

The logo for 'cientifica' features the word in a white, lowercase, sans-serif font. A small, stylized graphic of a yellow and orange flame or brushstroke is positioned above the letter 'i'.

Dendrimers

Technology White Papers
nr. 6

The background of the cover is a dark, abstract image. It features a horizontal band of purple and blue light at the top, with a bright cyan and green glow below it. The lower portion of the image is filled with numerous vertical, blurred streaks of light in various colors, including purple, blue, green, yellow, orange, and red, creating a sense of depth and movement.

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DENDRIMERS

Technology White Papers nr. 6

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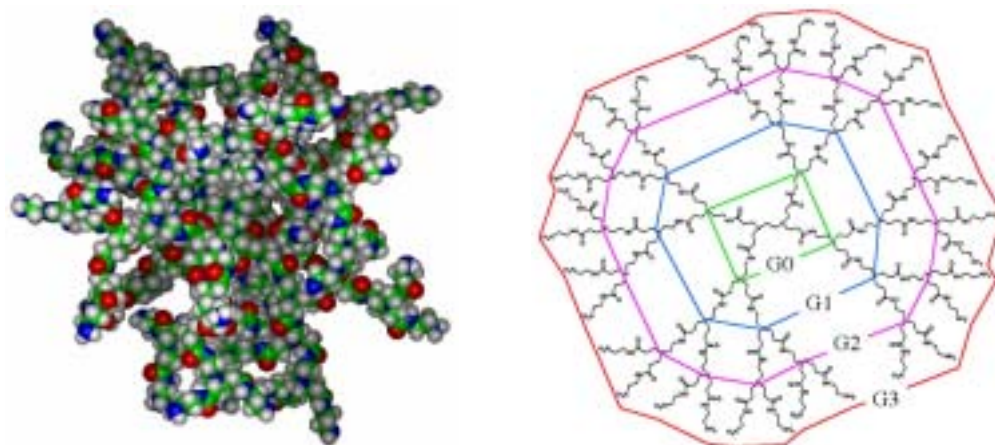
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Origin of Content

The free reports in this series are extracted from the technology reports that make up the Nanotechnology Opportunity Report collection and are designed to offer an introduction to the variety of technologies that fall under the nanotechnology umbrella. The full reports also include 'opportunities' sections, covering the various applications of the technology and their effects on markets, and a list describing the companies involved in the technology.

