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Organometallic dendrimers — molecular architecture and functions

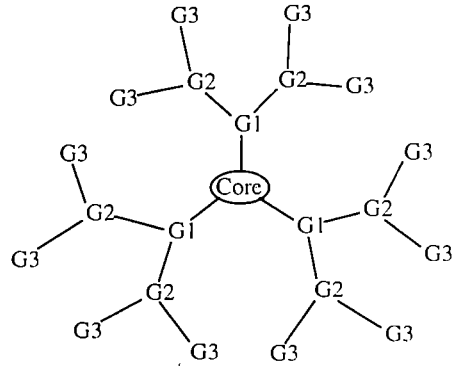
Summary — Two main methods of dendrimers synthesis — "divergent" (scheme B) and "convergent" one (scheme C) as well as the methods of their structures evaluations have been presented. Organometallic dendrimers differing in metal location: in the core [formulas (I)—(III)], at the interior [formulas (IV) and (V), Fig.1] and on the surface [formulas (VI)—(VIII)] have been discussed. Such dendrimers can work as the carriers and catalysts of chemical, polymolecular inter-phase processes. Especially they can be used as an excellent model systems simulating the action of catalytic centers of enzymes, based on metals.

Key words: organometalic dendrimers, synthesis, structure, metal location, application directions.

In early 40-ties Flory and Stockmayer predicted the possibility of synthesizing highly branched macromolecules [1, 2]. The first paper reporting controlled synthesis of so-called "cascade molecules" containing numerous amine groups at the outer shell was published however, by Fögtle and co-workers only in 1978 [3]. The name "dendrimer" appeared for the first time in a paper by Tomalia and co-workers in 1985 [4] as a combination of two Greek words *dendron* (tree) and *meros* (part). The present working definition for this class of compounds is: a regularly branched, highly ordered polymeric compounds, prepared *via* iterative synthesis. Each dendrimer consists of a core, several generations of concentric layers of branches and outer shell, with a well-defined number of functional groups of desired chemical properties.

A typical dendrimeric structure is shown in Scheme A.

Contrary to hyperbranched polymers, dendrimeric compounds can be isolated as single molecular species of well-defined molecular weight. Fundamental studies on synthetic methodology of dendrimers that allowed to synthesize large quantities of well-defined molecular species have been done independently by groups of Tomalia [5, 6] and Newkome [7]. Since then the scientific world has been fascinated by variability of molecular architecture and opportunity of incorporation of multiple active elements into dendrimeric macromolecules. Potential applications of dendrimers in contemporary technology [8—14] and medicine [15—21] make them particularly attractive objects of studies. The procedure of a synthesis usually involves repetition of sequence of several highly effective reaction steps, yielding different generation dendrimers.



Scheme A. General structure of dendrimer showing core and 3 generations of branches

Among different groups of dendrimers synthesized up to date, metallodendrimers attracted recently great deal of attention. Particularly in the area of biomedical research, metal-based dendrimers are believed to act as efficient reservoir-containing microdevices with a tailored size, shape, reservoir volume, and surface characteristics, that can be used as versatile delivery systems. It has been recognized that due to well-defined number of recognition sites and reactive centers flanked by stericaly hindered branches, dendrimers can be used as model systems, mimicking metal-based catalytic centers of enzymes. This review concentrates on the molecular architecture and functions characteristic for organometallic dendrimers.

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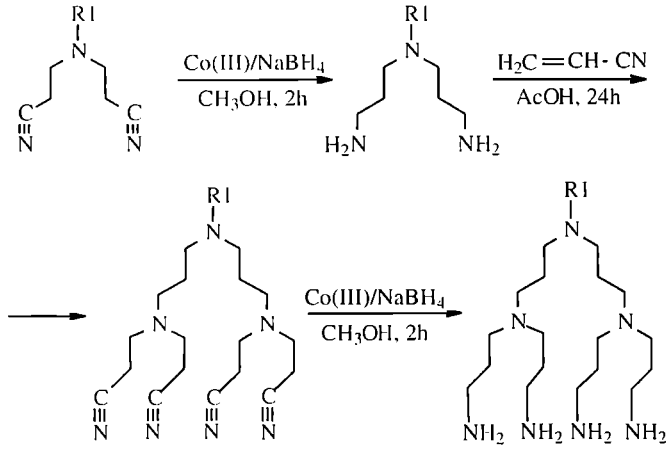
SYNTHESIS AND CHARACTERIZATION OF DENDRIMERS

