined using ^{1}H NMR spectroscopy. In addition, the final polymers were also characterized by SEC with refractive index detection; however, the absolute molecular weights of copolymers were determined using multiple detection SEC with a combination of refractive index and viscosity detectors and a MALLS light scattering detector. According to the obtained results, the weight-average MW (M_w) of the copolymer decreased after hydrolysis from 99 000 to 68 000 g mol^{-1}. The latter value is close to the theoretically expected molecular weight M_w = 66 000 g mol^{-1}, which attests to complete hydrolysis.

Neoh and co-workers[147] used a similar two-stage approach to synthesize two well-defined amphiphilic block-graft brushes with linear PSt or poly(glycidyl methacrylate) (PGMA) blocks and molecular brushes with

Structure 26

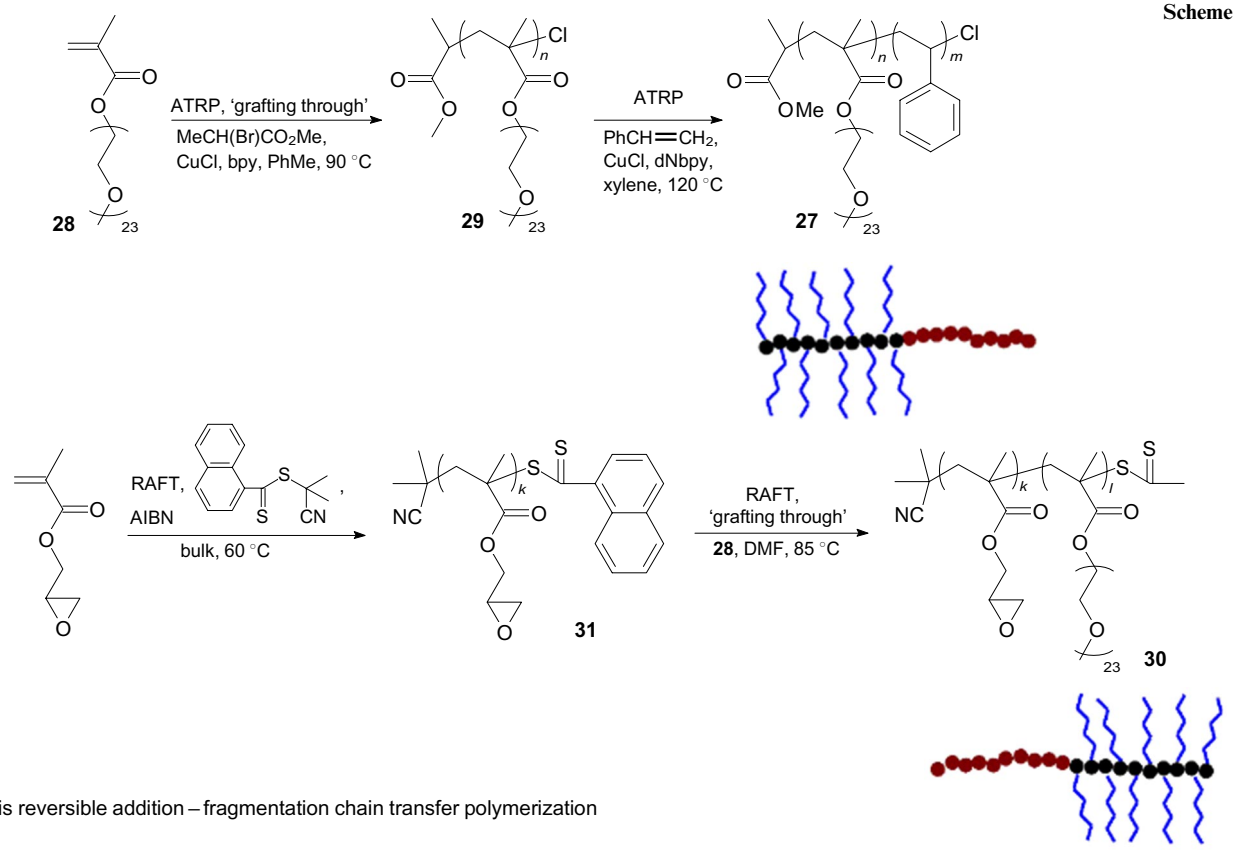


26

PGMA or PEO side chains, respectively, attached to them (Scheme 16). In order to prepare the first copolymer **27** using the 'grafting from' approach by ATRP of macromonomer PMPEGMA **28**, the monofunctional brush type macroinitiator **29** was pre-synthesized and then St was polymerized on this macroinitiator. For the synthesis of block copolymer **30**, RAFT synthesis of linear block PGMA **31** was accomplished in the first stage; then macromonomer **28** was RAFT-polymerized with **31**. The authors demonstrated that structure **30** is capable of self-assembly in water to give worm-like micelles with an average length of 80 nm and an average diameter of 25 nm. Meanwhile, copolymer **27** can be assembled in water into spherical micelles with an average diameter of about 60 nm.

Adamson and co-workers[148] synthesized molecular brushes with a similar structure in several stages (and called them toothbrush-like structures). These brushes consisted of the PSt-polyisoprene (PIp) block copolymer backbone with PEO side chains grafted to the PIp block with various grafting densities. First, anionic polymerization was carried out to prepare linear block copolymer backbone PSt-block-

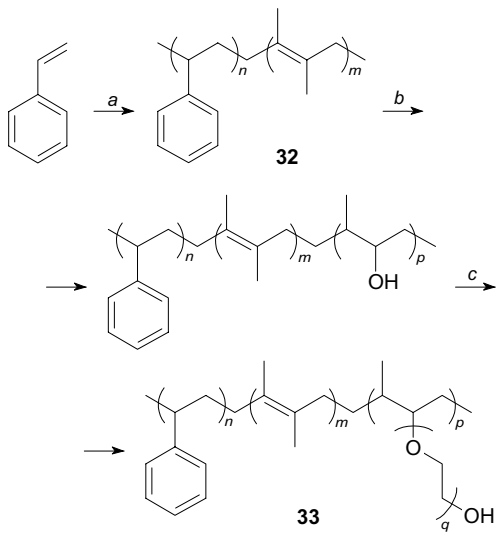
Scheme 16



28 **29** **27** **31** **30**

RAFT is reversible addition – fragmentation chain transfer polymerization

Scheme 17

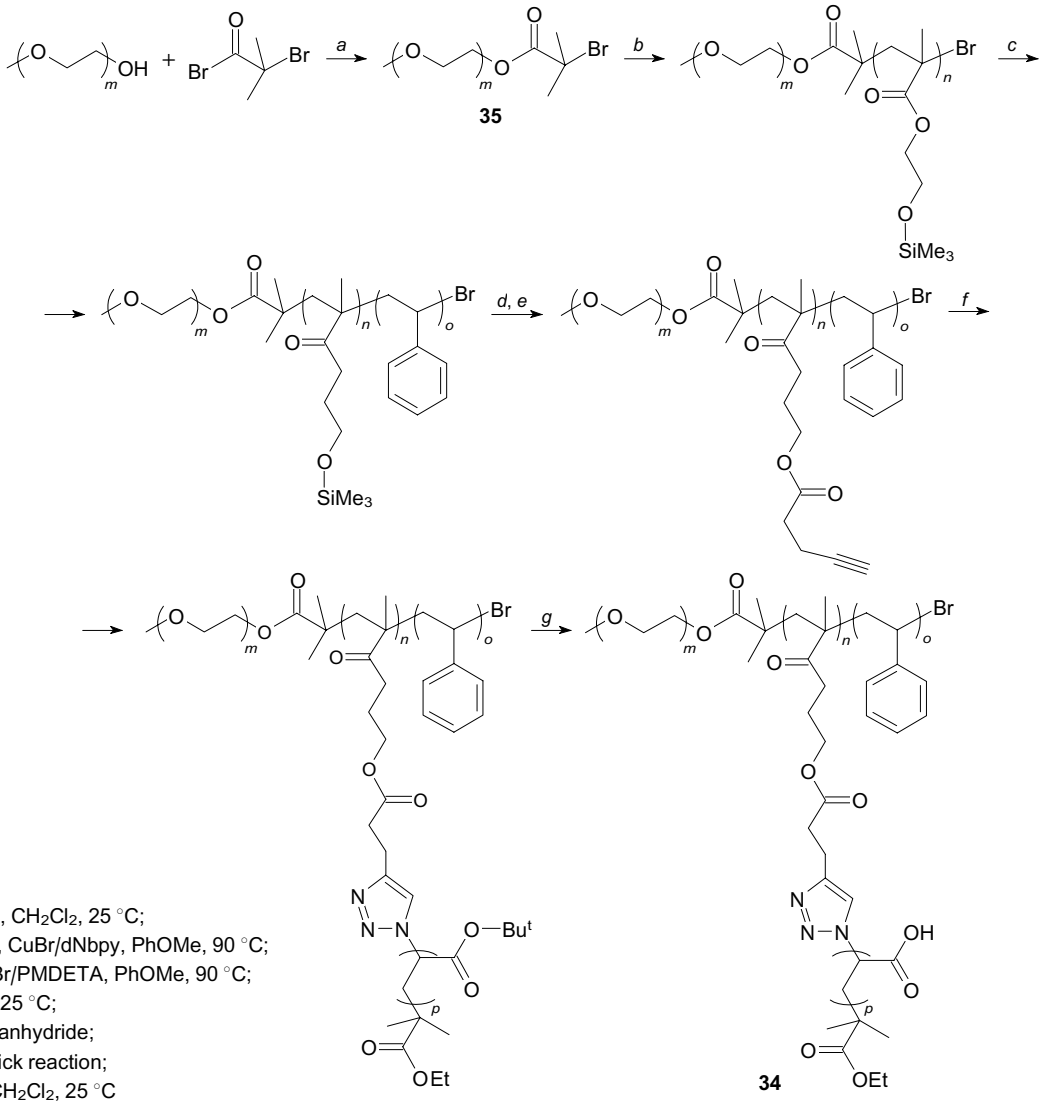


(*a*) 1) Bu^nLi, PhH, 25 °C; 2) Ip, 25 °C;
(*b*) 1) 9-BBN, THF, 50 – 70 °C; 2) 6 M NaOH, H_2O_2 (30 mass %), 0 °C;
(*c*) 1) potassium naphthalide, THF, 25 °C; 2) cooling < 0 °C;
3) ethylene oxide, 25 °C

PIp (**32**) with a low polydispersity index ($Đ$ = 1.05), which is inherent in the employed method. The second stage included modification of the PIp block at the double bonds by hydroboration on treatment with 9-borabicyclo[3.3.1]nonane (9-BBN) in order to produce the side OH functional groups. At the last stage, the anionic ROP of ethylene oxide initiated by the OH groups of the modified PIp block afforded toothbrush-like copolymer PSt-block-(PIp-graft-PEO) **33** (Scheme 17).

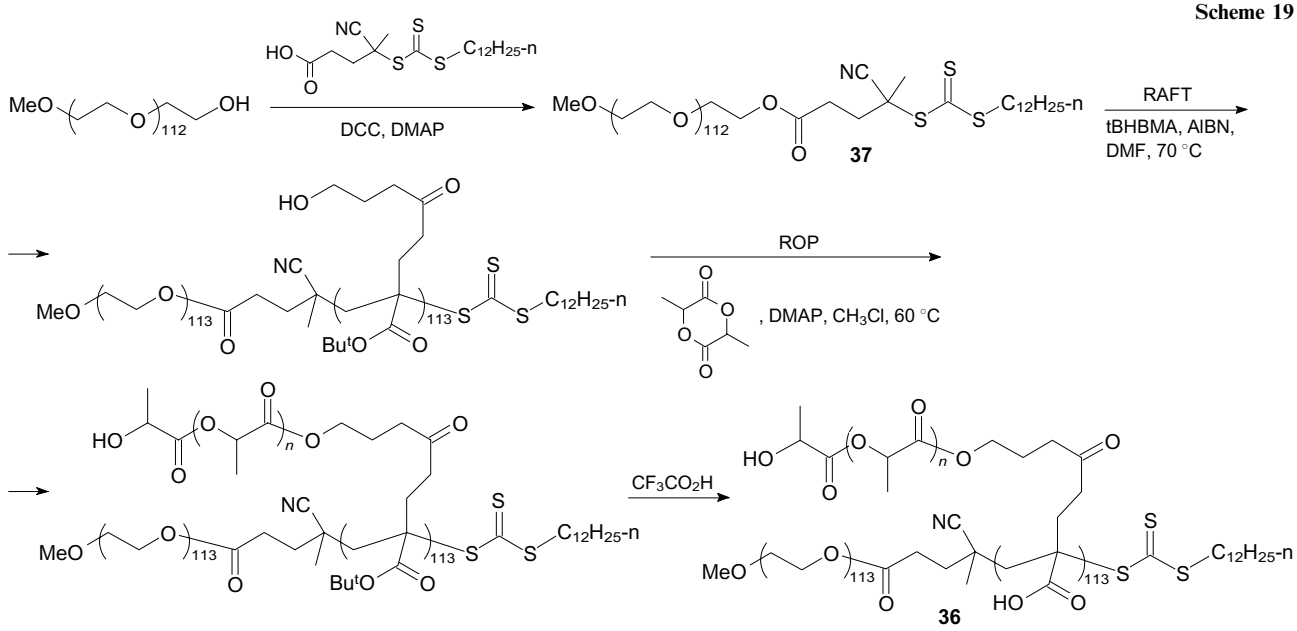
The self-organizing structures based on block-graft brushes **33** were prepared using a solvent mixture including both selective and non-selective solvents with respect to side chains. It was shown by DLS and TEM data that self-assembly considerably depended on the side chain grafting density in the brush block. Densely grafted copolymers formed only spherical micelles in selective solvents, while loosely grafted copolymers formed more highly organized structures such as cylindrical micelles and vesicles. It was also found that micelle coronas formed by densely grafted copolymers comprised the whole brush block, including the main hydrophobic part. However, the coronas of micelles formed by loosely grafted copolymers contained only the PEO side chains.

Scheme 18



(*a*) DMAP, Et_3N, CH_2Cl_2, 25 °C;
(*b*) HEMA-TMS, CuBr/dNbpy, PhOMe, 90 °C;
(*c*) styrene, CuBr/PMDETA, PhOMe, 90 °C;
(*d*) KF, Bu^n_4NF, 25 °C;
(*e*) 4-pentynoic anhydride;
(*f*) Pt-BA-N_3, click reaction;
(*g*) CF_3CO_2H, CH_2Cl_2, 25 °C

Scheme 19



tBHBMA is *tert*-butyl 2-[(4-hydroxybutanoyloxy)methyl]acrylate

Jia *et al.*[149] synthesized ABC block-graft molecular brushes **34** composed of a brush with a poly(2-methacryloyloxyethyl pentynoate) (PMAPA) backbone and PAA side chains as the middle block and linear PEO and PSt blocks on the opposite ends of the chain. These copolymers were prepared starting with successive ATRP of HEMA-TMS and St with macroinitiator PEO-Br **35**. Then PtBA side chains were 'grafted onto' the central block of the backbone by the CuAAC reaction, which was followed by their selective hydrolysis (Scheme 18). According to AFM data, depending on the ratio between the lengths of the central backbone block and side chains of the macromolecule, block-graft brushes **34** may have worm-like or spherical shape.

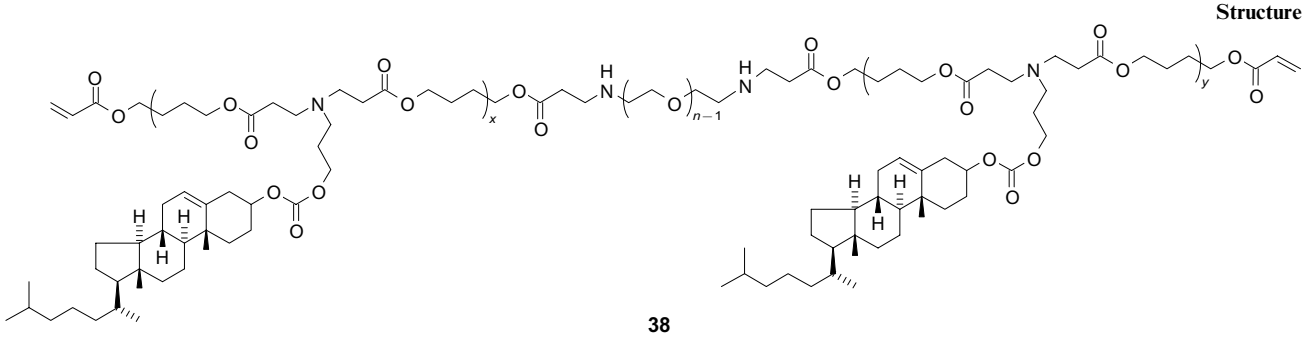
Asymmetric nanocomposite ABC type Janus rods were fabricated from brushes **34**, in which the PAA side chains functioned as a nanoreactor for the preparation of gold, nickel and silica NPs. The promising outlook for the use of such Janus nanorods as solid surfactants for stabilization of emulsions was demonstrated.

Qian *et al.*[150] prepared copolymers with a mixed linear-and-brush topology composed of hydrophilic poly(ethylene glycol) (PEG) blocks and hydrophobic PL side chains grafted to the hydrophilic poly(acrylic acid) block: PEG-block-(PAA-graft-PL) (**36**). These copolymers with narrowly dispersed blocks were synthesized by the successive use of RAFT polymerization to introduce the second precursor block, poly{*tert*-butyl 2-[(4-hydroxybutanoyloxy)methyl]acrylate}, into macroinitiator PEG **37** and ROP to graft PL side chains to this block. The subsequent acid hydrolysis of PtBA units furnished the PAA backbone for the brush block (Scheme 19). The degree of polymerization of PtBA and PL moieties was controlled by varying the initial reactant ratio. The final copolymers were investigated by SEC, and it was found that the products of the first and second polymerization stages had low polydispersity indices: $Đ \leqslant 1.10$ and 1.16, respectively. According to DLS and TEM data, the resulting amphiphilic copolymers were self-assembled in aqueous media to 70 – 110 nm spherical micelles.

One more example of mixed linear-and-brush copolymer is the amphiphilic pH-sensitive triblock copolymer **38** with a hydrophilic central linear PEG block and hydrophobic peripheral brush blocks with grafted cholesterol side chains.[151] An especially important feature of this copolymer is pH-sensitivity, which is due to the amino groups that frame the linear central block.

Studying the self-assembly of macromolecules of copolymer **38** in aqueous solutions revealed a strong dependence of CMC on the pH: CMC increased in the series 6.8, 12.6, 17.4 and 26.6 mg ml^{-1} as pH decreased in the series 7.4, 6.5, 6.0 and 5.0, respectively. Over the same

Structure 38



38

pH range, the size of micelles increased from 205.4 to 285.7 nm and simultaneously the ζ-potential of the micelle surface increased from 12.7 to 47.0 mV, respectively. As shown in Section 7, these dependences are of practical value.

5.4. Heterograft molecular brushes

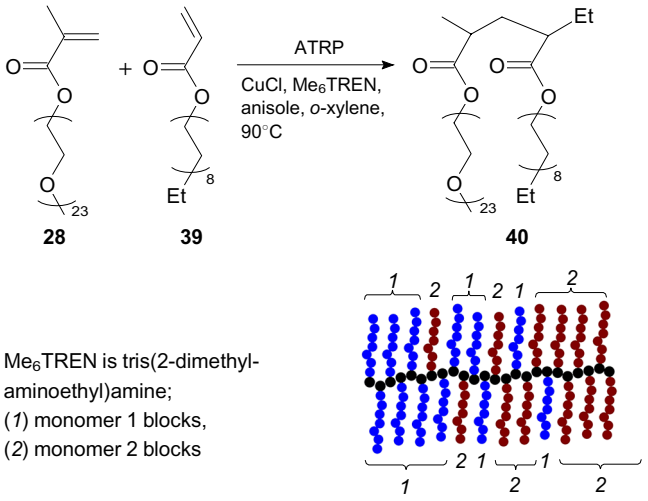
Molecular brushes with different side chains grafted to the backbone are usually called heterograft brush polymers. Chemically different side chains can regularly alternate along the backbone. If the side chains are randomly distributed along the backbone, the molecular brushes are called mixed, or random. The mixed heterograft molecular brushes are mainly prepared by 'grafting through' or 'grafting from' techniques or their combination.

As compared with other molecular brushes, those with grafted side chains of two different types possess an additional structural variability and unique aggregation properties.[152, 153] Grafting of side chains incompatible with one another to the backbone induces intramolecular phase separation.

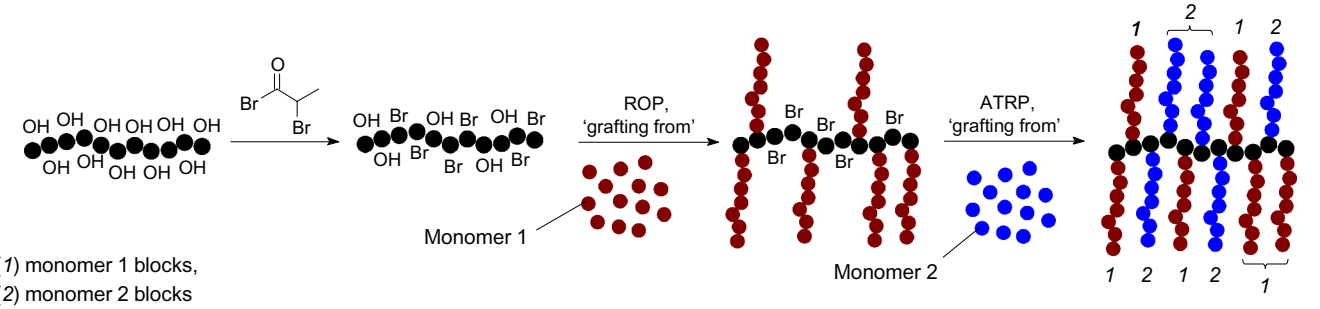
Molecular brushes with a grafting density gradient along the backbone were synthesized by the 'grafting through' approach[154–157] using ATRP. Neugebauer *et al.*[157] carried out ATRP-based copolymerization of macromonomers, PMPEGMA (**28**) and octadecyl acrylate (ODA, **39**) (Scheme 20) or octadecyl methacrylate (ODMA). The variation of comonomer ratio gave rise to amphiphilic heterograft copolymers **40** with different distributions of grafted chains and an average degree of polymerization of the backbone ranging from 300 to 500. Taking advantage of the higher reactivity of compound **28** compared with monomer **39**, the authors synthesized gradient type molecular brushes. For comparison with these copolymer brushes, they also prepared linear PODMA homopolymer with the average degree of polymerization $n = 165–435$ and $Đ = 1.15–1.3$: $n = 145$, $Đ = 1.5$ and PMPEGMA homopolymer ($n = 400$, $Đ < 1.1$). The molecular-weight characteristics of the brushes were determined using calibration-free multiple detection SEC analysis with three detectors: refractive index detector, viscosity detector and MALLS detector, whereas for analysis of the initial homopolymer macromonomers, calibration against linear PMMA standards was performed. The chemical composition of products and the conversion of macromonomers were determined from ^{1}H NMR data. It was found that the Cu^I/dNbpy catalytic complex provides a relatively low conversion of macromonomers (~60%), while the use of the more active catalytic complex Cu^I/Me6TREN [Me6TREN is tris(2-dimethylaminoethyl)amine] results in a >80% conversion. The polydispersity index $Đ$ of the mixed heterograft brushes was 1.1 – 1.4, that for the gradient brushes was 1.3 – 1.6. The combination of hydrophilic and hydrophobic segments in the polymer chains of these brushes induced microphase separation of the copolymer in the condensed state.

