Dendritic Materials- Design, Synthesis and Applications

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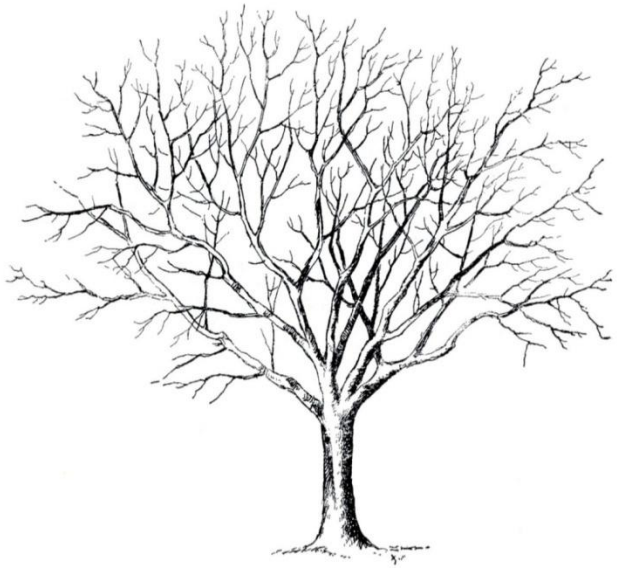
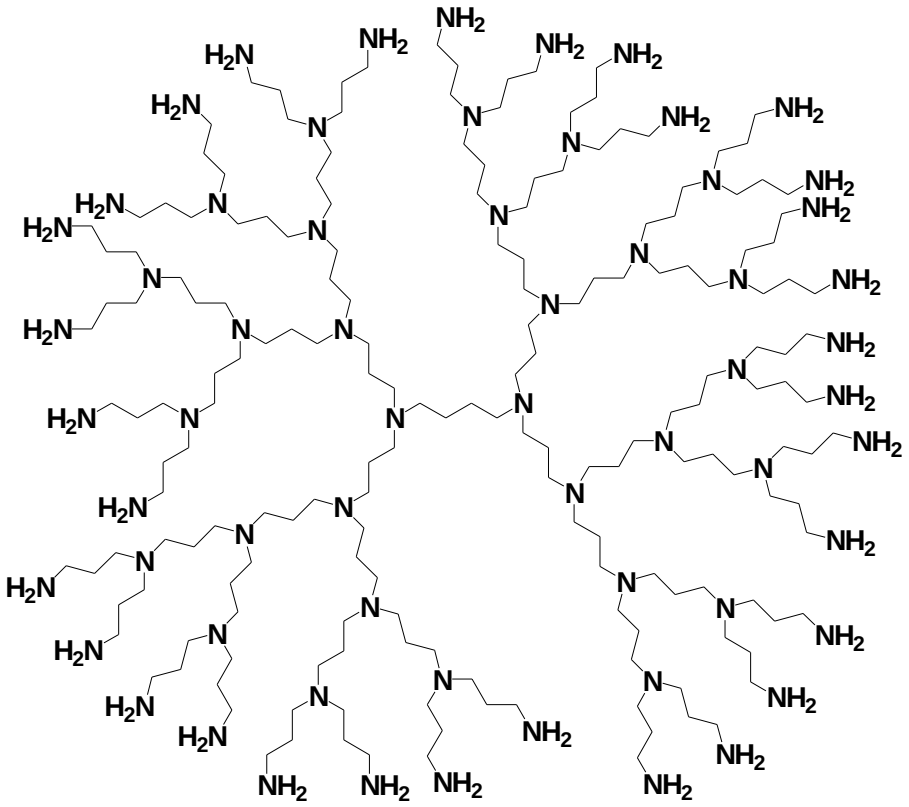
DENDRIMERS

- Novel class of branched polymers.
- Spherical polymers shaped like the head of a tree.
- *dendron* = tree and *meros* = units
- Synonyms: Arborols, cauliflower, starburst polymers.



Hawker, C. J.; Fréchet J.M.J. *J. Chem. Soc. Chem. Commun*., **1990**, 1010-13. (Review article)



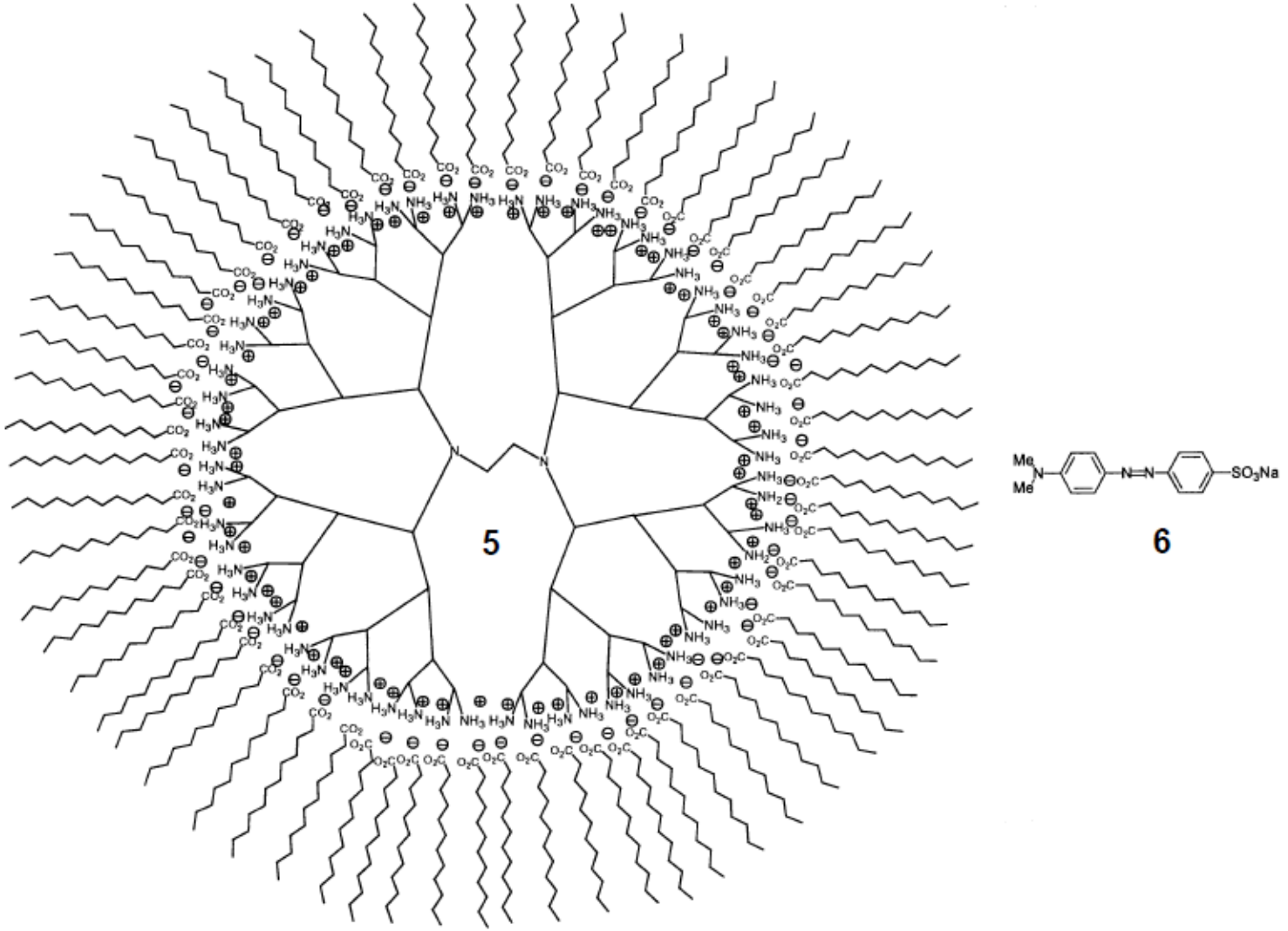


Fig. 3. Ionic assembly of PAMAM dendrimer and decanoic acid (5) studied by Crooks and co-workers. In water the assembly is capable of complexing methyl orange (6)

Evolution of Dendrimers

1952: Flory was the first to examine the potential role of branched units in a macromolecular architecture. (*J. Am. Chem. Soc.* 1952, *74, 2718.*)

1978: Vogtle developed iterative cascade method for the synthesis of low molecular weight branched amines. (*Synthesis* 1978, 155-158)

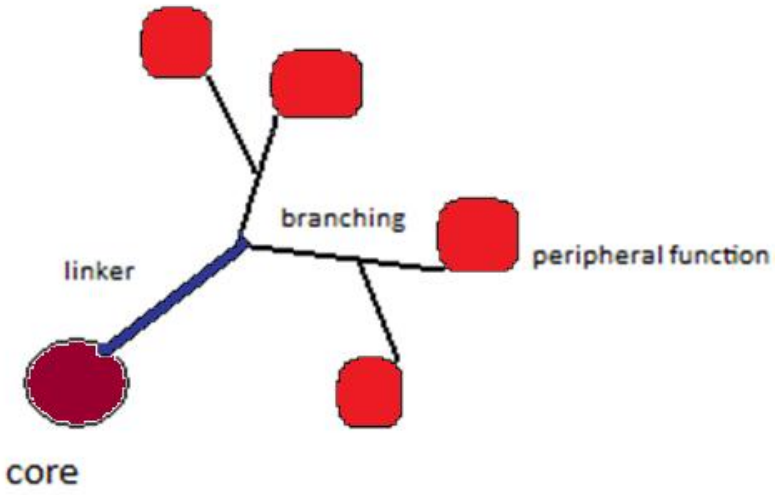
1984-85: D. A. Tomalia disclosed the synthesis of first family of dendrimers- Polyamidoamine (PAMAM dendrimers).(*Prepr.1st SPSJ Int. Polym. Conf., Soc. Polym. Sci. Jpn. (Kyoto) 1984,* 65.)

1985: Newkome reported preliminary results toward another family of trisbranched polyamide dendrimers. (*J. Org.Chem.* 1985, 50, 2003-2004.)

1989-1990: Hawker and Frechet introduced poly-benzylether dendrimers. (*J. Am. Chem. Soc.* 1990, 112, 7638-7647.)

1993: Improvements on Vogtle's original synthesis were disclosed by Meijer that enabled the production of poly(propylene imine) (PPI) dendrimers. (*Angew. Chem., Int. Ed. Engl.* 1993, 32, 1306-1308.)

Anatomy of a Dendrimer



Multifunctional core molecule with a dendritic wedge attached to each functional site. The core molecule is referred to as “generation 0”. Each successive repeat unit along all branches forms the next generation. Generation G_1, G_2, G_3 and so on until terminating the generation.

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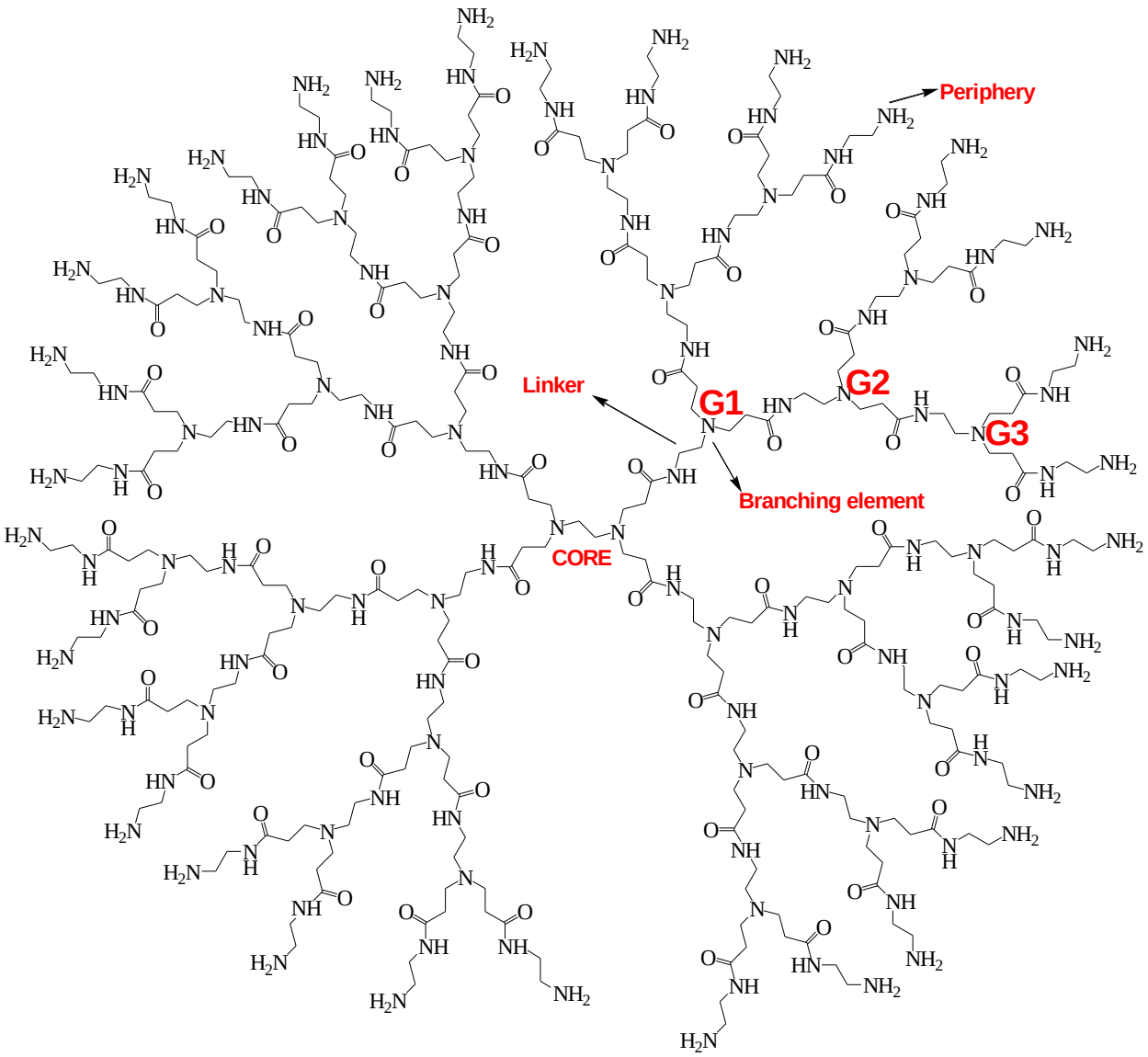
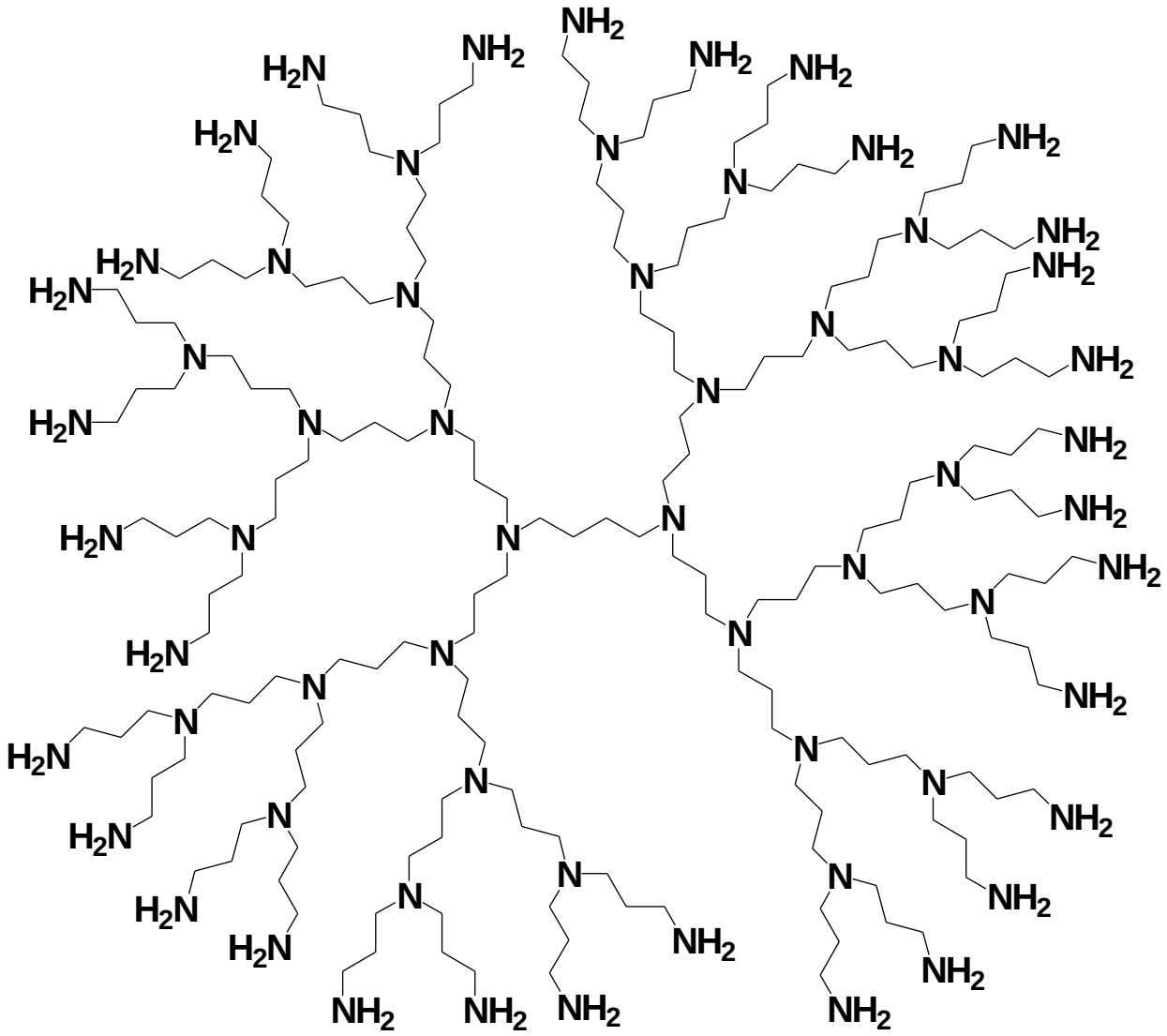
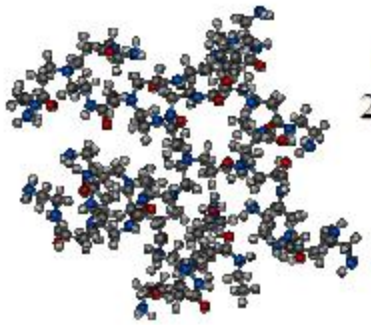
Structure of a G3 PAMAM dendrimer with ethylenediamine core.



