# Dendrimers and Hyperbranched Polymers as High-Loading Supports for Organic Synthesis

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**Abstract:** Polymeric supports have become a big necessity for automated synthesis and combinatorial chemistry, yet, the loading capacities of most polystyrene resins are very limited (typically $<1.5\,\mathrm{mmol\,g^{-1}}$). Dendrimers and hyperbranched polymers have been discussed for this application and now became readily available. These soluble polymers can either be used directly as high-loading supports for substrates, reagents, and catalysts or alternatively in hybrid polymers linked to conventional polystyrene resins.

**Keywords:** combinatorial chemistry • dendrimers • hyperbranched polymers • hybride polymers • solid-phase synthesis

## Introduction

The use of polymeric supports has revolutionized organic synthesis in the past decade and created a new field known as combinatorial chemistry.[1] Solid-phase synthesis on modified polystyrene microbeads, which was originally introduced by Merrifield,[2] still remains the major focus in this area.[1, 3] Although highly successful, solid-phase synthesis exhibits a number of problems due to the heterogeneous nature of reactions and the low concentration of functional groups (typically $\leq 1.5$ mmol substrate per g polymer). In addition, organic reactions on polystyrene microbeads require the use of expensive linker systems which can not be copolymerized. In order to obtain reasonable quantities of final products, substantial substrate loadings ($>1.5\,\mathrm{mmol\,g^{-1}}$) are required, which are difficult to achieve for most linker systems on polystyrene microbeads.[4] Hence, the scale-up of solid-phase reactions usually requires additional solution-phase synthesis in order to obtain mmol quantities of compound. This concept article summarizes and compares new developments in the field of high-loading polymeric supports for organic synthesis. The two major classes, solid phase polymeric supports and soluble polymeric supports are further classified by their polymer topology and will be discussed in due course.

## Solid-Phase Polymeric Supports

**Conventional solid phase supports**: The most frequently used approach for the synthesis of functionalized solid-phase supports is the modification of preformed polymers, for example cross-linked chloromethylated polystyrene microbeads (so-called Merrifield resin). The disadvantage of this method, however, are the limited versatility of the material properties[5] and the loading capacity of the final polymeric support, which is typically lower than that of the original resin ($<1.5\,\mathrm{mmol\,g^{-1}}$). Only in very few cases high-loading Merrifield resins ($4\,\mathrm{mmol\,g^{-1}}$) have been used successfully and the scale-up of reactions was possible directly on the resin.[6] The alternate approach, the copolymerization of monomers, which carry the desired functionality has often been tested in the "early days" of polymer-supported synthesis and has only recently become more attractive again.[7] This strategy can be advantageous because it generates a tailormade functional polymer. However, most highly functionalized solid supports employed today are still far from being ideal. In addition this approach is limited by the number of co-monomers suitable for radical suspension polymerization and the amount of co-monomer incorporation. This leads to loading capacities typically below $3\,\mathrm{mmol\,g^{-1}}$. Another problem of polystyrene-based solid supports is the poor swelling in highly polar and protic solvents and hence slow diffusion of reagents into the beads. In many cases, modification of the unpolar surface with PEG chains becomes necessary to enhance the solution-phase character of the reaction, especially for reactions in protic solvents and water.[8] A disadvantage arising from the grafting of long PEG chains onto the PS microbead certainly is the poor loading capacity obtained for the PEGylated resins, such as TentaGel ($\approx 0.3\,\mathrm{mmol\,g^{-1}}$).[9]

**High-loading solid-phase supports**: In order to increase the loading capacity of functionalized polystyrene microbeads,

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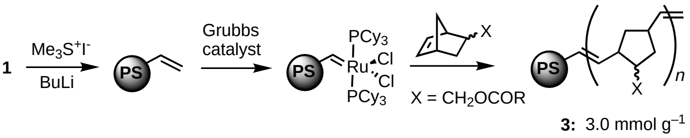
0947-6539/01/0702-0327 $ 17.50+.50/0

dendritic groups can be attached onto every functional group available. Such hybrids of conventional solid supports and dendrimers have been reported recently by several groups **2a–c** (Scheme 1).[10] In all cases the dendrimer synthesis was performed on the bead and the loading capacities increased considerably (up to 2.8 mmol$\,g^{-1}$). Another interesting observation for these hybrid materials is that the swelling characteristics of the microbeads are influenced by the dendritic groups. Similarly to TentaGel resins swelling in water was observed, when polar dendrimer groups are attached.[10] Many applications, such as high-loading supports for catalysts and combinatorial chemistry have been proposed for these hybrid materials.[10] For example, rhodium catalysts attached to the dendritic polymer **2a** have been used in hydroformylation reactions and showed high reactivities, which was assigned to the exposure of the ligands in the shell of the dendritic arms.[10d] Another advantage of these high-loading microbeads for combinatorial chemistry is the high-loading capacity of each individual bead. Up to 230 nmol per bead ($\approx$1 mmol$\,g^{-1}$) have been reported, which is sufficient for $^1$H NMR characterization of the product cleaved from a single bead.[10e] The tedious multistep synthesis of these dendrimer-functionalized polystyrene resins and the limited chemical stability of the polyamide dendrimer backbones, however, confine the general use of these hybrid materials as supports for organic synthesis.