Molecular brushes with mixed side chains can also be fabricated by successive grafting of two monomers to randomly arranged initiating sites of the backbone ('grafting from' approach). In this case, the final brush structure is the same as upon copolymerization of two macromonomers. Yan *et al.*[158] synthesized heterograft molecular brushes **41** using the cellulose backbone. The ATRP initiator with Br functional groups was prepared by functionalization of commercially available ethylcellulose (EC) containing hydroxyl groups. The OH : Br ratio of initiating groups in the backbone was controlled by varying the reaction time. In the first stage, ROP was performed to graft PCL to the OH functional groups. In the second stage, ATRP was carried out to graft *N*,*N*-dimethylaminoethyl methacrylate (DMAEMA) to the Br initiating groups to obtain amphiphilic heat- and pH-sensitive heterograft molecular brushes (Scheme 21). These brushes could not be synthesized in one stage because of the necessity to use different temperatures for ATRP (CuBr – PMDETA catalyst) and ROP [$Sn(Oct)_2$ catalyst]. In this study, the MW of brush **41** samples was determined using SEC analysis (with a single detector), ^{1}H NMR spectroscopy and calculations based on monomer conversion. The molecular weights found by different methods proved to be close to one another. It was found that the synthesized biocompatible

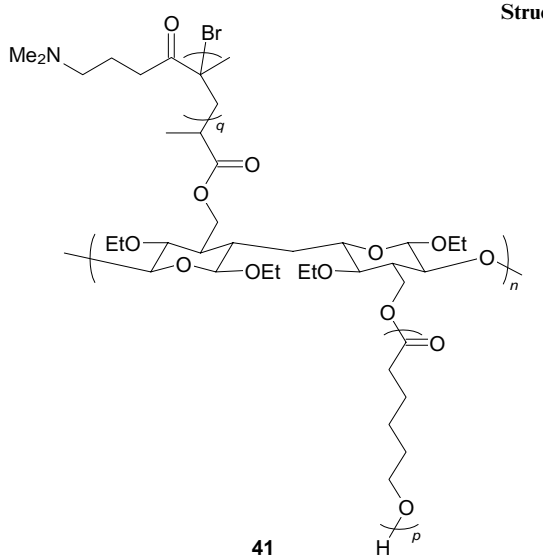
Scheme 20



Scheme 21



Structure 41

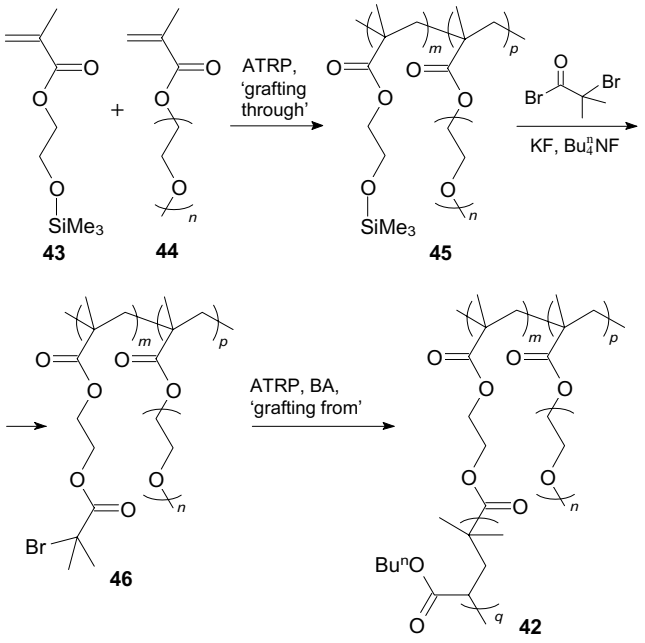


41

copolymers can be self-assembled to micelles in acidic aqueous solutions. As the pH of the medium changes, single micelles in aqueous solutions are assembled into micellar aggregates. As shown below, this pH sensitivity is promising for the creation of effective nanocontainers for targeted drug delivery.

Molecular brushes with mixed heterograft side chains can also be obtained by copolymerization of a macromonomer ('grafting through') with a monomer containing functional groups, precursors of the initiating groups for the subsequent 'grafting from' of the side chains. Matyjaszewski and co-workers [159, 160] synthesized heterograft brushes **42** with densely grafted PEO and PBA side chains. In the first stage, they performed ATRP of HEMA-TMS **43** with high-molecular-weight MPEGMA **44** ('grafting through') and thus obtained loosely grafted copolymer **45**. Then the HEMA-TMS side chains were converted to 2-(2-bromopropionyloxy)ethyl methacrylate groups, and the resulting copolymer **46** was used as the multicentre macroinitiator for the subsequent 'grafting from' of PBA by ATRP (Scheme 22). The specific macromolecular architecture of the brushes with a random distribution of chemically different side chains along the backbone suppressed the crystallization of PEO side chains. This finally gave amorphous, homogeneous materials that possessed typical properties of glassy systems.[159] Because of their sensitivity to the type and nature of the solvent, these polymers showed different behaviours in solvents of different nature. When dissolved in a non-selective solvent (chloroform), the macromolecules assumed a completely stretched conformation because of good solubility of both types of side chains. Meanwhile, in ethanol or methanol, which are selective solvents for side chains, polymer chains were significantly compressed, taking curved and globular shapes, respectively.[161]

Scheme 22

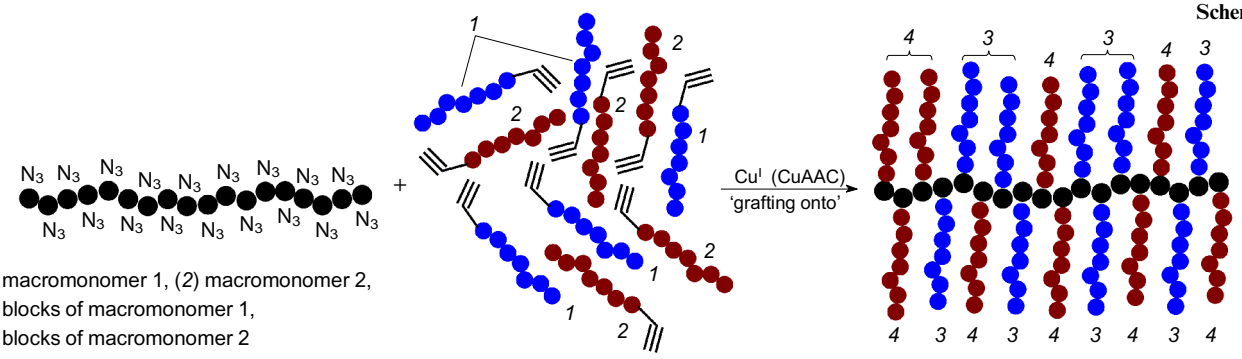


Xie *et al.*[160] synthesized a series of heterograft molecular brushes **42** with controlled structural parameters. The copolymer composition and the backbone length were controlled by varying the comonomer ratio, conversion, and monomer to initiator ratios. The length of hydrophilic side chains was controlled by using macromonomers **44** with different molecular weights. It was found that owing to the presence of both hydrophilic and hydrophobic blocks in the molecule, brushes **42** can stabilize water-in-oil emulsions at polymer concentrations below 0.01 mass %. The authors studied the effect of the side chain length and the backbone composition and length on the emulsifying properties of the brushes. The increase in the length and the fraction of hydrophilic side chains leads to higher efficiency of emulsification and to stabilization of the emulsion at a lower polymer concentration, probably, because of higher affinity for the aqueous phase.

The 'grafting onto' approach is used rather rarely for the synthesis of heterograft molecular brushes due to low grafting density. However, lately, this approach has been further developed. This is due to the use of highly efficient click reactions such as CuAAC in the polymer chemistry.[162 – 164] It was shown that the grafting density of the brushes prepared according to the 'grafting onto' approach is comparable with the grafting density attained in the 'grafting from' synthesis.[44, 128, 165, 166] Zhao and co-workers [167] synthesized heat-sensitive heterograft molecular brushes with high grafting density (~80%) of PEO and heat-sensitive poly(ethoxydiethylene glycol acrylate) (PEDEGA), the lower critical solution temperature (LCST) of which is 9 °C. The brushes were prepared within the framework of the 'grafting onto' approach by the CuAAC method (Scheme 23). According to DLS and AFM data, variations of the temperature of an aqueous solution are accompanied by a change in the size and shape of macromolecules, which are transformed from a stretched worm-like shape to a collapsed, but stable globular conformation (Fig. 3). It was found that PEO side chains stabilize the collapsed state.

The synthesis of heterograft molecular brushes with alternating chemically different side chains is a complicated task, which has been addressed in different ways. Initially, brushes of this type were formed by the 'grafting through' approach under thoroughly selected conditions of radical copolymerization of two macromonomers containing electron-donating and electron-withdrawing active end groups,

Scheme 23



(*1*) macromonomer 1, (*2*) macromonomer 2,
(*3*) blocks of macromonomer 1,
(*4*) blocks of macromonomer 2

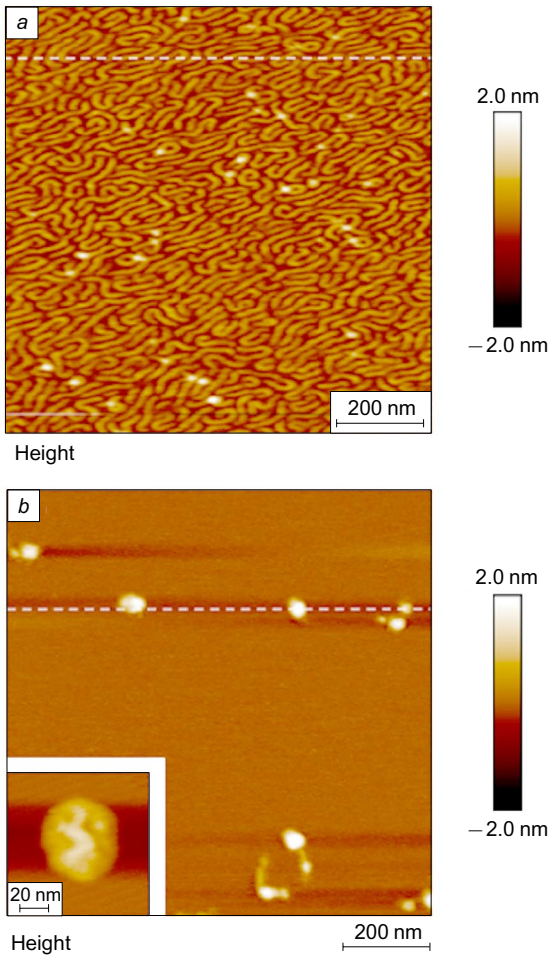
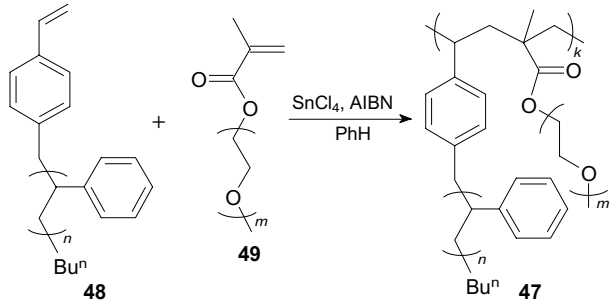


Figure 3. AFM image of PEO – PEDEGA heterograft brush molecules deposited by centrifuging on mica from aqueous solutions at $T = 0$ °C ($c = 0.1$ mg g^{-1}) (*a*) and $T = 40$ °C ($c = 0.01$ mg g^{-1}) (*b*).[167]

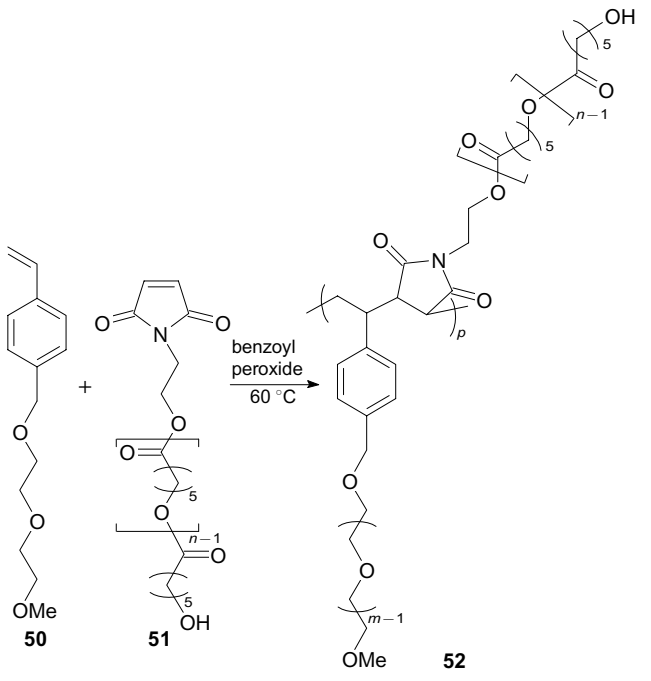
or by adding Lewis acid during the copolymerization of macromonomers. Ishizu *et al.*[152, 168, 169] obtained heterograft molecular brushes **47** (Scheme 24) by a procedure including radical copolymerization of PSt bearing vinylbenzyl terminal groups (**48**) with MPEGMA **49** in the presence of a Lewis acid. In a solvent selective to one sort of side chains, brushes **47** formed large core – shell cylinders in which the core was composed of insoluble side chains, while soluble side chains formed the shell.

Scheme 24

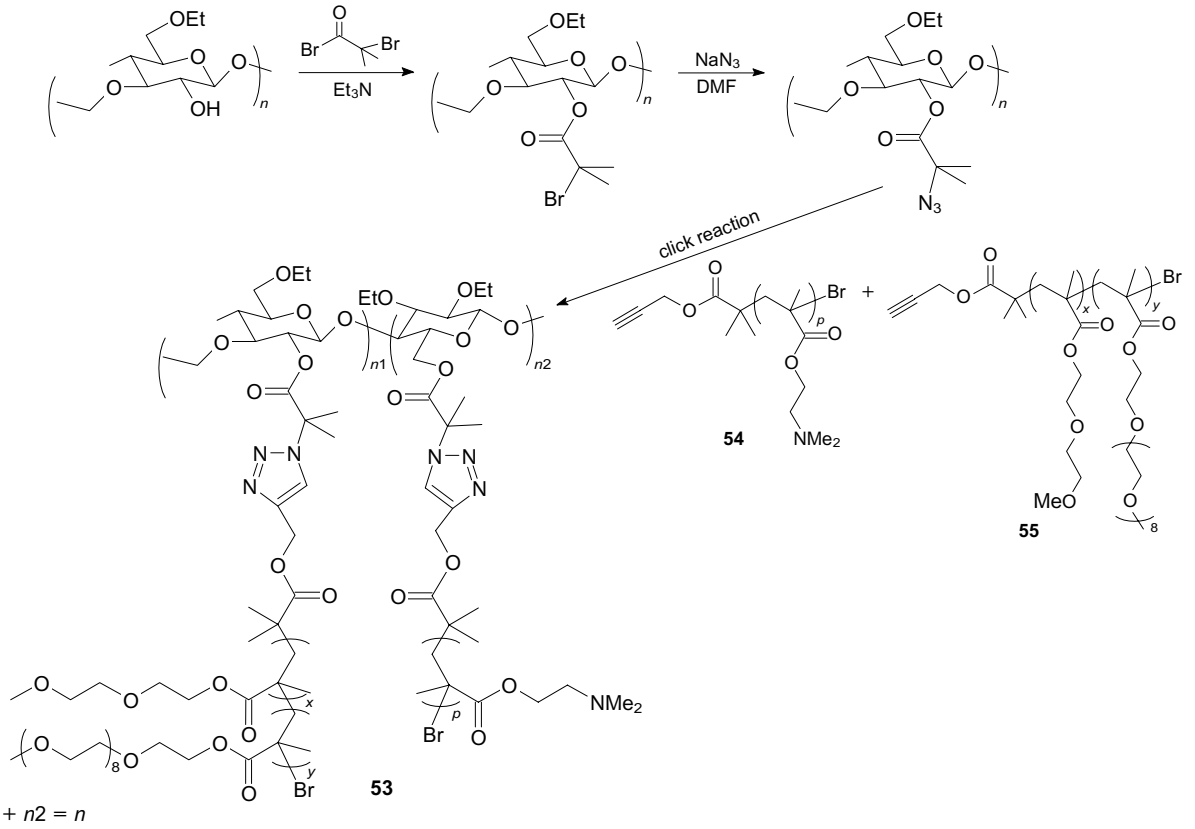


Chen and co-workers [170] synthesized heterograft brushes with alternating side chains using an approach based on the pronounced trend of macromonomers with vinylbenzyl and maleimide terminal groups for alternation. Radical copolymerization of the PCL macromonomer containing a maleimide functional group (**50**) and PEO macromonomer containing a vinylbenzyl terminal group (**51**) yielded heterograft molecular brushes **52** with alternating PEO and PCL side chains (Scheme 25).

Scheme 25



Scheme 26



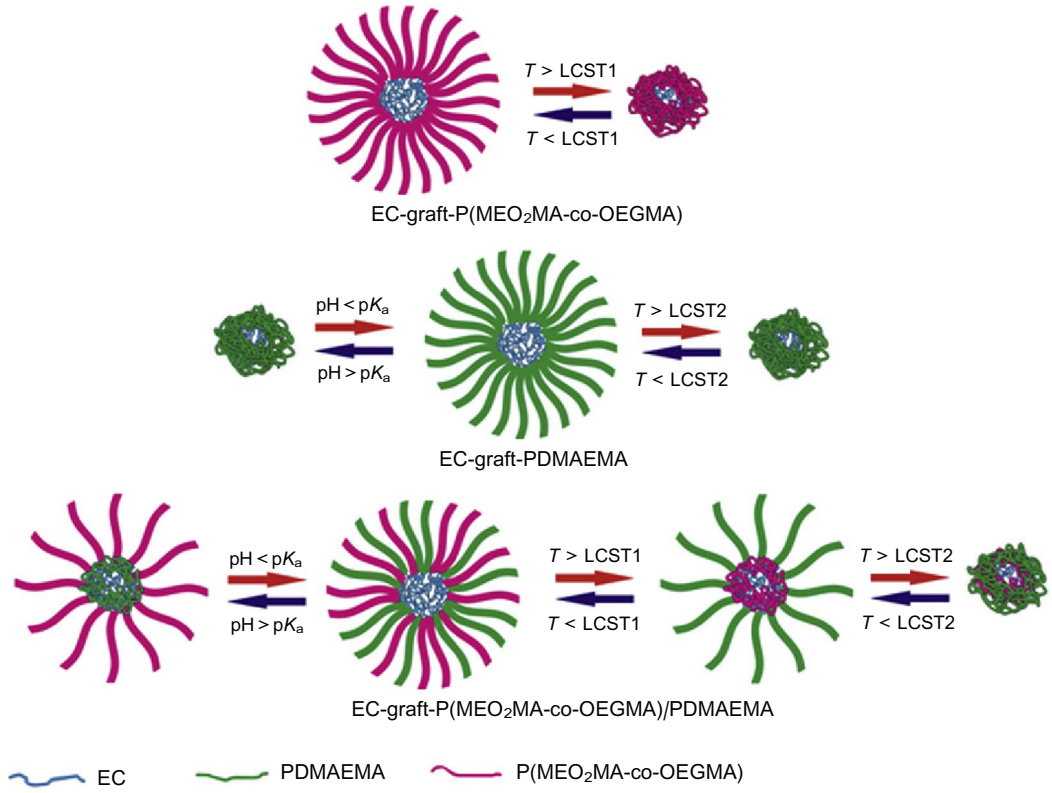
Ren and co-workers [171] utilized a combination of ATRP and click chemistry techniques to prepare amphiphilic molecular brushes **53** based on EC with poly[2-(2-methoxyethoxyethyl methacrylate)-co-oligoethylene glycol methacrylate] [P(MEO_2MA-co-OEGMA)] and PDMAEMA side chains (Scheme 26). The precursor side chains (**54**, **55**) were synthesized using ATRP. Then a click reaction was performed to graft these chains to azide-functionalized EC chains, with the molar ratio between P(MEO_2MA-co-OEGMA) and PDMAEMA side chains being varied by varying the amounts of these polymers. It was found that the obtained brushes can be spontaneously assembled in water into heat- and pH-sensitive spherical micelles (Fig. 4) and have a great potential for biomedical and smart materials applications. The studies showed that the cloud point of the solution and the size of micelles in the solution depend on the length of EC chains and the ratio between the heat-sensitive P(MEO_2MA-co-OEGMA) units and heat- and pH-sensitive PDMAEMA side chains.

5.5. Asymmetric molecular brushes

A special type of heterograft molecular brushes are asymmetric brushes, which are called centipede-like brushes. In these brushes, two side chains of different nature are grafted to one repeating unit of the backbone.

