

A Review of Synthesis, Characterization and Applications of Functionalized Dendrimers

Ebelegi Newton Augustus¹, Ekubo Tobin Allen², Ayawei Nimibofa^{1,*}, Wankasi Donbebe¹

¹Department of Chemical Sciences, Niger Delta University, Wilberforce Island, Nigeria

²Department of Chemistry, Federal University Otuoke, Nigeria

Abstract Dendrimers are multipurpose, nanosized particles that can be functionalized with various chemical procedures. The ability to control and engineer Critical Nanoscale Design Parameters such as architecture, shape, size, rigidity, flexibility, composition and surface chemistry offers a catalog of possibilities for utilizing dendrimers as modules for the thriving Nanotechnology industry. Contributions from researchers with various scientific backgrounds who have worked on different objectives that resulted to several applications of functionalized dendrimers are cited in this review.

Keywords Dendrimers, Functionalization, Synthesis and applications

1. Introduction

As part of a grand scheme to understand the evolution of natural building blocks, students of chemistry all over the world are trying to incorporate natural architectural techniques into the synthesis of compounds. This ushered in an era of macromolecules and polymers. In chemistry the term “macromolecule” means aggregates of two or more molecules held together by intermolecular forces. [1]

The term ‘dendrimers’ comes from two Greek words “dendron” which means tree and “meros” which means parts, therefore referring to the typical tree-like appearance of these compounds [2]. Dendritic polymers are recognized as the fourth major architectural class of polymers after the three well known types (linear, cross-linked and branched polymers). They have grown dramatically over their about 27 years history. Presently, over 50,000 patent and literature citations related to this important class of polymers have appeared [3]. Dendritic structures are wide spread motifs in nature that are often utilized where a particular function needs to be enhanced or exposed. Dendrimers are extremely branched, globular, multivalent, mono-dispersed molecules with synthetic elasticity and many possible applications [4]. The structure of a typical dendrimer is characterized by three distinct features namely; a central multifunctional ‘core’ generations or tiers of multifunctional repeating units which are attached to the core and the terminal or end groups. Manipulating these structural features of dendrimers allows controlled synthesis of a whole series of highly branched

end-functionalized macromolecules that are drawing increased attention for many potential applications [5].

The analysis of interactions between dendrimers and solid surfaces promises to provide very vital information that can expand the possibilities of using dendrimers adsorbed on solids as new adsorbents. Dendrimers can be used to modify properties of solid surfaces in order to produce composite materials that could be compactable with different kinds of environments therefore, enhancing the range of applications of dendrimer – surface supramolecule systems [6]. Because of the solvent accessibility of dendrimer voids, direct molecular design of dendrimers include; chemical modifications of their interior and periphery [7]. Rigid dendrimers seem to be suitable models for adsorption studies because they remain as solids in a wide range of temperature.

Dendrimers are used in drug delivery carriers, fuel cells, light emitting diodes liquid crystals chemical modification and membrane separation [8]. In recent times the attention of most researchers and scientific investigators has been focused on the free dendrimer while the properties and applications of functionalized dendrimers (supported dendrimers) are barely reported.

2. History of Dendrimers

In the design of plants and animals nature often ends up creating dendritic solutions to enhance particular properties as evidenced in the respiratory system of animals. Similarly, above the soil plants make use of their dendritic features to enhance the exposure of their leaves to sunlight also beneath the ground they have the maximum need to expose a large functional surface when collecting water from the soil. Therefore a dendrimer is both a covalently assembled molecule and a distinct nanoparticle [3]. The very first

* Corresponding author:

ayawei4acad@gmail.com (Ayawei Nimibofa)

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successful attempt to create and design dendritic structures by divergent synthesis was carried out by Fritz Vögtle and coworkers in 1978, followed by R.G. Denkewalter at Allied corporation in 1981, Donald Tomalia at Dow chemicals in 1983 and George Newkome in 1985. In 1990 Jean Frechet introduced the covagant synthetic approach. Although a lot of researchers have concluded work in studying the different properties and applications of dendrimers but another school of thought believes the research on the properties and applications of dendrimers is still in its infancy.

