Strategies for Supramolecular Chemistry with Dendrimers

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1. Introduction.

Dendrimers are highly branched, monodisperse macromolecules.[1] Dendritic architectures rely on repeating branching units and this type of structure is one of the most abundant in nature. In everyday life this type of architecture is common in ice-crystals, trees, roots and lightning. The word 'dendrimer' originates from the Greek words 'dendron' and 'meros' meaning 'tree' and 'part of' respectively.

About half a century ago, in theoretical studies, Flory was the first to study the role of branched units in macromolecular structures.[2] The first synthesis of a dendrimer was achieved in 1978 by Vögtle and co-workers in Germany.[3] The synthesis of the poly(propylene imine) dendrimer was later developed to a multi-kilogram preparation of large dendrimer structures thus allowing for commercialisation of the dendrimer (Figure 1). In the 1980's syntheses of a number of other types of dendrimers were developed (Figure 2). The family of poly(amido amine) dendrimers (PAMAM dendrimers, Figure 2) was also commercialised, and for this reason the PAMAM dendrimers and the poly(propylene imine) dendrimers have been studied extensively during the past three decades. In Figure 1 the structure of a fifth generation poly(propylene imine) dendrimer is shown illustrating some of the main features of the dendritic structure. In the dendrimer shown, the core is 1,4-diaminobutane, and this is sometimes referred to as 'generation zero'. To this end, the second 'generation' is also highlighted in the figure illustrating that each 'layer' of propylene imines constitutes a generation. Each amino functionality within the dendrimer is a branching point in the structure. The periphery (or surface) of the dendrimer is important as it determines many of the physical and chemical properties of the dendrimer. The dendrimer has 64 primary amino groups at the surface and is water soluble. If the amino groups at the periphery were modified with a fatty acid the dendrimer would resembles an inverted micelle and be soluble in organic solvents. When a dendrimer becomes sufficiently large the periphery of the dendrimer becomes 'saturated' and the three dimensional

structure of the dendrimer becomes spherical. With an appropriate choice of surface groups the dendrimer adopts a closed-shell with a hollow interior. This gives rise to some interesting phenomena that have been explored extensively since the discovery by Meijer and co-workers in 1994 that small molecules can be encapsulated (or imprisoned) within the dendrimeric structure.[4]

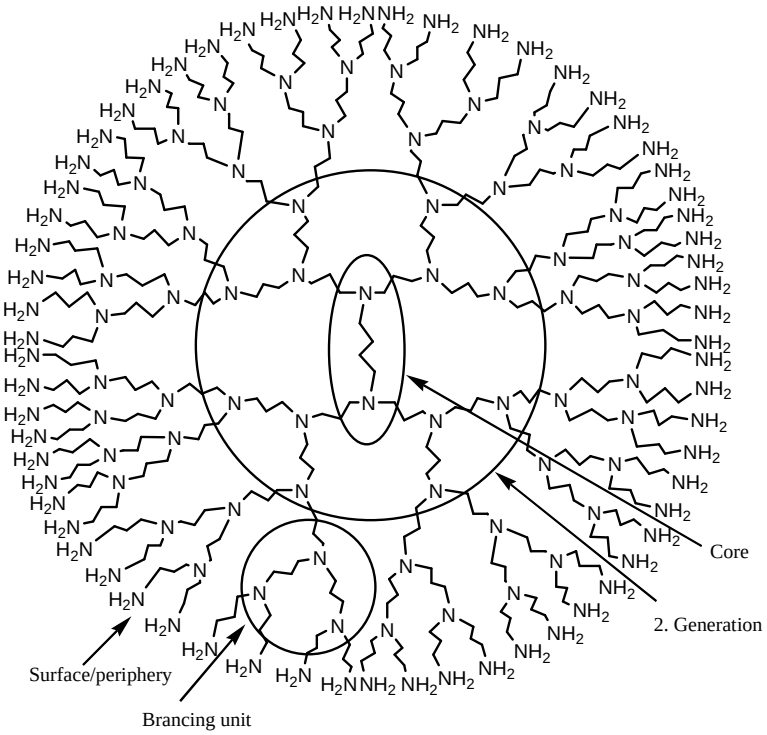

Figure 1. Structure and some features of a fifth generation poly(propylene imine) dendrimer.

The ability to chemically manipulate macromolecules is essential when aiming to understand the properties of both naturally occurring and artificial macromolecular systems. This is particularly true with the advent of interdisciplinary research areas such as molecular biology and nano-science. Indeed, the manipulation of polymers of amino acids (proteins) and nucleic acids (DNA, RNA) has been studied intensively in the past decades, and many successful chemically engineered systems have been disclosed, with PNA and LNA as prominent examples developed in Denmark.