This type of structure is exemplified by amphiphilic brushes **56** with hydrophilic PEG and hydrophobic PSt side chains grafted to one backbone unit.[172] The former were 'grafted through' to form backbone **57** *via* ATRP of the corresponding macroinitiator (Scheme 27). Then ATRP-initiating α-bromoester groups were introduced into polymer **57** on treatment with lithium diisopropylamide and α-bromopropionyl chloride. The authors selected conditions to introduce these groups into virtually each unit of the backbone, which was confirmed by ^{1}H NMR data. After that, the PSt side chains were attached by ATRP ('grafting from'). According to SEC data, copolymer structures obtained in the first and second ATRP stages had a narrow unimodal MWD ($Đ$ = 1.03 and 1.38, respectively). A study of micellization of brushes **56** demonstrated that their CMC values in aqueous solutions ($\sim 10^{-7}$ g ml^{-1}) were markedly lower than this parameter for linear amphiphilic block copolymers of the same nature.[172] The CMC of **56** decreases as the molecular weight of the copolymer increases as a result of increasing mass fraction of PSt, which was attributed to the branched topology of the brushes and to the increase in their asymmetry with increasing length of hydrophobic PSt side chains. Amphiphilic brushes **56** proved to be efficient stabilizers for hydrophobic nanoparticles, *e.g.*, β-carotene NPs. The high stabilizing capacity and specific morphology of this copolymer allowed the authors to generate ellipsoidal β-carotene NPs, whereas the use of linear diblock copolymers with similar hydrophilic and hydrophobic blocks can give only spherical NPs.

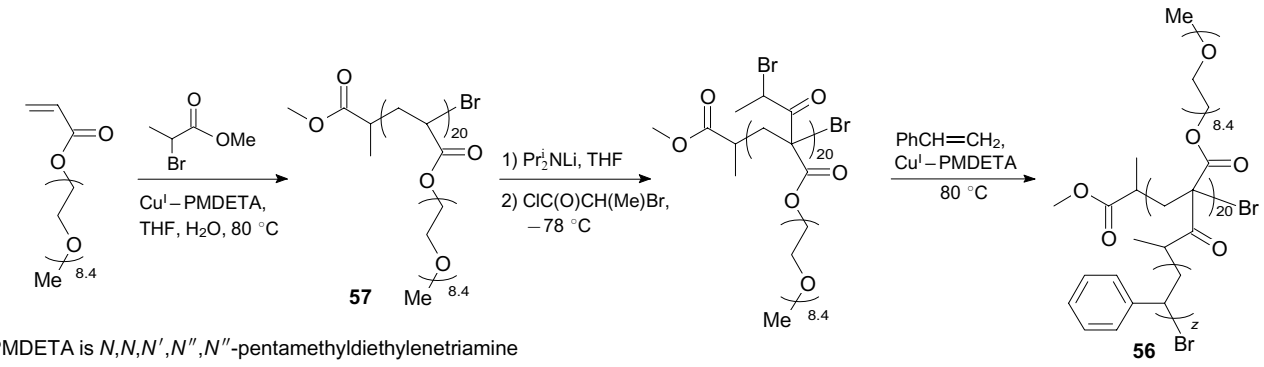
Non-spherical β-carotene NPs of unusual ellipsoidal shape or, which is even more remarkable, rod-shaped NPs were prepared using amphiphilic asymmetric brushes **58** with hydrophilic PEG side chains and hydrophobic poly(D,L-lactide) side chains as stabilizers.[173] These brushes were synthesized by a combination of CRP and click chemistry methods. For this purpose, the backbone with glycidyl side groups was synthesized by RAFT polymerization; under the action of sodium azide, these groups were converted to hydroxyl and azide side groups in each unit.



EC is ethyl cellulose, PDMAEMA is poly[2-(*N*,*N*-dimethylamino)ethyl methacrylate], OEGMA is oligo (ethylene glycol methacrylate), LCST is low critical solution temperature

Figure 4. Self-assembly of EC-graft-P(MEO_2MA-co-OEGMA) and EC-graft-P(MEO_2MA-co-OEGMA)/PDMAEMA molecular brushes at different temperatures and pH values.[171]

Scheme 27

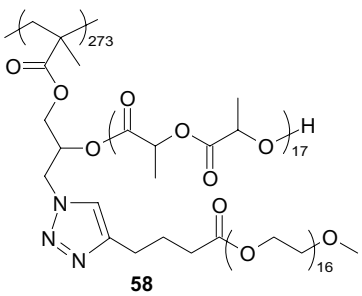


PMDETA is *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine

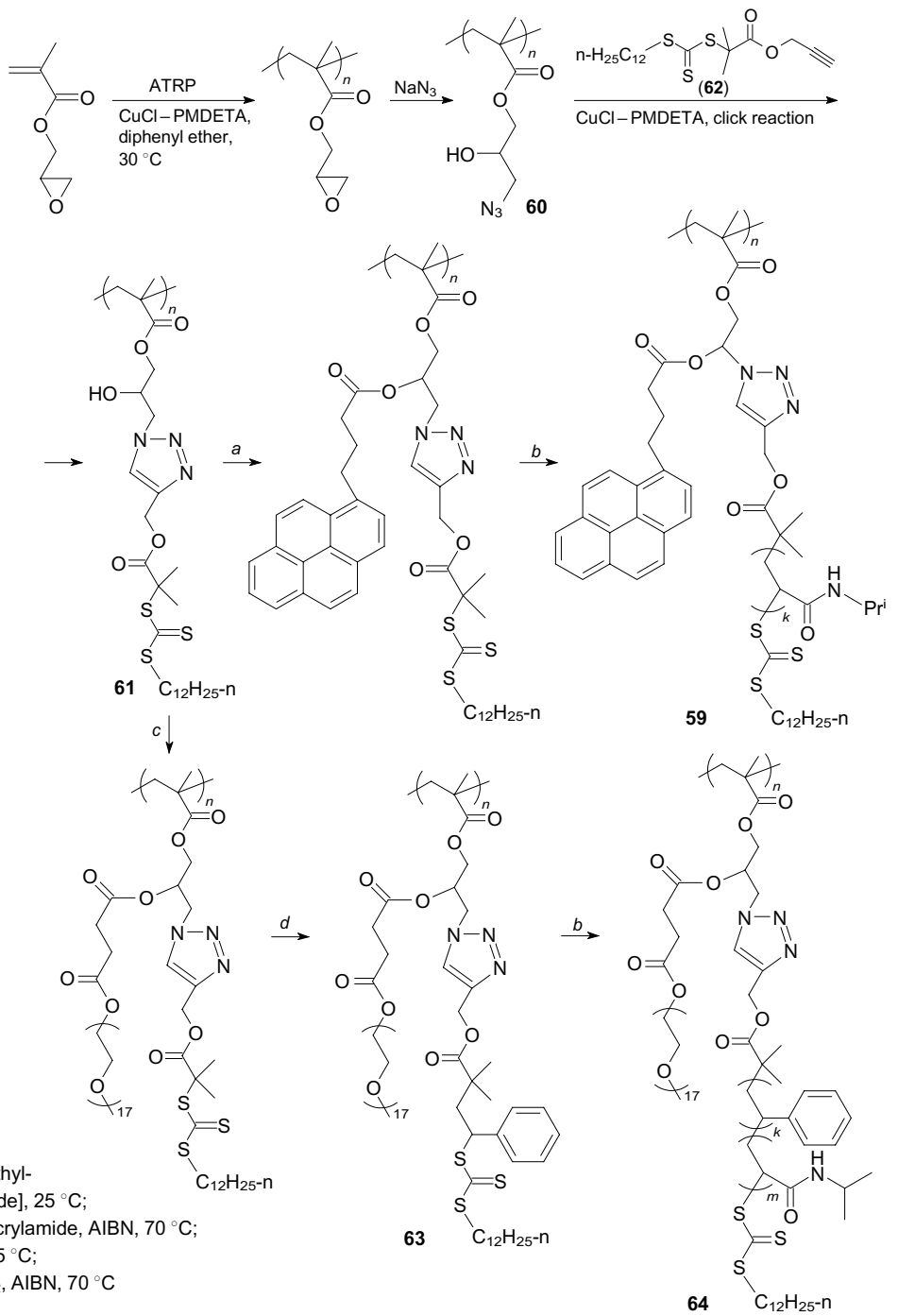
Then poly(D,L-lactide) side chains were attached through the hydroxyl groups *via* a ROP reaction, and the PEG chains were introduced according to the 'grafting onto' approach by the CuAAC reaction.

This combination of the 'grafting from' approach using CRP and click chemistry is often used to prepare asymmetric brushes. For example, Zhao *et al.*[174] obtained amphiphilic asymmetric brushes **59** with pyrene (Pyr) side groups and hydrophilic heat sensitive poly(*N*-isopropylacrylamide) (PNIPAM) side chains. First, ATRP of glycidyl methacrylate (GMA) and the subsequent treatment of the product with sodium azide gave backbone **60** with hydroxyl and

Structure 58



Scheme 28



azide side groups (Scheme 28). Then for the preparation of macro-RAFT agent **61**, RAFT-agent **62** and Pyr side groups were grafted to the backbone using click and esterification reactions, respectively. At the final stage, PNIPAM side chains were attached *via* RAFT polymerization (see Scheme 28 *b*). Transmission electron microscopy, DSC and DLS methods were applied to study the self-assembly and heat sensitivity of the resulting copolymers in water, which is a good solvent for PNIPAM side chains at temperatures below LCST and a precipitating agent for the Pyr side groups. It was found that the macromolecules are self-assembled in an aqueous solution to give vesicles, with their walls being composed of Pyr groups and the corona being formed by PNIPAM side chains (Fig. 5). Due to the presence of a heat-sensitive block in the structure, the size and morphology of the vesicles were markedly dependent on temperature. At temperatures above LCST for PNIPAM, its side chains in the vesicle coronae collapsed and the vesicle size decreased.

Micellization of brushes **59** in solvents of different thermodynamic quality for particular blocks and photophysical properties of the brushes were studied by UV spectroscopy, fluorescence spectroscopy and TEM. Analysis of UV and fluorescence spectra allowed the authors to control the formation of inter- or intramolecular pyrene excimers and determine the critical concentration of pyrene

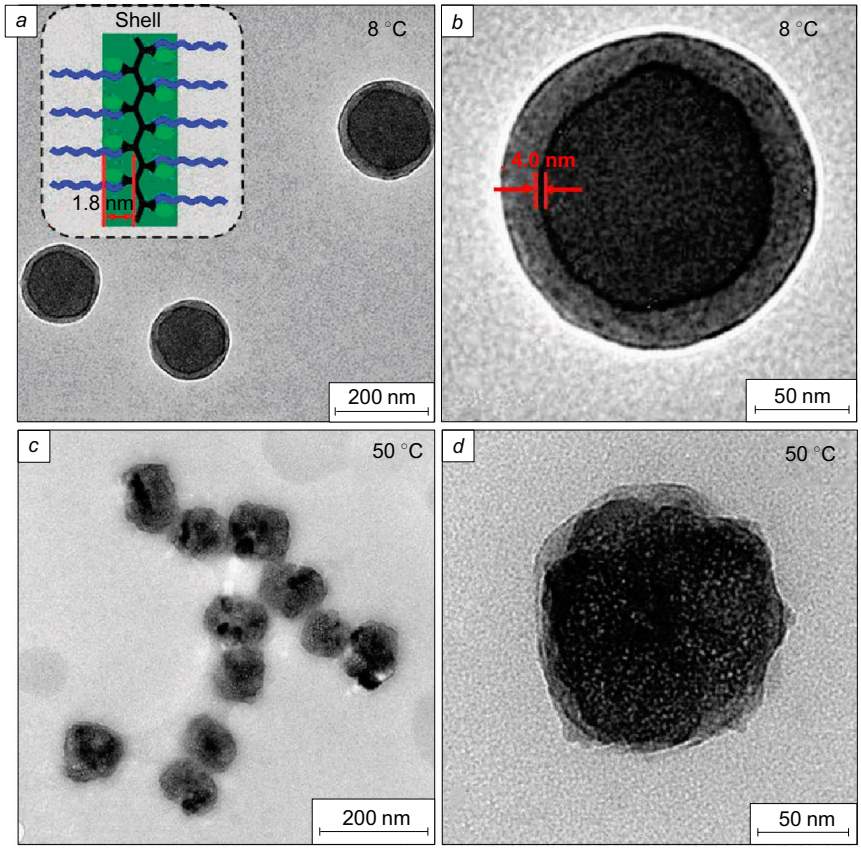


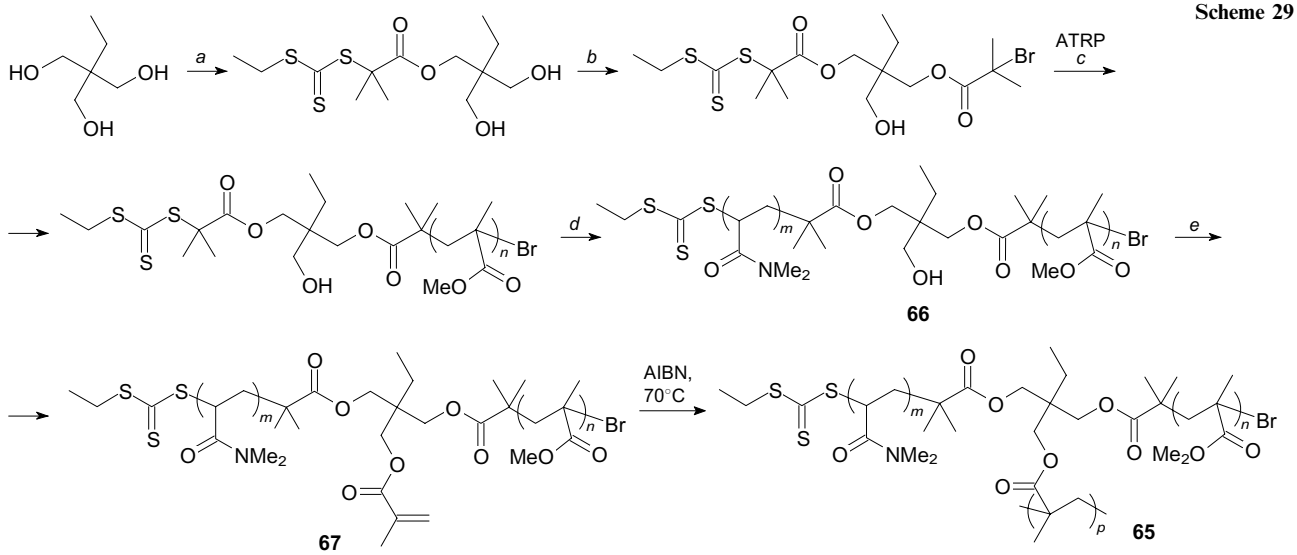
Figure 5. TEM images of the self-assembly of PGMA-graft-Pyr/PNIPAM macromolecules (c = 0.1 g litre^{-1}) in aqueous solutions at T = 8 (*a*, *b*) and 50 °C (*c*, *d*).[174] PGMA is poly(glycidyl methacrylate), Pyr is pyrene, PNIPAM is poly(*N*-isopropylacrylamide).

groups (1.7×10^{-4} mol litre^{-1}) in the copolymer solution below which intramolecular excimers are formed by pyrene groups grafted to one backbone. Above this concentration, intermolecular association of pyrene groups took place, that is, the conformation of the brush macromolecules was dictated by the copolymer concentration in an appropriate solvent. Meanwhile, in a selective solvent, copolymer chains formed vesicles with the pyrene side groups inside the vesicles and the outer shell made of PNIPAM side chains.

Lian *et al.*[6] also used a combination of CRP and click chemistry for the synthesis of amphiphilic asymmetric molecular brushes with hydrophilic PEO and hydrophobic PSt side chains (**63**) or PSt-block-PNIPAM block copolymer side chains (**64**) (see Scheme 28). The above-outlined strategy was employed to obtain macro-RAFT agent **61**, to the backbone of which PEO chains were attached by covalent bonds *via* an esterification reaction (see Scheme 28, pathway *c*). The PSt or PSt-block-PNIPAM side chains were grafted by one-stage or successive RAFT polymerization (see Scheme 28, conditions *b*, *d*). The copolymer structures were identified by spectral methods such as ^{1}H NMR, IR and UV spectroscopy. The molecular weight of the final branched copolymer was determined by SEC with an only refractive index detector and calibration against polystyrene standards. Due to the lack of reliability of the resulting values, the authors called these molecular weights apparent. For branched copolymers, these values differed by almost an order of magnitude from the molecular weights calculated from ^{1}H NMR data; however, for the initial homopolymers, these two methods gave similar results. The behaviour of the synthesized brushes was investigated in methanol and in water. In methanol, the asymmetric macromolecular brushes **63** were assembled into vesicles. The vesicle walls were composed of PSt side chains and the coronae were made of PEO side chains. The average size of aggregates increased with increasing length of the PSt chain. Conversely, macromolecular brushes **64** were self-assembled to give vesicles in aqueous solutions. The temperature had a considerable effect on the shape of aggregates. At temperatures above the PNIPAM LCST, the vesicle size decreased due to compression of the PNIPAM blocks in the corona.

A different approach to the preparation of asymmetric molecular brushes was proposed by Li *et al.*,[175] who synthesized brushes **65** with side chains based on PMMA and poly(*N*,*N*-dimethylacrylamide) (PDMAA) (Scheme 29). First, the chains were fabricated as a linear diblock precursor (PMMA-block-PDMAA, **66**) by successive ATRP and RAFT reactions. The subsequent functionalization of the diblock copolymer with methacryloyl (MA) groups yielded the macromonomer MA-PMMA-block-PDMAA **67**, which was then subjected to free radical polymerization to give the brush backbone. An interesting feature of the last-mentioned reaction is that it was conducted under heterogeneous conditions as emulsion polymerization. Micelles of **67** pre-synthesized in water and composed of a hydrophobic PMMA core, a hydrophilic PDMAA shell and MA groups at the interface between the

Scheme 29



(*a*) 2,2-bis(hydroxymethyl)butyl 2-[ethylthio(thiocarbonyl)thio]-2-methylpropanoate, DCC, DMAP, CH_2Cl_2, 25 °C;
(*b*) 2-bromoisobutyroyl bromide, Et_3N, CH_2Cl_2, 25 °C; (*c*) MMA, Cu^I – PMDETA, PhOMe, 60 °C; (*d*) *N*,*N*-dimethylacrylamide, AIBN, DMF, 70 °C

core and the shell were used as agents stabilizing the emulsion. Owing to these positions of groups, polymerization proceeded to a high degree of conversion in a controlled mode in the presence of the AIBN initiator pre-encapsulated into oil droplets.

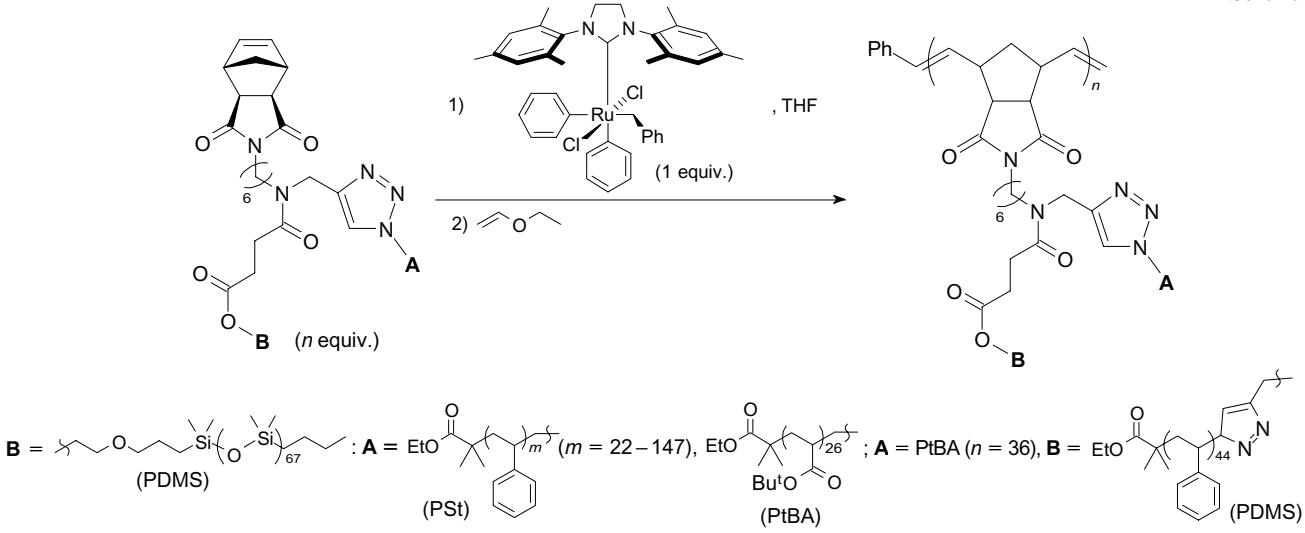
The ROMP process is also used to synthesize asymmetric molecular brushes. For example, Kawamoto and co-workers [176, 177] obtained asymmetric Janus brush copolymers by polymerization of norbornene-functionalized macromonomers with two different-type chains (Scheme 30). The authors called these compounds branched macromonomers. Brushes of this type proved to be of interest for studying the morphology of copolymer films.

