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ARTICLE

The dendritic effect illustrated with phosphorus dendrimers

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The dendritic (or dendrimer) effect is observed when a functional group behaves differently when it is alone or linked to a dendrimer; its property can even vary depending on the generation of the dendrimers. The dendritic effect can be observed with any type of dendrimers, and for any type of properties, even if it has been most generally tracked in catalysis and biology, and to a lesser extent in the field of materials. This review is mainly oriented towards the various types of dendritic effects observed with polyphosphorhydrazone dendrimers, even if many examples obtained with other types of dendrimers are given.

Key learning points

(1) Dendrimers are hyper-branched macromolecules, which can induce "the dendritic/dendrimer effect", i.e. the modifications of properties of a functional group when it is linked to a dendrimer.

(2) The properties can also vary depending on the dendrimers generation (size, number of layers).

(3) The dendritic effect may enhance the catalytic efficiency and enantioselectivity, and facilitate the recovery and reuse of catalytic entities linked to dendrimers.

(4) The properties of materials can be deeply modified when they are covered by dendrimers, or when they include dendrimers in their structure.

(5) The efficiency of dendrimers for drug delivery or as drug by themselves may also strongly depend on the generation of the dendrimers.

Introduction

Dendrimers are perfectly defined macromolecules, constituted of branches emanating radially from a central core, and comprising identical layers, which are called "generations". They pertain to the large family of polymers due to their repetitive structure, but they differ from classical polymers by the strict control of their structure. Indeed, dendrimers are never synthesized by polymerization reactions but step-by-step, most generally by the reiteration of two quantitative reaction steps. Many of the properties of dendrimers are connected to the nature of their terminal functions; they have found uses as catalysts, for the elaboration of materials, or for various purposes in the emerging field of nano-medicine.[1] One of their most intriguing property is the so-called "dendrimer (or dendritic) effect",[2] which is observed when a specific function has different properties (or efficiency), depending if it is grafted or not to a dendrimer. The dendrimer effect can take different aspects; i) if all the generations of a dendrimer have the same properties, but not the monomer, this effect is often called a multivalency effect; ii) if the effect varies when the generation increases, it is a generation effect, which concerns most generally the terminal functions, or sometimes the core under the influence of the branches. Of course the efficiency has to be compared for the same number of active sites, as illustrated in Figure 1 for both types of dendrimer effects.

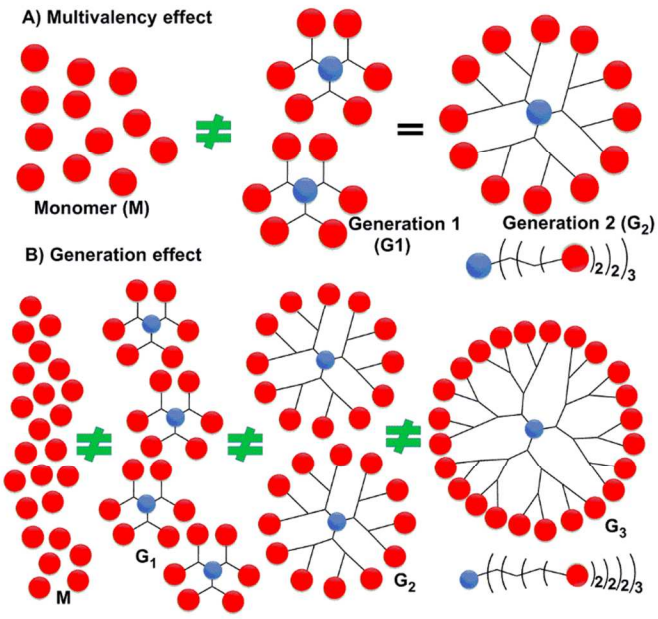


Fig. 1 Two types of dendrimer effect. The linear representation that will be used in most Figures of this paper are represented under G_2 and G_3.

The dendritic effect can be observed for any type of dendrimer properties, even if it has been most generally tracked in two main fields that are catalysis and biology, and to a lesser extent for the elaboration of functional materials. However, the very first reported dendritic effect concerned physical-chemical properties. In the interaction of pyrene with generations 1 to 9 of PAMAM (polyamidoamine) dendrimers (carboxylate terminal groups), the intensity of the the third to first vibronic peak of pyrene fluorescence increased when the generation of the dendrimer increased, indicating an increase of polarity of the internal structure.[3] The concept of "site isolation"[4] has been also elaborated to account for some specific effects occurring to the core upon the influence of the branches, mimicking the effects known at the active site of enzymes, or for proteins.[5] Such site isolation effects have been shown in particular for the fluorescence properties, for which an enhancement of both the fluorescence intensity and the lifetime has been observed when the generation of the dendrimer increases.[6]

It must be emphasized that the dendrimer effect is not always positive, but a bias is introduced in the literature. Indeed, many cases of negative dendritic effects are never published, because nowadays they are considered as non-interesting. However, the very first example of a dendritic catalyst reported a negative dendritic effect. The Kharasch addition carried out with Nickel complexes of a monomer, and of generations 0 and 1 of a carbosilane dendrimer, was more efficiently carried out with the monomer than with the dendrimers. Interestingly, only the dendrimers could be recovered and reused.[7] The dendritic effect can be positive up to a certain generation, and negative for the highest generations. Such behaviour has been first illustrated by the study of the transfection (introduction of genetic materials into cells) efficiency with PAMAM dendrimers ended by ammonium groups, and complexed to pCLUC4 Plasmid: the efficiency of the penetration inside cells increases by several orders of magnitude on going from the first to the sixth generation (Luciferase activity in the transfected CV-1 cells from 10^6 to 10^{10} light units per mg of cell protein), but decreases in the same proportion on going from generation 6 to generation 10.[8]

The dendritic effect can be (and has been) observed with any type of dendrimers, but it is very often not identified (or not named) by the authors, rendering difficult an exhaustive search on it. There exist many different families of dendrimers: PAMAM, PPI (polypropylene imine), polyether, polyphenylene, polytriazine, PETIM (polypropylethenimine), PURE (polyurea), polycarbosilane, and phosphorus-containing dendrimers, mainly of type polyphosphorhydrazone (PPH[9]). As we are specialized in the synthesis and study of properties of PPH dendrimers, this review will be mainly oriented towards the various types of dendritic effects that we have observed with this type of dendrimers, even if information afforded by other types of dendrimers will be frequently given.