Dendrimers are usually synthesized in step-by-step procedure by repetition of sequence of several, highly effective reactions. Each reaction sequence creates so-called "generation" of the dendrimer. Chemical versatility of dendrimers, *i.e.* their branching multiplicity, spacer lengths and 3D structure is achieved by chemical variety of building blocks [22]. Schemes B and C show two major synthetic strategies applied in dendrimer chemistry, named "divergent" and "convergent" approach. Tomalia and Newkome have introduced the "divergent method", where growth starts from the core and propagates towards dendrimer surface (Scheme B).



Scheme B. Divergent method of synthesis of poly(amino amine) type dendrimers

Even though a large excess of substrates is used to achieve high conversion ratio, the faulty pathways or incomplete reactions are common in higher generations. They are generated by steric hindrance and/or by non-covalent interactions, such as electrostatic, π-π stacking, hydrogen bonding *etc.*, within the dendrimer interior. This often creates problems with compounds isolation and their structural monodispersity. Therefore, recently, Fréchet and Hawker [23] introduced new synthethic methodology called "convergent approach", where smaller elements called "dendrons" are synthesized first and then coupled to the core (Scheme C). This method, in general, let to obtain structurally perfect, branched molecules, and makes purification procedure easier. However, linking together larger molecular fragments can be prohibited for higher generation dendrimers. Several other techniques are used less frequently. For example, a coupling of building blocks of metallodendrimers with application of supramolecular approach — called "non-covalent synthesis", proposed by Reinhoudt [24] or application of solid support methodology [25].

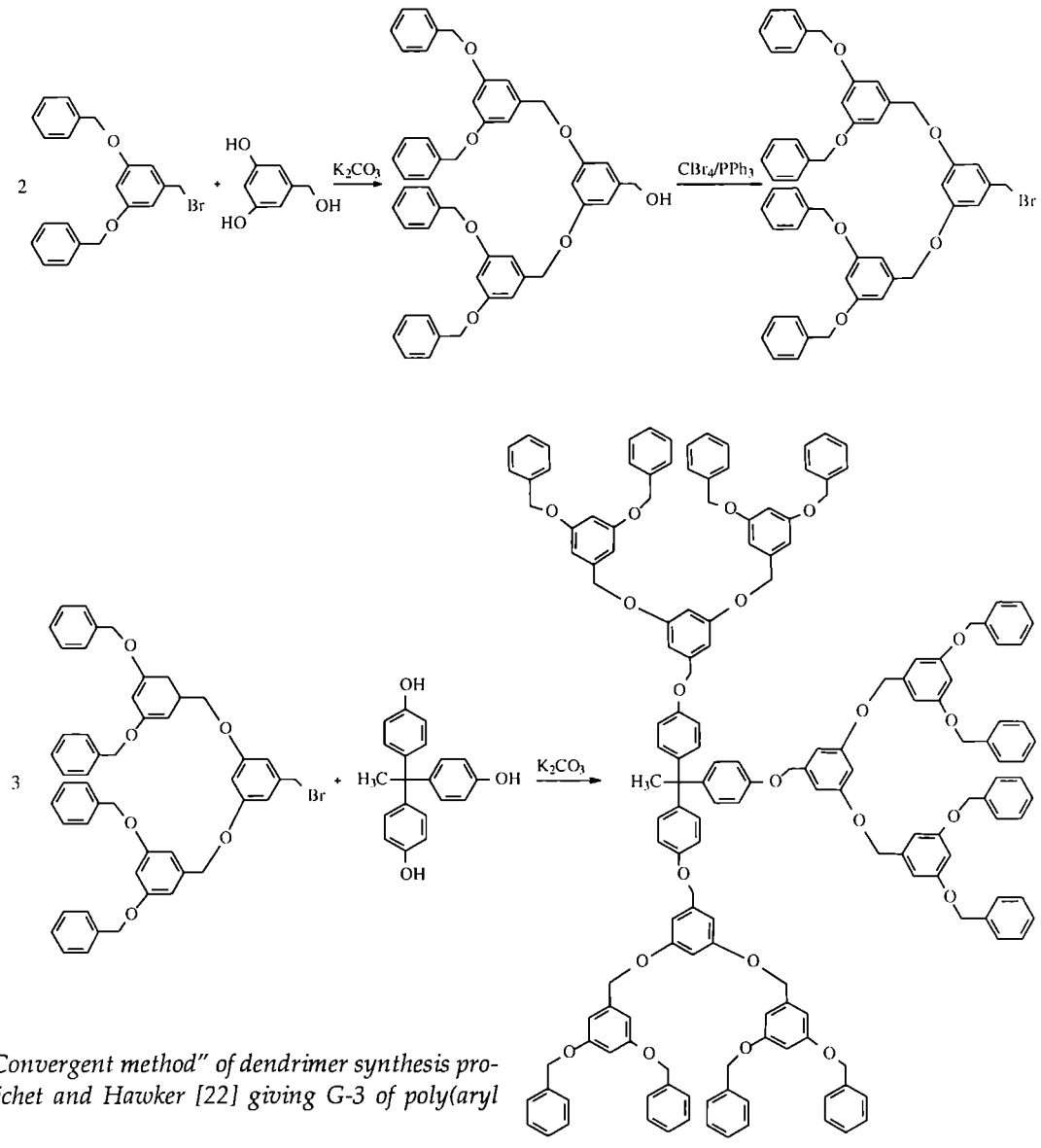
Multiplication of functional groups characteristic for dendrimers may lead to so-called "dendritic effect", *i.e.* enhancement of particular chemical, physical or biological effect with higher generations. This is not necessary always true as the secondary, ternary *etc.* structure of the inner part of dendrimer has to be considered.

