1. General introduction

In the last decades functional polymers have attracted increasing intrest in a wide range of applications, for example in medicine and pharmacy as polymer therapeutics[1-3] or in organic chemistry as supports for synthesis and catalysis.[4-6] Since about 20 years especially perfect dendrimers and hyperbranched polymers are of interest due to their unique properties.

1.1. Classification of polymers

Polymers can be divided into four classes: linear polymers, linear polymers with side-chains or side-functional groups, hyperbranched polymers,[7] and perfect dendrimers[8-11] (Figure 1). Additionally variations and combinations between those four classes have been investigated, for example linear polymers with dendronized side-groups[12-16] or linear/star-like polymers with dendritic head groups[17,18] (Figure 2).

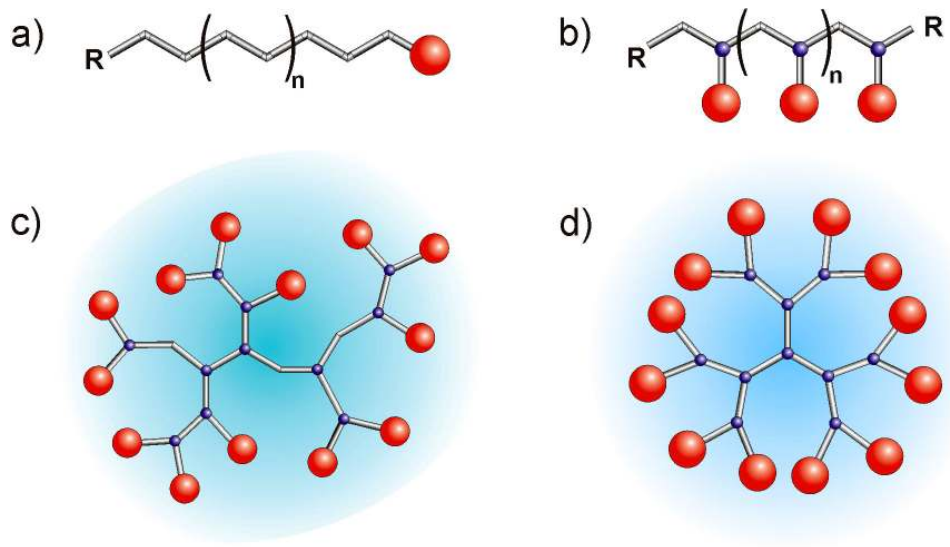


Figure 1. Schematic structures of linear and dendritic polymers: a) linear polymer with one functional endgroup, b) linear polymer with a functional group on every monomeric unit, c) hyperbranched polymer, d) perfect dendrimer.

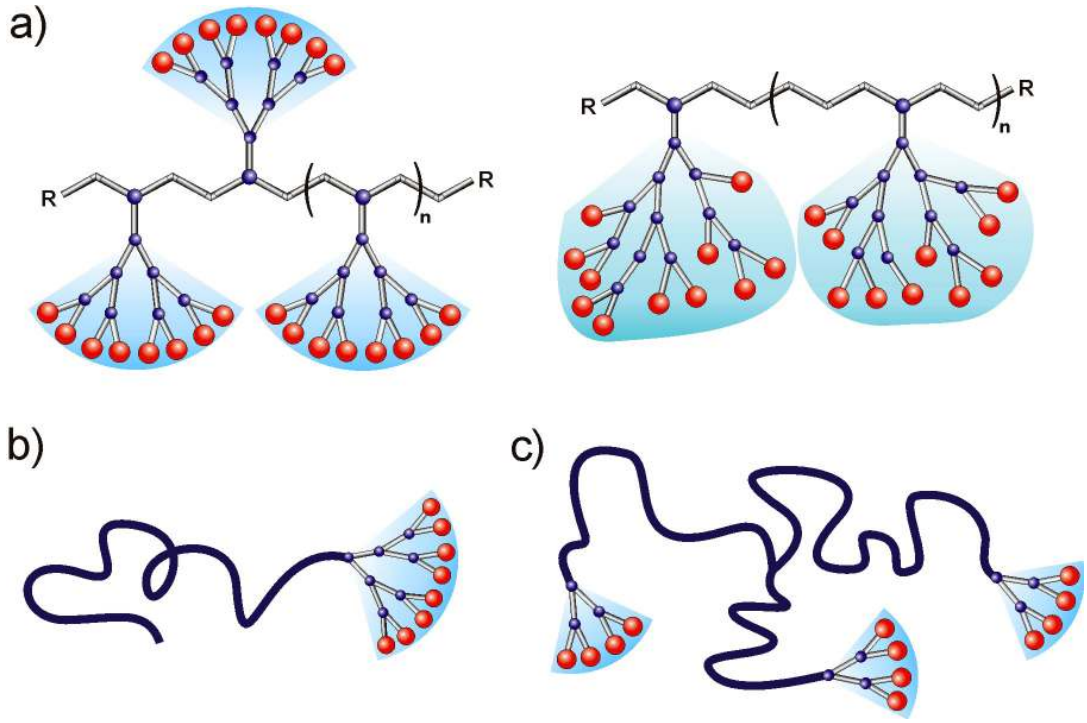


Figure 2. Dendronized polymers: a) functionalized at side-groups with dendrimers (left) and hyperbranched polymers (right), b) dendronized at endgroup, c) star-like polymer with dendrons on the end of the arms.

The properties of polymers are not only connected to their chemical composition but also to the geometrical shape of the macromolecules.[10] Therefore one of the most promising types of polymers are dendrimers and hyperbranched polymers. Due to their spherical, densely packed architectures those molecules reveal unique properties, such as globular shape, high density of functional groups, low viscosity, and amorphous material structure.[11] Additionally easy modifications allow the synthesis of tailor-made supramolecular structures, required for special applications.[5,7,19-24]

1.2. Dendrimers

Dendrimers represent a key stage in the ongoing evolution of macromolecular chemistry. Half a century ago, in theoretical studies, Flory examined the potential role of branched units in macromolecular architectures,[25] however, no progress in that field occurred during the next 26 years. The first report about cascade molecules based on poly(propylene imine) (PPI) was published by Vögtle in 1978.[26] Since then, dendrimers have been a growing field of research. The number of publications and patents concerning the topic “dendrimer” increased from 40 between 1986 and 1990 to 418 in 1991 to 1995, and up to 6216

publications in the years 2001 to 2005 (Figure 3). In 2005 almost 1500 articles have been published all over the world.

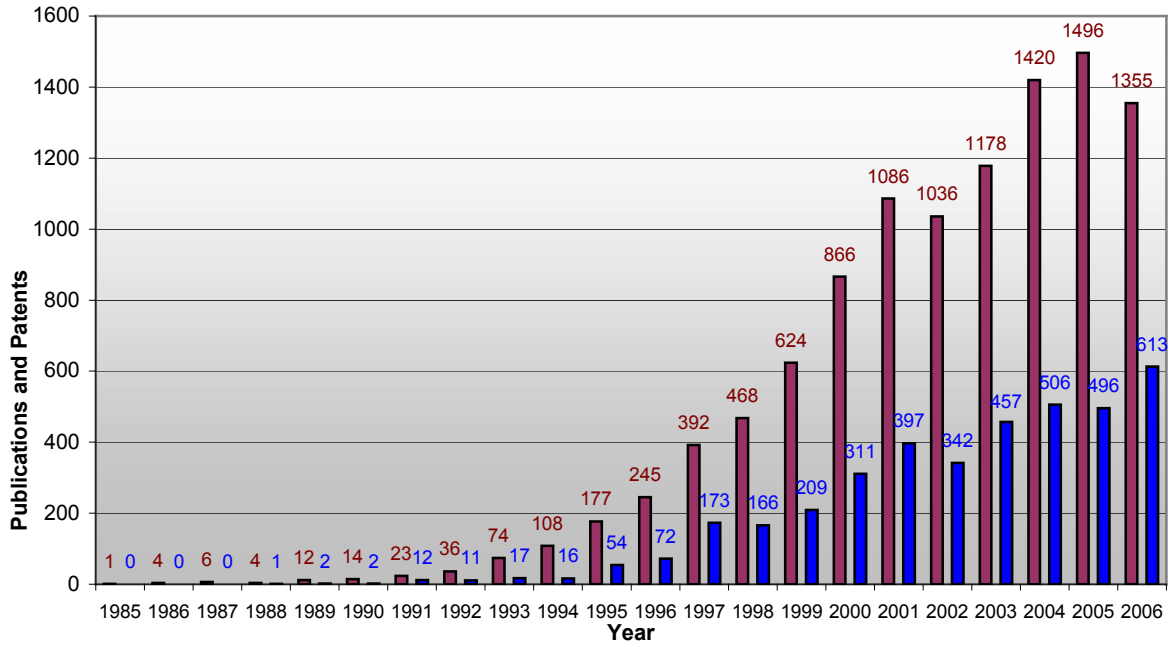


Figure 3. Number of publications and patents with the concept "dendrimer" (maroon) and "hyperbranched" (blue) in the years 1985 to 2006. (source: SciFinder Scholar 2006)

After the first publication about "cascade polymers" in the early 1980s, Denkewalter[27-29] patented the synthesis of L-lysine-based dendrimers. The patents describe structures up to high generations, although the characterization was only based on size exclusion chromatography (SEC).[30]

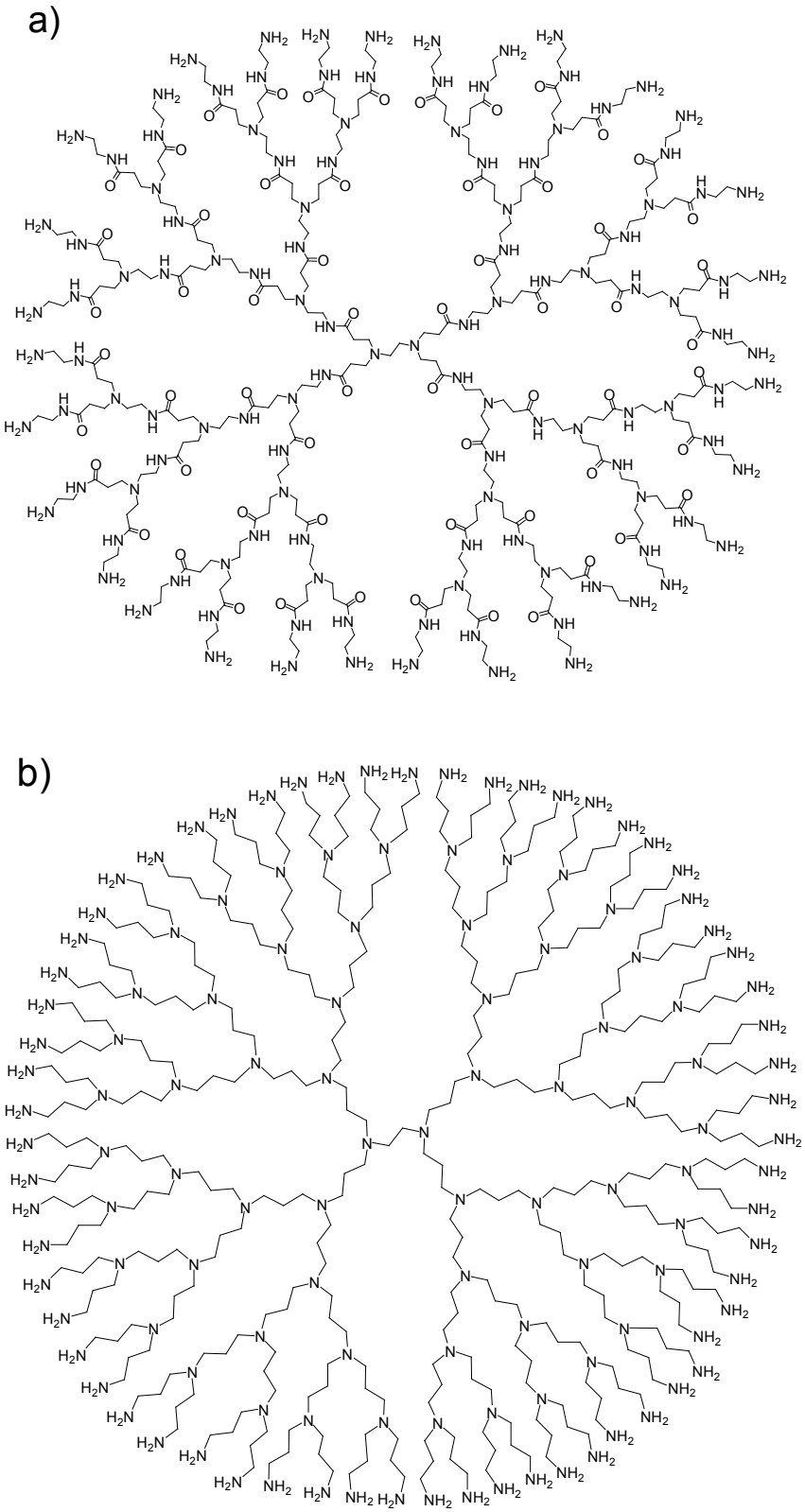


Figure 4. Chemical structure of: a) [G4]-PAMAM dendrimer and b) [G5]-PPI dendrimer.