Sheng and co-workers [178] performed theoretical simulation of self-assembly processes of amphiphilic asymmetric molecular brushes consisting of a solvophobic backbone with solvophilic and amphiphilic diblock copolymer side chains. Molecular brushes **64** obtained by Lian *et al.*[6] were used as the starting point for choosing parameters of the model. Depending on the length of blocks, molecular architecture and grafting density, multicomponent aggregates exhibited a large diversity of morphological conformations including five types of structures: porous aggregates, worm-like micelles, donut micelles, hamburger micelles and unimolecular micelles. For some molecular brushes, atypical asymmetric multilayer polymersomes were spontaneously formed. For the brushes containing a heat-sensitive block, the variation of temperature induced a morphology change from asymmetric four-layer to symmetric seven-layer polymersome. Correspondingly, the size of polymersomes substantially decreased when the solution temperature exceeded the PNIPAM LCST. The results of the simulation were in agreement with experimental data obtained in another study.[6]

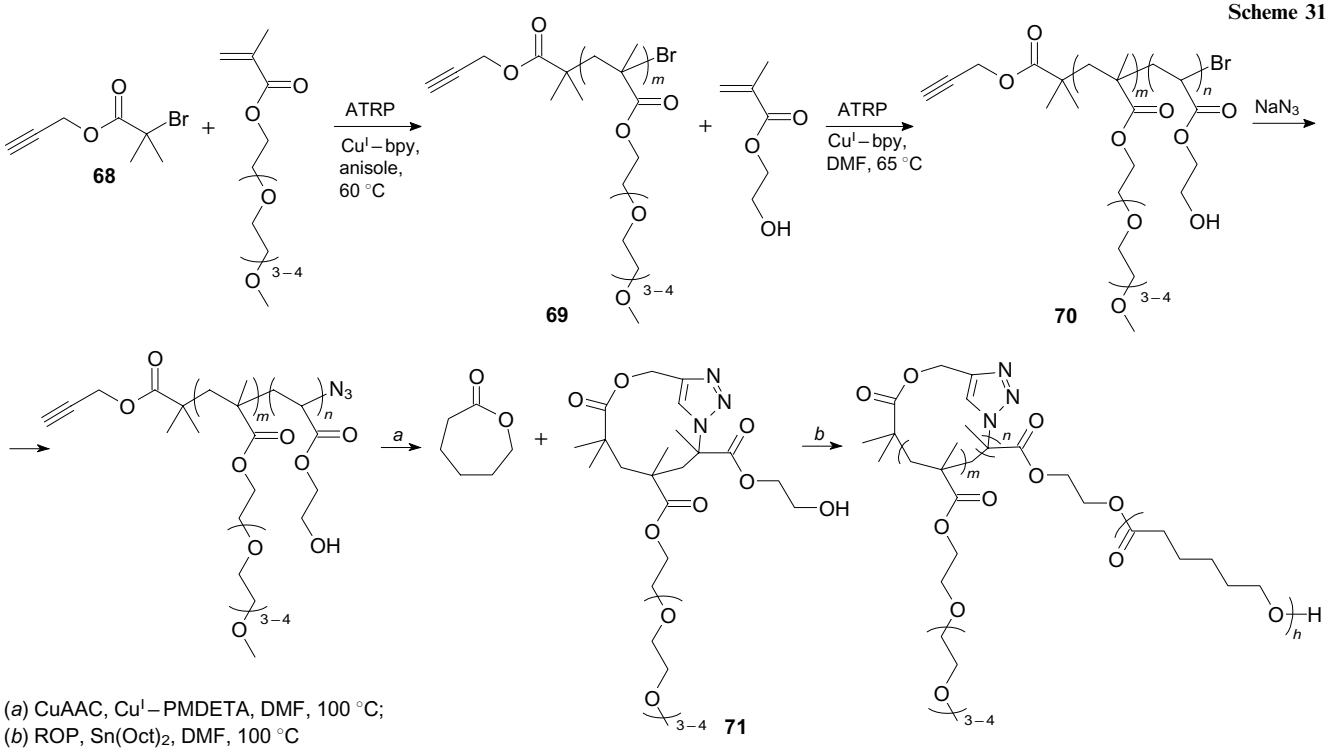
5.6. Cyclic molecular brushes

Amphiphilic cyclic molecular brushes [179 – 186] refer to a new class of complex polymers with toroidal topology and a

Scheme 30



Scheme 31



macrocyclic multicentre grafted chain (brush backbone). The brushes have a donut [179] or a sunflower [185] shape and a hydrophobic core and a hydrophilic corona of side chains. Owing to the unique topology and the ability to form unimolecular micelles in solutions, these structures behave as more efficient drug delivery systems than analogous acyclic brushes.

The cyclic brush structures are obtained by combination of various CP methods with click reactions, which serve to close the brush backbone into a macrocycle. The ring closure is performed either as a stage of the preparation of the cyclic multicentre macroinitiator [184] or after the formation of a classical brush with a linear backbone;[183] most often, this is done using the CuAAC reaction, with the terminal units of the backbone being pre-functionalized with azide and alkynyl groups.[179 – 183] Other cycloaddition reactions are also used.[181] The key methods for grafting side chains are ATRP,[179 – 181] RAFT [182] and ROP.[182, 183]

Amphiphilic cyclic molecular brushes with homopolymer,[182, 184] diblock copolymer [180, 181] or dendrimer [179] side chains have been prepared to date. Also, diblock copolymer and random copolymer cyclic brushes [18, 183, 185, 186] and heterograft cyclic brushes [187] have been reported. In other words, analogues of many of the above-described brushes, with the difference that their backbones are macrocyclic, have been obtained. The solubility in aqueous media and the amphiphilicity, which endow cyclic brushes with the ability to incorporate pharmaceuticals (most often, hydrophobic ones) into their hydrophobic cores, are provided by the choice of chemical structure of the hydrophobic cyclic backbone and hydrophilic side chains [182, 184] or their peripheral blocks.[180,181]

For example, a new interesting investigation object is represented by amphiphilic cyclic diblock copolymer brushes [181] synthesized in five stages (Scheme 31): (i) ATRP with initiator **68** gave the first brush block with hydrophilic oligoethylene glycol **69** side chains; (ii) the same method and brush **69** as a multicentre macroinitiator were used to prepare the second linear block of the copolymer with hydroxyl side groups (**70**) *via* polymerization of 2-hydroxyethyl methacrylate; (iii) on treatment with sodium azide, the terminal Br atom was changed to the azide group; (iv) intrachain cyclization was performed using click chemistry; (v) ROP with the second block of already cyclic copolymer **71** yielded hydrophobic oligo(ε-caprolactone) (OCL) side chains.

6. Self-assembly of amphiphilic multicomponent molecular brushes

A known characteristic feature of the macromolecules of linear block copolymers with different-type blocks is their self-assembly to ordered structures in solution, melt or solid phase. The spontaneous formation of micro- and nano-sized ordered domains with predominant content of some blocks accounts for the microphase separation in the solid phase typical of the morphology of copolymer materials. In solutions in selective solvents, self-assembly of copolymers induces micelle formation. Currently, self-assembly of linear amphiphilic copolymers has been studied most comprehensively;[7, 35, 188] it was shown that the properties of self-assembled aggregates depend on the chemical structure of the copolymer, the ratio of hydrophilic to hydrophobic blocks, the concentration and molecular weight of the copolymer, the preparation procedure of the aggregates and the solvent properties such as the composition, pH and ionic strength.[189 – 191]

Like linear block copolymers, multicomponent molecular brushes are also capable of self-assembly.[33, 192] These processes attract considerable interest because of their potential practical applications. Therefore, increasing number of recent publications have been devoted to the self-

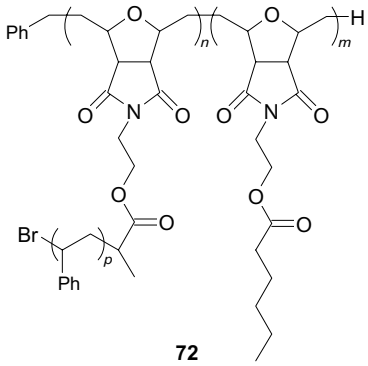
assembly of macromolecules of copolymer brushes in the solid phase and in solution and dependence of this process on the spatial organization (architecture) of the macromolecule and the block nature, relative length and type of coupling. The self-assembly of macromolecules of molecular brushes is largely affected by their structural features, in particular, the following. First, the interaction ('repulsion') of the densely grafted side chains dictates the conformation of molecular brushes and causes backbone and side chains to straighten, *i.e.*, gives rise to 'induced' rigidity of the macromolecule, depending on the length and grafting density of side chains. Second, molecular brushes, especially multicomponent ones, have fairly large molecular weights, which often exceed 10^6 g mol^{-1}, being much greater than the molecular weights of linear block copolymers.

Numerous data indicate that multicomponent molecular brushes can generate ordered cylindrical, thin layer (lamellar) or spherical areas in the solid phase, like linear block copolymers. According to the currently prevailing view, molecular brushes provide more freedom for the control over supramolecular assembly processes than linear block copolymers, since apart from the dependence on the nature and length of the backbone, self-assembly also depends on the nature, length and grafting density of side chains. The phase morphology of the brushes can be tuned by influencing the shape of domains *via* variation of the length and distribution of side chains and by influencing the size of domains *via* variation of the backbone length.[19] As distinct from linear block copolymers, brush block copolymers form larger domains in the solid phase (up to several hundred nanometres) as a result of microphase segregation. Their formed morphology is stable up to fairly high temperatures. The segregation is maintained by a relatively large length of the straightened brush backbone. The presence of side chains rigidly attached to the backbone prevents coiling of the macromolecule on heat treatment and, hence, contributes to the retention of the ordered morphology.[193] Asymmetric copolymer and block copolymer brushes were shown to form spherical or cylindrical domains. A linear dependence of the domain size on the backbone length was established for symmetric block copolymer brushes in numerous studies.

The self-assembly processes of block copolymer and asymmetric brushes in the solid phase were studied using thin-film or pressed and annealed disc-shaped samples. Larger size of the ordered structures formed by these molecular brushes in comparison with the ordered structures formed by linear block copolymer was noted for the first time by Runge *et al.*,[90] who demonstrated that diblock copolymer brushes **72** with PSt and PL side chains form 100 – 200 nm cylindrical domains in the solid phase. Later, the same research team identified a similar behaviour for a broad range of diblock copolymer brushes by detecting 100 – 300 nm plate-shaped, cylindrical or spherical domains depending on the relative length of the block with PL side chains.[18, 194] Furthermore, similar self-assembly in the solid phase was found for di-, tri- and tetrablock copolymer brushes with chemically different side chains and backbones.[195, 196]

Studies of the effect of the type of distribution (random, block and gradient) of the PSt and PL side chains in a copolymer molecular brush on the morphology of pressed and additionally annealed samples were reported.[19, 139, 193] The initial brushes had the same backbone, similar MW and

Structure 72



72

similar mole fractions of PSt and PL components. The size and shape of structures formed in the solid phase were studied by TEM and small angle X-ray scattering (SAXS) (Fig. 6). The obtained results indicated the formation of an ordered microdomain morphology differing in size and shape from the traditional morphology inherent in linear block copolymers. Block copolymer brushes formed an ordered lamellar structure with 70 – 150 nm lamellar domains.[19] Subsequently, it was shown[139, 193] that asymmetric block copolymer brushes and gradient copolymer brushes containing side chains of different length, but backbones of equal length are self-assembled into peculiar cylindrical domains, which was used to manufacture a nanoporous material.

For more in-depth study of the morphology of gradient copolymer brushes, the authors performed alkaline etching of the polylactide moiety of the brushes.[193] TEM and SAXS examinations of the resulting material revealed straight channels parallel to the sample surface and hexagonal pores with an average diameter of 15 nm perpendicular to the sample surface. This attests to a sample morphology composed of similar cylindrical domains, while their block copolymer brush analogues were packed into lamellar microstructures. The interplanar spacings of these structures regularly changed with changes in the percentage of block units with different side chains.

In the case of gradient copolymer brushes and AB block copolymer brushes, the interdomain gaps increased almost linearly with increasing number of repeating units along the brush backbone. However, the interdomain gaps were much smaller in gradient systems than in block copolymer analogues, with the backbone and side chain lengths being equal. This type of variation of this parameter was not observed for samples of linear copolymers and copolymer brushes with a random distribution of side chains.

Xia *et al.*[88, 102] utilized the 'grafting through' strategy and the ROMP reaction to synthesize narrow-disperse ($Đ = 1.05$) block copolymer and random copolymer brushes with PL and PBA side chains. Study of the self-assembly of the molecules of these brushes in thin films revealed a lamellar morphology with interplanar spacing of >100 nm for symmetric block copolymer brushes and a non-lamellar structuring with smaller periodic characteristics (40 – 60 nm) for asymmetric block copolymer brushes.

The morphology of the thin films of asymmetric Janus brushes with PSt and polydimethylsiloxane (PDMS) side chains was studied by scanning electron microscopy (SEM) and SAXS.[176, 177] Depending on the formation conditions of the films, the authors experimentally observed lamellar

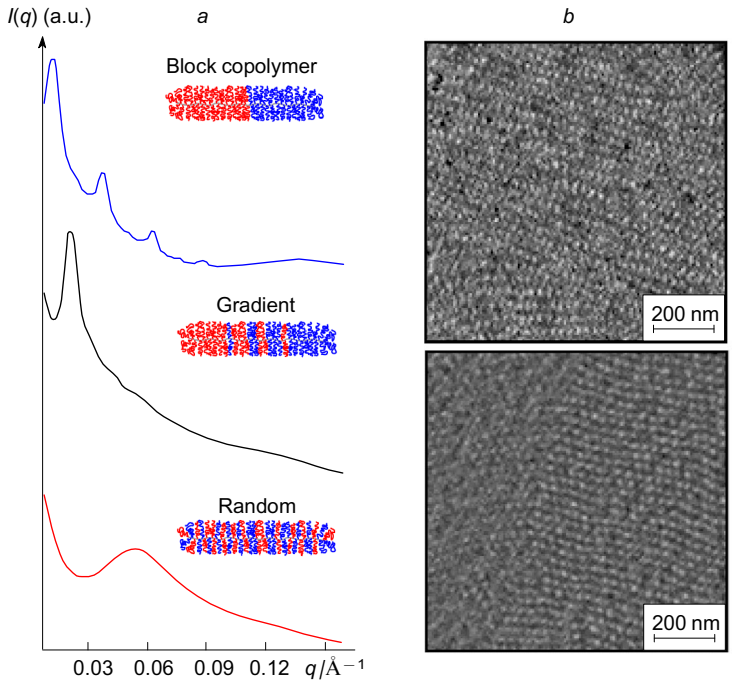


Figure 6. SAXS characteristics of nanostructures of molecular brushes with different side chain distribution in the solid phase (*a*) and TEM image of the morphology of brush nanostructures with gradient distribution of side chains (*b*);[193] *q* is scattering vector.

structures, hexagonal cylindrical domains and cylindrical microdomains with long-range periodicity; the domains formed a two-dimensional gyroid structure with interdomain distances of ~14–20 nm (Fig. 7). The experimental data were in good agreement with the results of computer simulation of the aggregation of brush macromolecules in the bulk and in thin films.

Grubbs and co-workers [197] ascertained that the presence of side chains and the grafting density are important structural parameters that have a significant effect on the physical properties of molecular brushes. They studied the effect of variation of the grafting density (z) in the $0 \leqslant z \leqslant 1$ range on the self-assembly of copolymer macromolecules in the solid phase. For this purpose, copolymers with well-defined structural parameters were synthesized by ROMP of macromonomers with PSt and PL chains and a norbornene terminal group. For the variation of the grafting density of PSt and PL side chains, the brush structure was 'diluted' with *endo*,*exo*-norbornenyl dimethyl ester. For comparison, linear block copolymer analogues with ultrahigh molecular weights were synthesized. By SAXS study of seventeen series of copolymers with variable z, the authors demonstrated that graft copolymers were assembled to long-range order lamellar structures. The range of periodicity monotonically decreased with decreasing z and showed a transition at $z \approx 0.2$ caused by a considerable change in the chain conformation.

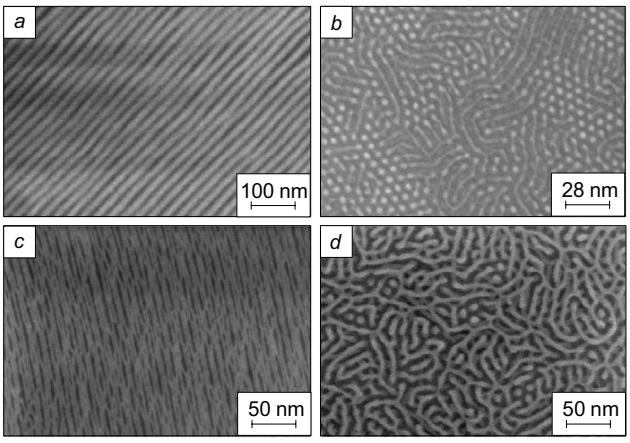
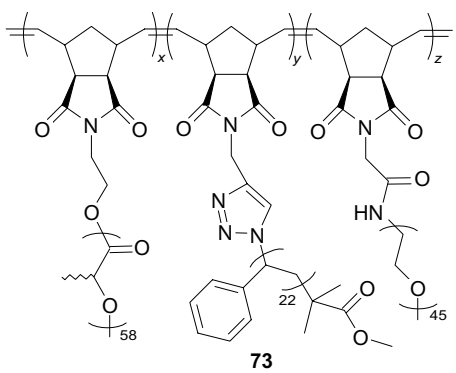


Figure 7. SEM images of the morphology of films of asymmetric brushes with PSt and PDMS side chains.[176]
(*a*) Drop-cast films; (*b*) centrifugal field-cast films; (*c*) films treated in a solvent atmosphere; (*d*) films treated by thermal annealing.

Grubbs and co-workers [198] studied the effect of the backbone conformation on the phase behaviour of a multicomponent block copolymer brush. As investigation objects, the authors used triblock copolymer brushes **73** containing brush blocks of variable length with PSt, PL and

Structure 73



73

PEO side chains synthesized using the 'grafting through' ROMP of the corresponding norbornene-containing macromonomers.

Instead of forming the expected lamellar morphology, brushes with the middle block bearing PSt side chains showed unusual phase behaviour at certain parameters and formed mixed medium-sized domains with decreasing range of periodicity upon increase in the length of the brush block bearing PEO side chains. For explaining the experimental and theoretical data, the authors suggested that in thin films a polymer brush is able to form loops, despite the steric rigidity of the backbone.

The influence of side chains and their grafting density on morphology and physical properties of multicomponent molecular brushes was also demonstrated for heterograft brushes with poly(ethylene glycol methacrylate) and octadecyl methacrylate (ODMA) side chains.[157] Both side segments of brushes synthesized in this study tend to crystallize at room temperature. The linear analogue PEGMA and its copolymer with ODMA form spherolites and hexagonal crystal structures, respectively. X-ray diffraction study revealed disorder of the packing of these segments in the graft copolymer to form an amorphous fraction instead of a partially crystalline one. The thermomechanical measurements showed rubber-like behaviour of graft copolymers.

In the last decade, equally extensive studies have been concerned with aggregation of copolymer macromolecules in solutions. It is known that the type of aggregation of amphiphilic copolymers and the CMC are substantially affected by the thermodynamic quality of the solvent with respect to its particular blocks, ionic strength of the solvent, micellization conditions, molecular weights of the copolymer and separate blocks and the copolymer architecture. So far, most of studies in this field have been focused on linear block copolymers. Meanwhile, the copolymer architecture has a considerable influence on the aggregation in solutions, and branched brush copolymers possess fundamentally different properties from those of linear copolymers.[31, 199 – 201] It was shown experimentally that, like linear block copolymers, amphiphilic multicomponent brushes form stable spherical, cylindrical and bilayer micellar structures such as vesicles.[15, 16, 23, 202] Quite a few examples of this type are given in Section 3 devoted to the synthesis of multicomponent brushes. As compared with linear block copolymer analogues with similar molecular weights, multicomponent molecular brushes tend to undergo faster micellization to give larger aggregates when dissolved in selective solvents and to be self-assembled even in very dilute solutions.

Of particular practical interest is the ability of amphiphilic multicomponent brushes to form micellar systems in water. The aggregation of brush macromolecules in solutions is studied by DLS, AFM and TEM methods, which are suitable for estimating the aggregate size, size distribution and shape. Based on the obtained results and MW of the copolymer, the degree of aggregation of micelles is calculated. Li *et al.*[98] investigated the behaviour in solutions of amphiphilic diblock copolymer molecular brushes **74** composed of blocks with PSt and PMAA side chains. These brushes were obtained by combination of RAFT polymerization (for the synthesis of macromonomers) and ROMP (for 'grafting through' preparation of the brushes).

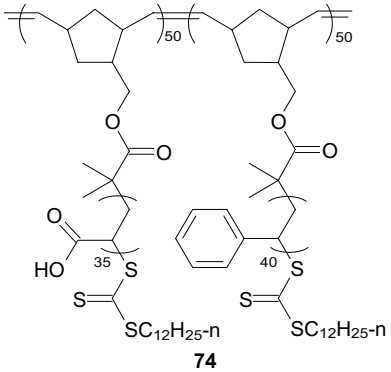
Using the phase segregation method of micelle formation, conventionally used for linear diblock copolymers, a solution of the synthesized diblock copolymer brushes was dialyzed against water in a solvent common to all polymer components (DMF). The degree of aggregation of micelles was determined from the known size of spherical micellar structures. The resulting value proved to be several times smaller than that usually observed for linear amphiphilic block copolymers, which is evidently caused by a larger size of the micelle building blocks.

Fenyves *et al.*[203] demonstrated the ability of amphiphilic diblock copolymer molecular brushes **75** with PL and poly(ethylene oxide methacrylate) (PEOMA) side chains to undergo supramolecular assembly; initially, a DMF solution of **75** was dialyzed against water. The micelle shape was visualized by cryo-TEM (Fig. 8).

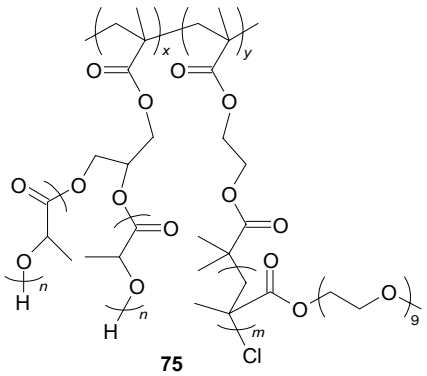
For these brushes, the CMC was 10^{-9} mol litre^{-1}, which is indicative of an excellent thermodynamic stability of the resulting micellar aggregates. The aggregate core diameter was $\sim$50 nm and the overall size of the micelle (including the corona) exceeded 100 nm. It was shown that a decrease in the size of the hydrophilic PEOMA block gives rise to structure asymmetry; as a result, a spherical micelle is converted to a cylindrical micelle or a bilayer lamellar structure. The authors noted that the identified trend of variation of the micelle size and shape can be described by a model developed for analysis of micellization of small surfactant molecules.