Analytical techniques used for molecules characterization depend on the dendrimer building blocks. For example, Fréchet characterized organic benzyloxy benzyl dendrimer with $C_{5585}H_{4860}O_{765}$ molecular formula using standard ^{1}H and ^{13}C NMR, FT-IR, and MAS spectroscopies [26]. On the other side, multicharged metallodendrimer of much smaller molecular mass containg 22 Ru^{2+} atoms could not be characterized easily due to poor solubility, high charge and complicated internal (secondary, ternary *etc.*) structure [27]. In the case of organometallic compounds extended X-ray absorption fine structure (EXAFS) and X-ray absorption near-edge structure (XANES) spectroscopies provide insight into coordination mode. X-ray crystallography, that usually provides good model, at the moment is mostly used for first, rarely second generation due to none or poor quality crystals. Mass spectrometry (MALDI TOF and ESI) is very often a method of choice confirming molecular formula, aggregation and charge of the molecule.

Interesting diversity of dendrimers, which made them very attractive to many chemists, is caused by the fact that almost every repeat unit can be used for dendrimers construction. Up to date, dendrimers based on amines, amides, esters, ethers, amino and nucleic acids, carbosilanes and various metallodendrimers were synthesized and characterized. Recently, as the basic synthetic procedures leading to monodisperse compounds have been established, studies performed in this field gradually turned towards application. Particularly, an interest in new, nanoscale materials for optics and electronics and high demand for new materials at the interfaces between technology and medicine directed research into metalloorganic derivatives. Recent reviews on metalloodendrimers are numerous [28, 29], and we shall concentrate here on 3D architecture of dendrimers and their potential applications as redox systems and catalysts.

METALLODENDRIMERS

Metallodendrimers are classified according to three possible metal locations: at the dendrimer core, at the interior or at the surface of the dendrimer. They are usually constructed as a combination of branched skeleton and various metalloorganic centres of known photo, electro, redox, catalytic and another properties. So far, metallocenes, porphyrines, phthalocyanines, anionic and cationic groups *etc.* have been inserted into dendritic systems or bound on the surface.