The first dendritic structures that have been thoroughly investigated were published by Newkome and Tomalia who synthesized higher generation cascade "arborol"[31][32] and poly(amidoamine) (PAMAM)[33-35] molecules (Figure 4a) and also established the term

"dendrimer".[9][36] Based on the preliminary work of Vögtle[26] in 1993 Mülhaupt[37] and Meijer[38] independently reported on the divergent synthesis of poly(propylene imine) (PPI) dendrimers up to the 4th generation (Figure 4b). Other well known dendrimers are the Fréchet type polyarylethers[39,40] introduced in 1990 (Figure 5a) which are easily accessible and have been studied widely, by several research groups. Other prominent examples are Moore's convergently produced polyacetylene dendrimers[41-44] (Figure 5b), and polyphenylene dendrimers[45,46] (Figure 5c) first described by Müllen et al. in 1997. Additionally, many other types of dendrimers with various architectures, defined nanoscopic dimensions, discrete number and type of functional end groups have been developed over the last years.[6,9,11,20,22-24,47-52]

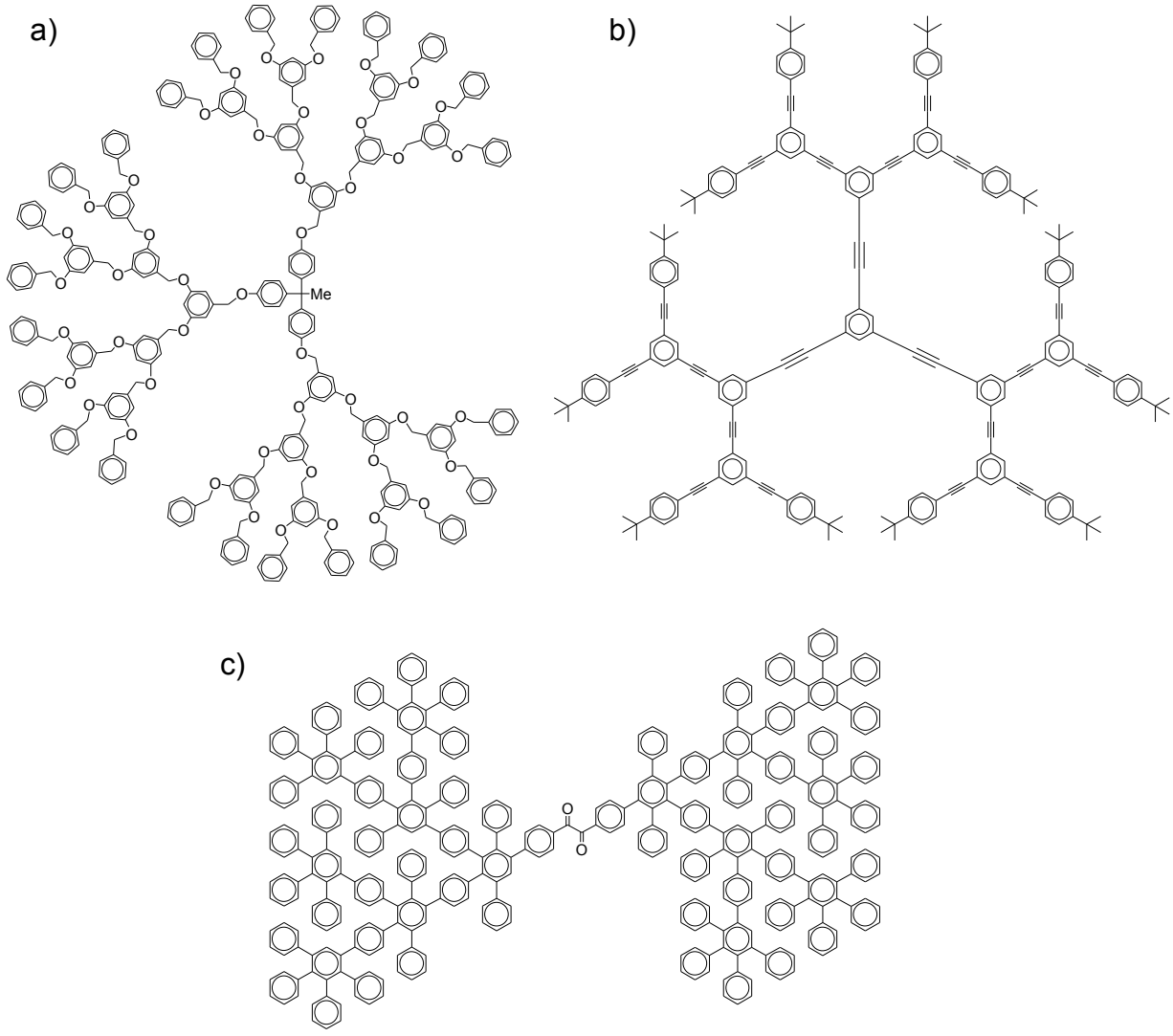
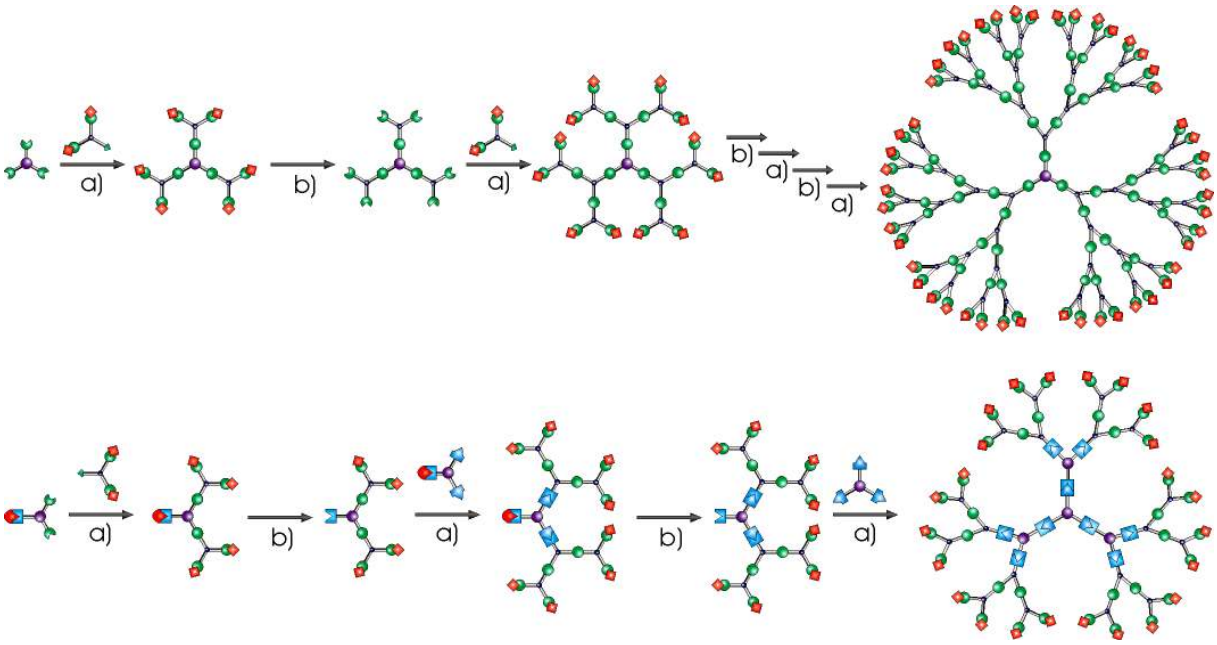


Figure 5. Chemical structure of: a) [G4]-polyarylether dendrimer, b) [G3]- polyacetylene dendrimer, and c) [G3]- polyphenylene dendrimer

There are two general synthetic approaches for the construction of high-generation dendrimers: the divergent approach and the convergent approach (Scheme 1). Both approaches are based on the repetition of coupling and activation steps and affect the creation of an additional generation of the dendrimer. In the divergent synthesis the growth of the dendrimer is initiated at what will become the core of the molecule and continues outwards with every coupling step. This strategy was used to synthesize PPI[37,38] and PAMAM[33-35] dendrimers as well as Newkome's arborols.[31] The convergent approach, first reported by Hawker and Fréchet in 1989-1990,[39,40] initiates the growth of the macromolecule from what will become the exterior of the dendrimer, and proceeds inward to the core.



Scheme 1. Divergent (upper) and convergent (lower) synthesis of dendrimers. Both approaches are based on the repetition of coupling (a) and activation (deprotection) steps (b).

The major challenge in the synthesis of dendrimers is the high purity of the final product that is required. In the divergent approach, especially for higher generation dendrimers, numerous identical reactions have to be performed on a single molecule. Consequently, every reaction has to be very selective and proceed with at least 99.9% conversion to ensure the integrity of the final product. As an example the synthesis of [G5]-PPI with an average selectivity 99.5 % per reaction (248 reactions total) will only result in 29 % (0.995^{248}) of defect free dendrimer. With a selectivity of above 99.9 % per reaction the final mixture will contain around 80 % of the perfect product. Because of only small differences in the masses of perfect and defect dendrimers, purification in case of the divergent synthesis is very problematic, especially for higher generations of dendrimers. Therefore, the statistical distribution of small defects in the structure of dendrimers

synthesized by this approach cannot be avoided. This situation is similar to the iterative synthesis of polypeptides or polynucleotides on a solid support.[53]

In the convergent route the big differences in the masses of perfect and imperfect dendrons allows an easier separation of product from side-products. Apart of the higher purity of the dendrimer, the convergent synthesis has some limitations. Because of the fact that in the last step of the synthesis the dendrons are attached to the central core molecule, the high sterical hindrance results in low selectivity of the reaction. Additionally, after the final coupling no further grow of the dendrimer is possible in a convergent fashion.

The globular structure of dendrimers results in a low viscosity in solution which seems to be not only dependent from the chemical composition but also dependent from the molecular weight. Therein they differ significantly from both high molecular weight chain-type polymers and suspensions of idealized spherical particles.[54] In addition to the good solubility in various solvent, determined by the properties of the periphery, the large number of functional endgroups and the highly defined structure make dendrimers attractive for many applications. Noteworthy, is also the use of dendrimers in medicine,[20,22,47,49,52,55-68] in host-guest chemistry,[19,69-97] in catalysis,[5,6,98-119] as chemosensors,[120-123] light harvesting structures,[24,48,61,124-131] and organic electronics.[132] Additionally, dendrimers can be used to mimic protein or coenzyme properties due to site isolation after encapsulation of an active center.[133,134] This phenomenon was also used for organic light emitting diodes (OLED) by localizing dyes inside the dendritic core.[135-137]

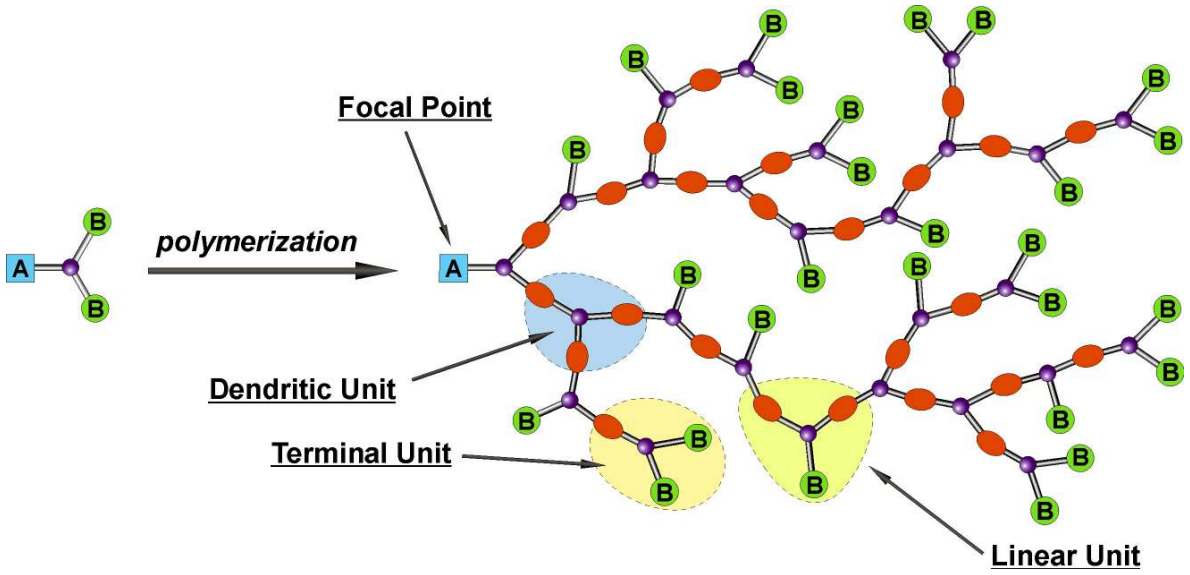
Nowadays the most popular dendrimers such as poly(propylene imine) (PPI, Astramol®) or poly(amidoamine) (PAMAM, Starburst®) are commercially available in kilogram quantities, although the unsolved problems of purification and multistep synthesis strongly influence the price and quality of the final materials. Additionally the backfolding of dendrons effect that the higher generation dendrimers (usually above [G3]) are never perfect structures.[21,138]

1.3. Hyperbranched polymers

In spite of the constant progress in development and optimization of dendrimer preparation,[139] the necessity of tedious, expensive multistep syntheses is still the major drawback in the commercial use of perfect macromolecules. As an alternative to dendrimers, hyperbranched polymers have been introduced. Hyperbranched polymers are a relatively old class of macromolecules which recently have attracted significant attention from both, academia and industry. In contrast to dendrimers, hyperbranched polymers are usually prepared in a one step process, most commonly by the polymerization of AB_n monomers ($n \geq 2$).

The history of hyperbranched macromolecules can be dated to the end of the 19th century, when Berzelius reported the formation of a resin from tartaric acid (A_2B_2 monomer) and glycerol (B_3 monomer).[140] Then the Watson Smith report of the reaction between phthalic anhydride (latent A_2 monomer) or phtalic acid (A_2 monomer) and glycerol (B_3 monomer) followed in 1901.[140] Kienle, et al.[140-142] studied that reaction further, obtaining results that are still used today. They observed a significantly lower viscosity of phtalic acid glycerol polymers in comparison to the linear polymers described by Staudinger.

In the 1940s, Flory et al.[143-146] used statistical mechanics to calculate the molecular weight distribution of tree-like polymers with tri- and tetrafunctional branching units, and developed the concepts of the “degree of branching” and “highly branched species”. In 1952 Flory[25] developed the theory that highly branched polymers can be synthesized without gelation by controlled polymerization of AB_n monomers ($n \geq 2$) (Scheme 2). Finally, in 1982 Kricheldorf[147] obtained highly branched polyester by copolymerization of AB and AB_2 type monomers. The name “hyperbranched polymer” was introduced by Kim and Webster[70,148,149] in 1988 with the synthesis of soluble hyperbranched polyphenylene. Since then hyperbranched polymers have attracted increasing attention due to their unique properties and easier availability compared to dendrimers. Nowadays companies such as the Perstorp Group (Boltorn®, aliphatic polyesters; Perstorp, Sweden), DSM Fine Chemicals (Hybrane®, poly(ester amides); Geleen, Netherlands), BASF AG (Polymin®, Lupasol®, poly(ethylene imines); Ludwigshafen, Germany), and Hyperpolymers GmbH (Polyglycerol®, aliphatic polyethers; Freiburg, Germany) produce commercially available hyperbranched polymers on large-scales.



Scheme 2. Theoretical polymerization of AB_2 monomers results in hyperbranched polymer with dendritic (D), linear (L), and terminal (T) units.