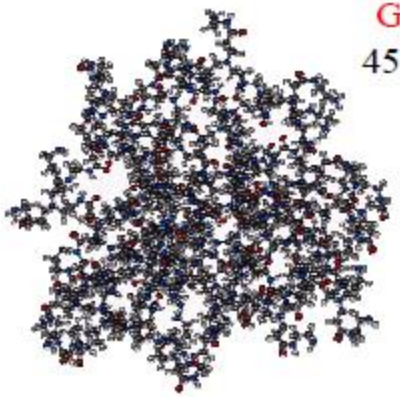
Structure of G3 PPI dendrimer with 1,4-diamonobutane as a core



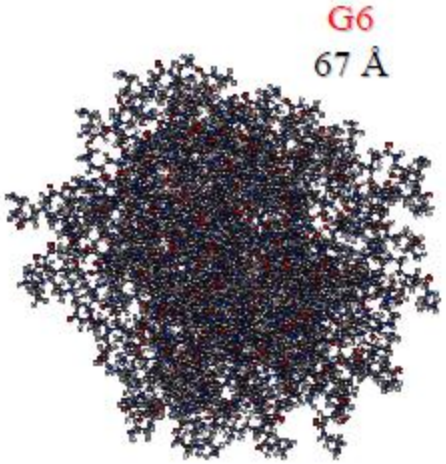
Increasing generations of G3 PPI dendrimer



G2
29 Å



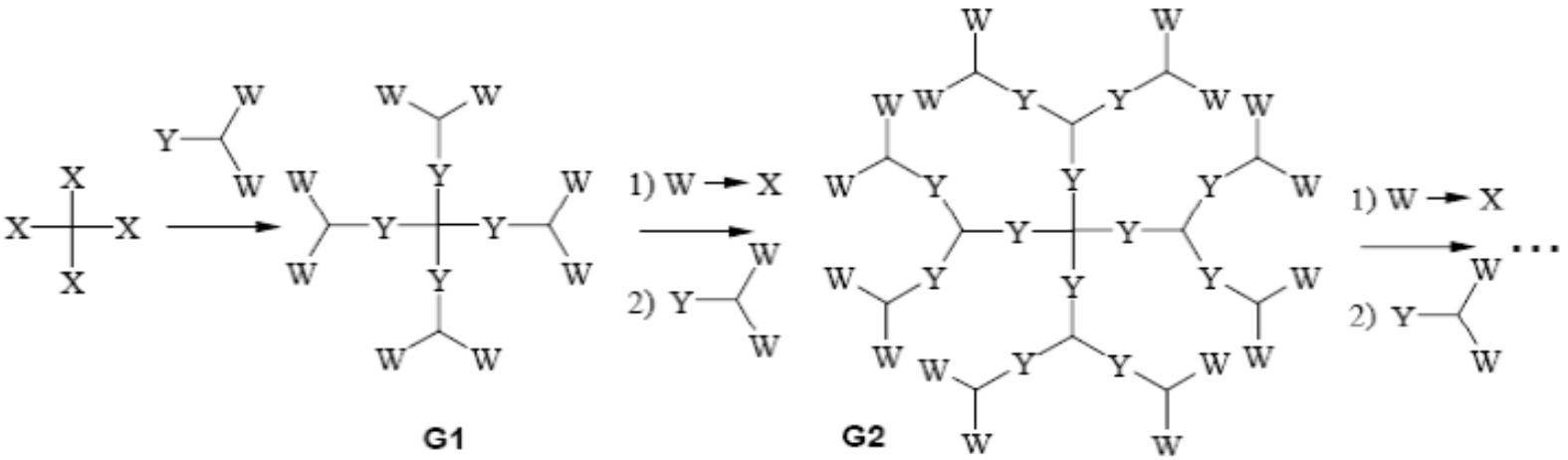
G4
45 Å



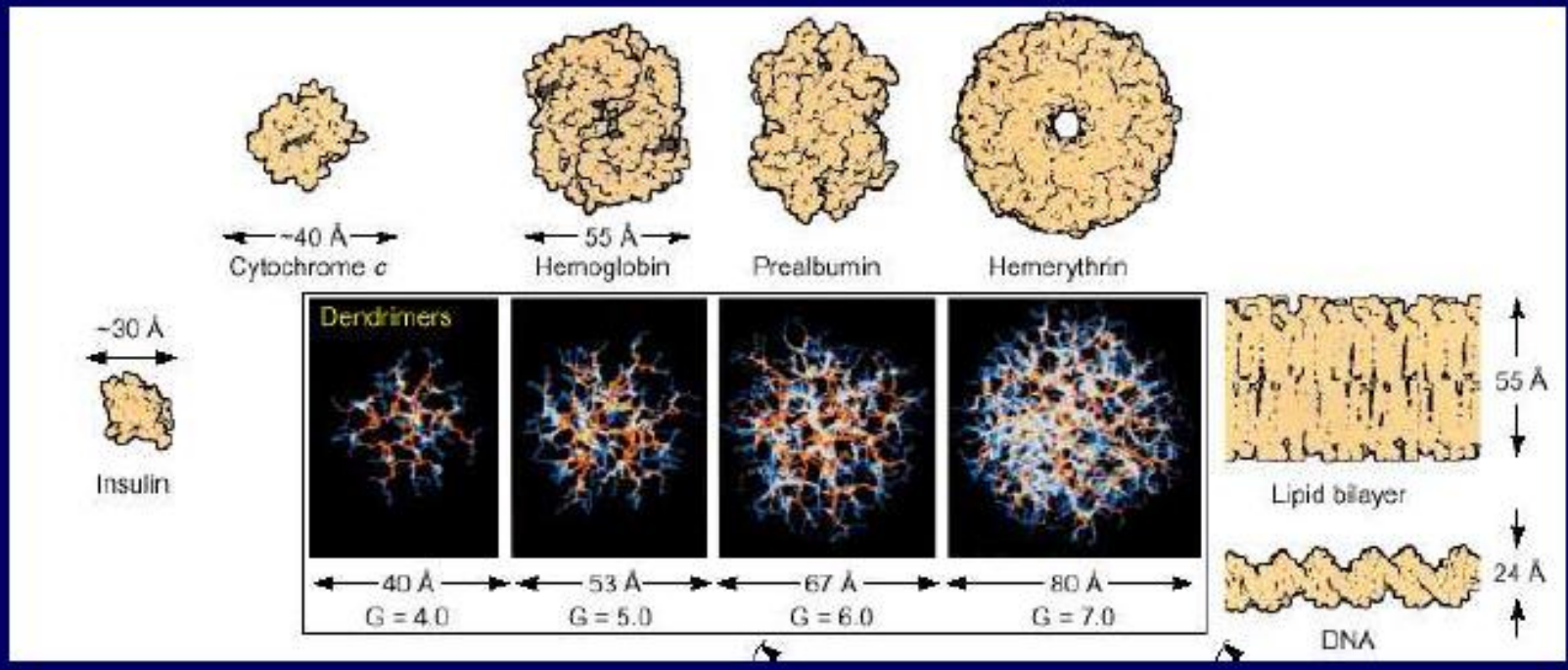
G6
67 Å

	# amines	
	3°	1°
G2	14	16
G4	62	64
G6	254	256
...		
G10	4094	4096
pKa	3-6	7-9

Generation-dependent increase in the number of surface groups



	G1	G2	G3	G4	G5	G6
	8	16	32	64	128	256
	12	36	108	324	972	2916



A dimensionally scaled comparison of a series of PAMAM dendrimers with a variety of proteins, a typical lipid bilayer membrane and DNA.

(Esfand and Tomalia, DDT Vol 6, 427-436, 2001)

Dendrimers vs Proteins

Similarities

- Size
- Weight
- Well defined chemical structure (known bonding structure)
- 3 dimensional position of each atom is difficult to determine - yet a consistent specific 3 dimensional structure exists
- Difficult to perform chemical analysis
- Easy for cell to uptake

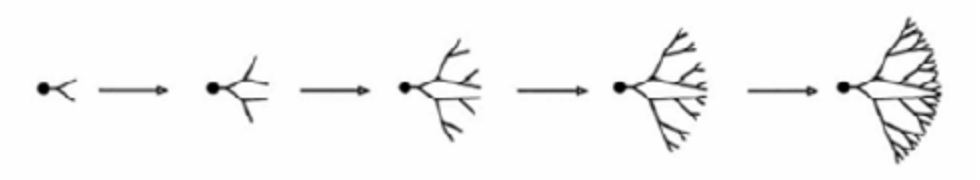
Main Difference

- Proteins are polymers made from 20 different monomers, while dendrimers are polymers made from two monomers.

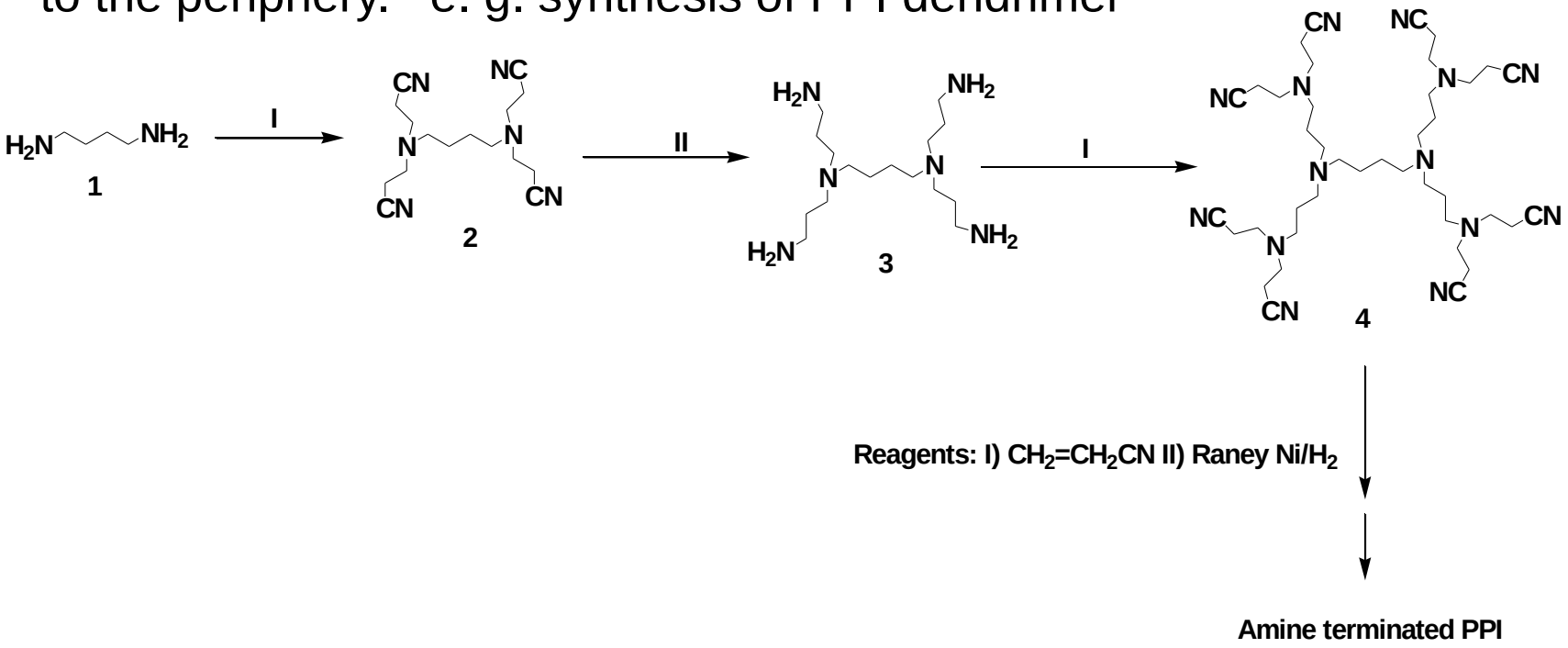
http://nano.med.umich.edu/Dendrimers.html

SYNTHESIS OF DENDRIMERS

Divergent Approach:



- A traditional approach also known as starburst method.
- Involves building the dendrimer layer-by-layer from a central core to the periphery. e. g. synthesis of PPI dendrimer



Angew. Chem., Int. Ed. Engl. 1993, 32, 1306-1308

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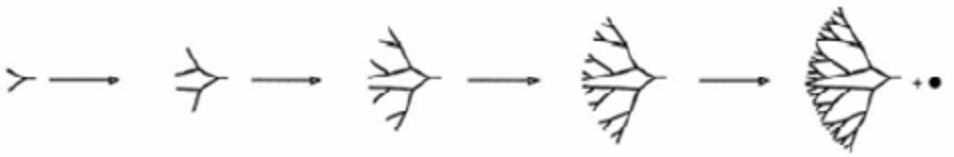
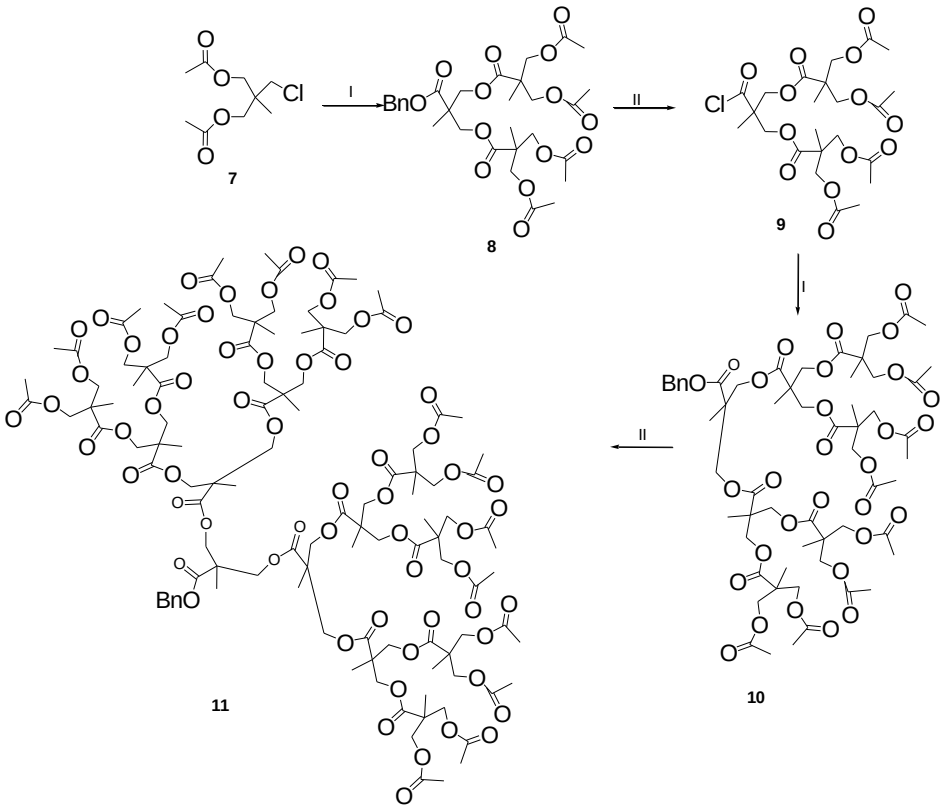
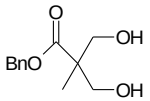
Convergent Approach



- It involves construction of dendrons followed by their attachment to a multifunctional core.

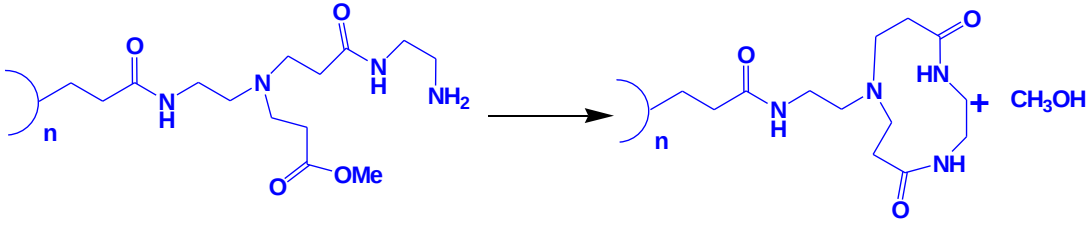
e.g. Synthesis of poly (alkyl ester) dendrimers utilizing a repeat unit based on 2,2-bis(hydroxymethyl)propanoic acid. (Ihre, H. et al. *J. Am. Chem. Soc,* **1996**, 118, 6388.)



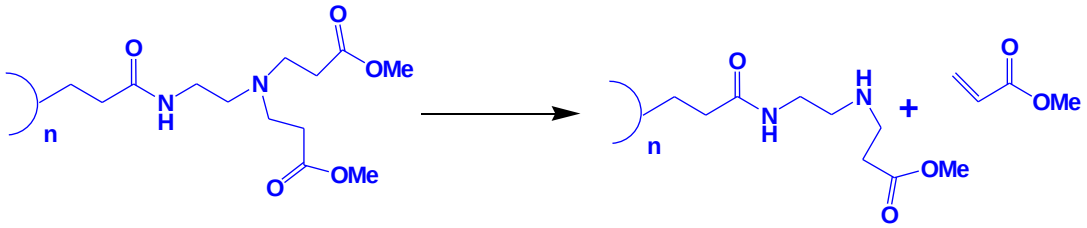
Reagents: I) DMAP, Et_3N,  II) i)Pd/C,H_2, ii) oxalyl chloride, cat. DMF

Unwanted reactions during dendrimer synthesis

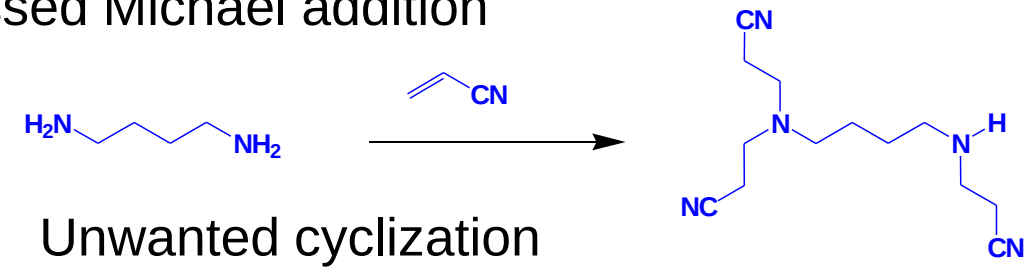
1. Lactam formation



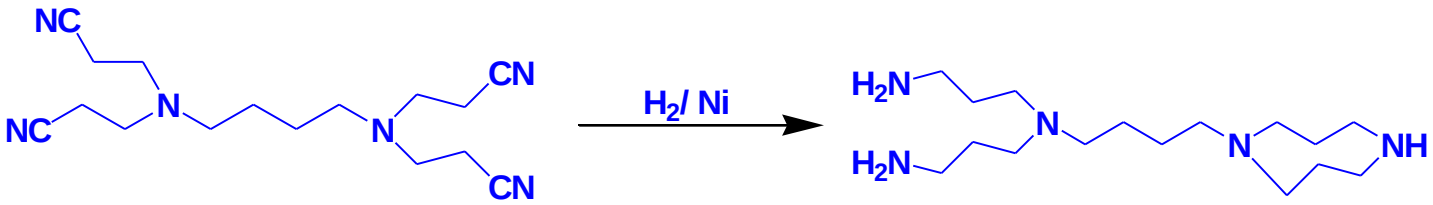
2. Retro-Michael reaction



3. Missed Michael addition



4. Unwanted cyclization



*Bosman, A.W. Et al. Chem Rev **1999**, 99, 1665-188*

ACCELERATED APPROACHES

✓ In response to the often tedious and purification intensive iterative dendrimer synthesis, many researchers have sought accelerated approaches that combine

the convergent and divergent strategies**.**

✓ Maintains the versatility and product monodispersity offered by the traditionalconvergent method, but reduces the number of linear synthetic steps required to access larger dendritic materials.

