Chapter 2

Photoresponsive Linear and Dendritic Macromolecules Functionalised with Porphyrins and Metalloporphyrins: an Overview

2.1 Introduction

A polymer is a large molecule built up by the repetition of small, simple chemical units. It is well known that polymers can possess different topological structures. They may be either be linear, branched or network. In contrast to the linear-chain molecules, some polymers have branched chains, often as a result of side reactions during the polymerization (Figure 2.1).

Branched polymers can be further subdivided into three different categories according to their topology: comb (the branching points distributed along one single chain), star (one single branching point), and hyperbranched polymers (the branching points are distributed randomly), as illustrated in figure 2.2.
Branched or hyperbranched polymers are a family of polymers with three dimensional dendritic architecture\(^3\). They are characterized by the peculiarity that there is no connecting line between any two end groups that passes all branching points. Generally dendritic polymers can be divided into two main categories: dendrimers with perfectly branched structure and hyperbranched polymers with randomly branched structure\(^4\).

The parameter degree of branching(DB) can be used to differentiate between linear, hyperbranched and dendritic polymers. According to Frey, the DB value can be calculated using the equation,\(^5\)

\[
DB_{\text{Frey}} = \frac{2D}{2D + L}
\]
Here D is the number of dendritic unit, while L is the number of linear unit.

![Figure 2.3. Comparison of polymeric architectures as a function of the degree of branching](image)

### 2.2 Linear Polymers as Core Materials for Photore sponsive Applications

**a. Polyvinyl alcohols (PVA)**

Polyvinyl alcohols are polymers of vinyl alcohol. Since the monomer vinyl alcohol cannot exist in the free form, poly vinyl alcohol (PVA) has so far manufactured by the polymerization of vinyl acetate. Polyvinyl acetate thus formed undergoes alcoholysis. PVA contains a large number of hydroxyl groups and they can be easily modified by the esterification with compounds containing COOH group. PVA can be synthesized by the hydrolysis of polyvinyl acetate, (Scheme 2.1). Even after prolonged hydrolysis, PVA contains around 1 to 2 mole percent of acetyl groups.

![Scheme 2.1. Synthesis of PVA](image)

Polyvinyl alcohol is a water-soluble synthetic polymer with excellent film forming, emulsifying, and adhesive properties. This versatile polymer offers outstanding resistance
to oil, grease, and solvents, plus high tensile strength, flexibility and high oxygen barrier. Suitable applications for PVA are largely determined by its properties.

Polyvinyl alcohol is used mainly in aqueous solution. Its solubility in water depends on its degree of polymerization and degree of hydrolysis, with the latter factor being especially significant. The presence of as little as 2-3 percent of residual acetate groups causes significant change in the solubility at 40-60°C. Fully hydrolyzed PVA is only slightly soluble, but approximately 97% hydrolyzed PVA is almost completely soluble. PVA is one of the few truly biodegradable synthetic polymers; the degradation products are water and carbon dioxide. The free hydroxyl functions of PVA can be easily functionalised by esterification or etherification. Photoresponsive groups such as tetrphenyl porphyrins can be anchored on to the PVA core by suitable functional modifications to generate photoactive systems for novel applications.

b. Polyethylene glycol (PEG)

Polyethylene glycols are linear homopolymers of ethylene oxide. They are available in a molecular weight range of 200 to 35,000. The physicochemical properties of PEG are essentially determined by the two free hydroxyl groups and the ether oxygen atoms. PEG are waxy materials available in different molecular weights grades and are commercially known as carbowax. They are soluble in water and many organic solvents. They find application in pharmaceutical preparations and cosmetics. Ethylene oxide can be polymerized with sodium methoxide or sodium hydroxide to give the polymer polyethylene glycol (scheme 2.2).

$$\begin{align*}
    n\text{H}_2\text{C}(-\text{CH}_2) + \text{NaOH} & \rightarrow \text{HO-}\left[\begin{array}{c}
    \text{CH}_2
    \end{array}\right]_{n-1}\text{-CH}_2\text{-CH}_2\text{O}\text{Na} \\
    \text{HCl} & \downarrow \\
    \text{HO-}\left[\begin{array}{c}
    \text{CH}_2
    \end{array}\right]_{n-1}\text{-CH}_2\text{-CH}_2\text{OH} & 
\end{align*}$$

Scheme 2.2. Synthesis of PEG
Polyethylene glycol possessing primary alcoholic terminal groups are accessible to common reactions such as esterification, etherification and reactions with isocyanates and epoxides. PEG is used as hydrophilic component in the synthesis of stearic and oleic esters.

PEG is used as additives and adjuvants in many different pharmaceutical and cosmetic applications on the basis of their physiological harmlessness. Their application profile reaches from maintaining moisture levels in creams and toothpastes to binding agents in tablets, water-soluble tablet coatings and use as actives in laxatives. PEG is used as non-volatile solvents and substrates for paints, inks and adhesives. Due to their reduced tendency to evaporate they prevent the mixtures from drying out and help disperse pigments.

c. Polyglycerol polyol (PG)

Polyol is a generic name for low molecular weight, water-soluble polymers and oligomers containing a large number of hydroxyl groups. Specific examples include glycols, polyglycols and polyglycerols. Polyols are used in water-base fluids as shale inhibitors and gas hydrate inhibitors.

Polyglycerol (PG) is a polyhydroxyl compound obtained by self-condensation of glycerol in the presence of alkaline catalysts. It is a very attractive polyol as a starter for the synthesis of polyether polyols for rigid polyurethane foams. It is liquid, easy to handle and has a very high average functionality of 420 (or more) hydroxyl groups/mol. A new technology for PG-based polyether polyols preparation was investigated. In the first step the self-polycondensation of glycerol to PG in the presence of potassium hydroxide or potassium methoxide as a catalyst was carried out. In the second step, the crude alkaline PG was alkoxylated without removing the catalyst, followed by purification of the resulting polyether polyols.

Polyglycerols and polyglycerol esters of 16 and 18 carbon-containing fatty acids are well known. They are, in fact, manufactured and sold for a wide variety of uses at the present time. When these compounds were fed to rats, no deleterious effects were noted in appearance, weight gains or cellular structure of the internal organs. Polyglycerols were
not deposited in the body fat. The nutritional value of the mono-, diesters formed by condensation of medium chain fatty acids (caproic, caprylic and capric) and polyglycerols is unknown. In contrast, the medium chain triglycerides have been shown to have unique nutritional properties. It was shown that these oils are readily absorbed via the portal system instead of the lymphatic route of most fats, and they are particularly effective in the treatment of malabsorption syndromes and allied clinical disorders. In this work it has been found there is a rapid, supplemental carrying effect or sparing action for protein and calcium ions which possibly may be explained by the greater surface activity, that is, the hydrophilic properties of medium chain monoglycerides. Since the caloric value of partial esters of polyglycerols is between that of carbohydrates and fats, they may find use in the formulation of dietary foods and supplements. The hydrophilic nature of these compounds should make them useful in altering properties of protein solutions and suspensions, in stabilizing agents, moisturizers and softeners, and in many other areas where the high water affinity of the partial esters can be useful.

All of the partial esters of the polyglycerols were liquids at room temperature; the glycerol mono-, diesters of capric, pelargonic and lauric acids were crystalline whereas the lower esters were liquid. The decaglycerol esters were heavy and so thick that they were barely pourable at room temperature. The viscosity of the triglycerol esters was the least of the polyglycerols but still greater than that of the glycerol mono-, diesters.

The ability to have polyglycerol esters of varying chain length and varying polymer length strongly indicates the broad scale range of hydrophilic to lipophilic products which should have potential utilization in the clinical and dietary applications.

A linear polyglycerol polyol, named, poly[di(ethylene glycol/glycerol-alt-adipic acid] polyol was used as a linear polymer core analogous to PVA and PEG core systems to mimic hyperbranched polyglycerol. This linear polymer was purchased from Aldrich and was used with out further purification. The sorbed water was removed by keeping the polymer in a vacuum oven at 60° for six hours.
2.3 Dendrimers as Photoresponsive Systems

By the development of synthetic macromolecules with more complex architectures, polymers with new properties can be attained. Elucidating the structure-property relationship of such materials is important in order to meet the demands for well-characterized materials in emerging research areas such as nanotechnology. In the recent past it has been found that the properties of highly branched macromolecules can be very different from conventional polymers. The structure of these materials has also a great impact on their applications.

Dendrimers were first discovered in the early 1980s by Donald Tomalia and co-workers. The term dendrimer, which was derived from the Greek words dendron, meaning tree and meros meaning part, was introduced in 1984 by Donald A. Tomalia, Ann Arbor, and coworkers. At the same time, Newkomes group independently reported the synthesis of similar macromolecules. They called them arborols from the Latin word arbor also meaning a tree. The term cascade molecule is also used, but dendrimer is the best established one.