The one-step procedure used for the preparation of dendritic polymers leads to an uncontrolled statistical growth. Consequently, the resulting structures are imperfect and polydisperse. Furthermore, unlike dendrimers, the control over layers or generations as well as over molecular mass deteriorates. Due to the additional availability of linear (L) units, the core-shell architecture of hyperbranched macromolecules is less defined compared to perfect dendrimers. Calculations suggest that dendritic (D) units are more likely to be found in the center of the polymer, linear (L) units are located statistically between the core and periphery of molecule and terminal (T) units are most likely to be found at the periphery.[150,151] Nevertheless flexible dendrimer structures exhibit backfolding of some branches which results in a distribution of the terminal units all over the diameter of the dendrimer. Therefore, it is not surprising that dendrimers and hyperbranched polymers show similar physicochemical properties due to their globular structure in solution.[152]

One of the most important features of hyperbranched polymers is the “degree of branching” (*DB*) or “branching factor”, which defines the ratio of branched, terminal, and linear units in the macromolecular structure. The degree of branching of a perfect dendrimers equals 1, while linear polymers have a *DB* of 0. Commonly, the *DB* is determined by NMR spectroscopy on the basis of low molecular weight model compounds, that posses structures similar to linear, dendritic, and terminal units in the respective hyperbranched polymers. The *DB* is obtained by comparing of the intensity of the signals for the respective units. Two different equations have been suggested for the calculation of the *DB*. The first definition, introduced by Fréchet and Hawker,[153,154] compares the sum of the dendritic and the terminal repeating units to the sum of all repeating units in the structure (Equation 1) where D, T, and L represent the number of dendritic, terminal and linear units per molecule. The second definition by Frey and co-workers[150,155] (Equation 2) does not include the terminal repeating units and is therefore claimed to be more accurate than equation 1 for polymers with low molecular mass.

$$DB_{Fréchet}(\%) = \frac{D+T}{D+T+L} \times 100 \qquad \text{(Equation 1)}$$

$$DB_{Frey}(\%) = \frac{2D}{2D+L} \times 100 \qquad \text{(Equation 2)}$$

Additionally, hyperbranched macromolecules are characterized by the molecular weight distribution (*MWD*) value (Equation 3). *MWD* of polymers synthesized by a semi-batch polymerization (with slow monomer addition) is strongly dependent on the functionality *f* of the initiator, where *f* is equal to the number of reactive groups.[156]

$$MWD = \frac{M_w}{M_n} \approx 1 + \frac{1}{f} \qquad \text{(Equation 3)}$$

The maximum achievable degree of branching depends on the synthetic pathways applied. Various factors, such as bulk polycondensation, slow monomer addition, but also the reactivity of the linear (L) units compared to the terminal (T) units, play an important role.[155,157] Bulk reaction conditions result in a maximum possible *DB* of 50% in theory, whereas slow monomer addition leads to a *DB* of up to 66% if the T and L units are equally reactive. A higher reactivity of the L units in comparison to the T units is necessary to obtain *DB* above 66%. Additionally, control over the topology of polymers can be obtained by changing parameters like temperature[158] or pressure.[159,160]

Most of the applications of hyperbranched polymers are based on the globular shape, the nature and large number of functional groups within a molecule, and by the absence of chain entanglements. The large number of functional groups allows the tailoring of their thermal, rheological, and solution properties and thus provides a powerful tool to design hyperbranched polymers for a wide variety of applications.[4,7,161-164]

In this work two different types of commercially available hyperbranched polymers: polyglycerol (PG) and poly(ethylene imine) PEI were used (Figure 6).

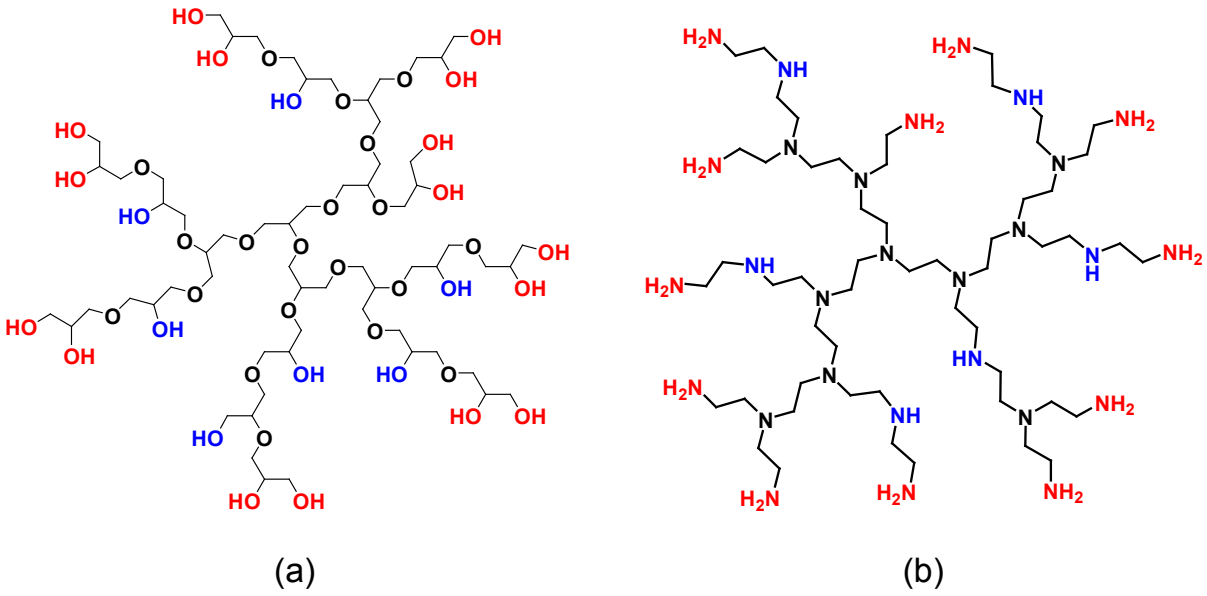
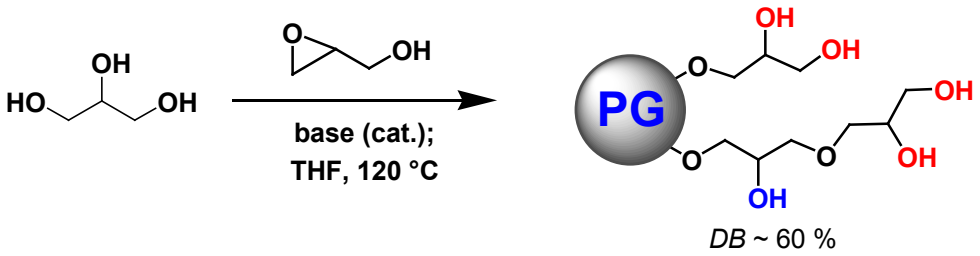


Figure 6. Chemical structure of hyperbranched (a) polyglycerol (PG) and (b) poly(etyhlene imine) (PEI); black = dendritic unit (D), blue = linear unit (L), and red = terminal unit (T); PG has a *DB* of 53 - 60 %, PEI has a *DB* of 62 – 73 %; the structures shown are small fragments of the large polymers.

Higher molecular weight PGs (Figure 6a) were first anionically polymerized by Vandenberg,[165] although final material was branched to the very limited extend. Later cationic polymerization of glycerol was reported by Penczek and Dworak.[166,167] In 1999 Frey and coworkers synthesized hyperbranched PG *via* an anionic ring-opening polymerization, using glycidol as a latent AB_2 monomer (Scheme 3).[168] A partially deprotonated triol (1,1,1-Tris-(hydroxymethyl)propane) was employed as the alkoxide initiator, therefore allowing control over the concentration of the active sites in the reaction mixture. The other key factor was a slow addition of the glycidol to the reaction mixture. This minimizes unwanted cyclization and enables to improve the control of molecular weights and to obtain lower polydisperities. The obtained hyperbranched polyglycerol possesses degrees of branching in the range of 53 % to 60 %, polydispersities are ranging from 1.1 to 1.5, and molecular weights are up to 10000 g mol^{-1}. During the synthesis of PG not all of the -OH groups are deprotonated and a rapid deprotonation/protonation takes place in a random fashion, resulting in a pseudo living anionic polymerizations.[161] The resulting narrow *MWD* is typical for living polymerization. To increase the degree of branching Haag and coworkers[169,170] proposed a three step synthesis to obtain pseudo-dendrimer polyglycerol with $DB \approx 100$ % and $M_w/M_n = 1.2$. Additionally, chiral and core-functionalized polyglycerols have been synthesized by using a functional starter and enantiomerically pure gylcidol.[171]

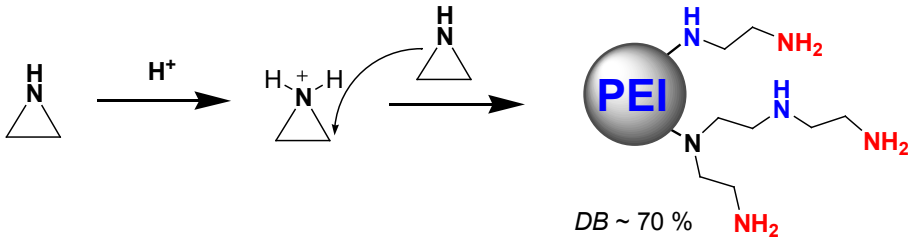
A different approach to synthesize very high molecular weight (M_n up to 700.000 g mol^{-1}) hyperbranched polyglycerol was proposed by Brooks and coworkers[172] who emulsified glycidol into nanodroplet and then started the anionic polymerization process.



Scheme 3. Synthesis of hyperbranched polyglycerol (PG). As a starter in this example glycerol has been used. The structure of the polymer is an abbreviation and corresponds to the structure shown in Figure 6a.

Hyperbranched poly(ethylene imine) (PEI)[173,174] (Figure 6b) is the oldest commercially available hyperbranched polymer. BASF produces PEIs in multi kilogram scale *via* an acid catalyzed ring-opening polymerization of aziridine (ethylene imine)[175] at 90 – 100 °C in water or organic solvents (Scheme 4) by slow monomer addition. Similar to hyperbranched polyglycerol the polymerization of aziridine can be described as pseudo living cationic. The higher reactivity of the secondary (linear) amino groups in comparison to

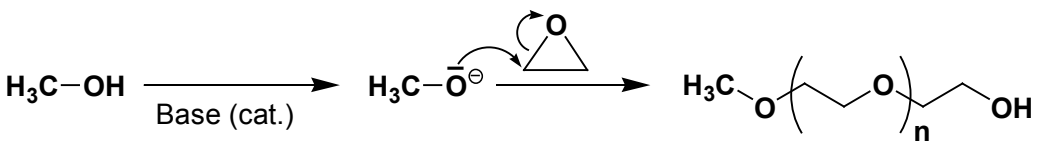
primary (terminal) amino groups leads to a faster reaction of the nitrogen atom of the L units with an aziridine monomer if the reaction is not dominated by steric hindrance. The degree of branching of PEI is therefore higher than theoretical 50 % and is in the range between 62 – 73 % (84 % in case of $PEI_{0,8}$, M_w = 800 g mol^{-1}). Poly(ethylene imine) can be obtained with narrow *MWD* (typically below 2.0) and molecular weights (M_n) up to 10000 g mol^{-1}. Higher molecular weight PEIs are accessible via crosslinking with bifunctional alkylation agents such as 1,2-dichloroethane. The hyperbranched PEIs have found application e.g. as crosslinkers (in coatings), in paper industry (as additives), gene delivery,[176] and for water treatment[177] due to their ability to form strong complexes with metal ions.[178]



Scheme 4. Synthesis of hyperbranched poly(ethylene imine) (PEI). As a starter in this example an activated aziridine unit has been used. The structure of the polymer is an abbreviation and corresponds to the structure shown in Figure 6b.

1.4. Biocompatible poly(ethers) as material for medical applications

Poly(ethylene glycol) (PEG), respectively poly(ethylene oxide) (PEO)[179] is a neutral, thermoplastic polymer with a high solubility in both water and organic solvents.[180,181] It is a linear polymer based on the $-CH_2CH_2O-$ repeating unit, and is prepared by a ring-opening polymerization of ethylene oxide.[182] PEGs with various molecular weights (from 200 – 8000000 g mol^{-1}) are commercially available in kilogram scale and with low polydispersities (M_w/M_n) of around 1.05 for polymers with molecular weights up to 10000 g mol^{-1}. The purity of PEG with a size greater than 10000 Da is reported to be diminished by the inclusion of branched structures and hydrophobic linking groups.[183] Ring-opening polymerization of ethylene oxide with methanol leads to products with one chain end blocked by a methoxy group (Scheme 5) – monomethyl poly(ethylene glycol) ether (mPEG).



Scheme 5. Synthesis of monomethyl poly(ethylene glycol) ether (mPEG) by anionic ring-opening polymerization.