Shi *et al.*[204] prepared disk-shaped micelles of hexagonally packed amphiphilic AbBA triblock copolymers **76** with a mixed linear-brush topology, where the block bB was represented by a molecular brush with densely grafted PtBA-block-PSt side chains, while the block A was represented by poly[*N*-(2-methacryloyloxyethyl)pyrrolidone] (PNMEP). In methanol, which is a selective solvent for the block A, the brush formed 2D supramolecular structures, in

Structures 74, 75



74



75

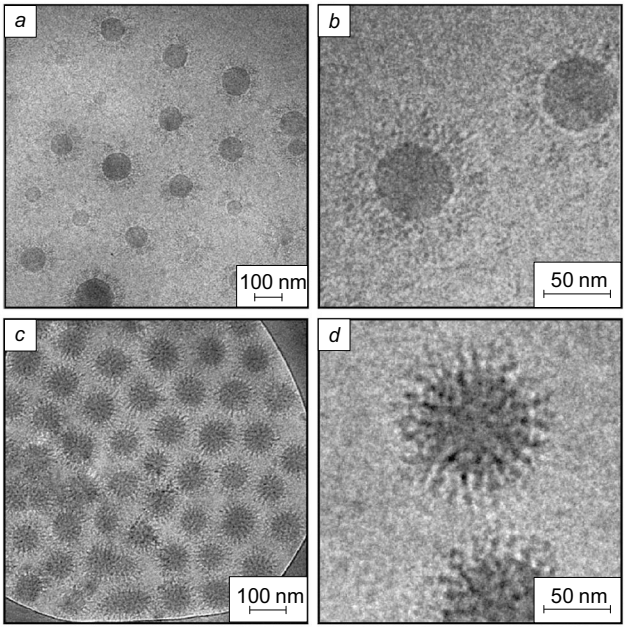
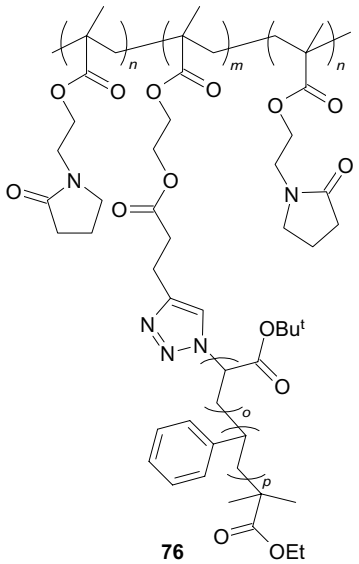


Figure 8. Cryo-TEM images of spherical micelle-like structures formed upon self-assembly in water of diblock copolymer brush **75** macromolecules with different side chain lengths of hydrophilic (*m*) and hydrophobic (*k*) blocks.[203]
(*a*, *b*) *m* (PL) = 90, *k* (PEOMA) = 56; (*c*, *d*) *m* (PL) = 82, *k* (PEOMA) = 27; PL is poly(L-lactide), PEOMA is poly(ethylene oxide methacrylate).

which the PNMEP block remained soluble and the block bB precipitated to form discs with a constant thickness (~33 nm) and a diameter of hundreds of nanometres.

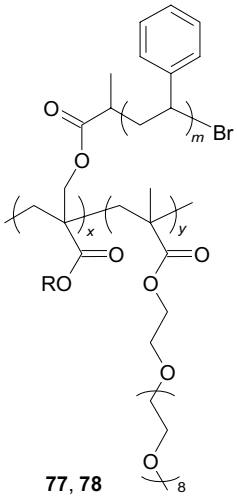
Structure 76



76

Huang and co-workers[205] synthesized two types of asymmetric molecular brushes with the PBA (**77**) or PAA (**78**) backbone and variable length of hydrophobic PSt side chains and variable grafting density of the hydrophilic MPEGMA side chains using successive RAFT and ATRP polymerizations and elucidated the effects of the grafting density and side chain length on the size of aggregates formed upon self-assembly. The CMC of the brushes was found to decrease with increasing length of the hydrophobic PSt side chains and to increase with increasing content of hydrophilic segments. In water, large spherical micelles with a diameter of 120 – 230 nm were generated. In these micelles, the MPEGMA side chains formed the corona, while the core consisted of numerous micelles with islands of PBA segments in the continuous phase of MPEGMA segments. For copolymers with invariable MPEGMA grafting density, the micelle size increased with increasing length of the PSt side chains. For brushes with invariable length of the PSt side chains, the micelle size decreased with increasing grafting density of MPEGMA side chains.

Structures 77, 78



77, **78**

R = Bu^t (**77**), H (**78**)

Herrera-Alonso and co-workers[206] studied self-assembly of amphiphilic copolymer brushes with alternating short PEG and PL side chains in water; the brushes were synthesized using a combination of 'grafting from' and 'grafting onto' strategies. The self-assembly processes were studied upon transfer of the copolymer into water by dialysis against water or during transfer to aqueous medium by replacing the solvent. Depending on the micellization conditions, the authors found a diversity of sizes and shapes of copolymer structures, in particular, the formation of toroidal structures upon fast replacement of the solvent was observed for the copolymer containing 26 mass % of PEG.

Schappacher and Deffieux[207] prepared well-organized polymer nanotubes based on cyclic molecular brushes. Polychloroethynyl vinyl ether served as the macrocyclic backbone, and PSt and PIp chains were randomly grafted to it. In a selective solvent (n-heptane), copolymer molecules formed up to 700 nm nanotubes ~100 nm in diameter. The fact that the diameter of these assemblies corresponded to the macrocycle diameter of the brush backbone was especially remarkable. Thus, the cyclic architecture of the brush determined the aggregation pattern of its macromolecules to give well-organized nanotubes (Fig. 9), which cannot be obtained from linear copolymers.

A unique feature of amphiphilic molecular brushes is their ability to form unimolecular micelles in a selective solvent, most often, in water.[208] The ability to exist in aqueous solutions as single molecules forming unimolecular

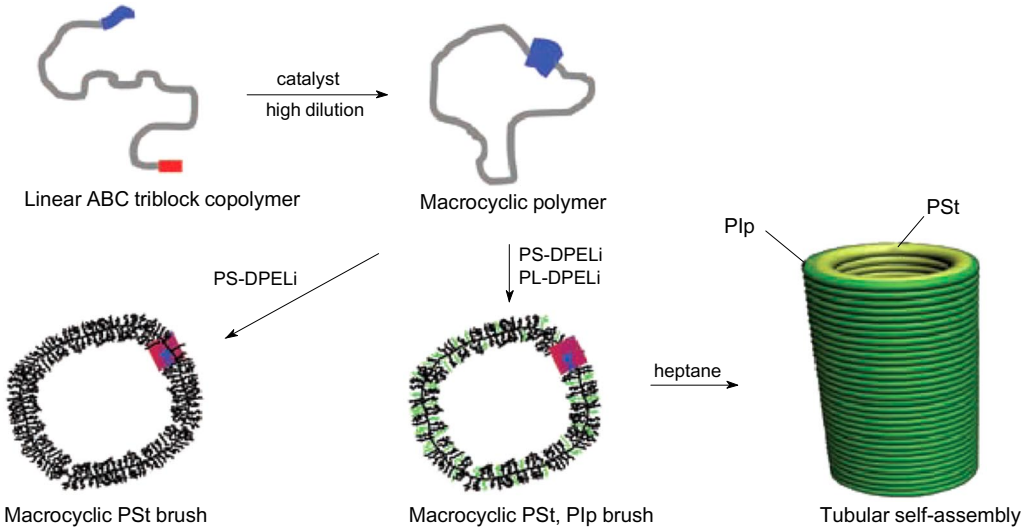


Figure 9. Structures based on cyclic molecular brushes with PSt and PIp side chains self-assembling in n-heptane.[207] PS-DPELi, PL-DPELi is (1,1-diphenylethylene)-terminated polystyryl- or polyisoprenyllithium.

micelles[209] with a core – shell structure is typical most of all of brushes with block copolymer side chains. Evidently, these micelles are stable under high dilution, which makes them especially attractive for the development of stable micelles for various applications.[210] For example, Gong and co-workers[211] obtained unimolecular micelles based on a molecular brush with the PHEMA backbone and PL-block-PEG block side chains for targeted delivery of anticancer drugs and non-invasive positron emission tomography.

The preparation of unimolecular core – shell micelles based on molecular brushes with various diblock copolymer side chains was described in a series of publications of Professor Müller's research team.[21,212–216] The brushes were obtained by combinations of living anionic polymerization and ATRP methods. According to cryo-TEM or AFM data, these polyelectrolytes with the PAA polyanionic block adjoining the backbone[21,213,216] are self-assembled into structures that were called pearl necklace (Fig. 10). It was found that these structures are sensitive to pH of the medium: they are formed at pH 7 and disappear at pH 4.[216] Core – shell cylindrical brushes with block copolymer chains obtained by 'grafting through' of diblock copolymer macromonomers were also described by Djalali *et al.*[217] The amphiphilic nature of the brush macromolecules was proved by TEM in combination with staining of macromolecules with RuO_4 vapour and selective staining of the core with a $HAuCl_4$ solution followed by reduction of these reagents, which was used to determine the core and shell sizes.

Recently, Chen and co-workers[218] reported the formation of unimolecular micelles in an aqueous medium, on the basis of three samples of a multicomponent brush with block copolymer PHEMA-graft-(PAA-block-PEG) side chains synthesized by combining living polymerization and click chemistry methods. For all samples, the degrees of polymerization of the PAA and PEG blocks were similar, while the degrees of polymerization of the PHEMA backbone were 57, 122 and 747. The authors demonstrated that with elongation of the brush backbone, the shape of the unimolecular micelle changes from spherical to rod-like and then to worm-like (Fig. 11).

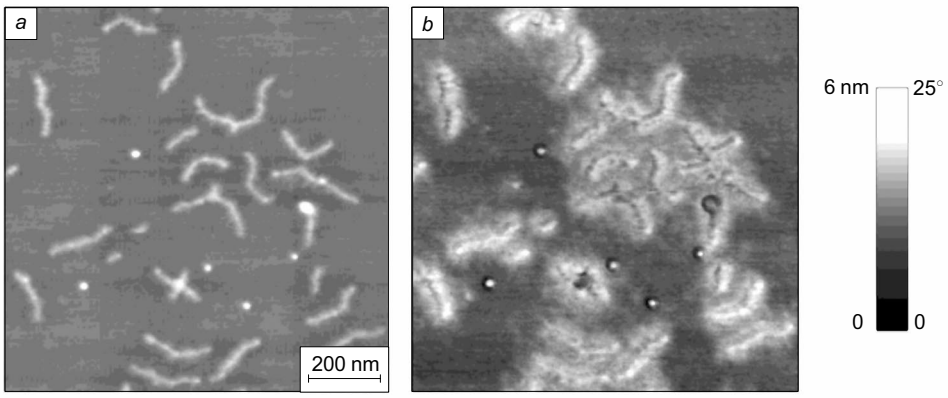


Figure 10. AFM images of molecular brush samples with diblock copolymer side chains PAA_{25}-block-PBA_{61}.[21] (*a*) Height, (*b*) phase; PAA is polyacrylic acid, PBA is poly(n-butyl acrylate).

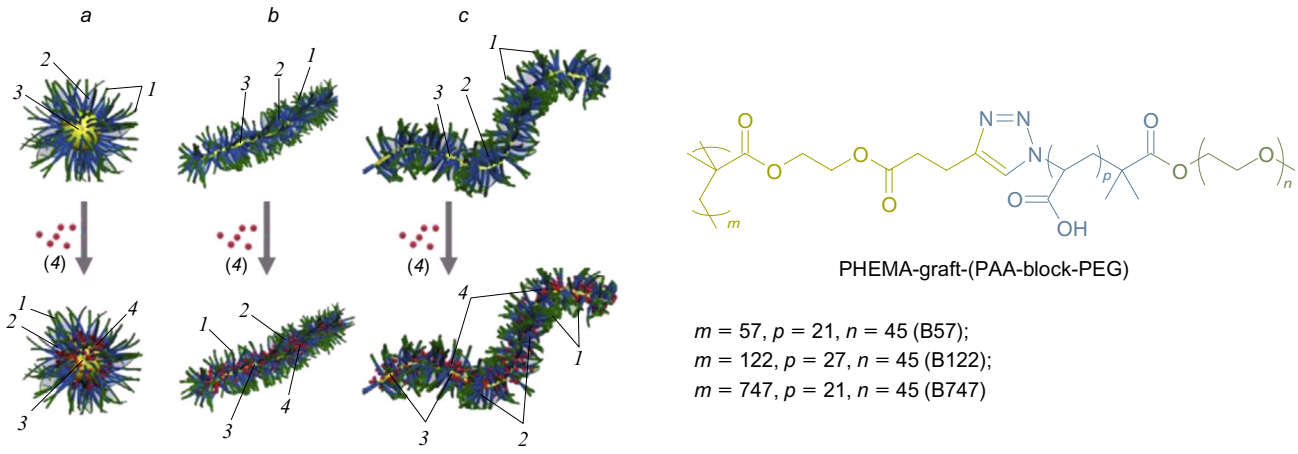


Figure 11. Diagram of the preparation of IR780 photothermal therapy drug-loaded unimolecular nanoparticles with spherical (*a*), rod-like (*b*) and worm-like (*c*) morphology.[218]
(*1*) PEG (polyethylene glycol), (*2*) PAA (polyacrylic acid), (*3*) PHEMA [poly(2-hydroxyethyl methacrylate)], (*4*) IR780.

According to AFM, spherical micelles had a diameter of 19 ± 3 nm, whereas the rod-like micelles were 18 ± 3 nm across and 60 ± 9 nm along, and the worm-like micelles were 18 ± 3 nm across and 171 ± 28 nm along. The authors noted good agreement between AFM and DLS results. The obtained micelles were successfully loaded with the IR780 drug. It was found that the unimolecular nature of the micelles was retained after loading, while the micelle size slightly increased.

In another publication, Chen's team[208] reported the synthesis of multicomponent brushes with a PCL backbone and block copolymer side chains of two types: poly(n-butyl acrylate)-block-poly(oligoethylene glycol acrylate) (PBA-block-POEGA) and poly(n-butyl acrylate)-block-polyethylene glycol (PBA-block-PEG). Brushes had a core – shell struc-

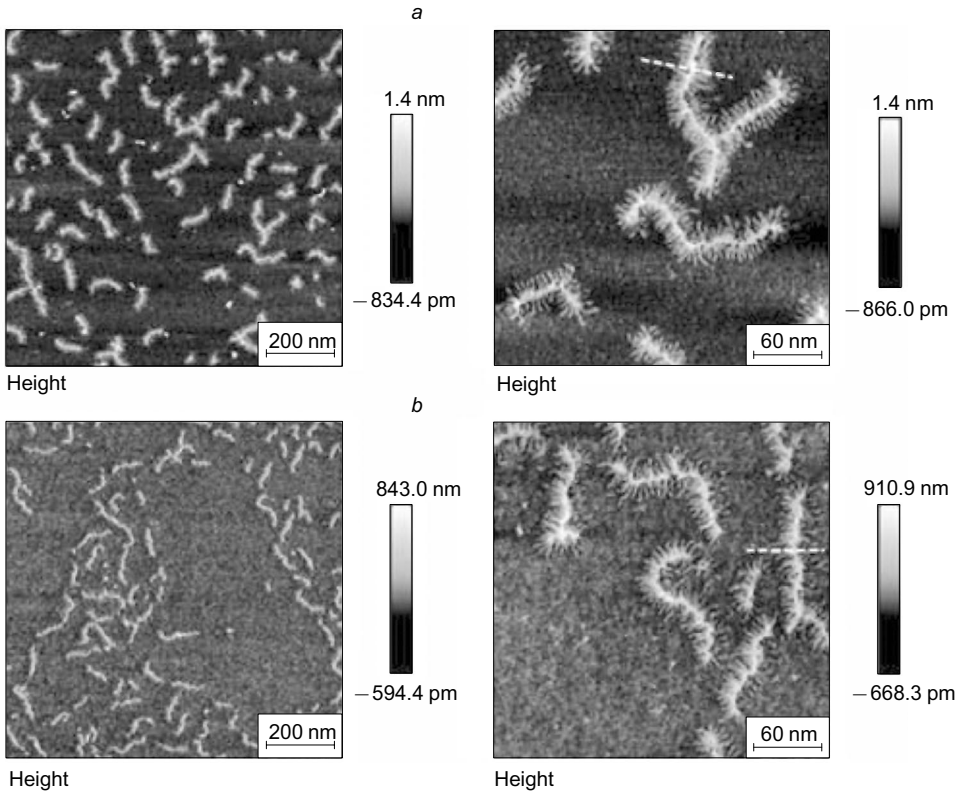


Figure 12. AFM images of PCL_{700}-graft-(PBA_{24}-block-$POEGA_{11}$) films deposited on mica by centrifuging solutions of polymers in water (*a*) and THF (*b*).[208]
PCL is polycaprolactone, PBA is poly(n-butyl acrylate), POEGA is poly(oligoethylene glycol acrylate).

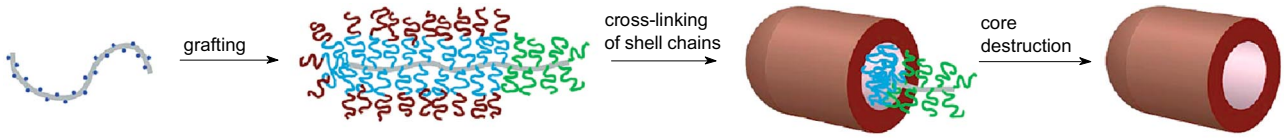


Figure 13. Diagram of the preparation of well-defined organic nanotubes based on multicomponent molecular brushes.[136]

ture of the same type, but were considerably different in the shell topology. In the case of poly(n-butyl acrylate)-block-poly(oligoethylene glycol acrylate) (PBA-block-POEGA) side chains, the outer block of side chains had a 'brush on brush' structure. The authors were able to obtain remarkably clear AFM images of these brushes (Fig. 12). In aqueous medium, unimolecular micelles of the brushes with different topology of the side chain outer block were formed. A comparison of the stability of micelles formed by brushes with the same backbone and the PBA block and a similar mole fraction of the side chain outer block revealed higher stability for brushes with branched outer blocks, whereas the brushes with linear outer blocks formed larger aggregates.

The unimolecular composition of the micelles of multicomponent brushes with block copolymer side chains made it possible to fabricate unusually shaped nanoobjects such as tubes. For example, multicomponent core – shell molecular brushes with PL blocks (core) and poly[4-(but-3-enyl)-styrene] blocks (shell) in the side chains were synthesized by combination of CP methods.[136, 219, 220] It was found that exact control of the functionality and structure of the macromolecules may allow the formation of cylindrical unimolecular micelles. After cross-linking of the shell chains and destruction of the PL core, the micelles turned into cross-linked shell-stabilized hollow nanotubes with a negatively charged inner surface (Fig. 13). The nanotube length and diameter were determined by the lengths of the backbone and side chains of polymer precursors. The nanotubes thus obtained were able to selectively encapsulate differently charged molecules.[16]

Unsal *et al.*[221] described the synthesis of amphiphilic multicomponent block copolymer brushes *via* ROMP of norbornene-functionalized macromonomers. By combining 'grafting from' and 'grafting through' approaches, the authors obtained four series of brushes with PL and PEO side chains. These series were characterized by different combinations of units with one grafted PL or PEO chain and units with two PL or PEO side chains grafted to one backbone unit. The PL side chains were functionalized at the ends by photoactive groups. According to DLS and cryo-TEM data, in aqueous solutions, all copolymers formed aggregates of the same shape and size with hydrodynamic diameters of 50 to 150 nm. After photo-cross-linking of chains of the shell, the resulting aggregates were used for efficient loading of anticancer drugs.

The effect of arrangement of different side chains along the backbone of the brush on the aggregation of macromolecules in solutions was investigated[222] in relation to random and block copolymer brushes with poly(3-hexylthiophene) and PL side chains. Brushes with the same molecular weight, but with different positions of these side chains were synthesized by ROMP of norbornene-containing macromonomers. It was shown that the degree of

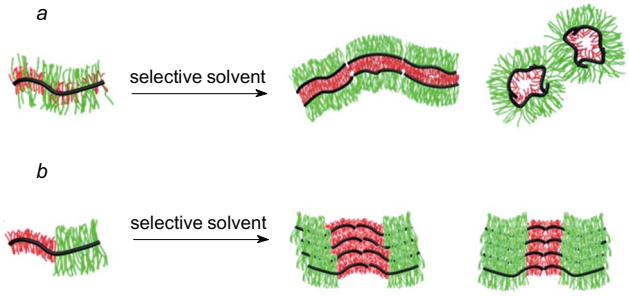


Figure 14. Self-assembly of molecular brushes with poly(3-hexylthiophene) and PL side chains in solution depending on the side chain composition and distribution.[222]
(*a*) Copolymer brush with random distribution of side chains, (*b*) block copolymer brush.

crystallinity and the properties of melts of these brushes do not depend on the positions of different type side chains, but are determined only by their relative contents. However, in a selective solvent, the random and block copolymer brushes were self-assembled in different ways (Fig. 14). As the selective solvent, a mixture of THF and ethyl acetate was used ($v/v = 60/40$). Tetrahydrofuran is a good solvent for both blocks, whereas ethyl acetate is selective to PL. In a mixture of these solvents, block copolymer brushes formed stable, strictly ordered nanofibrous structures, irrespective of the relative contents of blocks of different type, while in the case of random copolymer brushes, they formed unstable nanofibres and spheres. The appearance of large ordered structures in solutions of block copolymer brushes was facilitated by the intra- and intermolecular $\pi-\pi$ interaction of poly(3-hexylthiophene) side chains, which was the main driving force of the self-assembly. The formation of such structures was not observed in solutions of random copolymer brushes; the authors attributed this to weakening of $\pi-\pi$ interactions due to the influence of long PL side chains. An increase in the content of PL chains, inducing a decrease in the interaction between the poly(3-hexylthiophene) chains, in the random copolymer brushes gave rise to spherical aggregates. The type of aggregation in solution observed for different samples accounted for the corresponding morphology of thin films. Thus, it was shown that the architecture of brushes determined by the choice of methods for their synthesis can be used for targeted control of the morphology of thin films based on them, which is promising for optoelectronic applications.

