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Feature article

Grafting of hyperbranched polymers: From unusual complex polymer topologies to multivalent surface functionalization

Christoph Schüll [a,b], Holger Frey [a,*]

[a] Institute of Organic Chemistry, Johannes Gutenberg-University, Duesbergweg 10-14, 55128 Mainz, Germany
[b] Graduate School Materials Science in Mainz, Staudinger Weg 9, 55128 Mainz, Germany

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ABSTRACT

In this feature article, the grafting of hyperbranched polymers to different substrates is reviewed. Both grafting onto macromolecules with different topologies (homogeneous grafting) and the resulting complex polymer architectures containing highly branched segments as well as their applications are discussed. In the second part grafting of hyperbranched polymers on surfaces, i.e., planar surfaces and spherical particles (heterogeneous grafting), with respect to specific applications, such as bio-repellent surfaces or soluble carbon nanotubes is described. In all cases, the one-step synthesis and the resulting highly branched topology of the hyperbranched building blocks is beneficial for the convenient introduction of a large number of functional groups to the substrates. These multifunctional hybrid materials open interesting options for applications, e.g., for highly functional nanoparticles or nanocomposites.

1. Introduction

Hyperbranched polymers (HBPs) have become an established class of macromolecules since the first mentioning of the term "hyperbranched" by Kim and Webster in the late 1980s [1]. Their synthesis is usually achieved by a single reaction step, providing a highly branched polymer topology with a certain similarity to perfectly branched dendrimers, however, avoiding demanding multistep-synthesis and challenging purification procedures at the expense of a random branching pattern [2–4]. Within the last decade, progress in the synthesis of HBPs has paved the way for several highly branched polymer systems with controlled molecular weights, defined degree of branching and low polydispersities [5,6]. Besides the interest in hyperbranched homopolymers, grafted HBPs (=covalently or non-covalently attached to a substrate) have increasingly been used for the generation of hybrid structures, be it in the field of complex polymer topologies or for surface and particle functionalization. In this case, one has to distinguish between homogeneous grafting, if soluble substrates are used and heterogeneous grafting, if non-soluble substrates like metal nanoparticles or silicon wafers as surface substrates are used. HBPs are characterized by a high number of functional groups in combination with a rapid synthesis. The structures allow applications ranging from drug-delivery systems based on polymers with non-linear topologies to antimicrobial surfaces and therapeutic imaging compounds as well as sensors or other biomedical devices [7]. Another key aspect is their utilization as soluble supports in solutions or dispersions, if HBPs are grafted onto spherical particles, nanocrystals, beads or carbon nanotubes [8–10]. Here, the multitude of functional groups of the grafted HBPs promotes solubilization of the substrates in suitable solvents.

In this feature article, recent advances in the field of grafted HBPs are covered. We differentiate between several substrates depending on their macroscopic topology and "dimension" (Fig. 1). In the first part, complex polymer architectures containing grafted HBPs are discussed with respect to theory, synthesis and applications. In most cases, the HBPs are grafted from/to linear chains, which are 1-dimensional (linear) substrates, but also the grafting onto prefabricated hyperbranched polymers (3-dimensional) will be discussed (homogeneous grafting). Second, HBPs grafted on surfaces are reviewed (heterogeneous grafting). Here, one can distinguish between 2-dimensional substrates, such as planar

* Corresponding author. Tel.: +49 (0) 6131 39 25471.
E-mail address: hfrey@uni-mainz.de (H. Frey).

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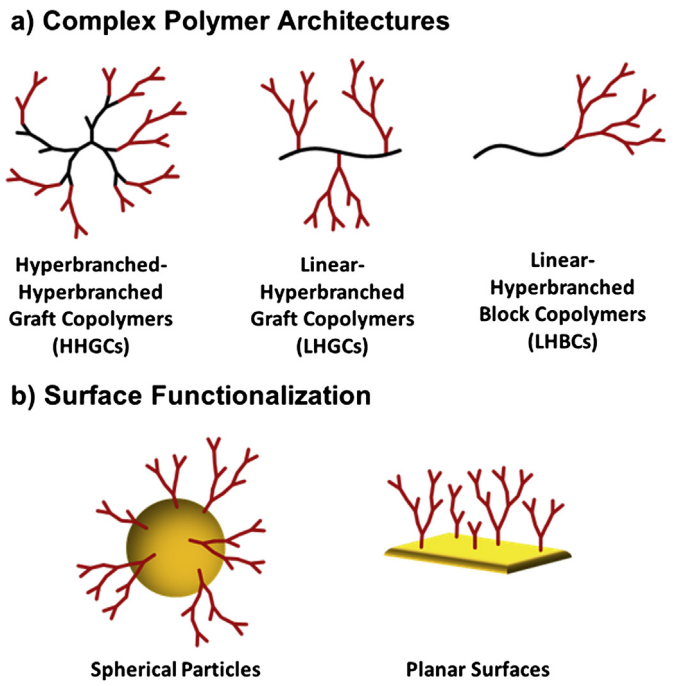


Fig. 1. Overview of various substrates for the grafting of hyperbranched polymer structures: a) complex polymer architectures by grafting from linear and hyperbranched polymer chains and b) functional planar surfaces and spherical particles grafted with hyperbranched polymers.

surfaces and 3-dimensional substrates, mainly spherical particles, which gives rise to multifunctional hybrid structures that are valuable for various applications, such as functionalized nanoparticles and nanocomposites. From a general perspective, the grafting of HBPs is a promising approach to enlarge the fundamental knowledge both in the synthesis and potential future applications of HBPs.

2. Complex polymer topologies by grafting onto single polymer chains

Besides composition and functionality, topology is one of the key parameters for synthetic polymers for the next generation of materials [11]. Especially the introduction of branching points that provide additional functional groups and changes in the overall topology lead to a significant variation in materials properties, such as hydrodynamic radius, viscosity or degree of crystallization compared to linear polymers [12]. Additional functional groups permit multiple derivatization reactions compared to linear polymers, where usually only two end groups are accessible. Copolymers containing a linear and a hyperbranched block or two hyperbranched blocks represent an interesting class of hybrid copolymer topologies. The major synthetic challenge in this context is the generation of defined structures with narrow molecular weight distribution, controlled molecular weights and degree of branching (DB) in the hyperbranched block. In this paragraph, we describe recent developments in both theory and synthesis of complex polymer architectures containing hyperbranched building blocks. An overview of the different topologies has been given in Fig. 1 and will be discussed in the following paragraphs in detail. Moreover, other properties, such as self-assembly, crystallization and potential applications are discussed.

2.1. Theoretical considerations for the hypergrafting concept

An important technique for the introduction of hyperbranched blocks into various copolymer topologies is the so-called hypergrafting (*grafting from*) strategy, which was first introduced by our group in 2001 [13]. In this case multifunctional (polydisperse) macroinitiator cores B_f are used for the polymerization of AB_m monomers. The hypergrafting methodology opens options towards non-conventional topologies (Fig. 1), such as hyperbranched–hyperbranched copolymers (using hyperbranched macroinitiators), linear-hyperbranched graft-copolymers (using multifunctional linear macroinitiators) or linear-hyperbranched block copolymers (using multifunctional block copolymer macroinitiators). Independent of the macroinitiator topology, the hypergrafting strategy can be applied universally. Multiarm star-polymers with a hyperbranched core and linear arms are another major class of complex polymer topologies with HBP building blocks. They have been covered in several reviews and will not be discussed here. [14,15].

A narrow molecular weight distribution is an essential structural parameter for defined complex polymer topologies. Efficient hypergrafting resulting in low polydispersity (PD) of the final polymer can be realized by the slow monomer-addition (SMA) strategy [16]. After initial theoretical works on the synthesis of hyperbranched polymers [17,18], Müller and coworkers derived an expression showing that the number of initiating groups f of multifunctional macroinitiators is a key parameter to obtain low polydispersities for the SMA of AB_2 monomers (Equation (1)). [19]

$$PD = 1 + \frac{1}{f} \tag{1}$$

thus, for increasing core functionality f, the polydispersity of the resulting hyperbranched polymer is reduced. In an independent work based on simulation studies, Hanselmann et al. proposed a more general expression to describe the polydispersity for the SMA of AB_m monomers, confirming Equation (1) (Equation (2)) [20].

$$PD = 1 + \frac{m-1}{f} \tag{2}$$

However, only monodisperse cores in the range of $f = 2$–12 were taken into account in this study, which are rather interesting for the synthesis of hyperbranched homopolymers. In a recent work by our group, a universal expression for PD valid for the SMA based on polydisperse macroinitiators was derived for the hypergrafting of arbitrary AB_m monomers from polydisperse macroinitiators B_f with a number average of functional groups $\bar{f}$ (Equation (3)) and a polydispersity of PD_f [21].

$$PD = PD_f + \frac{m-1}{\bar{f}} \tag{3}$$

This result simplifies to Equation (2) for the case of $PD_f = 1$ and $\bar{f} = f$, if monodisperse initiators are used. This shows that not only a high number of initiating moieties $\bar{f}$, but also a low PD_f value is crucial to obtain defined polymer architectures grafted with HBPs.