1) Multigenerational coupling

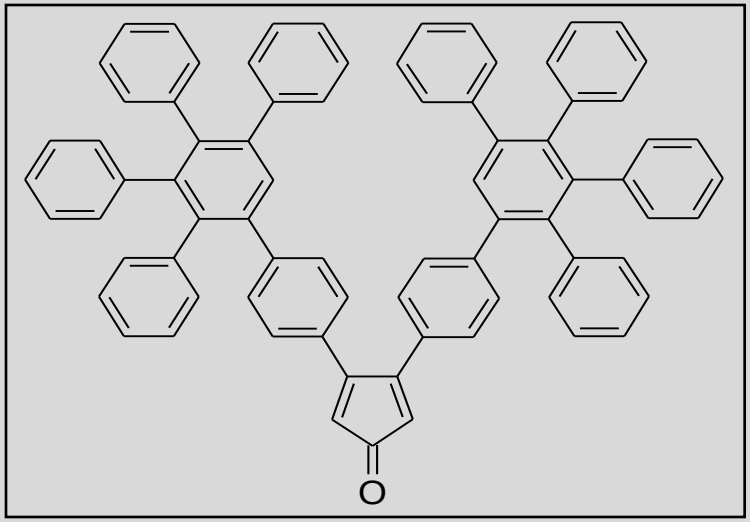
a) Hypercores
b) Hypermonomers
c) Double exponential growth

2) **Orthogonal syntheses**

Grayson S. M.; Frechet, J.M.J. *Chem. Rev.* **2001**, 101, 3819-67.

CLASSIFICATION OF DENDRIMERS DEPENDING ON BRANCHING ELEMENT

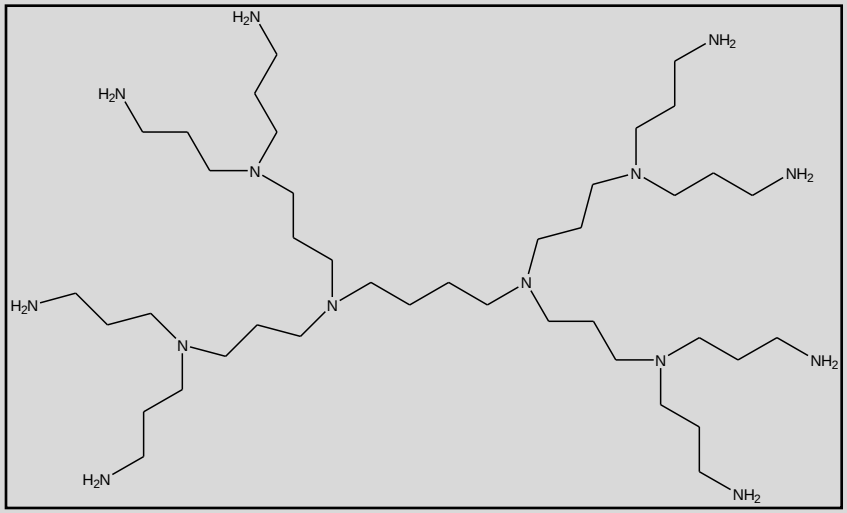
1. Phenyl branching element



Poly(phenylene) branching

Wiesler, U.M.; Mullen, K. *Chem Commun.*, 1999, 2293-2294.

2. Amine branching element



Poly propylene imine

Worner, C.; Mulhaupt, R. *Angew. Chem., Int. Ed. Engl.* 1993, 32, 1306-1308.

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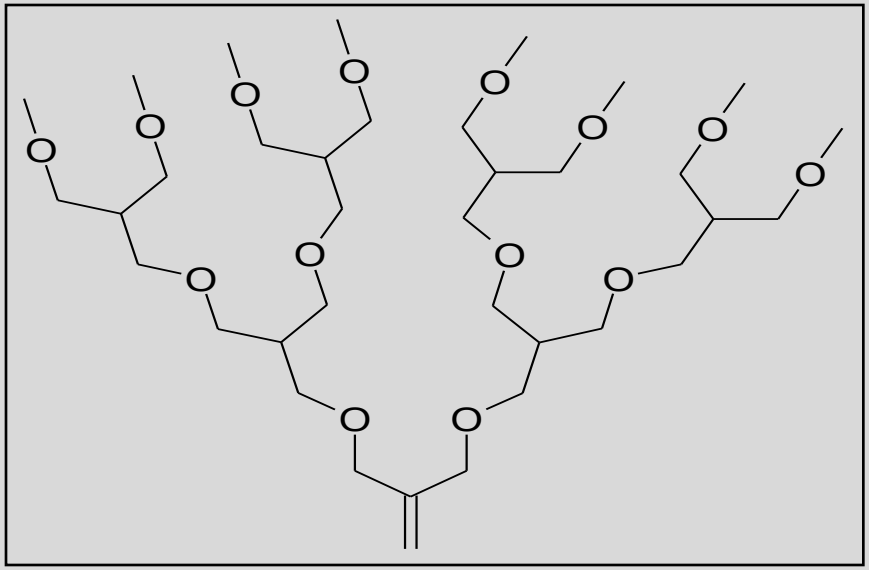
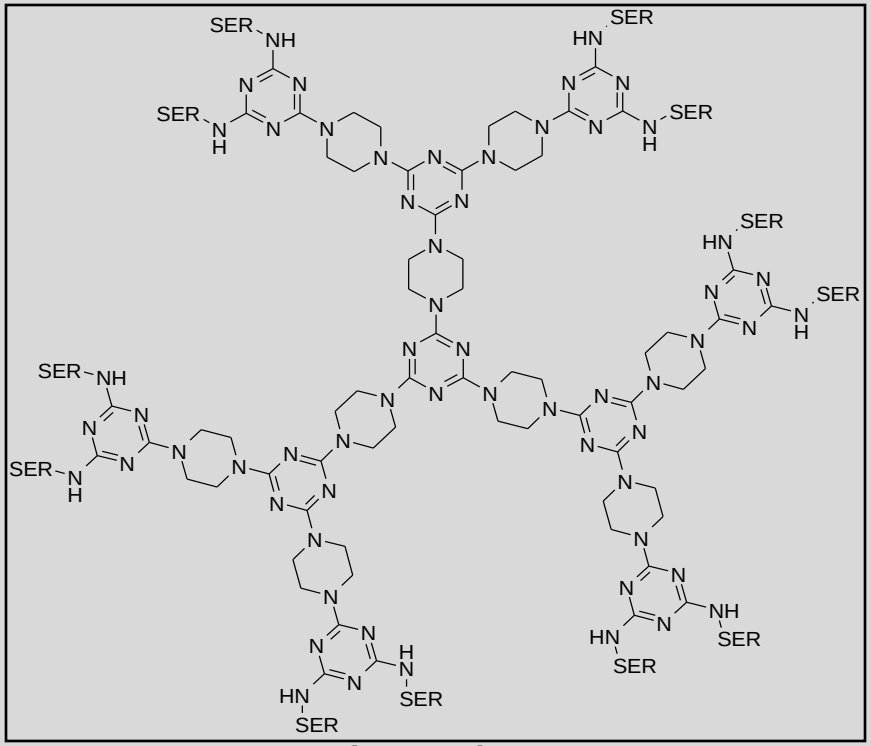
3. Alkyl branching element



Poly(alkyl ether) branching

Grayson, S. M.; Jayaraman, M.; Fre´chet, J. M. J. *Chem. Commun. 1999, 1329-1330*

4. Heterocyclic branching



Triazine branching

Pintea.M. *et al.* Heterocycl. Commun., 2006; 12, 135

DIFFERENT TYPES OF DENDRIMERS

1. **Glycodendrimer:**
   A general term used to describe wide range of architecture of dendrimer which incorporate carbohydrate into their structure.

a) ***carbohydrate-coated***,

b) ***carbohydrate-centered*** and

c) ***carbohydrate based***

Bhadra, A. K. et al. *Int. J Pharm*. **2005**, 295, 221–233.

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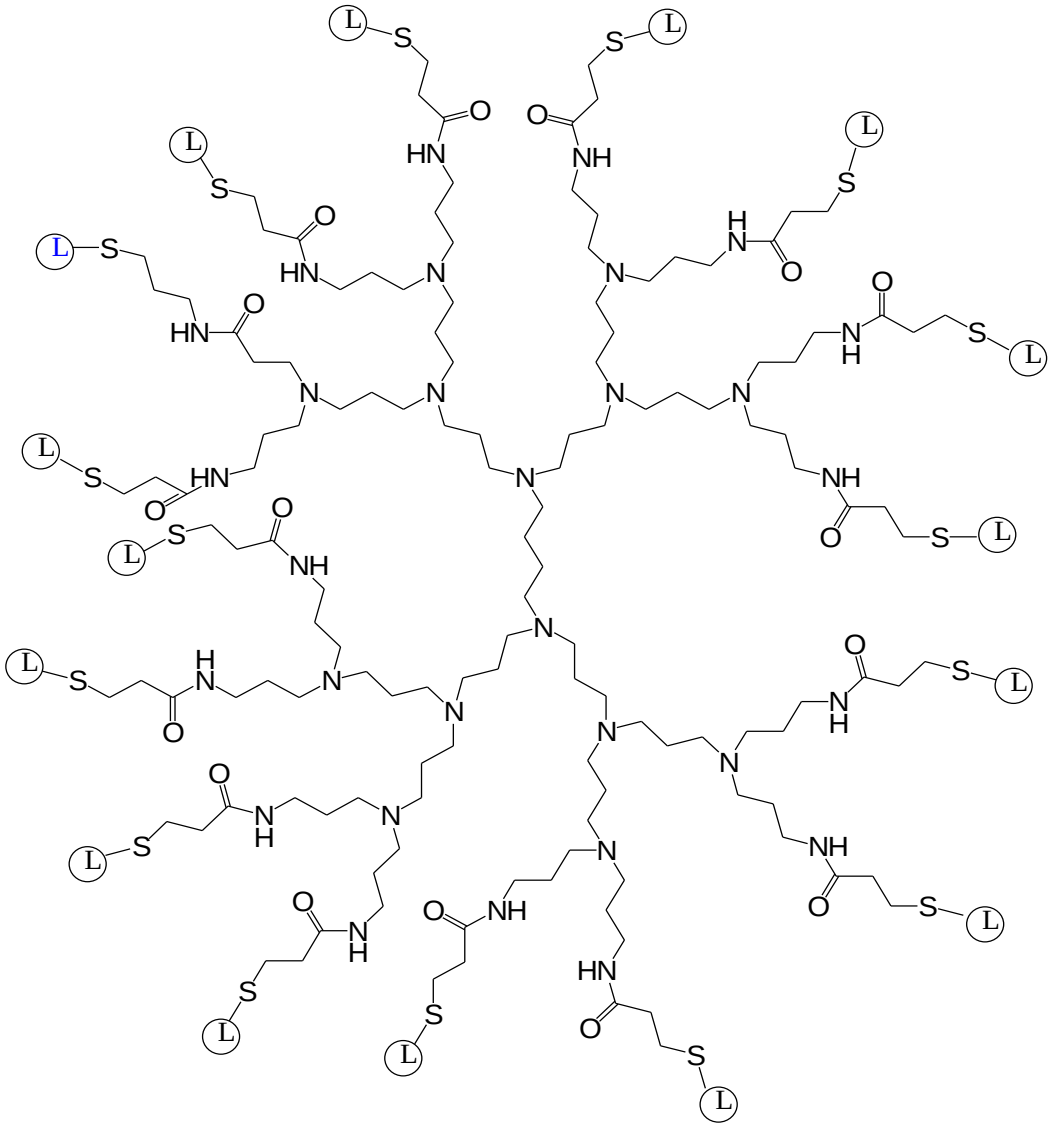
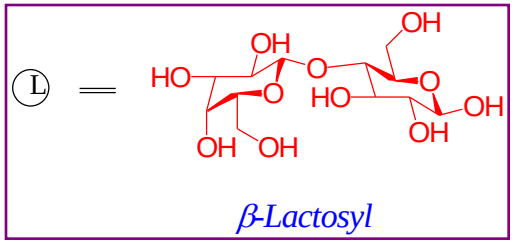
a) carbohydrate-coated dendrimer





*Pavlov, G.M. et al. Carbohydrate polymers, **1999**, 38, 195-202.*

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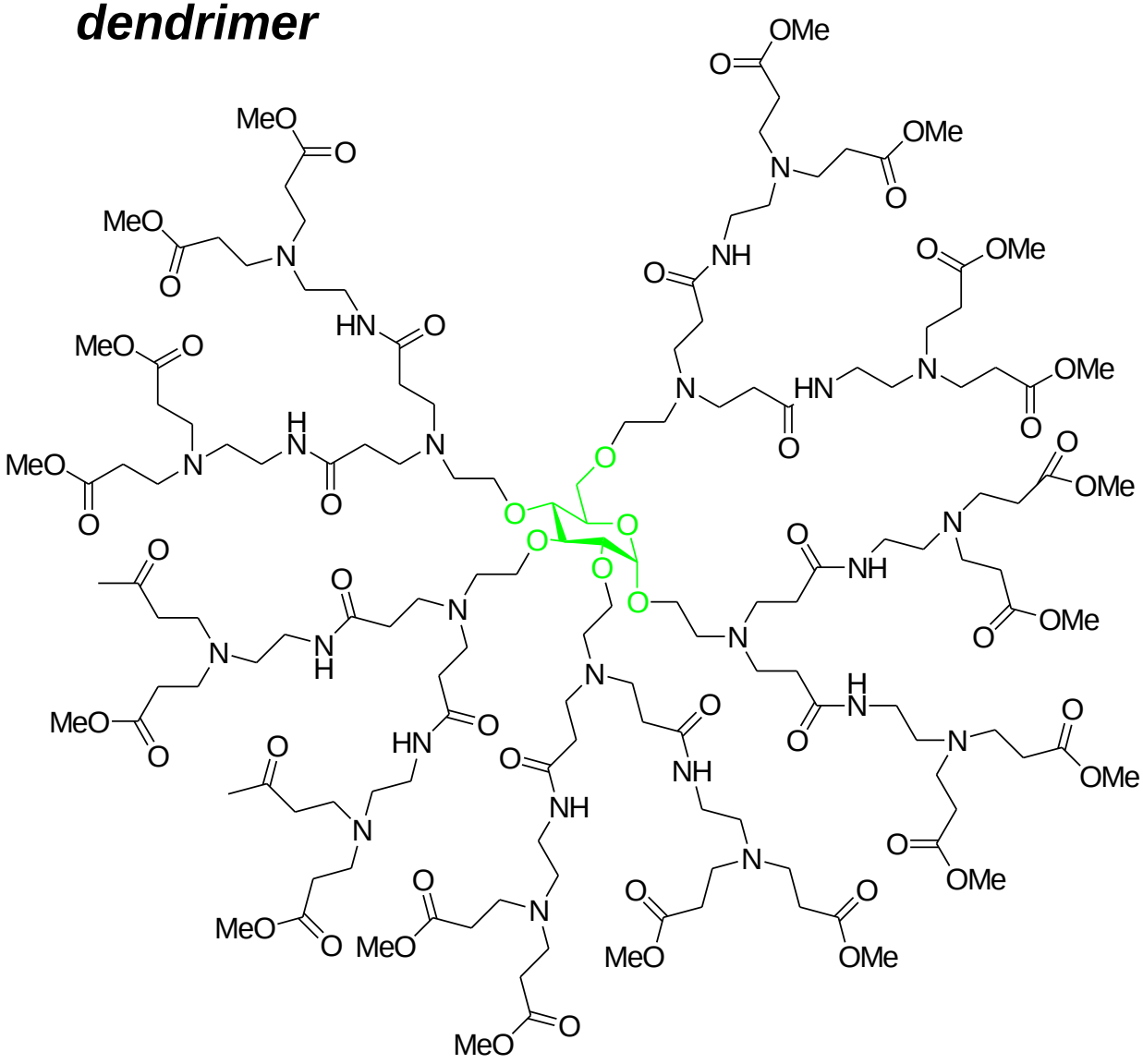
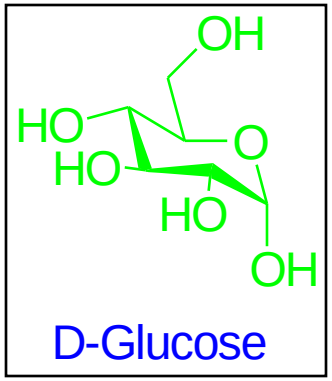
b) carbohydrate-centered dendrimer





Dubber, M.; Lindhorst, T.K. *Chem. Commun.*, **1998**, 1265-1266.