7. Application of multicomponent molecular brushes

In recent years, multicomponent molecular brushes have attracted increasing attention because of the unique set of

their properties promising for the preparation of new materials. The large size and anisotropy of macromolecules and their susceptibility for spontaneous ordering open up extensive possibilities of practical applications of molecular brushes, which are often difficult to attain using linear copolymers.

Numerous studies are directed towards the use of molecular brushes for targeted drug delivery, control of the rate of degradation of the polymer carrier at a desired drug release rate, protection of drugs from enzymatic degradation or hydrolysis during transportation and decrease in the toxicity.[223 – 225] Approximately 70% of new promising pharmaceutical drugs are insoluble in water,[173] which restricts their use and accounts for importance of the development of efficient water-soluble polymeric carriers.[226] In particular, the use of traditional cancer chemotherapy drugs such as doxorubicin (DOX), camptothecin (CPT) and paclitaxel (PTX), which have high cytotoxicity against various tumour cells, is restricted by their poor solubility in water and poorly controllable delivery to the tumour site.[227] Therefore, systems for drug delivery to the tumour and for suppression of drug uptake at other sites have been actively developed in the last decade. Among systems of this type, polymer micelles possess considerable advantages such as convenient synthesis, high drug loading, biological compatibility, low cytotoxicity and efficient controlled drug delivery.[228] Until recently, studies along this line have been mainly concerned with the micelles formed by linear amphiphilic block copolymers in aqueous medium.[229, 230] Meanwhile, recently it has been shown [151] that in comparison with these delivery systems, micelles based on copolymers with brush segments exhibit high stability, high drug loading capacity and ability to protect drugs from the action of biological environment, thereby ensuring long-term blood circulation and controlled drug release as a result of introduction of pH-sensitive segments into the copolymer.

Qian *et al.*[150] used a combination of RAFT and ROP methods and the 'grafting from' strategy to prepare a series of well-defined amphiphilic copolymers **36**. The authors demonstrated that copolymer macromolecules are assembled in water into micelles, which are shaped like spheres or vesicles depending on the structural parameters. Copolymer micelles do not have cytotoxicity by themselves, but show high capacity for drug loading *via* hydrophobic interactions. For example, DOX loaded into such micelles (6.2 mass %) exhibited much higher cytotoxicity than free DOX.

It is known that pH of tumours is lower than the normal physiological value ($\sim$7.4), for example, endosomal and lysosomal pH is 4.5$\sim$6.5.[231] Therefore, researchers pay much attention to the preparation of pH-sensitive polymer micelles.[232, 233] Huang *et al.*[151] described a three-stage approach for the synthesis of pH-sensitive triblock copolymer with the central hydrophilic linear PEG block and peripheral hydrophobic poly(β-amino ester)-graft-(cholesterol) blocks as a prolonged release drug delivery carrier for anticancer drugs.

According to potentiometric titration data, this copolymer possesses high pH sensitivity due to the protonation of amino groups, which results in transformation of hydrophobic segments into hydrophilic ones. The critical micelle concentrations of the copolymer are 6.8, 12.6, 17.4 and 26.6 μg ml^{-1} at pH of 7.4, 6.5, 6.0 and 5.0, respectively. The authors note that the tendency of CMC values to increase with decreasing pH attests to high stability of copolymer micelles, which may ensure longer time of their circulation in the body. The pH values also considerably affects the hydrodynamic diameter and ζ-potential of copolymer micelles. As pH is decreased from 7.4 to 5.0, the particle size and ζ-potential increase from 205.4 to 285.7 nm and from 12.7 to 47.0 mV, respectively. DOX-loaded polymer micelles with high degree of loading (20%) were prepared by dialysis technique. According to *in vitro* assays, the drug release rate and cumulative action depended on the pH.

Yakimansky *et al.*[234] demonstrated the good prospects of using water-soluble amphiphilic molecular brushes with the hydrophobic PI backbone and hydrophilic PMAA side chains as nanocontainers for solubilization of theranostic photodynamic agents based on cyanoporphyrazines. Later it was shown [235] that the brushes themselves have very low cytotoxicity, and their aggregates with porphyrazine formed in aqueous solutions have a size of about 100 – 200 nm, which is favourable for their use in photodynamic therapy, as opposed to the methylcellulose – porphyrazine and PEG – porphyrazine aggregates, which are an order of magnitude larger. The PI-graft-PMAA – porphyrazine aggregates provide the most efficient delivery of the photodynamic therapy agent to the tumour cells (in comparison with the delivery by other solubilizing water-soluble polymers), which was demonstrated for epidermoid carcinoma (A-431), cervical cancer (HeLa-M), bladder cancer (T24) and breast cancer (SK-BR-3) cells.

Multicomponent brush copolymers can serve as nanostructures efficiently loaded with hydrophobic drugs for various purposes. For example, micelles of mixed linear brush copolymers with a linear PEG block and a brush block with polylysine side chains were efficiently loaded with an anti-ischemic drug and showed sustainable drug release.[236, 237]

Yang *et al.*[238] carried out ATRP to obtain mixed linear brush copolymers with the linear [P(MMA-co-MAA)] block and the brush block prepared by polymerization of the PEGMA macromonomer with M_n = 300 Da (Fig. 15). The authors demonstrated that the macromolecules of this copolymer are self-assembled in water to give exceptionally stable spherical micelles. The average size of the drug-loaded micelles was 120 – 250 nm. For this purpose, the authors used ibuprofen, a water-insoluble anti-inflammatory drug, which was loaded into the polymer carrier *via* dialysis. It was found that the brush block with non-toxic hydrophilic PPEGMA side chains inducing no immune response is distributed over the micelle surface, thus acting as a tight protective layer maintaining the micelle stability during biological circulation. The hydrophobic PMMA fragments and pH-sensitive MAA fragments form the core encapsulating the drug. The release of ibuprofen from the micelles *in vitro* depended on the pH of the medium. In the simulated intestinal fluid (pH 7.4), 90% of the drug is released in 6 h. The results demonstrated that micelles of this type can deliver hydrophobic drugs to the intestine with a minor loss of the drug and, hence, they can be used as promising targeted delivery systems for poorly water-soluble drugs.

The ability of molecular brushes to form supramolecular structures with low CMC is also useful for the application of multicomponent brushes as drug carriers. For example,

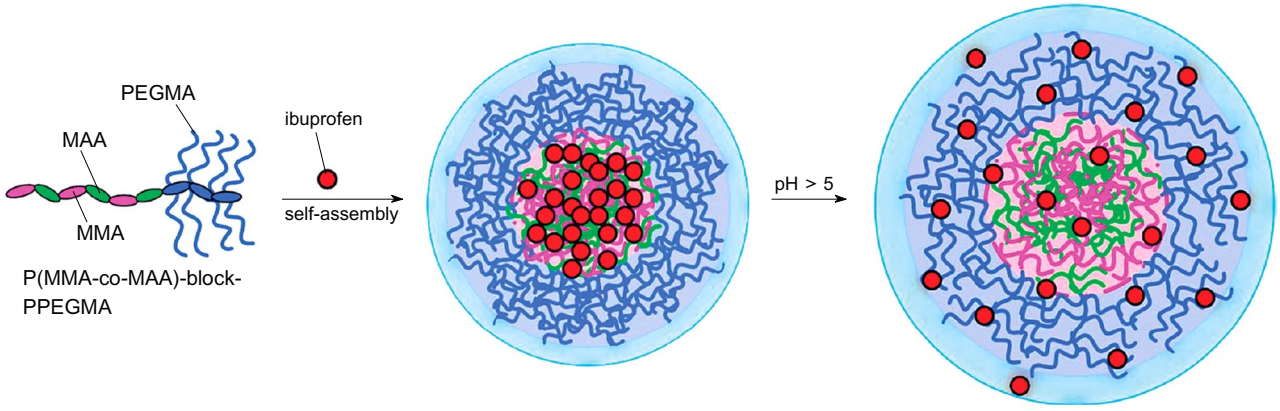


Figure 15. Diagram of micellization of P(MMA-co-MAA)-block-PPEGMA and pH-dependent drug release.[238] MAA is methacrylic acid, MMA is methyl methacrylate, PEGMA is poly(ethylene glycol methacrylate), PPEGMA is poly[poly(ethylene glycol)methyl ether monomethacrylate].

block copolymer brushes composed of a hydrophobic block with grafted functionalized cholesterol and a hydrophilic block with PEO side chains, with molecular weight in the $400-600\times10^3$ range and $Đ = 1.21-1.16$, were synthesized by ROMP.[239] The CMC of these copolymers in aqueous media was 5.4 – 15.3 mg litre^{-1}. It was shown that micellar structures formed by this amphiphilic copolymer brush can encapsulate DOX with a high degree of loading. The loaded micelles were efficiently internalized by human cervical cancer cells, with steady release of DOX from copolymer micelles being less than 2% per 24 h. An excellent circulation time *in vivo* was found for the loaded micelles compared with free DOX; furthermore, they were mainly accumulated in tumour tissue with a much lower uptake by heart and other vital organs.

Among all copolymer molecular brushes, the brushes with amphiphilic diblock copolymer side chains attract most attention because of their unique nanomolecular core – shell structure and the ability to form unimolecular micelles in selective solvents. The sizes of these micelles can be controlled by varying the molecular-weight characteristics of the backbone and side chains. Unimolecular micelles are a promising alternative to the aggregates formed *via* self-assembly of linear block copolymers, since the covalent bonding ensures stability of these micelles in highly dilute solutions. Structures of this type attract increasing interest for biomedical applications, especially as unimolecular micellar systems for targeted drug delivery.[211,240–242]

Heterograft molecular brushes, *e.g.*, those with hydrophilic PEG side chains and hydrophobic PL side chains, were also proposed as polymer carriers in the form of unimolecular micelles.[243] The authors showed that the transfer of the copolymer macromolecule from an organic solvent (DMSO) into water is accompanied by a collapse of the backbone and the hydrophobic PL block. However, in the presence of low concentrations of a hydrophobic compound, the brushes form unimolecular spherical micelles with high efficiency of encapsulation (Fig. 16). The parameters of micelles considerably depend on the nature of the dissolved compound.

The unimolecular micelles are used for the development of new pharmaceutical compositions for theranostics, that is, agents for both early diagnosis and therapy. For example, conjugated poly{fluorene-alt-[4,7-bis(hexylthien)-2,1,3-benzothiadiazole]} copolymer was used as a fluorescent backbone, with block copolymer side chains PCL-block-POEGMA being grafted to this backbone *via* successive ROP and ATRP reactions.[244]

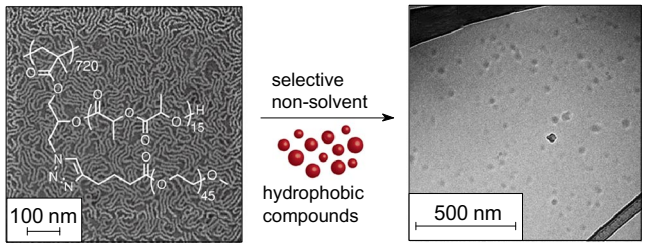


Figure 16. TEM images of the morphology of $PGMA_{721}$-graft-PEG_{45}/PL_{15} (on the left) and $PGMA_{721}$-graft-PEG_{45}/PL_{15} in the presence of hydrophobic Rose Bengal lactone (15 mass %) (on the right).[243]
PGMA is poly(glycidyl methacrylate), PEG is poly(ethylene glycol), PL is poly(L-lactide).

Owing to amphiphilic and branched structures of these brushes, it was possible to obtain unimolecular micelles with good dispersion capacity in aqueous media. Their optical properties and good biocompatibility made them promising as bioimaging probes for visuaization of biological systems. The presence of hydrophobic PCL blocks allowed efficient loading of these micelles with a hydrophobic anticancer drug (DOX).

Because of the possibility of formation of a core – shell or core – shell – corona structure and the presence of side chain blocks of different nature, molecular brushes with di- and triblock copolymer side chains are also promising as unimolecular templates or nanoreactors for the synthesis of organic and hybrid organic-inorganic nanostructures. An important advantage of these brushes as templates is that the CRP methods used to prepare them allow precise control of the positions of blocks that serve as matrices for nanoparticles. This, in turn, provides the possibility for targeted control over the size and distribution of the NPs formed. The beneficial combination of the polymer properties such as stability, elasticity and processibility with the

properties of inorganic NPs gives rise to soluble hybrid structures containing NPs in the core, with the shell isolating and stabilizing the NPs. Molecular brushes with di- and triblock copolymer side chains were used as templates for the design of organic nanotubes [15, 136, 220] and organosilicon hybrid nanotubes and nanowires.[20, 133, 134] For example, brushes bearing triblock copolymer side chains with the PtBA (core), PTMSPA (shell) and POEGMA (corona) sequence of blocks were used as unimolecular cylindrical templates for *in situ* formation of water-soluble organosilicon hybrid nanotubes.[133] Brushes with polyelectrolyte diblock copolymer side chains were used to obtain nanoparticles of noble metals (Au, Pt), semiconductors and magnetic materials in the polyelectrolyte core or in the shell.[21, 212 – 217, 245] Rzayev and co-workers [136, 220] employed brush templates to form polymer nanotubes. Mixed linear-brush block-graft amphiphilic brushes with peripheral linear blocks and a central brush block bearing PAA side chains were used as a nanoreactor and stabilizing agent for the generation of gold, nickel and silica NPs.[144]

One more promising area of practical application of multicomponent molecular brushes is for coatings to protect surfaces from protein adsorption. Thin film (less than 100 nm thick) coatings were obtained by deposition of dilute solutions of brushes on a substrate in a centrifugal field. For example, a film of amphiphilic asymmetric copolymer brush with hydrophobic PSt and hydrophilic PEG side chains was deposited on a glass surface.[246] The resulting film was shown to be an efficient anti-fouling system. Also it was shown that a surface coated by this brush acquires stimulus-responsive properties, in particular, it can respond to external stimuli such as treatment with selective solvents and to show hydrophobic or hydrophilic behaviour upon changes in the conformations of brush macromolecules.

In order to obtain new materials for devices with enhanced functional characteristics, polymer brushes can also be integrated into hybrid nanostructures.[247] Examples of these new materials are solid polymer electrolytes.[248] The replacement of liquid electrolytes by solids increases the safety of batteries by preventing evaporation or leakage and leads to higher thermal and mechanical stability of batteries. Solid electrolytes with high ionic conductivity at high temperatures (one of the highest values for PEO-based polymer electrolytes) for lithium ion batteries were developed on the basis of multicomponent molecular block copolymer brushes with norbornene groups in the backbone and PEO and poly{2,5-bis[(4-methoxyphenyl)oxycarbonyl]-styrene} side chains doped with lithium salts.[249]

Multicomponent molecular brushes are also promising as stabilizers for various purposes. Asymmetric brushes with PEG and poly(D,L-lactide) side chains [173] were proposed for efficient stabilization of β-carotene nanoparticles. Heterograft molecular brushes **42** with PEO and PBA side chains can serve as agents for the generation and stabilization of emulsions, for example the Pickering water – oil miniemulsion.[160] Comparison of brushes of various architecture (heterograft brushes and their diblock analogues) demonstrated that alternation of hydrophilic and hydrophobic side chains can enhance adsorption at the water – oil interface (Fig. 17). Jia *et al.*[149] described asymmetric nanocomposite ABC type Janus rods based on mixed linear brush copolymer **34**. Good prospects for the use of the obtained Janus rods as solid surfactants for stabilization of emulsions were demonstrated.

Particular attention is attracted by water-soluble polymer brushes with an LCST, the solubility of which decreases on heating and can even be completely lost at the cloud point. Changes of temperature, pH, polymer concentration and ionic strength of the solution and nature of the salt can be used to control the phase separation temperature and, hence, affect the final properties of the polymer material. These copolymer structures are usually obtained by introducing blocks of hydrophilic heat-sensitive polymers into

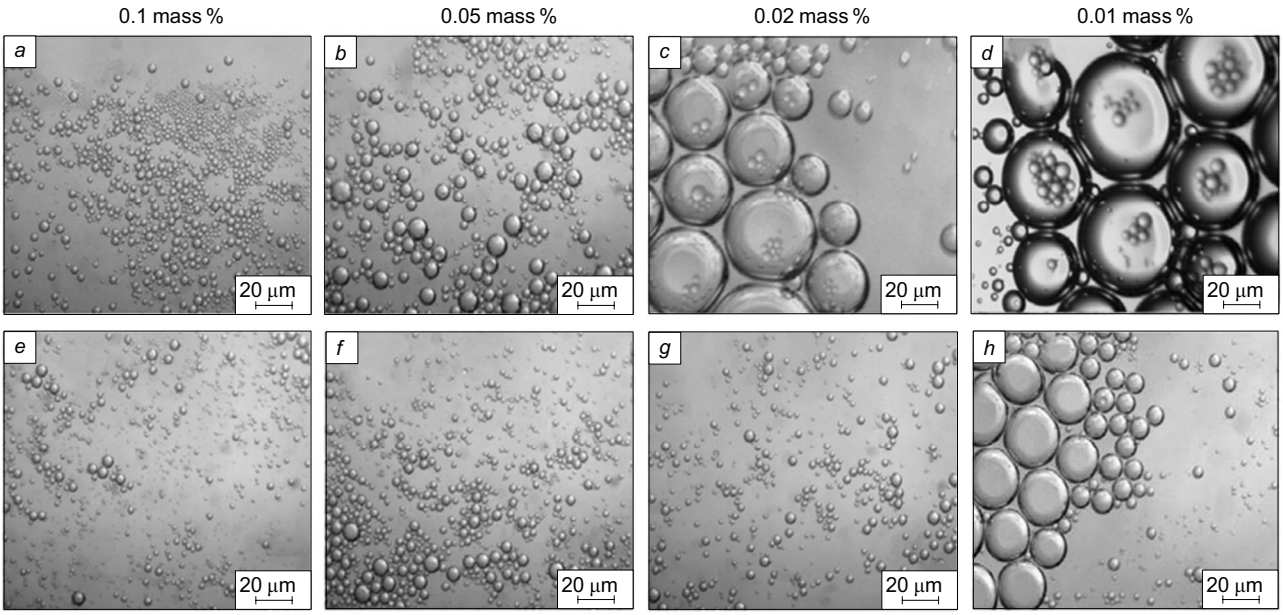


Figure 17. Optical microscopic images of dilute water – xylene emulsions of stabilized heterograft molecular brushes **42** with PEO and PBA side chains and hydrophobic to hydrophilic side chain ratios of ~1 : 3 (*a* – *d*) and ~1 : 1 (*e* – *h*).[160]

side chains. Heat-sensitive multicomponent brushes capable of spontaneously changing the shape of micelles in response to temperature changes are promising as templates. Kent *et al.*[250] demonstrated the possibility of controlling the shape of micelles based on stimulus-responsive brushes with diblock copolymer side chains by varying the solution temperature. The middle block of side chains was represented by heat-sensitive PDMAEMA, while the terminal block was poly(methoxytriethylene glycol acrylate). The brushes were obtained by CuAAC grafting of appropriate diblock copolymers to the backbone. Upon temperature change, the worm-like micelles turned to globules.

Grubbs and co-workers[17,251–253] made great advances in one more promising area of applications of multicomponent molecular brushes, namely, in the manufacture of photonic crystals. For example, it was shown[17] that block copolymer brushes with PSt and PL side chains obtained by ROMP of norbornene-terminated macromonomers are able to be rapidly self-assembled into a multilayer structure composed of alternating layers with different refractive indices (1D photonic crystals). The brushes had a high molecular weight (up to 6.5×10^6 Da) with relatively low polydispersity and 100% grafting density of side chains.

Müller and co-workers[216] synthesized brushes with diblock copolymer side chains (PtBMA-block-POEGMA) by two-stage ATRP; then the PtBMA block was hydrolyzed to give brushes with two hydrophilic blocks in side chains: PMAA-block-POEGMA. The final brushes were readily soluble in water and were pH-sensitive because of the polyelectrolyte properties of the PMAA block. These brushes were used to prepare superparamagnetic magnetite NPs.

Solid-phase di- and multicomponent polymer compositions are known to often undergo phase segregation. The addition of particular modifying agents into a segregated solid polymer blend contributes to the control of phase structure of composite materials.[254] Modifying agents of this type, called compatibilizers, are mainly located at the phase interface, thus changing the interfacial interaction. If some blocks of the compatibilizer are miscible with the dispersion medium and other blocks are miscible with the dispersed phase, the adhesion between the phases is enhanced, which leads to finer dispersion of the components during mixing.[255] Studies in this area were mainly carried out in relation to linear block copolymers. Meanwhile, Grubbs and co-workers[17] demonstrated that block copolymer brushes with PL and PSt side chains can serve as compatibilizers for a mixture of homopolymers of different types, *i.e.*, they can prevent macroscopic phase separation by stabilizing the interfaces. Interestingly, these brushes could also influence the distances between the lamellae, which enables control of the optical properties of polymer composite films.[251]

It is noteworthy that in recent years, a new alternative approach has been proposed to the design of elastomers based on multicomponent brush copolymers with mechanical properties unique for traditional synthetic linear homo- and copolymer elastomers.[256–258] It is known that, unlike biological tissues, which combine high elasticity and toughness, traditional synthetic elastomers show antiparallel patterns of variation of elasticity and toughness parameters (elastic modulus and toughness). Enhancing toughness characteristics of highly elastic polymers is a challenging task. This task is addressed, most often, by using empirical mixing techniques for the polymer and modifying and cross-linking agents. In the actively explored area of application of hydrogels as nature-mimicking materials, copolymerization methods are being developed. However, production of elastic and tough copolymer gels requires a precise combination of the density of hydrogen bonds and sparse chemical cross-linking and, hence, the thorough selection of the monomer natures and ratio.[259] Besides, for attaining a low elastic modulus, hydrogels should greatly swell in water, while brush structures are 'swollen' because of covalently attached side chains.

