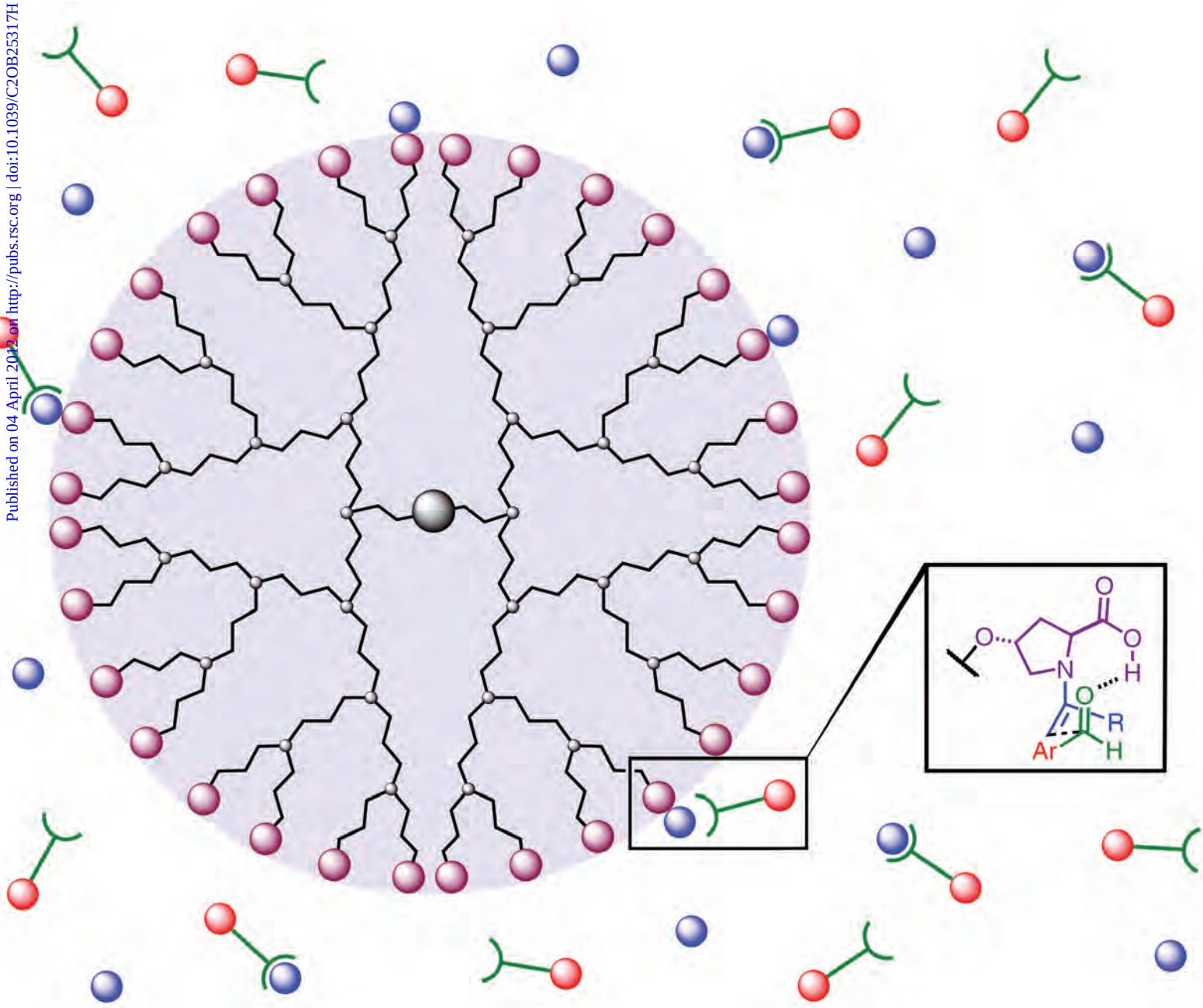
Organic & Biomolecular Chemistry

www.rsc.org/obc

Volume 10 | Number 25 | 7 July 2012 | Pages 4809–4988



ISSN 1477-0520

RSC Publishing

PERSPECTIVE

Brian Rasmussen and Jørn Bolstad Christensen

Organocatalytic dendrimers

Organic & Biomolecular Chemistry

Dynamic Article Links
View Online

Cite this: *Org. Biomol. Chem.*, 2012, **10**, 4821

www.rsc.org/obc

PERSPECTIVE

Organocatalytic dendrimers

Brian Rasmussen* and Jørn Bolstad Christensen

Received 13th February 2012, Accepted 3rd April 2012
DOI: 10.1039/c2ob25317h

Dendrimers are a class of synthetic macromolecules that bridge the gap between polymers and small molecules. The dendritic structure provides both the possibility for compartmentalization of reagents as well as offering a multivalent surface, and they are in that respect similar to globular proteins. This perspective article reviews the growing field of organocatalysis with dendrimers and highlights the possibilities that are unattainable for small molecule catalysts.

1. Introduction

Polymers can be divided into four different classes. These are the linear structures, the cross-coupled structures, the branched structures, and the dendritic structures.[1] Dendrimers constitute a subclass of the dendritic class and are characterized by a structure in which well-defined hyperbranched wedges of monomeric structure emanate from an inner core.[2] Dendrimers can be synthesized by an iterative procedure whereby a single layer is added and the product purified in each cycle of the iteration. Thereby, synthetic control is maintained in each step, and this results in well-defined structures that are characterized by the number of layers which is also called the generations. For the poly(propylene imine) and the poly(amido amine) dendrimers, the different generations are illustrated in Fig. 1.