Yet another approach towards high-loading solid-phase supports is based on cross metathesis between vinyl-substituted polystyrene microbeads and norbornene derivatives (Scheme 2).[11] The obtained “ROMP-spheres” **3** possess loading capacities up to 3 mmol$\,g^{-1}$, however, their swelling characteristics are not as good as those of conventional resins. Nevertheless, the utility of these high-loading supports was exemplified by a palladium-catalyzed coupling reaction between a resin bound bromo-benzoate and an aryl zincate in THF/MeOH 4:1.

The advances and the miniaturization in combinatorial chemistry require new high-loading solid-phase resins for single bead reactions and analysis. This need has not yet been fully satisfied, compared to the market potential of such materials. It is therefore necessary to improve and simplify the current approaches towards new high-loading solid-phase supports. A combination of high-loading soluble polymers linked to solid-phase resins are currently the most promising candidates for such hybrid materials.

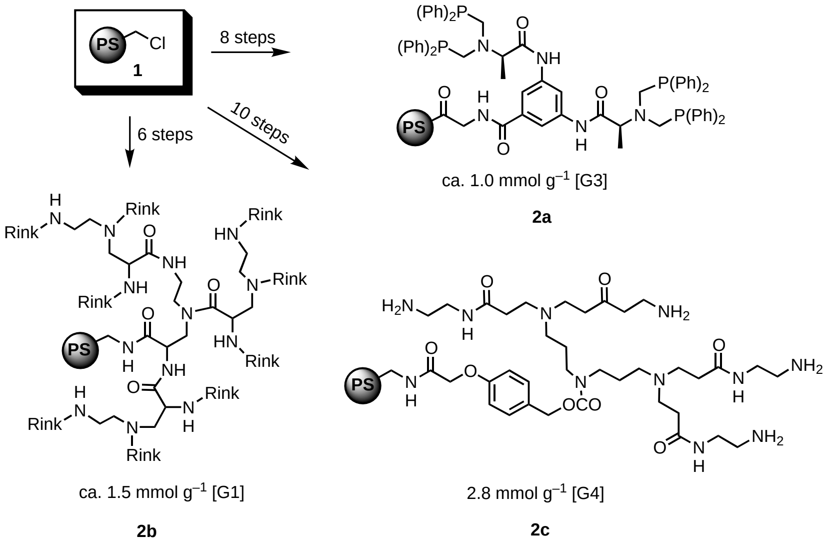


Scheme 2. Synthesis of “ROMP-spheres” **3** as high-loading solid-phase supports.[11]

## Soluble Polymeric Supports

Soluble polymeric supports have been proposed since the early seventies as an alternative to conventional solid-phase supports.[12, 13] The advantages of soluble polymeric supports are their high reactivity in solution due to the homogeneous conditions and their potential for high-loading capacities. In addition, soluble polymers can be used orthogonally—in one chemical reaction vessel—with conventional solid-phase supports and be separated sequentially.[14] For example, a solid phase bound alkene has been dihydroxylated with an osmium catalyst attached to a soluble PEG-polymer. Both polymers were separated by filtration and subsequent precipitation/filtration. It has been demonstrated that the soluble polymeric catalyst can be reused after isolation.[14b] In practice, however, these soluble polymers have not yet become as popular as solid-phase supports.[13]

It is generally believed that soluble polymeric supports, apart from their advantages, are difficult to separate from the reaction mixture. Therefore it is necessary to briefly summarize the multiple commercially available techniques for the separation of soluble polymers from the reaction mixture, that is low molecular weight compounds (Table 1).[15] There are several methods which have been used for the separation of macromolecules by size (dialysis, membrane filtration, and preparative SEC).[16] All of them are suitable for automation, however, little effort compared with the progress in solid-phase synthesis has been undertaken for multiparallel automation in this area. For efficient and fast separations by size homogenous polymeric supports should have medium molecular weights (5000–50000) and narrow molecular weight



Scheme 1. Polystyrene-dendrimer hybrid resins **2a–c**. For simplification only the first generation of the dendrimer arms are shown (**Rink**: Rink amide linker). The number of synthetic steps and the loading account for the highest generation [Gx] and the functional groups reported.[10]