Table 1. Names of dendrimer and their inventors

S/no	Type of Dendrimer	Inventor	Year
1	Poly(Propylene Imine) PPI dendrimer	Vögtle <i>et al.</i>	1978
2	PolyAmido-Amine PAMAM dendrimer	Tomalia <i>et al.</i>	1983, 1985
3	Arbosols	Newkome <i>et al.</i>	1985
4	Poly(aryl ether) dendrimer	Frechet and Hawker	1990
5	Polylysine dendrimer	Denkewalter <i>et al.</i>	1981
6	Polyether dendrimer	Frechet and Grayson	2001

3. Structure of Dendrimers

Each component of a dendrimer performs a specific function and at the same time defines some other properties as it grows from generation to generation [9]. The central core acts as the molecular information hub from which shape, size, multiplicity and directionality are articulated through a covalent connectivity to the functional groups at the periphery. The Generations are the branched cell amplification region which defines the type and volume of internal void space created as the dendrimer grows. The internal voids determine the extent and nature of guest – host properties that that can be achieved in any particular dendrimer family. The surface functional groups are reactive

or passive terminal groups that can perform numerous functions.

4. Synthesitic Routes

Dendrimers are generated by changing functionality in each of their constituent parts (core, inner shell and periphery) to index properties such as solubility, thermal stability and addition of compounds for particular applications. Dendrimers are assembled from multifunctional core which is extended outward by a series of reactions called Michael addition reactions [8]. Each step of the reaction must be driven to conclusion in order to prevent trailing generations (some branches becoming shorter than others). The presence of trailing generations (impurities) can create negative impacts on the symmetry and functionality of the dendrimer, besides dendrimers are very difficult to purify because the relative size difference between perfect and imperfect dendrimers is diminutive. It is also a known fact that synthetic procedure can be applied to manage the size and number of branches on a dendrimer. There are two established methods for dendrimer synthesis, divergent and convergent synthesis, the choice of method for synthesis depends greatly on the target end application.

Divergent Dendrimer Synthesis

In the very early years of dendrimers, the synthetic approach to produce the two major dendrimers (PPI and PAMAM) relied on a step by step divergent strategy. Here the creation of the dendrimer takes place in a stepwise manner which begins from the core, followed by the build-up of the molecule towards the periphery using two basic operations namely; coupling of the monomer and secondly transformation of the monomer end-group to create a new reactive surface for the coupling of a new monomer. These two steps can be repeated several times to form different generations (tiers) of dendrimers with each generation having arms from previous generations [10].

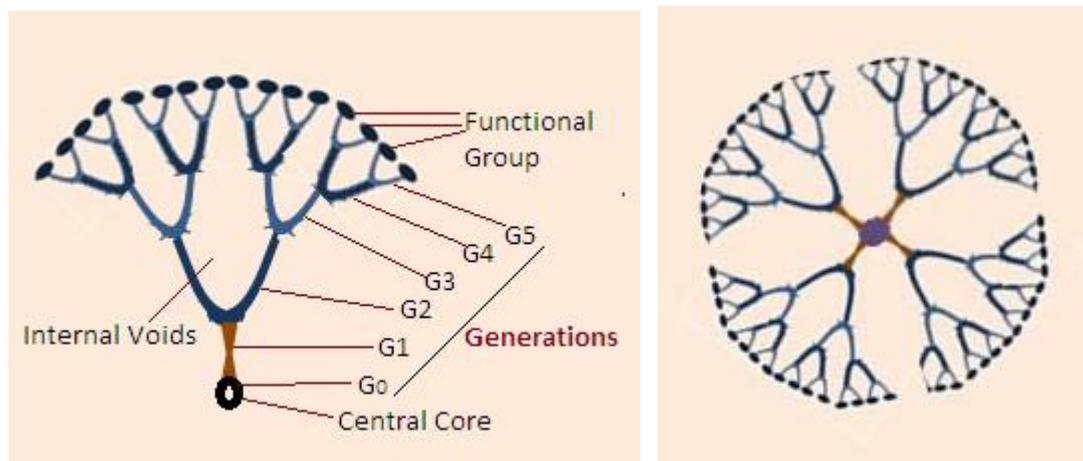


Figure 1. Schematic representation of the Dendrimer Structure. Adopted from reference [42]

This divergent route for dendrimer synthesis is believed to be advantageous and very useful for commercial scale production because of high yield but with low purity. Impurities are encountered in the divergent synthesis of dendrimer as a result of either of the following side reactions missing repeating units, intra molecular/intermolecular cyclization or retro-Michael addition.

Convergent Dendrimer Synthesis

This method of dendrimer synthesis constructs a dendrimer from its surface and inwards towards the core via a one to one coupling of monomers thereby creating dendritic segments of increasing sizes as the synthesis progresses. During convergent synthesis of dendrimers the number of reactive sites found during the proliferation stage is usually minimal and this results to faster reaction rates with better yields. There is a large molecular difference between reactant molecules and products and this in turn facilitates the separation of products from reactants during purification. The convergent route of dendrimer synthesis is a practical means of producing dendrimers with mixed structural features because different segments are coupled together to generate dendrimers that possess heterogeneous morphologies [11, 12]. The creation of dendrimers with heterogeneous morphologies opens up the fascinating fields of incorporating multiple active sites in one dendrimer to develop macromolecules with multifunctional design.