This review will be organized depending on the three fields in which the dendrimer effect is mostly observed (catalysis, materials, biology).

The dendrimer effect in catalysis

Many reviews concern the use of dendrimers in homogeneous catalysis,[10-11] but few are specifically about the dendrimer effect in catalysis.[12] Several consequences of dendritic effects have been identified, such as the influence on the rates of reaction, substrate activation, or selectivity. The main reasons proposed for such effects are site isolation, confinement, or cooperativity between proximal catalytic sites in the dendrimer structure. Such effects and others will be illustrated below, mainly with polyphosphorhydrazone (PPH) dendrimers having catalytic properties.

The recovery and re-use of dendritic catalysts

As already indicated for the first example of dendritic catalysts,[7] their recovery and re-use, which is a clear difference in comparison to monomeric catalysts, is of paramount importance. A first reason is that dendritic catalysts are generally expensive due to their step-by-step syntheses (in addition to the use of expensive metals in many cases); a second reason is to simplify the purification processes of the products, which is particularly interesting for the catalysed synthesis of compounds of pharmaceutic interest. A few methods have been proposed for the recovery and reuse of dendrimers, either based on separation membranes for continuous flow catalysis or dialysis, or more generally on precipitation when changing the solvent. Indeed, the solubility of dendrimers is often lower than that of the reagents and products. Only a few examples of the use of separation membranes for dendritic catalysts have been reported, since a particular equipment is needed.[13] Furthermore, the dendritic catalysts interact unfavourably with the membrane by blocking its pores in several cases. On the contrary, the use of a non-solvent or bad solvent for the dendrimer (to precipitate it selectively) can be carried out in any laboratory, and with almost any type of dendritic catalyst. The principle is illustrated in Figure 2. The efficiency of the method depends both on the stability of the metal-ligand complexes and on the percentage of precipitation of the dendritic catalyst. The choice of the solvent for precipitation is particularly important, since it must be both a good solvent for the products and be a bad solvent for the dendritic catalysts.

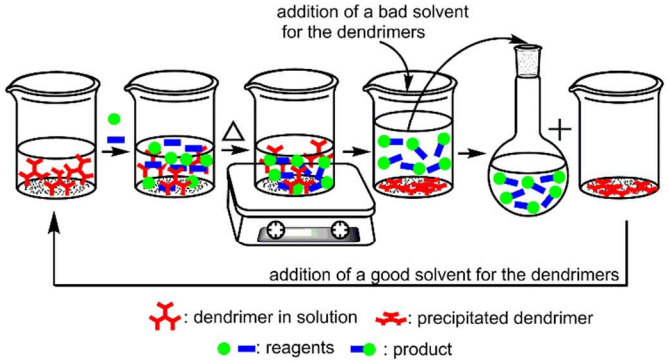


Fig. 2 Principle for the recovery and re-use of dendritic catalysts by selective precipitation, using a bad solvent.

This method can be extremely efficient, as illustrated by eleven recovery and re-uses of a dendritic terpyridine-scandium complex based on generation 4 (G_4) polyphosphorhydrazone (PPH) dendrimers having a hexafunctional cyclotriphosphazene core (N_3P_3), for catalysed Friedel-Craft acylations under micro-wave (MW) irradiation, starting from a variety of reagents. The efficiency of the catalysis is dependent on the reagent, but not on the number of reuses of the catalysts. Indeed, identical yields were obtained for run 4 (after 3 recoveries) and run 12 (after 11 recoveries), starting from identical substrates. Diethylether was used as the bad solvent for the catalytic dendrimer and good solvent for the products (Figure 3).[14]

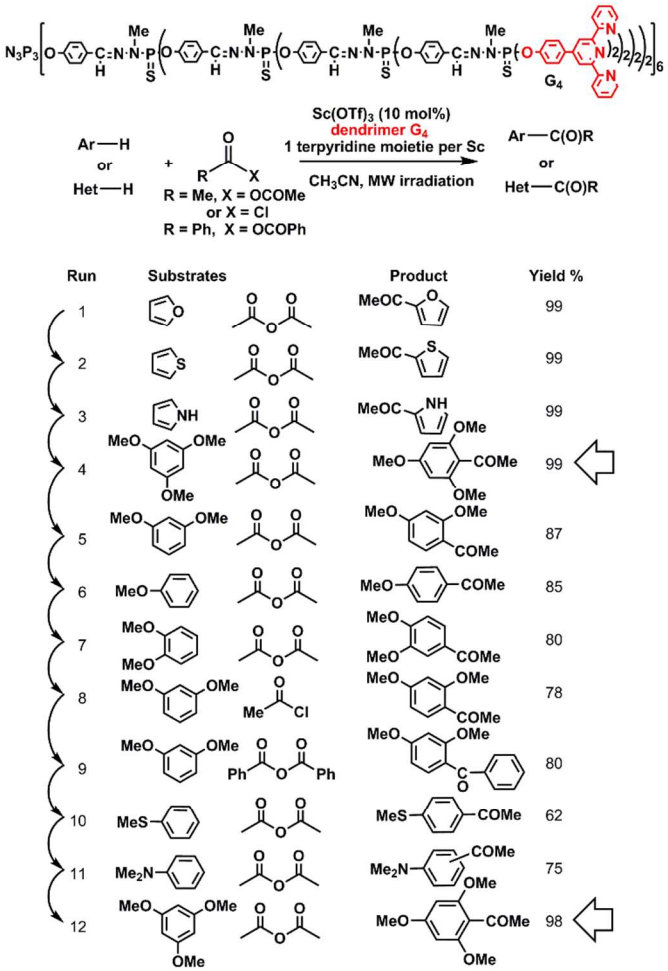


Fig. 3 Recycling experiments carried out by precipitation with diethylether of the scandium complex of dendrimer G_4 ended by terpyridine moieties. The linear formalism is used to draw the dendrimer; this is another way to represent the 3-dimensional structure of dendrimers (see also Figure 1). The corresponding Sc complexes are used for catalysed Friedel-Craft acylations with different substrates for each run.[14] The arrows on the right corresponds to the same reaction carried out at runs 4 and 12.