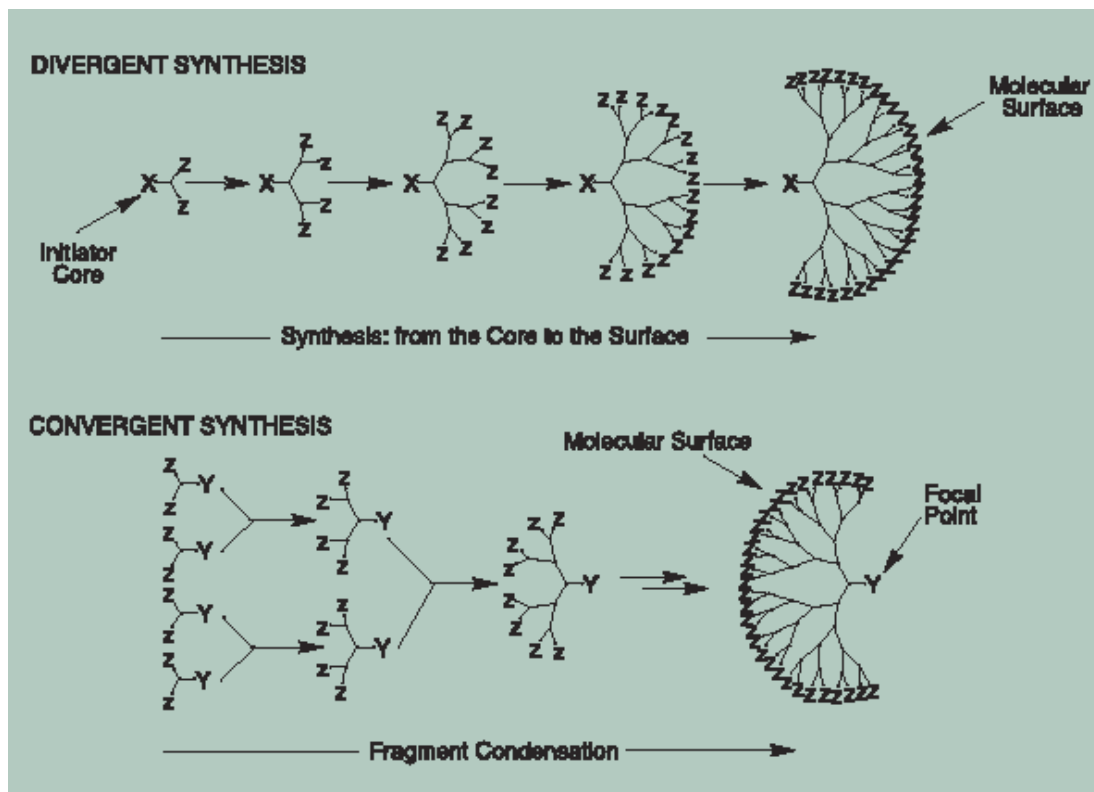
Introduction to Dendrimers



Dendrimer structure. Courtesy of Dendritech

Dendrimers are large and complex molecules with very well-defined chemical structures. From a polymer chemistry point of view, dendrimers are nearly perfect monodisperse (basically meaning of a consistent size and form) macromolecules with a regular and highly branched three-dimensional architecture. They consist of three major architectural components: core, branches, and end groups.

Dendrimers are produced in an iterative sequence of reaction steps, in which each additional iteration leads to a higher generation dendrimer. The creation of dendrimers, using specifically-designed chemical reactions, is one of the best examples of controlled hierarchical synthesis, an approach that allows the 'bottom-up' creation of complex systems. Each new layer creates a new 'generation', with double the number of active sites (called end groups) and approximately double the molecular weight of the previous generation. One of the most appealing aspects of technologies based on dendrimers is that it is relatively easy to control their size, composition and chemical reactivity very precisely.



Divergent and convergent methods for dendrimer synthesis

It has been suggested that the need to repeat reaction steps many times could lead to high manufacturing costs and thus hinder commercialization. However, the synthesis is, in most cases, just the iterative sequence of two straightforward chemical reactions, the reactants are normally cheap chemicals, and with each step the product practically doubles its weight. Consequently, the manufacture of dendrimers can be a cost-effective process and large-scale production is, in general, technically and economically viable. PPI and PAMAM dendrimers (explained later) are already being produced on a large scale by companies such as DSM and Dendritech, and can be ordered through the Sigma-Aldrich catalog, like any other common chemical compound.

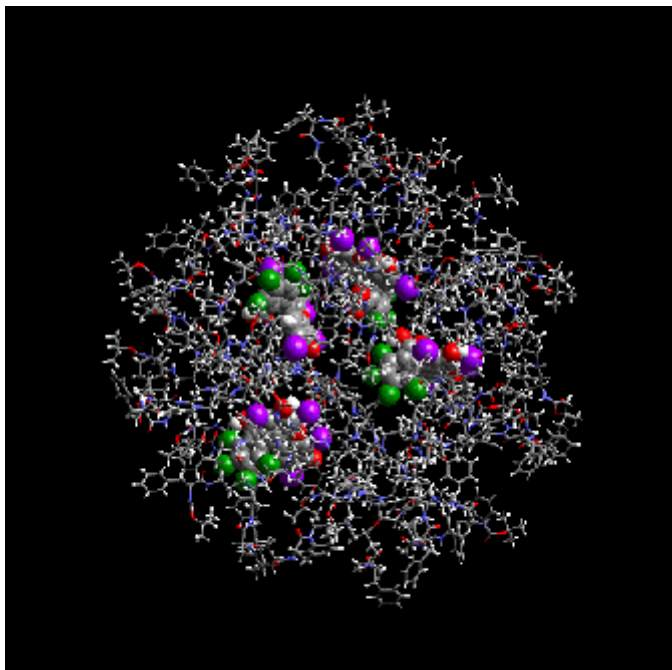
Derivatives of the classical well-defined dendrimers are currently being evaluated as potential alternatives offering lower production costs. Dow Corning Corporation, in collaboration with the Michigan Molecular Institute, has developed a new class of dendrimers, which contain PAMAM (see later) interiors and organosilicon (OS) exteriors. These nanobuilding blocks can form films, membranes and coatings with controlled hydrophilic (water-loving) and hydrophobic (water-hating) domains. They can be applied to the preparation of printed wire boards, sensors, catalysts, and drug delivery systems.