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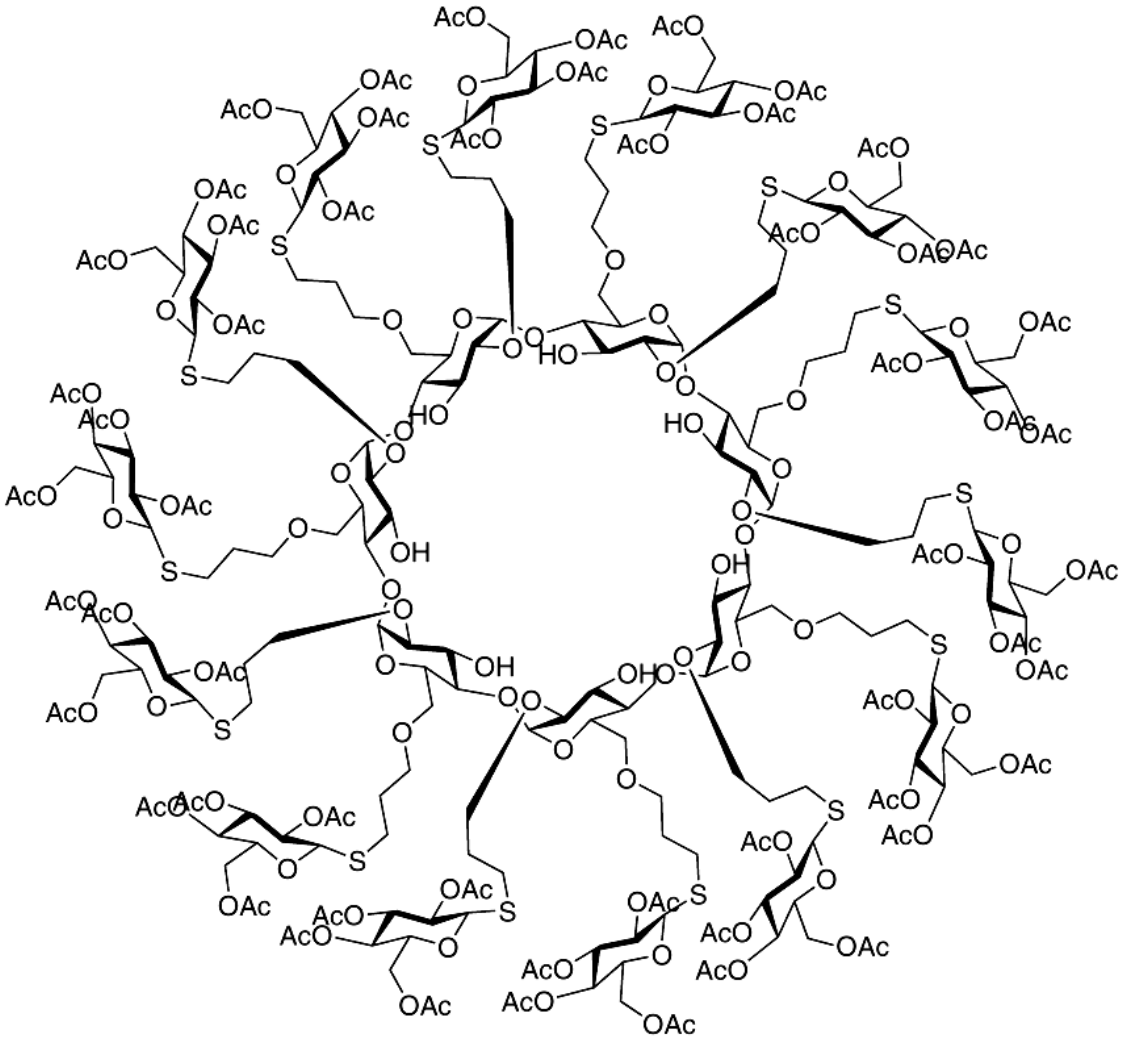
c) carbohydrate based dendrimer



β *-cyclodextrin core and 14 copies of a glycosylthiol residue*

Fulton, D. A.; Stoddart, J. F. Org. Lett. ***2000****, 2, 1113-1116.*

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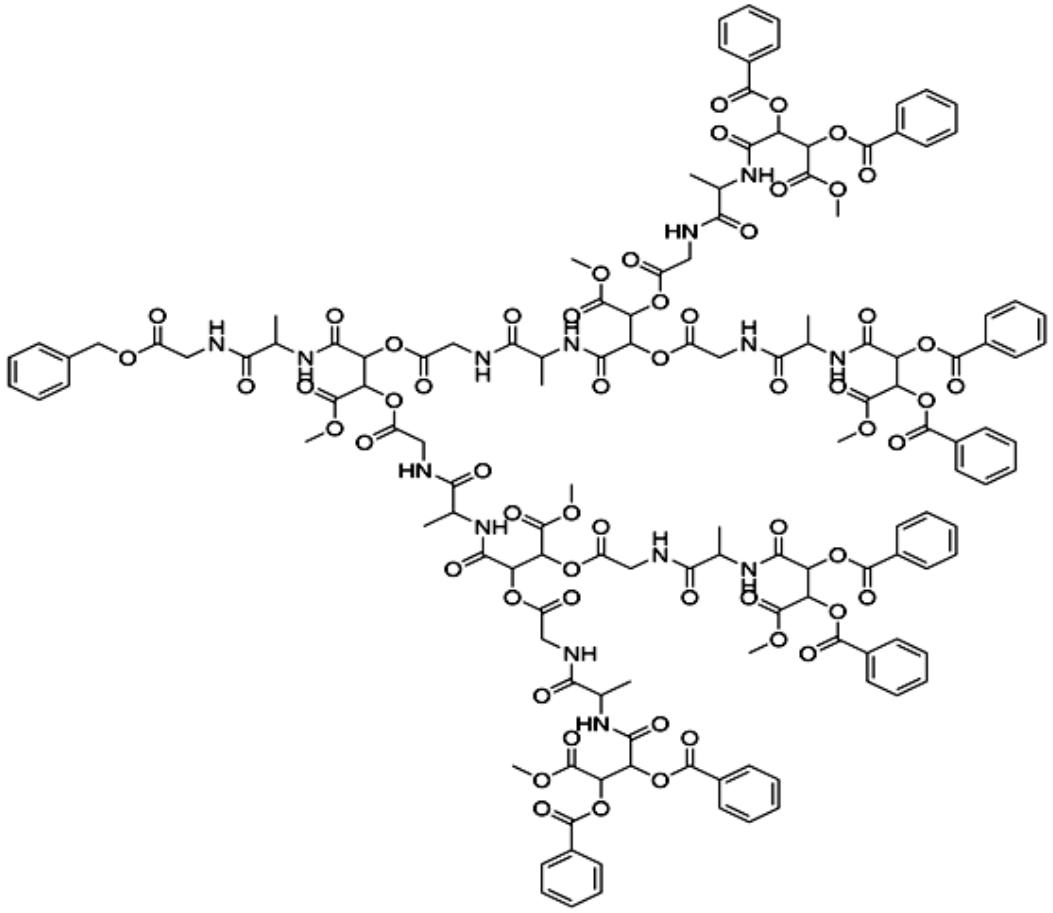
2. Peptide dendrimers:

Highly branched structures of non-natural origin that contain peptide bonds.



Structure of a third generation depsipeptide dendrimer

Kress, J.; Rosner, A.; Hirsch, A. Chem. Eur. J. ***2000****, 6, 247-257.*

Continued…

3. Janus dendrimers:

✓Name derived from ancient Romanian GOD of beginnings and transitions having two faces on his head, facing opposite directions.

A statue representing *Janus Bifrons* in the Vatican Museums

✓Formed by linking two chemically distinct dendritic building blocks, thereby **breaking the roughly spherical symmetry that characterizes most dendrimers.**

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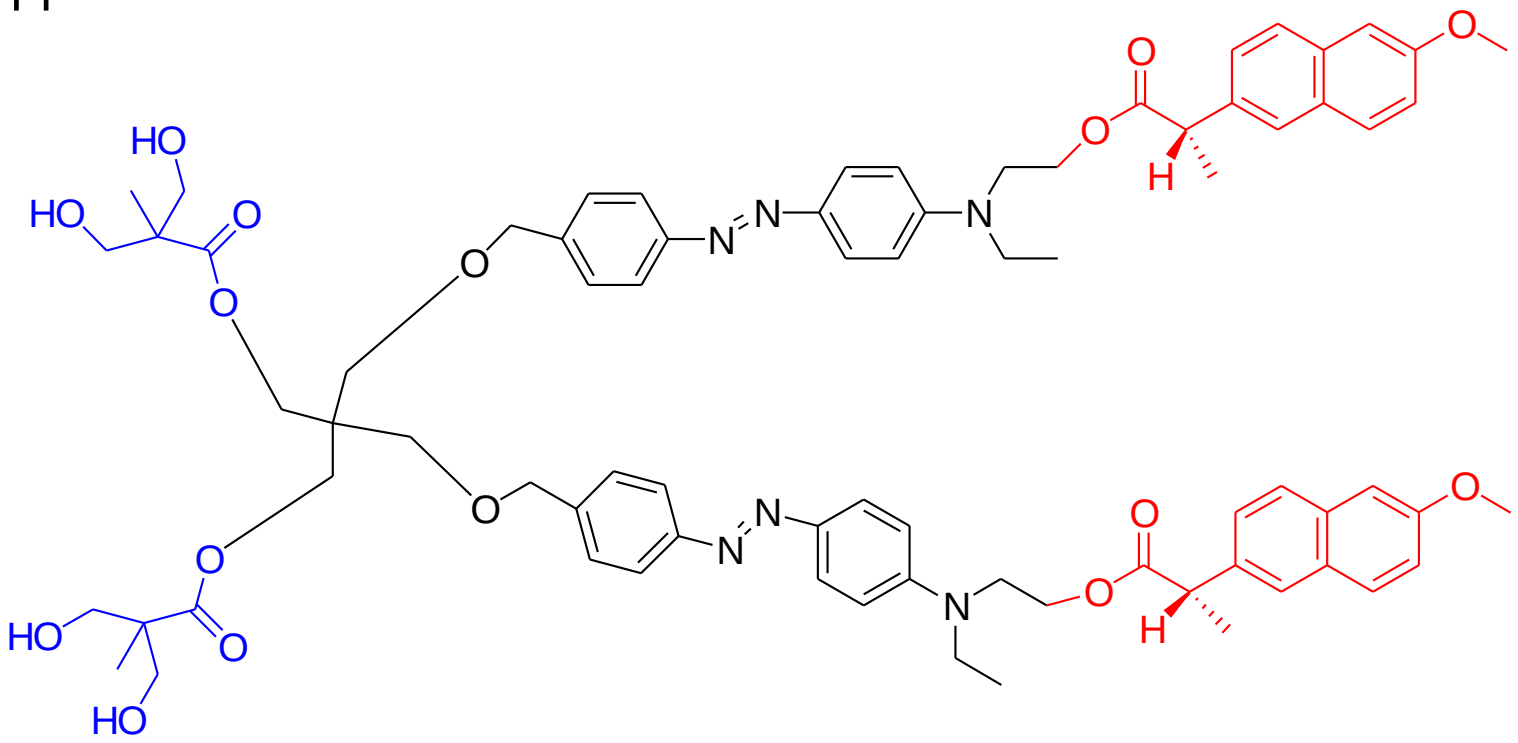
What has attracted research is the Janus thing?

Has two sides, polar on one and non polar on another (*amphiphilic).*
This bipolar configuration is very useful to molecular chemists for wide variety of applications.



Chiral azobenzene dye functionalized G1 Janus dendrimer

Chemical & Engineering News, May 24, 2010, Volume 88, Number 21, p. 7
Tuuttila, T. et al. Tetrahedron, ***2008****, 64, 10590-10597.*

4. Metallodendrimers:
Complex of a dendrimer with metal.

Structure of a first generation PPA dendrimer-metal complex

Refat, M.S. et al. *Spectrochim Acta, Part A* , **2009**, 72, 772-782.

CHARACTERISTIC FEATURES OF DENDRIMERS

1.Monodisperse single compounds.

2.Large number of end groups that increase exponentially with generations.

3.Lower molecular density.

4.More compact molecules.

5.Steric limitation to growth (*De Gennes dense packing limit*) results in more globular conformation as generations increases.

CHARACTERIZATION OF DENDRIMERS

Size and symmetry makes characterization rather difficult. Techniques used are-

1. Elemental Analysis
2. HPLC
3. NMR (^{1}H, ^{13}C, ^{15}N, ^{31}P)

Above techniques can't reveal small amounts of impurities in higher generations.

For in depth analysis-

1. ESI-MS
2. MALDI-MS
3. L-SIMS

PROPERTIES OF DENDRIMERS

Investigated by comparative studies between predictions based on theoretical calculations and experimental results by chemical analysis.

1. **Shape:**

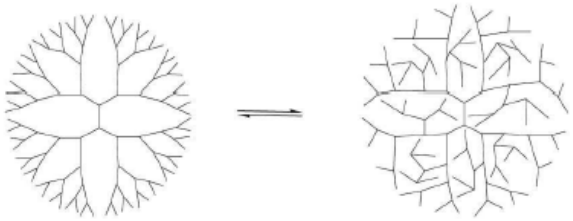
   Globular- In good solvent or bulk of the material and when the end groups are bulky.

   Flat- after interaction with the surface

   Shape deformation after coming in contact with the substrates.

2. Back folding:

- Folding of dendrons into the interior of the dendrimer towards the core.
- Observed when dendrimers are not in solver

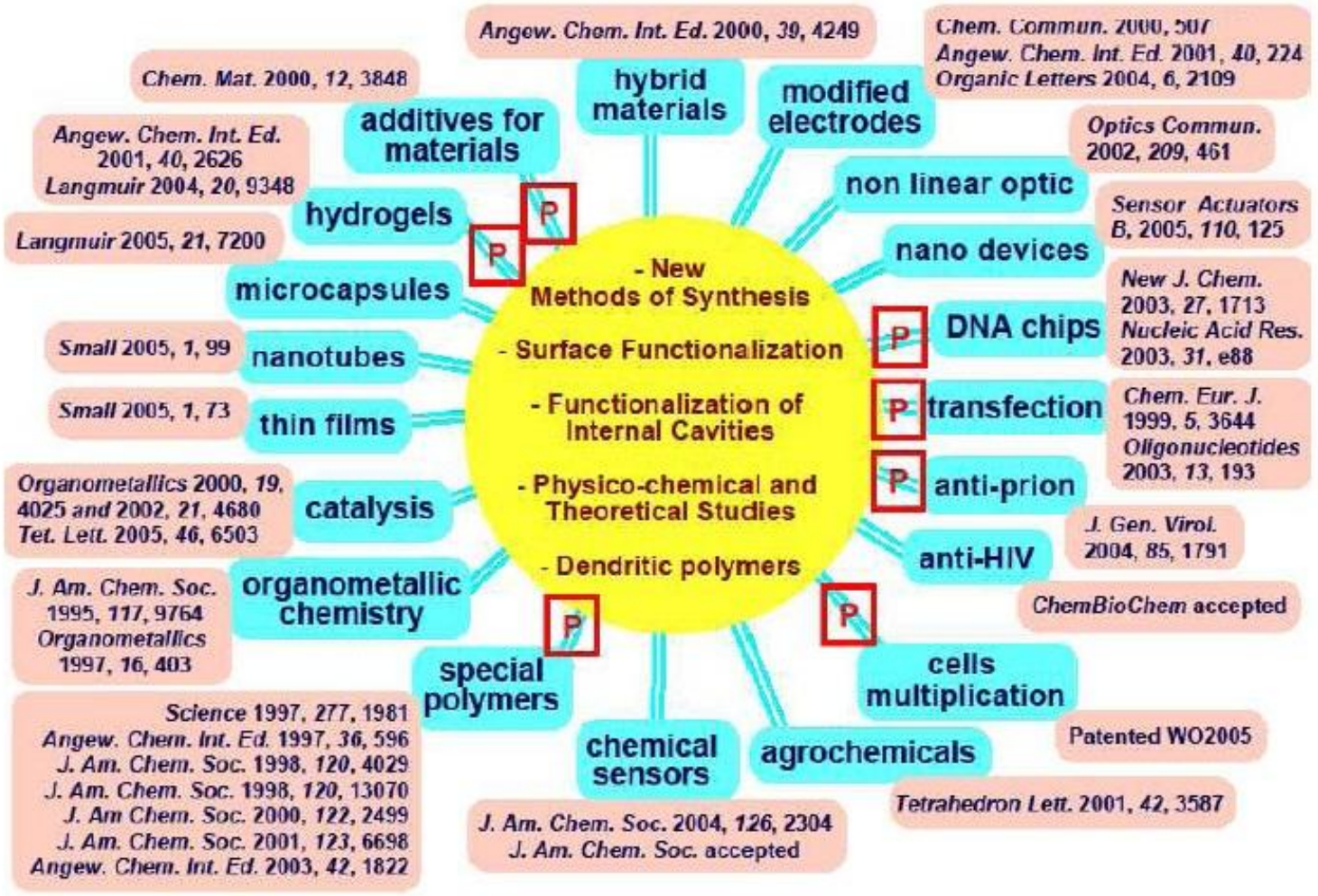


3. Intrinsic viscosity:

Does not increase with increase in the molecular weight but reaches a maximum at a certain dendrimer generation.

*a)Percec, V. et al. J. Am. Chem. Soc., **1998**, 120, 11061-70.; b)Haberecht, M.C. et al. Angew. Chem. Int. Ed., **2008**, 47, 1662-67.*

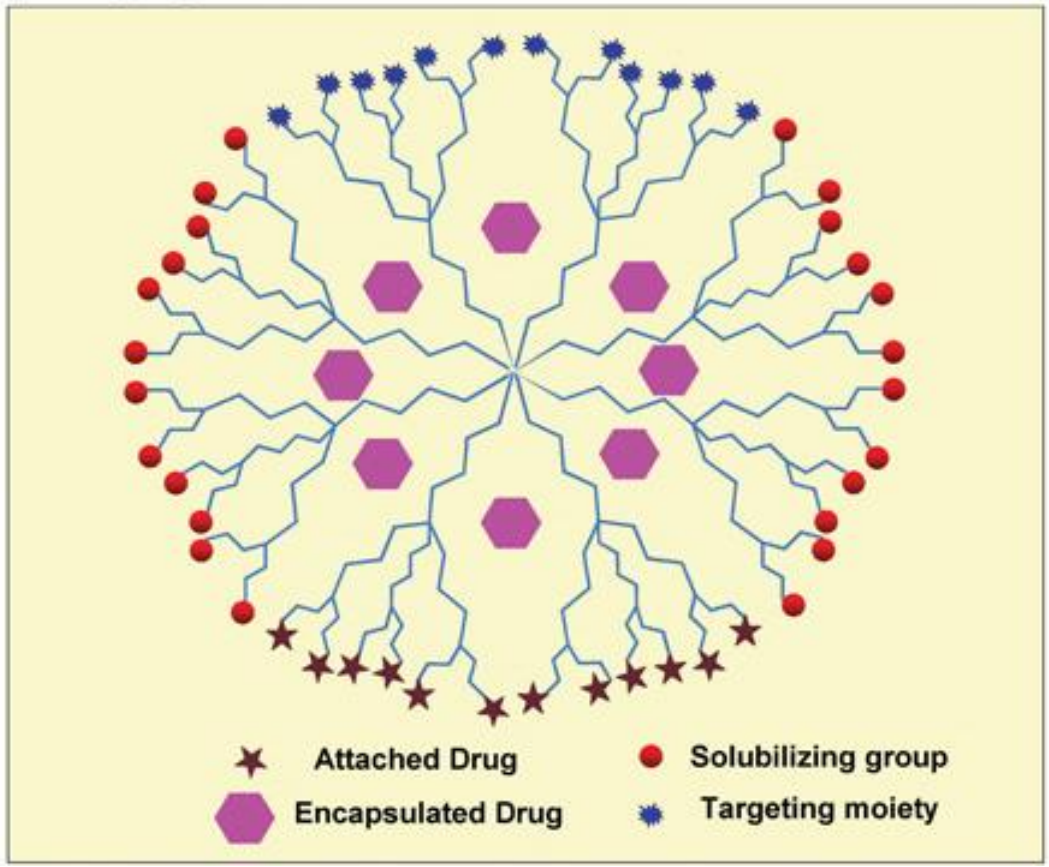
Applications of Dendrimers



Dendrimer in Pharmaceutical Technology

PHARMACEUTICAL APPLICATIONS OF DENDRIMERS

1. Vehicles for drug delivery, solubility enhancement of poorly soluble or practically insoluble drug molecules and controlled release of drugs.