Scheme C. "Convergent method" of dendrimer synthesis proposed by Fréchet and Hawker [22] giving G-3 of poly(aryl ether) wedge

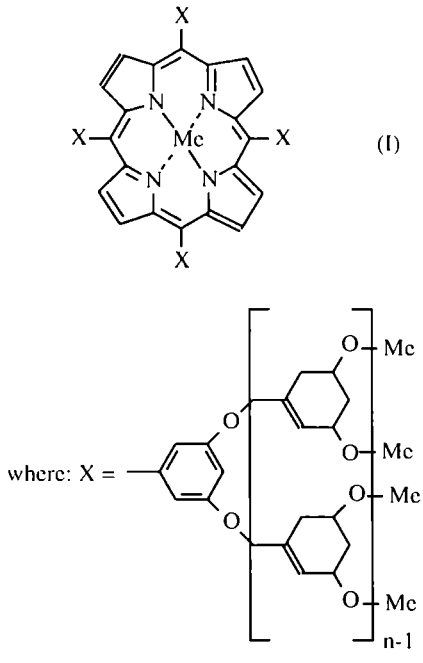
Encapsulated core — mimics of enzymes active site

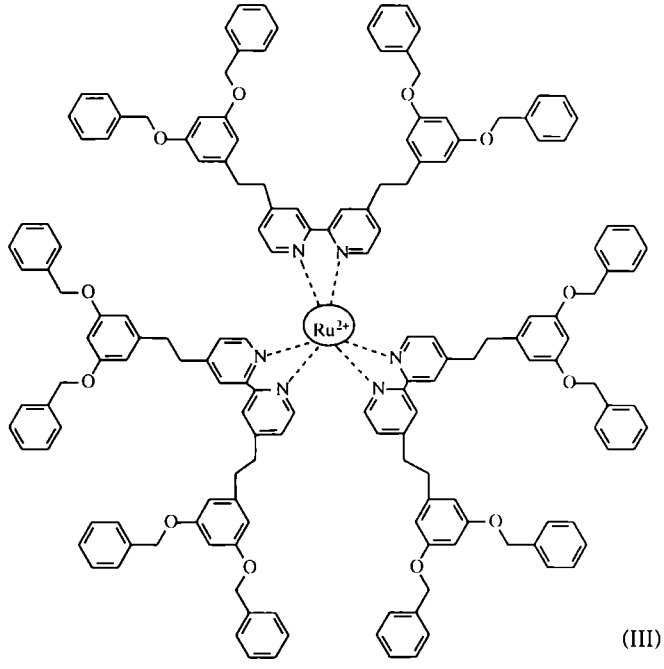
Single catalytic groups located at the core can elegantly mimic biological systems and allow to observe how these properties are modified by dendritic environment. The controlled encapsulation prevents interactions of the active centre with solvent molecules and induces selectivity towards natural ligands.

Synthesized, by Aida and co-workers [30], family of dendrimers, mimicking located on metalloporphyrin unit active centre of haeme proteins, are the first branched macromolecules of this type. Dendrimer of Formula (I) (reprinted with permission from [31], copyright 1996 The Royal Society of Chemistry) built around zinc-porphyrine core, shows a remarkable property of selective interactions with imidazole-functionalized aryloxy-dendrimers (haeme centre — histidine interactions are known in natural systems). The dendritic effect of this relatively rigid dendrimer is manifested by generation-dependent selectivity. The 1:1 complex is formed regardless of generations of the two complementary dendrimers up to G-4 of both partners.

Although, binding constants became smaller with increase of the dendrimers generations, complex formation could not be possible without significant deformation of the globular structure and/or arms interpenetration of the two complementary partners. This is perhaps the first experimental evidence of very complex molecular recognition events between dendrimeric molecules. Even more interesting are properties of Fe^{2+} derivative of the dendrimer of Formula (I). In the presence of 30-fold excess of 1-methylimidazole, five-coordinated iron(II) atom selectively and reversively binds oxygen molecule [31]. The G-5 adduct with O_2 molecule is stable over several months at room temperature and at atmospheric pressure. When exposed to carbon monoxide it still exhibits a half-life time *ca.* 50 h.