Hyperbranched structures are built in a similar way to dendrimers and they have a similar structure, but their architecture is not as precisely controlled (not all the

molecules in a batch look the same: they miss branches; there are more holes in the structure and fewer active chemical groups at the surface of the molecule). To make these 'imperfect' molecules, a far less rigorous optimization of the production process is needed (less care is required in ensuring that the synthesis steps have been completed). In some cases far fewer steps are necessary to produce hyperbranched structures, which leads to reduced production costs.

For many applications dendrimers do not have to be perfect to be useful and it is important to remember that hyperbranched structures could replace dendrimers in many such cases. Think, for example, of additives for lowering viscosity (where the requirement is simply for globular structures) or decontamination agents (where larger holes could even be an advantage for binding larger molecules). On the contrary, if multivalency (a large number of active chemical groups located at the surface of the dendrimer) and well-defined structure are needed, as is the case for biomedical applications, dendrimers are much better candidates.

The cavities present in dendrimers can be used as binding sites for small guest molecules, analogous to the way enzymes (natural catalysts, or promoters of chemical reactions) work in living organisms.



Dendritic box. Courtesy of the Eindhoven University of Technology, the Netherlands

The potential of dendrimers as hosts (containers) for small molecules was strikingly demonstrated in 1994 by Bert Meijer, chemistry professor at Eindhoven University of Technology in the Netherlands.

The 'dendritic box' was constructed by building a hard shell around the soft-core dendrimer once a small 'probe' molecule was encapsulated into the dendrimer. This structure

yielded a molecular container of nanoscopic dimensions.

Dendrimers are generally roughly spherical molecules with very well defined size and shape. This physical characteristic, combined with their thermally decomposable organic nature, makes them especially suitable for use as porogen (a pore-generating material). This can be applied in the creation of foams with optimized nanoscale pore sizes and distributions, such as synthetic zeolites for catalysis or low dielectric

constant materials (in simple terms, good insulators) for use in ever-shrinking integrated circuits. They have also been used as templates to obtain larger structures with particular characteristics. Recently, the first example of the formation of amorphous calcium carbonate by artificial methods was reported. The structures created used dendrimers as an organic template in an attempt to imitate nature in the way it constructs shells and bones (an example of the power of this sort of nanostructuring is nacre, or mother-of-pearl, which is extremely tough despite being largely made of the same material as chalk). However, the process is not yet completely understood and applications in the manufacture of artificial bone currently look remote, with other approaches a lot closer to market, such as the coating of artificial joints with nanograins of hydroxyapatite.

Dendrimers can also be grown around a template (acting as the core) and then cross-linked to fix the structure. The core can then be removed to create a cavity that selectively binds to the original template. This creates a structure that is imprinted at the molecular level and that has a specific binding site (like an artificial antibody) that can separate enantiomers (mirror image versions of a molecule, only one of which usually has the desired function), remove pollutants or catalyze reactions.