Poly(ethylene glycol) is claimed to be non-toxic and biocompatible. The biocompatibility (toxicity and bioaccumulation) were studied by Carpenter et al.[184] after intravenous injection of PEG4000 (M_w = 4000 g mol^{-1}) in dogs. They found no detectable toxic or cumulative effects of PEG after repeated injections of doses ranging up to 90 mg/kg per day. Carbon-14-labelled PEG was used to determined that 24h after an intravenous injection, the major portion of the polymer was excreted in the urine. Further researches proved that polymers with molecular weights below 30 kDa are eliminated from the body by kidneys and by faeces (for PEGs > 20 kDa).[185,186] Studies in rats on the acute and subacute oral, intravenous, and dermal toxicity of PEGs ranging in size from 200 g mol^{-1} to 10000 g mol^{-1} have shown that these compounds exhibit low toxicity.[187] However, in some cases, severe reactions such as seizure and anaphylactic shock have been observed in humans after oral use.[188] Also allergic reactions have been observed in a few patients after using medications containing PEG.[189] In recent years the accumulation of poly(ethylene glycol)s in finger capillaries has been observed (palmar-plantar erythrodysesthesia).[190]

Poly(ethylene glycol) is approved by the FDA (Food and Drug Administration)[191] and is one of the mostly widely used biocompatible polymers. It is the basis of a number of laxatives (Movicol®, MiraLax®), many skin creams, lubricants, gels, and eye drops. It is used in a number of toothpastes as a dispersant. PEG is used as a polar domain of nonionic surfactants (Pluronix®)[192,193] and as a solvent in organic reactions.[194] Last but not least, poly(ethylene glycol) is in generall the polymer of choice for protein and peptide conjugation. The development of protein and peptide drugs for therapeutic purposes has increased the interest in methods to enhance their delivery (In 2000, sales of polypeptide drugs were estimated at US $15 billion worldwide[195]). The creation of polymer-protein conjugates increase dramatically the bioavailability, solubility and stability of protein drugs and at the same time decreased immunogenicity. These altered properties improve the delivery and efficacy of proteins/peptides and impart the flexibility of their clinical usage. The covalent conjugation of PEG to proteins is referred to as “PEGylation”.[196,197] The amount of PEG/mPEG connected to a single protein can be varied by changing the number of polymer chains per molecule and/or by the modification of the molecular weight of a single polymeric chain. In general it is proved that the in the most tolerogenic conjugates 60 to 70 % of molecular weight comes from mPEGs and 30 – 40 wt% come from protein. Higher or lower mPEG/polymer ratios were found to be less effective.[198] Up to now the FDA has approved several pegylated polypeptides as therapeutics and more are undergoing clinical investigations. The most prominent are pegademase (Adagen®), pegaspargase (Oncaspar®), peginterferon α2b (PegIntron® - with PEG 12 kDa, Pegasys® - with branched

PEG 40 kDa),[199,200] pegvisomant (Somavert®), and pegfilgrastim (Neulasta® - pegylated form of the earlier drug Neupogen®).[186]

In the recent years also linear and hyperbranched polyglycerols were reported to be a highly biocompatible polymers based on their similarities to the PEG.[201,202] Comparison tests performed for PG and PEG revealed very similar biocompatibility profile for both polymers. *In vitro* tests of blood compatibility, red blood cell aggregation (including total blood viscosity), and complement activation showed no or insignificant influence of the polymer on measured values. The studies performed with fibroblasts and endothelial cells showed very limited cytotoxicity of linear and hyperbranched PG, with about 80 % cell valibility observed even at a high concentration after 72 h of incubation. No significant difference was observed between hyperbranched and linear polyglycerol in terms of biocompatibility for compounds with low molecular mass (below 6000 g mol^{-1}). In all mentioned aspects PG behaved as well or better than PEG. Moreover, hyperbranched polyglycerol is thermally and oxidatively more stable than poly(ethylene glycol).[203]

In vivo studies performed only for hyperbranched PG with low (4250 and 15400 g mol^{-1})[201] and high (106000 and 540000 g mol^{-1})[202] molecular masses revealed no sign of toxicity at mice after injection of the dose up to 1 g/kg. Also on autopsy all organs appeared normal. For the high molecular mass compounds the plasma half-life was 32 or ~54 hours for polymers with M_n = 106000 g mol^{-1} or 540000 g mol^{-1}, respectively. Therefore PG polymers are potential candidates for drug delivery and imaging applications where a long circulating polymer is highly desirable. However, due to very limited urinary excretion and slow polymer degradation, accumulation of the high molecular mass PG in the liver and spleen was observed for at least 30 days after application.

In the last years oligoglycerols (up to 12 monomer units) have been approved by FDA as a food additives.[204]

1.5. Supramolecular systems for nanocompartmentation

1.5.1. General aspects of nanocompartmentation

The generation of nanocompartments for homogeneous complexation and dissolution of active agents is an unsolved problem for many applications, for example, in catalysis, drug delivery, solubilization and stabilization of molecules.

In catalysis, homogenous catalysts are usually helpful for high activity and selectivity. Nevertheless, in industrial processes heterogeneous catalysts are still dominant. The decisive drawback of homogeneous catalysts results from the loss of active catalyst during the isolation of the products. Recovery of a (noble) metal catalyst is useful not only from obvious economic reason but also because the contamination of a product with heavy metal

impurities is undesirable and must be limited to sub-ppm levels.[205,206] Therefore, the creation of homogeneous catalysts with highly effective strategies for recovery and reuse (retention) by, for example, nanofiltration will allow to combine both: high activity and high retention of catalyst in one system. This can be achieved by coupling of catalysts to a polymeric backbone (linear or dendritic)[4,113,119,207,208] or encapsulation[117,118,209,210] inside macromolecules.

In medicine, the physicochemical properties of new drugs are important factors regarding whether they will be successful *in vivo*. Many potent drug candidates fail in preclinical studies because of their limited solubility, stability, and high toxicity. Today, the vast majority of clinically used drugs are low-molecular-weight compounds (typically under 500 g mol^{-1}) that unfortunately exhibit a short half-life in the blood stream and a high overall clearance rate. Thus a number of macromolecular drug delivery systems are under investigation to overcome transport problems[192,193,211-222] and to improve the potential of new or existing drugs.

In general macromolecular delivery systems can be divided into two classes: drug-polymer conjugates and nanoparticulate drug delivery systems. Drug-polymer conjugates consist of a drug which is covalently linked to polymers such as proteins, polysaccharides, or synthetic polymers. This concept received an important impetus from 1975 onwards with the development of monoclonal antibodies by Milstein and Köhler[223] the monoclonal antibodies and from Ringsdorf's notion of a general model of drug-delivery systems based on synthetic polymers (Figure 7).[224,225] In this model drug molecules are bound to a macromolecule through a special cleavable spacer to ensure release of the drug at the site of interest. Additionally, the polymer conjugate can contain special moieties, such as targeting groups (antibodies or sugars) and/or groups groups which increase the solubility. To this group of polymer therapeutics belong the pegylated polypeptides mentioned before: pegademase, pegaspargase, peginterferon α2b, and pegvisomant.[186,199,200]

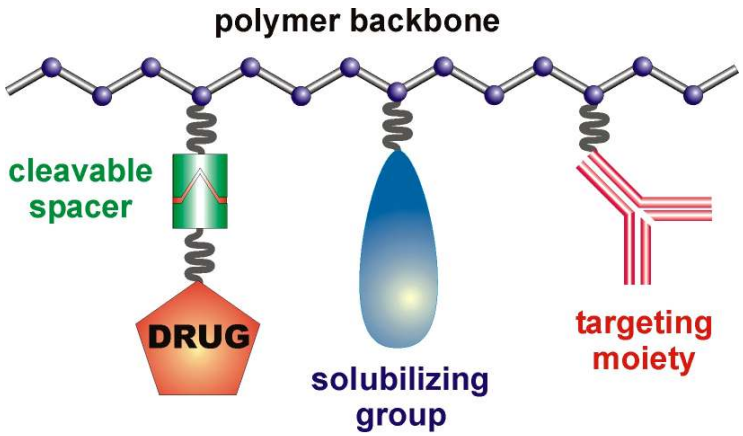


Figure 7. Ringsdorf's model for drug-delivery systems based on synthetic polymers.

In nanoparticulate drug delivery systems drugs are physically incorporated into nanoparticles including emulsions, liposomes, and others noncovalent polymeric carrier systems. These include: a) polyanionic polymers for the inhibition of virus attachment and as heparin analogues; b) polycationic complexes with DNA or RNA; and c) polymeric micelles with covalently bounded or encapsulated drugs as well as dendritic core-shell architectures for the encapsulation of drugs.

The reason for using macromolecules as efficient carriers for drugs, is based on a few general aspects.

The biological rational of polymeric carriers for the specific delivery of active agents into solid tumor tissue is based on the pioneering work of Maeda [226-228] and Jain.[229,230] Their work describes the biochemical and physiological differences of healthy and tumor tissue that allow the passive accumulation of macromolecules in the tumors. This phenomenon has been termed: “enhanced permeability and retention effect” (EPR effect) (Figure 8).

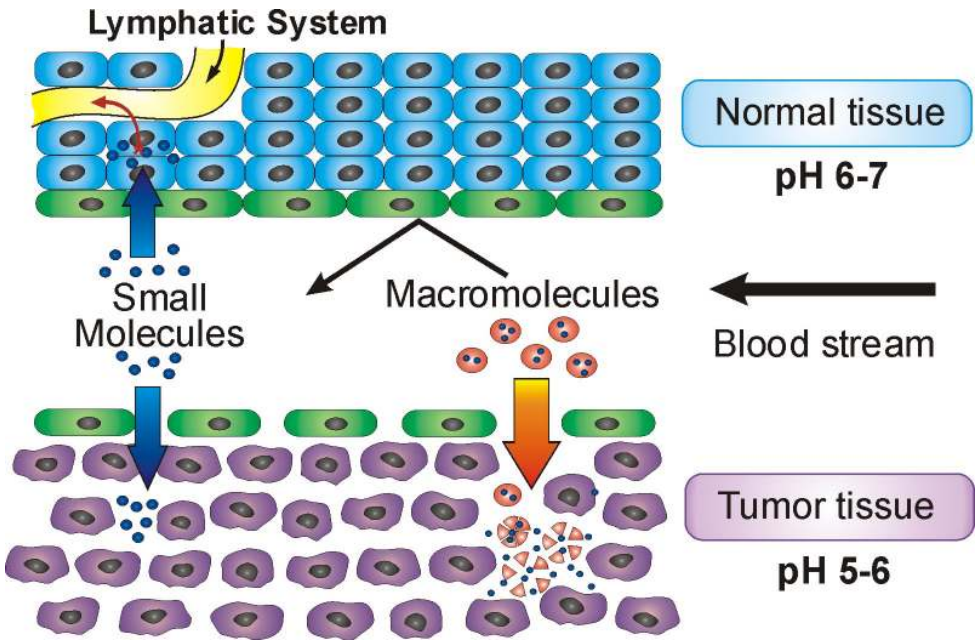


Figure 8. Schematic representation of the anatomical and physiological characteristics of normal and tumor tissue with respect to the vascular permeability and retention of small and large molecules (EPR effect). Also the average pH values are given.

Low molecular weight compounds diffuse into normal and tumor tissue through the endothelia cell layer of blood capillaries. Macromolecules and other nanoparticles, however, cannot pass the healthy endothelial layer, but penetrate into the tumor tissue. In contrast to normal tissues, the endothelial layer of capillaries in the tumor is fenestrated and leaky. Additionally, the defect lymphatic drainage system causes that macromolecules are retained and can subsequently accumulate in solid tumors. The size of macromolecules is the crucial factor with respect to the uptake by the tumor and was determined to be in the range from 20

to 200 kDa. It is generally assumed that in a healthy organism the renal threshold is in the range of 30-50 kDa to avoid leakage of body proteins into the bladder.[231]

Besides this simple passive drug targeting by size, cell-specific targeting using antibodies, oligosaccharides, and peptides has also been investigated by many research groups.[232]

As a second important aspect it should be pointed out that macromolecules are taken up by the cell through receptor-mediated endocytosis, adsorptive endocytosis, or fluid-phase endocytosis (Figure 9).[233] These pathways for cellular uptake allow the nonspecific delivery through a membrane. Additionally, a significant drop of pH value form the physiological value (7.2-7.4) in the extracellular space to pH 6.5-5.0 in the endosomes and around pH 4.0 in lysosomes is important. A large number of lysosomal enzymes become active in the acidic environment of these vesicles. This gives the possibility to release conjugated/encapsulated drugs from polymeric matrices into the cell by unspecific hydrolysis by enzymes, reduction, or in a pH-dependent manner.

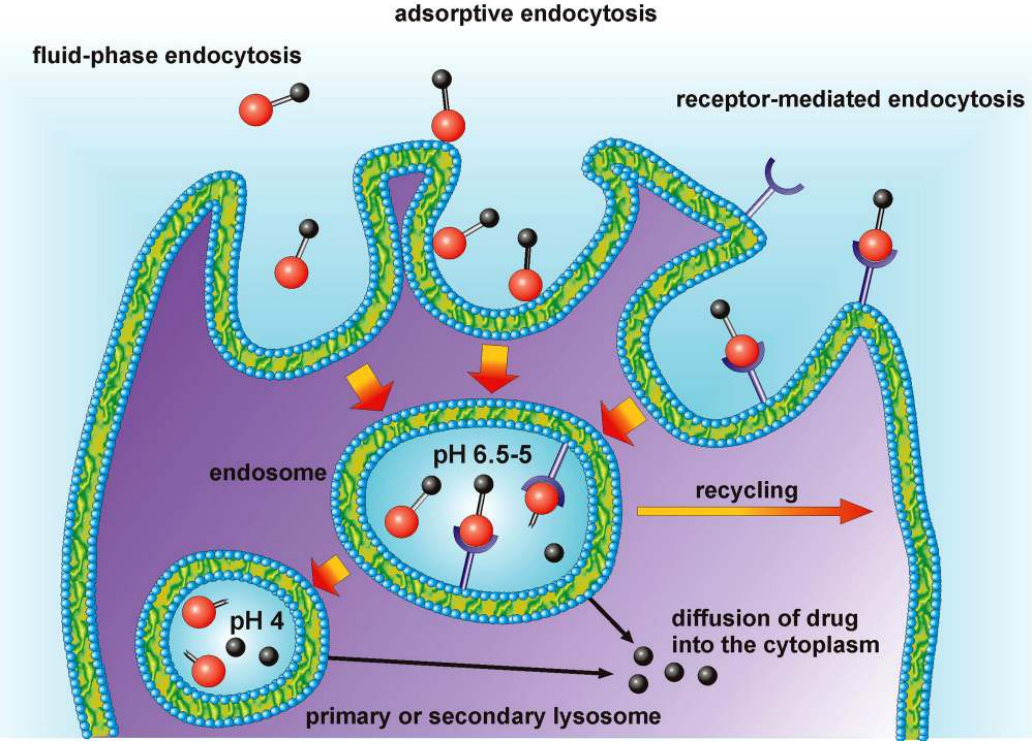


Figure 9. Endocytotic pathway for the cellular uptake of macromolecules and nanocarriers for drug delivery.

In the ideal case the release of the drug is triggered by a biochemical or physiological property which is unique for the addressed target. This approach leads to a high local concentration of active agent and therefore increases the selectivity and efficacy of the drug which is crucial in anticancer therapy.

Finally, the stabilization of the drugs conjugated or complexed by polymeric carrier prolonged their half-life in the blood plasma (Figure 10) and reduced side effects. These facts and the possibility of multivalent drug interactions locates polymer therapeutics in the center of interest for drug development all over the world.[3]

Due to the specificity of the topic of this thesis only micellar, liposomal, and dendritic core-shell architectures will be described and discussed in the next chapters of this work with respect to their applications in naanomedicine.