Adapted from: Dendrimers & Dendrons: Facets of Pharmaceutical Nanotechnology: Sakthivel and Florence, Drug Delivery Technology, www.drugdeliverytech.com, accessed 10/02/2006

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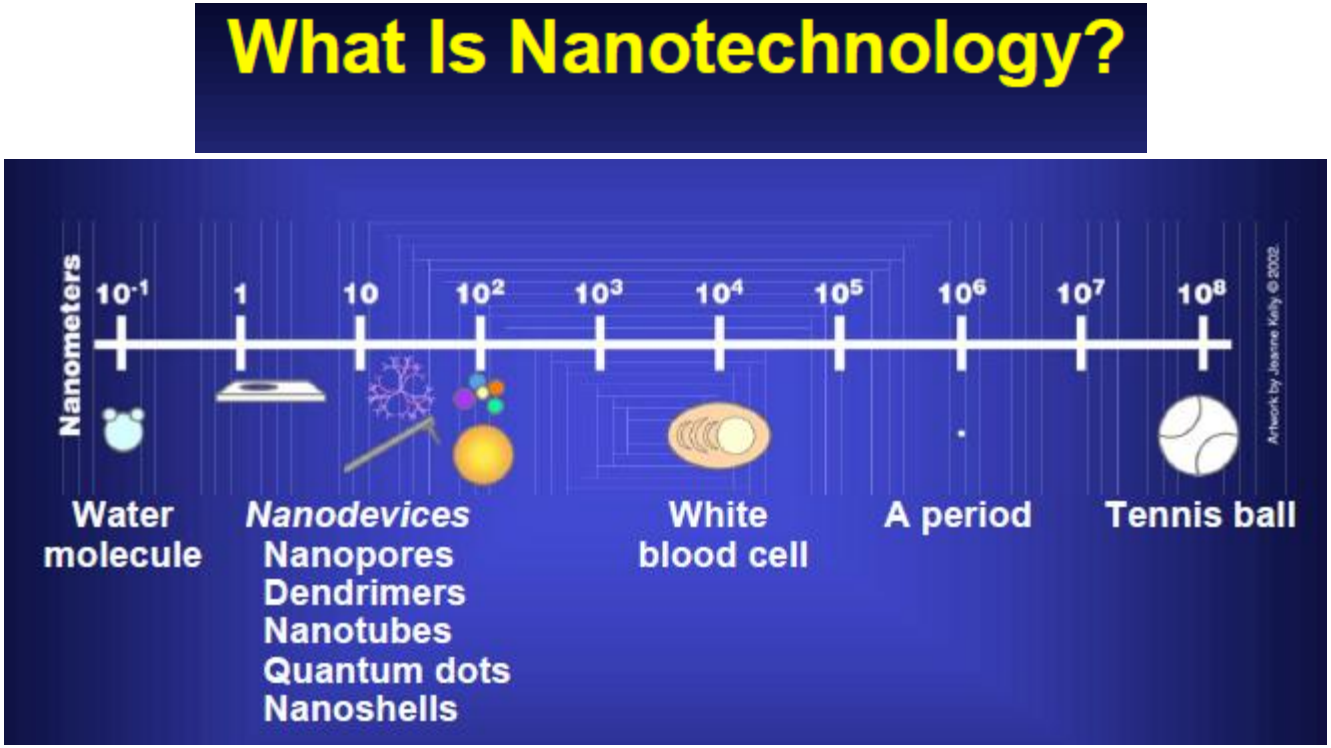
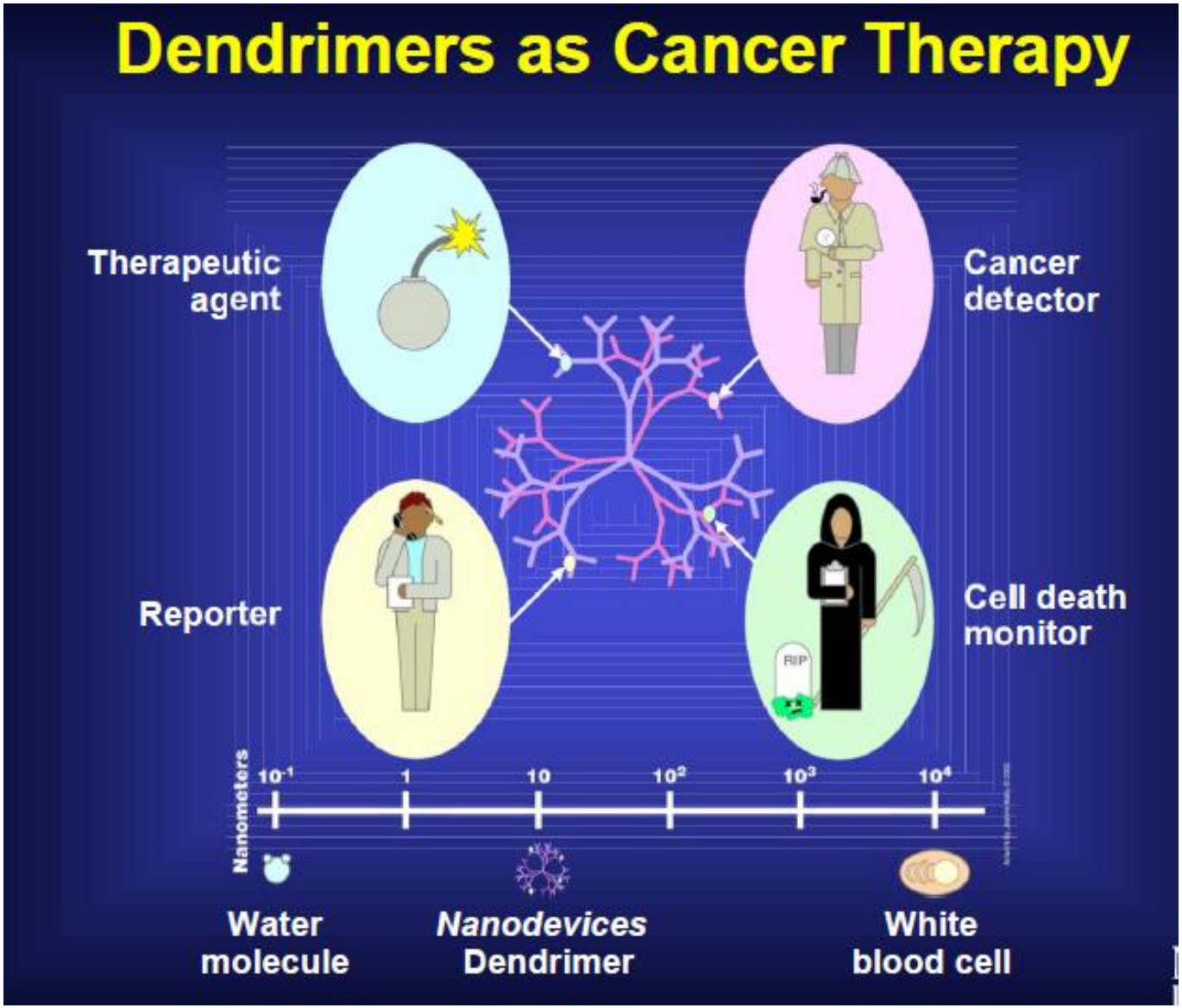
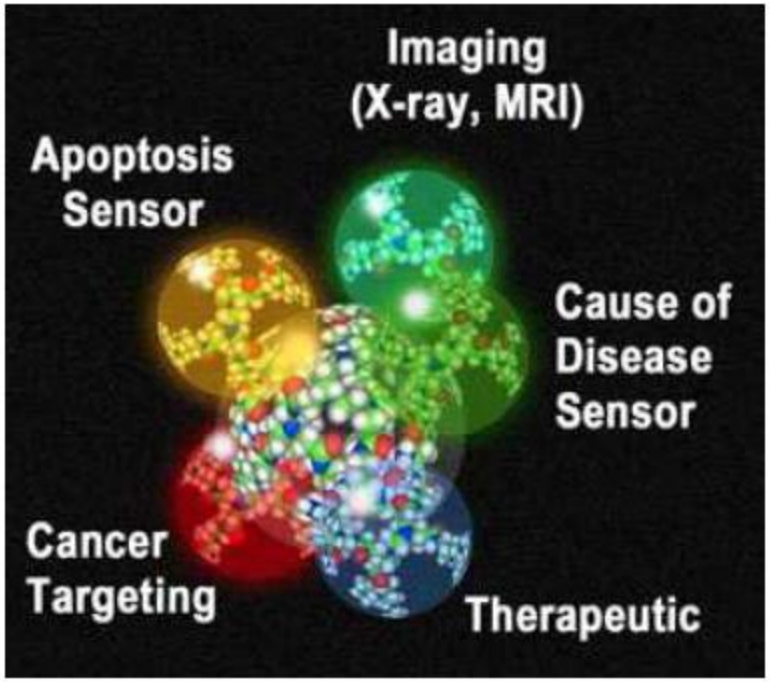
Nanodevices





A single dendrimer can carry a molecule that recognizes cancer cells, a therapeutic agent to kill those cells, and a molecule that recognizes the signals of cell death. Researchers hope to manipulate dendrimers to release their contents only in the presence of certain trigger molecules associated with cancer. Following drug release, the dendrimers may also report back whether they are successfully killing their targets.

Tagged Dendrimers: Various Applications



Various tags can be associated with the dendrimer to:

- Recognize target (cancer cells)
- Diagnose cause of the disease
- Deliver drug to target
- Report location (of tumor)

Targeted drug delivery: *Cancer cell targeting*

Doxorubicin polyester dendrimers complex with a clevable acetal shell. The drug could be delivered after hydrolysis of the acetal functions under mild acidic conditions, similar to the pH present in endosomes, with the hope of obtaining better delivery to the cancer cells.

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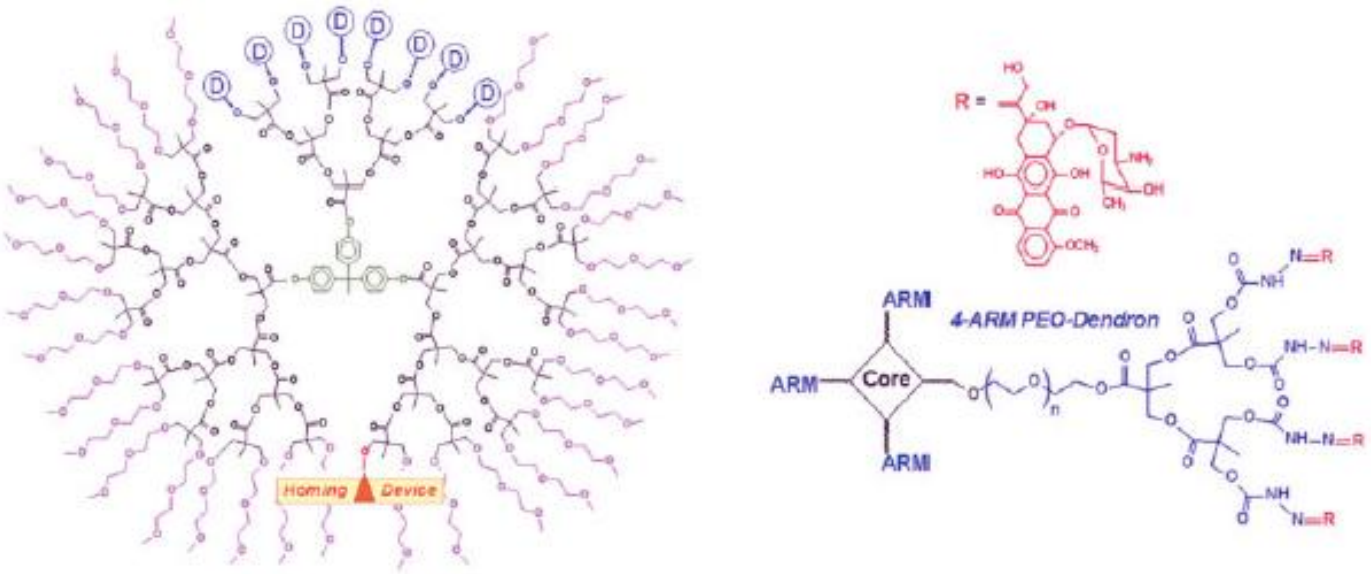
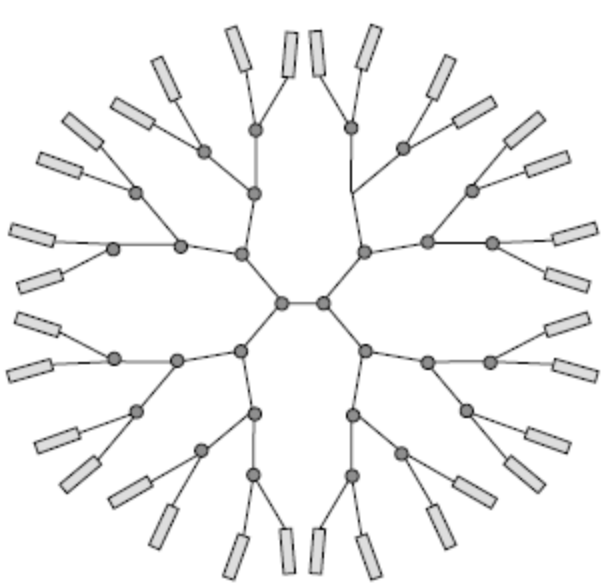


Figure 11. General concept of the targeted dendrimer–drug conjugate with multiple copies of the drug (D) attached to the dendrimer by a cleavable linkage (left) and a four-arm PEO dendron used for the delivery of the anticancer drug doxorubicin (right; refs. 98–100).



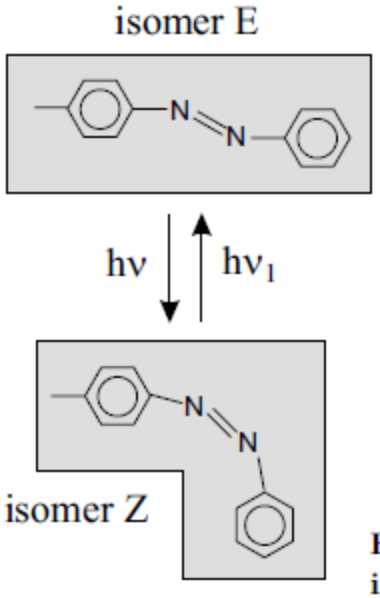


Figure 6. Dendrimer terminated in azobenzene groups [16].

A fourth generation polypropylene imine dendrimer with 32 end groups was terminated in azobenzene groups (Fig. 6). 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.

Vaccines:

Peptide dendrimers for vaccine and immunization purpose.

Preparation of the prodrugs:

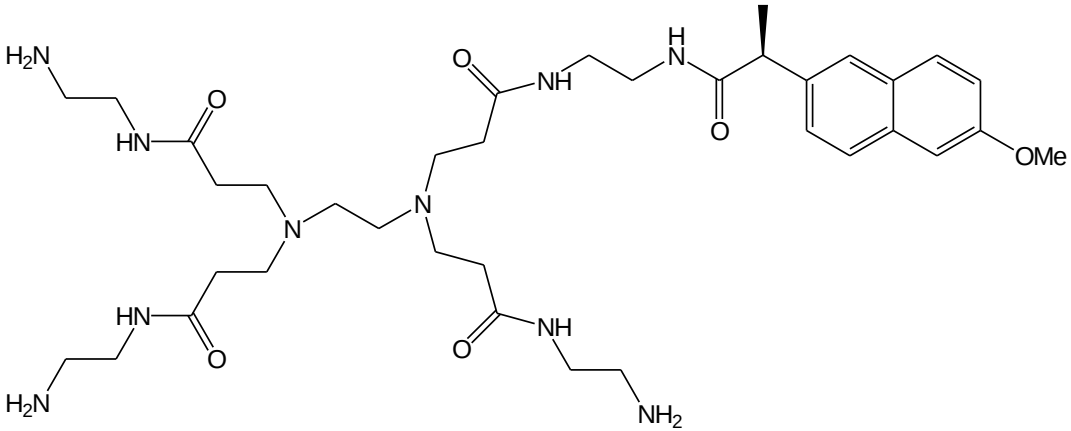


Fig. G0-PAMAM-Naproxen prodrug

*Moreno, R. et al. ChemBioChem, **2001**, 2, 838-843; **2002**, 3, 270.*

*Najlah, M. et al., Int. J. Pharm., **2006**, 308, 175-182.*

Continued

7. As drugs:

a) Antiinflammatory properties of naked, unmodified PAMAM.
b) Antibacterial activity of anionic amphiphilic dendrimers.

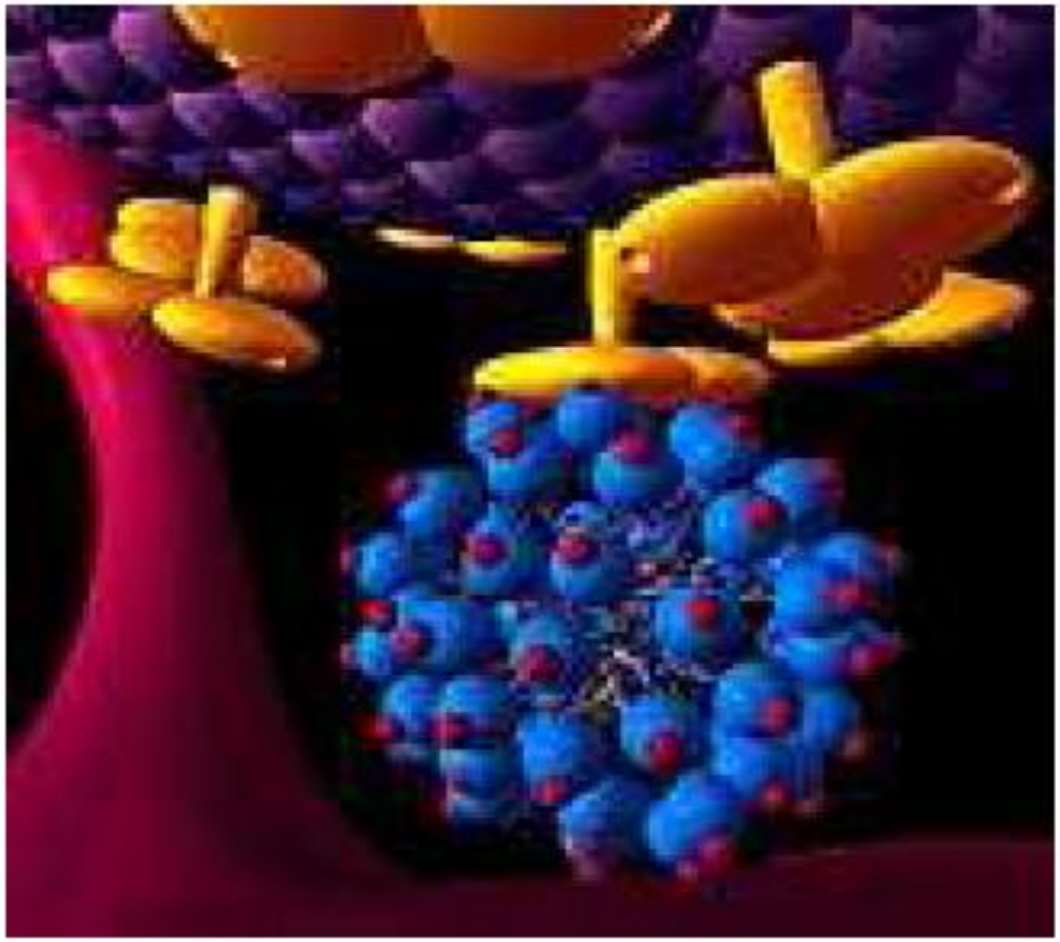
8. As HIV prophylactic:

starpharma

- Viva gel® developed by Australian company -
- *Active ingredient*: G4 polylysine dendrimer called SPL7013
- Molecule's surface is decorated by the thirty-two naphthalene disulfonate moieties, attached via amide linkages.
- Polyanionic structure binds to the gp120 glycoprotein receptors on the virus surface.