Since the discovery of dendrimers, the research interest for developing new synthetic routes as well as finding new applications for dendrimers are ever increasing. In contrast to the ordinary synthetic polymers, dendrimers are virtually monodisperse highly branched polymers.

Each layer of ABX monomers builds up one generation. One wedge of a dendrimer is called a dendron. Because of the branching of the repeating unit, the number of end groups increase with each generation, resulting in a large number of terminal units at high generations. Dendrimers are typically well-defined globular macromolecules constructed around a core unit (figure 2.4).

During synthesis, each successive reaction step leads to an additional generation of branching. Ideally, dendrimers exhibit monodispersity, which means that all the molecules are exactly the same in terms of their structure, composition, and molecular weight.
2.3.1 Synthesis

There are two main synthetic routes for construction of high-generation dendrimers, that is, the convergent and the divergent routes\textsuperscript{14} (figure 2.5). The synthesis starts from the AB\textsubscript{x} monomers. Such monomers possess one A functionality and x complimentary B groups.

In the convergent route, the synthesis starts at the end groups and grow towards the core. Each step involves the coupling of the focal point of the dendron to the AB\textsubscript{x} monomer and finally to the core molecule, forming the dendrimer in the last step\textsuperscript{16}. In the divergent route, the chemistry starts off at the core, and the generations are added sequentially to the end groups of the dendrimer\textsuperscript{17}.

In the divergent synthesis, the dendrimer is grown in a stepwise manner from a central core, implying that numerous reactions have to be performed on a single molecule. Consequently, every reaction has to be very selective to ensure the integrity of the final product. Since every new generation of divergently produced dendrimer can hardly be purified, the presence of a small number of statistical defects cannot be avoided\textsuperscript{18}. The two methodologies have their own characteristics, and therefore, the perfection of the final dendritic product is related to this synthetic approach.

In the convergent approach, starting the synthesis of dendrimers from the periphery
and ending it at the core have overcome the difficulty of many reactions that have to be performed on one molecule. In this fashion, a constant and low number of reaction sites are warranted in every reaction step throughout the synthesis. As a consequence, only a small number of side products can be formed in each reaction, and therefore, every new generation can be purified. It becomes possible to introduce subtle engineering into the dendritic structure by precise placement of functional groups at the periphery of the macromolecule. The convergent approach does not allow the formation of high generations because steric problems occur in the reactions of the dendrons and the core molecule. Thus, convergently produced dendrimers, which can be seen as dendrimers prepared in an organic chemistry approach, can be defect-free.

Figure 2.5. Formation of dendrimers: A. The divergent growth method; B. The convergent growth method

At higher generations, the dendrimers will adopt a more globular structure due to their branched structure. The highly branched structures in combinations with the large number of end groups gives rise to a number of unique dendritic properties for e.g., high solubility, unusual rheological behaviour, and site isolation phenomena. Because of the highly branched structure of dendrimers, properties such as solubility, glass transition temperature and size can be altered by varying the generation number, the type of repeating unit, and the functionality of the end groups. Because of the high
number of end groups, most dendritic properties are strongly end dependent and by end-group tailoring, properties such as hydrophilicity/ hydrophobicity can be introduced.

The first synthesised dendrimers were poly-amidoamines (PAMAMs)\textsuperscript{24}. They are also known as starburst dendrimers. Ammonia is used as the core molecule. In the presence of methanol it reacts with methyl acrylate and then ethylenediamine is added:

\[ \text{NH}_3 + 3 \text{CH}_2=\text{CH}(\text{OCH}_3) \rightarrow \text{N}(\text{CH}_2\text{COOCH}_3)_3 \]

\[ \text{N}(\text{CH}_2\text{COOCH}_3)_3 + 3 \text{H}_2\text{NH} \rightarrow \text{N}(\text{CH}_2\text{COOCH}_3)_3 + 3 \text{CH}_3\text{OH} \]

\textbf{Scheme 2.3. Synthesis of PAMAM}

At the end of each branch there is a free amino group that can react with two methyl acrylate monomers and two ethylenediamine molecules. Each complete reaction sequence results in a new dendrimer generation. The half-generations PAMAM dendrimers (e.g., 0.5, 1.5, 2.5) possess anionic surfaces of carboxylate groups. The number of reactive surface sites is doubled with every generation. The mass increases more than twice.

The molar mass of the dendrimer can be predicted mathematically\textsuperscript{25}

\[ M = M_c + n_c \left[ M_m \cdot \frac{1}{n_m G - 1} \right] + M_t \cdot n_m G \]

Where:
- \( M_c \) is the molar mass of the core,
- \( M_m \) is the molar mass of the branched monomer,
- \( M_t \) is the molar mass of the terminal groups,
- \( n_c \) is the core multiplicity,
- \( n_m \) is the branch-juncture multiplicity,
- \( G \) is the generation number\textsuperscript{23}.

\subsection*{2.3.2 Molecular structure}

Dendrimers of lower generations (0, 1, and 2) have highly asymmetric shape and possess more open structures as compared to higher generation dendrimers. As the chains
growing from the core molecule become longer and more branched (in 4 and higher generations) dendrimers adopt a globular structure\textsuperscript{26}. Dendrimers become densely packed as they extend out to the periphery, which forms a closed membrane-like structure. When a critical branched state is reached dendrimers cannot grow because of a lack of space. This is called the starburst effect\textsuperscript{27}. For PAMAM dendrimer synthesis, it is observed after tenth generation, the rate of reaction drops suddenly and further reactions of the end groups cannot occur. The tenth generation PAMAM contains 6141 monomer units and has a diameter of about 124 anstrom\textsuperscript{25}. The increasing branch density with generation is also believed to have striking effects on the structure of dendrimers. They are characterized by the presence of internal cavities and by a large number of reactive end groups.

2.3.3 Properties

Dendrimers are usually drawn in a highly symmetrical fashion. The molecular structure is displayed with all tiers, having the characteristic algorithmic growth pattern pointing outward, the end groups are invariably located at the surface and overall picture suggests that the dendrimer is a spherical entity\textsuperscript{17}.

Dendrimers are monodisperse macromolecules, unlike linear polymers. The classical polymerization process that results in linear polymers is usually random in nature and produces molecules of different sizes, whereas size and molecular mass of dendrimers can be specifically controlled during synthesis.

Because of their molecular architecture, dendrimers show some significantly improved physical and chemical properties when compared to traditional linear polymers. In solution, linear chains exist as flexible coils; in contrast, dendrimers form a tightly packed ball. This has a great impact on their rheological properties. Dendrimer solutions have significantly lower viscosity than linear polymers\textsuperscript{28}.

When the molecular mass of dendrimers increases, their intrinsic viscosity goes through a maximum at the fourth generation and then begins to decline \textsuperscript{21}. Such behaviour is unlike that of linear polymers. For classical polymers the intrinsic viscosity increases continuously with molecular mass. The presence of many chain ends is responsible for high solubility and miscibility and for high reactivity\textsuperscript{29}. Dendrimers solubility is strongly
influenced by the nature of surface groups.

Numerical calculations using the kinetic growth model of Lescanec and Muthkumar predict a monomeric decrease in density on going from the center of the dendrimer to its periphery\textsuperscript{30}. As a consequence, the ends of the branches are not positioned at the surface but are severely back folded (figure 2.6).

Dendrimers terminated in hydrophilic groups are soluble in polar solvents, while dendrimers having hydrophobic end groups are soluble in nonpolar solvents. In a solubility test with tetrahydrofuran (THF) as the solvent, the solubility of dendritic polyester was found remarkably higher than that of analogous linear polyester.

A marked difference was also observed in chemical reactivity. Dendritic polyester was de-benzylated by catalytic hydrogenolysis whereas linear polyester was unreactive. Lower generation dendrimers which are large enough to be spherical but do not form a tightly packed surface, have enormous surface areas in relation to volume (up to 1000 m\textsuperscript{2}/g)\textsuperscript{24}. Dendrimers have some unique properties because of their globular shape and the presence of internal cavities. The most important one is the possibility to encapsulate guest molecules in the macromolecule interior.

Figure 2.6. Representation of a backfolded trifunctional fifth generation dendrimer

The hydroxyl group containing poly (alkyl aryl ether) dendrimers are soluble in alkaline solutions. In this respect, initial studies have shown that water insoluble aromatic substances become progressively soluble better as the generation number of the dendrimer advanced. Taking advantage of the solubilization properties of the dendrimers, few organic
reactions were conducted. Ramamurthy offered methods to test the dendritic medium in photochemical studies\textsuperscript{31}. Several photochemical reactions were thus conducted and from these studies, it was established that (i) dendritic microenvironments not only restrict the mobility of the reactive intermediates, but also rigidly encapsulates the substrates, intermediates and the products and (ii) dendritic media offer much better constraint than some of the traditional micelles, such as, sodium dodecyl sulfate and sodium deoxycholate.