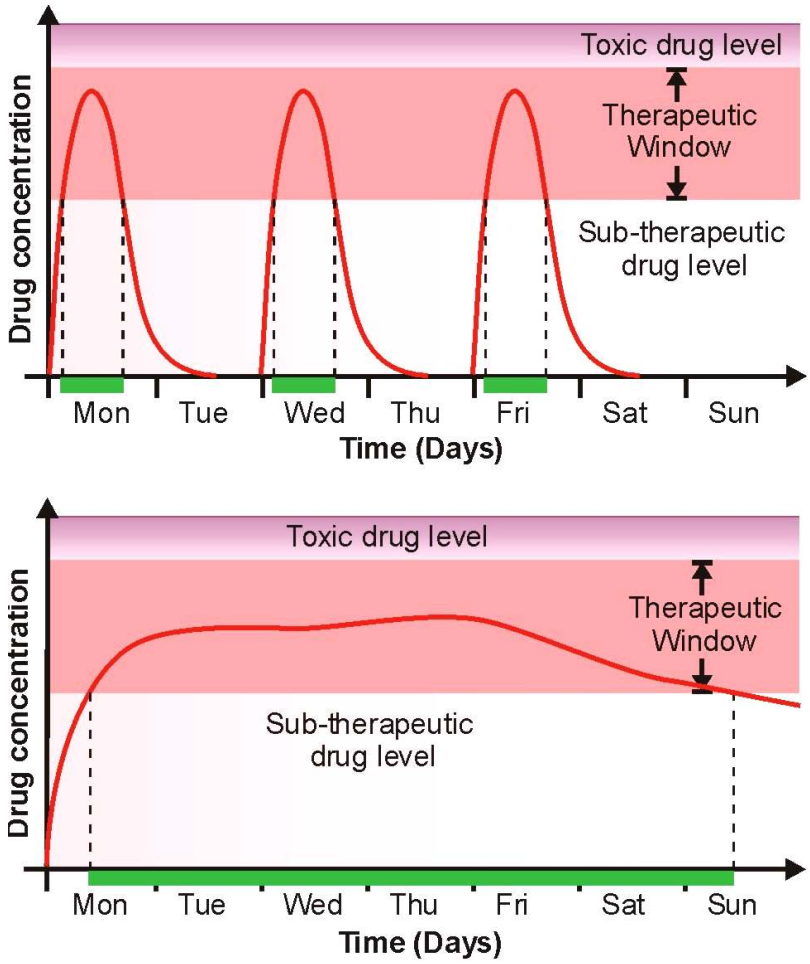


Figure 10. Circulation life-time difference between unmodified drug and polymer-drug conjugate on example of pharmacokinetic profile of Interferon (top) and Pegasys® - Interferon conjugated to branched PEG 40 kDa (bottom).[199,200] These graphs represent the concentration of the drug in human blood. Interferon (top) is injected every two days and its short life-time leads to pulse blood concentration levels with a very short time at the effective (therapeutic) concentration (green bars on the horizontal scale). Pegasys® has a long circulation life-time due to a presence of PEG_{40kDa}, and one weekly injection leads to a nearly constant blood concentration at the level of the therapeutic window (bottom). Therefore the effective drug concentration remains constant for up to one week (green bar).[186]

1.5.2. Block-copolymer micelles

Since the beginning of the last century small amphiphilic molecules are well know to form micelles. Such supramolecular aggregates are formed in water, and aliphatic chains are orientated towards the center of the micelle, while polar, neutral or ionic “heads”, are exposed on the periphery of the sphere (Figure 11). An important parameter in the study of micellar systems, is the so-called critical micelle concentration (CMC). The CMC is defined as the narrow concentration range of surfactant (amphiphile) at which the micelles first become detectable, usually by some change in the physical properties, such as interfacial tension, electric conductivity, specific heat, pH, viscosity, and spectroscopic properties of the solution.[234] Amphiphilic block-copolymers show similar properties in the formation of micelles, although the tendency for micellarization is overall much higher in block-copolymers compared to low molecular weight surfactants since the exposure of a long hydrophobic block to water is more unfavorable. Formed polymeric micelles possess cores with limited motion ability. ^{1}H NMR and fluorescent sample studies provide an evidence for the existence of rigid cores with little relaxation.[235,236] The thermodynamic stability of polymeric micelles is characterized by low CMC values which are usually in the micromolar range. This contrasts typical millimolar CMC levels of low molecular weight surfactants.[235,237-239] Also the kinetic stability of polymeric micelles with rigid cores is in sharp contrast to surfactant micelles which tend to break up in milliseconds upon dilution below the CMC value and are in continuous exchange with their unimers in solution. The slow dissociation rates (in hours and days) have been reported for polymeric micelles even under concentrations below their CMC (Figure 11).[237]

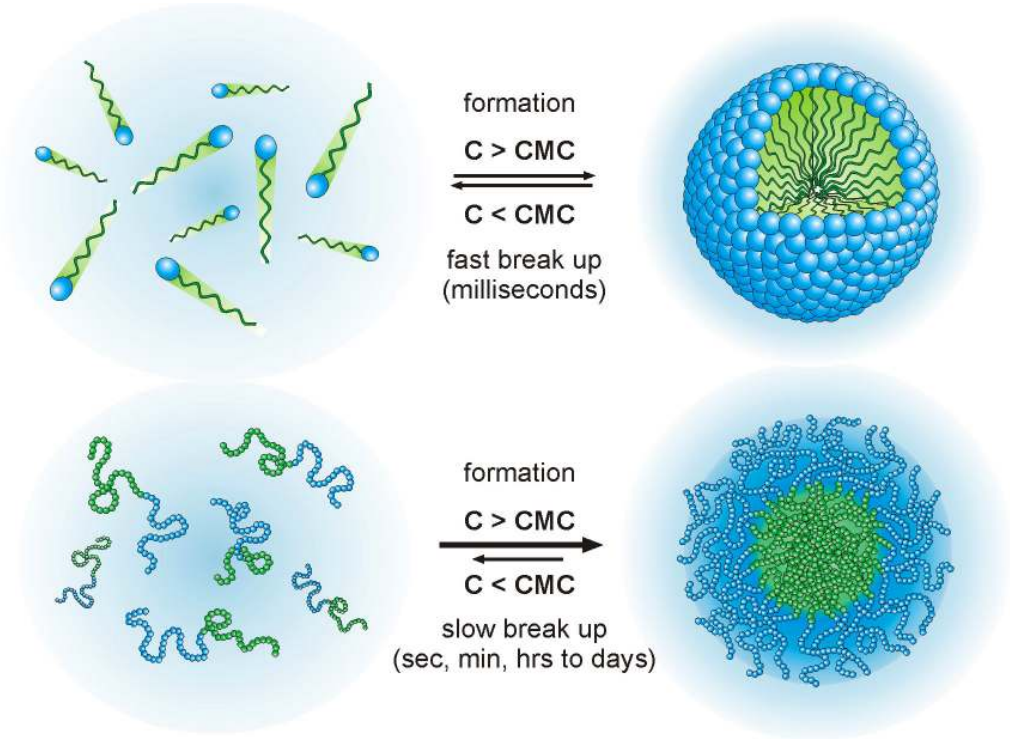


Figure 11. Formation and break up of low molecular weight surfactants micelles (top) versus polymeric micelles (bottom).

In the past two decades polymeric micelles have attracted growing interest in the field of drug- and gene delivery.[240-242] Similar to the micelles formed by conventional detergents, polymeric micelles solubilize poorly water-soluble drugs by incorporating them into their hydrophobic core thus allowing to increase the bioavailability.[243-245] Thereby polymeric micelles often allow extended circulation times, favorable biodistribution and lower toxicity of drugs.[243-245] The pharmaceutical efficiency of polymeric micelles can be further increased by targeting micelles to organs or tissues of interest. In case of tumors the targeting is achieved *via* the EPR effect. Another targeting approach uses the fact that certain pathological processes are associated with a local temperature increase and/or acidosis.[246,247] The use of polymeric micelles prepared from thermo- or pH-sensitive block-copolymers ensures their disintegration and the release of incorporated drugs specifically at the site of interest.[244,248-250] Additionally the micelles can be modified by attaching special targeting groups such as antibodies, peptides, lectine, saccharides, and hormones to their surface. This effect can be easily obtained by mixing two different block-copolymers, one with covalently connected drug molecules at the hydrophobic domains and the other with a targeting group attached to the end of the hydrophilic part of the amphiphile (Figure 12).[251]

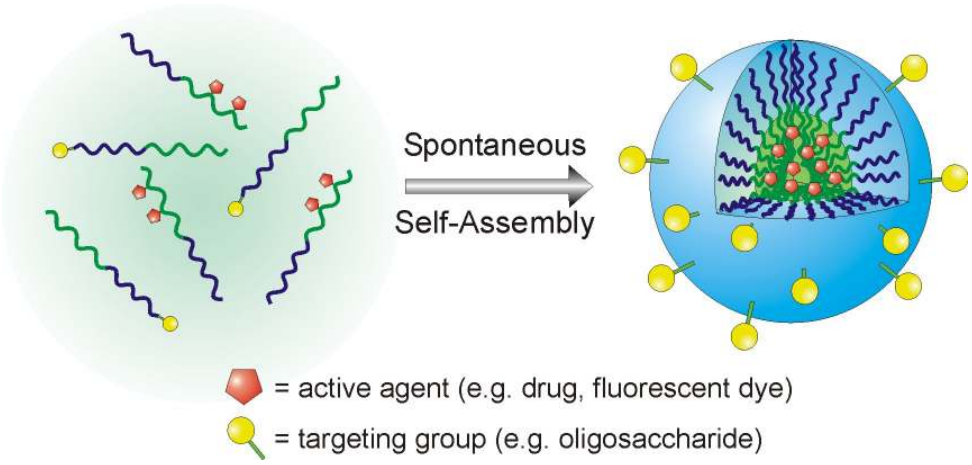


Figure 12. Architecture of block-copolymer micelles formed by self-assembly in water with covalently attached active agent and targeting groups. Typical examples of block-copolymers are PEO-*b*-PPO, PEO-*b*-PCL, and PEO-*b*-Pasp.

The most commonly used polymer to form hydrophilic domains is PEG (PEO).[191,220,252] As mentioned in chapter 1.4 poly(ethylene glycol) is a biocompatible polymer and therefore its use as a shell forming material results in low toxicity of the obtained micelles. In PEG-based systems, the shell contributes to the steric stability of the micelles by physically blocking the flocculation and preventing non-specific interaction with blood components. The circulation time of polymeric micelles depends on the length and density of the polymer chains. In general, longer chains prolonge the half-lifetime of micelles in the blood stream. An example for PEG-based polymeric micelle drug delivery systems, developed by Kataoka and co-workers, [253] is poly(ethylene glycol)-*b*-poly(aspartate-hydrazone-doxorubicin) block-copolymer (PEG-*b*-p(Asp-Hyd-DOXO)). The hydrophobic domain consists of poly-aspartate with doxorubicin (DOXO) connected to the polymeric backbone *via* a pH-sensitive hydrazone linker (Figure 13). The hydrazone bond is cleaved under acidic conditions (pH below 6.5) and the drug is released from the polymeric micelle after endocytotic cellular uptake.

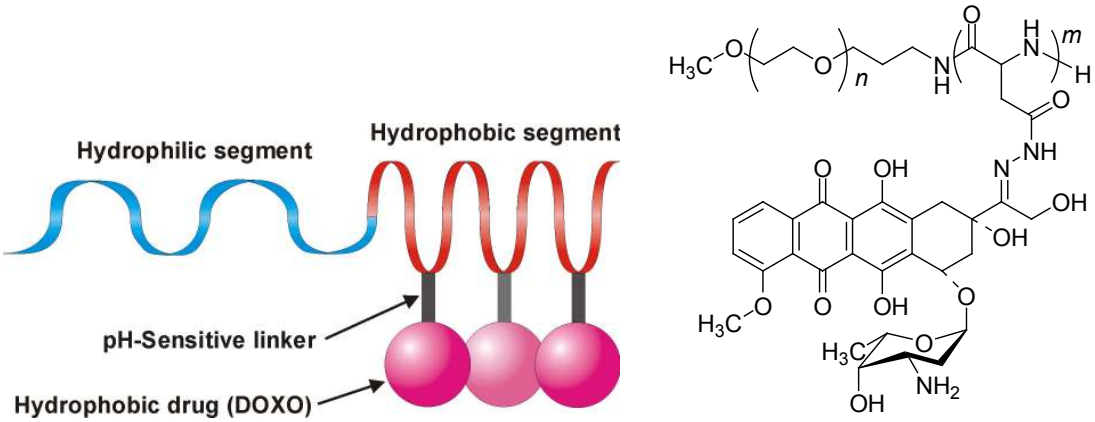


Figure 13. Schematic picture of block copolymer and chemical structure of PEG-*b*-p(Asp-HYD-DOXO).[253]

Other polymers used as polar and nonpolar building blocks of amphiphilic block-copolymers for polymeric micelles are: poly(vinylpirolidone) (PVP),[254] poly-(2-vinylpyridine),[255-257] *N*-(2-hydroxypropyl)methacrylamide (PHPMA), poly(acrylic acid) (PAA), poly-N-isopropyl acrylamide (PNIPAM),[250,258] poly(methacrylic acid) (PMAA),[259-261] N,N-dimethylacrylamine (DMAAm),[262] poly(L-lysine) (PLL),[263-265] Poly(D,L-lactic-co-glycolic acid) (PLGA),[266,267] poly(D,L-lactide) (PDLLA),[268] 2-(acrylamido)-2-methyl-propanesulfonate,[269-271] Poly((dimethylamino)alkyl methacrylate) and similar,[272-280] poly(orthoethers) (POE),[281] polyisohexylcyanoacrylate (PIHCA),[282] poly(L-aminoacid) (PLAA),[252] Heparin, poly (dicarboxylatophenoxyphosphazene) (PCPP), Chitosan and others[191,192,213,217,219,221,239,283-295] (Figure 14).