Independently, another nature mimicking system — iron(II) porphyrine functionalized dendrimers with more flexible arms (Formula (II) — reprinted with per-

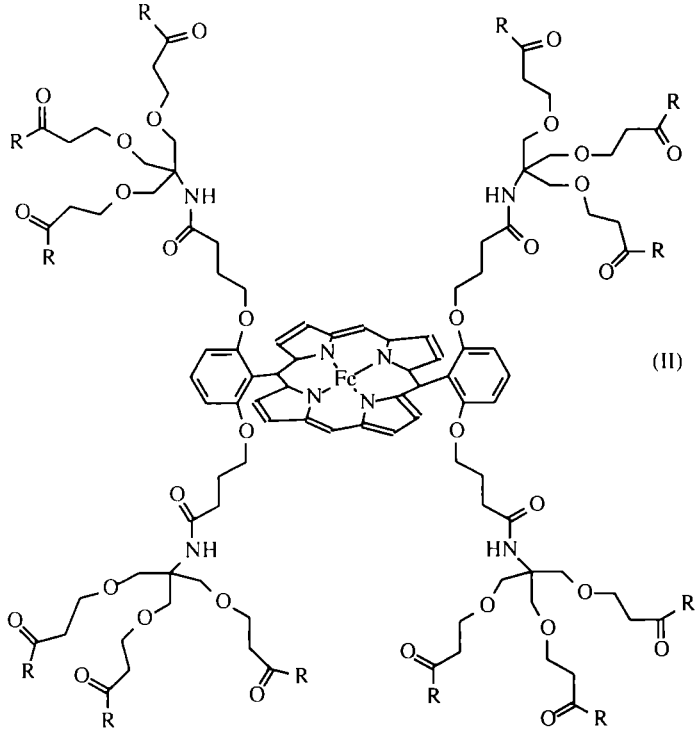


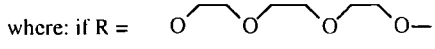


mission from [32]; copyright 1997, The Royal Society of Chemistry] have been designed by Collman, Diederich and co-workers [32].

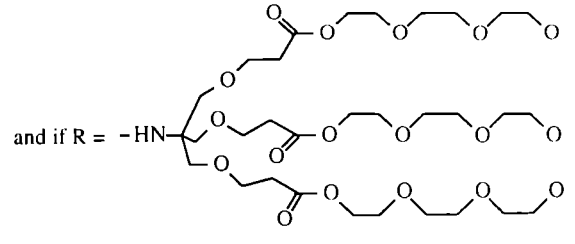
These two groups of dendrimers are models for studying the processes of oxygen storage and distribution in biological systems. Due to the fact that O_2 affinity, observed in toluene, is significantly higher than CO affinity, they are superior than any other model designed previously, including "picket fence" model provided by Fe(II) porphyrin itself [33].

Moore, Suslick and co-workers [34] designed dendrimers with core-encapsulated Mn(III)-porphyrine unit. Branched part was built of phenyl ester units and these dendrimers worked as catalysts in epoxidation of alkenes. It was observed that for higher generation dendrimers more congested catalytic surface selectively preferred substrates with less sterically hindered double bonds. Ferrocene-containing carbohydrate dendrimers designed by Stoddart and co-workers [35] and photoactive Ru(2,2'-bipyridine)$_3^{2+}$ [Ru(bpy)] unit encapsulated





structure of formula (II) is designed as G1-Fe^{II}

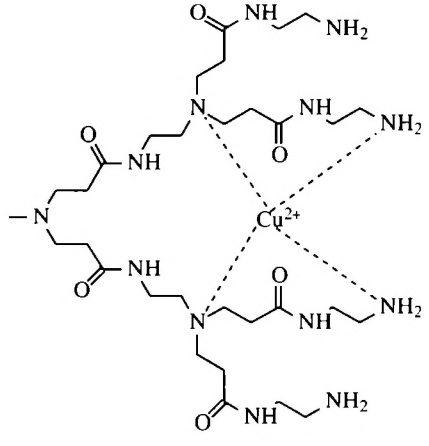


structure of formula (II) is designed as G2-Fe^{III}

in G-1 dendrimer [Formula (III)], designed by Vögtle and co-workers [36], constitute another two important families of dendrimeric macromolecules that are photo- and redox-active systems.