*Chauhan, A.S. et al. Biomacromolecules, **2009**,10, 1195-1202.*
*Meyers, S.R. et al. J. Am. Chem. Soc., **2008**, 130, 14444-45.*

Continued……



The dendrimers (blue and red) in VivaGel interact with protein structures (yellow) on the surface of HIV, blocking the interaction of HIV (purple) with healthy human cells (pink) that results in HIV infection.

Possible Adverse Effects

- **Cytotoxicity** (increases with both, concentration and generation of the dendrimer)

- *In vivo* study by Roberts at al. with PAMAM 3rd, 5th and 7th gen. (J. Biomed. Mater. Res., 30,1996, 53-65): no behavioral toxicity, normal growth pattern, no macroscopic or microscopic abnormalities, no immunoresponse or carcinogenicity were observed ($5 \cdot 10^{-9}$ - $5 \cdot 10^{-7}$mol/kg)

- Broader range of PAMAM, polypropyleneimine (PPI) and polyethylene oxide (PEO) grafted carbosilane dendrimers was tested *in vitro* by Malik et al. (*J. Control. Release* 83, 2000, 133-148). Dendrimers possessing amino groups were the most toxic – charge-dependent negative outcomes. In general, regardless the structure, **cationic dendrimers were hemolytic and cytotoxic**. On the other hand, dendrimers with carboxylate or PEO groups on the surface were neither hemolytic nor cytotoxic towards a panel of cell lines.

- i.v. administration of amino-terminated PAMAM changes red blood cell (RBC) morphology (echinocytic transformation, irregular contour due to the folding of the periphery) eventually leading to **hemolysis**.

- *In vitro* clustering (**agglutination**) of RBCs – likely the aggregation and adhesion to the walls of blood vessels is caused by diminishing natural electrostatic repulsion among RBCs by cationic PAMAM.

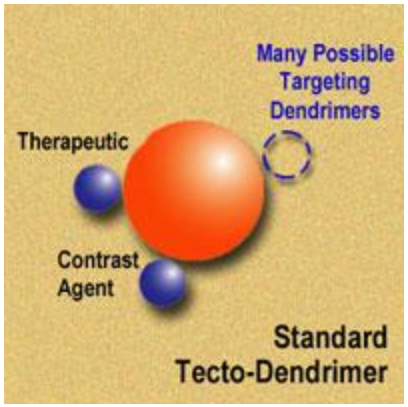
- It is possible to modify the positively charges surface functionalities by polyethylene glycol (PEG) or by lauroyl chains or use melamine dendrimers.

- Undesirable effects for cationic dendrimmers are expected to be compensated by low concentrations of dendrimers necessary to use.

RECENT ADVANCEMENTS

1. Tecto-dendrimers:

Consists of a central dendrimer as a core with multiple dendrimers at its periphery.



The surrounding dendrimers are of several types holding promise for multidrug delivery and environmental remediation applications.

Each type designed to perform a function necessary to a smart therapeutic nanodevice.

- *Diseased cell recognition*
- *Diagnosis of disease state*
- *Drug delivery*
- *Reporting location*
- *Reporting outcome of therapy*

Continued….

Possible outcomes from tecto-dendrimers

Cancer treatment, Treatment of viral infections, Cure of parasitic infections
Possibility of targeting parasites which are hiding inside human cells.
e.g. malaria.

http://nano.med.umich.edu/platforms/Tecto-Dendrimers.html (browsed on August 10, 2011)

Welch, P.M.; Welch, C.F. *Macromolecules*, **2009**, 42, 7571-7578.

2. Dendrimersomes and other complex architectures:

Self-assembly of amphiphilic Janus dendrimers results in-dendrimersomes, cubosomes, disks, tubular vesicles and helical ribbons.

Types of Dendrimersomes:

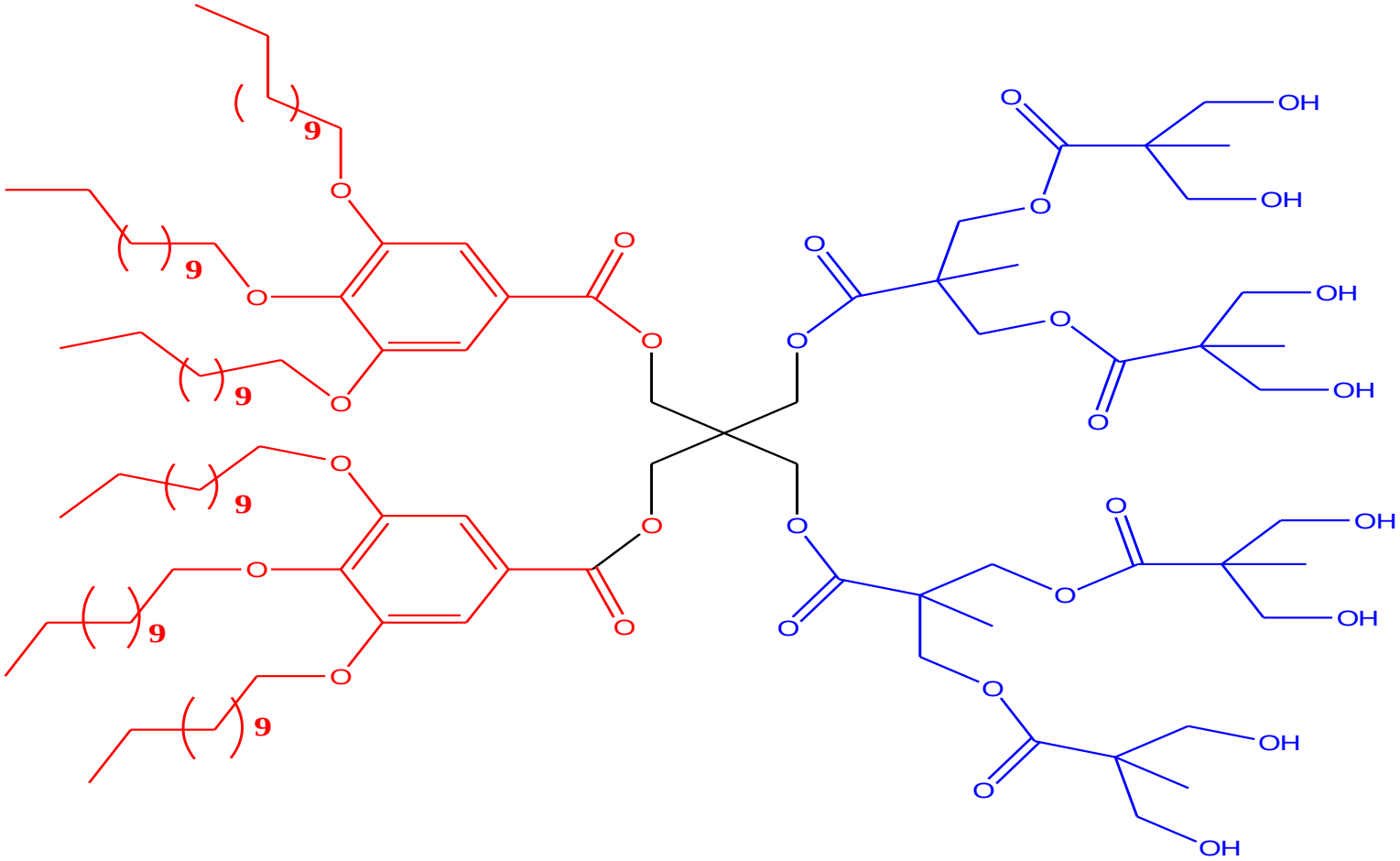
1. Small Unilamellar Dendrimersomes (SUD)
2. Large Unilamellar Dendrimersomes (LUD)
3. Giant Unilamellar Dendrimersomes (GUD)

Methods of Preparation:

a. *Solvent Injection* and
b. *Film Hydration*

Continued……

Structure of G1 Janus dendrimer forming dendrimersomes

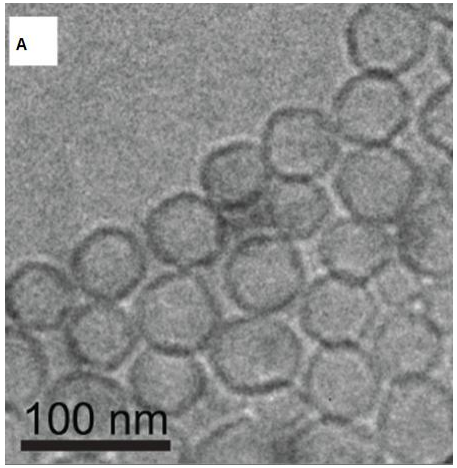


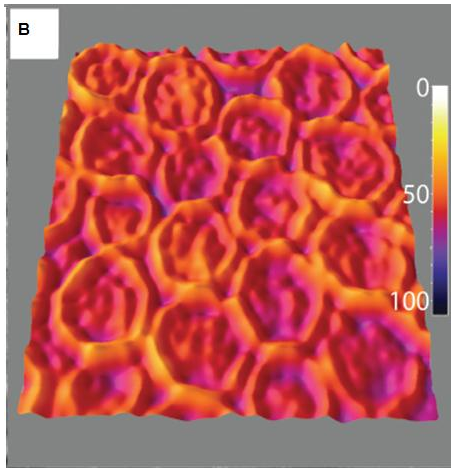
Advantages over polymerosomes and liposomes:

a) Stable for longer periods of time, b) Highly uniform in size, c) Have proper dimensions to accommodate membrane-spanning proteins, d) Easily functionalized

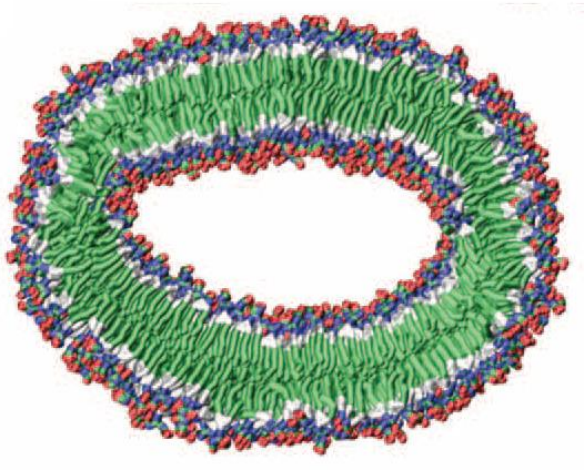
Continued…..

Virgil Percec et al. *Science*, 21 May **2010**, 328, 1009-1014.





(A) Cryo-TEM of dendrimersomes in ultrapure water formed by ethanol injection and (B) their 3D intensity profile.



Dendrimersome: cross-section shows its cell-membrane-like bilayer by CG molecular dynamics.

OTHER APPLICATIONS

Light Harvesting

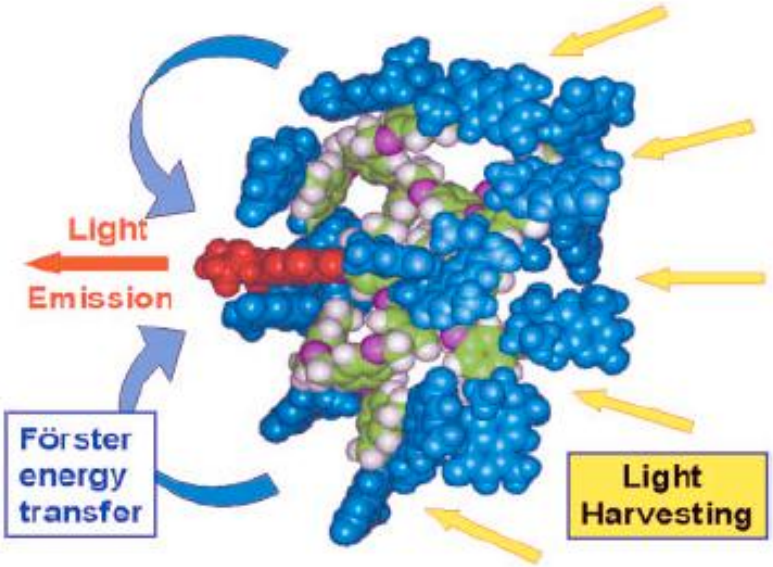


Figure 4. Light-harvesting antenna. Light harvested by all the chromophores (blue and red) is concentrated at the focal-point (red) acceptor chromophore and re-emitted as monochromatic radiation.

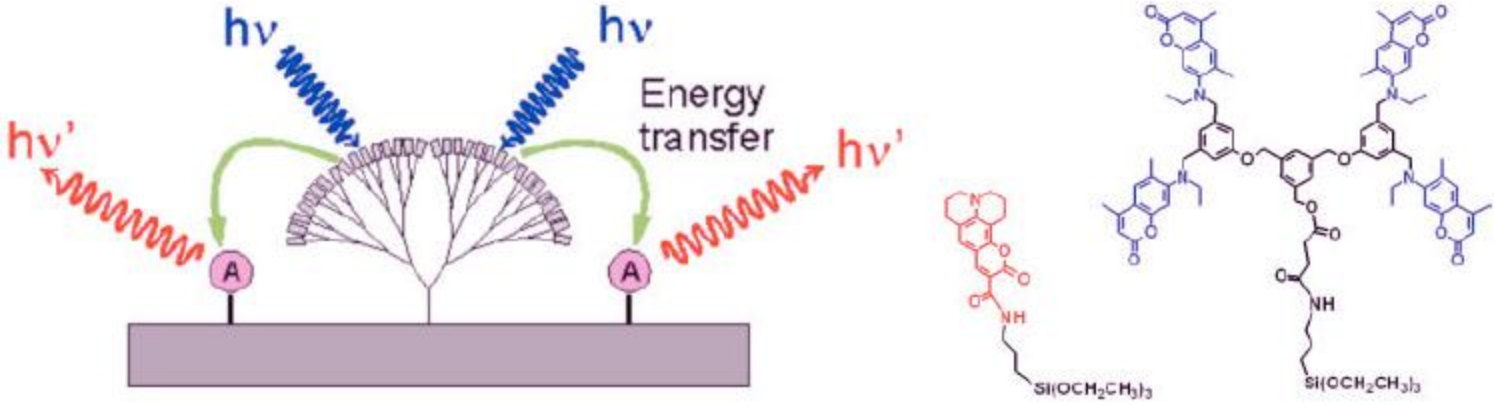
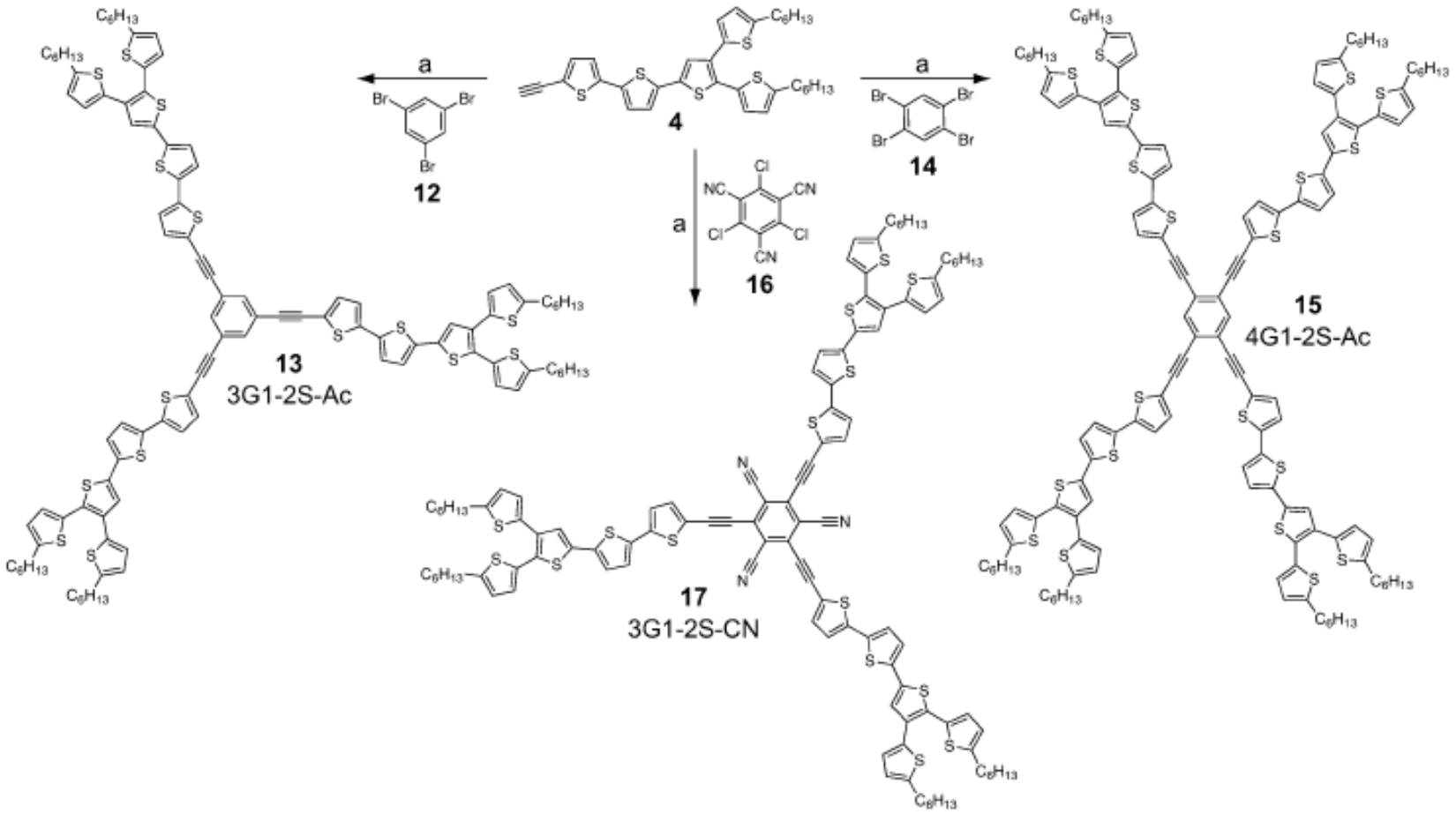
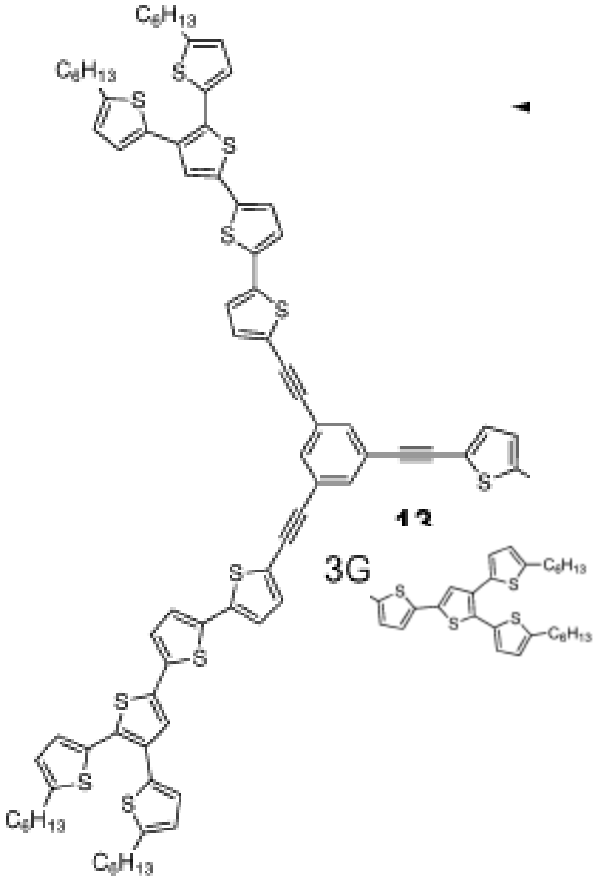
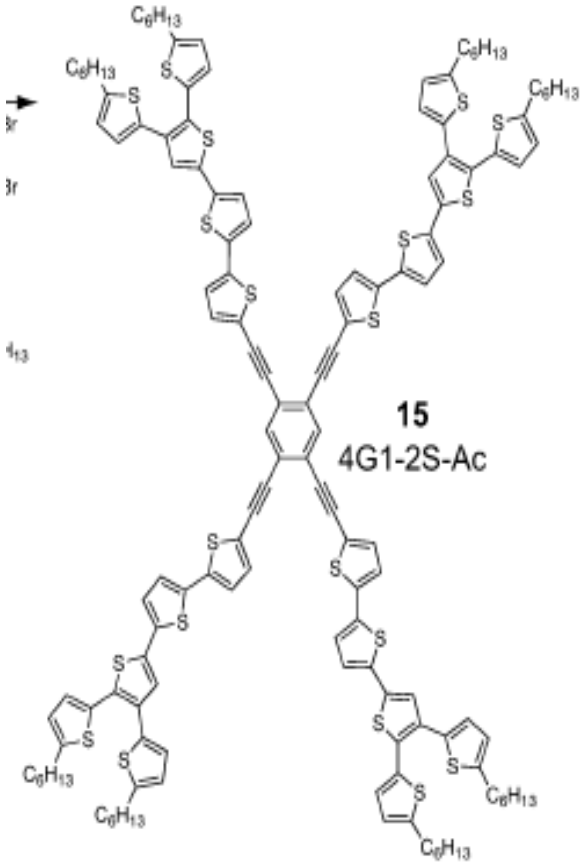