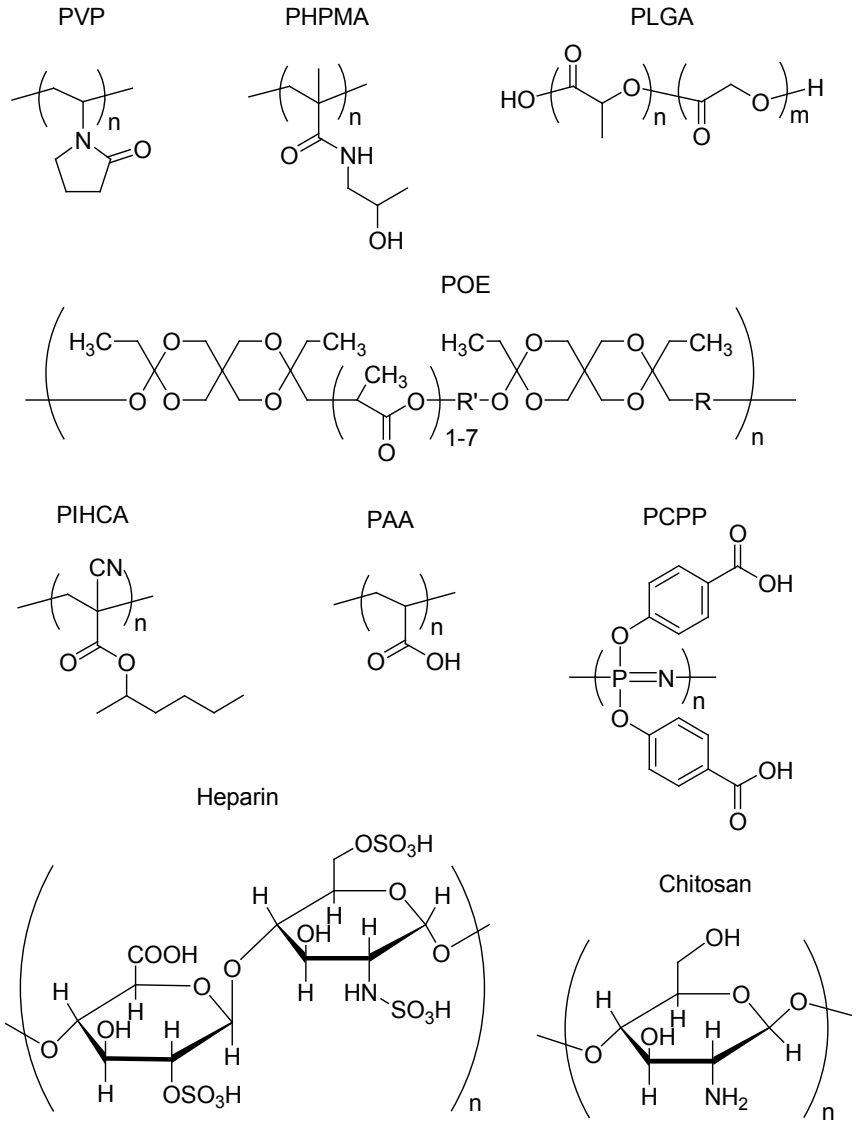


Figure 14. Chemical structure of various types of polymers used as building blocks for polymeric micelles.

Additionally to drug- and gene delivery polymeric micelles attracted increasing interest in the field of catalysis[296] and as nanoreactors.[297]

1.5.3. Liposomes, polymeric liposomes, and "stealth" liposomes

Liposomes have been discovered more than 40 years ago by Alec D. Bangham[298-300]. Since then ongoing progress in the modification of liposomes and the development of new applications can be observed, especially for their use as vehicles for pharmaceutical, diagnostic, and cosmetic agents.

Liposomes can be classified as association colloids, build up of amphiphilic lipid molecules that self-assemble in aqueous media into spherical, self-closed structures (Figure 15) with a diameter in the range from 20 nm up to 50 μm.[301]

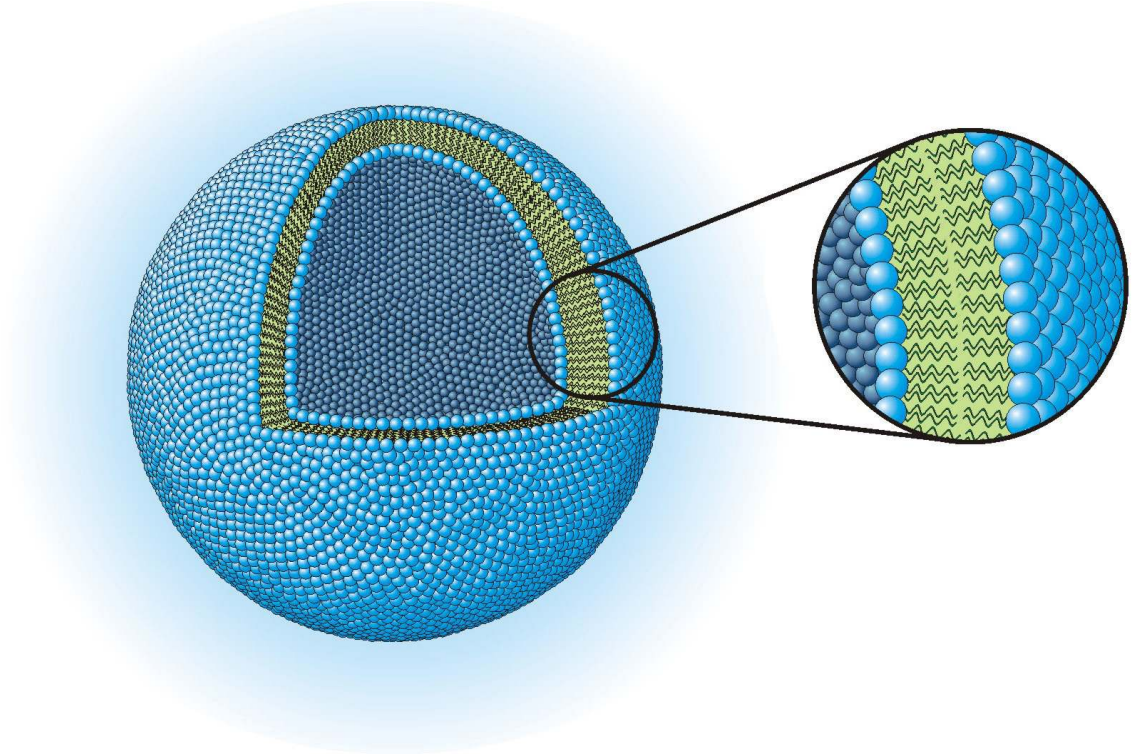


Figure 15. Schematic structure of a liposome with a bilayer membrane.

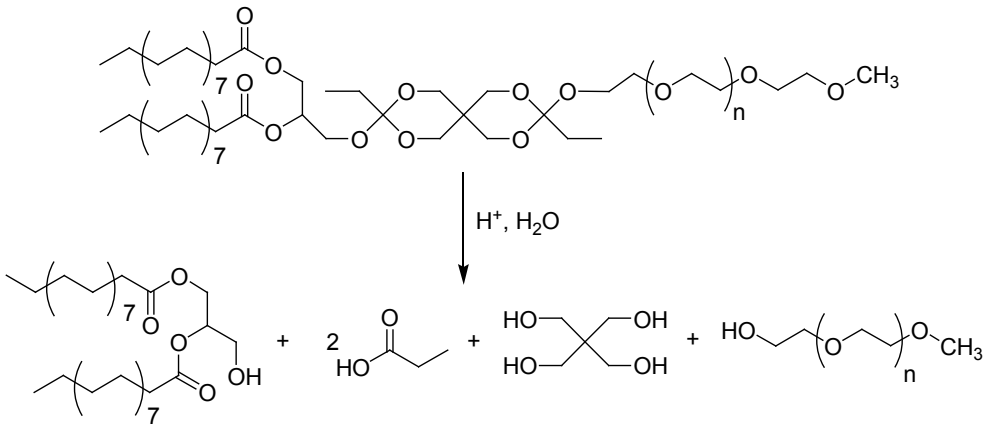
As shown in Figure 15, liposomes are an assembly of lipid molecules that are in a lamellar phase formed of two monolayers which are arranged back to back to give a bilayered membrane with encapsulated aqueous media inside. A similar basic lipid bilayer structure as that exhibited by liposomes is surrounding every living biological cell. Therefore lipid bilayers have been used extensively as a model system for studies that aim to understand the complexities of cell membrane properties, structure, and functions. As in the cell, the lipid bilayers act as chemical, mechanical, and electrical barrier that sequesters an internal aqueous solution and separates it from the external environment. Thus liposomes provide a biocompatible system (biodegradable, non-toxic, with low induction of immune response) for encapsulation and release of internally trapped aqueous soluble active agents.[211,302,303] Furthermore, they tend to encapsulate nonpolar guest molecules inside their lipid bilayer.[304] Therefore, one of the most promising applications of liposomes is drug, enzyme, oligonucleoide and gene delivery to various targets (organs and tissues). Notable progress in transferring liposome mediated systems from the laboratory to clinic[305-307] raises hope to obtain a new family of modern, highly selective drug carrier systems that are free from side effects. The use of modern polymer-conjugated lipids in the creation process of

vesicles allows to increase the circulation lifetime of liposomes.[302,308,309] This improvement was based on an analogy to PEGylated proteins with prolonged plasma stability. Liposomes with surface-grafted PEG chains showed from 1 up to 2 orders of magnitude longer circulation times (up to several days) in the blood stream[302] and therefore can accumulate in the targeted organs/tissues or cells better than unmodified ones. The clearance mechanism of liposome from the blood is, however, still not fully understood. Probably PEG stabilizes membrane bilayers and inhibits membrane fusions,[310,311] presumably due to a decreased ability of opposing membranes to come into close approximation. As well as molecular shape that prevents the formation of essential non-bilayer intermediates. Additionally, the coating of liposomes surface with a PEG significantly reduces the interaction of vesicles with blood components and cannot be detected by the immune system. This lead to the term “stealth liposome”.

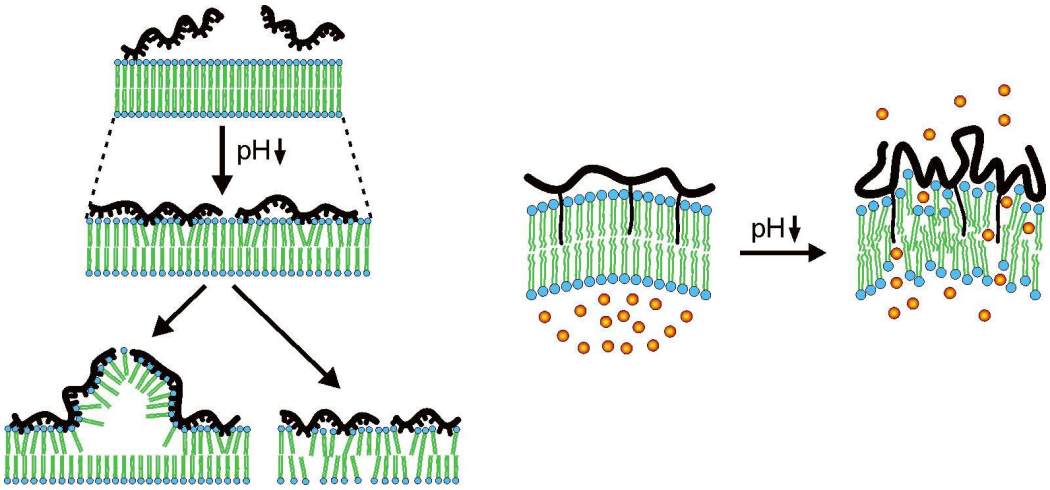
The second aspect for the development of a successful system for active agent delivery is the selective release of encapsulated molecules. Initially the payload needs to remain inside the vesicle. Premature leakage of the drug from the liposome will decrease the amount of active agent that reaches the target site and results in systematic toxicity. After accumulation in targeted tissue or cell the load of drug has to be effectively released by specially designed mechanisms of destabilization of the vesicle. The strategies developed to induce such triggered liposomal leakage in response to an environmental stimulus include the formation of defects and channels in the bilayer, lamellar-micellar and lamellar-hexagonal phase transition, lipid phase separation, and liposome fusion.[303,312-317] The stimuli to induce release can be divided into systems triggered by externally applied stimulations such as heat[318,319] and light,[320,321] and those triggered by a biologically supplied stimulus such as enzymatic cleavage, change of pH, and change of a redox potential.[322]

In general, liposomes are transported into the cells through an endocytotic pathway[323,324] and are delivered to the lysosomes (see Figure 9) where the pH drops from 7.4 to 5.0. Decrease of pH is also implicated in many other pathological processes such as inflammation, infection, tumor growth, and myocardial ischemia. Therefore pH sensitive mechanisms of drug release are one of the most promising and intensively studied ones.[303,307,312,313] There are four different models of pH-triggered liposome destabilization. (1) Neutralization of negative lipids in the bilayer *via* protonation of carboxylate groups. This leads to a reduction of the surface area of the head group of the amphiphile and causes the collapse of the liposome.[313,325] (2) The ionization of neutral surfactants into their positive, surface-active conjugated acids, this leads to an increase of the surface area of the head group of the surfactants and destabilization of the liposome due to strong repulsive interactions between the amphiphiles.[326,327] (3) The acid-catalyzed hydrolysis of bilayer-stabilizing lipids into destabilizing detergents or conical lipids (Scheme 6).[281,328-334]

(4) Protonation of negative polymers or peptides, which adsorb to the bilayer and destabilize their structure by lysis, phase separation, pore formation or fusion.[303,312,335-343] Peptides used for destabilization of a membrane usually possess numerous flexible glycine rich regions like the natural peptides corresponding to the putative fusion sequences of viral and cellular fusion glycoproteins. Additionally, many of these peptides are amphiphilic in nature. It has been shown that anchoring of the peptide in the bilayer can increase the effectiveness of membrane destabilization up to 1000 fold.[344] Acid-triggered liposome destabilization/fusion is generally achieved by using non-peptidic polyelectrolytes. Acid titration of the polymers is usually accompanied by a modification of the polymer conformation and/or association with liposome bilayer which result in its destabilization (Scheme 7). The mechanism of membrane disturbance varies depending on whether the polyelectrolyte is a weak base (polycation) or a week acid (polyanion). Polycations at high pH values act neutral but acquire a positive charge as the pH decreases. In solution such ionized polymers can interact with negatively charged membranes, perturb lipid packing and promote aggregation and fusion of liposomes. Week acid polyelectrolytes differ from polycations as they can trigger leakage of the contents from neutral as well as charged vesicles. Fusion is not always involved in the destabilization process and its mechanism depends on the polymer structure, concentration, and molecular mass.



Scheme 6. Structure of diortho ester conjugate of PEG and distearoyl glycerol and its decomposition under acidic conditions as example of one of the most promising pH-sensitive linkers for drug delivery systems.



Scheme 7. Theoretical mechanism of lipid membrane disturbance by poly(2-ethylacrylic acid) (PEAA) polymer proposed by Tirrell and Thomas[312,340,341] (left) and mechanism proposed by Leroux[343] for N-isopropylacrylamide (NIPAM) copolymers (right) as an example of polymer-liposome pH-sensitive delivery systems.