Table 1. Separation techniques for homogeneous polymeric supports.[16]

| Parameter | Dialysis | Ultra-filtration | SEC | Precipitation/filtration | Liquid/liquid phase-separation |
|---|---|---|---|---|---|
| separation method | hydrodynamic volume | hydrodynamic volume | hydrodynamic volume | solubility | solubility |
| minimum MW of polymer | $>1000\,\mathrm{g\,mol^{-1}}$ | $>1000\,\mathrm{g\,mol^{-1}}$ | – | $>3000\,\mathrm{g\,mol^{-1}}$ | – |
| typical sample volume | 10 mL – 1 L | 1 – 100 mL | < 1 mL | 1 – 100 mL | 10 mL – 1 L |
| commercially available | yes | yes | yes | – | – |
| suitable for automation | yes | yes | yes | no | yes |
| suitable for high-throughput synthesis | no | yes | yes | no | yes |
| limitations | unsuitable for final cleavage step | – | – | not suitable for multistep syntheses | different solubilities required |

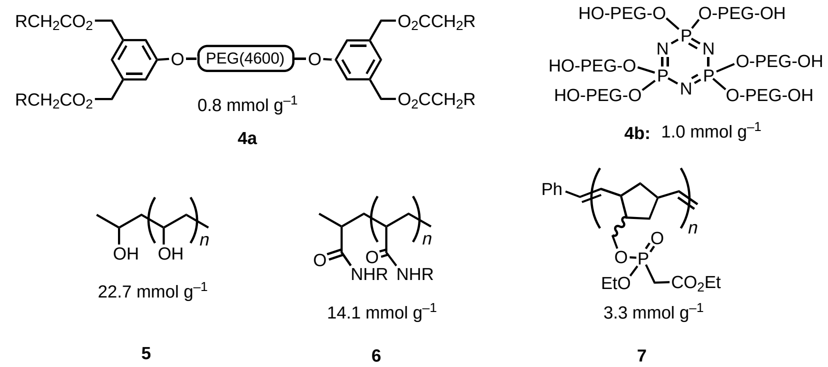


Figure 1. Multiarm PEG-supports with functional groups only at the terminal positions **4a**,**b** and high-loading linear polymers with one functional group per monomer unit **5**–**7**. The given loading capacities correspond to the respective functional groups (R = H).

distributions (<1.5). In addition, macromolecules with a more globular (branched) structure are preferable to a linear polymer structure.

Other separation techniques for soluble polymers, such as precipitation/filtration and liquid–liquid phase separation rely on polymer properties rather than their molecular weight. Precipitation is frequently used in polymer chemistry to purify the polymer from low molecular weight impurities. This method works especially well, when the polymer is crystalline and the $T_g$ is above ambient temperature. It has been frequently applied for the separation of functionalized PEG-supports **4a, b**.[13, 17, 19] Precipitation, however, is not suitable for multistep syntheses because often impurities remain trapped in the polymer. In addition, large solvent volumes are required to perform quantitative precipitations and hence automation of the process is difficult. Another relatively simple separation technique, which is suitable for the separation of organic molecules from water-soluble polymers is based on liquid–liquid phase separation between an organic phase which contains the cleaved organic product and an aqueous phase containing the water soluble polymer.[12c, 13, 15] This separation technique, however, is limited to systems with opposite solubilities of the components in the two phases.

**Linear polymeric supports**: The most widely used soluble polymeric support in organic synthesis is monomethylated polyethylene glycol (typically MPEG 5000), soluble in many organic solvents and easily precipitated in nonpolar solvents (e.g. diethyl ether).[12, 13] Due to the linear topology of this polyether, it contains only one reactive functionality and hence exhibits a rather poor loading capacity ($0.2\,\mathrm{mmol\,g^{-1}}$). In order to increase the loading capacity, bifunctional PEGs endcapped with benzyl ether dendrons **4a** (Figure 1) have been prepared and used for the synthesis of $\beta$-lactams.[17] Another approach is the coupling of PEG-arms onto a multifunctional core to give a PEG-star polymer. Such multiarm PEG-star polymers have been recently introduced as supports for organic synthesis based on hyperbranched polyglycerol (see below)[18] and cyclotriphosphazene **4b**.[19] The advantages of these polyethers are their high chemical stability and good reactivity of the functional groups in homogeneous phase. The achieved loading capacities of polymer **4a** and **4b** (0.8 and $1.0\,\mathrm{mmol\,g^{-1}}$, respectively), however, are only marginal improvements compared with the commercially available mono- and bifunctional PEG derivatives.