2.2. Hyperbranched–hyperbranched graft-copolymers

When hyperbranched polymers are grafted onto a hyperbranched polymer core, hyperbranched–hyperbranched graft-copolymers (HHGCs) are obtained (Fig. 1a). These materials can be viewed as core–shell structures, which are interesting for a variety of transport applications if polymers with different polarity are used, comparable to multiarm star-polymers with a hyperbranched core and linear chains as a shell [5,15]. Interestingly, only

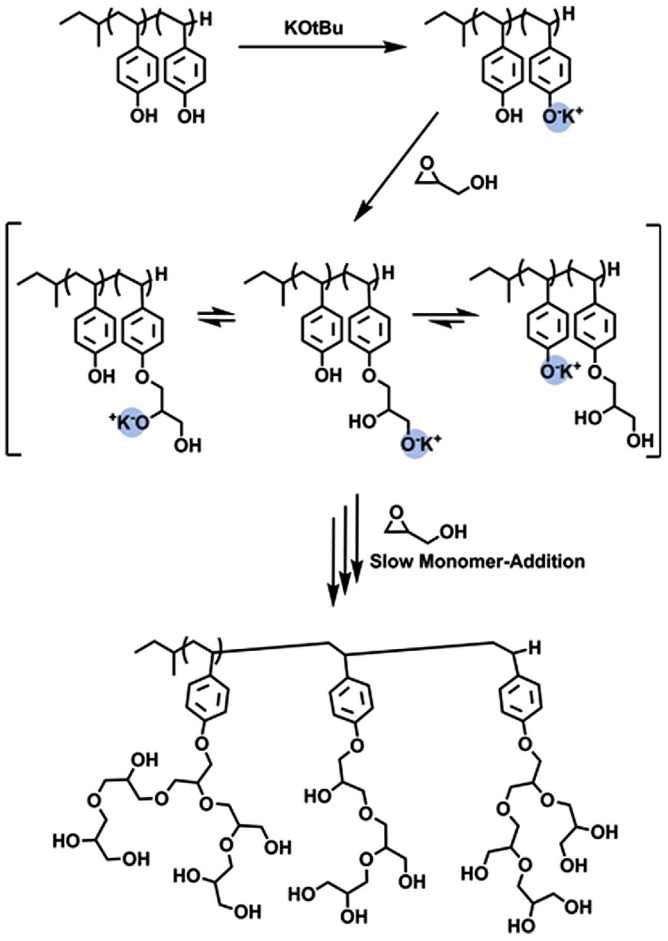
few examples of HHGCs have been described in the literature. The first HHGCs were described by Gao and coworkers who combined the cationic ring-opening multibranching polymerization (ROMBP) of 3-ethyl-3-hydroxymethyl oxetane (EHMO) and glycidol to obtain HHGCs with a hydrophobic hyperbranched PEHMO core and a hydrophilic hyperbranched polyglycerol (*hb*PG) shell [22]. The excellent biocompatibility [23] of *hb*PG renders these HHGCs interesting for biomedical transport purposes [7,24] as well as other applications, such as catalyst supports or for use in biomineralization. [25] *Hb*PG has also been hypergrafted from low molecular weight *hb*PG macroinitiators to obtain *hb*PG homopolymers with increased molecular weights [26]. Recently, Haag and coworkers presented the hypergrafting of *hb*PG from hyperbranched polyethylene to obtain amphiphilic core–shell structures [27]. These polymers showed unimolecular transport of poorly water-soluble model dyes such as Nile Red into living cells. Undoubtedly, this area is far from being mature and is likely to develop strongly in the years to come.

2.3. Linear-hyperbranched graft-copolymers

Linear polymers grafted with hyperbranched side chains, i.e., linear-hyperbranched graft-copolymers (LHGCs) represent an interesting approach towards macromolecules with cylindrical topology in bulk or solution (Fig. 1a), inspired by the concept of dendronized polymers (DenPols). DenPols consist of a linear polymer backbone with densely packed perfectly branched dendrons, which force the linear backbone into an elongated conformation due to steric repulsion [28]. The dendron side chains require comparably high synthetic effort due to the inevitable stepwise construction [29]. Nevertheless, in an impressive work by Schlüter et al. cylindrical polymers in the size-range of the tobacco mosaic virus were realized [30]. The intriguing benefit of the substitution of dendrons by hyperbranched building blocks lies in the comparably simple one-step synthesis of the side chains. It is an intriguing question, whether hyperbranched side chains may lead to a stretching of the linear backbone in a similar manner, despite the random branching pattern involving less dense packing within each side chain. So far, no experimental work has been able to provide an answer to this challenging question. For the synthesis of LHGCs three major approaches can be applied: (i) hypergrafting, (ii) grafting-to (covalent attachment of hyperbranched dendron analogues with a single focal functionality to a reactive linear backbone) and (iii) the macromonomer strategy with hyperbranched dendron analogues containing a single focal polymerizable group. Other works utilized special polymerization conditions of AB_m monomers to promote the preferred formation of linear repeat units, which leads to rather ill-defined LHGCs. [31].

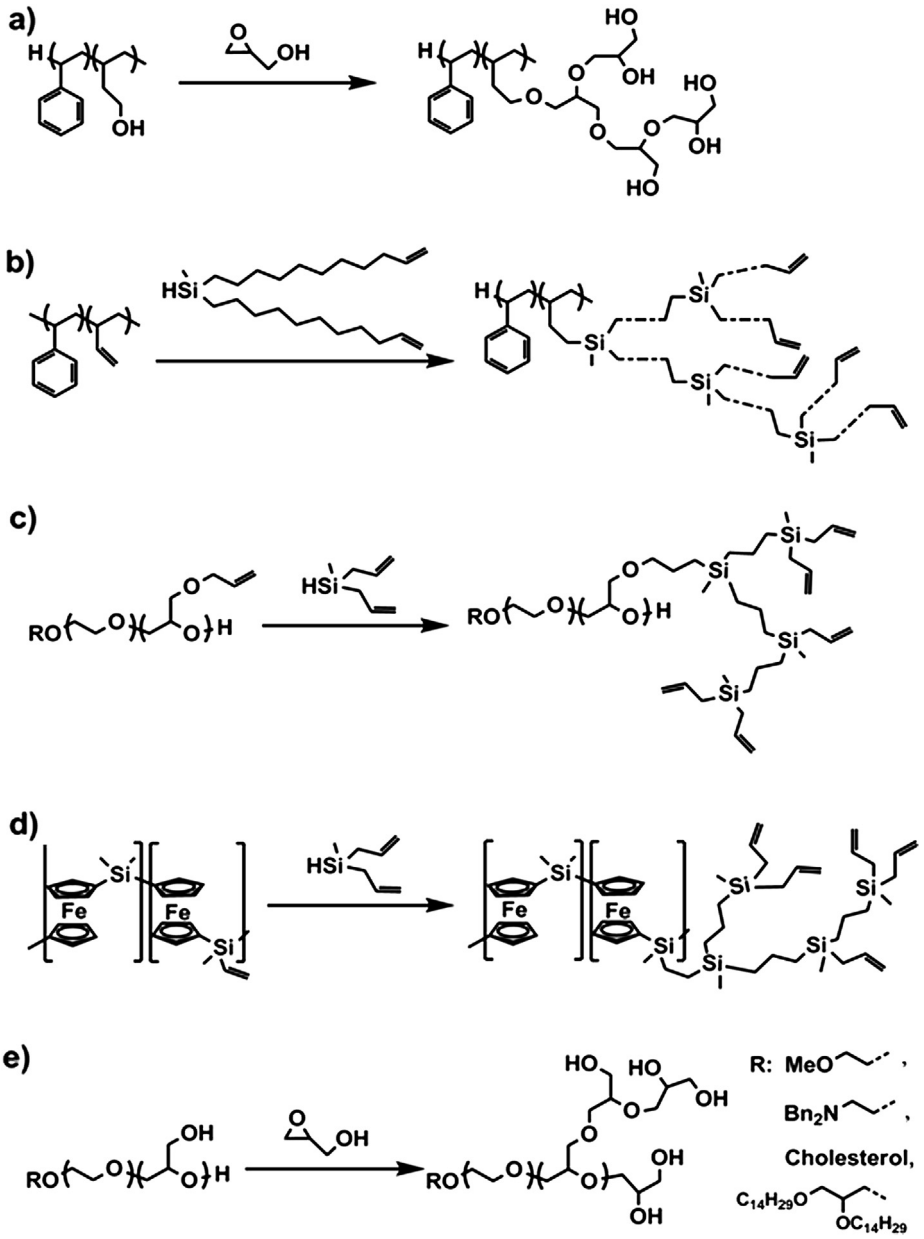
The first controlled synthesis of LHGCs was realized by Lach et al., in 1998, who polymerized hyperbranched carbosilanes with a focal oxazoline functionality by cationic polymerization [32]. The macromonomer approach was also realized by the polymerization of several linear and hyperbranched polyglycerols with focal acrylate or methacrylate moieties by free radical polymerization or atom transfer radical polymerization (ATRP) [33,34]. The hypergrafting strategy was first applied to graft hyperbranched poly(ethylene imine) from a poly(allyl amine) macroinitiator [35]. The authors did not provide detailed polymer characterization data, but showed that the LHGCs are able to form stable complexes with Cu^{2+} ions, which is interesting for potential catalyst recovery applications. Recently, we presented the hypergrafting of glycidol from a linear poly(4-hydroxy styrene) (PHOS) macroinitiator (Scheme 1) [36].