Mechanical testing of materials based on molecular brushes demonstrated fast deformation-induced stiffening for such systems not inherent in linear polymer.[254] The authors attributed this phenomenon to the stretched conformations of the backbone and side chains typical of molecular brushes, which is caused by the steric repulsion of side chains. Relying on these data, Matyjaszewski and co-workers[256,258] proposed introducing a macromolecular brush as a central block into ABA copolymers in order to attain a combination of high elasticity and toughness for elastomeric polymers. A considerable advantage of the proposed linear-brush elastomeric copolymers is the possibility to fabricate highly elastic materials able to enhance toughness characteristics during deformation without chemical modification or addition of a solvent.[256,258] The authors developed a physical model for programming the mechanical properties for this type of elastomers at the stage of copolymer synthesis by preparing brush blocks of different chemical structure, but with specified parameters such as the brush block length, side chain length and grafting density. This model was confirmed experimentally for copolymer networks based on structures containing brushes with polydimethylsiloxane side chains.[256,258] It is of interest that the synthesis of copolymers with multiblock architecture comprising a central brush block and peripheral linear blocks gave rise to a regular two-phase morphology[257] with a controlled formation of nano-sized phase areas. According to structural studies, despite the amorphous nature, these polymer systems possess long-range order similar to that observed, for example, for LC polymers and low density polyethylene.

8. Conclusion

The active interest in molecular polymer brushes is due to significant difference of their properties from those of linear copolymer analogues. Molecular brushes have a high concentration of side chains and, hence, a large number of chain ends bearing functional groups and greater persistence length of macromolecules caused by a stretched conformation of backbones resulting from steric repulsion of side chains. They also have more compact conformations of macromolecules in solutions and a lower degree of entanglements in the condensed state than linear copolymers. This largely determines the specific properties of molecular brushes. Multicomponent brushes possess additional structural flexibility and unique aggregation properties, compared with homopolymer brushes, as a result of incompatibility of different types of side chains. Great promise is held by combining linear and brush blocks in mixed-topology copolymers. The pronounced distinctive features of these copolymer structures offer a variety of

practical applications, which are often impossible for linear block copolymers.

The synthesis and study of brush copolymer structures with different-type blocks became possible owing to advances in the development of new synthetic methods of polymer chemistry, first of all, living polymerization. The achievements in the field of controlled (living) polymerization made it possible to synthesize an exceptionally wide range of multicomponent brushes. Variations of copolymer design were directed along the brush backbone, along the side chains or in both directions, thus giving rise to alternating, block, gradient or another structures. Apart from the synthesis of copolymers of specified chemical composition, living polymerization provides precise control of structural parameters such as the length, type of combination and the sequence of chain blocks and the grafting density of side chains. More efficient control over the copolymer architecture allowed researchers to generate new properties by targeted molecular design. This opens up pathways to new high-tech materials for various applications.

Among living polymerization methods and strategies of fabrication of brush blocks described in Section 3, the 'grafting from' approach implemented by controlled radical polymerization methods has been most popular over two decades. During this period, the ATRP method was used most often, but lately the use of RAFT has increased. One more recent trend is the more active use of the 'grafting through' strategy, which is the most facile approach for introduction of chemically different side chains into the brush molecule. Currently, this method is often used for polymerization of macromonomers with norbornene terminal groups. However, virtually each case of preparation of a complex multicomponent brush includes a combined use of different polymerization processes. The high complexity of multistage syntheses of multicomponent brushes is largely counterbalanced by more extensive opportunities for the control (tuning) of self-assembly of macromolecules in solutions and in the condensed state and, hence, the properties of materials based on them, as compared with linear copolymers.

Owing to the significant advances in the synthesis of complex copolymers *via* combination of different polymerization methods, diversified multicomponent copolymer brushes, capable of self-assembling, in solutions or in the condensed state, to nano-sized building blocks of nanostructured materials have been obtained to date. An increasing number of recent studies have been devoted to these processes. Micellization processes in solutions receive special attention. In a number of recent publications such as a paper of Stenhaus *et al.*,[145] the synthesis and structure determination of multicomponent brushes are given in the supplementary material, while the main body of the paper is devoted to structurization issues. The same is indicated by the change in the main subject matter of reviews considering molecular brushes. Whereas earlier reviews address mainly the development of living polymerization techniques and characterization of the copolymer products, in recent years the focus has shifted towards self-assembly issues, properties and practical applications of these products.[33, 34]

The diverse properties and broad prospects for practical use of multicomponent brush copolymer structures account for the interest of researchers in this area. The design and development of the syntheses of these copolymers of complex architecture and extensive studies of their properties are currently among the predominant trends of polymer chemistry. It is beyond doubt that these copolymer structures have a great future for fundamental science and practical purposes.

This review was prepared with financial support of the Ministry of Education and Science of the Russian Federation (Mega-grant of Government of the Russian Federation, contract No 14.W03.31.0022).

Figures 3, 5 – 8, 10, 13, 15 – 17 are courtesy of American Chemical Society publishers; Figures 4, 11, 12 are courtesy of Elsevier; Figure 9 is courtesy of American Association for the Advancement of Science; Figure 14 is courtesy of Royal Society of Chemistry publishers.

References

1. A.Narumi, T.Matsuda, H.Kaga, T.Satoh, T.Kakuchi. *Polymer*, **43**, 4835 (2002)
2. W.Zhao, P.Fonsny, P.FitzGerald, G.G.Warr, S.Perrier. *Polym. Chem.*, **4**, 2140 (2013)
3. J.Wang, K.Yao, C.Wang, C.Tang, X.Jiang. *J. Mater. Chem. B*, **1**, 2324 (2013)
4. H.Lee, J.Pietrasik, S.S.Sheiko, K.Matyjaszewski. *Prog. Polym. Sci.*, **35**, 24 (2010)
5. Y.-L.Lin, H.-Y.Chang, Y.-J.Sheng, H.-K.Tsao. *Macromolecules*, **45**, 7143 (2012)
6. X.Lian, D.Wu, X.Song, H.Zhao. *Macromolecules*, **43**, 7434 (2010)
7. G.Riess. *Prog. Polym. Sci.*, **28**, 1107 (2003)
8. K.Okamoto, C.K.Luscombe. *Polym. Chem.*, **2**, 2424 (2011)
9. F.Wurm, H.Frey. *Prog. Polym. Sci.*, **36**, 1 (2011)
10. J.Zhang, X.-F.Chen, H.-B.Wei, X.-H.Wan. *Chem. Soc. Rev.*, **42**, 9127 (2013)
11. X.Guo, B. Choi, A.Feng, S.H.Thang. *Macromol. Rapid Commun.*, **39**, 1800479 (2018)
12. S.S.Sheiko, M.Möller. *Chem. Rev.*, **101**, 4099 (2001)
13. S.S.Sheiko, B.S.Sumerlin, K.Matyjaszewski. *Prog. Polym. Sci.*, **33**, 759 (2008)
14. S.S.Sheiko, S.A.Prokhorova, K.L.Beers, K.Matyjaszewski, I.I.Potemkin, A.R.Khokhlov, M.Möller. *Macromolecules*, **34**, 8354 (2001)
15. K.Huang, D.P.Canterbury, J.Rzayev. *Chem. Commun.*, **46**, 6326 (2010)
16. K.Huang, J.Rzayev. *J. Am. Chem. Soc.*, **133**, 16726 (2011)
17. B.R.Sveinbjornsson, R.A.Weitekamp, G.M.Miyake, Y.Xia, H.A.Atwater, R.H.Grubbs. *Proc. Natl. Acad. Sci. USA*, **109**, 14332 (2012)
18. M.B.Runge, N.B.Bowden. *J. Am. Chem. Soc.*, **129**, 10551 (2007)
19. J.Rzayev. *Macromolecules*, **42**, 2135 (2009)
20. J.Yuan, Y.Xu, A.Walther, S.Bolisetty, M.Schumacher, H.Schmalz, M.Ballauff, A.H.E.Müller. *Nat. Mater.*, **7**, 718 (2008)
21. M.Zhang, M.Drechsler, A.H.E.Müller. *Chem. Mater.*, **16**, 537 (2004)
22. K.Huang, A.Jacobs, J.Rzayev. *Biomacromolecules*, **12**, 2327 (2011)
23. Y.Q.Yang, X.D.Guo, W.J.Lin, L.J.Zhang, C.Y.Zhang, Y.Qian. *Soft Matter*, **8**, 454 (2012)
24. J.A.Johnson, Y.Y.Lu, A.O.Burts, Y.Xia, A.C.Durrell, D.A.Tirrell, R.H.Grubbs. *Macromolecules*, **43**, 10326 (2010)
25. X.Lu, T.-H.Tran, F.Jia, X.Tan, S.Davis, S.Krishnan, M.M.Amiji, K.Zhang. *J. Am. Chem. Soc.*, **137**, 12466 (2015)
26. D.M.Ilgach, T.K.Meleshko, A.V.Yakimansky. *Polym. Sci., Ser. C*, **57**, 3 (2015)

27. J.Yuan, A.H.E.Müller, K.Matyjaszewski, S.S.Sheiko. In *Polymer Science: A Comprehensive Reference*. (Eds M.Moeller, K.Matyjaszewski). (Amsterdam: Elsevier, 2012). P. 199
28. D.Neugebauer. *Polymer*, **72**, 413 (2015)
29. W.Hadasha, B.Klumperman. *Polym. Int*., **63**, 824 (2014)
30. M.Müllner, A.H.E.Müller. *Polymer*, **98**, 389 (2016)
31. R.Verduzco, X.Li, S.L.Pesek, G.E.Stein. *Chem. Soc. Rev*., **44**, 2405 (2015)
32. J.Rzayev. *ACS Macro Lett*., **1**, 1146 (2012)
33. T.Pelras, C.S.Mahon, M.Müllner. *Angew. Chem., Int. Ed*., **57**, 6982 (2018)
34. G.Xie, M.R.Martinez, M.Olszewski, S.S.Sheiko, K.Matyjaszewski. *Biomacromolecules*, **20**, 27 (2019)
35. Y.Mai, A.Eisenberg. *Chem. Soc. Rev*., **41**, 5969 (2012)
36. J.Raez, I.Manners, M.A.Winnik. *J. Am. Chem. Soc*., **124**, 10381 (2002)
37. S.J.Holder, N.A.J.M.Sommerdijk. *Polym. Chem*., **2**, 1018 (2011)
38. M.L.Adams, A.Lavasanifar, G.S.Kwon. *J. Pharm. Sci*., **92**, 1343 (2003)
39. A.Halperin, S.Alexander. *Macromolecules* **22**, 2403 (1989)
40. M.Zhang, A.H.E.Müller. *J. Polym. Sci., Part A: Polym. Chem*., **43**, 3461 (2005)
41. Y.Tsukahara, K.Tsutsumi, Y.Yamashita, S.Shimada. *Macromolecules*, **23**, 5201 (1990)
42. Y.Tsukahara, K.Mizuno, A.Segawa, Y.Yamashita. *Macromolecules*, **22**, 1546 (1989)
43. M.Schappacher, C.Billaud, C.Paulo, A.Deffieux. *Macromol. Chem. Phys*., **200**, 2377 (1999)
44. H.Gao, K.Matyjaszewski. *J. Am. Chem., Soc*., **129**, 6633 (2007)
45. M.Schappacher, A.Deffieux. *J. Am. Chem. Soc*., **130**, 14684 (2008)
46. K.L.Beers, S.G.Gaynor, K.Matyjaszewski, S.S.Sheiko, M.Möller. *Macromolecules*, **31**, 9413 (1998)
47. H.G.Börner, K.Beers, K.Matyjaszewski, S.S.Sheiko, M.Möller. *Macromolecules*, **34**, 4375 (2001)
48. M.Zhang, T.Breiner, H.Mori, A.H.E.Müller. *Polymer*, **44**, 1449 (2003)
49. H.C.Kolb, M.G.Finn, K.B.Sharpless. *Angew. Chem., Int. Ed*., **40**, 2004 (2001)
50. C.Cheng, E.Khoshdel, K.L.Wooley. *Nano Lett*., **6**, 1741 (2006)
51. J.Zhao, G.Mountrichas, G.Zhang, S.Pispas. *Macromolecules*, **43**, 1771 (2010)
52. B.S.Sumerlin, D.Neugebauer, K.Matyjaszewski. *Macromolecules*, **38**, 702 (2005)
53. D.Neugebauer, B.S.Sumerlin, K.Matyjaszewski, B.Goodhart, S.S.Sheiko. *Polymer*, **45**, 8173 (2004)
54. K.Matyjaszewski, S.Qin, J.R.Boyce, D.Shirvanyants, S.S.Sheiko. *Macromolecules*, **36**, 1843 (2003)
55. G.Cheng, A.Böker, M.Zhang, G.Krausch, A.H.E.Müller. *Macromolecules*, **34**, 6883 (2001)
56. A.V.Yakimansky. *Polym. Sci., Ser. C*, **47**, 1 (2005)
57. M.Szwarc, M.Levy, R.Milkovich. *J. Am. Chem. Soc*., **78**, 2656 (1956)
58. M.Szwarc. *J. Polym. Sci., Part: A Polym. Chem*., **36**, 9 (1998)
59. W.A.Braunecker, K.Matyjaszewski. *Prog. Polym. Sci*., **32**, 93 (2007)
60. In *Anionic Polymerization: Principles, Practice, Strength, Consequences and Applications*. (Eds N.Hadjichristidis, A.Hirao). (Tokyo: Springer Japan, 2015). P. 1082
61. F.T.Wall. *Science*, **119**, 555 (1954)
62. P.J.Flory. *J. Am. Chem. Soc*., **62**, 1561 (1940)
63. D.F.Grishin. *Polym. Sci., Ser. C*, **53**, 3 (2011)
64. R.P.Quirk, B.Lee. *Polym. Int*., **27**, 359 (1992)
65. M.Yu.Zaremskii, V.B.Goluber. *Polymer Sci., Ser. C*, **43**, 81 (2001)
66. G.V.Korolev, A.G.Marchenko. *Russ. Chem. Rev*., **69**, 409 (2000)
67. K.Matyjaszewski, N.V.Tsarevsky. *J. Am. Chem. Soc*., **136**, 6513 (2014)
68. In *Controlled and Living Polymerizations*. (Eds K.Matyjaszewski, A.H.E.Müller). (Weinheim: Wiley-VCH, 2009). P. 612
69. C.J.Hawker, A.W.Bosman, E.Harth. *Chem. Rev*., **101**, 3661 (2001)
70. J.Nicolas, B.Charleux, O.Guerret, S.Magnet. *Macromolecules*, **38**, 9963 (2005)
71. J.Nicolas, Y.Guillaneuf, C.Lefay, D.Bertin, D.Gigmes, B.Charleux. *Prog. Polym. Sci*., **38**, 63 (2013)
72. L.E.N.Allan, M.R.Perry, M.P.Shaver. *Prog. Polym. Sci*., **37**, 127 (2012)
73. E.V Kolyakina, D.F.Grishin. *Russ. Chem. Rev*., **78**, 535 (2009)
74. J.Chiefari, Y.K.(Bill) Chong, F.Ercole, J.Krstina, J.Jeffery, T.P.T.Le, R.T.A.Mayadunne, G.F.Meijs, C.L.Moad, G.Moad, E.Rizzardo, S.H.Thang. *Macromolecules*, **31**, 5559 (1998)
75. S.G.Karaj-Abad, M.Abbasian, M.Jaymand. *Carbohydr. Polym*., **152**, 297 (2016)
76. W.Wei, A.Balamurugan, J.H.Dwyer, P.Gopalan. *ACS Macro Lett*., **7**, 100 (2018)
77. M.K.Brinks, A.Studer. *Macromol. Rapid Commun*., **30**, 1043 (2009)
78. J.-S.Wang, K.Matyjaszewski. *J. Am. Chem. Soc*., **117**, 5614 (1995)
79. M.Kato, M.Kamigaito, M.Sawamoto, T.Higashimura. *Macromolecules*, **28**, 1721 (1995)
80. N.M.L.Hansen, K.Jankova, S.Hvilsted. *Eur. Polym. J*., **43**, 255 (2007)
81. G.Moad, E.Rizzardo, S.H.Thang. *Aust. J. Chem*., **65**, 985 (2012)
82. B.Klumperman, E.T.A.van den Dungen, J.P.A.Heuts, M.J.Monteiro. *Macromol. Rapid Commun*., **31**, 1846 (2010)
83. C.-S.Ha, J.A.Gardella. *Chem. Rev*., **105**, 4205 (2005)
84. C.-S.Xiao, Y.-C.Wang, J.-Z.Du, X.-S.Chen, J.Wang. *Macromolecules*, **39**, 6825 (2006)
85. A.Kowalski, J.Libiszowski, K.Majerska, A.Duda, S.Penczek. *Polymer*, **48**, 3952 (2007)
86. C.W.Bielawski, R.H.Grubbs. *Prog. Polym. Sci*., **32**, 1 (2007)
87. T.-P.Lin, A.B.Chang, H.-Y.Chen, A.L.Liberman-Martin, C.M.Bates, M.J.Voegtle, C.A.Bauer, R.H.Grubbs. *J. Am. Chem. Soc*., **139**, 3896 (2017)
88. Y.Xia, B.D.Olsen, J.A.Kornfield, R.H.Grubbs. *J. Am. Chem. Soc*., **131**, 18525 (2009)
89. J.A.Johnson, Y.Y.Lu, A.O.Burts, Y.-H.Lim, M.G.Finn, J.T.Koberstein, N.J.Turro, D.A.Tirrell, R.H.Grubbs. *J. Am. Chem. Soc*., **133**, 559 (2011)
90. M.B.Runge, S.Dutta, N.B.Bowden. *Macromolecules*, **39**, 498 (2006)
91. S.Jha, S.Dutta, N.B.Bowden. *Macromolecules*, **37**, 4365 (2004)
92. C.Cheng, K.Qi, E.Khoshdel, K.L.Wooley. *J. Am. Chem. Soc*., **128**, 6808 (2006)
93. C.Cheng, E.Khoshdel, K.L.Wooley. *Macromolecules*, **40**, 2289 (2007)
94. D.-J.Liaw, C.-C.Huang, E.-T.Kang. *Polymer*, **47**, 3057 (2006)
95. R.M.Kriegel, W.S.Rees, M.Weck. *Macromolecules*, **37**, 6644 (2004)
96. G.Morandi, G.Mantovani, V.Montembault, D.M.Haddleton, L.Fontaine. *New J. Chem*., **31**, 1826 (2007)
97. G.Morandi, S.Pascual, V.Montembault, S.Legoupy, N.Delorme, L.Fontaine. *Macromolecules*, **42**, 6927 (2009)
98. Z. Li, J.Ma, C.Cheng, K.Zhang, K.L.Wooley. *Macromolecules*, **43**, 1182 (2010)
99. S.C.Radzinski, J.C.Foster, R.C.Chapleski, D.Troya, J.B.Matson. *J. Am. Chem. Soc*., **138**, 6998 (2016)