On the other hand linear polymers, carrying functional groups on every monomer unit, for example polyvinylalcohol **5**, polyacrylic acid, polyacrylamide **6** have also been used as high-loading supports for organic synthesis.[13] For example the commercially available polyvinylalcohol (PVA) **5** (Figure 1) has been used as soluble support for oligonucleotide synthesis and a loading of up to $10\,\mathrm{mmol\,g^{-1}}$ of mononucleotide was reported, however, polymeric supports with a lower capacity and better solubility in polar organic solvents were recommended.[20] In addition, PVA **5** cannot be transformed in high yields into the respective polyacetals upon reaction with aldehydes or ketones and hence is less suitable as polymeric support for carbonyl compounds.[21] Other plausible reasons for the limited use of PVA **5** as soluble polymeric support are its poor solubility in organic solvents and the need of harsh reaction condition for functionalization.[13]

Another potentially high-loading linear polymeric support is polyacrylamide **6**.[13, 22] It has been used in a soluble noncross-linked form for the liquid-phase synthesis of oligonucleotides and in the form of cross-linked microbeads for the enzymatic synthesis of glycopeptides.[23] A limiting factor for the general use of polyamide supports, however, is their reduced chemical stability compared with polystyrene or polyethers, especially for reactions with organometallic reagents and strong bases.

More recently high-loading ROMP-based polymers have been introduced as polymer-supported reagents.[24] A "ROMPGEL" **7** containing phosphinoxide sidechains (loading $\approx 3.3\,\text{mmol}\,\text{g}^{-1}$) has been used as polymer reagent in Horner–Emmons reactions (Figure 1). This polymer has a gel-like behavior when solvated in organic solvents and can be removed from the reaction mixture by filtration through a silica cartridge. Other "ROMPGELs" have been used for the scavenging of amines and hydrazines, as acylation reagent and for the synthesis of oxadiazoles.[25] A general problem of these "ROMPGELs" are the tedious preparation of the norbornene monomers and the sensitivity of the double bonds in the final polymer towards heat and oxygen.

In general, linear polymeric supports have potentially high loading capacities, however, their polymer characteristics, such as solubility and chemical stability as well as their materials properties are problematic in some cases for broad application in organic synthesis.

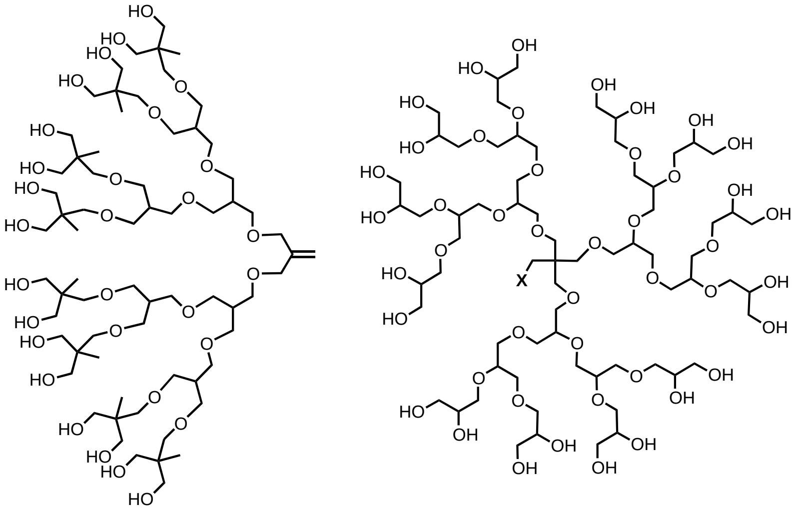
**Dendritic and hyperbranched polymeric supports**: The disadvantages of linear polymers, such as limited solubility in many organic solvents, gel formation, and problematic thermal behavior (high melting points and $T_g$s) in some cases can be overcome by the use of branched polymer architectures. An extreme in terms of tree-like branching are the perfectly branched dendrimers.[26] These well-defined macromolecules are soluble in many organic solvents (depending on their end functionalities) and possess a maximum capacity of functional groups in their periphery. However, the relatively high price and limited chemical stability of the commercially available polyamidoamine or polyamine dendrimers might well be the reasons for their limited use as supports in organic synthesis.[27] Despite these problems, polyamidoamine dendrimers have been sucessfully used as high-loading supports in the synthesis of indoles.[28] The separation of the macromolecules from low molecular weight species was performed by size-exclusion chromatography (SEC, Table 1) in this case.

In contrast to dendrimers, hyperbranched polymers are easily available in one reaction step. They contain dendritic, linear and terminal monomer units in their skeleton and hence can be considered as intermediates between linear polymers (degree of branching DB = 0 %) and dendrimers (DB = 100 %) with an approximate DB between 40 and 60 %.[29] The potential loading capacity of these hyperbranched polymers is similarly high as for dendrimers (5–14 $\text{mmol}\,\text{g}^{-1}$) and some hyperbranched polymers are even commercially available.[30] The use of these commercial materials as supports for organic synthesis, however, is limited due to the chemical stability of the respective polymer backbone (e.g. polyamines, polyesters) and the relatively broad molecular weight distributions (typically $>2$).