The exo-receptor properties of poly (alkyl aryl ether) dendrimers were evaluated. In this instance, the photochemical trans-cis and thermal cis-trans isomerizations of azobenzene, presented at the peripheries of the dendrimers, were assessed\textsuperscript{32}. While solution phase studies of the isomerization showed that the azobenzene units within a molecule behaved in an independent and unconnected manner. Solid-state studies, performed by Das and co-workers, revealed an anomalous fluorescence of the azobenzene in dendrimers\textsuperscript{33}. Such fluorescence behavior was absent for the monomeric azobenzene alone. These studies illustrate that dendritic architectures influence properties of functional units that are otherwise non-existent in the monomer unit alone.

\subsection{2.3.4 Functional modifications}

Since Tomalia and Newkome reports on dendrimers\textsuperscript{10,11} research on these branched molecules has mainly focused on the preparation and molecular characterization of a wide variety of dendritic macromolecules. Gradually, the interest in this field of chemistry has shifted to research in which specific functions of and particular applications for dendrimers are addressed. From the beginning, applications in the fields of medicinal chemistry (e.g., in drug delivery systems), host-guest chemistry and catalysis have been foreseen\textsuperscript{34−39}. Dendrimers have some unique properties because of their globular shape and the presence of internal cavities. The most important one is the possibility to encapsulate guest molecules in the macromolecule interior. Meijer and co-workers\textsuperscript{40,41} trapped small molecules like Rose Bengal or p-nitrobenzoic acid inside the dendritic box of poly(propylene imine) dendrimer with 64 branches on the periphery. Then a shell was formed on the surface of the dendrimer by reacting the terminal amines with an amino acid (L phenylalanine) and guest molecules were strongly encapsulated inside the box.
Hydrolysing the outer shell could liberate the guest molecules. The shape of the guest and the architecture of the box and its cavities determine the number of guest molecules that can be entrapped. Meijers group described experiments in which they had trapped four molecules of rose bengal or eight to ten molecules of p-nitrobenzoic acid in one dendrimer. Archut and co-workers\textsuperscript{42} developed a method in which boxes could be opened photochemically.

\begin{figure}
\centering
\includegraphics[width=0.5\textwidth]{figure2.7}
\caption{Dendrimer box encapsulating the guest molecule}
\end{figure}

A fourth generation polypropylene imine dendrimer with 32 end groups was terminated in azo-benzene groups is shown in figure 2.8.

\begin{figure}
\centering
\includegraphics[width=0.5\textwidth]{figure2.8}
\caption{Dendrimer terminated in 32 end groups}
\end{figure}

The azobenzene groups undergo a fully reversible photoisomerization reaction. The E isomer is switched to the Z form by 313 nm light and can be converted back to the E
form by irradiation with 254 nm light or by heating. Such dendrimers can play the role of photoswitchable hosts for eosin Y. Photochemical modifications of the dendritic surface cause encapsulation and release of guest molecules. Archuts experiment demonstrated that the Z forms of the fourth generation dendrimers are better hosts than the E forms. It is possible to create dendrimers, which can act as extremely efficient light-harvesting antennae\textsuperscript{43,44}. Absorbing dyes are placed at the periphery of the dendrimer and transfer the energy of light to another chromophore located in the core. The absorption spectrum of the whole macromolecule is particularly broad because the peripheral chromophores cover a wide wavelength range. The energy transfer process converts this broad absorption into the narrow emission of the central dye. The light harvesting ability increases with generation due to the increase in the number of peripheral chromophores.

Biological properties of dendrimers are crucial because of the growing interest in using them in biomedical applications. Cationic dendrimers (e.g., amine terminated PAMAM and poly (propylene imine) dendrimers that form cationic groups at low pH) are generally haemolytic and cytotoxic. Their toxicity is generation-dependent and increases with the number of surface groups\textsuperscript{45}.

PAMAM dendrimers (generation 2, 3 and 4) interact with erythrocyte membrane proteins causing changes in protein conformation. These changes increase with generation number and the concentration of dendrimers. The interactions between proteins and half-generation PAMAM dendrimers (2.5 and 3.5) are weaker\textsuperscript{11}. Anionic dendrimers, bearing a carboxylate surface, are not cytotoxic over a broad concentration range. Incubation of human red blood cells in plasma or suspended in phosphate-buffered saline with PAMAM dendrimers causes the formation of cell aggregates\textsuperscript{46}.

The dendritic core is at least to some extent-shielded from the medium, implying a microenvironment inside the medium. This knowledge is inspired many scientists to prepare dendrimers with specific functionalities at the core. Porphyrin based dendrimers have attracted a lot of attention in this research field. Porphyrins are found in many natural systems, where they play an essential role as photoactive, redox, guest-binding, and catalytic entities\textsuperscript{26}. Dendrimers with phthalocyanine cores also display several characteristics\textsuperscript{47,48}. 
2.3.5 Applications

There are now more than fifty families of dendrimers, each with unique properties, since the surface, interior and core can be tailored to different sorts of applications. Many potential applications of dendrimers are based on their unparalleled molecular uniformity, multifunctional surface and presence of internal cavities. These specific properties make dendrimers suitable for a variety of high technology uses including biomedical and industrial applications.

There are attempts to use dendrimers in the targeted delivery of drugs and other therapeutic agents. Drug molecules can be loaded both in the interior of the dendrimers as well as attached to the surface groups. The biocompatibility and pharmacokinetics of dendrimers are important factors when in vivo applications are considered. The therapeutic effectiveness of any drug is strictly connected with its good solubility in the body aqueous environment. There are many substances that have a strong therapeutic activity but due to their lack of solubility in pharmaceutically acceptable solvents have not been used for therapeutic purposes. Water-soluble dendrimers are capable of binding and solubilising small acidic hydrophobic molecules with antifungal or antibacterial properties. The bound substrates may be released upon contact with the target organism. Such complexes may be considered as potential drug delivery systems. Sialylated dendrimers, called sialodendrimers, have been shown to be potent inhibitors of the haemagglutination of human erythrocytes by influenza viruses (figure 2.9).

![Figure 2.9. A Glycodendrimer consisting of an L-lysine core and 16 sialic acid residues](image-url)

Figure 2.9. A Glycodendrimer consisting of an L-lysine core and 16 sialic acid residues.
Frachet and co-workers at Berkeley are investigating the use of dendrimers to harvest broadband light to convert the energy in to monochromatic light with amplification, in to electricity through charge separation, or in to chemical energy. The systems consist of light harvesting dendrons with numerous laser dye chromophores, such as coumarins, at the periphery. The light is harvested over a wide area on the surface of the dendrimer and funneled by dipole-dipole interactions to the single active sites at the core where energy conversion takes place. Dendrimers are likely to play an important role in artificial photosynthesis and information processing at the molecular level. Dendrimers containing photoactive units can also be exploited for sensing metal ions.

Balzani, Vogtle and their teams have studied up to fifth generation poly (propylene amine) dendrimers functionalized at the periphery with strongly fluorescent dansyl [1-dimethyl amino-1-naphthaqlene-5-sulfonyl] units.

Figure 2.10. Light harvesting dendrimer

Hawker, Frchet, and their co-workers at Berkeley and IBM have developed dendrimers as nanoscale reactors for catalysis. They introduced polar groups in the inner building blocks of a convergent polymer to build a dendritic macromolecule that contains a high concentration of the polar groups within the cavity of the dendrimer. The researchers demonstrated that the internal polarity of the dendrimer enabled simple nucleophilic substitution and elimination reactions to occur in catalytic fashion. The globular shape of dendrimers offers a unique opportunity to design artificial systems. Brunner and co-workers prepared a so-called dendrizyme by growing chiral dendritic branches around a
achiral metal chelate to catalyse the cyclopropanation of styrene with ethyl diazoacetate to form the cyclopropane carboxylates\textsuperscript{52,53}. Placing the catalytic group at the center of the dendrimer allows special control of functionalities; this enables steric, photophysical and electrochemical properties are to be controlled\textsuperscript{54}.

Dendrimers due to their properties are highly suited for use as image contrast media. Several groups have prepared dendrimers containing gadolinium ions chelated on the surface\textsuperscript{55,56}. Preliminary tests show that such dendrimers are stronger contrast agents than conventional ones. They also improve visualisation of vascular structures in magnetic resonance angiography (MRA) of the body. It is a consequence of excellent signal to noise ratio\textsuperscript{57}. S.C. Zimmerman and S. Micheal reported the first example of cored polymersynthesised by cross-linking the dendrimers peripheral groups and then removing the groups by hydrolysis\textsuperscript{58}.

2.3.6 Applications in future

The chemistry of dendrimers is blossoming day by day. The first International Dendrimer Symposium was organized by DECHEMA, a Frankfort based German Nonprofit Society concerned with chemical engineering, chemical technology and biotechnology. Topics included potential applications of dendrimers, their design, synthesis, structure, analysis and properties. The developing applications of dendrimers take full advantage of their precise nanometer size, high functionality, and regular structural features.