Recovery by precipitation is the most widely used technique for dendritic catalysts, but a few other types of recycling experiments have been carried out in specific cases. This includes in particular the use of magnetic cobalt nanoparticles covered by graphene. Dendrons having a pyrene as core and catalytic entities as terminal groups interact by π-stacking with the graphene of the nanoparticles, at room temperature but not when heating. The dendrons catalyse the reaction in homogeneous conditions when heating. On cooling when the reaction has gone to completion, the dendrons deposit again onto the magnetic nanoparticles. These nanoparticles covered by the catalytic dendrons are simply recovered using a magnet, and reused as illustrated in Figure 4.

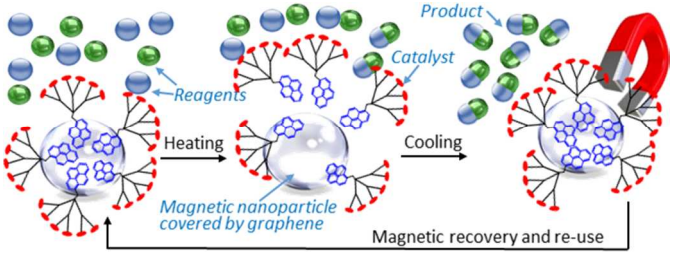


Fig. 4 Principle of magnetic recovery of the dendritic catalyst, interacting by π-stacking with a magnetic nanoparticle covered by graphene.

This principle has been applied to Suzuki couplings with phosphine-palladium complexes as terminal groups of PPH dendrimers. Such method has produced in particular the anti-inflammatory drug Felbinac in quantitative yields, even after 11 recycling and re-uses, as illustrated in Figure 5.[15]

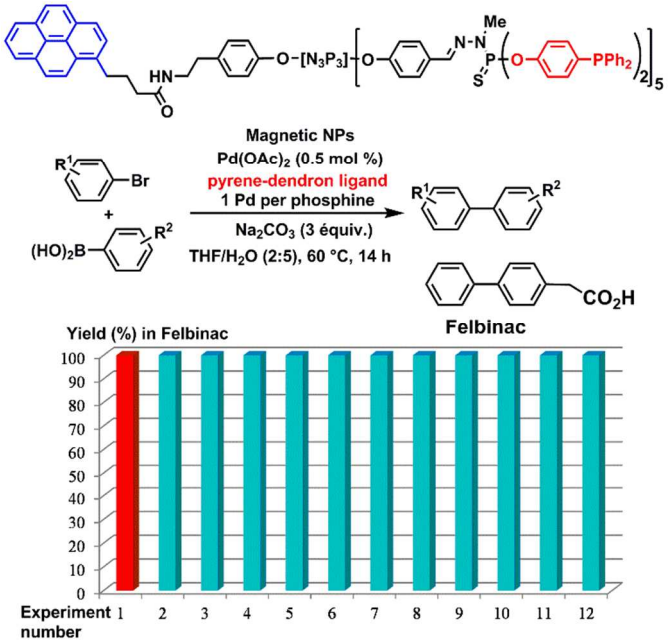
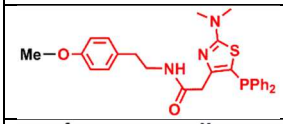
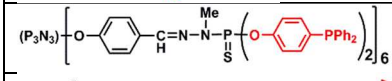
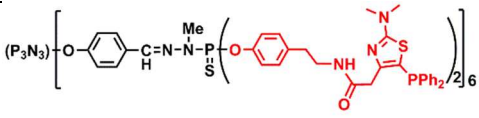


Fig. 5 Suzuki coupling applied to the synthesis of the anti-inflammatory drug Felbinac, using the process shown in Figure 4 for the recovery and reuse of the dendritic catalyst.[15]

An efficient recovery and re-use of dendritic catalysts can be carried out only if the complex is stable, it means if the leaching of metal is reduced to become undetectable. A reduced

leaching is also a positive point for "green chemistry" and for simplifying the purification of the products. A large difference in leaching has been measured by ICP-MS (Inductively Coupled Plasma Mass Spectrometry) in Suzuki couplings with monomeric or first generation PPH dendrimers Pd-complexes of triphenylphosphine and thiazolylphosphine. An influence of the type of ligand is also observed, and the leaching can become undetectable in the case of the dendrimer ended by the thiazolyl phosphine, illustrating a multivalency effect (Table 1).[16]

Table 1. Palladium leaching in the solutions containing the products, after Suzuki couplings, using the ligand-Pd complexes as catalysts (1 Pd per phosphine).[16]

Ligand	Pd leaching (ppm)
PPh_3	2227 (±63)
	1432 (±46)
	173 (±3)
	<0.55[a]

a: undetectable (limit of detection by ICP-MS)

Influence of dendrimers on the catalytic efficiency

Most generally, the dendritic catalysts can be recovered and reused, except if the dendrimer is cleaved during the catalytic process.[17] However, a positive dendritic effect concerning the efficiency is not so frequently observed. Indeed, in many cases, grafting a catalytic entity to a dendrimer has a neutral or even detrimental effect on the efficiency of catalysis.[18] It must be emphasized that the catalytic efficiency is given each time in relation to the number of catalytic sites. For instance if a dendrimer has 12 catalytic moieties as terminal groups, its efficiency will be compared with that of 12 equivalents of the corresponding monomeric catalyst.

When positive, the dendritic effect can have a dramatic influence on the rate of the catalysis. The most spectacular example in this field is certainly the ester hydrolysis catalysed by peptide-dendrimers composed of histidine-serine in the whole structure, as enzyme models. The catalytic rate constants are directly proportional to the total number of histidine residues per dendrimer. In the best case, the dendrimer of generation 4 was 140,000-fold more efficient than the reference catalyst for ester hydrolysis, amounting to a 4500-fold acceleration per histidine side-chain.[19] This example is particular since the whole structure is composed of catalytic entities. Most generally the catalytic entities are only located at the outer-shell of the dendrimers.