The fact that dendrimers are generally depicted as spherical molecules can be misleading. Dendrimers generally have a globular shape when they are held in a good solvent, or in a bulk material, or when the end groups are so bulky that they get in the way of each other's ability to move around, making the structure rigid (this is known as steric hindrance). However, 'bare' dendrimers are very flexible structures. When secondary interactions are introduced into the system (for example, those based on the affinity of the end groups for a particular surface or hydrophobic (water-hating) interactions that can lead to self-assembly), dendrimers have the ability to completely change their conformation to form layers or even self-assembled lipid-like structures. They can transform their shape from spherical to almost completely flat, if the interactions with the surface are adequate.

Self-organization, or self-assembly, is an approach to the construction of new nanomaterials, such as coatings, non-linear optic materials, polymer electronics, etc., that is receiving a lot of attention. The paradigm is being explored extensively in areas such as sol-gel chemistry and self-assembled monolayers. Many such applications are geared toward creating bulk materials, coatings being a predominant example. The self-assembly paradigm, however, also offers the possibility of creating discrete functional nanostructures, or even nanodevices, rather than bulk materials. The creation of nanocapsules or quantum dots in liquid phase (as opposed to creating them on a surface), for example, holds great promise for applications such as drug delivery or bioanalysis. Central to many of these approaches is the use of amphiphilic substances, which have hydrophobic (water-hating) and hydrophilic (water-loving) regions that cause them to spontaneously form nanostructures such as capsules, by virtue of one part of the molecule being repelled by the surrounding medium and another part being attracted by it. Dendrimers can be amphiphilic (see glossary) and thus can be persuaded to self-organize into nanoscale structures but have the added advantage that they can be designed with a very wide variety of chemical and physical

properties. These can be leveraged to produce self-assembled complex multifunctional units that really start to warrant the description of a nanodevice. Some examples will be given later.

Some of the most interesting applications for dendrimers, in a technical and commercial sense, are in the pharmaceutical and biomedical area. Dendrimers can be created that are biologically active or inert, and one of the attractions is that they can be designed for such properties from the bottom up. The molecules are small enough to pass into cells and can be used to deliver substances such as drugs, genetic material or chemical markers right into the cell. James Baker of the University of Michigan in Ann Arbor has built multi-purpose dendrimers that can deliver a drug, document that the drug is there and report back on the cell's response. This is a real example of a multifunctional nanodevice.

On a slightly simpler level, the ability to engineer all sorts of behavior into dendrimers holds promise for a number of biotechnology and medical applications. For example, dendrimers have been deployed as transfection agents (carrying and incorporating foreign genetic material into cells), for mediating transport across cell membranes, or for binding particles to inhibit an immune response.

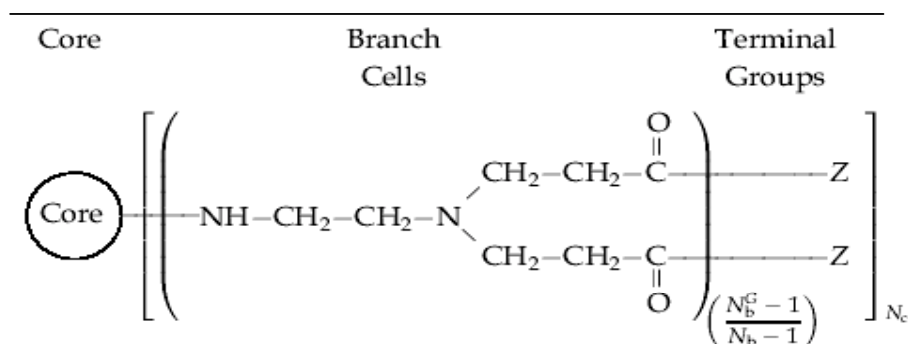
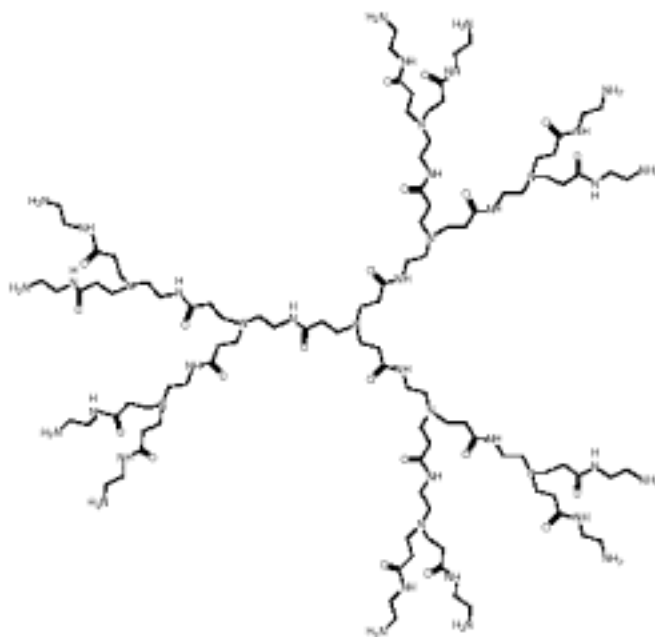
Types of Dendrimers