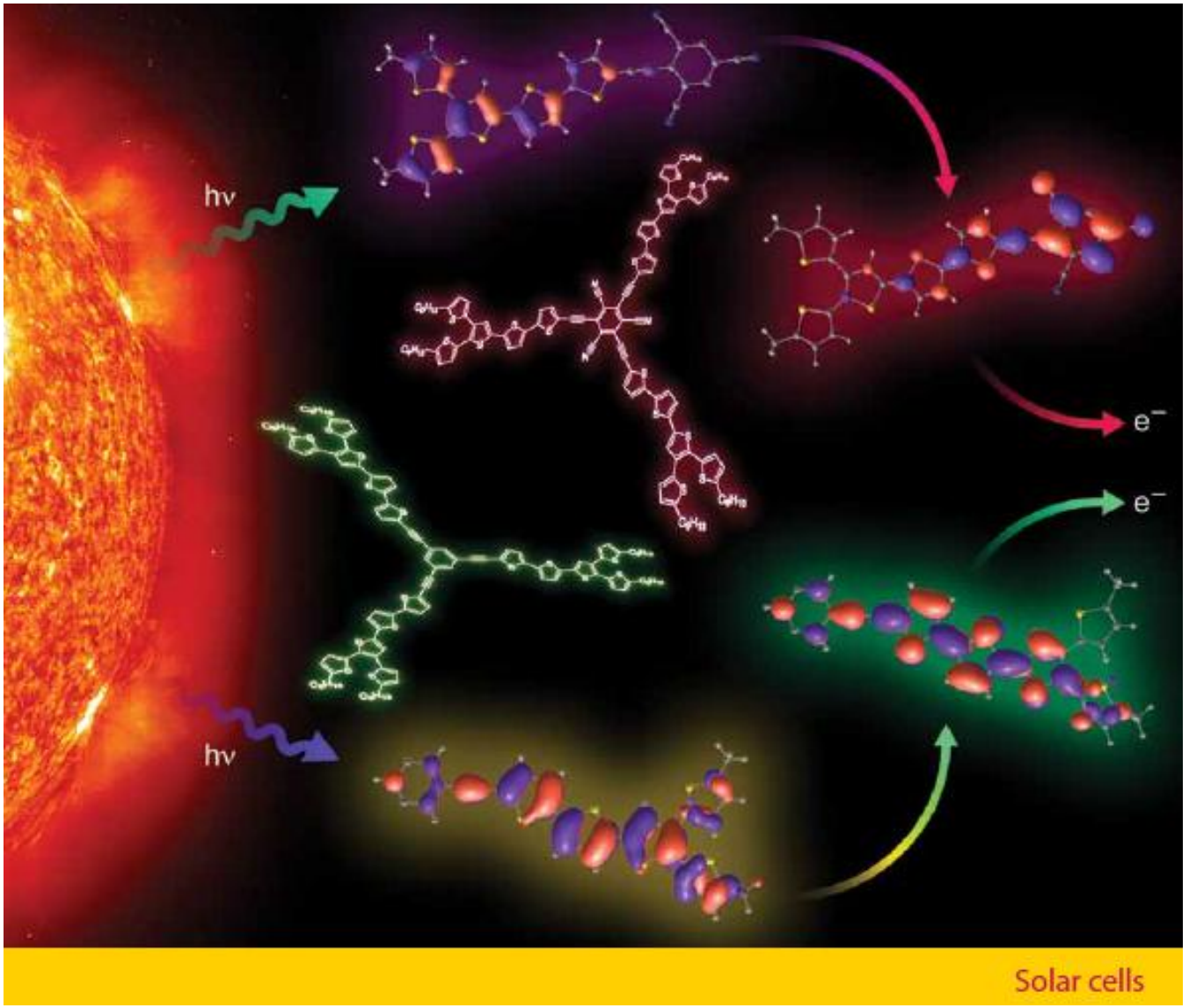
Figure 5. Multichromophoric light-harvesting antenna self-assembled on a surface such as silicon (right) and the donor (blue) and acceptor (red) chromophores used to prepare the light-harvesting monolayer (left).

http://www3.interscience.wiley.com/cgi-bin/fulltext/106558159/PDFSTART


a
12
4
a
14
a
16
13
3G1-2S-Ac
15
4G1-2S-Ac
17
3G1-2S-CN


3G


15
4G1-2S-Ac


hν
hν
e⁻
e⁻
Solar cells

Organic Light Emitting Diodes

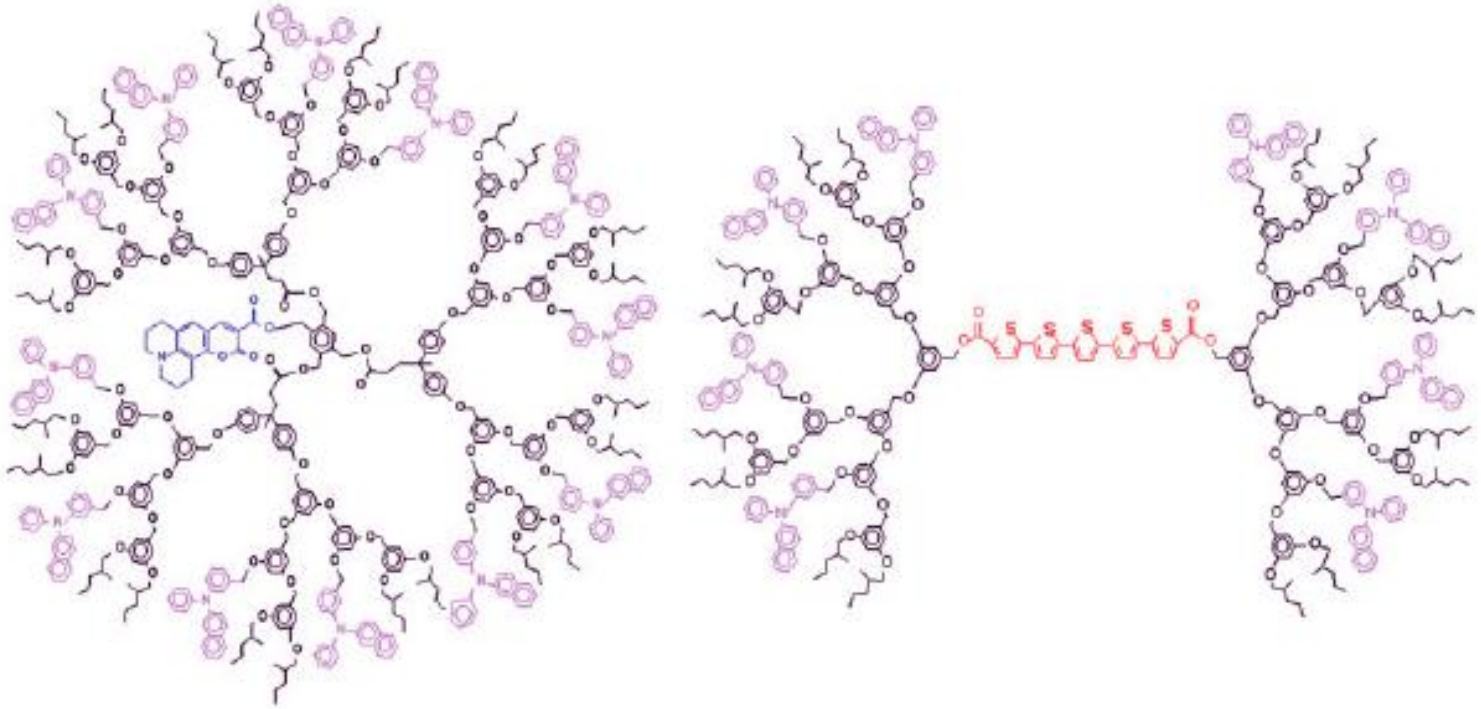


Figure 7. Two encapsulated chromophores used as a mixture capable of simultaneous emissions in an organic light-emitting diode. The coumarin moiety (the blue structure on the left) has been enlarged for clarity.

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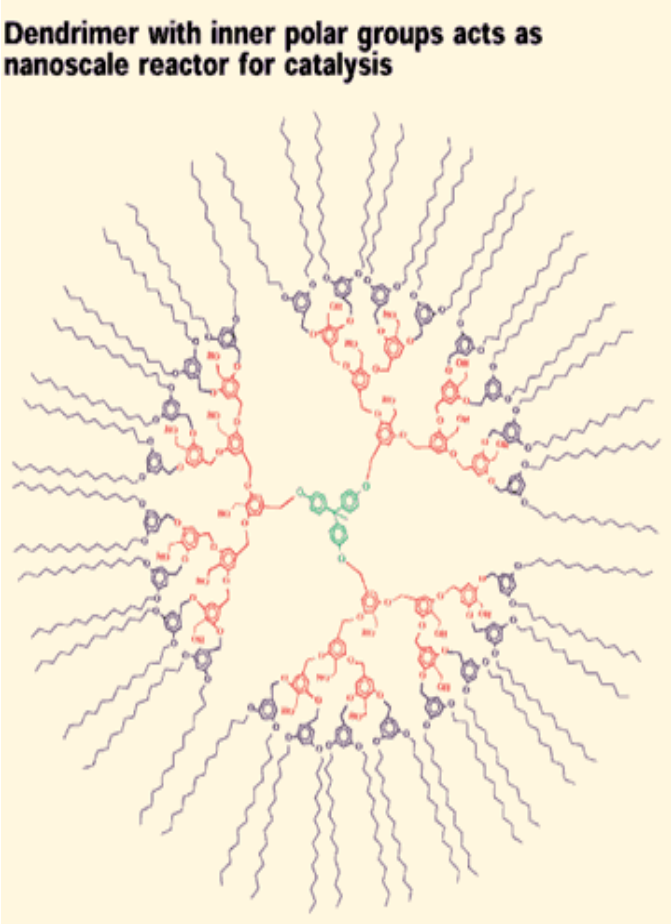
Catalysis



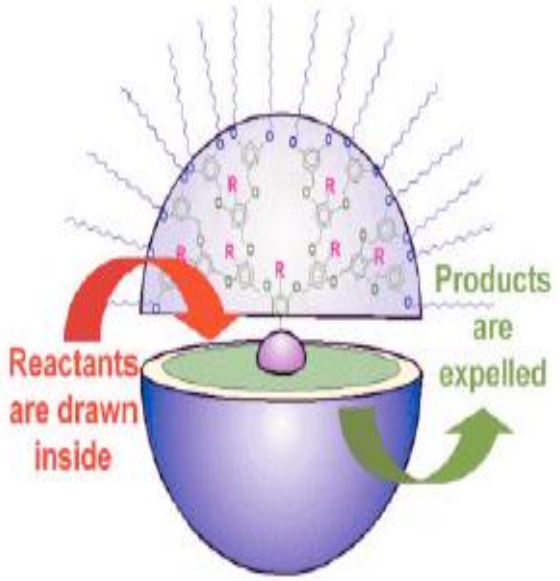
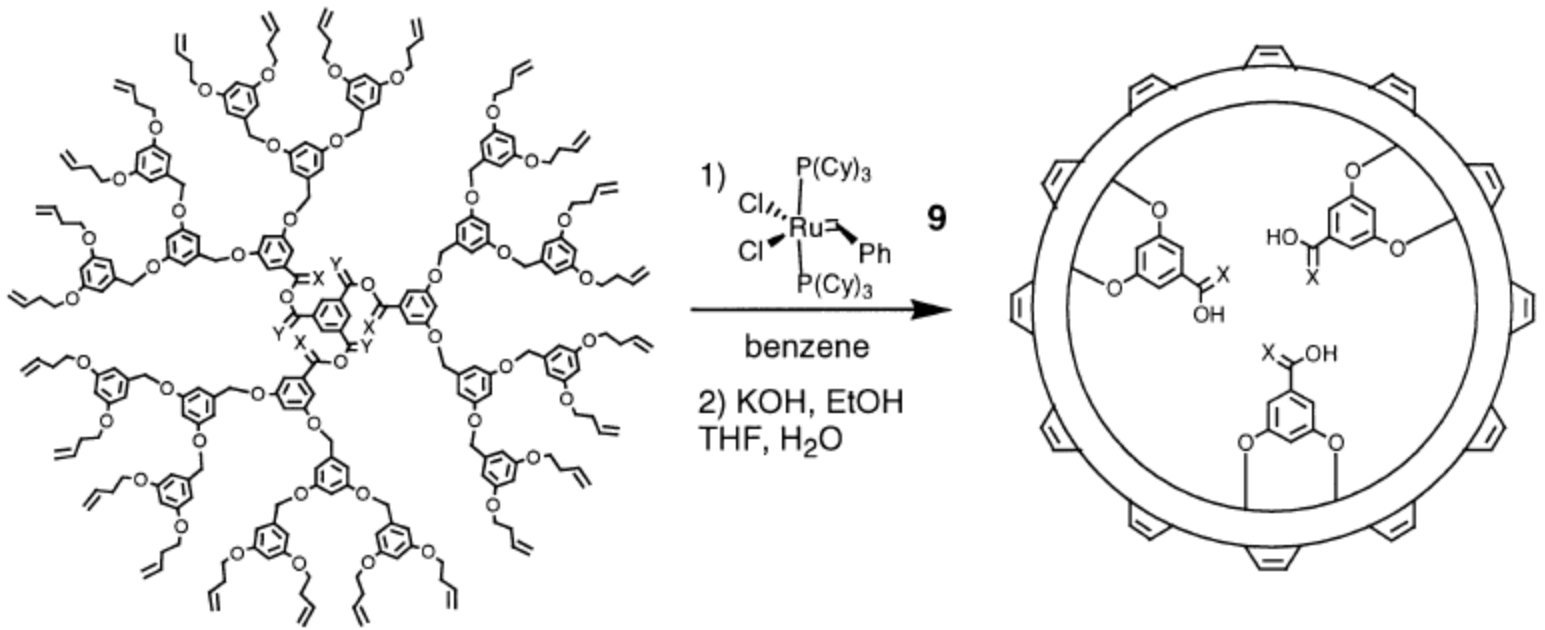


Figure 9. Dendrimer as a catalytic nanoreactor ensuring mass transfer in and out of the dendrimer interior in which the reaction takes place.