The PHOS macroinitiator was polymerized by anionic polymerization of a protected styrene derivative to ensure high



Scheme 1. Synthesis of poly(4-hydroxy styrene)-*graft*-hyperbranched polyglycerol (PHOS-g-*hb*PG) by hypergrafting with a high side chain density [36]. Adapted with permission from Schüll, C.; Frey, H. *ACS Macro Lett.* **2012**, 1 (4), 461–464. Copyright 2012 American Chemical Society.

definition and a narrow molecular weight distribution of the precursor. Due to the higher acidity of the phenolates compared to the aliphatic alkoxides during the slow monomer-addition, a high grafting density at the backbone could be achieved, as proven by ^{13}C NMR spectroscopy. A high side chain density is crucial to promote a cylindrical, elongated backbone caused by steric repulsion of the highly branched side chains. Moreover, linear polyglycerols (*lin*PG) were used as macroinitiators for the hypergrafting of glycidol to study structural parameters like the degree of branching [21]. For both macroinitiators (PHOS and *lin*PG) low polydispersities of the resulting LHGCs were found, confirming theoretical considerations of the hypergrafting concept and Equation (3). These are valuable results for other fields of research, as the hypergrafting strategy has also been widely applied for the synthesis of linear-hyperbranched block copolymers (cf. Section 2.4). To increase the molecular weights of the LHGCs with *hb*PG side chains, a grafting-to strategy was developed by our group [37]. Here, hyperbranched polyglycerol dendron analogues with a single focal amino functionality were selectively grafted to linear poly(pentafluorophenyl methacrylate) backbones with reactive ester moieties to obtain LHGCs with molecular weights exceeding 126,000 g mol^{-1} and polydispersities (M_w/M_n) below 1.3 (SEC data). The excellent biocompatibility of *hb*PG[23] opens perspectives for novel polymer therapeutics with non-linear topologies, since upon partial attachment of the dendrons residual poly(pentafluorophenyl methacrylate) repeat units could be



Scheme 2. Synthesis of various linear-hyperbranched block copolymers (LHBCs) by hypergrafting from linear multifunctional block copolymers. a) polystyrene-*block*-hyperbranched polyglycerol (PS-*b*-*hb*PG) [43], b) polystyrene-*block*-hyperbranched polycarbosilane (PS-*b*-*hb*PCS) [44], c) poly(ethylene glycol)-*block*-hyperbranched polycarbosilane (PEG-*b*-*hb*PCS) [45], d) poly(ferrocenylsilane)-*block*-hyperbranched polycarbosilane (PFS-*b*-*hb*PCS) [46], e) poly(ethylene glycol)-*block*-hyperbranched polyglycerol (PEG-*b*-*hb*PG) with various single focal functionalities for multipurpose applications [47–51]

functionalized with dyes, drugs or biomedical imaging compounds.

2.4. Linear-hyperbranched block copolymers

Linear-dendritic block copolymers, i.e., block copolymers consisting of a hyperbranched or dendrimer block linked to the chain-end of the linear block (Fig. 1a), have gained increasing attention in the field of complex polymer architectures [38–40]. The dendritic block adds functional groups to the linear segment and exerts a significant influence on the crystalline properties of the linear block. In analogy to DenPols and LHGCs, the preparation of linear-hyperbranched block copolymers (LHBCs) is an interesting alternative to the synthesis of linear-dendrimer block copolymers due to the considerably reduced synthetic effort. Additionally, increased yields provide larger amounts of available material for fundamental research and future technologies. However, a major challenge results from the fact that only few HBPs can be polymerized with control over molecular weight, low polydispersity and defined degree of branching.

Generally speaking, the synthesis of LHBCs can be realized by three major strategies: (i) “chain first”: hypergrafting from linear chain with initiation moieties utilizable for the polymerization of the hyperbranched block, (ii) “coupling strategy”: attachment of a monofunctional dendron analogue and an end-functional linear block with suitable reactive groups and (iii) “core first”: polymerization of a linear block from a hyperbranched dendron analogue with a single initiation group [39].

Following a work by Kricheldorf et al., in 1998 [41], our group described the first controlled synthesis of LHBCs consisting of a linear poly(propylene oxide)-*co*-poly(ethylene oxide) (PPO-*co*-PEO) and a hyperbranched polyglycerol (*hb*PG) block in 2003 [42]. To this end, PPO-*co*-PEO with an amino end group was first modified with two equivalents of glycidol to introduce four hydroxyl groups that initiate the ring-opening multibranching polymerization (ROMBP) of glycidol. A single amino group is not sufficient for the hypergrafting process, as is described in the theory section (Equations (2) and (3)), since this leads to broad molecular weight distributions. The use of linear macroinitiators, prepared by anionic polymerization techniques, for the hypergrafting strategy has been investigated by our group intensively (Scheme 2). Defined molecular weights and low PDIs of the macroinitiators are beneficial for the overall polydispersity of the LHBCs, as derived from Equation (3).

LHBCs with a linear polystyrene and a *hb*PG block formed self-assembled micellar structures, despite the isomerism of the hyperbranched block, as shown by AFM [43]. The synthesis was realized by using a polystyrene-*block*-poly(buta-1,2-diene) (PS-*b*-PBD) precursor prepared by carbanionic polymerization. The PBD moieties were derivatized by hydroboration to create hydroxyl functionalities, which were subsequently used for the hypergrafting of glycidol (Scheme 2a). The same macroinitiators were also employed for the hypergrafting of AB_2 type carbosilane monomers to give hyperbranched poly(carbosilane) blocks (*hb*PCS) (Scheme 2b) [44]. These LHBCs exhibit molecular weights between 70 and 100 kg mol^{-1} and polydispersities below 1.1. Morphological studies by TEM, AFM, and SAXS demonstrate that a variety of nanophase segregated morphologies can be obtained that depend on the fraction of the hyperbranched block. The results hint at an increased curvature induced by the hyperbranched carbosilane block that leads to steric crowding at the interface. Furthermore, Wurm et al. developed amphiphilic LHBCs with *hb*PCS blocks and linear poly(ethylene glycol) (PEG) segments and poly(ferrocenyl silane) (PFS) blocks [45,46]. For PEG-*b*-*hb*PCS, a linear poly (ethylene glycol)-*block*-poly(allyl glycidyl ether) precursor was synthesized by oxyanionic polymerization and subsequently used for hypergrafting by hydrosilylation (Scheme 2c). TEM studies demonstrated unusual anisotropic microstructures in solution depending on the size of the *hb*PCS block. Metal-containing PFS-based LHBCs could also be synthesized by hypergrafting (Scheme 2d) and showed strongly anisotropic morphologies in TEM and tunable electrochemical response depending on the monomer ratio, as investigated by cyclic voltammetry. For the hypergrafting of carbosilane monomers no slow monomer-addition is necessary, since the high reactivity of the linear macroinitiator is sufficient to control molecular weight and polydispersity of the resulting LHBCs.