In collaboration with F. C. Szoka, Frechet and his team are working on the use of dendrimers for targeted delivery of toxic drugs used in chemotherapy. Dendrimers can act as carriers, called vectors, in gene therapy. Vectors transfer genes through the cell membrane into the nucleus. Currently liposomes and genetically engineered viruses have been mainly used for this. PAMAM dendrimers have also been tested as genetic material carriers\textsuperscript{59,60}.

Dendrimers containing photoactive groups can also be exploited for sensing metal ions. On addition of cobalt (II) and copper (II) ions to solutions of dansyl-functioalized POPAM (poly propylene amine) dendrimers, the dansyl fluorescence is strongly quenched. This is a very interesting result since it shows that the extraction of transition metal ions
on fluorescence labels appended to the dendrimers\textsuperscript{15}.

Based on their dimensional length scaling, narrow size distribution and other biomimetic properties, dendrimers are often referred to as artificial proteins\textsuperscript{61}. Within the PAMAM family, they closely match the sizes and contours of many important proteins and bioassemblies, for example, insulin (3nm), cytochrom C (4nm) and hemoglobin (5.5nm) are approximately the same size and shape as ammonia-core PAMAM dendrimers generations 3,4,5, respectively. Surface modified dendrimers themselves may act as nano-drugs against tumors, bacteria, and viruses\textsuperscript{61}.

2.4 Hyperbranched Polymers

Hyperbranched polymers and dendrimers belong to the same group of polymers with densely branched structures and a large number of reactive groups. They resemble each other in that they are both polymerized from monomers with mixed reactivities, commonly denoted A\textsubscript{2}B or A\textsubscript{3}B monomers, thus giving branched structures with exponential growth, in both end group functionalities and molecular weights. However there are also differences. Dendrimers are defined as monodisperse hyperbranched polymers, while ordinary hyperbranched polymers are polydisperse. The fundamental synthetic approach differs between the two. Whereas dendrimers require absolute control of all synthesis steps, manufacturing of ordinary hyperbranched polymers is accomplished by a simplified approach similar to conventional resin technology\textsuperscript{62,63}. Dendrimers are polymers with perfectly branched structure while hyperbranched polymers are with randomly branched structure\textsuperscript{64} (figure 2.11).

Over the past 15 years, hyperbranched polymers have received much attention due to their unique chemical and physical properties as well as their potential applications in coatings, additives, drug and gene delivery, macro-molecular building blocks, nanotechnology and supramolecular science\textsuperscript{65–67}.
2.4.1 History

In 1940s, Flory et al used statistical mechanics to calculate the molecular weight distribution of three-dimensional polymers with trifunctional and tetra functional branching units in the state of gelation, and developed the degree of branching and highly branched species concepts\textsuperscript{68}. In 1952, Flory developed the theory that highly branched polymers can be synthesized without the gelation by polycondensation of a monomer containing one A functional group and two or more B functional ones capable of reacting with A\textsuperscript{69}. Finally in 1982, Kricheldorf obtained highly branched polyesters by copolymerization of AB and AB\textsubscript{2} type monomers\textsuperscript{70}.

![Figure 2.11. (a) perfect dendrimer and (b) hyperbranched polymer with a core B (A in the periphery)](image)

The term Hyperbranched polymer was first coined by Kim and Webster in 1988\textsuperscript{71,72}. They synthesized soluble hyperbranched polyphenylene. Since then, hyperbranched polymers have attracted increasing attention owing to their unique properties and greater availability as compared with dendrimers\textsuperscript{67}. Although dendrimers have been studied extensively for their size, shape and surface functional group related properties, their large scale synthesis has been limited to only a few structures because of the inherent difficulties in the stepwise growth pattern\textsuperscript{73}. The synthesis of hyperbranched polymers can often be simplified compared to dendrimers, as it does not require the use of protection/deprotection steps.
According to Holger Frey, the hyperbranched polymers, prepared in a controlled manner in two or three steps, might be able to perform just as well as dendrimers prepared in 10 or 12 steps\textsuperscript{65}. Hyperbranched polymers combine some of the features of dendrimers, such as highly branched architectures and high content of functional groups, with cheap and easy preparation procedures.

2.4.2 Synthesis

The synthesis of hyperbranched polymers can often be simplified compared to that of dendrimers, as it does not require the use of protection/deprotection steps. This is due to the fact that hyperbranched polymers always contain a fraction of linearly incorporated A\textsubscript{n}B monomers\textsuperscript{66}. The most common synthetic route follows a one-pot procedure, where A\textsubscript{n}B monomers are condensed in the presence of a catalyst.

Hyperbranched polymers have been synthesized by self condensation polymerization using an A\textsubscript{n}B type monomer in which A and B are functional groups that react with each other and not with themselves. This method comes under the category called single-monomer methodology (SMM). According to the reaction mechanism, the SMM category includes at least four specific approaches: (1) polycondensation of A\textsubscript{n}B monomers (2) self-condensing vinyl polymerisation (SCVP) (3) self-condensing ring opening polymerization (SCROP) (4) proton transfer polymerization (PTP). The other category contains methods of the double monomer methodology (DMM) in which the direct polymerization of two types of monomers or a monomer pair generates hyperbranched polymers\textsuperscript{67}.

(i) SMM-Polycondensation of A\textsubscript{n}B monomers

Flory et al described the condensation reaction of A\textsubscript{n}B monomers from a theoretical point of view and predicted that such a polymer will have a highly branched structure and a multitude of end groups\textsuperscript{74,75} (scheme 2.4).

Here the growth of the polymer starts only at the already existing reaction sites A and B; in other words there is no generation of a new site during the polymerization. If z monomers are coupled together, the resulting molecule will contain only a single B group
and \((fz-2z+1)\) A groups, where \(f\) is the total number of functional groups on the monomer.

![Diagram of hyperbranched polymer]

**Scheme 2.4.** General strategy for the synthesis of hyperbranched polymers with \(A_2B\) monomer

Some examples of this class are hyperbranched polyphenylenes, polyesters, polyethers, polyurethanes, polyamines, polyamides, and polysiloxanes.

(ii) SMM- Self condensing vinyl polymerization (SCVP)

In the second strategy to prepare hyperbranched polymer is termed self-condensing vinyl polymerization (SCVP) defined by Frechet in 1995. The applicable monomer denoted by \(AB^*\) contains an initiating moiety in addition to a double bond. The initiating moiety is activated, and then, reacted with a double bond to form a covalent bond and a new active site on the second carbon atom of the double bond, as shown in scheme 2.5.

The number of activation sites increases proportionally to the propagation reaction in SCVP where as two functional groups are always consumed during the self-poly condensation of the \(ABx\) monomers. If the new activation sites generated during the polymerization have different reactivity from the activation sites generated from the initiating moiety of the original polymer, the difference dramatically affects the structure of the resulting polymer. The activated species could be a living free radical, an electrophilic cationic moiety or a carbanion. Examples of this class include polystyrene and poly acrylates.
The third category is the ring opening polymerization of latent ABx monomers, which was termed multibranching polymerization by Suzuki in 1992\textsuperscript{84}. Branching units are generated during the ring-opening reaction, while the starting AB monomers do not contain branching points. The polymerization is initiated by the addition of proper initiators to generate active sites, which may allow for control over the molecular weight and molecular weight distribution of the resulting polymers.

Although the properties of hyperbranched polymers are intermediate between those of dendrimers and linear polymers, the low cost for the synthesis of hyperbranched polymers permits to produce them on a large scale, giving them an advantage over dendrimers in applications. Hyperbranched polymers are thus considered as an alternative to dendrimers for different applications both in academia and in industry\textsuperscript{64,65}. 
2.4.3 General properties

There are three major parameters used to describe hyperbranched polymers. They are molecular weight, polydispersity and functionality and degree of branching (DB). The third parameter degree of branching can be used to tell the difference between dendrimer and hyperbranched polymers. Recently, Frey et al. introduced an expression for degree of branching where the degree of polymerization is also taken into account. The DB can be calculated using the following equation:

$$DB_{Frey} = \frac{2D}{2D + L}$$

Here D is the number of dendritic unit, while L is the number of linear unit.

The degree of branching has a limiting value of 0.66 with slow monomer addition at high degree of conversion.

Dendrimers do not possess linear units and in this case, the degree of branching, DB, is calculated as 1, while on the other hand, linear polymers do not possess dendritic units, the DB value can be calculated as zero. Accordingly hyperbranched polymers should then exhibit an intermediate DB value between zero and one (figure 2.12).

It is of vital importance to understand how the DB value affects the properties of a hyperbranched polymer. One way to obtain polymers with higher degrees of branching is to use performed dendron- monomers. This concept was used by Hawker and Chu and it was found that the resulting polymers with the highest degree of branching also exhibited the highest solubility in organic solvents.