For instance, the arylation of pyrazole catalyzed by the copper complexes of pyridine-imine ligands (monomeric or linked as terminal groups of generations 1 to 3 of PPH dendrimers) induced both types of dendritic effects displayed in Figure 1. Indeed, arylation with PhI proceeds in almost quantitative yields with all the generations of the dendrimers, but the monomer is practically non-active, illustrating a multivalency effect. On the other hand, arylation with PhBr is more difficult than with PhI, and a clear generation effect is observed on going from the monomer (non-active) to generation 3, which is the most active (Figure 6).[20]

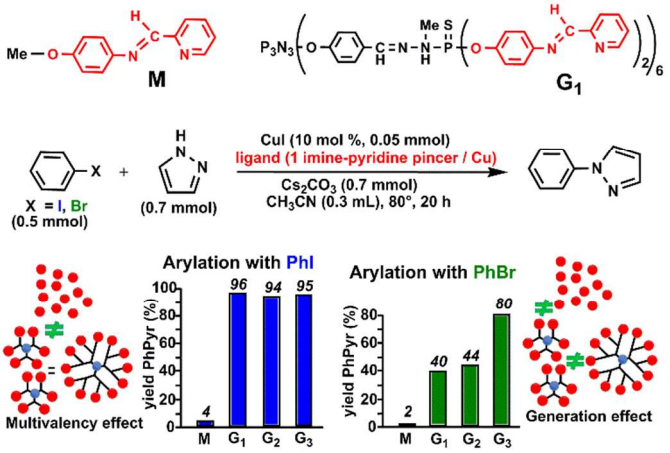


Fig. 6 Catalyzed arylations using monomeric and dendritic copper complexes, displaying two types of dendritic effects: a multivalency effect in the case of PhI, and a generation effect in the case of PhBr.[20]

The reasons for the dendritic effect are usually linked to the idea of cooperativity between the terminal groups. Such cooperativity has been proved in particular for catalyzed asymmetric ring opening in the hydrolytic kinetic resolution of terminal epoxides, using PAMAM dendrimers having salen-Co complexes as terminal groups. The mechanism involves simultaneous activation of both the epoxide and the nucleophile by different salen-Co units.[21]

Besides an increased efficiency concerning the rate or yield of the catalysis, an influence on the enantioselectivity has been also reported in some cases.[22] The most important effect to date has been observed for [2+2+2] cycloaddition reactions between N-tosyl-1,6-diyne and 2-methoxynaphthalene alkynyl derivatives, catalyzed by PPH dendrimers containing terminal phosphoramidite ligands complexing Rh. A strong positive dendritic effect has been observed in both the yield and the enantioselectivity. Such effect is not a simple cooperative effect between two catalytic centers, as the branch (association of two monomers) is not more efficient that the monomer M (Figure 7). These data point to an effect due to a large number of chiral entities in close proximity.[23]

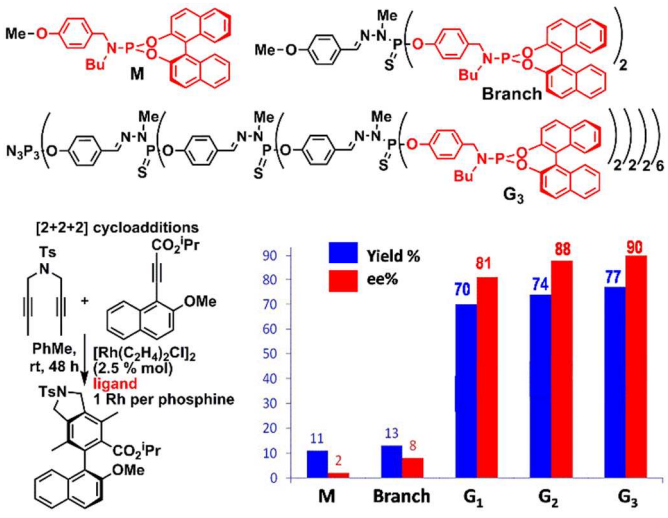


Fig. 7 [2+2+2] cycloadditions catalyzed by phosphoramidite ligands complexing Rh. Effect of the monomer, branch, and generations of the dendrimers on the yields and enantioselectivity (ee).[23]

In summary, the dendritic effect in catalysis can induce different properties. The most straightforward and most frequently observed property concerns the easy recovery and reuse of dendritic catalysts. The recovery is related to the size and the different solubility, the reuse is related to a reduced leaching. Such behaviour is in sharp contrast with the behaviour of monomeric catalysts, but it is not specific to dendrimers, as it can be observed also with polymers. Specific and dramatic dendritic effects can be observed on the efficiency of the catalysis, i.e. on the rate, the yield, or the enantioselectivity. These effects can be observed either on going from a monomer to any generation of the dendrimer, or can be dependent on the generation. The influence on the rate of catalysis has been brilliantly illustrated by a dendrimer of generation 4 that is 140,000-fold more efficient than the reference catalyst.[19] The dendritic effect on the yield of the catalysis is illustrated by an almost non-active monomer, which induces close to 100% yield when linked to dendrimers.[20] The influence on the enantioselectivity has been observed with a monomer having almost 0% ee, whereas the ee is above 80% when the same monomer is linked to a dendrimer.[23] Cooperativity and/or multivalency effects are generally proposed to account for these effects, even if they are often not fully understood. However, these positive dendritic effects on the catalysis outcomes should be relativized, as negative effects are frequently observed, but not always reported.

The dendrimer effect for the elaboration / modification of materials

Dendrimers have been used since a long time for the elaboration or modification of materials.[24] In connection with the previous paragraphs about catalysis, dendrimers or more generally dendrons (dendritic wedges) linked to the surface of materials, have been used for heterogeneous (supported) catalysis.[25] For instance, Wang polystyrene supports were functionalized with 3 generations of 3 types of dendrons (polyarylbenzyl ether, polyarylbenzyl thioether, and polyaryl benzyl amine), decorated with phosphine ligands on the periphery and complexed with Pd(0). A positive dendritic effect has been observed for the catalysis of the Heck and Suzuki reactions of bromobenzene, using the first to third generations supported dendritic catalysts.[26]

As shown above, the dendritic effect is almost systematically searched in the case of catalysis. On the contrary, it has been rarely searched in connection with materials. The use of dendrimers for elaborating sensitive bio-arrays is the very first example of dendrimers for commercial applications. Dade Behring has been using PAMAM dendrimers in its diagnostic technology since 1998, as a key component in the Stratus CS instrument for cardiac analysis.[27] As they are 3-dimensional spacers, the dendrimers keep the biological entities away from the solid surface, so that the biological entities behave almost as if they were in water. The principle of synthesis of DNA bio-arrays (DNA chips) is shown in Figure 8, applied to various generations (G_1-G_7) of PPH dendrimers ended by aldehydes.