LHBCs consisting of a linear PEG block and a *hb*PG block are of special interest due to their facile synthesis with excellent control over molecular weight and polydispersity. The chemical inertness of the polyether structure as well as the biocompatibility of both block segments provides access to potential applications in the field of polymer therapeutics with unusual non-linear polymer topologies. PEG-*b*-*hb*PG is synthesized by oxyanionic polymerization of ethylene oxide and subsequent polymerization of a short segment of an acetal-protected glycidyl ether (1-ethoxyethyl glycidyl ether, EEGE). Upon mild acidic treatment, the released primary hydroxyl groups can be used for the hypergrafting of glycidol (Scheme 2e) [47]. In this context, a work by Gnanou and coworkers should be mentioned, where star-hyperbranched block copolymers, i.e., LHBCs which are coupled to a trifunctional core, have been synthesized [52]. More advanced topologies, such as hyperbranched-linear-hyperbranched triblock copolymers, *hb*PG-*b*-PEG-*b*-*hb*PG, were synthesized by the same strategy [53], inspired by earlier works by Dworak [54]. In other works, hyperbranched-linear-hyperbranched triblock copolymers with hyperbranched poly(3-ethyl-3-hydroxymethyl oxetane) blocks and a linear PEG block [55] or a linear poly(tetrahydrofuran) and *hb*PG blocks have been described [56]. Control over molecular weight, polydispersity and degree of branching of the *hb*PG block has been studied further in a recent work on a synthetic model system of linear-hyperbranched graft-copolymers (see previous section) [21]. By using suitable initiators for the synthesis of the linear macroinitiators, the focal end group of the PEG block can be modified. For example, the introduction of amino functionalities was realized, which were subsequently used for protein conjugation [48,57]. Moreover, the introduction of pyrene anchor groups afforded functionalization and solubilization of carbon nanotubes [49]. By using the monoalcohol cholesterol as an initiator, amphiphilic copolymers can be obtained that were used for liposome preparation. Polyether based lipids are interesting for sterically stabilized liposomes in biomedical transport applications [50]. Additionally, dyes or drugs can be attached by "click"-chemistry at the *hb*PG block, exploiting the multifunctionality of *hb*PG [51]. Moreover, it was shown that the focal cholesterol moiety supports the formation of monolayers and is able to crystallize. [58] Detailed investigation by AFM revealed the influence of the polymer topology on the morphology of the resulting polymers. The comparison of linear poly(ethylene glycol), linear polyglycerol, LHBCs (PEG-b-*hb*PG) and *hb*PGs with single focal cholesterol groups shows a varying aggregation behaviour depending on the polymer topology. Fig. 2 exemplifies the AFM height images of cholesterol-containing linear polyglycerol ($DP = 15$) and cholesterol-containing hyperbranched polyglycerol ($DP = 35$). The hyperbranched polyglycerol segments give rise to larger aggregated structures compared to linear polyglycerol, resulting from the more bulky structure of the hyperbranched architecture.

For the hypergrafting approach it should be mentioned that a certain fraction of hyperbranched homopolymer might be present that cannot be attached to the *hb*PG block, since the focal group has been cyclized with one of the multiple end groups. Still, purification by precipitation mostly enables separation and removal of undesired hyperbranched homopolymer.

The "coupling approach" has only been applied in few examples [59,60]. Disadvantageous work-up procedures (removal of an excess of polymer) and unselective coupling due to the limited availability of hyperbranched dendron analogues with a single focal functionality render this approach synthetically challenging so far. However, in an elegant work Yan and coworkers prepared LHBCs by coupling of a linear adamantane-functionalized long alkyl chain and a hyperbranched block (*hb*PG-grafted from β-cyclodextrin) via non-covalent coupling [61]. These LHBCs could self-assembly into unimolecular vesicles with great ductility and disassembled upon addition of a competitive host for β-cyclodextrin. In a recent follow-up work, the synthesis of the first amphiphilic hyperbranched–hyperbranched block copolymer by non-covalent coupling was realized [62]. For the core first approach, some examples have been described, but mostly without clear evidence for the presence of exactly one linear block or with strong limitations with respect to applicable monomers [63–65]. In a recent work, our group described the synthesis of a hyperbranched polyglycerol macro chain transfer agent that was used for the synthesis of LHBCs by the "core first" strategy via RAFT polymerization. Various monomers, such as biocompatible methacrylamides or thermoresponsive methacrylates could be attached as defined linear blocks [66].

LHBCs represent the most widely studied class of complex polymer topologies containing grafted hyperbranched segments. The miscellaneous examples based on hypergrafting demonstrate the high usefulness of this technique for the preparation of LHBCs. Potential applications lie in the field of polymer therapeutics or drug-delivery, especially for polyether based LHBCs. Since mostly

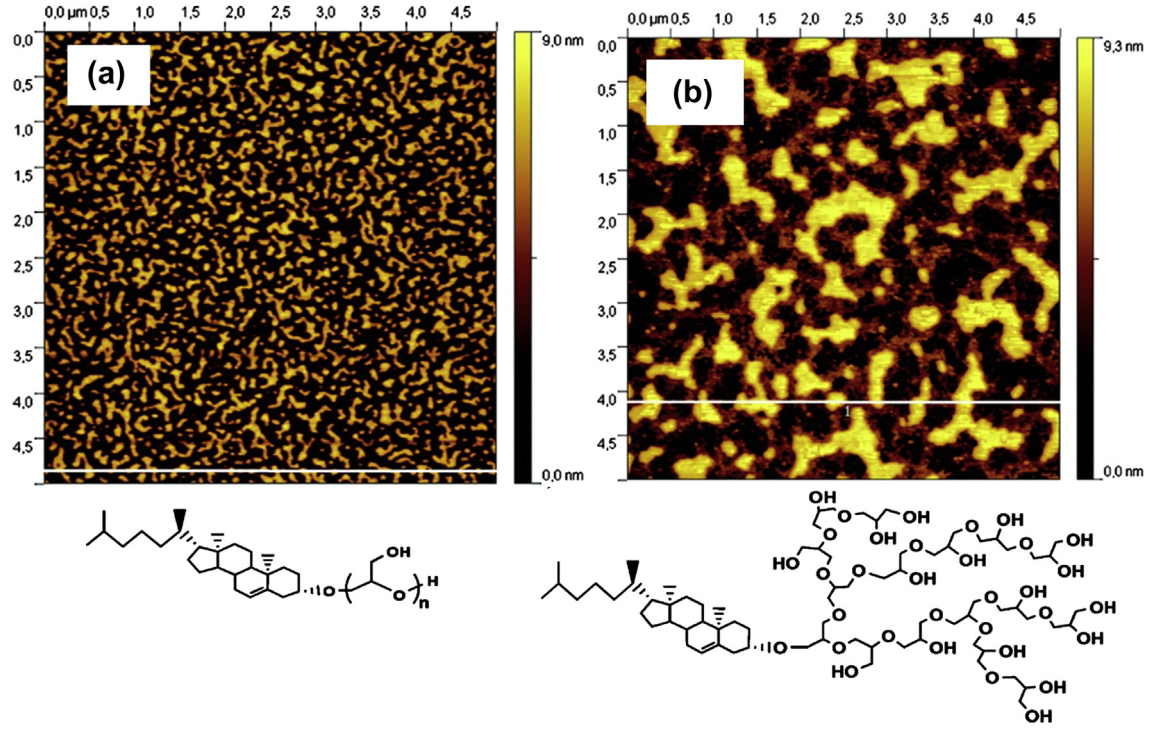


Fig. 2. AFM height images of cholesterol-containing linear polyglycerol (DP = 15, left) and cholesterol-containing hyperbranched polyglycerol (DP = 35, right) with schematic representation of the chemical structures. Adapted with permission from Reuter, S.; Hofmann, A. M.; Busse, K.; Frey, H.; Kressler, J. *Langmuir* **2011**, 27 (5), 1978–1989. Copyright 2010 American Chemical Society.

anionic polymerization techniques were used so far, the tremendous progress in controlled radical polymerization surely will lead to further innovations in this field.

3. Grafting onto surfaces

It is well-known that the properties of planar surfaces (2D) or spherical particles (3D) can be tailored by the attachment of functional polymers [67,68]. Specific polymer modifications can be made to adjust the friction behaviour, adhesion or wettability of a planar surface, which is interesting for applications as "smart" materials (e.g., switchable surfaces) or in biomedicine with bio-repellent or bio-adhesive surfaces for medical devices or tissue engineering, respectively. Grafting of hyperbranched polymers (HBPs) to spherical particles increases their solubility, dispersibility and is a versatile method for the introduction of a large number of functional groups. HBPs combine a facile synthesis, a large number of functional groups and a globular topology, which ensures efficient coverage of the surface by a densely packed polymer layer [69–71]. Different synthetic methods for the introduction of HBPs onto surfaces are available (Fig. 3): (i) step-by-step, (ii) graft-on-graft, (iii) hypergrafting (grafting from) and (iv) grafting-to [70]. All methods have in common that grafting can usually only take place after introduction or in presence of functional groups at the surface (B, Fig. 3), if covalent attachment is desired.

In the following, surfaces grafted with HBPs are discussed depending on the synthetic strategy applied. Several applications of the HBP-functional surfaces will be presented and discussed as well.