100. L.Su, G.S.Heo, Y.-N.Lin, M.Dong, S.Zhang, Y.Chen, G.Sun, K.L.Wooley. *J. Polym. Sci., Part A: Polym. Chem.*, **55**, 2966 (2017)
101. Z.Li, K.Zhang, J.Ma, C.Cheng, K.L.Wooley. *J. Polym. Sci., Part A: Polym. Chem.*, **47**, 5557 (2009)
102. Y.Xia, J.A.Kornfield, R.H.Grubbs. *Macromolecules*, **42**, 3761 (2009)
103. U. Tunca, Z.Ozyurek, T.Erdogan, G.Hizal. *J. Polym. Sci., Part A: Polym. Chem.*, **42**, 4228 (2004)
104. W.Jakubowski, J.-F.Lutz, S.Slomkowski, K.Matyjaszewski. *J. Polym. Sci., Part A: Polym. Chem.*, **43**, 1498 (2005)
105. F.Zhu, T.Ngai, Z.Xie, C.Wu. *Macromolecules*, **36**, 7405 (2003)
106. J.Dawkins. *Pure Appl. Chem.*, **54**, 281 (1982)
107. P.J.Wyatt. *Anal. Chim. Acta*, **272**, 1 (1993)
108. K.Se, T.Sakakibara, E.Ogawa. *Polymer*, **43**, 5447 (2002)
109. L.K.Kostanski, D.M.Keller, A.E.Hamielec. *J. Biochem. Biophys. Methods*, **58**, 159 (2004)
110. A.V.Gidh, S.R.Decker, T.B.Vinzant, M.E.Himmel, C.Williford. *J. Chromatogr. A*, **1114**, 102 (2006)
111. M.Shakun, H.Maier, T.Heinze, P.Kilz, W.Radke. *Carbohydr. Polym.*, **95**, 550 (2013)
112. M.A.Haney. *J. Appl. Polym. Sci.*, **30**, 3037 (1985)
113. R.Mendichi, L.Šoltés, A.Giacometti Schieroni. *Biomacromolecules*, **4**, 1805 (2003)
114. D.Lecacheux, J.Lesec, C.Quivoron, R.Prechner, R.Panaras, H.Benoit. *J. Appl. Polym. Sci.*, **29**, 1569 (1984)
115. M.W.F.Nielen. *Anal. Chem.*, **70**, 1563 (1998)
116. G.Montaudo, F.Samperi, M.S.Montaudo. *Prog. Polym. Sci.*, **31**, 277 (2006)
117. A.Ah Toy, P.Vana, T.P.Davis, C.Barner-Kowollik. *Macromolecules*, **37**, 744 (2004)
118. H.Ma, Q.Wang, W.Sang, L.Han, P.Liu, J.Chen, Y.Li, Y.Wang. *Macromol. Rapid Commun.*, **36**, 726 (2015)
119. G.D.Fu, E.T.Kang, K.G.Neoh, C.C.Lin, D.J.Liaw. *Macromolecules*, **38**, 7593 (2005)
120. A.V.Yakimanskii, T.K.Meleshko, D.M.Il'gach, N.N.Bogorad, E.N.Vlasova, T.D.Anan'eva. *Russ. Chem. Bull., Int. Ed.*, **61**, 999 (2012) [*Îb. AH. Cep. xùü.*, 994 (2012)]
121. S.S.Sheiko, M.da Silva, D.Shirvaniants, I.LaRue, S.Prokhorova, M.Moeller, K.Beers, K.Matyjaszewski. *J. Am. Chem. Soc.*, **125**, 6725 (2003)
122. H.Lee, W.Jakubowski, K.Matyjaszewski, S.Yu, S.S.Sheiko. *Macromolecules*, **39**, 4983 (2006)
123. K.Min, S.Yu, H.Lee, L.Mueller, S.S.Sheiko, K.Matyjaszewski. *Macromolecules*, **40**, 6557 (2007)
124. K.Mukumoto, Y.Li, A.Nese, S.S.Sheiko, K.Matyjaszewski. *Macromolecules*, **45**, 9243 (2012)
125. C.M.F.Oliveira, E.F.Lucas. *Polym. Bull.*, **24**, 363 (1990)
126. R.Djalali, N.Hugenberg, K.Fischer, M.Schmidt. *Macromol. Rapid Commun.*, **20**, 444 (1999)
127. K.Tsubaki, K.Ishizu. *Polymer*, **42**, 8387 (2001)
128. Y.Yan, Y.Shi, W.Zhu, Y.Chen. *Polymer*, **54**, 5634 (2013)
129. N.B.Bowden, M.Dankova, W.Wiyatno, C.J.Hawker, R.M.Waymouth. *Macromolecules*, **35**, 9246 (2002)
130. T.K.Meleshko, I.V.Ivanov, A.V.Kashina, N.N.Bogorad, M.A.Simonova, N.V.Zakharova, A.P.Filippov, A.V.Yakimansky. *Polym. Sci., Ser. B*, **60**, 35 (2018)
131. K.Ishizu, H.Kakinuma. *J. Polym. Sci., Part A: Polym. Chem.*, **43**, 63 (2005)
132. J.-Z.Du, L.-Y.Tang, W.-J.Song, Y.Shi, J.Wang. *Biomacromolecules*, **10**, 2169 (2009)
133. M.Müllner, J.Yuan, S.Weiss, A.Walther, M.Förtsch, M.Drechsler, A.H.E.Müller. *J. Am. Chem. Soc.*, **132**, 16587 (2010)
134. M.Müllner, T.Lunkenbein, M.Schieder, A.H.Gröschel, N.Miyajima, M.Förtsch, J.Breu, F.Caruso, A.H.E.Müller. *Macromolecules*, **45**, 6981 (2012)
135. S.Onbulak, J.Rzayev. *J. Polym. Sci., Part A: Polym. Chem.*, **55**, 3868 (2017)
136. K.Huang, J.Rzayev. *J. Am. Chem. Soc.*, **131**, 6880 (2009)
137. H.Lee, K.Matyjaszewski, S.Yu-Su, S.S.Sheiko. *Macromolecules*, **41**, 6073 (2008)
138. Z.Cheng, X.Zhu, G.D.Fu, E.T.Kang, K.G.Neoh. *Macromolecules*, **38**, 7187 (2005)
139. J.Bolton, T.S.Bailey, J.Rzayev. *Nano Lett.*, **11**, 998 (2011)
140. K.Ishizu, J.Satoh, A.Sogabe. *J. Colloid Interface Sci.*, **274**, 472 (2004)
141. D.Wu, C.Zhao, J.Tian, H.Zhao. *Polym. Int.*, **58**, 1335 (2009)
142. D.Zehm, A.Laschewsky, M.Gradzielski, S.Prévost, H.Liang, J.P.Rabe, R.Schweins, J.Gummel. *Langmuir*, **26**, 3145 (2010)
143. D.Han, X.Tong, Y.Zhao. *Macromolecules*, **44**, 5531 (2011)
144. Y.Wang, R.Ren, J.Ling, W.Sun, Z.Shen. *Polymer*, **138**, 378 (2018)
145. A.Steinhaus, T.Pelras, R.Chakroun, A.H.Gröschel, M.Müllner. *Macromol. Rapid Commun.*, **39**, 1800177 (2018)
146. S.Ohno, A.Nese, B.Cusick, T.Kowalewski, K.Matyjaszewski. *Polym. Sci., Ser. A*, **51**, 1210 (2009)
147. Z.Cheng, X.Zhu, E.T.Kang, K.G.Neoh. *Langmuir*, **21**, 7180 (2005)
148. A.P.Martinez, Z.Cui, C.Hire, T.A.P.Seery, D.H.Adamson. *Macromolecules*, **48**, 4250 (2015)
149. F.Jia, F.Liang, Z.Yang. *Langmuir*, **34**, 1718 (2018)
150. W.Qian, X.Song, C.Feng, P.Xu, X.Jiang, Y.Li, X.Huang. *Polym. Chem.*, **7**, 3300 (2016)
151. X.Huang, W.Liao, G.Zhang, S.Kang, C.Y.Zhang. *Int. J. Nanomed.*, **12**, 2215 (2017)
152. K.Ishizu, J.Satoh, K.Tsubaki. *J. Mater. Sci. Lett.*, **20**, 2253 (2001)
153. K.Tsubaki, H.Kobayashi, J.Sato, K.Ishizu. *J. Colloid Interface Sci.*, **241**, 275 (2001)
154. D.Neugebauer, Y.Zhang, T.Pakula, S.S.Sheiko, K.Matyjaszewski. *Macromolecules*, **36**, 6746 (2003)
155. Ya.Li, Y.Zhang, D.Yang, Yo.Li, J.Hu, C.Feng, S.Zhai, G.Lu, X.Huang. *Macromolecules*, **43**, 262 (2010)
156. D.Neugebauer, Y.Zhang, T.Pakula, K.Matyjaszewski. *Macromolecules*, **38**, 8687 (2005)
157. D.Neugebauer, M.Theis, T.Pakula, G.Wegner, K.Matyjaszewski. *Macromolecules*, **39**, 584 (2006)
158. Q.Yan, J.Yuan, F.Zhang, X.Sui, X.Xie, Y.Yin, S.Wang, Y.Wei. *Biomacromolecules*, **10**, 2033 (2009)
159. D.Neugebauer, Y.Zhang, T.Pakula, K.Matyjaszewski. *Polymer*, **44**, 6863 (2003)
160. G.Xie, P.Krys, R.D.Tilton, K.Matyjaszewski. *Macromolecules*, **50**, 2942 (2017)
161. D.Neugebauer, B.E.Carson, S.S.Sheiko, K.Matyjaszewski. *ACS Polym. Prepr.*, **44**, 510 (2003)
162. R.K.Iha, K.L.Wooley, A.M.Nyström, D.J.Burke, M.J.Kade, C.J.Hawker. *Chem. Rev.*, **109**, 5620 (2009)
163. B.S.Sumerlin, A.P.Vogt. *Macromolecules*, **43**, 1 (2010)
164. Y.Shi, X.Cao, H.Gao. *Nanoscale*, **8**, 4864 (2016)
165. P.Zhao, Y.Yan, X.Feng, L.Liu, C.Wang, Y.Chen. *Polymer*, **53**, 1992 (2012)
166. H.Tang, Y.Li, S.H.Lahasky, S.S.Sheiko, D.Zhang. *Macromolecules*, **44**, 1491 (2011)
167. D.M.Henn, W.Fu, S.Mei, C.Y.Li, B.Zhao. *Macromolecules*, **50**, 1645 (2017)
168. K.Ishizu, X.Shen, K.-I.Tsubaki. *Polymer*, **41**, 2053 (2000)
169. K.Ishizu, N.Sawada, J.Satoh, A.Sogabe. *J. Mater. Sci. Lett.*, **22**, 1219 (2003)
170. H.Zhu, G.Deng, Y.Chen. *Polymer*, **49**, 405 (2008)
171. W.Yuan, J.Zhang, H.Zou, T.Shen, J.Ren. *Polymer*, **53**, 956 (2012)
172. L.Gu, Z.Shen, S.Zhang, G.Lu, X.Zhang, X.Huang. *Macromolecules*, **40**, 4486 (2007)
173. H.Luo, D.Raciti, C.Wang, M.Herrera-Alonso. *Mol. Pharm.*, **13**, 1855 (2016)
174. C.Zhao, D.Wu, X.Lian, Y.Zhang, X.Song, H.Zhao. *J. Phys. Chem. B*, **114**, 6300 (2010)

175. He.Li, H.Miao, Y.Gao, Hu.Li, D.Chen. *Polym. Chem.*, **7**, 4476 (2016)
176. K.Kawamoto, M.Zhong, K.R.Gadelrab, L.-C.Cheng, C.A.Ross, A.Alexander-Katz, J.A.Johnson. *J. Am. Chem. Soc.*, **138**, 11501 (2016)
177. H.V.T.Nguyen, N.M.Gallagher, F.Vohidov, Y.Jiang, K.Kawamoto, H.Zhang, J.V.Park, Z.Huang, M.F.Ottaviani, A.Rajca, J.A.Johnson. *ACS Macro Lett.*, **7**, 472 (2018)
178. H.-Y.Chang, Y.-L.Lin, Y.-J.Sheng, H.-K.Tsao. *Macromolecules*, **45**, 4778 (2012)
179. B.A.Laurent, S.M.Grayson. *J. Am. Chem. Soc.*, **133**, 13421 (2011)
180. X.Fan, G.Wang, J.Huang. *J. Polym. Sci., Part A: Polym. Chem.*, **49**, 1361 (2011)
181. X.-Y.Tu, C.Meng, X.-L.Zhang, M.-G.Jin, X.-S.Zhang, X.-Z.Zhao, Y.-F.Wang, L.-W.Ma, B.-Y.Wang, M.-Z.Liu, H.Wei. *Macromol. Biosci.*, **18**, 1800022 (2018)
182. S.Zhang, L.Yin, W.Zhang, Z.Zhang, X.Zhu. *Polym. Chem.*, **7**, 2112 (2016)
183. Z.Liu, Y.Huang, X.Zhang, X.Tu, M.Wang, L.Ma, B.Wang, J.He, P.Ni, H.Wei. *Macromolecules*, **51**, 7672 (2018)
184. X.Tu, C.Meng, Z.Liu, L.Sun, X.Zhang, M.Zhang, M.Sun, L.Ma, M.Liu, H.Wei. *Polymers*, **9**, 301 (2017)
185. H.Wei, C.E.Wang, N.Tan, A.J.Boydston, S.H.Pun. *ACS Macro Lett.*, **4**, 938 (2015)
186. X.-Y.Tu, C.Meng, Y.-F.Wang, L.-W.Ma, B.-Y.Wang, J.-L.He, P.-H.Ni, X.-L.Ji, M.-Z.Liu, H.Wei. *Macromol. Rapid Commun.*, **39**, 1700744 (2018)
187. M.Liu, L.Yin, S.Zhang, Z.Zhang, W.Zhang, X.Zhu. *Polymers*, **11**, 240 (2019)
188. M.D.Ward, P.R.Raithby. *Chem. Soc. Rev.*, **42**, 1619 (2013)
189. D.E.Discher. *Science*, **297**, 967 (2002)
190. L.Zhang, A.Eisenberg. *Macromolecules*, **32**, 2239 (1999)
191. H.Cui, Z.Chen, K.L.Wooley, D.J.Pochan. *Macromolecules*, **39**, 6599 (2006)
192. R.J.Williams, A.P.Dove, R.K.O'Reilly. *Polym. Chem.*, **6**, 2998 (2015)
193. L.Jiang, D.Nykypanchuk, A.E.Ribbe, J.Rzayev. *ACS Macro Lett.*, **7**, 619 (2018)
194. M.B.Runge, C.E.Lipscomb, L.R.Ditzler, M.K.Mahanthappa, A.V.Tivanski, N.B.Bowden. *Macromolecules*, **41**, 7687 (2008)
195. M.B.Runge, J.Yoo, N.B.Bowden. *Macromol. Rapid Commun.*, **30**, 1392 (2009)
196. J.Yoo, M.B.Runge, N.B.Bowden. *Polymer*, **52**, 2499 (2011)
197. T.-P.Lin, A.B.Chang, S.-X.Luo, H.-Y.Chen, B.Lee, R.H.Grubbs. *ACS Nano*, **11**, 11632 (2017)
198. D.F.Sunday, A.B.Chang, C.D.Liman, E.Gann, D.M.Delongchamp, L.Thomsen, M.W.Matsen, R.H.Grubbs, C.L.Soles. *Macromolecules*, **51**, 7178 (2018)
199. L.Y.Qiu, Y.H.Bae. *Pharm. Res.*, **23**, 1 (2006)
200. K.Matyjaszewski, N.V.Tsarevsky. *Nat. Chem.*, **1**, 276 (2009)
201. Y.Tezuka, H.Oike. *Prog. Polym. Sci.*, **27**, 1069 (2002)
202. W.Hadasha, M.Mothunya, N.Akeroyd, B.Klumperman. *Aust. J. Chem.*, **64**, 1100 (2011)
203. R.Fenyves, M.Schmutz, I.J.Horner, F.V.Bright, J.Rzayev. *J. Am. Chem. Soc.*, **136**, 7762 (2014)
204. Y.Shi, W.Zhu, D.Yao, M.Long, B.Peng, K.Zhang, Y.Chen. *ACS Macro Lett.*, **3**, 70 (2014)
205. B.Xu, G.Gu, C.Feng, X.Jiang, J.Hu, G.Lu, S.Zhang, X.Huang. *Polym. Chem.*, **7**, 613 (2016)
206. H.Luo, J.L.Santos, M.Herrera-Alonso. *Chem. Commun.*, **50**, 536 (2014)
207. M.Schappacher, A.Deffieux. *Science*, **319**, 1512 (2008)
208. Y.Chen, H.Zhou, Z.Sun, H.Li, H.Huang, L.Liu, Y.Chen. *Polymer*, **149**, 316 (2018)
209. J.Xu, S.Luo, W.Shi, S.Liu. *Langmuir*, **22**, 989 (2006)
210. M.C.Lukowiak, B.N.S.Thota, R.Haag. *Biotechnol. Adv.*, **33**, 1327 (2015)
211. J.Guo, H.Hong, G.Chen, S.Shi, T.R.Nayak, C.P.Theuer, T.E.Barnhart, W.Cai, S.Gong. *ACS Appl. Mater. Interfaces*, **6**, 21769 (2014)
212. J.Yuan, Y.Lu, F.Schacher, T.Lunkenbein, S.Weiss, H.Schmalz, A.H.E.Müller. *Chem. Mater.*, **21**, 4146 (2009)
213. M.Zhang, C.Estournès, W.Bietsch, A.H.E.Müller. *Adv. Funct. Mater.*, **14**, 871 (2004)
214. J.Yuan, M.Drechsler, Y.Xu, M.Zhang, A.H.E.Müller. *Polymer*, **49**, 1547 (2008)
215. J.Yuan, F.Schacher, M.Drechsler, A.Hanisch, Y.Lu, M.Ballauff, A.H.E.Müller. *Chem. Mater.*, **22**, 2626 (2010)
216. Y.Xu, J.Yuan, B.Fang, M.Drechsler, M.Müllner, S.Bolisetty, M.Ballauff, A.H.E.Müller. *Adv. Funct. Mater.*, **20**, 4182 (2010)
217. R.Djalali, S.-Y.Li, M.Schmidt. *Macromolecules*, **35**, 4282 (2002)
218. H.Li, H.Liu, T.Nie, Y.Chen, Z.Wang, H.Huang, L.Liu, Y.Chen. *Biomaterials*, **178**, 620 (2018)
219. K.Huang, M.Johnson, J.Rzayev. *ACS Macro Lett.*, **1**, 892 (2012)
220. K.Huang, D.P.Canterbury, J.Rzayev. *Macromolecules*, **43**, 6632 (2010)
221. H.Unsal, S.Onbulak, F.Calik, M.Er-Rafik, M.Schmutz, A.Sanyal, J.Rzayev. *Macromolecules*, **50**, 1342 (2017)
222. S.Ahn, J.Nam, J.Zhu, E.Lee, S.M.Kilbey. *Polym. Chem.*, **9**, 3279 (2018)
223. A.Kumari, S.K.Yadav, S.C.Yadav. *Colloids Surfaces, B*, **75**, 1 (2010)
224. K.S.Soppimath, T.M.Aminabhavi, A.R.Kulkarni, W.E.Rudzinski. *J. Control. Release*, **70**, 1 (2001)
225. J.Nicolas, S.Mura, D.Brambilla, N.Mackiewicz, P.Couvreur. *Chem. Soc. Rev.*, **42**, 1147 (2013)
226. Y.Kawabata, K.Wada, M.Nakatani, S.Yamada, S.Onoue. *Int. J. Pharm.*, **420**, 1 (2011)
227. F.Du, H.Meng, K.Xu, Y.Xu, P.Luo, Y.Luo, W.Lu, J.Huang, S.Liu, J.Yu. *Colloids Surfaces, B*, **113**, 230 (2014)
228. A.Rösler, G.W.M.Vandermeulen, H.-A.Klok. *Adv. Drug Deliv. Rev.*, **64**, 270 (2012)
229. M.Gou, X.Zheng, K.Men, J.Zhang, B.Wang, L.Lv, X.Wang, Y.Zhao, F.Luo, L.Chen, X.Zhao, Y.Wei, Z.Qian. *Pharm. Res.*, **26**, 2164 (2009)
230. B.Xue, Yi.Wang, X.Tang, P.Xie, Yu.Wang, F.Luo, C.Wu, Z.Qian. *J. Biomed. Nanotechnol.*, **8**, 80 (2012)
231. D.Schmaljohann. *Adv. Drug Deliv. Rev.*, **58**, 1655 (2006)
232. A.E.Felber, M.-H.Dufresne, J.-C.Leroux. *Adv. Drug Deliv. Rev.*, **64**, 979 (2012)
233. S.-S.Han, Z.-Y.Li, J.-Y.Zhu, K.Han, Z.-Y.Zeng, W.Hong, W.-X.Li, H.-Z.Jia, Y.Liu, R.-X.Zhuo, X.-Z.Zhang. *Small*, **11**, 2543 (2015)
234. A.V.Yakimansky, T.K.Meleshko, D.M.Ilgach, M.A.Bauman, T.D.Anan'eva, L.G.Klapshina, S.A.Lermontova, I.V.Balalaeva, W.E.Douglas. *J. Polym. Sci., Part A: Polym. Chem.*, **51**, 4267 (2013)
235. N.Y.Shilyagina, N.N.Peskova, S.A.Lermontova, A.A.Brilkina, V.A.Vodeneev, A.V.Yakimansky, L.G.Klapshina, I.V.Balalaeva. *J. Biophotonics*, **10**, 1189 (2017)
236. D.Liu, X.Tang, X.Li, W.Xia, F.Tong. *Int. J. Nanomed.*, 1717 (2016)
237. F.Tong, H.Zhang. *Kidney Blood Press. Res.*, **42**, 495 (2017)
238. Y.Q.Yang, L.S.Zheng, X.D.Guo, Y.Qian, L.J.Zhang. *Biomacromolecules*, **12**, 116 (2011)
239. T.-H.Tran, C.T.Nguyen, L.Gonzalez-Fajardo, D.Hargrove, D.Song, P.Deshmukh, L.Mahajan, D.Ndaya, L.Lai, R.M.Kasi, X.Lu. *Biomacromolecules*, **15**, 4363 (2014)
240. P.Zhao, L.Liu, X.Feng, C.Wang, X.Shuai, Y.Chen. *Macromol. Rapid Commun.*, **33**, 1351 (2012)
241. M.Müllner, S.J.Dodds, T.-H.Nguyen, D.Senyschyn, C.J.H.Porter, B.J.Boyd, F.Caruso. *ACS Nano*, **9**, 1294 (2015)

242. M.Müllner. *Macromol. Chem. Phys.*, **217**, 2209 (2016)
243. H.Luo, M.Szymusiak, E.A.Garcia, L.L.Lock, H.Cui, Y.Liu, M.Herrera-Alonso. *Macromolecules*, **50**, 2201 (2017)
244. C.Yang, S.Huang, X.Wang, M.Wang. *Polym. Chem.*, **7**, 7455 (2016)
245. J.Yuan, A.H.E.Müller. *Polymer*, **51**, 4015 (2010)
246. B.Xu, C.Feng, J.Hu, P.Shi, G.Gu, L.Wang, X.Huang. *ACS Appl. Mater. Interfaces*, **8**, 6685 (2016)
247. J.M.Giussi, M.L.Cortez, W.A.Marmisollé, O.Azzaroni. *Chem. Soc. Rev.*, **48**, 814 (2019)
248. T.Morinaga, S.Honma, T.Ishizuka, T.Kamijo, T.Sato, Y.Tsujii. *Polymers*, **8**, 146 (2016)
249. J.Ping, H.Pan, P.Hou, M.-Y.Zhang, X.Wang, C.Wang, J.Chen, D.Wu, Z.Shen, X.-H.Fan. *ACS Appl. Mater. Interfaces*, **9**, 6130 (2017)
250. E.W.Kent, D.M.Henn, B.Zhao. *Polym. Chem.*, **9**, 5133 (2018)
251. R.J.Macfarlane, B.Kim, B.Lee, R.A.Weitekamp, C.M.Bates, S.F.Lee, A.B.Chang, K.T.Delaney, G.H.Fredrickson, H.A.Atwater, R.H.Grubbs. *J. Am. Chem. Soc.*, **136**, 17374 (2014)
252. G.M.Miyake, V.A.Piunova, R.A.Weitekamp, R.H.Grubbs. *Angew. Chem., Int. Ed.*, **51**, 11246 (2012)
253. G.M.Miyake, R.A.Weitekamp, V.A.Piunova, R.H.Grubbs. *J. Am. Chem. Soc.*, **134**, 14249 (2012)
254. D.R.Paul, C.B.Bucknall. In *Polymer Blends: Formulation and Performance*. (New York: Wiley, 2000). P. 1224
255. A.Hotta, S.M.Clarke, E.M.Terentjev. *Macromolecules*, **35**, 271 (2002)
256. M.Vatankhah-Varnosfaderani, W.F.M.Daniel, M.H.Everhart, A.A.Pandya, H.Liang, K.Matyjaszewski, A.V.Dobrynin, S.S.Sheiko. *Nature (London)*, **549**, 497 (2017)
257. M.Vatankhah-Varnosfaderani, A.N.Keith, Y.Cong, H.Liang, M.Rosenthal, M.Sztucki, C.Clair, S.Magonov, D.A.Ivanov, A.V.Dobrynin, S.S.Sheiko. *Science*, **359**, 1509 (2018)
258. W.F.M.Daniel, J.Burdyńska, M.Vatankhah-Varnoosfaderani, K.Matyjaszewski, J.Paturej, M.Rubinstein, A.V.Dobrynin, S.S.Sheiko. *Nat. Mater.*, **15**, 183 (2016)
259. X.Hu, M.Vatankhah-Varnoosfaderani, J.Zhou, Q.Li, S.S.Sheiko. *Adv. Mater.*, **27**, 6899 (2015)