The convergent synthetic route for dendrimer synthesis has been used for the synthesis of a wide range of dendrimers bearing different core functionalities, where the core is introduced at the last step of synthesis [12]. Therefore this methodology has facilitated the development of dendrimers with different core functions. Additionally, dendrimers synthesized by this route have less impurities with more monodispersity and symmetry because better purification is achieved before dendrons are finally attached to the core. However, the size of dendrimers synthesized via this route have limitations due to steric hindrance between dendrons trying to get attached to the core.

5. Functionalization of Dendrimers

Functionalization of dendrimer is the process of incorporating multiple active sites in dendrimers in order to create macromolecules with multifunctional architecture. Functionalized dendrimers also known as structurally controlled dendrimers have at least six well defined nanoscale features known as Critical Nanoscale Design Parameters (CNDPs) such as size, shape, surface chemistry, flexibility, rigidity, architecture and elemental composition [13].

These Critical Nanoscale Design Parameters may be thoroughly manipulated to produce a wide range of new emerging properties that may be desirable and also critical for many industrial and commercial applications.

Owing to systematic considerations, functionalization is

usually introduced into the dendrimer framework at either the core or periphery or even both [14]. X, Shi *et al.*, reported the crucial role played by dendrimers in the synthesis of dendrimer-stabilized Nano-Particles, the metal ion is usually complexed with dendrimer ligands such as interior tertiary amines and surface functional groups through coordination or electrostatic interactions [15]. Similarly, Harmilton *et al.*, investigated the hydrophobic modification of G5 hydroxyl terminated PAMAM dendrimer by conjugation with dodecyl chloroformate and cholesteryl formate [16]. Welton and Stoddart also gave an account of the hydrolysis of ester-terminated PAMAM dendrimers with hydroxides of group I elements resulted in the formation of white hygroscopic powders (salts) [17].

6. Characterization of Dendrimers

Dendrimers concern both molecular chemistry because of the step by step synthesis approach used during their synthesis and Polymer chemistry due to their repetitive structures that are made up of monomers. Therefore they are usually characterized using analytical techniques from both fields. Analytical techniques are used to investigate the chemical composition, morphology, shape, polydispersity, homogeneity, synthesis, conjugation, reaction rates, molecular weight, structural defects and purity of dendrimers [18]. They include spectroscopic methods, scattering techniques, microscopic methods, chromatographic techniques, electrical techniques and rheological / physical properties analysis.

Spectroscopic Techniques

Spectroscopic analytical methods are based on measuring the amount of radiation produced or absorbed by molecular or atomic species of interest. Spectroscopic methods have provided perhaps the most widely used tool for elucidation of molecular structure as well as quantitative and qualitative determination of both inorganic and organic compounds [19].

Ultraviolet – Visible Spectroscopy: This technique provides the proof of synthesis as well as surface modification on dendrimers due to characteristic absorption maximum or shift in value of lambda max (λ_{max}). UV-Visible spectroscopy is also used to detect the functional moieties attached to dendrimer molecules. Characteristic curves in UV-Vis spectroscopy shows the specific maximum absorption peaks at specific wavelengths which is ascribed to the contribution of a conjugated moiety. Tulja *et al.* reported the use of UV- Vis spectroscopy for the characterization of dendrimer – Gold Nanocomposite material [20].

Infra – Red Spectroscopy: Infra-Red (IR) spectroscopy provides information for routine analysis of the chemical transformations at the surface of dendrimers [3]. Thus it is an analytical technique applied for the determination of synthesis, functional groups, conjugation and drug-dendrimer interaction. Kolev *et al.* investigated the

occurrence of hydrogen bonding in Polypropylene Imine(PPI) glycine functionalized dendrimers [21]. Similarly, Kolhe *et. al.* showed that the disappearance of aldehydes during the synthesis of PMMH dendrimers reflects synthesis and surface modifications [22].

Nuclear Magnetic Spectroscopy: Nuclear Magnetic Resonance spectroscopy allows the determination of structure and dynamics of molecules in solution [19]. Victoria *et. al.* used one-dimensional and two-dimensional NMR studies to probe the conformation of melamine dendrimer which bears unique NMR signals from the core to the periphery [23].

Raman Spectroscopy: Raman spectroscopy is a technique used to study vibration, rotational and other low-frequency forms in a system. This technique was applied by Furer *et. al.*, in the study of cyclodehydration of polyphenylene dendrimers and the characterization of polypropylene Imine(PPI) and phosphorus dendrimers [24].