It is important to mention that liposome-based drug delivery systems are no longer only "laboratory" type studies but at least six of them have been already approved by FDA as drug formulations, for example the Doxil® - pegylated liposomal formulation of doxorubicin,[345] and many more are concurrently under clinical trials.

1.5.4. Core-shell architectures with dendritic and hyperbranched cores and their applications

In contrast to the previously described micellar and liposomal transport systems, dendritic core-shell architectures are claimed to be unimolecular host-guest systems. Unfunctionalized dendrimers are often described in the literature as core-shell structures due to the differences between interior and exterior of the molecules. Nevertheless, further selective modification of terminal (T) or dendritic/linear units of dendritic polymers results usually in new types of nanomaterials with more pronounced core-shell architecture and properties which can be adjusted by variation of the polymer building blocks (core and shell domains).[10] The most important property of core-shell architectures is the capability of host-guest chemistry.[19] Therefore core-shell type macromolecules attracted a lot of interest especially in medicine (drug delivery vesicles, gene transfection agents, imaging agents),[47,251,346] and for the preparation of nanoparticles e.g. for catalysis.[5] Since these molecules often possess an amphiphilic character, core-shell architectures are also described as "unimolecular micelles".

For the first time this expression was used by Kim and Webster[70] in 1990 for fully aromatic water-soluble hyperbranched poly(phenylene)s with carboxylic end groups. Later in 1991 Newkome[347] described a saturated hydrocarbon dendrimer (micellanoic acid) containing 36 carboxylic acid moieties converted into ammonium and tetramethylammonium salts as “unimolecular micelle” (Figure 16). The diameter of the monomers were in the range of 30 to 40 Å. Fluorescence spectroscopy experiments with lipophilic diphenylhexatriene (DPH) indicate that DPH molecules were associated within the lipophilic interior of the polycarboxylate microenvironment like in real micelles. A similar system has been reported by Hawker et al.[348] with a Fréchet-type dendritic core.

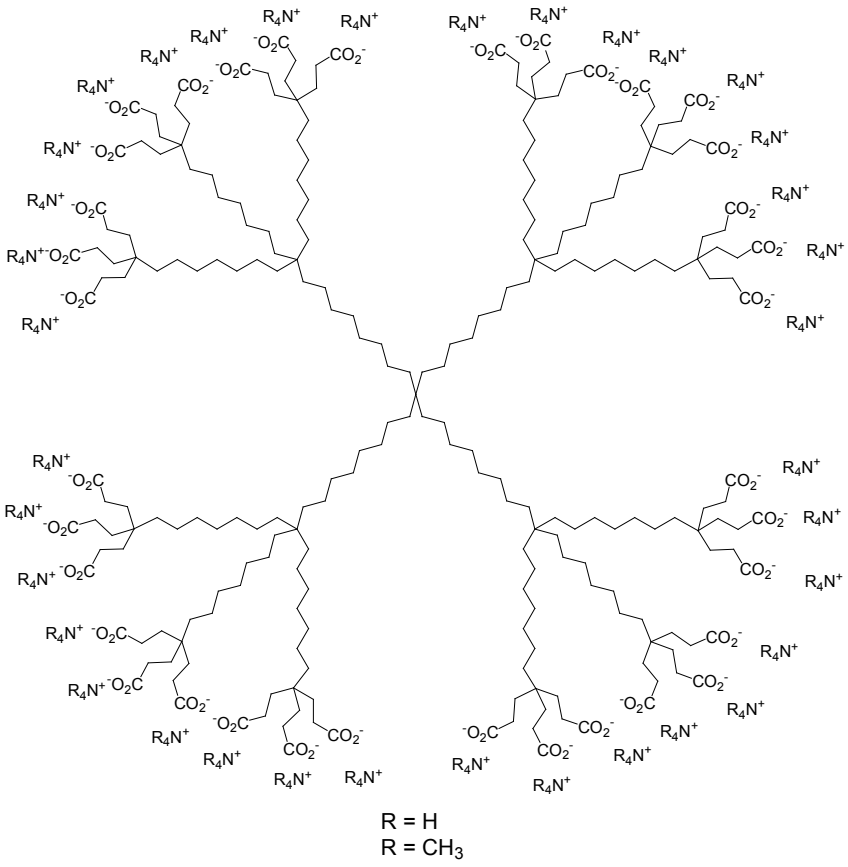
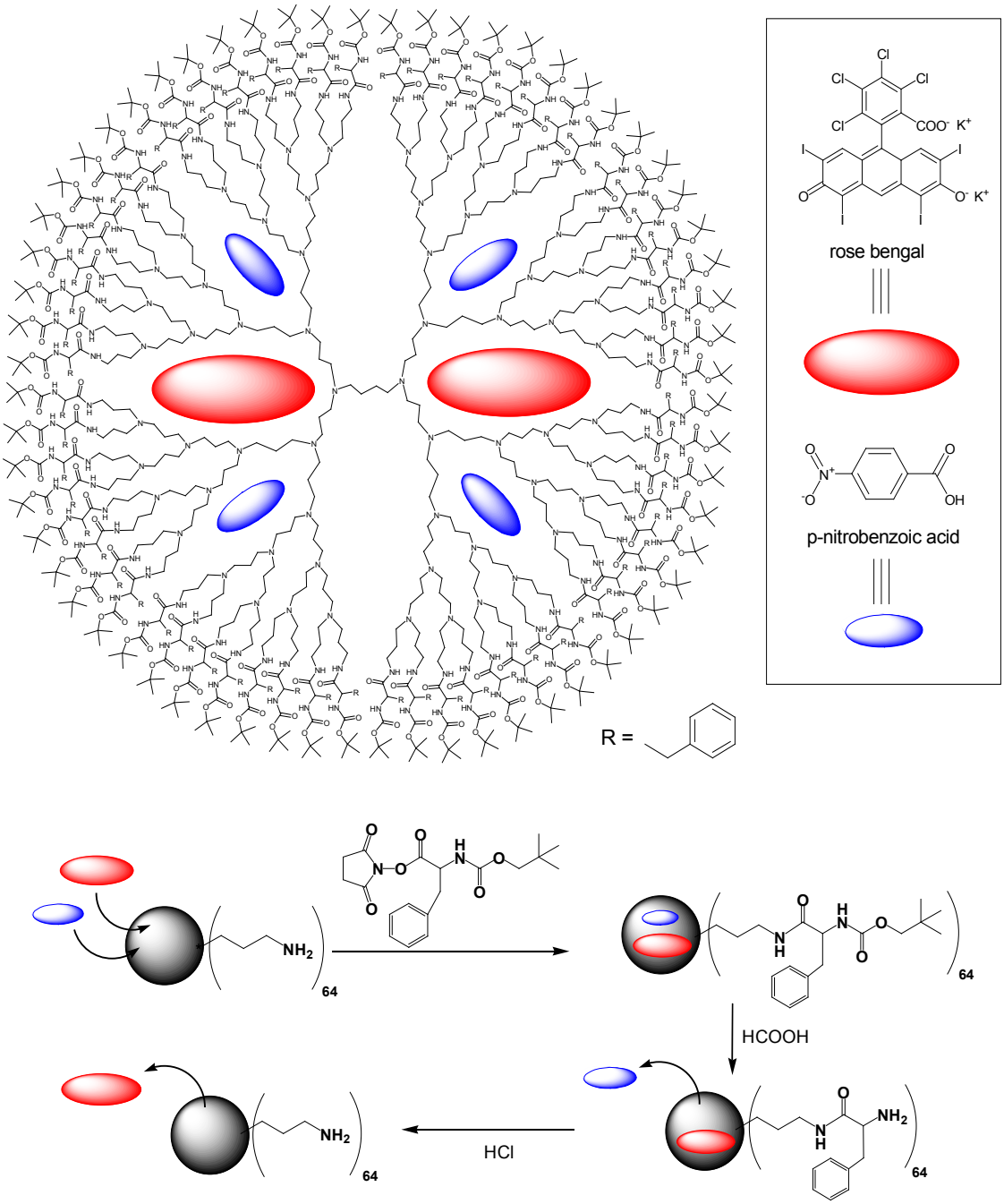


Figure 16. Chemical structure of micellanoic acid cascade polymer with carboxylic acid ammonium salts as a shell – unimolecular micelle.

The first pH-sensitive dendritic core-shell architectures have been reported by Meijer and coworkers in 1994.[71,72] The presented system was named “dendritic box”, based on dendritic polypropylenimine PPI core functionalized with *tert*-butoxy-protected amino acids (Scheme 8). Inside the core exist cavities, which are able to encapsulate guest molecules of various-sizes, e.g. rose bengal and *p*-nitrobenzoic acid. After functionalization of the core with *t*-BOC-amino acids, the sterical hindrance of the introduced groups prevented the

leakage of the load from the interior. After partial removal of the shell by lowering of the pH-value, only smaller guest molecules were liberated from the “perforated” dendritic box. Additional cleavage of the amino acids leads to the release of the larger guest molecules (Scheme 8). It is important to mention, that the “dendritic box” can also be described as “unimolecular micelle”, due to its polar core and nonpolar exterior.



Scheme 8. *t*-BOC-phenylaniline functionalized PPI [G5] dendrimer with encapsulated guest molecules inside the core (upper). Mechanism of encapsulation and selective release of first smaller and later bigger guest molecules from the dendritic box (bottom).

Modification of polar PPI dendrimers with nonpolar end groups like palmitoyl and adamantyl units yield macromolecules with an unimolecular inverted micellar structure with polar core and nonpolar periphery (Figure 17).[73,349] The inverted micellar character was confirmed by encapsulation experiments with rose bengal. The hydrophilic dye was first solubilized together with the core-shell polymer in ethanol, allowing the dye to enter the core and than the complex was precipitated in acetonitrile and solubilized in n-hexane to obtain a colored organic phase. Also liquid-liquid extraction of polar molecules (rose bengal, fluorescein, 4,5,6,7-tetrachlorofluorescein) from water into organic solvents, like dichloromethane and toluene, resulted in a quantitative phase transfer of the dyes from polar to nonpolar solvents (for dendritic extractant to dye a 1 to 1 molar ratio). The maximum loading capacity of the G5 based core-shell architecture was approximately 50 rose bengal molecules per one host-molecule.[75] Further studies of this phenomenon with watersoluble 3,4,5-tris-(tetraethyleneoxy)benzoyl-functionalized dendritic poly(propylene imine) (Figure 18) revealed a very strong interaction between guest molecules and the core of the host.[80] In buffered aqueous media at pH 7 the preferential location of the guest molecules was in the interior of the dendrimer as could be confirmed by UV/Vis titration and SAXS measurements.

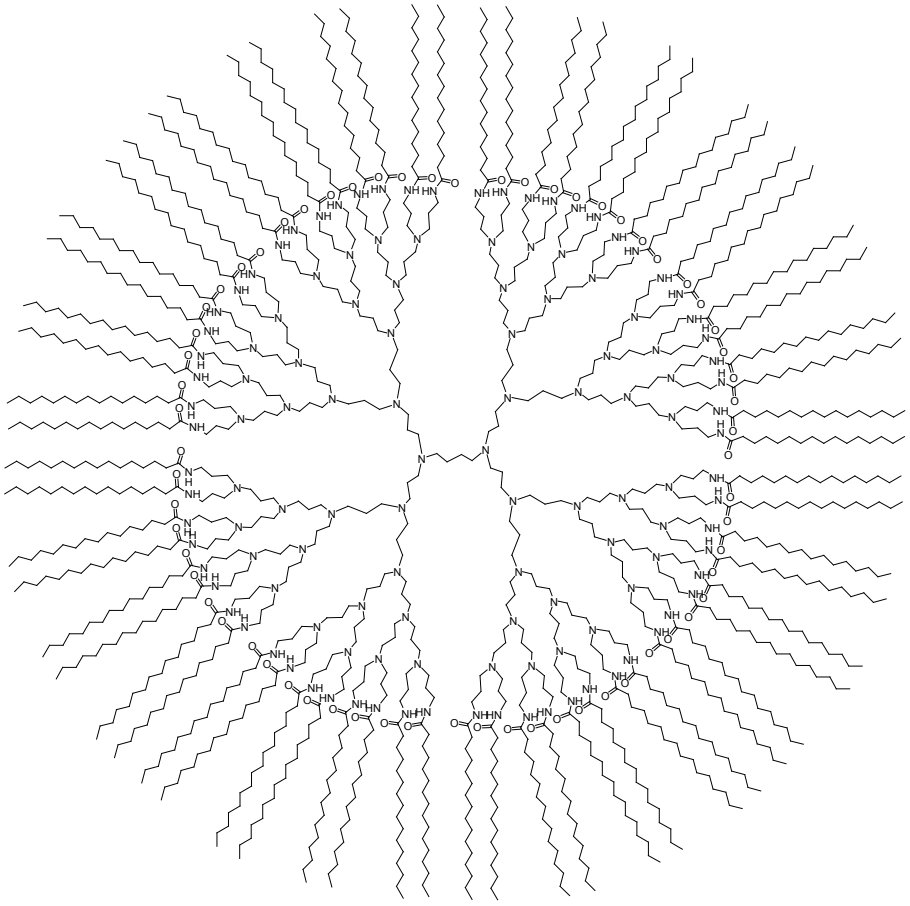


Figure 17. Chemical structures of palmitoyl-modified dendritic poly(propylene imine) [G5].