The well-defined aspect of the structures of dendrimers is what differentiates these molecules from polymers in the three non-dendritic classes. In the synthesis of polymers from these latter classes, uncontrolled procedures lead to products with rough variations in both the degree of branching and the number of attached monomers. These variations result in polymers with a high polydispersity, and this stands in contrast to dendrimers which are either monodisperse or have a very narrow molecular weight distribution.

Due to the high degree of branching in dendrimers, the number of functionalities at the surface increases fast relative to the overall size of the molecule. Therefore, important differences exist between the overall shape of low and high generation

Department of Chemistry, The H.C. Ørsted Institute, University of Copenhagen, Universitetsparken 5, 2100 Denmark.
E-mail: bris@kiku.dk; Tel: +45 3532 0168

Brian Rasmussen

Brian Rasmussen was born in 1980 in Denmark and initiated his chemistry studies at the University of Copenhagen in 2001. Under the guidance of associate professor Jørn B. Christensen, his BS work concerned supramolecular chemistry at dendrimer surfaces, whereas his PhD was concentrated on dendrimer synthesis and the development of new organocatalytic dendrimers for the Diels–Alder reaction. From 2010, he has been employed as a Post Doc at the University of Copenhagen under the guidance of assistant professor Michael Pittelkow where he is mainly working with organoselenium chemistry, supramolecular chemistry, and dynamic combinatorial chemistry.

Jørn B. Christensen

Jørn B. Christensen obtained his PhD degree in organic chemistry in 1994 from University of Copenhagen in Denmark working with Professor Klaus Bechgaard. He was appointed assistant professor in 1994 and associate professor in 1997. He was a visiting scientist in Professor E. W. "Bert" Meijer's group at the Technical University of Eindhoven in 1997 and in 2001 and a visiting professor at The National Dendrimer & Nanotechnology Center at Central Michigan University in 2008. His main research interests lie in the synthesis and applications of dendrimers in catalysis, nanomedicine and as tools for investigating molecular interactions.