Fluorescence spectroscopy: Fluorescence spectroscopy is a type of electromagnetic spectroscopy which analyzes fluorescence from a sample. Fluorescence spectroscopy provides valuable information regarding the interaction between chemical additives and dendrimers. Size and shape of molecules can be determined with the help of fluorescence spectroscopy [19]. Wang and Imae reported a strong fluorescence emission from fourth generation(G4)NH₂ – terminated PAMAM dendrimer upon adjusting the pH value [25].

Atomic force microscopy (AFM): AFM provides a three-dimensional surface profile and better resolution. Atomic force microscopy (AFM) is a very useful technique to characterize the structure and behavior of the dendrimer agents. Pan *et. al.*, fabricated and characterized Polyamidoamine dendrimer modified multiwalled carbon nanotubes by AFM [26].

X-ray photoelectron spectroscopy (XPS): X-ray photoelectron spectroscopy is also known as Electron Spectroscopy for Chemical analysis (ESCA). It is a quantitative spectroscopic technique utilized to measure elemental composition, empirical formula, chemical state, thickness of one or more thin layered dendrimers (1–8 nm) and electronic state of the elements that exist within dendritic framework [19]. Gates *et. al.*, studied the synthesis and characterization of melamine-based dendrimers [27].

Microscopic Techniques

Scanning Electron Microscopy (SEM): Scanning Electron Microscopy is usually applied in the study of the surface topography of dendrimers. Dadapeer *et. al.*, applied Scanning Electron Microscopy (SEM) in studying a phenyl-OH terminated dendrimer in order to get a deeper understanding of its surface properties [28].

Transmission Electron Microscopy (TEM): Transmission Electron Microscopy (TEM) is a microscopic technique in which a beam of electrons is transmitted through an ultra-thin specimen, interacting with the specimen as it passes through it. An image is formed from this interaction

and it is magnified onto an imaging device. Jackson *et. al.*, applied TEM in examining Poly(Amidoamine) PAMAM dendrimer molecules in order to ascertain average size, shape and size distributions for G10 to G5 [29].

Electro analytical Techniques

Electro analytical techniques are capable of producing low detection limits and a lot of characterization information describing electrochemically accessible systems such as Stoichiometry and rate of interfacial charge transfer, rate of mass transfer, the extent of adsorption and the rates and equilibrium constants for chemical reactions [30]

Electron Paramagnetic Resonance (EPR): This technique is applied in studying chemical species with one or more unpaired electrons such as organic and inorganic free radicals or inorganic complexes possessing transition metal ions. Ottaviani *et. al.* reported the use of Electron Paramagnetic Resonance in the investigation of the adsorption of dendrimers on homoporous silica, activated alumina and zeolite [7].

Electrophoresis: This technique provides useful information about the purity and homogeneity of several types of water-soluble dendrimers. Ottaviani *et. al.* investigated the purity of Poly(Amidiamine) dendrimers with the use of gel electrophoresis, mass spectrometry and ¹³C NMR spectroscopy [7].

Electrochemistry: In an inquiry about Copper adsorption on ChloropropylSilica gel surface modified with Nano structured DAB – AM-16 dendrimer Carmo *et. al.* employed cyclic-voltametry to identify the presence of a Reduction - Oxidation process which was attributed to a Copper complex [8].

Titrimetry

Titrimetry is usually applied in the determination of terminal groups in dendrimers. X. Shi *et. al.* used potentiometric titration to determine the number of primary amine and tertiary amine groups on the surface of functionalized Poly(Amidoamine) dendrimers [31].

Thermo Gravimetric Analysis (TGA)

Thermo gravimetric analysis measures weight changes in a sample with respect to changes in temperature. In the same way, Differential Thermal Analysis (DTA) reveals if the changes were exothermic or endothermic. Therefore TGA-DTA measures heat flow and weight changes in a material as a function of temperature in a controlled atmosphere. Dadapeer *et. al.* considered the thermogravimetric analysis of a phosphorus containing dendrimer with diphenylsilanediol as core unit. The thermal stability and changes in weight with respect to change in temperature of dendrimer molecules were studied by TGA-DTA [28].

7. Applications of Dendrimer

In view of the fact that the core, interior and surface of

dendrimers can be functionalized to suit various applications, more than fifty families of dendrimers with unique properties have been developed [32]. Their unmatched molecular consistency, multifunctional surface and unique internal cavities makes dendrimers suitable for a number of wide range high technology uses as shown in Fig.2 below.