This section is quite technical in nature.

Thanks to recent advances in synthetic chemistry and characterization techniques, a rapid development of this new kind of polymer has been possible and a variety of dendritic scaffolds has become accessible with defined nanoscopic dimensions (3-5 nm for high generations) and discrete numbers of functional end groups.

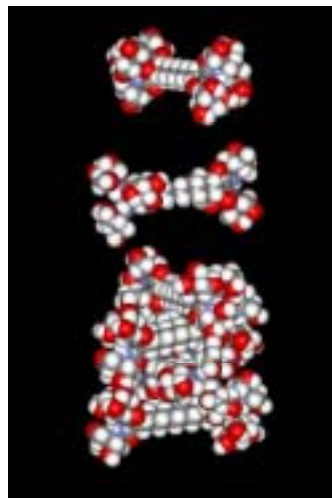
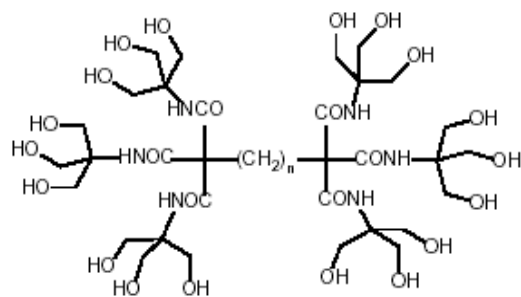
The first example of an iterative synthetic procedure towards well-defined branched structures was reported by Vögtle in 1978, who named this procedure a 'cascade synthesis'. In the early 1980s, Denkewalter patented the synthesis of L-lysine-based dendrimers. The patents describe structures up to high generations. However, no detailed characteristics of the materials were given.

The first dendritic structures that were exhaustively investigated and that received widespread attention were Tomalia's PAMAM (poly(amidoamine)) dendrimers and Newkome's 'arborol' systems.



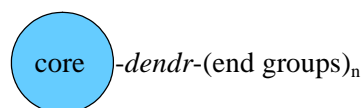
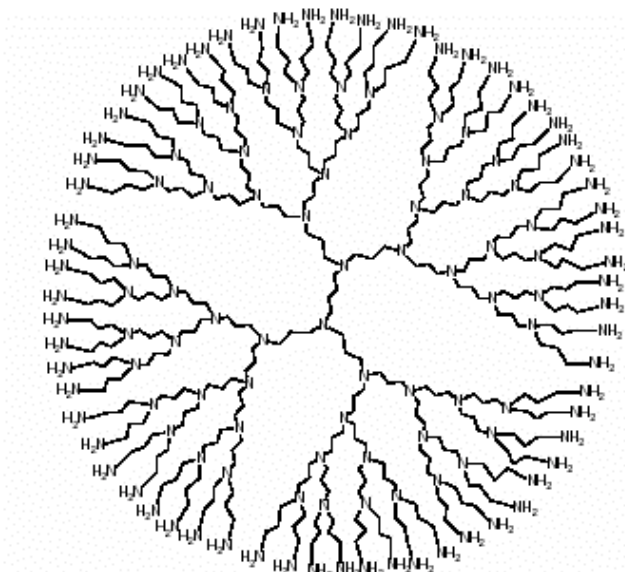
Poly(amidoamine), or, PAMAM dendrimer. Trade name: StarburstTM