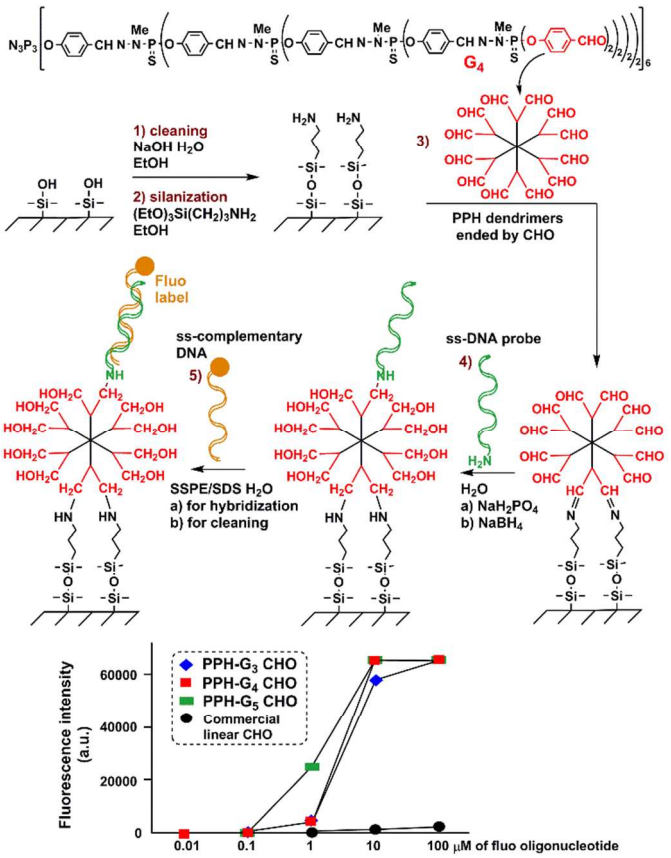


Fig. 8 Principle of synthesis of DNA chips with dendrimers as spacers (SSPE: saline sodium phosphate ethylene diamine tetraacetic acid; SDS: sodium dodecylsulfate). Comparison of the efficiency of generations 3-5 of PPH dendrimers, with that of a linear aldehyde, for the detection of fluorescent oligonucleotides.[28]

The test consisted in measuring the fluorescent signal-to-background ratio after hybridization of a 15mer Cy5-labelled complementary single strand (ss) to a 35mer ss-DNA probe. An increase of the signal-to-background ratio was observed on going from a linear aldehyde up to generation 4, but no more increase was found with dendrimers G_4-G_7[28] (data shown for G_3-G_5 in Figure 8). This work is at the origin of the creation of the startup Dendris™ dedicated to biological and environmental diagnosis.

The dendritic effect has been observed by serendipity in the case of PPH dendrimers bearing triazatriene macrocycles as terminal groups. Their reaction with $Pt_2(dba)_3$ (dba = dibenzylidene acetone) induces the formation of Pt nanoparticles (NPs) in mild conditions. Remarkably, these NPs are organized in branched supramolecular assemblies composed of dendrimers and coalesced Pt-NPs. The length of the branches of the network of coalesced Pt nanoparticles surprisingly depends on the generation of the dendrimers, and more precisely on the number of macrocycles per dendrimer. The branches of the network become larger when the generation of the dendrimers increases; this is a very unique organization of organic dendritic structures interweaved with inorganic dendritic structures (Figure 9).[29]

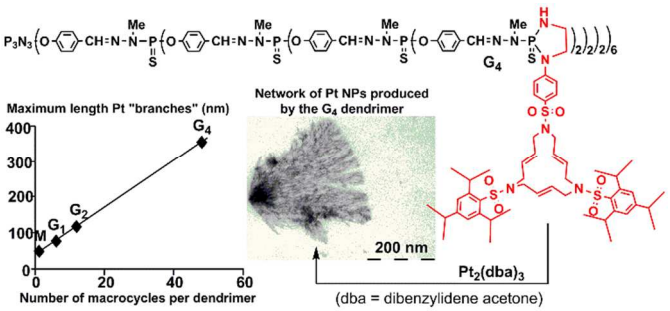


Fig. 9 Reaction of dendrimers ended by triazatriene macrocycles with $Pt_2(dba)_3$ inducing the formation of Pt nanoparticles (NPs), and organizing them in dendritic-like networks (photo by electron microscopy in the centre). The size depends on the generation of the dendrimer (graph).[29]

Dendrimers ended by ammonium groups have many biological properties (see later), but they are also useful for the layer-by-layer (LbL)[30] elaboration of materials, in particular nanotubes[31-32] and microcapsules. In the latter case, negatively charged DNA and generations 1 to 4 of positively charged PPH dendrimers were deposited LbL on the surface of microspheres of melamine formaldehyde. The destruction in acidic conditions (pH 1.2-1.6) of the internal part of the microspheres, without destroying the dendrimers-DNA layers, induces the formation of microcapsules. The stiffness of these microcapsules has been assessed, by measuring force-deformation curves with the atomic force microscope (AFM). These experiments clearly show that the stiffness of the microcapsules increases when the generation of the dendrimers increases (Figure 10).[33]

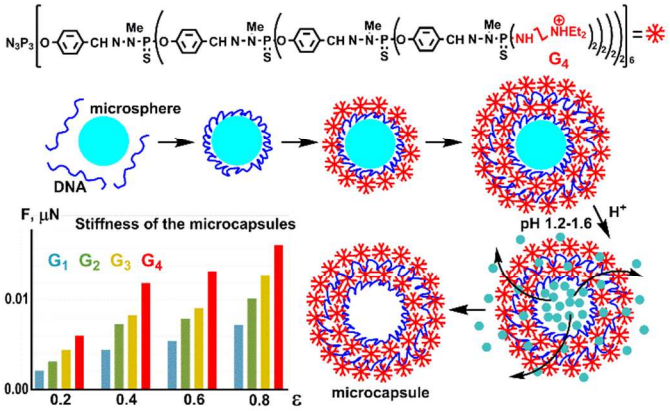


Fig. 10 Microcapsules elaborated by LbL deposit of dendrimers and DNA on microspheres, followed by the destruction into pieces of the microspheres in acidic conditions. (left) applied force (µN) versus deformation (ε) measured with AFM for the capsules made with generations 1 to 4 of the positively charged dendrimers.[33]