The influence of end groups on the properties of linear polymers is negligible at a sufficiently high molecular weight. However, every hyperbranched polymers have a large number of end groups. The end groups have been demonstrated to be easily accessible for chemical modifications and the nature of the end groups determine the thermal (e.g. Tg) and physical properties of the hyperbranched polymers to a great extent. The high degree of branching enables them to be amorphous since branching prevents or impedes crystallization.
Kim and Webster\textsuperscript{96} reported that hyperbranched polyphenylenes had very good solubility in various solvents as compared to linear polyphenylenes that have very poor solubility. The solubility depended to a large extent on the structure of the end groups, and thus highly polar end-groups such as carboxylates would make the polyphenylenes even water-soluble.

Furthermore, hyperbranched polymers are characterized by the absence of chain entanglements, at high molecular weight they are found to be globular, contrarily to the linear polymers they behaved more like molecular miscelles, which results in low melt and solution viscosities\textsuperscript{64}, this bring great benefit to the processing. Frechet presented a comparison between linear polymers, hyperbranched polymers and dendrimers with respect to intrinsic viscosities as a function of molecular weight, which clearly shows the
difference induced by variations in the backbone architecture\textsuperscript{97}. The slope of the plot for the hyperbranched polymers is smaller than that for linear polymers although intrinsic viscosities increase with increase in molecular weight (figure 2.13)

![Graph showing log M vs log η for different types of polymers](image)

**Figure 2.13.** Relationship between log M and log η for macromolecules (η = solution viscosity, M = molecular weight)

Flory predicted that the number of entanglements would be lower for polymers based on A\textsubscript{x}B monomers, with subsequent reduction in mechanical strength\textsuperscript{98}. Not only good solubility but also solution behavior differs for hyperbranched polymers compared to linear polymers. For example, the hyperbranched aromatic polyesters, described by Turner et al\textsuperscript{99,100} exhibit very low η value (less than 0.5) in the Mark-Houwink-Sakurada equation (η = kM\textsuperscript{a} and low intrinsic viscosities. This suggests a spherical shape for the molecules in solution. In GPC measurements, the retention volume for hyperbranched polymers tends to be larger than that for linear polystyrene having the same molecular weight. This also suggests a more compact form for hyperbranched polymers in solution compared to linear polymers\textsuperscript{95}.

Another special feature of hyperbranched polymers is the possibility to combine an interior structure with one polarity, with a shell (end groups) having another polarity, for instance a hydrophobic inner structure and hydrophilic end groups\textsuperscript{73}. The dilution properties of hyperbranched polymers also differ from those of linear polymers. In a comparison between two alkyd resin systems, where one was a conventional high solid alkyd system and the other based on hyperbranched aliphatic polyester, the conventional
high solid alkyd was seen to exhibit a higher viscosity\textsuperscript{64}.

Molecular modeling of the hyperbranched polymer reveals a large number of empty cavities between branches. Kim and Webster speculated that a complex would form between hyperbranched polyphenylene and other aromatic groups through intercalation of the aromatic rings. Existence of such complexation was confirmed by a NMR study of carboxylated polyphenylene and p-toludine\textsuperscript{72}. Tg is one of the properties that have been reported for most of the hyperbranched polymers.

Values of Tg for a series of hyperbranched aromatic polyesters with end groups have been presented in a review paper by Voit\textsuperscript{101}. Tg shifted as much as 100\textdegree{}C on going from carboxylic acid to acetate end groups. This and other reports show the large impact of end group on the Tg.

The thermal stability of hyperbranched polymers is related to the chemical structure in the same manner as for linear polymers; for example, aromatic esters are more stable than aliphatic ones. In one case, the addition of a small amount of hyperbranched polyphenylene to polystyrene was found to improve the thermal stability of the blend as compared to the pure polystyrene\textsuperscript{96}.

The rheological properties of hyperbranched polymers are characterized by a Newtonian behavior in the molten state; i.e., no shear thinning or thickening is observed, indicating a lack of entanglement for these polymers. The non-entangled state imposes rather poor mechanical properties, resulting in brittle polymers. This has limited the use of these polymers as thermoplastics to applications where mechanical strength is of minor importance\textsuperscript{64}. The large amount of branching also makes most of the polymers amorphous. Hence, these polymers are mainly suitable as additives or as thermo sets when high mechanical strength is required for certain applications. The melt behavior has been shown to be greatly affected by the structure of end-groups where an increase in polarity of the end groups can raise the viscosity by several orders of magnitude. This is of great importance in applications where low viscosity is essential for the processing of the material.
2.4.4 Functional modifications

The properties of hyperbranched polymers are often affected by the nature of the backbone and the chain end functional groups, the degree of branching, chain length between branching points, and the molecular weight distribution. Hyperbranched polymers are often modified to tailor their properties for a specialized purpose. Based on the highly branched architecture and the large number of terminal functional groups of hyperbranched macromolecules, five modification manners have been developed: (1) end capping with short chains or organic molecules, (2) terminal grafting via living polymerization, (3) growing hyperbranched polymers on the surface or grafting from/on to the surface and (4) hypergrafting to obtain hyperbranched polymers with a linear macromolecular core.

(i) End capping

The large number of end groups attached to the linear and terminal units of hyperbranched polymers can be conveniently end-capped with small organic molecules. In the end-capping process three major purposes are emphasized (1) to exclude the influence of some functional groups on the measurement of molecular weight, (2) to investigate the effect of terminal groups on the properties of hyperbranched polymers, (3) to fabricate novel functional polymeric materials. Many experiments demonstrated the influence of terminal functional groups on the Tg value. The Tg value of hyperbranched polyphenylene was found to vary over a wide range, from $96^\circ$C for the polymer with a-vinyl phenyl end groups to $223^\circ$C for the polymer with p-anisol end groups although the modified hyperbranched polymers have the same backbone.

Salazar et al. synthesized hyperbranched amino terminated poly glycidols by end modification of terminal hydroxy groups with toyl sulfonyl chloride (TsCl), followed by nucleophilic substitution of the toyl sulfonyl groups with secondary aliphatic amines. The hyperbranched amino terminated polymers obtained can be used as macromolecular ligands in an oxidative coupling reaction of phenyl acetylene. It is found that amino-terminated polyglycidols-CuCl complexes are more effective catalysts for the oxidative
coupling reaction than the reference monomeric tertiary amines CuCl, while less effective than the most efficient N,N,N,N-tetramethylethylenediamine-CuCl complexes. The performance improvement for the hyperbranched polymeric ligands may be attributed to two factors: (1) the better complexation abilities, and (2) local increase of the reagent concentration.

Scheme 2.6. Schematic representation of end capping process

The thermal and mechanical characters of hyperbranched polymers can be conveniently manipulated via the end capping method on the basis of the relationship between terminal groups and properties. Generally alkyl and ether groups terminated hyperbranched polymers will have relatively low Tg values, low melting viscosity and low mechanical strength, and carboxylic acid and hydroxy- terminated hyperbranched ones have relatively high Tg values, high melt viscosity and high mechanical strength.67

(ii) Terminal grafting

Terminal grafting can also be called grafting from. Grafting polymers from macromolecular initiators prepared by modification of the functional groups of hyperbranched polymers affords core-shell multi-arm star polymers or hyperstars. Some properties such as polarity, solubility and flexibility of the hyperbranched scaffolds can be conveniently tailored through terminal grafting modification.102
Three polymerization methods (e.g. anionic, cationic and living/controlled radical polymerizations) have been adopted to fabricate the hyperstars via reaction processes including macromolecular initiator-first and in situ grafting.

(iii) Surface growing

The method to modify the specific surface or interface with hyperbranched macromolecules or to graft hyperbranched polymers is denoted as surface growing. The grafted hyperbranched polymers can be regarded as so-called polymer bushes, which are typically anchored to the surface by one end of the polymer chain, such that the polymer can extend away from the surface\(^\text{104}\). Surface grafting is an efficient strategy to fabricate inorganic/organic-hyperbranched polymer hybrid materials and functional devices or improve the properties of surface objects.

(iv) Hypergrafting

Hypergrafting represents grafting hyperbranched macromolecules to a multifunctional polymeric core, and the resulting hybrid material is called a hypergrafted polymer. If the core used is linear polymer, a new sort of comb-like polymer cylinder will be formed\(^\text{105}\).

![Figure 2.14. Schematic representation of surface grafting](image_url)
2.4.5 Applications

Hyperbranched polymers due to their potential for developing advanced nanometerials, biomaterials and biological and rheology modifiers, structural hydrogels, functional cross linkers, dental components and catalytic support based on the low viscosity and high functionality have achieved increased academic and industrial interest\textsuperscript{65,68}.