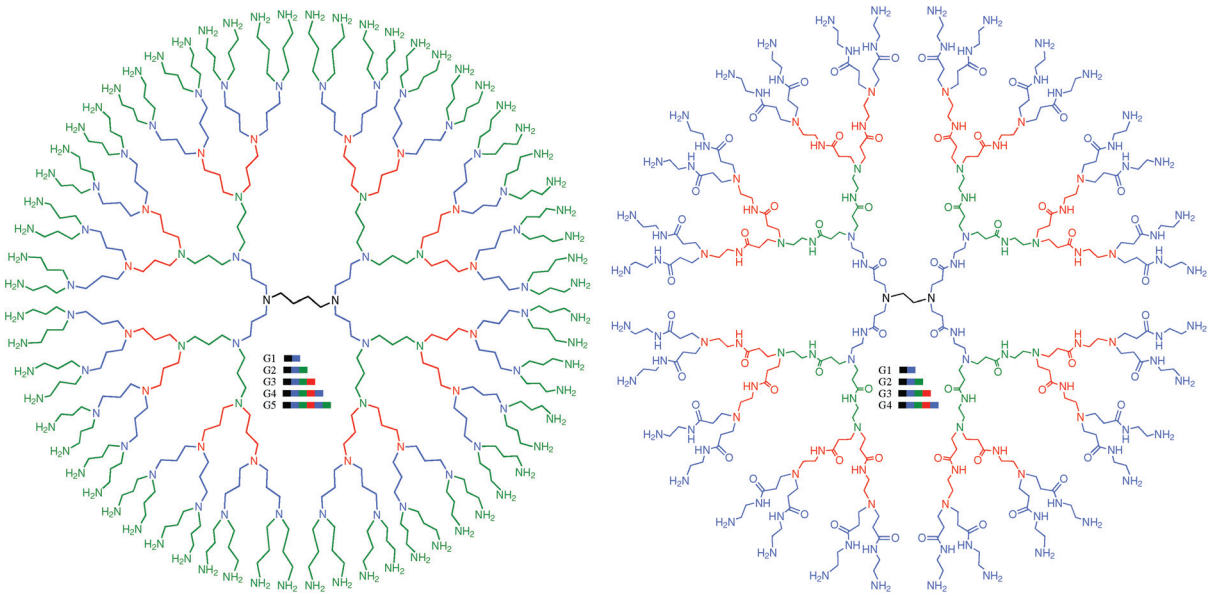


Fig. 1 On the left, the structure of a fifth generation poly(propylene imine) (PPI) dendrimer, and on the right a similar illustration of a fourth generation poly(amido amine) (PAMAM) dendrimer.

dendrimers. The latter can be thought of as spheres with closely situated surface functionalities that isolate the dendritic interior, whereas the low generation structures are non-spherical open structures.

Thus, by increasing the generation of a dendrimer, a differentiation will gradually arise between the structure's interior and the exterior, and thereby the overall properties become different from what is obtainable for small molecules. Non-dendritic polymers possess the same ability to isolate parts of their structure, but these micro environments are, due to a less controlled synthesis, poorly defined. Hence, dendrimers constitute in a unique way structures which can be precisely designed for a desired function, and these properties have opened application areas such as catalysis,[3–7] nanomedicine,[8] surface chemistry,[9] light-harvesting systems,[10] *etc.*

In the following sections, a part of the first of the above-mentioned areas, namely catalysis, will be covered from its beginning in 1994 to 2011.

2. Catalytic dendrimers

Catalytic dendrimers can be divided into two main types. In the first type, the combination of a dendrimer and an already catalytically-active transition metal constitutes the catalytic system, and in the second type the dendrimer alone constitutes an organocatalytic system. The metal loaded systems have been the subject of numerous reviews and will not be covered here. Instead, this review focuses exclusively on the organocatalytic systems wherein the catalytic activity originates from the dendrimer alone.

The reactions used to test for possible catalytic activity of a new dendrimer take place either in the dendritic interior or at the exterior close to the surface groups. This difference is used in the following description to categorize the different examples, and in section 2.1 the interior-based systems are presented, while section 2.2 covers the surface-based systems.

2.1. Organocatalysis in the dendritic interior

In general, organocatalysis is the acceleration of a reactions with a substoichiometric amount of an organic compound which does not contain a metal atom. The field of organocatalysis has grown tremendously over the last decade and a large number of systems have been described.[11,12] Many of these systems involve small molecules acting as nucleophilic catalysts and by this way of action the systems imitate several enzymatic processes. Enzymes possess, however, the extra advantage that the protein structure surrounding the active site can provide a compartment that facilitates the catalyzed reaction, and this is unobtainable with a small molecule catalyst. By the transition to dendritic systems this extra advantage is potentially possible and this makes dendrimers interesting candidates for the development of new organocatalysts.