## Design of New Hyperbranched and Dendritic Polymers

A very promising class of high-loading polymeric supports are dendritic aliphatic polyethers as highly branched analogues of PEG. Aliphatic polyether dendrimers containing terminal 1,3-diol **8** and 1,2-diol units **9** have recently been prepared in a seven- and six-step synthesis, respectively (Figure 2).[31, 32] They are chemically stable, soluble in many organic solvents, show good accessibility and reactivity of the functional groups and possess a high concentration of OH-groups (11 and 14 $\text{mmol}\,\text{g}^{-1}$, respectively). However, the general drawback of any dendrimer is the tedious multistep preparation of higher generations (molecular weight exceeding 1500 $\text{g}\,\text{mol}^{-1}$), which is the lower limit for dialysis and ultrafiltration procedures (cf. Table 1). For this reason, perfectly branched dendrimers have mainly been used as supports for valuable transition metal catalysts with ligands attached to the core[33] and the shell of the macromolecule.[34] Yet another problem of high-generation dendrimers appears to be steric hindrance and site–site interaction at the outer functional shell.[35] This problem might be overcome by using randomly branched polymer structures as supports.

Recently, the controlled synthesis of well-defined hyperbranched polyglycerols **10** has been achieved, by using both racemic and enantiomerically pure glycidol monomers (Scheme 3).[36] These polyether polyols are conveniently prepared in a one-step synthesis on a multi-gram scale,[37] and possess molecular weights ($M_n$) up to 30000 $\text{g}\,\text{mol}^{-1}$ with molecular weight distributions ($M_w/M_n$) typically below 1.5.[38]



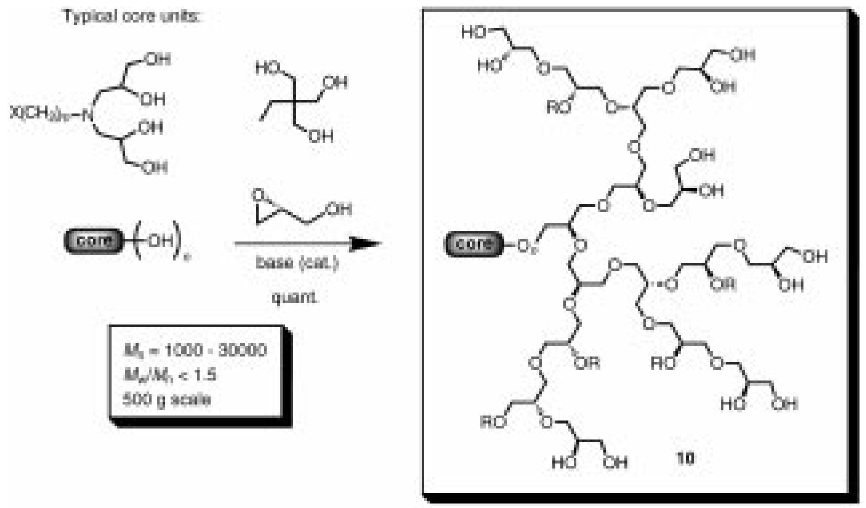
5.6 mmol diol $\text{g}^{-1}$

**8**

7.1 mmol diol $\text{g}^{-1}$

**9**

Figure 2. Dendritic supports based on aliphatic polyether dendrimers containing 1,3-diols **8**[31] and 1,2-diols **9** (X = core functionality).[32]

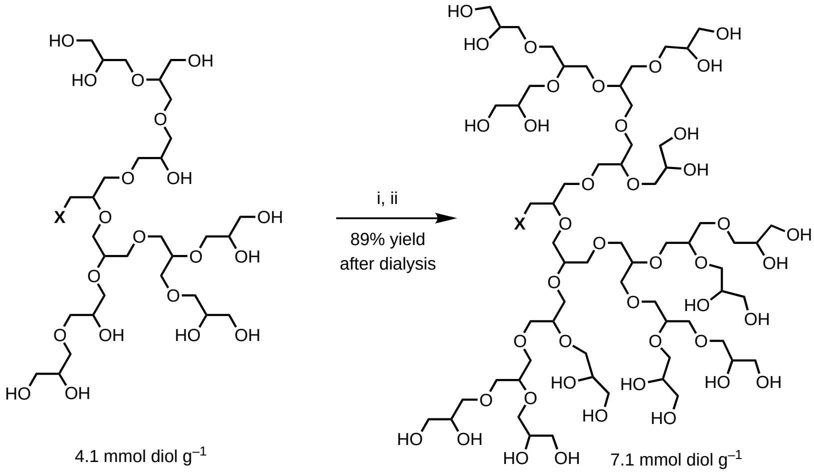


Scheme 3. Synthesis of achiral and chiral hyperbranched polyglycerols **10** (R = H).[36] For simplification only a small fragment of the hyperbranched structure is represented. Exclusively diol-functionalized polyglycerols **10** (R = Me, Et, allyl, Bn) can be prepared by selective synthetic modification.[39] A functional core unit (X = alkene, $NH_2$, SH) can also be introduced.[36b]

Due to anionic polymerization mechanism (ring-opening multibranching polymerization) quantitative polymer yields are obtained and the molecular weight is controlled by the monomer/initiator ratio. The dendrimer-like structure of the hyperbranched polyglycerol **10** is characterized by exactly one core unit with multiple hydroxyl groups randomly incorporated as linear (OH groups) and terminal groups (1,2-diols). The total density of functional groups in polymer **10** is 13.5 mmol OH per g polymer, of which approximately 60% (8.2 mmol OH per g) are terminal 1,2-diols. These terminal diols (see below) can directly be used as linker functionalities for many applications in organic synthesis.