Ulrich S. Schubert, predicted the possibilities of hyperbranched polymers for applications for medical purposes. An important application of hyperbranched polymers in medicine is advanced drug-delivery systems. These polymers control the drug concentration and delivery rate in the body. Hyperbranched polyesters have been suggested for such systems.

Hyperbranched polymers are receiving increasing attention in biomaterials application\textsuperscript{106}. In this field, hyperbranched polymers can play two main roles: biocarriers and biodegradable materials. As carriers, hyperbranched polymers can offer their interior or peripheral functional groups to covalently fix bio objects, or depending on their core-shell architecture, to sequester guest molecules\textsuperscript{68}.

Dendritic and hyperbranched polymers based on amide linkages have received considerable attention due to the fact that polyamides are commercially important and these linkages are the backbone of all the naturally occurring proteins and enzymes. E.W. Meijer et al. synthesized and characterized the first example of urea based hyperbranched polymer which could be an alternative fibre-forming polymers\textsuperscript{74}. Bergbreiter et al have demonstrated that hydrophobic, fluorinated, hyperbranched poly acrylic acid can passivate and block electrochemical reactions on metal surfaces, thereby preventing corrosion\textsuperscript{105}.

Hyperbranched polymers have been used as the base for various coating resins, such as powder coatings\textsuperscript{107,108}, high solid coatings\textsuperscript{109}, flame retardant coatings\textsuperscript{110}, and barrier coatings for flexible packing\textsuperscript{111}, depending on their high solubility, low viscosity and abundant functional groups.

Hyperbranched polymers and their substitutes can be used as nanomaterials for host-guest encapsulation and the fabrication of organic-inorganic hybrids, and even directly used as nanoreactors for some reactions\textsuperscript{112}.
Hyperbranched polyester, containing 3, 6 di-acceptor substituted carbazole chromophores, was suggested for use in Non linear optical (NLO) applications\textsuperscript{114,114}. The lack of mechanical strength for thermoplastic hyperbranched polymers makes them more suitable as additives in thermoplastic applications. Hyperbranched polyphenylenes have been shown to act as rheology modifiers when processing linear thermoplastics. A small amount added to polystyrene resulted in reduced melt viscosity\textsuperscript{77}.

Toughness properties of thermosets can be improved by various additives. It is important that the additives should not affect the thermo mechanical properties of the thermosetting material. Manson et al. have demonstrated that by using an epoxy-modified hyperbranched polyester as toughner the critical energy release rate, $G_{1c}$, of carbon fiber reinforced epoxy was improved from 1400 to 2500 Jm\textsuperscript{-2} \textsuperscript{115,116}.

### 2.5 Hyperbranched Polyglycerols

Over the past decade, perfect dendrimers have received immense interest from academic as well as industrial researchers. However, commercial applications of these perfectly branched materials are scarce, since the tedious multistep synthesis result in unacceptable costs for most applications. H. Frey et al. developed an efficient method to generate well-defined hyperbranched polyglycerol (HPG), based on ring- opening multibranching polymerization of glycidol under slow monomer addition technique that proceeds by a reversible activated chain-end mechanism\textsuperscript{117} (scheme 2.7).

The epoxyalcohol glycidol can be very efficiently polymerized under anionic conditions by applying self- assembled monolayer techniques. The resulting polyglycerol comprises up to several hundred hydroxyl end groups rendering it a versatile scaffold for subsequent functionalisation.
Scheme 2.7. Synthetic route and structure of hyperbranched polyglycerol

The polymer obtained by this process possesses relatively narrow molecular weight distribution (Mw/Mn is around 1.5), determined by size exclusion chromatography vs. poly (propylene oxide) standards, compared this PDI with the normal range 3-5, and molecular weight can range from 1000 to 25000g/mol.

The HPG obtained by Frey group is a clear, viscous liquid. The glass transition temperature is considerably below room temperature, typically around -25°C. At room temperature it is highly viscous, the viscosity increasing with molecular weight. By simple heating to elevated temperatures (80°C) it becomes a free flowing liquid. HPG is highly soluble in water and also in polar organic solvents such as methanol. By comparison to linear, the solution-viscosity of non-branched polymers is considerably lower. Polyglycerols are essentially non-volatile at room temperature. Hyperbranched polyglycerol possesses an inert polyether scaffold. Each branch ends in a hydroxyl-function, which renders HPG a highly functional material, e.g., a molecule with a molecular weight of 5000g/mol possesses 68 hydroxyl end groups. The high functionality in combination with the versatile and well-investigated reactivity of hydroxyl functions is the basis for a broad variety of derivatives.

Many possible applications can be proposed for these materials. The low viscosity in combination with the high functionality is useful for functional crosslinkers, additives, and
rheology modifiers to components in adhesives, advanced coatings, structured hydrogels, and dental composites\textsuperscript{119}. Such polymers might also be of interest in nanotechnology, for example, as building blocks for nanoscale reaction compartments, as a template for nanoporous materials with low dielectric constants (scheme 2.8), or for the fabrication of defined hybrid particles (e.g. biomineralisation techniques)\textsuperscript{120,121}. Other fields considered are biochemistry and biomedicine, where such macromolecule can act as carriers, either highly loaded for diagnostic purposes (e.g. for magnetic resonance imaging (MRI) of blood vessels) or as host compartments for controlled drug-release. Finally their use as homogenous supports for recyclable catalysts and for supported organic and biochemical syntheses have been suggested.

\textbf{Scheme 2.8}. Nanocapsules and nanoreactors from PG

Partial esterification with fatty acids yields amphiphilic materials, which behave as nanocapsules. Such nanocapsules can, for example, incorporate polar molecules as guests and solubilize them in an apolar environment\textsuperscript{122}. Selective modification can be achieved utilizing the reactivity of 1,2-diol units, located preferentially at the periphery of the molecule\textsuperscript{119,123}. Complimentary to functionalization by reactions of the large number of hydroxyl-groups, a single functionality can also be introduced selectively as the core of the molecule. A number of single core functionalities, such as a vinylic group, amines and
thiols, have been incorporated\textsuperscript{118,122–124}. Apart from these modifications, HPG is also employed as core molecules to build different star-branched block copolymers.

Biocompatibility is one particularly advantageous feature of polyglycerol. It can be used as a delivery agent for biologically active compounds, cosmetics etc. HPG consists of an inert polyether backbone with functional hydroxyl bonds at each branch-end. This structural feature of HPG resembles the well known poly (ethylene glycol) (PEG) that is accepted for various for biomedical applications\textsuperscript{125,126}. The polyether back bone of HPG, taking the biocompatibility of aliphatic polyether structures such as PEG in to account, makes HPG an attractive polymer for biomedical and pharmaceutical applications\textsuperscript{121,122,127,128}. Additionally the hydrophilicity in combination with its hydroxyl functionalities makes HPG very suitable for the design of hydrogels. Hydrogels, hydrophilic networks are of wide spread interest for applications in the pharmaceutical, biomedical and biotechnological fields\textsuperscript{126,129}.

\section*{2.6 Photochemical Modification of Dendrimers and Hyperbranched Polymers}

Dendritic macromolecules, such as dendrimers and hyperbranched polymers, deserve much attention for their unique physical and chemical properties. It is reported that both of them, usually amorphous, show good solubility in organic solvent, and low melt and solution viscosity. Photochemical reactions which occur in small molecules can also be induced to occur in macromolecules. Though, in macromolecular environments the macromolecules which may coil, branch, or be chemically cross-linked increasing the order of complexity. The free volume available to a reactive site or dissolved probe controls the course of photophysical and photochemical processes, for example. Likewise, molecular mobility plays an important role in determining, the course of photochemical reactions in polymers and is related to the size of the molecule, the flexibility of the polymer chain, and whether the polymer is in solution or the solid state. In order to fully understand these effects, it is useful to select one or two simple photochemical reactions, which are
well known, and to study them in a macromolecular environment. Such a photochemical reaction is the cis-trans isomerism of an azobenzene.

A photoresponsive smart material was made by incorporating a photochromic azobenzene compound into a side chained dendritic polyester. Upon irradiation at a specific wavelength of light, the azobenzene compound undergoes changes in its overall structure and properties that can be used to produce physical property changes in the polymer. The development of smart materials that can reversibly change shape or properties by simple photoirradiation, could allow for components that are lighter and capable of responding faster than current adaptive materials. One important factor is that the material must be strong enough to be formed and retain physical strength. This requires a bulkier azobenzene, which poses a difficult dilemma. The nitrogen double bond on the azobenzene isomerizes from its stable trans to its less stable cis conformation during photoirradiation. Adding bulky substituents to the aromatic group of the azobenzenes can hinder this process and reduce the photoresponsiveness of the material. Polyamidoamine (PAMAM) dendrimer wedges allow a large unit to be readily added to a single linear chain. The resulting functionalized macromolecule was reacted with an azobenzene to form a photoresponsive side chain dendritic polyester (SCDPE). PAMAM dendrimers were incorporated into photoresponsive polymers with the goal of increasing stability without losing the photoefficiency of the polymer. Further work, must be focused on enhancing the PAMAM dendrimer design by implementing additional photoresponsive groups onto the peripherals of the dendrimer wedges. The incorporation of these dendrimer wedges to the linear polymer will be used to increase the photoefficiency of the polymer. Thin films of the polymer will be cast onto a flexible substrate that will aid in converting the light energy provided upon irradiation into a mechanical response, resulting in a reversible deformation of the smart material\textsuperscript{130–132}.