The development of dendritic catalysts with the interior tailor made for a given test reaction was initially motivated by the similarities between earlier developed catalytic micelle systems and dendrimer's properties as unimolecular micelles. Years before the synthesis of the first dendrimer, surfactants forming micelle-based reaction vessels had already shown interesting catalytic possibilities. These micelle systems could accelerate a reaction by causing high local concentration of the reagents and in some cases enhance reactivity due to encapsulation. This approach to catalysis has been successfully used in reactions like epoxidations,[13] nucleophilic substitutions,[14] and pericyclic reactions.[15]

Despite the success of the micellar systems, the strategy of using surfactants as building blocks for the reaction environments has its limitations. Firstly, micelles are not formed when the concentration of the surfactants is below the so-called critical

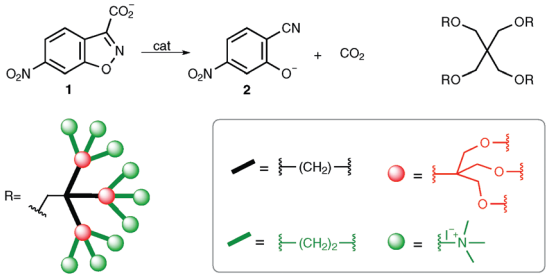


Fig. 2 An illustration of the test reaction and the dendritic catalyst in Ford's studies.

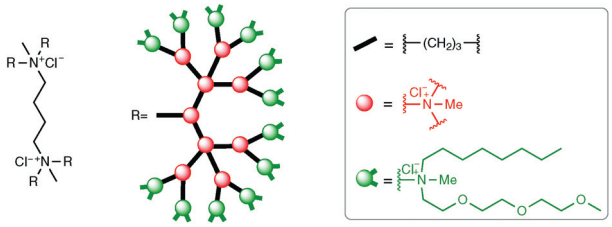


Fig. 3 Schematic representation of Ford's dendrimer with the highest catalytic activity.

micelle concentration. This is a parameter that depends on both solvent and temperature, and hence the conditions under which a given test reactions can be carried out are narrowed in the micellar approach. Secondly, formation and decomposition of micelles are dynamic processes. This means that the micelles continuously decompose and reform, and this is problematic when encapsulation of reagents is crucial for catalytic activity.

Both these drawbacks can be overcome with dendritic systems. Firstly, due to the unimolecular nature of dendrimers no critical concentration exists, and thus the reaction conditions can be chosen with fewer restrictions. Secondly, covalent bonds hold the molecule together and not the weaker supramolecular forces operating in the micelle systems. Therefore, no decomposition of dendrimers is likely within the normal range of reaction temperatures. This removal of drawbacks does not happen at the expense of catalytic potential. Dendrimers still possess the same possibilities to encapsulate reactants and tune the reactivity as seen in micellar systems.

An early example of a dendritic system taking advantage of the properties of the interior was presented in 1994 by Ford and co-workers.[16] To study the additional potential of dendrimers, one of the test reactions Ford examined had already been studied in micelle-based systems. This reaction was the decarboxylation of 6-nitrobenzisoxazole-3-carboxylate, **1**, taking place in an aqueous medium with and without dendrimer present, of the type illustrated in Fig. 2.

Ford designed the catalytic system to create a dendrimer with a nonpolar aprotic interior and a polar periphery. The polar end groups controlled the hydrophilicity of the dendrimer, and the aprotic interior enhanced the reactivity of the reagent. In the protic media outside the dendrimer, both the carboxylate **1** and the transition state leading to the phenolate **2** are stabilized by hydrogen bonding. When the substrate is transferred to the interior of the dendrimer, this stabilizing interaction is lost. Due to a relatively localized negative charge in the ground state, strong stabilizing interactions are lost, whereas only weaker interactions are lost in the transition state where the negative charge is more delocalized. Hence, the energy barrier for the reaction is lowered by encapsulation, and a catalytic effect is expected. A comparison of the reaction in an aqueous medium with and without the dendrimer present showed that the dendrimer caused a twenty-fold increase in the rate. However, this result was around ten times lower than what was obtainable by different ammonium ion based latexes.