From a topological point of view, dendrimers can (if properly engineered) be thought of as a hollow sphere with a densely packed surface. Dendrimers functionalised at the periphery can be further non-covalently modified using a newly developed, purely organic guest-host approach. The surface functionalisation of dendrimers using this approach can potentially be explored in drug design where the multivalency of the dendrimer gives advantages over traditional monovalent drug molecules.

When viewing the dendrimer as a hollow sphere, the possibility of filling the dendrimers with 'guest' molecules is attractive. Dendrimers can be filled with certain metal ions that can be reduced to metal nanoparticles. This gives the unique possibility of tuning the size of the metal particles to have the dimensions of the dendrimer (typically 1-5 nanometer), and this constitutes an interesting entry into metal mediated catalysis.

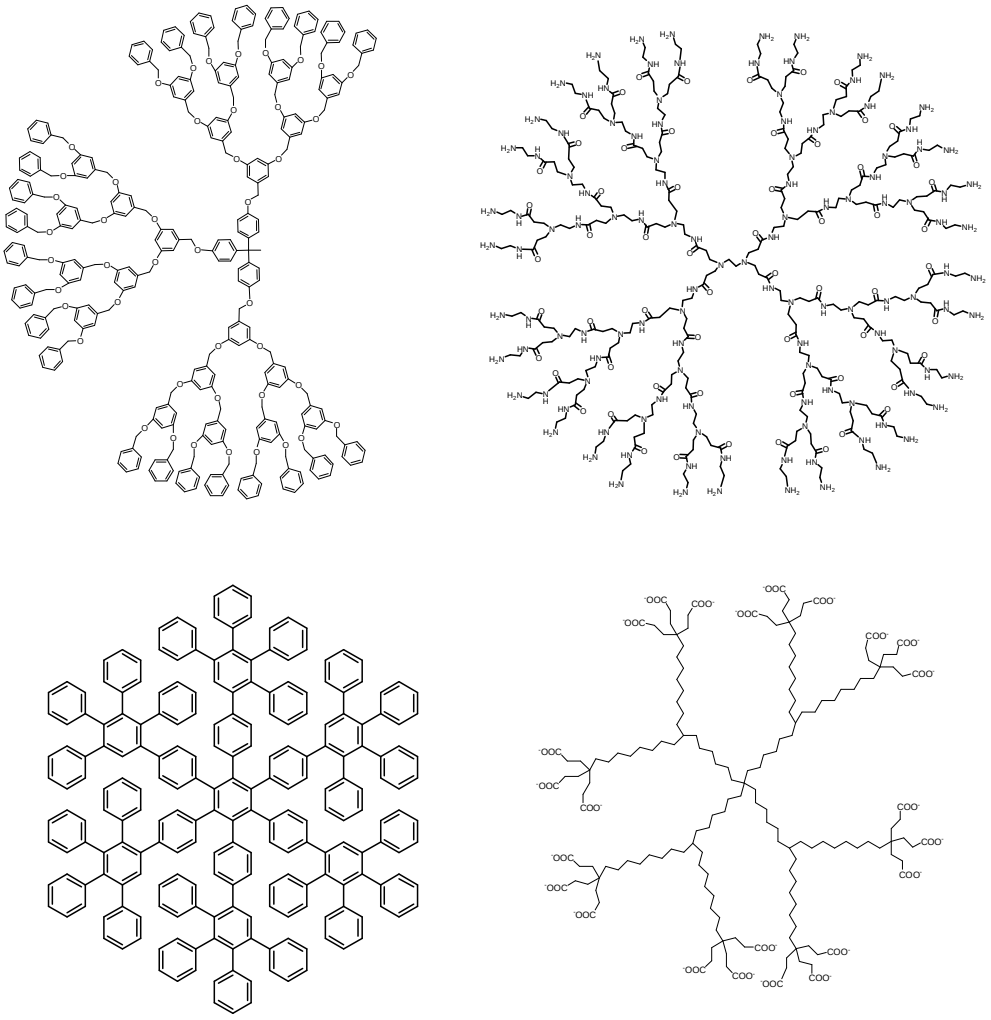

Figure 2. Structure of some common dendrimers. Top left: poly(aryl ether) dendrimer. Top right: PAMAM dendrimer. Bottom left: poly(phenyl phenylen) dendrimer. Bottom right: Micellanoic^{TM} dendrimer.