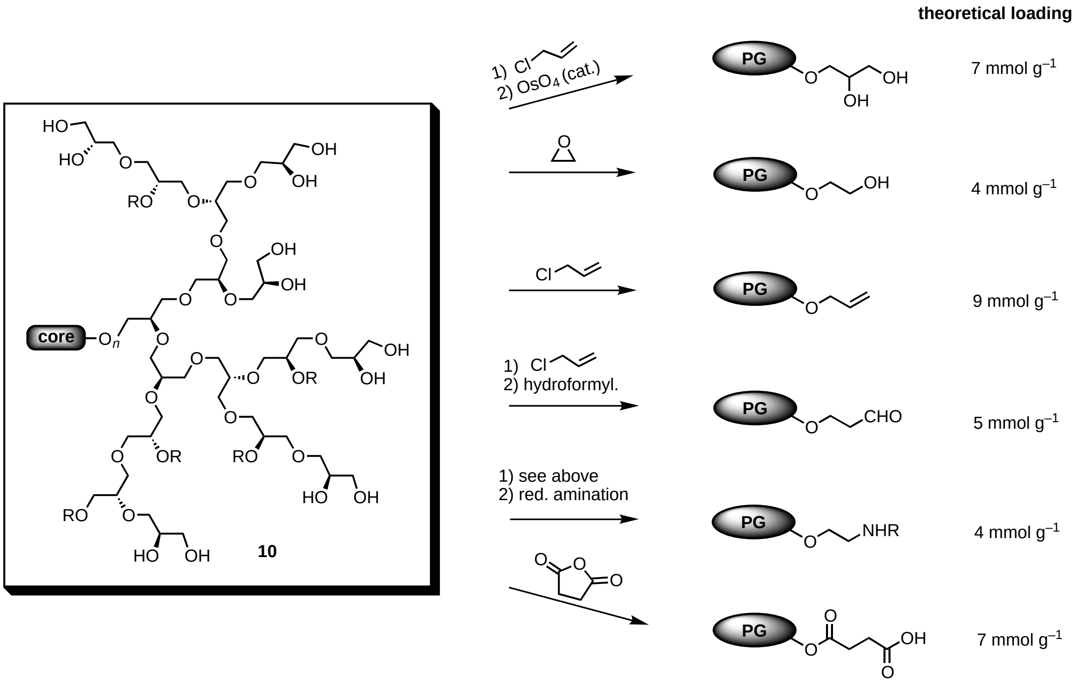
The complete derivatization of the terminal diols in polyglycerol **10** (R = H), with for example acetals, leaves about 40% of the OH groups unaffected (cf. Scheme 3). These remaining OH groups might limit the scope of this new polymeric support for some synthetic applications. For the preparation of a chemically inert polyether support **10** these residual OH groups can be selectively alkylated (R = Me, Et, Allyl, Bn) by using phase transfer conditions to obtain dendritic polymers with exclusively diol linkers.[39] This approach also permits to introduce a second type of functional groups and tune the solublity of the polymer in various organic solvents. In order to further increase the loading capacity of the polyglycerol support the linear glycerol units can also be converted into terminal 1,2-diols. For this purpose the hyperbranched polyglycerols **10** (R = H) can be transformed into perfectly branched structures, designated "pseudo-dendrimers" **11** (Scheme 4) by applying one dendrimer synthesis step (allylation and dihydroxylation) subsequent to the preparation of the hyperbranched polymer **10**.[32] This strategy increases the capacity of the terminal 1,2-diol units from 4.1 mmol g$^{-1}$ for the hyperbranched polymer **10** to 7.1 mmol g$^{-1}$ for the pseudo-dendritic structure **11** and preserves all advantages of the polyether scaffold. For comparison we have also prepared the perfectly branched glycerol dendrimer **9** (DB = 100%) in a six-step synthesis, which is monodisperse and possesses only two types of glycerol units (dendritic and terminal). As expected, the pseudo-dendritic polyglycerol shows identical $^1$H and $^{13}$C NMR spectra and hence must consist of the same structural units.[32] The pseudo-dendrimer **11**, however, is not centrosymmetric and monodisperse as required for perfect dendrimers. It still remains an intriguing question, whether molecular weight distribution and the topological difference between **9** and **11** lead to different chemical behavior and materials properties. On the other hand, for many applications currently discussed for dendrimers—especially as high-loading supports in organic synthesis—these aspects are of minor concern and the easily available pseudo-dendrimers can be alternatively used.