In summary, the dendritic effect has not been frequently reported in connection with materials, but it has found an important use for the elaboration of sensitive bio-arrays, in which the dendrimers play the major role of a 3-dimensional spacer. Such property is in particular at the origin of the first commercial use of dendrimers (in 1998), as a key component in an instrument for cardiac analysis.[27]

The dendrimer effect in biology/nanomedicine

Nanomedicine is an emerging interdisciplinary field, in which dendrimers occupy a predominant place,[34] thanks to their multivalency, reminiscent to the multivalent (or polyvalent) interactions widely found in the Nature. The multivalent interactions concern for instance the adhesion ability of the gecko lizards induced by a large number of microscale setae on their footpads, or the large number of interaction of carbohydrates with proteins. Multivalent interactions can be collectively much stronger than the corresponding monovalent interactions, in particular through multiple ligand – receptor interactions.[35] Dendrimers, which are inherently multivalent species have found many uses in biology,[36] essentially for two main types of experiments:[37] for drug delivery, and as drugs by themselves.

Drug delivery with dendrimers

Drug delivery is a complex process, which necessitates in most cases three main steps: the carriage (interaction drug/carrier), the targeting, generally (but not always) followed by the drug release. Many reviews have gathered references about the use of dendrimers for drug delivery, through covalent or non-covalent assemblies.[38-40] "Drug" has to be understood in a wide sense, as it covers classical drugs, but also DNA, RNA, siRNA, nucleic acids, and so on.

Transfection is the terminology used for the deliberate introduction of nucleic acids (normally in the form of plasmids) into cells and up to the nucleus, generally carried out in view of gene therapy. A vector for carrying the nucleic acids is generally needed. Viruses have naturally such property, but even when inactivated, their use is difficult, eventually dangerous, thus many researches focus on the search for non-viral vectors. The use of dendrimers as transfection agents, for the delivery of nucleic acids into cells, is among the very first uses proposed for dendrimers,[8] and a lot of work has been (and is still) carried out in this field.[41] Most generally positively charged dendrimers are used to interact with the negatively charged nucleic acids. The nature of the terminal groups, generally ammoniums, is particularly important, as it should be adaptable to the pH variations encountered in different parts of cells, for delivery to the nucleus. In the case of PPH dendrimers, a drastic difference in the efficiency has been observed between tertiary and quaternary ammonium terminal groups. The former displays a positive dendritic effect with increasing generations, whereas the latter displays a negative dendritic effect, mainly related to an increased toxicity (Figure 11).[42]

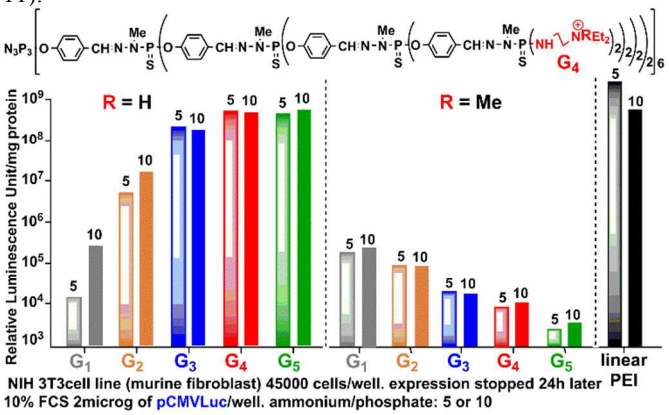


Fig. 11 Transfection efficiency of several generations of dendrimers ended by $-NHEt_2$ (left) or $NMeEt_2$ (right) groups, compared with the efficiency of a standard chemical transfection agent (Polyethyleneimine (PEI)), for the luciferase plasmid. 5 and 10 refers to the ratio ammoniums of the dendrimers to phosphates of the plasmid. The efficiency of the transfection is detected by luminescence.[42]

The dendritic effect can be also related to the shape of the dendrimers. Indeed, dendrimers built from a tri-functional core have a cauliflower shape, whereas dendrimers built from a hexa-functional core should have a more spherical structure. Both types of structures were obtained with PPH dendrimers, either built from $S{=}PCl_3$ or from $(N{=}PCl_2)_3$ as core, and ended by carboxylic acid moieties. These dendrimers form saline species with an aminolactitol M, affording multisite analogues of Gal$\beta_1$cer, which is a glycolipid of the membrane of cells. Gal$\beta_1$cer has a highly specific affinity for the V3 loop region of the gp120 viral envelope protein of HIV-1. The saline assemblies dendrimers/aminolactitol have been synthesized with the aim of blocking HIV infection prior to the entry of the virus into human cells. The efficiency of HIV1 inhibition has been evaluated in vitro on CEM-SS cells (human T4-lymphoblastoid cell line). All dendrimers are more efficient than the aminolactitol alone. In order to compare the efficiency of all compounds, IC_{50} values (the concentration which induces 50% of inhibition) have been replaced by RIC_{50} values, which corresponds to IC50 x Number of aminolactitol moieties in the assembly. An original dendritic effect is observed, as it appears that the number of aminolactitol moieties is less important than the shape of the assembly. The hexa-functional core is more efficient that the trifunctional one (compare the efficiency of G_1 (PS) and G_0 (N_3P_3), both having 6 aminolactitol moieties, in Figure 12).[43]

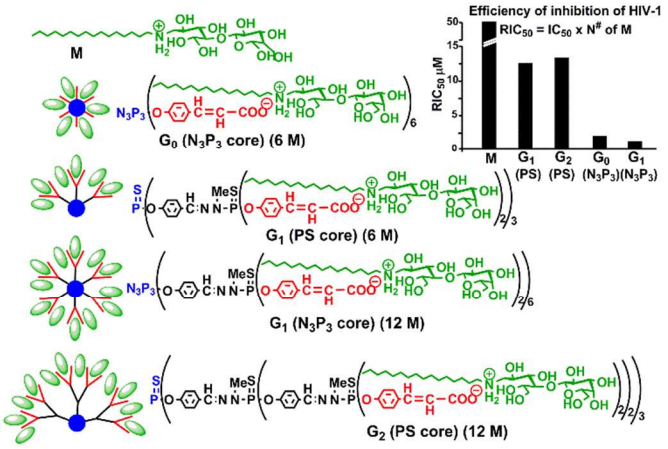


Fig. 12 Structure of the assemblies between the aminolactitol M and dendrimers built from a tri- or hexa-functional core. RIC_{50} is used instead of IC_{50}, to compare the efficiency for the inhibition of HIV1.[43]

Dendrimers as drugs by themselves

Known drugs can be covalently grafted to the surface of dendrimers, affording other examples of "drug delivery" if the link is cleavable.[44] However, there exists also dendrimers which have strong biological properties, whereas the monomer they bear as terminal groups has not at all these properties when it is alone. Such compounds are called "drugs by themselves" or "drugs per se". They afford certainly the most striking examples of dendritic effects in biology.