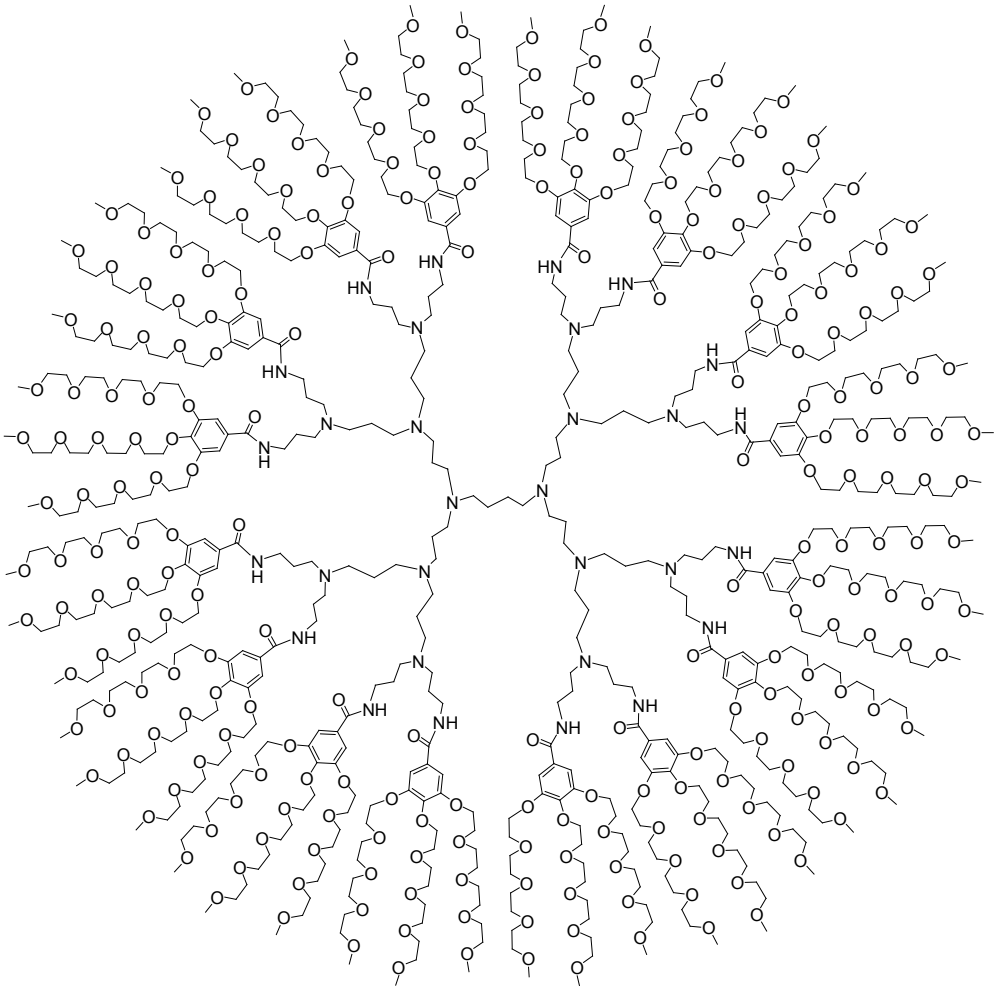
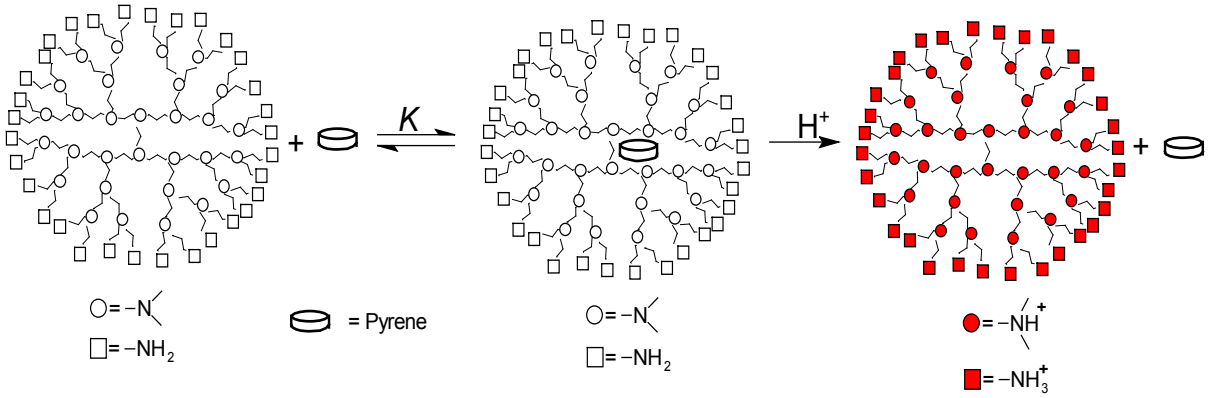


Figure 18. Chemical structure of dendritic 3,4,5-tris(tetraethyleneoxy)benzoyl-functionalized poly(propylene imine) [G3].

Moreover, host-guest properties of functionalized PPI systems[19,349] were found to be fully reversible and dependant on the pH value of the aqueous solution. At pH 6 dyes can be extracted into the organic phase with quantitative yield. All dye molecules in the organic media could be recovered if the pH level of the aqueous solution was increase above 10.[75] Reverse situation has been observed for encapsulation and liberation of nonpolar molecules from unfunctionalized poly(propylene imine) dendrimer.[78] With the decrease of the pH value from pH 11 to the level of pH 2 a release of pyrene was observed by fluorescence studies. Liberation of polar molecules with increase of the pH value and release of nonpolar guest-molecules with decrease of pH depends on the protonation or deprotonation of terminal and dendritic amino groups of the dendrimer (Scheme 9).[78] At low pH all tertiary amino groups are protonated and therefore the interior of the dendrimer is hydrophilic and can encapsulate polar molecules. With increasing pH value (pH 6 – 9) deprotonation of amino groups shifts the polarity of the dendritic core from being polar to nonpolar and polar guest molecules are release form the core. Such nonpolar core is then suitable for the encapsulation of nonpolar

guest-molecules. With decreasing of pH amino groups start to undergo protonation and the environment becomes sufficiently polar again to repel nonpolar molecules and encapsulate polar ones. Modification of terminal amino groups of dendrimer affects the protonation titration profile and leads to the release/encapsulation of guest-molecules within a narrowed and/or shifted pH region.[81,82]



Scheme 9. Incorporation of pyrene inside a PPI-dendrimer and release in acidic media due to protonation of amine groups.

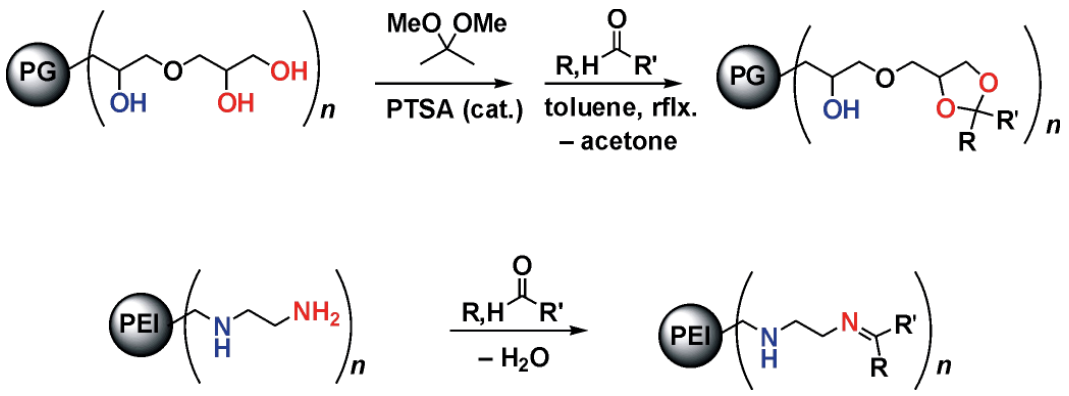
Extraction of polar dye molecules (acid red 1; Azoploxine) and copper(II) salt from water into nonpolar organic media have also been observed for stearyl acrylate modified poly(amidoamine) dendrimer.[87] The maximum loading capacities with dye in case of G3 and G4 dendrimers were determined to be 8 and 24, respectively. No aggregation of dendritic structures has been observed and SAXS experiment proved the change in the size of the inverted unimolecular micelle before and after the encapsulation from 2.6 nm up to 4.3 nm in diameter for G4 dendrimer.

PAMAM dendrimers with grafted mPEG chains were designed as novel drug carriers which possess an interior for the encapsulation of drugs and a biocompatible surface.[57,85] Encapsulation tests were performed for anticancer drugs, doxorubicin and methotrexate, in water by extraction with chloroform from mixtures of core-shell polymer and various amounts of the drugs. The encapsulation ability increases with increasing dendrimer generation and monomethyl poly(ethylene glycol) ether chain length. The highest transport ability (6.5 doxorubicin molecules or 26 methotrexate molecules per dendrimer molecule) was achieved by a polymer with a G4 core and a shell composed of mPEG with the average molecular weight of 2000 g mol^{-1}. However, in isotonic solution, both of the drug types were readily released from the poly(ethylene glycol)-attached dendrimer due to weakening of the electrostatic interaction between the drug molecules and core-shell dendrimer. In another attempt, Yang et al.[350] used a G3 PAMAM dendrimer and conjugated it with mPEGs of different molecular weight (750, 2000, 5000 g mol^{-1}). The result suggested that the PEG arm

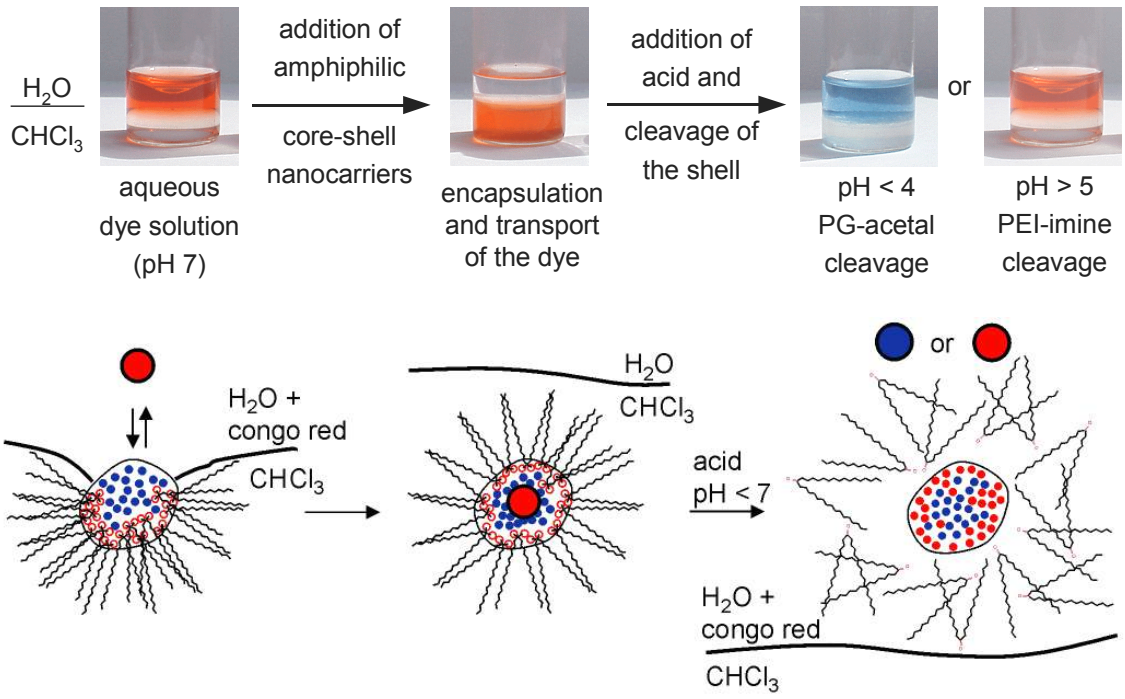
length has a significant effect on the pyrene solubility in water. The optimal length was determined to be ~ 2000 g mol $^{-1}$ so the PEG chains can create a thick network at the dendrimer surface and offer additional cavities for guest molecules. Shorter poly(ethylene glycol) chains cannot create shells with the right thickness to enhance the transport ability and too long chains cause agglomeration (regarding to authors) and interpenetration of PEG chains which limits the available cavities for transported molecules. Many others core-shell architectures of PAMAM and PPI (and others) dendrimers have been reported as active agents and drug delivery systems.[8,19,23,47,50,77,79,351]

In the past few years it was shown that also hyperbranched polymers with a narrow *MWD* can be modified to obtained core-shell architectures with host-guest abilities.[251,352-360] Although in case of perfect dendrimers only terminal units can be modified to obtain core-shell structures, hyperbranched polymers possess additional linear units that can be functionalized. Conversion of both T and L groups of the polymer results in a less pronounced core-shell architecture of macromolecule.[150,151] Therefore the selective modification of only terminal or linear units of hyperbranched polymers will lead to a more defined core-shell structure similar to one based on perfect dendrimers.

By the modification of terminal groups of hyperbranched poly(ethyleneimine) polymer with palmitic and stearic acids, Krämer et al.[361,362] obtained core-shell architectures, that possess similar properties like inverted micellar structures based on PPI dendrimers with aliphatic chains.[73,349] Encapsulation abilities have been tested using liquid-liquid extraction between water and chloroform phase and congo red as polar guest molecules. Up to 100 molecules of congo red could be encapsulated per one molecule of polymer in neutral pH for the polymers with the PEIs with a molecular weight (M_n) of ~10000 g mol^{-1} (what corresponds to ~[G6] PPI dendrimer). It was also shown that the conversion of diol-units to acetal units in case of hyperbranched PG or amine groups to imine groups in case of PEI results in acid cleavable core-shell structures (Scheme 10).[356] These amphiphilic systems are able to encapsulate and transport hydrophilic guest molecules from the aqueous phase to an organic phase as it was demonstrated using congo red (Scheme 11). After lowering the pH of the aqueous phase cleavage of the shell and release of dye could be observed. In case of the PG-acetals the cleavage takes place at pH 2 – 3 dependent on the degree of functionalization and in case of the PEI-imines based on aldehydes at pH 6 after 4 days (Scheme 11).



Scheme 10. Conversion of diol units of PG to acetal units after attachment of hydrophobic ketone or aldehyde; conversion of amine groups of PEI to imine groups after addition of aldehyds or ketons; in both cases core-shell structures with hydrophobic shell and hydrophilic core are obtained.



Scheme 11. Encapsulation and transport of guest molecules, here congo red, into the organic phase; cleavage of the shell leads to the release of the encapsulated guest molecule. Below schematic representation of encapsulation, transport, and release of guest molecule.

In contrast to hyperbranched PEI or PG functionalized at the periphery, selective functionalization of linear groups of PG leads to novel core-shell micelle-like structure with nonpolar interior, and polar exterior.[359] This micelle-like structure possesses good water solubility and can encapsulate nonpolar molecules inside the core. As test molecules the hydrophobic drug nimodipine-N and pyrene were used. The use of polymeric core-shell architectures allows to enhance the water solubility of guest molecules by a factor of 10^3 at concentration of a 10 weight %.

Besides the use of core-shell architectures as drug delivery systems, many others applications such as gene transfection,[51] stabilization of nanoparticles, and catalysis[6,10,210,363-365] were reported by many researchers in the last decade.