For a more general application of polyglycerol **10** in organic synthesis and in order to increase the scope of possible reactions on this support, the conversion of the hydroxyl groups into various other linker functionalities by postsynthetic transformations has been explored (Scheme 5).[40, 41] In



**10** **11**

Scheme 4. Synthesis of pseudo-dendritic polyglycerol **11** from the readily available hyperbranched polyglycerol **10** (X = functional core unit): i) allyl chloride, NaOH, tetrabutylammonium bromide; ii) *N*-methyl morpholine-*N*-oxide, osmium tetroxide (cat.), water/acetone 1:1.[32]



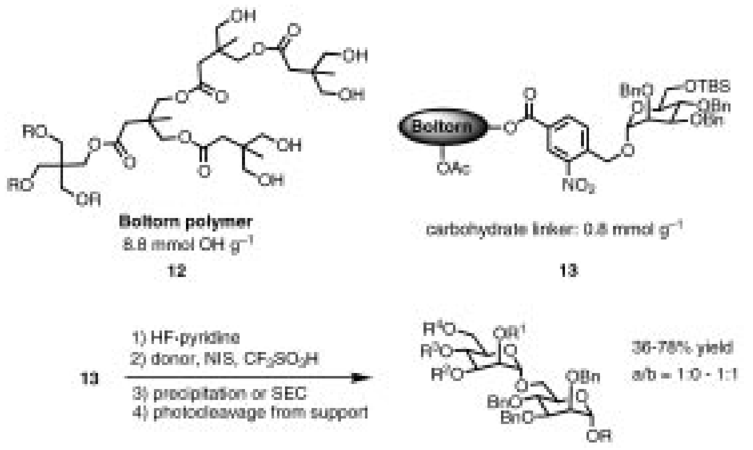
Scheme 5. Synthesis of multifunctional polyglycerols as high-loading supports for organic synthesis with various reactive linkers groups.[40, 41]

1–2 synthetic steps after the polymerization several reactive linker functionalities, such as alkenes, aldehydes, amines, carbonic acids, and esters are accessible in good yields and with high-loading. For many applications (see below), however, the native polyglycerols **10**, with "built-in" diol-linkers, can be directly used as support and no additional linker synthesis is required.

## Application of Dendritic and Hyperbranched Polymers in Organic Synthesis

Recently, hyperbranched polymers have been introduced as soluble supports in organic synthesis.[42, 43, 46] A hyperbranched polyester support **12** containing 1,3-diols as terminal units was used for the synthesis of disaccharides (Scheme 6).[42] Theoretically, these polyesters have a relative high loading capacity (8.8 mmol OH per g) but the experimentally achieved loading with monosaccharides attached to a photo-labile linker **13** was reduced due to the weight of the linker functionality (0.8 mmol g$^{-1}$). For better compatibility, the remaining OH functionalities were converted into acetates. The general use of this hyperbranched polymer **12** as support is limited due to the chemical sensitivity of the polyester backbone. In addition, these commercially available polyesters, have rather low molecular weights ($M_n = 1500-2000$), and molecular weight distributions in the range of $M_w/M_n = 2-2.5$.[44] This is especially problematic for the separation by dialysis or ultrafiltration with a minimum molecular weight cut off (MWCO) of 1000 g mol$^{-1}$ (cf. Table 1).

Dendritic and hyperbranched polyglycerols **10**, **11** on the other hand can be prepared with much higher molecular weights and narrow molecular weight distributions (see above). They are readily soluble in many organic solvents and can easily be separated from low molecular weight compounds by dialysis or ultrafiltration with a typical MWCO of 1000 g mol$^{-1}$. Due to the high flexibility of the branches, the terminal 1,2-diol groups show excellent accessibility and can be used directly as linker groups for various applications in organic synthesis (Figure 3). An important application is the support of carbonyl compounds, because they are pres-



Scheme 6. The use of hyperbranched polyesters **12**, (R = other polymer branches) **13** as homogeneous supports for the synthesis of disaccharides.[42]

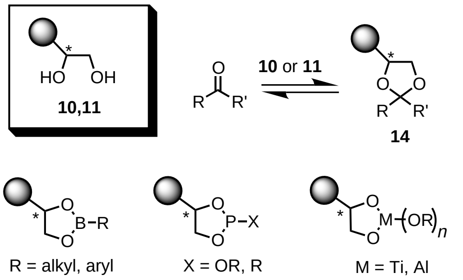


Figure 3. Potential applications for polymeric supports with 1,2-diols linkers, as reversible supports for carbonyl compounds **14**,[43] reagents and catalysts. The $C_2$-carbon of the linker is a stereogenic center and can be used to generate chiral polyglycerol supports (cf. Scheme 3).[36b]

ent in many synthetic building blocks, natural product and drug molecules. The acetal protection group is stable towards many reagents from basic to weakly (aprotic) acidic media and can be cleaved under protic acidic conditions. In addition, acetal cleavage liberates the carbonyl compound and regenerates the diol linker group.