PAMAM dendrimers are synthesized by the divergent method starting from ammonia or ethylenediamine initiator core reagents. They are constructed using a reiterative sequence consisting of (a) a double Michael addition of methyl acrylate to a primary amino group followed by (b) amidation of the resulting carbomethoxy intermediate with a large excess of ethylenediamine. Products up to generation 10 (a molecular weight of over 930,000 g/mol) have been obtained (by comparison, an atom of carbon weighs 12 g/mol, the molecular weight of human hemoglobin is approximately 65,000 g/mol).



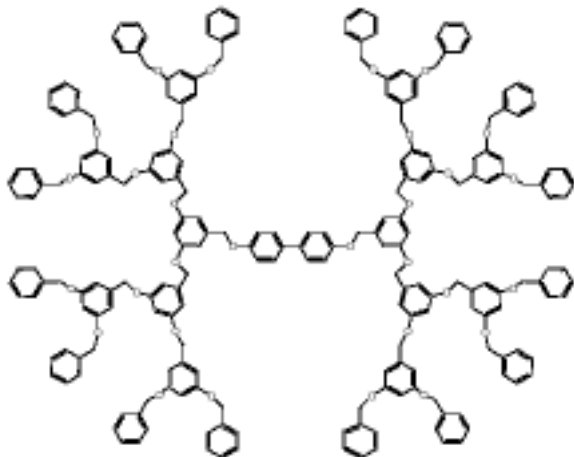
Newkome's arborol dendros

In 1993, based on the original work of Vögtle, divergently produced (from the core to the periphery) poly(propylene imine) dendrimers were created by Meijer at DSM of the Netherlands. Today, these PPI dendrimers are synthesized in large quantities by DSM and are commercially available.



Polypropyleneimine dendrimers, or, PPI dendrimers. Trade name: Astramol™

PPI dendrimers are synthesized by the divergent method starting from 1,4-diaminobutane. They are grown by a reiterative sequence consisting of (a) a double Michael addition of acrylonitrile to the primary amino groups followed by (b) hydrogenation under pressure in the presence of Raney cobalt. Products are made up to generation 5. DSM uses its own designation to describe its dendrimers: where the core is diaminobutane, *dendr* indicates the interior dendritic branch cell; and *n* is the number of end groups.



Fréchet's aromatic polyether dendrimer

In 1990, Fréchet introduced the convergent approach to create dendrimers. In convergent synthesis, the procedure is started at the periphery and elaborated to the core. Fréchet's aromatic polyether dendrimers are easily accessible and have been studied frequently by various researchers.

In the early 1990's, phenylacetylene dendrimers were created by Jeffrey Moore using the convergent method.

In the last 5 years, many other types of interesting dendritic systems have appeared, although they have been less widely investigated and many have not left the lab.

Glossary

Amphiphilic

From the Greek meaning "both" (amphi) and "lover" (philos). An amphiphile is a molecule that has a strong attraction towards both polar solvents, such as water (hydrophilic), and non-polar solvents (hydrophobic), and will be generally located at the interface between the two. When dispersed in either a polar or non-polar solvent an amphiphile has a tendency to form capsules with the ends of the molecules that are not compatible with the solvent on the inside. Liposomes are an example with a long history.

Apoptosis

A Greek word meaning "the dropping of leaves from a tree". A normal series of events in a cell that lead to its self-destruction. Apoptosis is a vital biological process (an organism's housekeeping mechanism) by which it maintains health through ridding itself of aging, infected, or mutated cells.