Two main factors determine the rate of the decarboxylation. These are the position of the equilibrium between encapsulated and non-encapsulated reagent, and the rate constant for the reaction taking place in the dendritic interior. Kinetic studies gave a measure for both factors, and a comparison with similar results for the earlier examined latex systems showed that the superiority of these systems was a result of higher rate constants for encapsulated reagent. Therefore, Ford's original study was followed up by the synthesis of dendrimers with small variations aimed at obtaining as isolated an interior as possible.[17–19]

The dendrimers used in these studies were PPI dendrimers that were functionalized both at the surface and at each branching point. The two key differences between these structures and the originally studied dendrimer were that (*i*) the cationic centers were moved from the periphery to the interior, and (*ii*) hydrophobic chains were attached to the dendrimer surface (Fig. 3). The cationic centers in the interior were planned to move the anionic reagent further inside the dendrimer, and the hydrophobic chains at the surface should create an isolating layer. Therefore, both these changes helped to isolate the reaction environment more efficiently. Catalytic studies with the new dendrimers showed both a higher rate constant and a more favorable equilibrium constant for the encapsulation of **1** compared to the original study.

In 2005, Kaneda and co-workers developed a catalytic system very similar to Ford's optimized dendrimer.[20] The test reaction in Kaneda's study was the Mukaiyama reaction between various aldehydes and with 1-methoxy-2-methyl-1-(trimethylsilyloxy) propene as the enol equivalent. The catalysts were third generation PPI dendrimers with the branching points methylated and the surface functionalities amidated with fatty acids.

Control experiments with dendrimers missing the quaternary ammonium centers in the interior showed no measurable reaction. The reason for this difference was deduced from the differences in NMR data for the silyl enol ether in the presence of the catalytic dendrimer and in the presence of the non-catalytic dendrimer. As illustrated in Fig. 4 the dendrimer with cationic centers caused a lower ppm value for the carbon in the β-position. Low ppm values correspond to a high degree of shielding, which corresponds to high electron density at that position. This higher electron density gave rise to increased nucleophilicity, and hence the catalytic effect.

The two dendrimer's ability to alter the electrophilicity of the aldehydes was also examined. This examination showed no difference in the chemical shifts for the carbonyl carbon when encapsulated in the catalytic and non-catalytic dendrimer, respectively. Overall, this suggested that the catalytic effect arose as a consequence of base interactions between the counter ion of the ammonium centers and the silyl enol ether. This is contrary

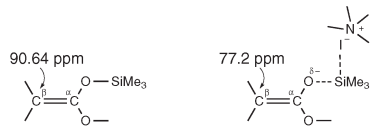


Fig. 4 A comparison of the ppm values for Kaneda's silyl enol ether in a mixture with the non-catalytic dendrimer (left) and in a mixture with the catalytic dendrimer (right).

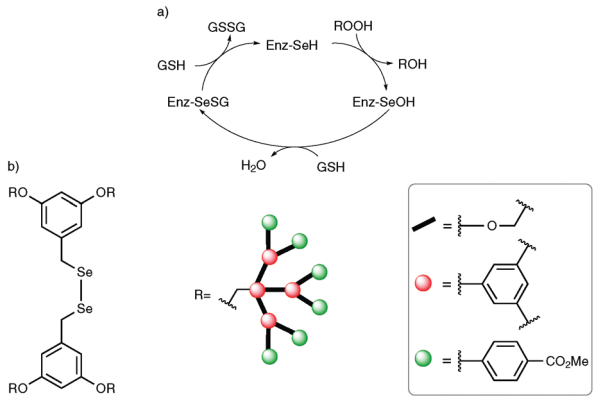


Fig. 5 (a) The catalytic cycle for glutathione peroxidase. (b) The structure of Zhang's third generation enzyme mimicking dendritic system.

to the conventional Mukaiyama reaction, wherein Lewis acids activate the electrophile in the reaction.

To examine the factors causing the catalytic activity further, the test reactions were also carried out in the presence of non-dendritic ammonium iodides like $N(n\text{-}C_6H_{13})_4I$ and $N(n\text{-}C_4H_9)_4I$. These tests showed that the ammonium iodides caused a small catalytic effect, but nothing that was comparable to the dendritic catalyst. This difference was proposed to result from an isolated and highly polar reaction environment in the dendritic case, which earlier studies had shown were favorable for the Mukaiyama reaction.

Both Ford's and Kaneda's dendritic systems illustrate that the properties of the interior can be controlled and used to cause a catalytic effect. Such control is very similar to what is seen in catalysis with enzymes where for instance hydrophobic pockets contribute to control of substrate selectivity and provide optimized conditions for the catalyzed reaction. With these similarities as the motivation, new organocatalytic dendrimers have been developed to catalyze biologically interesting reactions.