3.1. Step-by-step and graft-on-graft strategy

Both, the step-by-step and the graft-on-graft methodology are multistep procedures to graft highly branched polymers on/from surfaces. Both methods have been described in several comprehensive reviews [69–71] and will be covered just briefly in this feature article, including the presentation of some selected examples. The step-by-step strategy proceeds in analogy to the divergent

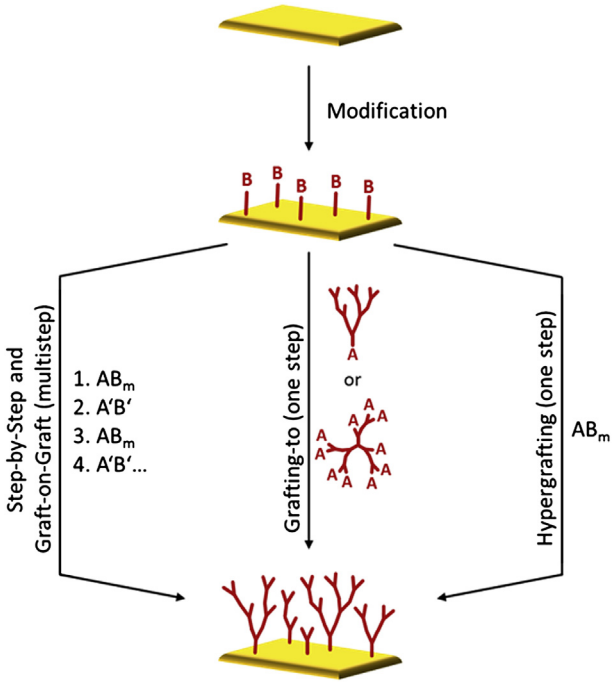


Fig. 3. Preparation strategies for surfaces with grafted hyperbranched polymers. The pathways are analogously valid for the grafting on spherical particles. The formation of covalent bonds is selectively possible between A/A′ and B/B′ groups. AB$_m$: branching (macro-)monomers with $m \geq 2$, A′B′: low or high molecular weight building blocks.

dendrimer synthesis. Here, low molecular weight branching AB_m building blocks are used, which are stepwise attached to the functional surface alternating with A′B′ building blocks to form a highly branched layer. In the case of partial conversion in each step, a HBP-layer is obtained despite the dendrimer synthesis character of the approach. A widely used approach is the generation of poly (amido amine) (PAMAM) at amino-functional surfaces by repetitive Michael addition of methyl methacrylate and amidation with ethylenediamine, which was realized in pioneering works on silica [72] and chitosan [73] as substrates. Similar approaches using multifunctional acrylates have also been described [74]. Grafting on silica is a promising approach for various applications [75] (see section 3.4). Nevertheless, other substrates like carbon black have also been grafted with PAMAM [76] or polyesters [77] by the step-by-step method.

One major drawback of the step-by-step method is the limitation in thickness of the polymer layer that grows during each reaction step at the surface. This is in analogy to the synthesis of dendrimers with high generation/molecular weight by the divergent method. The graft-on-graft technique overcomes this problem by using macromolecular building blocks for grafting the polymer onto the surface, again in a stepwise fashion. This "macromonomer" strategy has widely been used by Bergbreiter [69] for the functionalization of surfaces by using diamino-terminated poly(*tert*-butyl acrylate) as macromonomer. Upon attachment to the surface, this building block was "reactivated" by hydrolysis yielding poly(acrylic acid) for the preparation of the respective next "generation" with diamino-terminated poly(*tert*-butyl acrylate) [78]. The surface properties of grafted gold surfaces were studied by AFM [79] and could further be functionalized by a variety of derivatization reactions [80].

3.2. Grafting-to strategy

While the step-by-step and the graft-on-graft strategy are based on multistep procedures and bear obvious analogy to the divergent dendrimer synthesis, the grafting-to strategy allows the attachment of preformed HBPs to surfaces in one-step. The homogeneous size of the surface-grafts is a major advantage over the step-by-step and the graft-on-graft strategy, if well-defined HBPs are used. The grafting-to of HBPs on surfaces can be realized by the attachment of HBPs using a single focal group or some of the multiple end groups (A, Fig. 3). One has to distinguish between covalent binding or mere adsorption of the HBPs on the surface, e.g., by ionic interactions. The latter case can be realized, e.g., using layer-by-layer self-assembly [81].

Tsukruk and coworkers adsorbed hyperbranched polyesters of different molecular weight on silica surfaces and found a higher adsorption amount for lower molecular weight HBPs, as expected [82]. Moreover, hyperbranched hydroxyl functional polyesters were attached to epoxide-functionalized surfaces to provide stable carboxyl-functional films that swell at different pH values, which results in a different film thickness [83]. Vice-versa, epoxide-containing hyperbranched polyesters with additional hydrophobic moieties were attached to silica to afford hydrophobic surfaces with higher film thickness compared to self-assembled monolayers with conventional alkyl chains [84]. Voit and coworkers used electron beam irradiation for the patterning of grafted hyperbranched polyesters [85] and UV-curing, e.g., to obtain epoxy network layers, creating surfaces with increased hardness and scratch resistance [86]. In other works, hyperbranched poly (ethylene imine)s were attached to silica by adsorption [87] or linked via coupling reagents leading to amino-functional surfaces [88]. A prominent technique for the functionalization of surfaces is layer-by-layer self-assembly (LbL), where polyelectrolytes are deposited onto charged surfaces [81]. LbL is comparable to the graft-on-graft method: While the graft-on-graft method utilizes covalent (chemical) grafting, LbL is achieved by non-covalent grafting (physical adsorption via ionic interactions) of macromolecular building blocks, e.g., by using amino-functional HBPs [89,90] or metal-complexes [91].

Due to the excellent control over molecular weight, polydispersity and degree of branching, hyperbranched polyglycerol (*hb*PG) has been widely used as a well-defined hyperbranched material for the grafting-to strategy on surfaces. *Hb*PG is of special interest as an alternative bio-repellent surface layer compared to the established poly(ethylene glycol) (PEG). A detailed discussion on the bio-repellent properties of *hb*PG on surfaces can be found in Section 3.4. Haag and coworkers functionalized *hb*PG with a disulfide linker-group and attached it to gold surfaces [94]. Recently, *hb*PGs containing additional amino functions were attached to gold surfaces allowing further derivatization reactions, e.g., for the introduction of selective cell-targeting ligands (Fig. 4a) [92]. Moreover, other molecular weights and polyglycerol derivatives, such as perfectly branched polyglycerol dendrons and linear polyglycerol brushes with thiol-anchors were also investigated [95,96]. The thiol groups were introduced either by post-polymerization

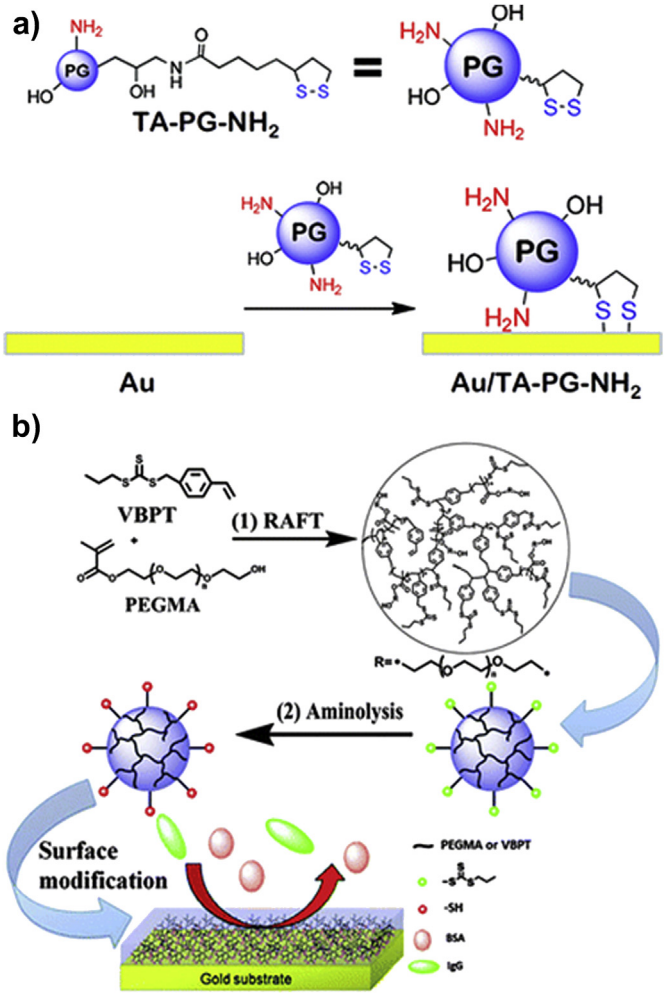


Fig. 4. Grafting of hyperbranched polyethers to gold surfaces by grafting-to. a) *hb*PG on gold surfaces by using lipoic acid anchors. Reproduced from Ref [92] with permission of The Royal Society of Chemistry. b) Grafting-to of HBP containing linear polyether segments, prepared by RAFT polymerization. Reproduced from Ref 93 with permission of The Royal Society of Chemistry.

modification of *hb*PG or by using suitable starting molecules for the synthesis of the polyglycerol dendrimers.