Further advantages of polymeric supports containing 1,2-diol linkers are their general applicability in organic synthesis, for example as supports for reagents, ligands, and catalysts (Figure 3). For example, boronic acids and phosphites can be easily treated with a diol linker and subsequently be used as reagents or ligands, respectively. Due to the chelating effect of a 1,2-diol to oxophilic metals, such as titanium and alumina, it can also be directly used as ligand. Despite these multiple advantages 1,2-diols have not yet been widely recognized as linker groups for polymeric supports and only few examples have been reported so far.[45]

We have developed several synthetic strategies for the selective coupling of carbonyl compounds on the terminal 1,2-diol units of polyglycerols **10**, **11**.[43] In all cases the polymer supported acetals **14** were isolated in high yields after purification by dialysis. The coupling reaction also occurs with quantitative conversion as demonstrated by $^{13}C$ NMR spectroscopy. Acetal cleavage can be performed with a solid phase acidic ion exchange resin (e.g. DOWEX-50) in aqueous methanol. The latter clearly demonstrates the orthogonal use of two polymers (soluble and insoluble) in *one* reaction mixture with sequential separation.[14, 43] Various chemical transformations have been successfully performed on functionalized polymer-bound acetals, such as nucleophilic substitutions, catalytic C–C-coupling reactions, selective reductions, and Wittig-reactions.[43, 45] This demonstrates the general applicability of polymer supports with 1,2-diol linker groups for organic synthesis.

## Scope and Limitations of High-Loading Polymeric Supports

Every new polymeric support has to compete with the current benchmark, the so-called Merrifield resin and its derivatives. Therefore new high-loading supports must i) be easily accessible in large quantities, ii) have a loading capacity >1.5 mmol linker per g polymer, iii) contain reactive groups, which are conveniently functionalized by standard solution phase chemistry, iv) be chemically and mechanically stable and v) be easy to separate by standard laboratory techniques. For ecological and financial reasons new polymeric supports should also allow mmol-scale synthesis and the complete recycling of the support after cleavage of the product.

None of the previously mentioned high-loading supports is perfect, however, dendritic and highly branched soluble polymeric supports or hybrids of these with solid-phase resins are among the most promising candidates to fulfill the requirements for new high-loading supports in organic synthesis. Such hybrid resins are especially attractive because they can combine several materials properties and allow the full characterization of the product by standard analytical techniques (including $^1H$ NMR!) after cleavage from a single microbead.

For many synthetic applications new linker systems are developed, however, in some cases the synthetic effort and final loading capacity of the polymeric support (due to the weight gain from the linker) are not considered. The development of new high-loading polymeric supports should therefore focus on simple and general linker systems, which do not dramatically decrease the loading capacity of the polymeric support. "Built-in" linker systems, such as the terminal diol units in polyglycerol supports **10**, **11** require a minimum synthetic effort and are most efficient.

Another important criterion for high-loading polymeric supports certainly is the possibility of intramolecular cross-reactions in these highly functional supports.[4] However, site isolation in dendritic and hyperbranched polyglycerol derivatives is less problematic due to the randomized 3D-orientation of the terminal groups as compared to a linear high-loading polymer, such as PVA **5** and perfectly branched dendrimers, for example **9** (see above). Nevertheless, it is necessary to find an optimum between accessibility, flexibility, and loading of functional groups in these dendrimer-like polymer scaffolds. In recent work we have shown that the degree of branching in polyglycerols can be adjusted from 0–100% by copolymerization with other glycidyl ethers and postsynthetic modification.[40, 41] By this method the diol-loading of the polyether support is adjustable from 0–7.1 mmol g$^{-1}$ and can provide an answer to this interesting question.

Whether or not a new polymeric support is suitable for general application in organic synthesis can only be determined by application in diverse chemical syntheses in a multiparallel fashion. At present we investigate the potential of these soluble high-loading polyglycerol supports **10**, **11** for application in multistep liquid phase combinatorial syntheses (LPCS) and for fabrication of new high-loading hybrid supports.

## Acknowledgement

The author would like to thank his co-workers and colleagues who are mentioned in the papers for their contribution. He is especially indebted to Dr. Alexander Sunder and Dr. Holger Frey for careful proof-reading of this manuscript and helpful discussions; Prof. Rolf Mülhaupt for his generous support, the Fonds der Chemischen Industrie and Bayer AG for financial support.

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