Since dendritic polymers have excellent characteristic physical properties such as low viscosity, good solubility, and many functional groups, compared with corresponding linear polymers, they have been of great interest in the field of polymer chemistry. Among them, hyperbranched polymers have great possibility as high performance and new photo-curable polymers and oligomers in chemical industry\textsuperscript{133}. 
2.7 Porphyrins as Biologically Important Macroyclic Compounds

2.7.1 The porphyrin macrocycle

Porphyrins (which comes from the Greek for purple) are a ubiquitous class of naturally occurring molecules involved in a wide variety of important biological processes ranging from oxygen transport to photosynthesis, from catalysis to pigmentation changes\textsuperscript{134,135,136}. The common feature of these molecules is the basic structure of porphine macrocycle, which consists of 16-atoms ring containing four nitrogen atoms, obtained by linking four tetra pyrrolic sub units with four methine bridges, as shown in figure 2.15.

\textbf{Figure 2.15.} (a): Structure of porphyrine macrocycle and (b) tetraphenyl porphyrin. \( R = \text{alkoxy, amino, carboxyl, carbomethoxy, halogeno and nitro groups.} \)

This macrocycle is an aromatic system containing 22 \( \pi \) electrons, but only 18 of them are delocalized according to the Huckels rule of aromaticity. The size of the macrocycle is perfect to bind almost all metal ions and indeed a number of metals (e.g. Fe, Zn, Cu, Ni and Co) can be inserted in the center of the macrocycle forming metalloporphyrins.

There are several biologically important porphyrin bearing macrocycles employed in living system by nature to carry out many functions specifically with maximum efficiency. Since the properties and functions of molecules are cumulative effect of several factors, biomimeticists design porphyrin assemblies with various substituent groups, metal ions and
different oxidation states. Careful studies with such compounds under different conditions throw light on to several fundamental aspects of life process. It also helps to design several highly useful catalysts and molecules of unusual properties.

Porphyрин based fundamental biological representatives include hemes, chlorophylls, vitamin B-12, and several others. Heme proteins which contain iron porphyrins (figure 2.18) serve many roles, like $O_2$ storage and transport (myoglobin and Hemoglobin), electron transport (cytochrome P 450 and cytochrome oxidase) (figure 2.16).

![Figure 2.16. The structure of heme, the ligand-iron porphyrin complex in hemoglobin](image)

Chlorophyll (which have central magnesium ion) and pheophytins (which are metal free) are found in the photosynthetic apparatus of plants and bacteria, while vitamin B12 (which contains cobalt) is present in bacteria and animals. The chlorophyll ring system is a porphyrin derivative in which a double bond in one of the pyrrole rings has been reduced. A fused cyclopentanose ring is also present. Chlorophyll absorbs wide range of visible radiations including low energy light in far-red region (700nm). The exact frequency depends on the nature of the substituents on chlorophyll. Structure of chlorophyll is as given in figure 2.17.

In view of the capabilities of porphyrins to bind and release gases and to act as active center in catalytic reactions in biological systems, porphyrin-based films on metal or semiconductor surfaces are extremely appealing as chemical and gas sensors as well as nanoporous catalytic materials, in novel synthetic bio-mimetic devices etc.
Moreover, the role of porphyrins in photosynthetic mechanisms indicates a good attitude of these molecules to mediate visible photon-electron energy transfer process. As shown in figure 2.19, the UV-visible absorption spectrum of highly conjugated porphyrin macrocycle exhibits an intense feature at about 400 nm (the soret band), followed by several weaker absorptions (Q bands) at higher wavelength (from 450 to 700 nm). While variations of the peripheral substituents on the porphyrin ring often cause minor changes to the intensity and wavelength of the absorption features, protonation of the two inner nitrogen atoms or the insertion /change of metal atoms in to the macrocycle usually strongly change the visible absorption spectrum for this reason.

In recent years, porphyrins and porphyrin-metal interfaces are of major interest for applications in optoelectronics, data storage and solar cells$^{142,143}$ and a still increasing number of covalently linked donor-acceptor supramolecular porphyrin-based assemblies have been studied for these purposes$^{144}$. 

![Figure 2.17. The structure of chlorophyll](image-url)
The involvement of porphyrins in many biological processes and the possibility to tailor their physical and chemical properties at the molecular level—including very large dipole moments, polarisability, non-linear optical response absorption spectrum, energy transfer and catalytic properties make porphyrins and metalloporphyrins extremely versatile synthetic base materials for research projects in many discipline of chemistry and physics, like electronics, optoelectronics, electrochemistry, catalysis and photophysics.

Hemoglobin and myoglobin are respiratory proteins which serve to transport and store oxygen essential to the life of all vertebrates. Myoglobin, the oxygen binding protein in muscle tissues, responsible for the storage and transport of oxygen across membranes, is composed of 153 residue peptide and iron (II) protoporphyrin complex. The active site in hemoglobin and myoglobin is the heme tightly bound to a protein (globin) through about 80 hydrophobic interactions and a single co-ordinate bond between the imidazole of the proximal histidine and iron.

In most of the biological systems mentioned above, the porphyrin moiety (heme part) occurs as one of the units in big protein assembly. The heme is often covered and buried at specific sites by the long chain of the protein residue. The steric crowding of protein chains around it can cause some tilt or puckering in the planar π frame work of the metalloporphyrins. Such a distortion would cause a decrement in the extent of overlap.

**Figure 2.18.** UV-visible absorption spectrum of porphyrin
of certain \( \pi \)molecular orbitals of the macrocycle with symmetry matching metal orbitals thus causing an enforced strain in the molecule. The tendency of this entatic species would be to release the strain, which is supposed to be the driving force for this species to behave as biological catalyst. The capped porphyrins along with many others specifically designed metalloporphyrins have modeled\(^{147}\).

The versatile characteristics of haemoglobin and myoglobin ubiquitous porphyrin molecule can be attributed to the highly delocalized \( \pi \) electron system, which is very sensitive to various factors. It has been proved that the electronic structures and the redox potential of the macromolecule can be modified in many ways. A thorough knowledge of the various factors and their effects is necessary to modify the compound for ones advantage. The important factors to be considered are the following. (i) The nature of the peripheral substituents has a great ability to tune the electronic levels of porphyrins and metallophrphyrins. Electron withdrawing groups on the pyrrole \( \beta \)- carbons make them better oxidizing agent while electron releasing groups give them reducing characteristics. (ii) The nature of the central ion has a pronounced effect on the electronic property of porphyrin. The nature of the interaction between the metal ion and the porphyrinato moiety is such that both the species mutually influence their electronic levels. (iii) The porphyrinato moiety is capable of stabilizing metal ions in their unusual oxidation states. Since the ligand d electron count and relative energy of orbitals get altered on changing the oxidation states, the nature of resulting metalloporphyrin also get modified. (iv) There is a thermodynamic drive for square planar complexes to add on axial ligands if available so as to get octahedral geometry. Both the metal electronic levels and porphyrinato orbital energies get affected by such change in geometry. (v) Steric effect of large bulky groups attached and structural distortion thus arising will affect the properties of porphyrins. When large bulky groups are attached on the \( \beta \)-pyrrole positions, planarity of the molecule will be lost and distortion will take place. Such distortions are supposed to play an important role in altering the electronic structure.

Porphyrins and their metal derivatives exhibit enormously rich and novel photochemistry, which is widely used in carrying out several special reactions and in mimicking biological systems. Model light harvesting complexes are prepared by zinc and porphyrin
free base building blocks\textsuperscript{148}. Many issues concerning the origin of different light harvesting phenomena in natural systems remain unclear. In artificial systems notably in photodynamic therapy\textsuperscript{149} more emphasis is placed on generating singlet molecular oxygen and reaction usually proceeds through the longer-lived triplet excited state of the porphyrin.