Base

A subunit of a nucleic acid (such as DNA or RNA). Complementary bases are held together by hydrogen bonding. In DNA, base pairing occurs between A (adenine) and T (thymine) and between G (guanine) and C (cytosine). In RNA thymine is replaced

by uracil (U). Technically, the base is the portion of a nucleotide that makes it an A, G, T (or U) or C. Often referred to as the letters of the genetic alphabet.

Enzyme

A natural (organic) catalyst, i.e. a substance that, simply put, facilitates a chemical reaction.

Hybridization

Binding of complementary sequences of nucleic acids (DNA or RNA) through specific pairing of bases (see entry under 'Base'). Hybridization is generally used to detect particular DNA or RNA sequences by complementary base pairing of tagged probes. The probes are usually nucleic acids containing the chemical label biotin (a water soluble vitamin from the B vitamin complex that can be easily detected because it can be made to contain a radioactive isotope of phosphorus or iodine, or a molecule that fluoresces, so that it can be detected during analysis).

Hydrophilic

From the Greek words for "water" (hydro) and "love" (philos). A hydrophilic compound is one that has affinity for water and easily dissolves in it. Having potential for hydrogen bonding or having a charge will make a compound hydrophilic. Most inorganic salts and many organic molecules, like ethanol, are hydrophilic.

Hydrophobic

From the Greek words for "water" (hydro) and "fear" (phobos). A compound is hydrophobic if it "hates" water and will not dissolve in it. Having low polarity (variation in charge from one end of the molecule to the other) and no net charge makes a molecule hydrophobic. Most industrial organic molecules, such as hexane and toluene, are hydrophobic.

Lipid

An organic compound composed of chains of carbon atoms that have two (or fewer) hydrogen atoms attached to each of them. Lipids are commonly known as fats and oils, and belong to the family of molecules known as hydrocarbons. They are important as major fuels in cell metabolism. Polar lipids have amphiphilic (cf.) properties and are the building blocks of cell membranes and liposomes.

MEMS

Microelectromechanical systems. Generally used to refer to systems that can respond to a stimulus or create physical forces (sensors and actuators) and that have dimensions on the micrometer scale. They are almost exclusively made using the

same lithographic techniques that are used to make silicon chips for computing. Miniature accelerometers are the most successful product in this field and are used to trigger air bags in cars. When such systems can be made with nanoscale dimensions they can be classified as NEMS.

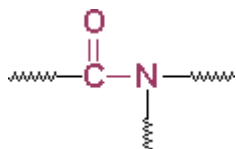
NEMS

Nanoelectromechanical systems. Nanoscale MEMS (cf.).

Non-linear optical materials

NLO materials are used for wavelength conversion. The most common optical properties, such as refraction, can be related to the polarizability of the molecule. Polarizability is the change in the dipole moment when an electric field is applied (a first derivative). Non-linear optical properties depend upon the hyperpolarizability of the molecule. Hyperpolarizability is the change in the change in dipole moment due to an electric field (a second derivative). An example of a non-linear optical property is frequency doubling, where the light emitted from a material is twice the frequency of the light being sent into the material.

PAMAM



Poly AMido AMine dendrimers. Dendrimers containing tertiary amines (a nitrogen (N) atom bonded to three carbon (C) atoms) as branching points and amide groups (carbon (C), oxygen (O) and nitrogen (N) atoms arranged in the manner shown in the figure) as branches in their structure.

PPI

Poly(Propylene Imine) dendrimers. Dendrimers containing tertiary amines (a nitrogen (N) atom bonded to three carbon (C) atoms) as branching points and propylene groups (three carbon (C) atoms) as branches in their structure.

Self-assembly

The process whereby components spontaneously organize into larger or more complex objects. An approach to construction used widely in natural systems and a central theme in much of nanotechnology, where the term bottom-up is often used interchangeably (though self-assembly is just one example of bottom-up construction).