In 2004, Zhang and co-workers reported on the design and synthesis of such an enzyme mimicking dendrimer and examined it for glutathione peroxidase (GPx) activity.[21] GPx is a selenium-based antioxidant that protects biomembranes from oxidative damage. As illustrated in Fig. 5a, the selenium-containing enzyme is the central part of a cycle that reduces hydroperoxides with glutathione (GSH) as the reducing agent. The active site of the enzyme involves selenocystein and the protein forms a hydrophobic pocket around this moiety. In Zhang's dendritic system, selenium was introduced in the core as illustrated in Fig. 5b and a hydrophobic environment around this core was established by attaching nonpolar poly benzyl ether dendrons (so-called Fréchet-type dendrons) of generation one to three.

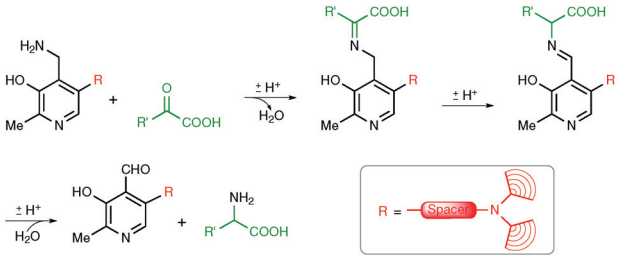


Fig. 6 Assumed reaction sequence in the catalyzed transfer of an amino group from pyridoxamine to an α-keto-acid.

As an alternative to glutathione, benzenethiol was used in testing of the dendrimer and H_2O_2 was chosen as the target substrate. Initial rates of the reduction were measured for all three generations and showed that the catalytic effect was largest for the G3 dendrimer and then declined with decreasing generation.

A closer examination of the system showed that the positive dendritic effect was most evident in the transition from generation two to three. Computer simulations suggested that the marked superiority of the third generation dendrimer was a consequence of this structure's size and ability to efficiently create a hydrophobic pocket around the selenium-containing core. In addition, measurements of the association constants between benzenethiol and each of the three dendrimers showed the highest affinity to the third generation dendrimer.

Another example of a dendritic system synthesized to mimic enzymes has been reported by Breslow and co-workers.[22] In this example, PAMAM dendrimers of generation one to six with a pyridoxamine based core were tested for their ability to transfer an amino group from the pyridoxamine moiety to α-keto-acids. As illustrated in Fig. 6, every step in the reaction sequence leading to this transfer requires reorganization of protons. The numerous amine functionalities in the dendritic structure were planned to catalyze these steps.

Three series of dendrimers with different spacer units were tested for transaminase activity with the two substrates pyruvic acid and phenylpyruvic acid. Regardless of the spacer, Michaelis–Menten kinetics were observed as well as a positive dendritic effect. As in Zhang's studies, this effect was not linear and an evident enhancement was clear from generation four and forward. The best results were observed with phenylpyruvic acid as substrate and a more than 7000-fold rate (k_2/K_M) increamse was observed relative to the same reaction with pyridoxamine without PAMAM dendrons attached.

The k_2/K_M-values for phenylpyruvic acid were about 0.5-, 1-, and 5-fold larger than those for pyruvic acid when tested in dendrimers of generation one, three, and six, respectively. These differences were mainly the result of smaller K_M-values for the substrate containing a phenyl group, and this was interpreted to originate from a hydrophobic binding effect that gradually becomes more efficient with increasing generation.

Without the combination of Breslow's transaminase process to a reaction that regenerates the dendrimer core, the system is not a true catalyst. Later, this weakness was addressed with studies on a related dendritic system which constituted a true catalyst in one of the tested reactions.[23] The pyridoxamine in the original core was changed to a pyridoxal moiety and the studied reactions