2. Manipulating the surface of dendrimers.

Manipulation of the surface of adamanty urea functionalized poly(propylene imine) dendrimers was achieved by developing a novel series of guest molecules that have specific affinity for the surface of the dendrimer (Figure 3 shows the binding motif).[5] The guest molecules interact via a combination of non-covalent interactions with an electrostatic acid-base interaction and multible hydrogen bonding as the main attractive forces. By tuning the acidity of the guest molecules, the affinity for the dendrimer was shown to vary (sulfonic acid binds stronger than phosphonic acid which binds stronger that carboxylic acid).

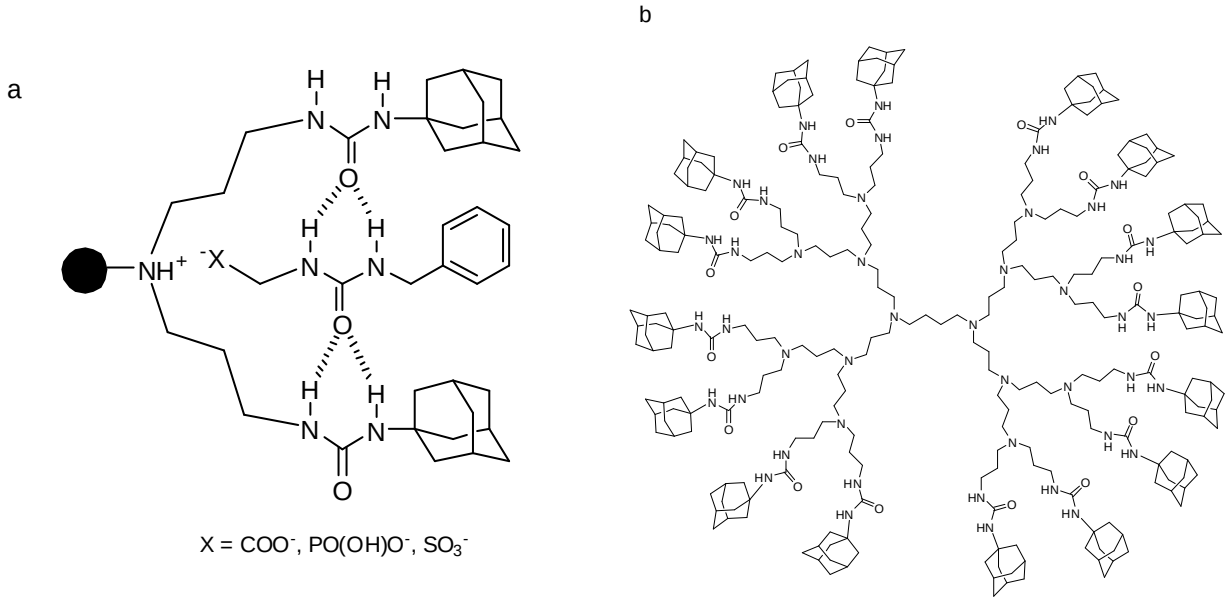

Figure 3. a) Structure of guest-host motif. b) Structure of a third generation poly(propylene imine) dendrimer covalently functionalised with adamantly urea.

This stability of the guest-host interactions between the third generation poly(propylene imine) dendrimer in Figure 3 and a series of different guest molecules was studied using a variety of techniques including collision induced dissociation mass spectrometry.[6] The third generation dendrimer is capable of binding eight guest molecules at its periphery. Upon addition of guests with different binding strengths to the dendrimer and introduction of this macromolecular complex into an electrospray mass spectrometer it is possible to select a specific complex between the dendrimer and two different guest molecules. If this complex is collided with an inert gas the complex fragments. The energy of this process can be controlled in such a way that the guest molecule that binds less strongly to the dendrimer is released before the guest molecule that is bound more strongly. In Figure 4 the most simple type of experiment is shown, where a dendrimer-guest complex with four guest molecules attached to the dendrimer is disassembled in the mass

spectrometer, one guest at the time. This type of study is important as it gives qualitative information of the binding of small molecules to large macromolecules. In a subsequent study the qualitative binding observations have been verified in solution using a number of different spectroscopic techniques such as 2D NOESY NMR experiments and fluorescence titration experiments.[5b]