The first example of dendrimers as drugs by themselves was certainly provided by PAMAM and PPI dendrimers ended by ammonium groups. Both dendrimers was found efficient to purge PrP^{Sc}, the protease-resistant isoform of the prion protein, from scrapie-infected neuroblastoma (ScN2a) cells in culture, but only generations 4 were tested.[45] Prion diseases are transmissible spongiform encephalopathies which affect the brain and nervous system of many animals and of humans. In the case of PPH dendrimers, generations 3, 4 and 5 terminated by ammonium groups (see structure in Figure 11, for G_4 and R = H) were tested against several prion strains. Generation 4 was found the most efficient, illustrating a specific effect with this generation. This dendrimer was also found very efficient in vivo, when injected to scrapie-infected mice (Figure 13).[46]

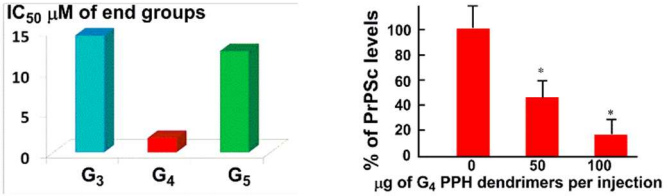


Fig. 13 Left: specific efficiency of PPH dendrimers ended by ammonium groups (see structure in Fig. 11 for G_4, with R = H). Right: dose dependent effect of G_4 injected every two days for 1 month to scrapie-infected mice; efficiency expressed in % compared to untreated mice.[46]

Dendrimers may have also strong anti-inflammatory properties. A series of PPH dendrimers ended by a variable number of mannose derivatives (from 1 to 3 at each terminal point) was synthesized with the aim of mimicking the bioactive supra-molecular structure of mannose-capped lipoarabinomannan (ManLAM), which is a major virulence factor of *Mycobacterium tuberculosis*. Indeed, the cluster of ManLAM has an anti-inflammatory effect, depressing the immune response of the host, in favor of the survival of the invading pathogen. Despite the difference in size (about 30 nm for Man LAM cluster, less than 10 for the G_4 dendrimer), several dendrimers ended by two (G_3-D and G_4-D) or three (G_3-T) mannose derivative on each terminal point have efficiencies comparable to that of the ManLAM cluster for the binding to membrane-expressed DC-SIGN (Figure 14). DC-SIGN is a C-type lectin receptor present on the surface of macrophages, which recognizes and binds to mannose type carbohydrates. Furthermore, G_3-T was found efficient *in vivo* for preventing acute lung inflammation in mice exposed to aerosolized LPS (lipopolysaccharide, a strong inflammatory agent). Prior administration of this mannodendrimer G_3-T *per os* (orally) was found to significantly reduce lung inflammation for mice exposed to LPS.[47]

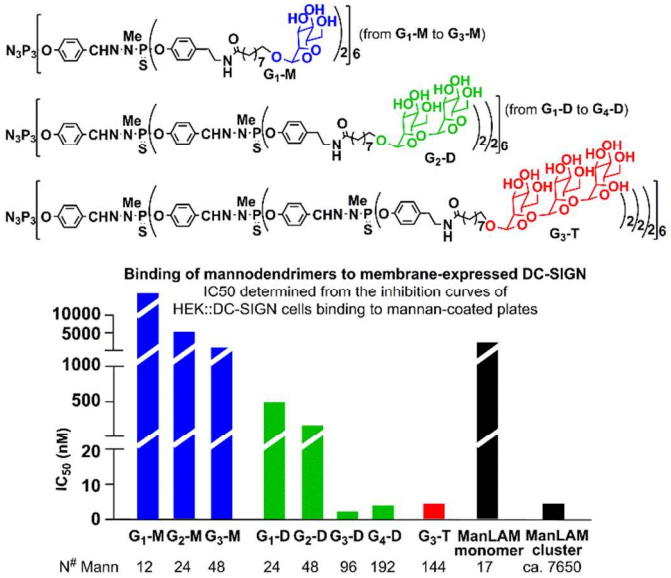


Fig. 14 Structure of some PPH mannodendrimers, and their efficiency for binding to membrane expressed DC-SIGN, compared to natural monomeric ManLAM and ManLAM cluster.[47]

Another example of anti-inflammatory properties of dendrimers was provided by PPH dendrimers ended by azabisphosphonic derivatives. These dendrimers trigger cells of the human immune system, and are in particular able to activate monocytes[48] via an anti-inflammatory pathway. These dendrimers are also able to induce the multiplication of the Natural Killer cells (NK), which play a key role in immunity by fighting against cancers and infections. Three generations of this dendrimer (G_0 to G_2) were tested for the multiplication of NK cells. Generation 1 is the most efficient to multiply NK cells, both in number and in percentage (Figure 15).[49] Recent developments have shown that this dendrimer has also an anti-osteoclastic activity (osteoclasts are giant cells responsible for bone resorption). Combination of this anti-osteoclastic property with the anti-inflammatory property has resulted in a strong activity against a model of rheumatoid arthritis, demonstrated on mice suffering from a comparable disease, which received the G_1 dendrimer either by injection or orally.[50]