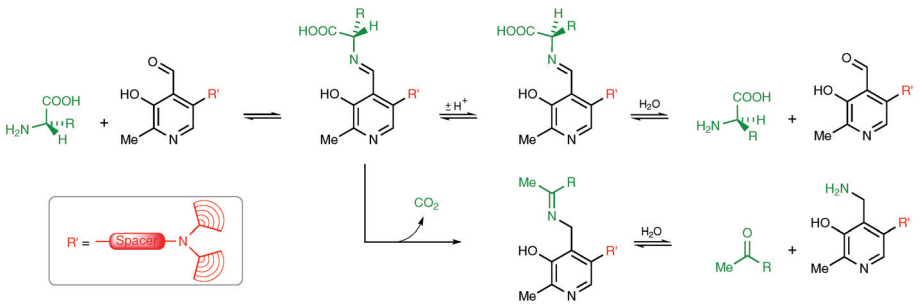


Fig. 7 The assumed reaction sequences in the racemization of amino acids (top) and combined decarboxylation and amino group transfer of amino acids (bottom).[23]

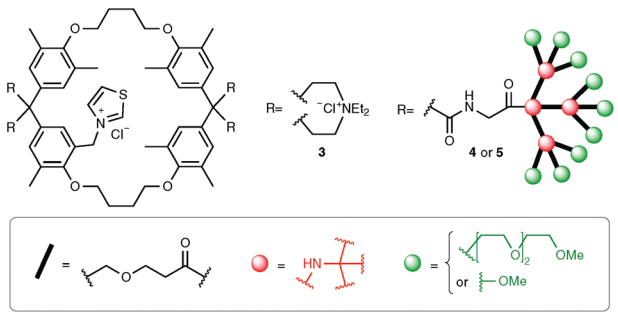


Fig. 8 The structure of Diederich's oxidase active cyclophane and dendrophanes.

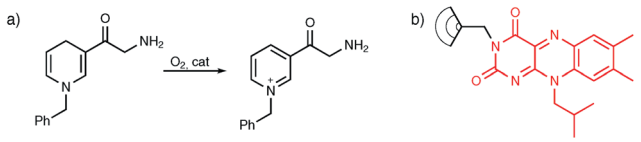


Fig. 9 (a) The test reaction in Cooke's studies, and (b) a schematic representation of the dendrimers highlighting the flavine-derived core.

were (*i*) racemizations of amino acids, and (*ii*) combined decarboxylation and amino group transfer. The proposed reactions sequences in these two processes are shown in Fig. 7.

As in the original study, Breslow and co-workers observed a positive dendritic effect on both reactions. The sixth generation dendrimer accelerated the rate of racemization by a factor 97 relative to the same reaction between the amino acids and the core molecule without dendrons attached. In the enhancement of the decarboxylation, the rate was more than tripled by the sixth generation dendrimer relative to a similar reference reaction.

In 1999 Diederich's group published an example of an oxidase mimicking dendritic catalysts.[24] The test reaction was the oxidation of naphthalene-2-carbaldehyde to methyl naphthalene-2-carboxylate. Prior to Diederich's dendritic studies, catalysis of this reaction had been studied with different small molecular candidates. The thiazolio-cyclophane **3** in Fig. 8 was such a candidate and it catalyzed the oxidation of aromatic aldehydes with a flavin derivative as the oxidizing agent.

Mechanistic studies of the oxidation suggested a transition state with a low polarity. Motivated by these findings, Diederich turned to a dendritic system wherein attachment of low polarity dendrons to the already tested cyclophane moiety was planned to create a non-polar reaction environment. The structure of theses so-called dendrophanes (*i.e.*, dendritic cyclophanes) **4** and **5** are illustrated in Fig. 8.

Initial rates of the oxidation were measured on the test reaction in a methanol solution with a phosphate buffer (pH 7.5) and a flavine derivative as the oxidizing agent. A comparison of these measurements and the results for the non-dendritic studies with cyclophane **3** showed that the catalytic activity of dendrophanes **4** and **5** were 50 and 160 times lower, respectively. Based on a closer analysis of the kinetics, the authors proposed an explanation for the low efficiency of the dendritic system. Different rate equations for the dendrophane-catalyzed and the cyclophane-catalyzed reactions were observed, and this was interpreted as being the result of different rate-determining steps in the two systems. Hence, the basis for the initial design of the dendritic systems might be directed towards the wrong factors.

A final example of a dendritic system that catalyzes a biologically interesting reaction has been published by Cooke and co-workers.[25] As in Diederich's work, the aim of this study was oxidase activity. As illustrated in Fig. 9, the dendritic system was based on Fréchet-type dendrons and a flavin derivative as the core. The attached lipophilic dendrons were designed to provide the same isolation that Diederich was trying to create, and both molecular dynamic simulations and UV-Vis measurements indicated increasing isolation with increasing generation.