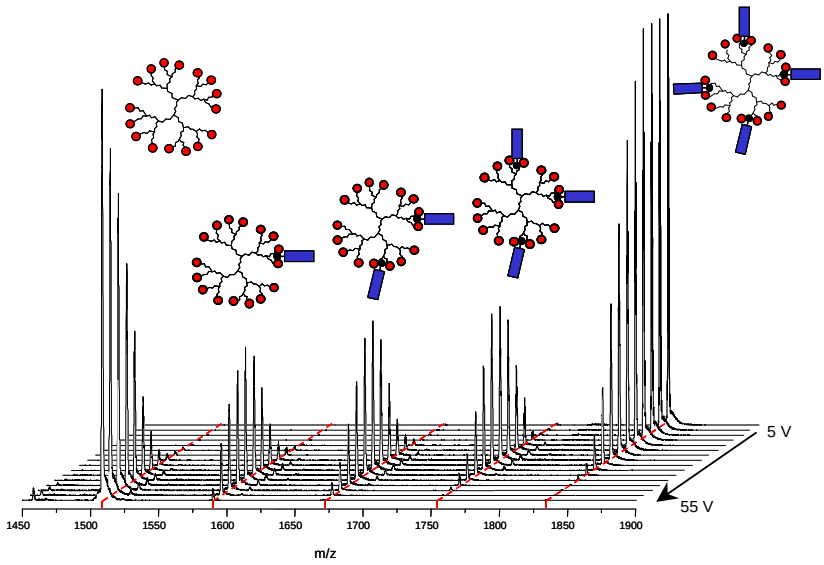

Figure 4. Selection of one ion (Dendrimer•guest$_4$) followed by a collision with increasing acceleration voltage in the collision cell results in sequential dissociation of the guests from the dendrimer.

3. Manipulating the interior of dendrimers.

A dendrimer with an interior that facilitates the coordination of a metal ion and a surface that has no affinity for that metal ion can be used as a 'sponge' for the metal ions. If the inside of a dendrimer is saturated with metal ions (for example Pd^{2+}) and subsequently reduced by an external reducing agent, metal nanoparticles (Figure 5) of the size of the dendrimer are obtained (typically 1-5 nm). The metal nanoparticles (typically Pd or Pt) are effective and recyclable catalysts for organic reactions. An attractive research target is to introduce chirality into the dendrimer encapsulated metal nanoparticles for use in enantioselective catalysis. This goal has been pursued actively, and the first synthesis of a series of internally chiral PAMAM dendrimers has been completed.[7] The introduction of chiral centers inside the dendrimers makes it possible to prepare metal nanoparticles where the chirality is transferred from the dendrimer (organic) to the metal particle (inorganic).[8] This is the first example of the use of dendrimers as a template for chiral metal nanoparticles. The next step of this research is to target chiral induction in organic reactions using the chiral metal nanoparticles as the catalyst.

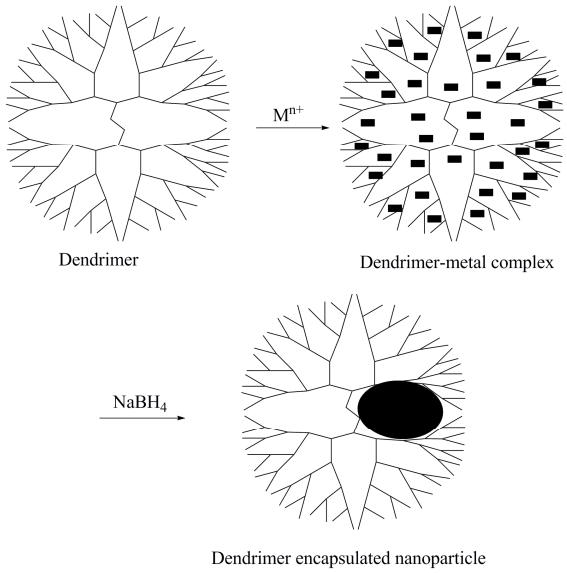

Figure 5. Synthetic scheme for encapsulation of metal nanoparticles inside dendrimers.

4. Outlook.

Basic studies of dendrimers and their role in supramolecular chemistry is important for understanding how to manipulate macromolecules and for understanding how small molecules interact with macromolecules. The future seems promising for the field of dendrimer research, both in academia and in more applied fields: The first drug based on dendrimers (an anti-HIV agent, VivaGel^{TM}) is soon to be launched and effective catalysts based on dendrimers have been developed. Dendrimers have been shown to form stable complexes with DNA and RNA and can be used in gene transfection. Finally, dendrimers have been shown to have promising results as Gadolinium based contrast agents for MR scanning and many other discovered and undiscovered areas.

5. Bibliography

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