### 2.7.2 Synthesis of porphyrin

The mechanism for the formation of the porphyrin macrocycle from the reaction of pyrrole and aldehyde has been proposed by several workers\textsuperscript{150–154}. The reaction between pyrrole and aldehyde in acid medium leads to the formation of protonated aldehyde which attacks the 2-position of the pyrrole with the loss of water molecule (scheme 2.9).

\[ \begin{align*}
\text{Scheme 2.9.} \quad \text{The reaction between pyrrole and benzaldehyde} \\
\text{The carbonium ion formed attacks the free } \alpha \text{-position of another pyrrole and functional group of which continue further condensation. This chain building process results in tetrapyrrolylcarbinol and polypyrrolyl by-products. These open chain tetrapyrrolylcarbine can undergo cyclisation to form porphyrinogen, chlorine, phlorin and other cyclic tetrapyrroles (scheme 2.10).}
\end{align*} \]

The phlorin formed by ring closure could either rearrange to chlorin or get oxidized to porphyrin. There are two general approaches to obtain a desired porphyrin: (1) by modification of a naturally occurring porphyrin (e.g. heme); or (2) by total synthesis. Although convenient, modification of naturally occurring porphyrins poses great limitations on the choice of peripheral substituents because certain substituents cannot be modified easily. In most cases, such limitations can be overcome by total synthesis, which involves the syntheses of the pyrrole sub units having the required substituents.
Scheme 2.10. Synthetic tracks to TPP

The following are the methods commonly used in porphyrin total synthesis.

- Tetramerisation of monopyrroles
- Condensation of dipyrrolic intermediates
- Cyclisation of open chain tetra pyrroles
- Other methodologies

To synthesize porphyrins containing only one type of substituent, tetramerization of monopyrroles is often used. One approach involves the reaction between a 2,5-disubstituted pyrrole and an aldehyde providing the bridging methine carbons (scheme 2.11). This method has also been used in the synthesis of various meso-tetraarylporphyrins, including meso-tetraphenylporphyrin (scheme 2.12).

Scheme 2.11. Synthesis of substituted porphyrins
Another approach of monopyrrole tetramerization involves the self-condensation of 2-acetoxymethylpyrrole or 2-N,N-dimethylaminomethylpyrrole (scheme 2.13). More recently, similar condensation with 2-hydroxymethylpyrroles have been carried out to synthesize various porphyrins, including porphyrins that are centrosymmetric (containing two types of substituents situated in alternate positions).

**Scheme 2.13.** Synthesis of substituted porphyrin

### 2.7.3 Functionalisation of porphyrins of porphyrin

The chemical transformation of natural and synthetic porphyrin macrocycles and their peripheral substituents have been an important research area\textsuperscript{134}. Through the modification of hemin and its biosynthetic precursors, nature produces a wide variety of biologically important molecules. Thus, many of the synthetic modified porphyrin compounds have been used as models for natural porphyrin systems. Based on theoretical electron density calculations, the nucleophilic and electrophilic substitution reactions occurring on porphyrins take place preferably at the meso positions and, on chlorins, the favoured meso positions are those adjacent to the reduced pyrrole ring. Steric considerations are
very important since the bulky peripheral substituents shielded some of the sites on the porphyrin periphery.

2.7.4 Introduction of new substituents

Porphyrs undergo a number of chemical reactions typical of aromatic compounds. For example, electrophilic substitution reactions are often performed on porphyrins. The methine (meso) carbons and the beta-pyrrolic carbons participate in these reactions. Furthermore, certain substituents on a porphyrin molecule can be modified. This leads to the availability of a variety of different porphyrins. Another important feature of porphyrins is their ability to be metallated and demetallated. A number of metals (e.g. Fe, Zn, Cu, Ni) can be inserted into the porphyrin cavity by using various metal salts. Removal of the metal (demetallation) can usually be achieved by treatment with acids of various strengths.

(a) Electrophilic substitution

The Vilsmeier formylation (using POCl$_3$/DMF) of the copper (II) and nickel (II) complexes of porphyrins and chlorins is an efficient and reproducible method, widely used for over 30 years for the preparation of meso- and $\beta$-substituted porphyrins and chlorins. Poly formylation is achieved upon prolonged treatment of the metalloporphyrins and metallochlorins with excess Vilsmeier reagent.$^{155,156}$

(b) Nucleophilic substitution

The $\pi$-cation radicals of metalloporphyrins and metallochlorins react with various nucleophiles (e.g. nitrite, pyridines, imidazole, cyanide, thiocyanate, triphenyl phosphine, chloride, acetate, azide) affording the corresponding meso-substituted metalloporphyrins and metallochlorins.$^{157,158}$ Demetallation then gives the meso-substituted porphyrins and chlorins.

The porphyrin ring is very stable to concentrated acids (e.g. sulphuric acid), and can exhibit characteristics of both acids and bases. Strong bases such as alkoxides can remove
protons from the inner nitrogen atoms of a porphyrin to form a dianion. Conversely, the two pyrrolic nitrogen atoms bearing lone pairs of electrons can be protonated easily with acids such as trifluoroacetic acid$^{159-160}$. The aromatic character of porphyrin has also been established with visible and NMR spectroscopy.

## 2.8 Porphyrin Bound Linear and Dendritic Macromolecules

In recent years, several types of polymeric porphyrin systems have been synthesized. Polyvinyl alcohol, polyethylene glycol, and linear polyglycerol are linear polymeric systems having free hydroxyl functional groups which can be used to bound with any macrocyclic molecules having functional groups which can undergo condensation reaction with the OH groups. Porphyrin macrocycle which can be functionalized at its meso position easily with COOH, SO$_3$OH etc groups can undergo condensation reactions with the OH groups of the linear or dendritic polyglycerol systems. This polymer supported porphyrin system found many applications in the field of biomimetics, catalysis, NLO, drug-delivery system etc.

Absorption anisotropy and emission anisotropy measurements of polyvinyl alcohol-porphyrin derivatives are reported. Wavelength dependent absorption anisotropy in oriented PVA films, and wavelength dependent excitation spectrum of emission anisotropy of fluorescent porphyrin derivatives in anisotropic PVA films indicate the presence of multiple transition moments with different well-defined orientation. Comparison of linear dichroism and orientation behavior in stretched PVA films of deuteroporphyrin and its iron derivative reveals significant out-of-plane transition moment components. A considerable participation of out-of-plane polarized absorption components is also observed for metal substitutions in porphyrin rings, do not produce circular degeneration of electronic transition moments. Instead, the presence of metal induces absorption components orthogonal to the porphyrin plane$^{161}$.

The catalytic efficiency of porphyrin complexes can be improved by coupling it with a
polymeric system with ionic polymer-porphyrin linkage because of the ideal compatibility of these systems with polar medium when employed for catalytic reaction\textsuperscript{162}.

The single step synthesis of a Fe (II) porphyrin cored hyperbranched polymer, possessing similar size and topology to the natural heme containing proteins, is reported. UV spectroscopy successfully demonstrated the ability of this polymer to reversibly bind oxygen\textsuperscript{163}. A suitably functionalised porphyrin unit could act as an initiator core and be incorporated at the center of a HBP. If the environment around the central porphyrin could be controlled, then a hemoglobin/myoglobin mimic could be obtained using just one synthetic step. A porphyrin cored hyperbranched polyester was therefore synthesized by reacting an excess of the branching monomer, 3-5 diacetoxy benzoic acid (95mol\%, with a small amount of the core unit tetrakis(4-acetoxyphenyl)porphyrin (5mol\%) under reversible trans esterification conditions (scheme 2.13)\textsuperscript{163}. The purified polymer had a MW of 37,0000D and a relatively narrow polydispersity of 2.25 (relative to HBPs synthesized with out core units) and a degree of branching equal to 49\%. This polymer could reversibly bind oxygen, with the potential to be applied as a future artificial blood product\textsuperscript{164–168}.

The above said oxygen binding polymer-porphyrin system is not water soluble and less biocompatible compared to water-soluble and amphiphilic, porphyrin cored hyperbranched polyglycerol (figure 2.19). Hence studies are progressing on this and related polymers for use as a biocompatible and safe artificial blood product for human use\textsuperscript{169}.

\textbf{Figure 2.19.} Schematic representation of a water-soluble hyperbranched polyglycerol for application as an artificial blood product
Scheme 2.14. Porphyrin cored hyperbranched polymer having oxygen-binding capacity

2.9 Porphyrin Bound Linear and Dendritic Polymers for Photophysical and Medical Applications

The porphyrins and their derivatives find a lot of applications and are used in photodynamic therapy of cancer, in laser technology, in light to electrical energy conversion, in optoelectronics and others. Consequently the investigations of processes occurring after light absorption are needed. Attaching different substitutes to the tetrapyrrole ring can modify Photophysical properties of porphyrin dyes. The high amount of coloured compounds is a powerful tool to design material for processes driven by the visible light with good efficiency\textsuperscript{170}.

The dendrimers and hyperbranched polymers have proven to be extremely versatile, al-
ollowing complete control over locations, as well as overall solubility. The aliphatic polyether
dendrimer, terminated by alcohol groups are water-soluble and appeared to be harmless
in recent animal studies. These polymers are ideally suited for applications as varied as
targeted drug delivery, light harvesting, and energy conversion.

2.10 References

   34, 925-934 (1996).


164. http://www.biopolymer.group.shef.ac.uk