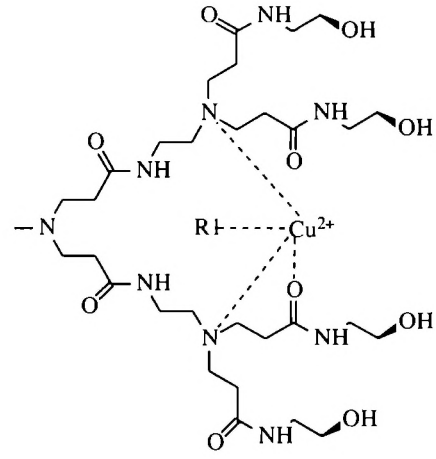
Dendrimer interior — superb hosting system

The idea and successfull preparation of dendrimers, which encapsulate and release in controlled fashion organic molecules (organic dyes or 2,2,3,4,5,5-hexamethyl--3-imidazolinium-1-yloxy methyl sulfate) crossing lypophilic/hydrophilic barrier prompted several groups to use dendrimers as host molecules [37, 38]. Possibility of transport of hydrophobic molecules through polar phase and release them in apolar medium (and conversely transport of polar molecules through hydrophobic phase and release in hydrophilic solvent) has immediate application in medicine (markers and drug delivery systems), and chemistry and technology as catalysts. One of the first examples of encapsulation of Cu^{2+} ions in poly(amidoamine) (PAMAM) or PAMAM(OH) (PAMAM dendrimer with OH as the end groups) based dendrimers was reported by Crooks and co-workers in 1998 [39]. Detailed studies on interactions between Cu^{2+} ions and PAMAM or PAMAM(OH) dendrimers, performed with the use of UV-VIS, ENDOR, MALDI TOF and EPR techniques showed, that well-defined, generation-dependent number of copper ions can be incorporated into the dendrimer [40, 41]. According to these studies binding mode involves two amine groups: one located at the surface and second from the interior of the dendrimer. Probable coordination modes of Cu^{2+} cations within PAMAM or PAMAM(OH) dendrimers [40] are presented by formulas (IV) and (V), respectively.



(IV)

Moreover, due to the fact that branching (and molecular density) at the periphery of the macromolecule is much higher than around a core (see Fig. 1), it is possible to obtain dendrimer molecules highly loaded also with Pd^{2+} and Pt^{2+} ions. These, when reduced *in situ* with BH_4^-, yield neutral monodisperse metal clusters of



(V)

nanometric size that can be used in homogeneous hydrogenation catalysis [42].

Very stable PAMAM(OH) dendrimer with encapsulated Pt^{2+} nanoparticles, prepared by the same method, has been used as efficient electrocatalyst for O_2 reduction

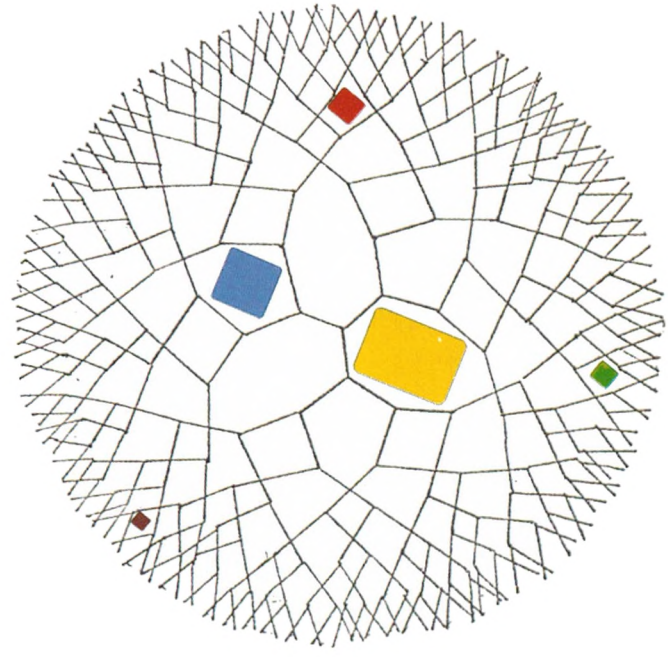


Fig. 1. Inclusion of metal clusters within the dendrimer interior is dependent on the generation, cavity size and coordination properties

[43]. Zhao and Crooks have found recently that G-6 PAMAM dendrimer containing clusters of 55 Cu(0) atoms when exposed to a solution of more noble metals, exchanges Cu(0) for Au or Pt metal clusters giving rise of formation of wider range of nanocomposite materials for homogeneous catalysis [44].