http://perceco2.chem.upenn.edu/~percec/inthenews/denx.html

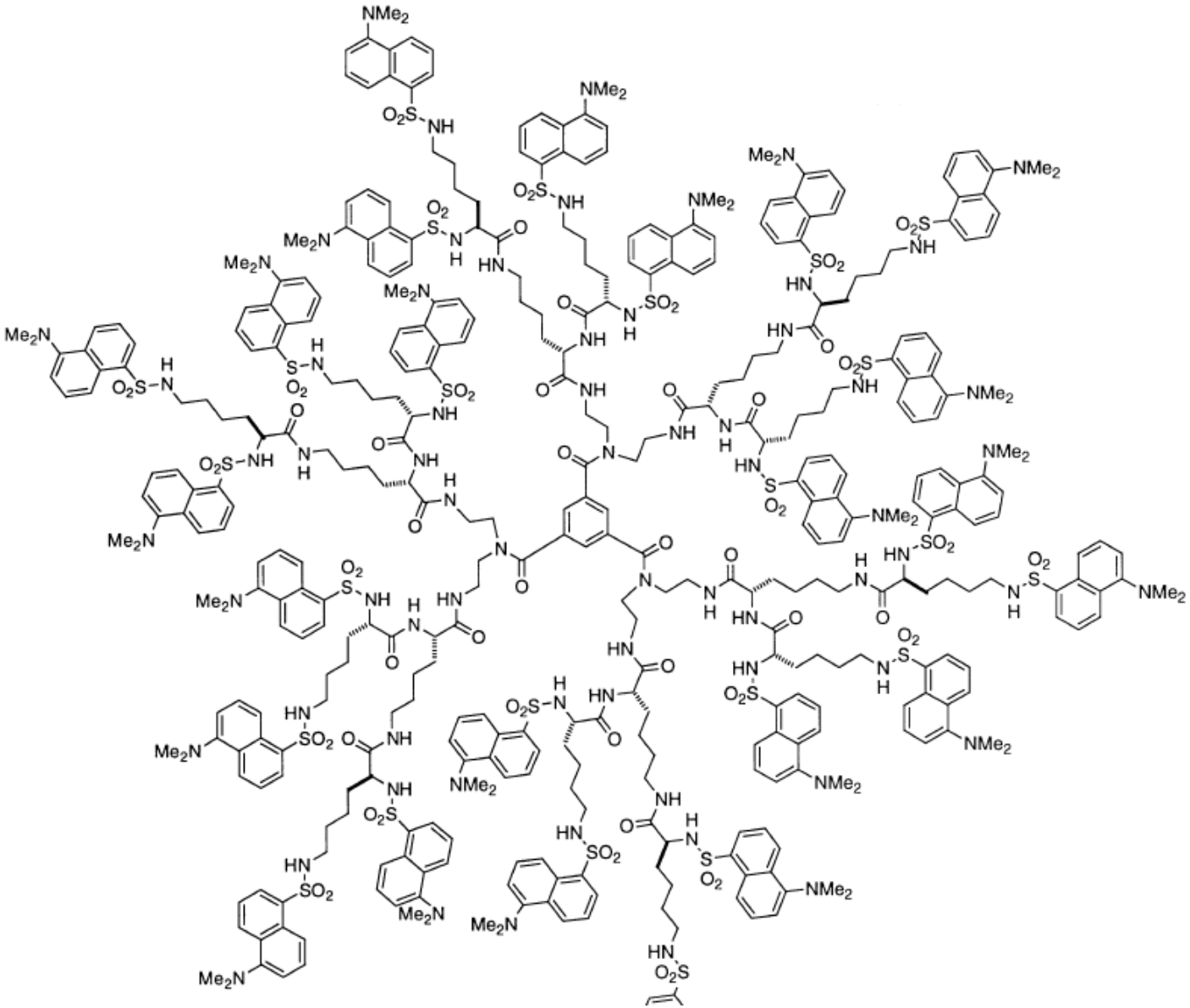
http://www3.interscience.wiley.com/cgi-bin/fulltext/106558159/PDFSTART



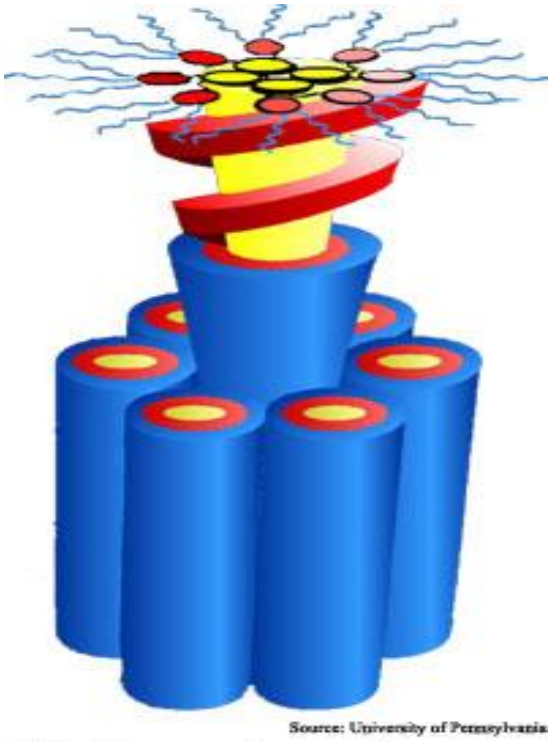
7 : X = H,H; Y = O
8 : X = O; Y = H,H

10 : X = H,H
11 : X = O

Scheme 1. Wendland and Zimmerman process for "coring" dendrimers. Cross-linking with the ring closing metathesis reaction is followed by basic hydrolysis/alcoholysis which removes the core unit



Nanowires



This diagram shows microscopic wires made from electrically-conductive molecules attached to branched polymers that spiral around the cores to form insulating layers. The electrically-conductive cores are yellow and the polymers are red and blue.

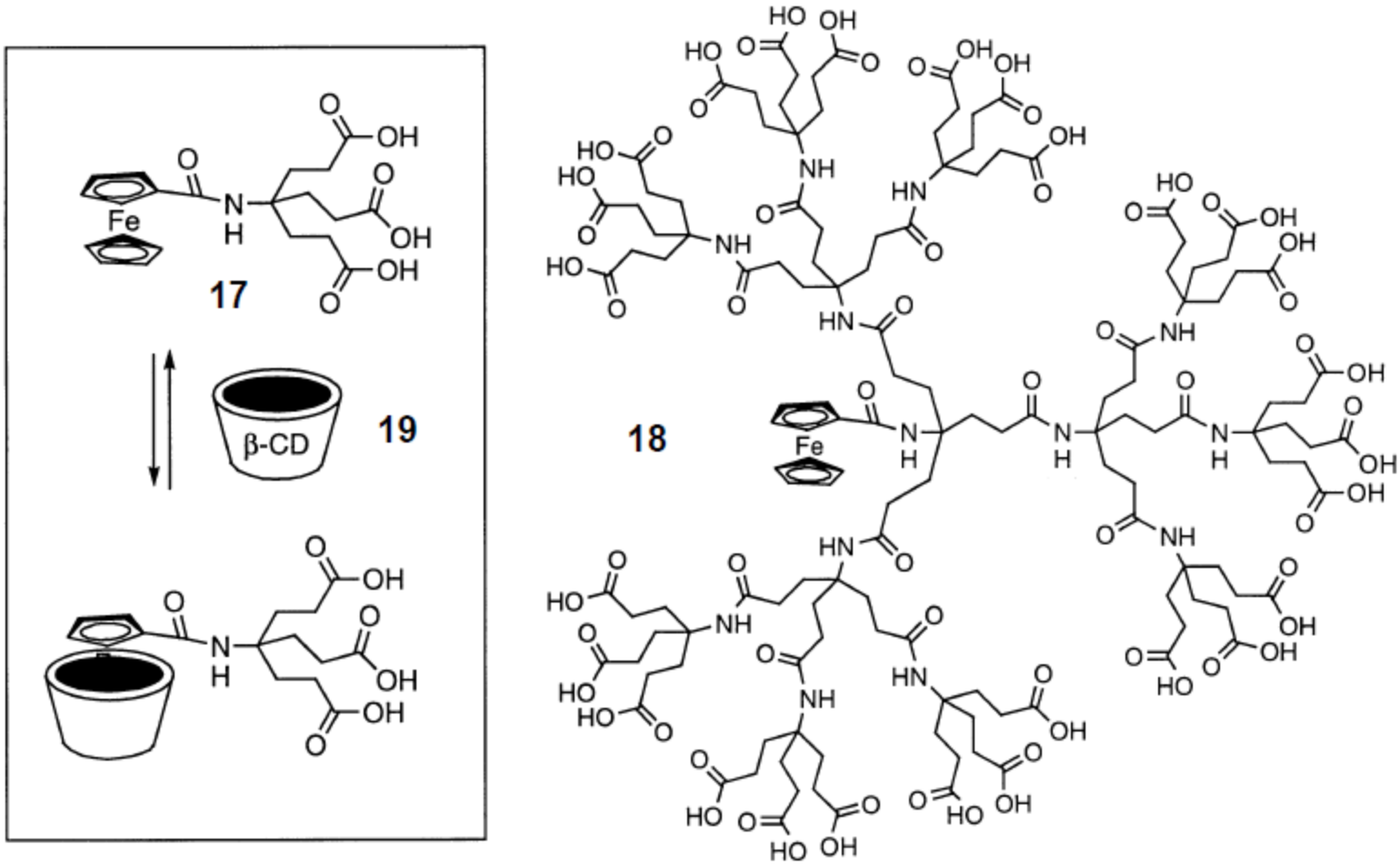
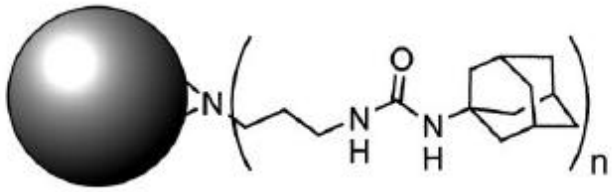
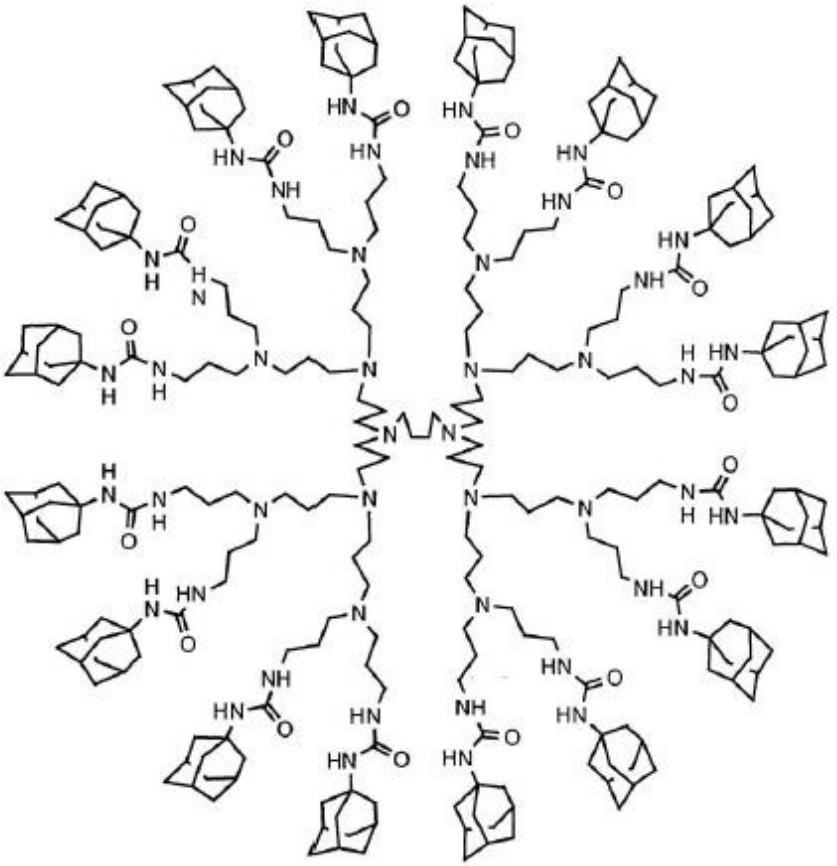


Fig. 4. Kaifer's third-generation Newkome-type dendrimer with a ferrocene core (18). Equation showing ferrocene complexation (first generation, 17) into the secondary side of β-cyclodextrin (19)



n	compd no.
4	**24a**
8	**24b**
16	**24c**
32	**24d**
64	**24e**



24c

Fig. 7. Adamantane-tipped PPI dendrimers developed by Meijer and Reinhoudt, complex multiple β-cyclodextrin units in water

MOLECULER ASSEMBLIES - DENDRIMERS

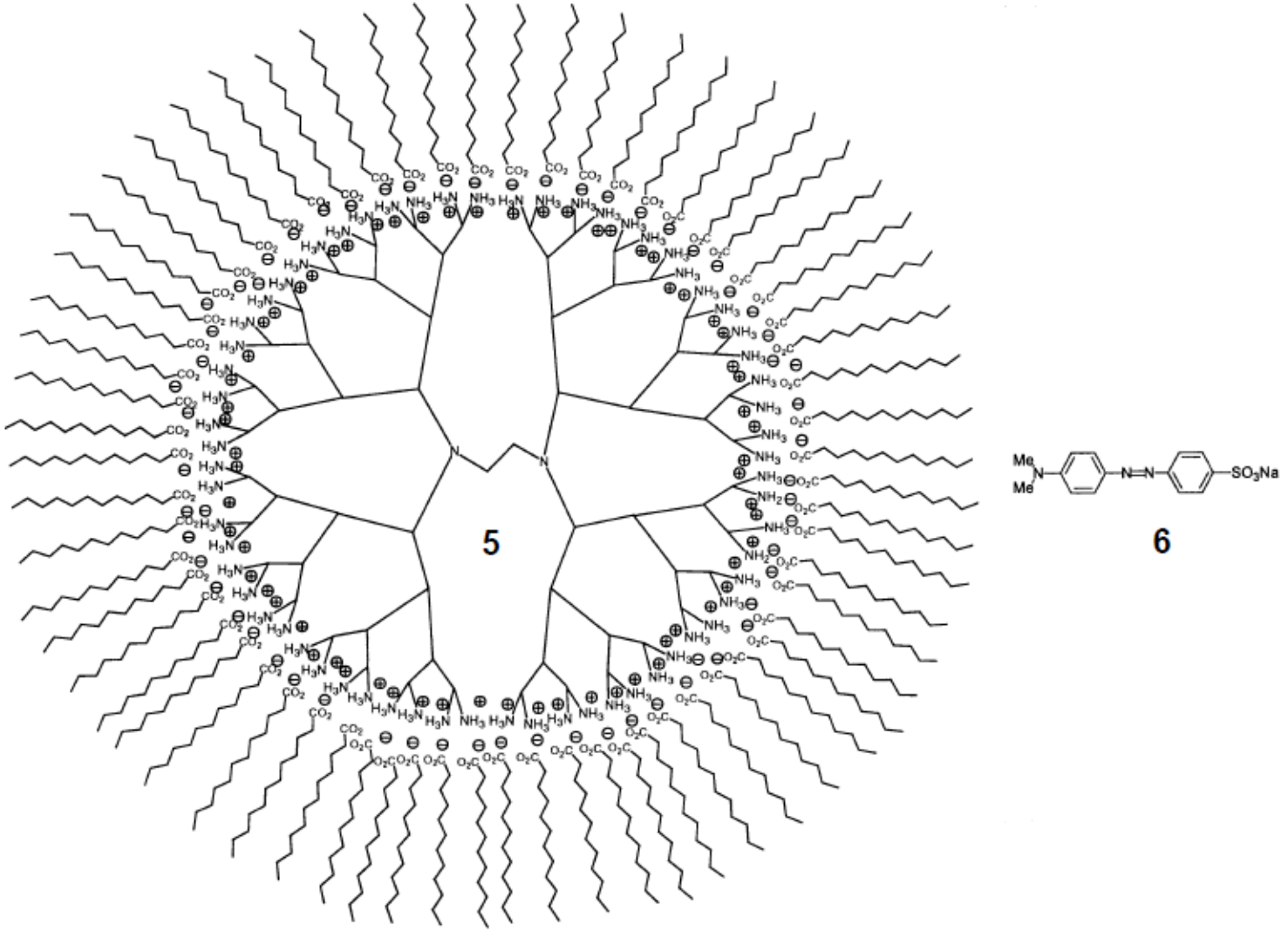
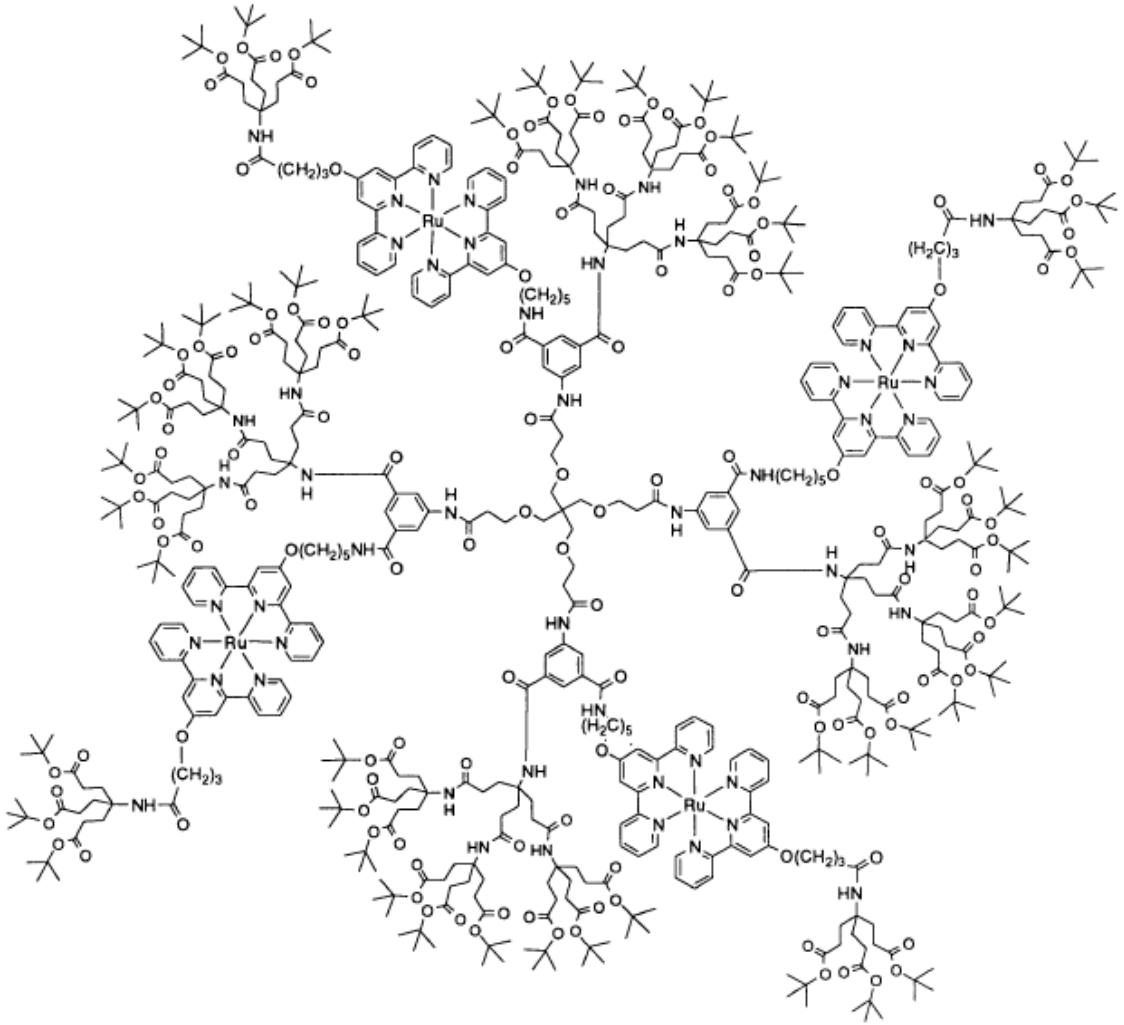


Fig. 3. Ionic assembly of PAMAM dendrimer and decanoic acid (5) studied by Crooks and co-workers. In water the assembly is capable of complexing methyl orange (6)



28

Fig. 9. Newkome's isomeric Ru-trpy self-assembled dendrimers 27 and 28