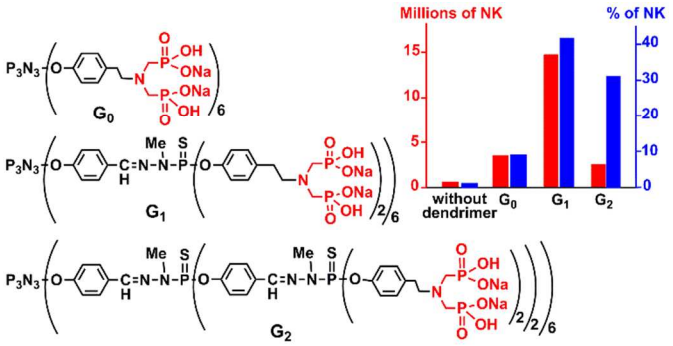


Fig. 15 PPH dendrimers ended by azabisphosphonic functions, and their efficiency for the multiplication of human Natural Killer cells.[49]

In summary, the dendritic effect in biology has been observed with dendrimers used both for drug delivery and as drugs by themselves. The first case includes in particular the transfection efficiency, for which a positive dendritic effect when the generation of the dendrimer increases has been frequently observed.[41] This efficiency is often related to a more efficient screening of the negative charges of the nucleic acids by the positively charged dendrimers. However, the most astonishing results in biology were obtained for dendrimers used as drugs by themselves, and for which the monomer has no activity. Early examples concerned the strong interaction of positively charged dendrimers with the prion protein, which decreases the level of the infective form,[45] including *in vivo*.[46] More recently, it has been shown that several types of dendrimers have strong anti-inflammatory properties, including *in vivo*.[47,50] In these cases, the dendritic effect is reminiscent to the "cluster glycoside effect" widely known in biology, in which a large number of weak interactions results in a very strong interaction.

Conclusions

The dendritic (dendrimer) effect is a true non-linear effect, which is not always positive, but when it is, it can induce quite remarkable properties, unobtainable by other means. The dendritic effect has a very broad scope; it has been observed in different fields, with an emphasis on the catalytic properties and the biological properties. The origin of the dendrimer effect is not always fully understood, even if some constants can be identified. When the function is located at the core, the dendritic effect originates from the influence of the branches towards the core, modifying the polarity of the environment, or shielding the effect of the solvent, in particular water.

However, most of the dendritic effects are observed with functions located at the surface of the dendrimers. In those cases, cooperativity, taken in a large sense, is certainly the most important factor to account for such effect. Cooperativity can concern two or a few neighbouring sites in close proximity, but more generally a large part of the functions located at the surface of the dendrimers. High local concentration of functions within well-defined nanoscopic reaction volumes can be attained. Such behaviour affects the molecular interactions between the dendrimers and their surroundings at the interface (substrates for catalysis, receptor or biological entities), which in turn affects the activity and selectivity.

These phenomena cannot be replicated in a randomly dispersed monomeric or even a polymeric system, emphasizing the specificity of dendrimers amongst all types of molecules and polymers. The molecular design of dendrimers has to be carried out taking into account the search for the dendritic effect, which can be attained even with small generations of the dendrimers. This opens new avenues for future researches in the expanding field of dendrimers.

Acknowledgements

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Notes and references

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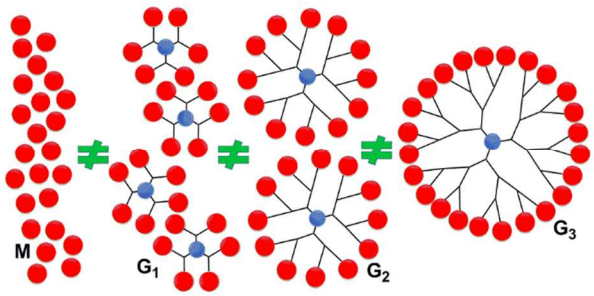
Graphical abstract



The dendritic effect occurs when the properties of a functional group become different when it is linked to a dendrimer.

Anne-Marie Caminade is Director of Researches at the CNRS in Toulouse since 1997 and head of the "Dendrimers and Heterochemistry" group at the LCC-Toulouse since 2006. After two PhDs in Toulouse and two Post-docs (IFP-Paris and Von Humboldt fellow in Saarbrücken), she was recruited by the CNRS in 1985. She developed several aspects of phosphorus chemistry, including low coordinated compounds, transition metal coordination, and macrocycles. Her current research interest is on dendrimers, in particular on their use as catalysts, for nanomaterials and biology. She is the co-author of about 385 publications, 40 book chapters and 30 patents (h index 55).

Armelle Ouali received her PhD from the University of Montpellier in 2005 in the field of copper-catalyzed arylation of nucleophiles (Dr M. Taillefer). After a post-doc in the synthesis of phosphorous and silicon-based dendrimers for biological applications (Drs J.-P. Majoral and A.-M. Caminade, Toulouse), she moved to the University of California for a post-doc in carbene chemistry (Prof. G. Bertrand, Riverside). She joined the group of Dr A.-M. Caminade in 2008 where she is involved in the development of new catalytic systems for various applications in organic synthesis. Her current interest is the design of dendrimeric metal-based or organic catalysts.

Régis Laurent was born in Porvoo (Finland) and studied chemistry at the University of Toulouse (France) where he received his PhD in 1994 (Pr. J. Dubac and A. Laporterie, microwave activation in organic chemistry). After post-doctoral studies at the University of Saarbrücken (Germany, M. Veith), and at the University of Toulouse (L. Gorrichon), he got in 1996 a CNRS researcher position in Toulouse (LCC, J.P. Majoral). His research interests are in the synthesis and characterization of phosphorus-containing dendrimers, their applications in catalysis and in material sciences. He is in charge of the technological platform Technopolym.

Cédric-Olivier Turrin was born in 1974 in Rouen, France. He studied chemistry at the Engineering School in Lyon (CPE-Lyon) before receiving his PhD thesis in Toulouse (France) in 2000. He is currently working at the LCC/CNRS where he holds a CNRS researcher position since 2001. His research interests include the study of phosphorus-containing dendrimers and hyper-branched polymers for biomedical applications, biomaterials and hybrid systems.

Jean-Pierre Majoral is Emeritus Director of Research at the CNRS in Toulouse. His research interest is focused on the design and the properties of macrom-olecules such as phosphorus dendrimers and hyperbranched polymers. Main efforts are directed to the use of dendrimers in medicinal chemistry and material sciences. Emphasis is also laid on immobilization of molecular and macromolecular organo- and metal catalysts and their use for fine chemical synthesis. He is a member of several Academies of Sciences worldwide and an author of 545 publications, 5 books, 28 book chapters, and 45 patents.