The same group reported the first example of a carbon-carbon coupling reaction catalyzed by a poly(propylene imine) (PPI) dendrimer-templated nanomaterial containing Pd(0) particles. Although such catalyst

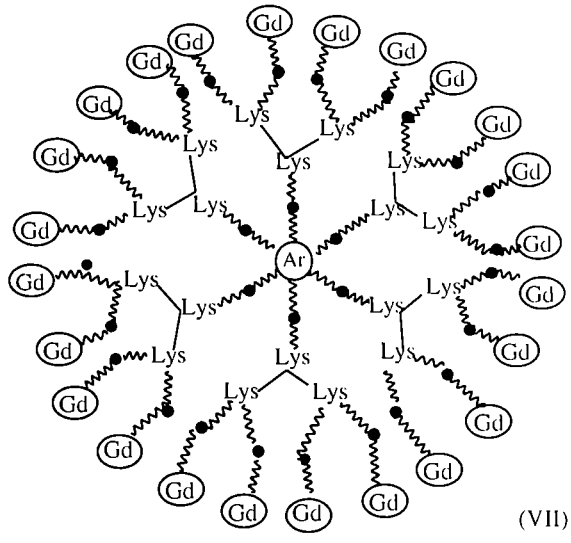
worked only at elevated temperatures and was sensible towards several inhibitors, it was 100% selective yielding *n*-butyl-*trans*-formylcinnamate from aryl halides and *n*-butylacrylate (Heck coupling reaction) [45]. Although the presence of metal clusters is confirmed by various physicochemical methods, actual location and mechanism of metal cluster-dendrimer interactions remain unclear.

Vögtle and co-workers [46] have recently reported an interesting study on the coordination mode of Co^{2+} ions in the interior of poly(propylene amine) dendrimers. Fluorescence spectra of the above dendrimeric Co^{2+} complexes containing fluorescent dansyl groups at the surface, allowed to speculate about interplay between reversible coordination of metal ions in the interior of the dendrimers and generation-dependent interactions with dansyl residues located at the surface.

Dendrimer surface — controlled policentered recognition site

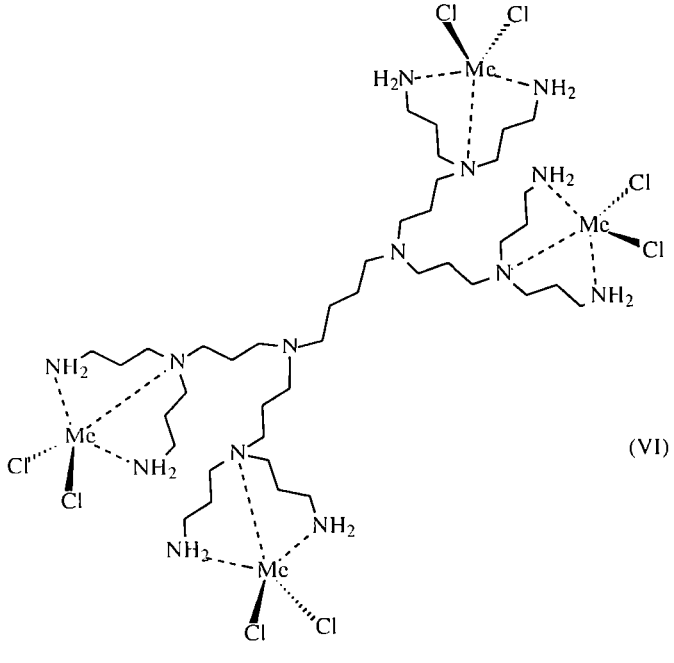
Finally, catalytic groups can be incorporated at the surface of dendrimers. Typically, such dendrimers are synthesized by "divergent method" and then modified by introduction of groups capable of metals chelation. Amines, amides, crown ethers, pyridine, bipyridine, phosphine, sulfur *etc.*, are the most common examples of functional groups used for chelating purposes. Van Koten and co-workers synthesized first organometallic silane dendrimers containing terminal arylnickel(II) groups which worked as catalysts in model addition reaction of tetrachloromethane to methyl methacrylate [47]. Cu(II), Co(II), Zn(II), and Ni(II) transition metal complexes bind stechiometrically to bis(3-aminopropyl)amine moieties of poly(propylene imine) dendrimers. Such dendrimer with DAB-core [Formula (VI)] — has been used as catalyst in hydrolysis of *p*-nitrophenyl diphenyl phosphate in water (DAB — diaminobutene). The best hydrolysis rate has been observed for lower generations of the Cu(II)-dendrimer complexes [48].