In a different strategy, disulfide-containing initiators (2,2′-dihydroxyethane disulfide) have been used for the polymerization of glycidol. After reduction and cleavage of the disulfide, *hb*PG with a single thiol group was obtained that was grafted to gold surfaces [97]. *Hb*PG was also grafted to glass surfaces by utilizing a triethylsilane anchor, efficiently preventing the adsorption of proteins [98]. Besides the various works on *hb*PG on surfaces, Yan and coworkers recently described a different route to graft hyperbranched polyethers to surfaces. By copolymerization of the inimer (4-vinyl) benzyl-propyltrithiocarbonate with poly(ethylene glycol)methacrylate by RAFT polymerization, a hyperbranched polyether was obtained that could be linked to gold surfaces after aminolysis of the trithiocarbonate groups (Fig. 4b) [93].

3.3. The hypergrafting strategy

As demonstrated for the synthesis of complex polymer architectures, the hypergrafting strategy is a general technique for the direct grafting of HBPs onto surfaces. After the introduction of suitable functional groups to the surface, these can directly be used as initiators for the polymerization of branching monomers (Fig. 3). For this procedure, no previous polymer synthesis or post-polymer modification of the HBP for the introduction of surface attaching moieties is necessary. The monomers are polymerized at/from the surface, which can be carried out either in batch- or in slow-addition mode. The various polymerization techniques that can be used for the grafting of linear polymers from surfaces were covered in several excellent reviews [99,100]. This paragraph focuses on controlled polymerization techniques to obtain well-defined functional surfaces. However, polycondensation is also applicable for hypergrafting from surfaces [101–103].

In pioneering works by Mori and Müller, planar bromide-functionalized silica-surfaces were used for the hypergrafting of methacrylate inimers by self-condensing vinyl polymerization (SCVP) via atom transfer radical polymerization (ATRP) [104,105]. This concept was also applied for hypergrafting of methacrylates from spherical silica particles [106]. Moreover, sugar-containing "glyco-inimers" were hypergrafted from surfaces [107,108], which leads to hydrophilic planar surfaces, as shown by contact angle measurements. Besides silica, other surfaces like stainless steel [109] or ZnO nanoparticles [110] were used for hypergrafting by SCVP. In all works, the surfaces were characterized in detail by typical methods such as AFM and ellipsometry to investigate the modified surfaces properties.

Ring-opening multibranching polymerization (ROMBP) is an established technique for the controlled synthesis of hyperbranched polymers [16]. Especially highly strained cyclic monomers like glycidol and aziridines have been used for surface functionalization by hypergrafting. Kim and coworkers prepared surfaces functionalized with up to 66 amines per nm^2 by hypergrafting of aziridine. Remarkably, the concentration of available amines on the surface is strongly increased compared to surfaces with linear poly(ethylene imine) grafts [111]. This concept was expanded to silica, glass and other surfaces, yielding functional surfaces with high thermal and pH stability [112]. Other amino-functional monomers like oxazolidones have also been described [113]. The excellent applicability of the latent monomer glycidol for hypergrafting has already been discussed for complex polymer topologies (see Section 2). Huck and coworkers hypergrafted glycidol at SiO/SiO_2 surfaces (wafers and gels) using the slow monomer-addition technique [114].

Huck et al. investigated the branching of the *hb*PG grafts after cleavage from the surface with HF by ^{13}C NMR spectroscopy and found the typical repeat units known for *hb*PG homopolymers. However, the degree of branching was lower compared to *hb*PG homopolymers, which might be caused by the steric congestion on the surface during polymerization. Moreover, it has been found that for increasing reaction temperature the surface layer thickness increases up to approximately 15 nm (Fig. 5a). To further increase the surface thickness, a "reinitiation" approach has been used. Here, *hb*PG-grafted surfaces were deprotonated again to re-start the polymerization of glycidol. The increased number of hydroxyl functionalities promotes the formation of layers with a thickness up to 70 nm after two reinitiation cycles (Fig. 5b). In recent works, different substrates, such as polystyrene or poly(ethylene terephthalate) were used for the hypergrafting of glycidol [115]. In this context, in a recent work Buchmeiser and coworkers introduced the initiation moieties by oxygen plasma treatment. In other works, the hypergrafting was realized from hydroxylated polystyrene-beads [116] and amino-functional silicon surfaces [117].

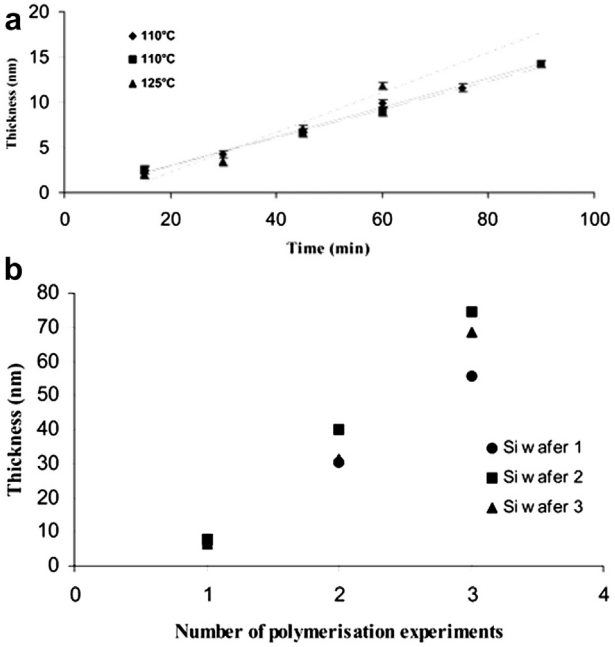


Fig. 5. Thickness of the *hb*PG surface layer prepared by hypergrafting (data determined by ellipsometry) [114]. (a) Dependency on polymerization time and reaction temperature. (b) Dependency on the number of reinitiation experiments. Reprinted with permission from Khan, M.; Huck, W. T. S.; *Macromolecules* **2003**, 36 (14), 5088–5093. Copyright 2003 American Chemical Society.

In summary, the synthetic strategies, especially the grafting-to and the hypergrafting approach have widely been used to obtain well-defined hypergrafted surfaces. Both approaches permit surface functionalization in one-step procedures, if suitable functional groups are located at the surface for the attachment of HBPs or the hypergrafting of corresponding monomers. Functional surfaces, i.e., planar surfaces, spherical particles or other heterogeneous substrates, grafted with hyperbranched polymers are interesting for a variety of applications, as will be described in the following paragraph.

3.4. Applications of surfaces, particles, cells, carbon nanotubes and other substrates grafted with HBPs

The multiple functional end groups and the branched polymer topology render surface grafted HBPs interesting as soluble supports, e.g., for metal nanoparticles, carbon nanotubes and others. The improved solubility and/or dispersibility as well as the suppression of aggregation facilitates processing and applications in

biological media. Moreover, the bio-repellent properties of hyperbranched polyethers are interesting for antifouling surfaces in medical devices and materials or for the grafting to various cell types, which is for example interesting for enhanced camouflage of therapeutic cells in physiological environments. Furthermore, the grafting of HBPs to other substrates like nanocrystals [10] and nanodiamonds [118] has been realized to improve the processability of these materials. Grafting on substrates like silica or metal particles, cellulose and others leads to an immense variety of interesting materials for applications like CO_2 capture [119–121], H_2O purification [122], flame-retardant materials [123], cellulose with increased thermal stability [124], corrosion-inhibiting coatings [125], supports for heavy-metal ion removal [126] or catalysis [127,128].