Biomedical: Functionalization of dendrimers creates room for possible control over architectural design, shape, size, branching, density and surface functionality. The formation of particulate systems with well-defined sizes and shapes is of prominent interest in certain medical applications such as drug delivery [33].

Pravinkumar *et al.*, reported the possibility of encapsulating drug molecules within the branches of dendrimers that it offers the potential of dendrimers to interact with poorly soluble drugs, enhance drug stability, bioavailability and control of drug release [34]. Their size, ease of preparation, functionalization and possibility to attach multiple surface groups renders dendrimers as suitable vehicles for ophthalmic drug delivery [35]. Vandamme *et al.*, reported improved residence time of Pilocarpine in the eyes with the use of Poly(Amidoamine) dendrimer with carboxylic or hydroxyl surface groups [36]. Wang *et al.*, also investigated the utilization of Polyhydroxylalkanoate (PHA) and G-3 Poly(Amidoamine) dendrimer in novel transdermal drug delivery systems [37].

Environment: Dendrimers have large number of surface functional groups with which they can attach to different surfaces, such dendrimer supported surfaces could act as useful adsorbents for analytical and electro-analytical procedures in environmental studies. Shahbazi *et al.*, accounted the use of functionalized SBA-15 mesoporous silica gel with Poly(Amidoamine) dendrimer (PAMAM-SBA-15) for the removal of Cu(II), Pb(II) and Cd(II) ions from aqueous solutions [38]. Similarly, Carmo and Piam reported their investigation of Copper adsorption

on Chloropropylsilica gel surface functionalization with G-3 Poly(Propyleneimine)hexadecaamine dendrimer (Dab-Am-16) [8]. In like manner, Defever *et al.*, investigated the remediation of Naphthalene by 3rd – 6th generation Poly(Amidoamine) dendrimer and graphene oxide(GrO). The report reveals the potential applications of these nanomaterials in removing PolyAromatic Hydrocarbon (PAH) contaminants from water [39].

Sensors: The unique structures and properties of dendrimers evolved interest in interfacing nanoscale dendrimers in the sensing of chemical and biological species. It is on record that various nanoparticles are used in the development of miniaturized, rapid, ultrasensitive and inexpensive environmental monitoring devices. Touzani reported that a Poly(Amidoamine) dendrimer with 1,8-Naphthalinamide surface groups is capable of acting as a Photo induced Electron Transfer (FET) fluorescent sensor for rare earth metals and metal cations, his investigation showed that the presence of metal ions evolves a Photo induced Electron Transfer (PET) leading to an enhancement in the fluorescence [33].

Nanotechnology: Organic electronic devices such as organic thin-film transistors, organic solar cells and organic optical detectors are described as linear or branched dendrimer compounds incorporating a specific component that acts as hole-injecting, hole-transporting or hole-blocking materials [36]. One feature of dendrimers that has attracted attention is its nanostructure. Dendrimers can encapsulate insoluble materials such as metals and transport them into a solvent within their interior [8]. Cooper *et al.*, accounted for the extraction of strongly hydrophilic compounds from water into liquid CO₂ using fluorinated dendrimers [40]. In the same vein X, Shi *et al.*, reported the synthesis, characterization and manipulation of dendrimer-stabilized Iron Sulfide nanoparticle that is very active in the reductive dechlorination of chlorinated hydrocarbons [15].



Figure 2. Schematic representation of applications of functionalized dendrimers

Catalyst: Dendrimers have been used in large quantities as catalysts because of their many active sites which make them intermediates between homogenous and heterogeneous catalysts and also the possibility of encapsulating a single catalyst site whose activity can be enhanced by the dendritic superstructure. Mizugaki et al. examined the selective hydrogenation of conjugated dienes to monoenes using an atmospheric pressure of hydrogen gas at 25°C by the dendritic catalyst DAB-dendr-[N(CH₂PPh₂)₂PdCl₂]₁₆ [40]. Newkome [41], Brunner [42], Majoral [43] and other researchers are working hard to find the best catalysts with very good efficiency.

Industrial Processes: Dendrimers have been applied for the improvement of most industrial processes such as; catalysis, micro fabrication, photodynamic therapy, optical data storage, environmental remediation, adsorption, printing/photography and membrane filtration.

8. Conclusions

An elevated level of control over the structural design of dendrimers has been demonstrated by the evolving tapestry of emerging techniques for the synthesis of dendrimers. Structural and functional groups can be incorporated into dendrimers in specific positions potentially giving the chemist so much control over dendritic architecture and functionality. However, more work should be done in order to make the process of functionalizing dendrimers more cost effective.

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