Recently, Schering AG group has designed a new dendritic contrast reagents that let performing medical diagnostics of soft tissues with the use of Magnetic Resonance Imaging (MRI) method [49]. Compound called Gadomer-17 [Formula (VII)] has already entered clinical studies [50]. The macromolecule contains 24 gadolinium (Gd) ions complexed with crown ether functionalized

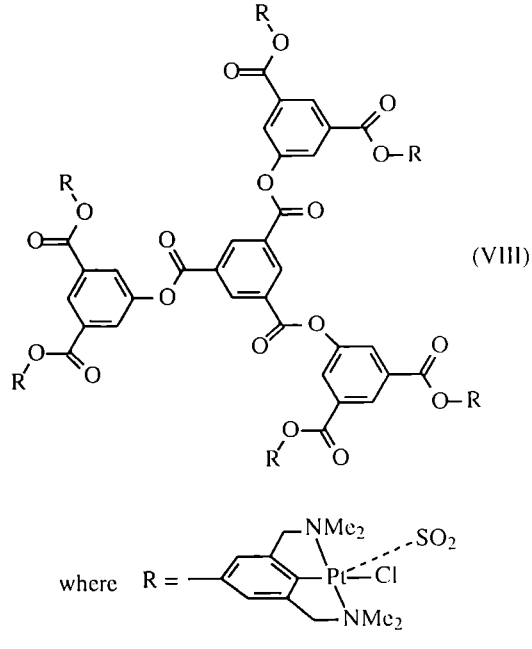


(VII)

lysine-based dendrimer. Contrary to other Gd-chelating contrast reagents used nowadays in medical practice, this one shows promising pharmacokinetic behavior, in-



(VI)



(VIII)

cluding an extended lifetime, and almost exclusively intravascular distribution after *i. v.* injection.

Another spectacular example of small dendrimer with potential industrial application is G-1 complex [Formula (VIII)] containing coordinated platinum(II)--chelating systems [51]. It forms molecular aggregate with gaseous SO_2 both in CH_2Cl_2 solution and in solid state. The complex is formed instantaneously in the presence of SO_2 with the change of color; thus the process can be investigated reliably by UV-VIS or ^1H NMR techniques.

CONCLUSIONS

The process of dendrimer formation can be controlled in order to produce macromolecules with a high degree of monodispersion. Dendrimers present a highly branched architecture with an opportunity of incorporation of controlled number of active groups. Because of these unique properties they are believed to be prospective molecular devices providing multi-center recognition and multi-center response. It has been shown that their metal derivatives can act as carriers and catalysts in the chemical inter-phase polymolecular processes. Dendritic branches are able to provide high degree of steric hindrance. Therefore, dendrimers have been used as superior model systems, mimicking natural situation of metal-based catalytic centers in enzymes. Metallodendrimers have also been shown to display regioselective catalysis. Interactions of metal ions with the branched interior of dendrimers and subsequent reduction afforded encapsulation of polymetallic nanoparticles. They are very useful because of their ability to isolate chemical species from the outside and for their catalytic properties.

ACKNOWLEDGMENT

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