3.4.1. Functional nanoparticles for biomedical applications

The use of magnetic nanoparticles is of high interest for biomedical applications, e.g., imaging, drug-delivery, magnetic cell separation or tumour therapy by hyperthermia [129–131]. Grafting of HBPs on the surface of magnetic nanoparticles allows for derivatization reactions and supports the biocompatibility and solubility of the particles in physiological media. Especially biocompatible HBPs, e.g., *hb*PG, are interesting for these purposes. Wang and coworkers synthesized multihydroxyl-functional Fe_3O_4 nanoparticles (superparamagnetic iron oxide nanoparticles, SPIONs) by hypergrafting of glycidol [132]. They showed that the particles are non-cytotoxic and stable in cell culture medium for months. Moreover, Komatsu and coworkers functionalized similar particles with the RGD tripeptide and showed that selective cell uptake of the hypergrafted particles in tumour cells is possible [133]. Additionally, their magnetic properties (Fig. 6) render these particles interesting for tumour visualization by magnetic resonance imaging (MRI) [134]. In a different approach, iron oxide-silica nanoparticles have been grafted with carboxylated *hb*PG, which allows for the adsorption of dyes and drugs [135]. Moreover, the grafting of *hb*PG onto CdTe quantum dots (CdTe@HPG) has been realized [136]. The CdTe@HPG quantum dots show strong fluorescence, water-solubility, low toxicity and are able to conjugate functional biomolecules. All these remarkable results in this field confirm the highly interesting potential of hybrid materials consisting of metal nanoparticles and grafted biocompatible *hb*PG for biomedical applications.

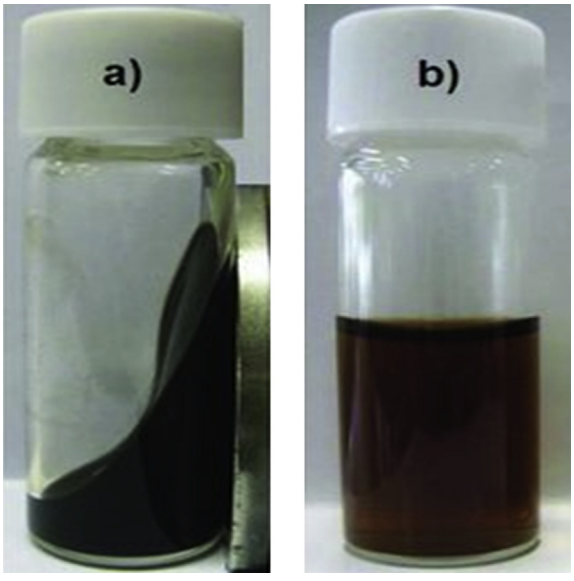


Fig. 6. Photographs of a) an aqueous solution of SPION-*hb*PG in response to a permanent magnet and b) SPION-hbPG, functionalized with RGD tripeptide dissolved in PBS buffer [133]. Zhao, L.; Chano, T.; Morikawa, S.; Saito, Y.; Shiino, A.; Shimizu, S.; Maeda, T.; Irie, T.; Aonuma, S.; Okabe, H.; Kimura, T.; Inubushi, T.; Komatsu, N. *Adv. Funct. Mater.* **2012**, 22, 5107–5117. Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission.

On the other hand, amino-functional PAMAM-hypergrafted magnetic particles can be used for magnetic DNA extraction [137]. Due to the efficient complexation of DNA by PAMAM, DNA could be extracted from blood by an automated method [138].

3.4.2. Bio-repellent surfaces and other biomedically relevant surface modifications

In a number of works, hyperbranched polyglycerols (*hb*PG) have been attached to gold and glass surfaces to prevent protein adsorption, which is a key feature for the fabrication of materials for medical and marine applications (Fig. 4) [94,97,98]. The major advantage of *hb*PG over other established systems like poly (ethylene glycol) (PEG) or dextran stems from the fact that the hyperbranched topology and the multiple hydroxyl groups lead to an increased thermal and oxidative stability of the functional surface layer. Haag and coworkers compared different topologies and chemically modified polyglycerols on gold surfaces with respect to their protein repellent properties. For small polyglycerol dendrons they showed comparable protein resistance as for high molecular weight *hb*PGs [95]. Moreover, brush-type polyglycerols with perfect dendritic side chains show enhanced protein repulsion compared to brush-type polyglycerols with linear side chains [96]. The suppression of non-specific protein adsorption using grafted *hb*PG was also shown for magnetite nanoparticles [139]. Other PEG-containing branched copolymers, e.g., synthesized by RAFT and attached to gold surfaces by a grafting-to procedure were described to efficiently prevent protein adsorption [93].

Furthermore, layer-by-layer self-assembly of hyperbranched polyethers with linear poly(ethylene imine) on aminolyzed quartz slides and silicon wafers resulted in cell-adhesive surfaces that were further evaluated as local drug-delivery systems [90]. Besides hyperbranched polyethers, other HBPs have been used in this area. For example, cotton fabrics were treated with PAMAM-modified chitosan to introduce antimicrobial properties [140]. By using a layer-by-layer (LbL) assembly of disulfide-containing PAMAMs, simultaneous complexation of DNA during the film assembly process was realized. Subsequently, DNA could be released upon treatment of the assembly under physiological reducing conditions, which is appealing for gene delivery concepts [89]. Besides DNA, also proteins like glucose oxidase and others were immobilized by LbL assembly using hyperbranched PAMAM, which might be applicable for biosensors [141]. Moreover, Wooley and coworkers presented crosslinked hyperbranched flouropolymer/PEG surface coatings on glass that efficiently prevented biofouling upon exposure to various proteins [142,143]. In a different structural concept, it was shown that the adsorption of aromatic amino acids by $\pi-\pi$ interactions at poly(phenylene vinylene) (PPV) depends significantly on the topology, since linear and hyperbranched PPVs show different adsorption behaviour, which is an important observation [144].

3.4.3. Grafting onto cells

Kizhakkedathu and coworkers realized the grafting-to of succinimidyl succinate functionalized *hb*PG (and PEG) on different cells, including red blood cells, leukocytes and others [145]. The highly branched polymer topology of *hb*PG on the cell surface might lead to an increased camouflage of surface proteins and opens options, e.g., as universal donors for red blood cells (RBCs). Interestingly, they showed that the presence of nonreactive "additive" polymers such as PEG, dextran and *hb*PG during the grafting

process enhances the grafting efficiency, probably due to improved penetration of the reactive polymer into the glycocalyx of the cell membrane. In follow-up works, they investigated the clearance, circulation and biodistribution of tritium-labelled *hb*PG-grafted RBCs [146]. They found a minimal accumulation in organs other than liver and spleen, suggesting a normal clearance mechanism compared to unmodified RBCs (Fig. 7).

Moreover, *hb*PG-grafted RBCs possess a reduced degree of cell membrane deformation compared to PEG-grafted RBCs and significant higher levels of CD47 self-protein accessibility, which possibly affects their in vivo survival [147]. In a different study, Zimmerman and coworkers recently developed the synthesis of *hb*PGs modified with octyl chains and vasculature binding peptides (VBPs) [148]. The octyl chains allow binding to cell membranes by hydrophobic interactions, while the VBPs can selectively guide the modified cells, e.g., to inflammatory endothelium or other desired tissues, if selective targeting motives are used. The grafting of HBPs to cells is a promising novel approach for novel cell-based drug-delivery systems. Multiple functional groups and a densely packed hyperbranched polymer structure are beneficial compared to linear polymers with respect to camouflage effects and efficient derivatization of cells.

3.4.4. Multifunctional carbon nanotubes and graphene sheets

Carbon nanotube (CNT)-polymer hybrids are promising materials to improve the processing of CNT in composite materials, providing high mechanical strength and unique electrical properties [149]. Therefore, the suppression of aggregation of CNTs and improved solubility or dispersibility is desired for improved processing from solution. Moreover, solubilization in biological media is of high interest for drug-delivery applications. In general, grafting of hyperbranched building blocks (or dendrimers) is often favoured over grafting with linear polymers to substrates for several reasons: (i) The introduction of multiple functional groups is achievable with few initiation or coupling groups on the CNTs, thereby reducing the destruction of the CNTs by inevitable chemical modification. (ii) The large number of functional groups and the branched topology of HBPs are usually more effective to avoid aggregation by their reduced solution viscosity and reduced degree of crystallization. (iii) The numerous functional groups from HBPs facilitate a broad range of possibilities for further functionalization reactions. The hypergrafting strategy was applied to covalently attach hyperbranched polyethers to CNTs. H*b*PG [150] or hyperbranched poly(3-ethyl-3-hydroxymethyl oxetane) (PEHO) (Fig. 8) were hypergrafted from several pre-introduced hydroxyl groups at the surface of CNTs [151]. The multiple hydroxyl groups of the HBPs on the CNTs are readily available for derivatization reactions.

Non-covalent interaction was exploited by our group to solubilize CNTs with *hb*PG-containing polymers bearing a single pyrene or myristyl unit [49]. In various works by Reich and Haag, the non-covalent interaction of CNTs with polyglycerol-based amphiphiles were investigated. The amphiphiles consist of alkyl chains and aromatic moieties as hydrophobic segment and perfectly branched polyglycerol dendrons as hydrophilic segment [152,153]. The chemical similarity of perfectly branched polyglycerol dendrons compared to *hb*PG is promising for the efficient solubilization of CNTs using highly branched polyether polyols. Solubility in water, biocompatibility of the polyglycerol-"coating" and the excitation transfer between the aromatic units of the amphiphiles and the CNTs render these hybrid materials interesting for applications in non-invasive biomedical diagnostics, e.g., by near-infrared spectroscopy [154,155].

Hyperbranched polyimides were attached by hypergrafting of aziridine from amine-functionalized CNTs using cationic polymerization. These modified CNTs were then applied for DNA delivery [156]. Besides ring-opening polymerization, controlled radical polymerization could also be utilized. For example Müller and coworkers hypergrafted glucose-containing inimers by ATRP to obtain biocompatible, water-soluble CNTs [157]. By hypergrafting of methacrylate inimers by ATRP, the solubilization of multiwalled CNTs in organic solvents such as chloroform or THF could be achieved [158]. More examples of synthetic strategies, including a focus on non-covalent grafting techniques which have not been discussed here, can be found in a recent review article [9].

In the context of CNTs, the functionalization of graphene or graphene oxide sheets should also be mentioned. The exploration of the vast application potential of graphene is a current topic of intense research. Modification of graphene sheets with multifunctional HBPs might lead to reduced aggregation and thereby improved processing in large scale applications. Graphene sheets have been functionalized at the edges with hyperbranched aromatic polyamides, which allows for better dispersibility in common solvents [159] or the incorporation into polymer-based composite materials with high moduli and tensile strength [160]. In another work, Gao and coworkers prepared interesting nacre-mimics using

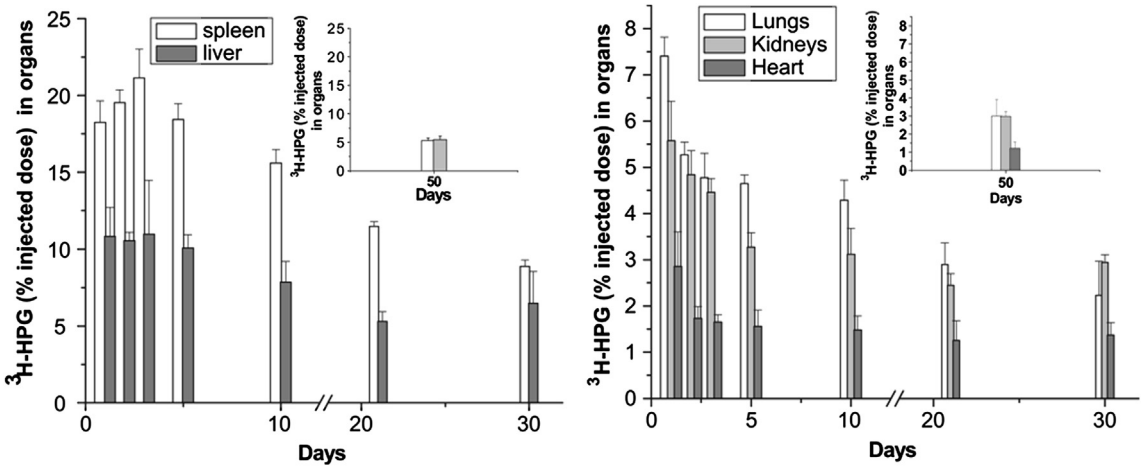


Fig. 7. Percentage of tritium-labelled *hb*PG-modified red blood cells injected dose detected in various organs after digestion. Reprinted from *Biomaterials* 33(10), Chapanian, R.; Constantinescu, I.; Brooks, D.E.; Scott, M.D.; Kizhakkedathu, J.N. *In vivo circulation, clearance, and biodistribution of polyglycerol grafted functional red blood cells*, pp. 3047–3057, Copyright 2012, with permission from Elsevier.

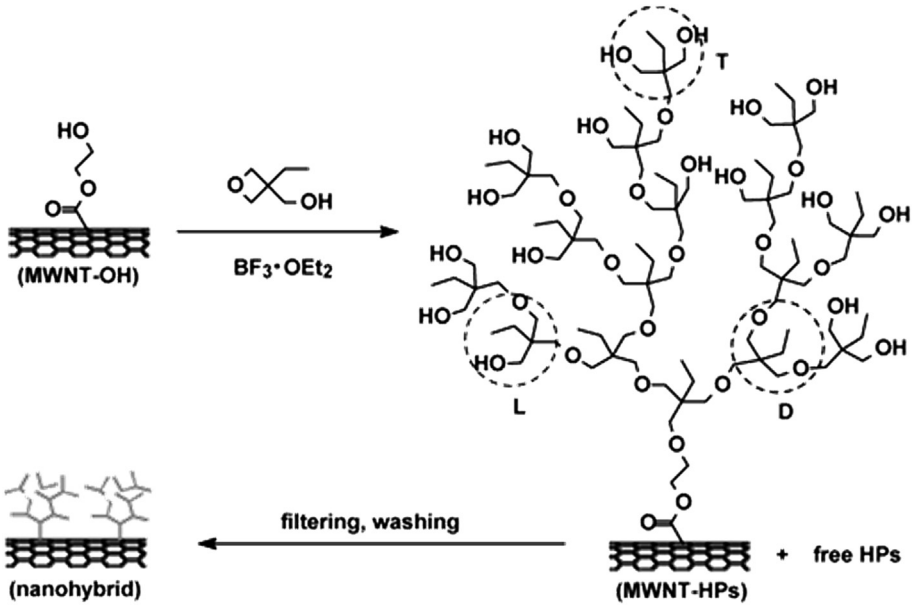


Fig. 8. Preparation of multiwalled CNT (MWNT)-HBP nanohybrids by cationic hypergrafting of 3-ethyl-3-(hydroxymethyl) oxetane [151]. The different repeat units of the HBP are: T: terminal, L: linear, D: dendritic. Reprinted with permission from Xu, Y.; Gao, C.; Kong, H.; Yan, D.; Jin, Y. Z.; Watts, P. C. P. *Macromolecules* **2004**, 37 (24), pp 8846–8853. Copyright 2004 American Chemical Society.

a composites of *hb*PG and graphene sheets [161]. Just recently, Mülhaupt and coworkers presented the grafting of hyperbranched poly(3-ethyl-3-hydroxymethyloxetane) onto graphene nanosheets and the subsequent functionalization with alkylimidazolium cations [162]. These hybrid materials are readily dispersed in water, resulting in stable dispersions without the need for surfactant addition or high shear mixing and self-assemble on surfaces, forming stable films. Carbon/polymer hybrid materials in general represent a highly promising field of research for mechanically demanding applications in materials science.

4. Conclusion

In summary, the grafting of hyperbranched polymers (HBPs) to homogeneous substrates (or functional polymers) is a valuable, recent technique for the convenient preparation of a wide range of complex polymer architectures containing branched elements and usually strongly increased functionality. Moreover, grafting onto heterogeneous substrates like planar surfaces, spherical particles and other "nano-materials" like carbon nanotubes or even macroscopic objects like cells, provides multifunctional hybrid materials. Especially, the grafting-to and the hypergrafting (grafting from) strategies allow a precise attachment of the HBPs to the substrates.

This review underlines the high potential of HBPs as building blocks for the convenient preparation of complex copolymer topologies with branching motives such as linear-hyperbranched block- and graft-copolymers. In the case of surface modification, HBPs provide soluble metal nanoparticles for biomedical imaging, bio-repellent surfaces for medical devices, soluble carbon nanotubes for mechanically stable composite materials and many more. The grafting of HBPs to cells is a major step towards advanced cell engineering. For all systems, the convenient synthesis of the HBP block as well as the multiple end groups permit subsequent derivatization reactions and lead to improved solubilization of heterogeneous substrates. Undoubtedly, both homogeneous and heterogeneous grafting of hyperbranched structures represents an emerging area.

Acknowledgements

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Christoph Schüll studied Biomedical Chemistry at the Johannes Gutenberg-University of Mainz with a temporary stay at the University of Massachusetts Amherst (USA). Since 2010, he is working on his Ph.D. thesis at the University of Mainz in the group of Prof. Holger Frey as a fellow of the Graduate School "Materials Science in Mainz". His research interests focus on the synthesis and applications of complex polymer architectures containing hyperbranched building blocks.

Holger Frey studied Chemistry at the University of Freiburg. Following a stay at Carnegie Mellon-University in Pittsburgh (Kris Matyjaszewski) he obtained the Ph.D. for research on polysilane copolymers at the University of Twente (NL) in the group of Martin Moeller (1993). After his Habilitation at the University of Freiburg (1998) on polycarbosilanes, he moved to the Johannes Gutenberg-University (JGU) at Mainz in 2001. Since 2003 he has been holding a Full Professorship in Organic and Macromolecular Chemistry at JGU. His research interests are directed at novel linear and branched functional polymer structures with unusual topology and biomedically relevant materials in general.