The studied test reaction was the aerobic oxidation of a substrate containing the same reduced form of nicotinamide as found in NADH. Three generations of the dendritic catalyst were studied, and as a reference catalyst riboflavin was used. Initial rates of the reaction with the four different catalysts showed a gradual increase in efficiency within the dendritic series, and in addition that all dendrimers caused faster reaction than riboflavin. The authors suggested that the positive dendritic effect was the result of a gradually higher association between the dendrimer and the substrate.

In the enzyme mimicking examples above, dendrimers were designed to catalyze reactions that, in advance, were known to be catalyzed by enzymes. Thereby, these studies centered around the test reaction. However, other strategies for constructing artificial enzymes exist where, for example, the mimicking aspect lies in the structure of the dendrimer. In 2001 Smith and co-workers illustrated such a strategy by synthesis of polypeptide dendrimers.[26] The branching structure of these dendrimers was based on the amino acid L-lysine and the core of the dendrimer was tris

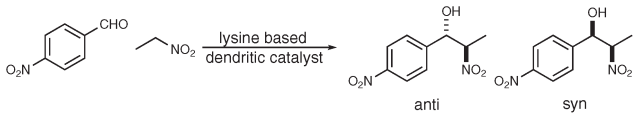


Fig. 10 The test reaction used in Smith's studies of catalytic activity of lysine based dendrimers.

(2-aminoethyl)amine. The test reaction in Smith's catalytic dendrimers was the Henry reaction between nitroethane and 4-nitrobenzaldehyde as shown in Fig. 10.

The tertiary amine in the center of the dendrimer was the active catalyst, and therefore the efficiency of the dendrimers could be compared with the catalytic activities of the tertiary amines triethylamine and *N*,*N*-diisopropylethylamine. This comparison showed that similar yields were obtainable by the dendritic and non-dendritic catalysts, respectively. However, the dendrimers required considerably longer reaction times to give these yields. The effect of generation was also studied, and a comparison between the first and second generation dendrimers showed two interesting differences. Firstly, the required reaction times were very different as exemplified by 92% yield after 48 hours with the first generation dendrimer and 94% after only 24 hours for the second generation structure. Secondly, the induced diastereoselectivity was different for the two dendrimers. The first generation dendrimer slightly favored the *anti* product, whereas the second generation dendrimer favored the *syn* product.

The Henry reaction has also been studied by Morao and Cossío and in other types of dendrimers.[27] As in Smith's study, the dendrimers were build around a tertiary amine core, but instead of a lysine branching structure, nonpolar Fréchet-type dendrons were attached. The catalytic tests of these dendrimers showed (*i*) that longer reaction times were required relative to non-dendritic catalyst, and (*ii*) that an increase in generation caused lower efficiency. This work was followed up with a combination of molecular dynamics simulations and kinetic studies of how the catalytic efficiency was related to small variations in the dendritic structure.[28] The dendrimers were all based on benzyl ether dendrons but with differences in the degree of branching. Despite these differences, an increase in generation resulted in a decrease in activity for every type of dendrimer.

Dendritic catalysts have also found use as phase transfer catalysts. In 2000 van den Broeke and co-workers published a study in which PPI dendrimers functionalized at the periphery with perfluorooctanoyl end groups were used to transfer reagents between an acidic aqueous phase and supercritical carbon dioxide.[29] The reactions were (*i*) the nucleophilic displacement of chloride from BnCl by bromide, and (*ii*) the diesterification of oxalic acid by reaction with pentafluorobenzyl bromide. In both reactions, anionic species which were insoluble in the supercritical carbon dioxide phase were transported by the dendrimer. Presumably, this transport was a consequence of ion–ion interactions between the nucleophiles and protonated amine functionalities in the dendritic interior.

Dendrimers of generation two, three, and four were used in both reactions. The highest catalytic activities were observed at the intermediate generation, and at this generation, 3- and 5-fold accelerations were found in reaction (*i*) and (*ii*), respectively. The decrease in activity from generation three to four was proposed to result from a more difficult mass transport in the more congested G4 dendrimer.

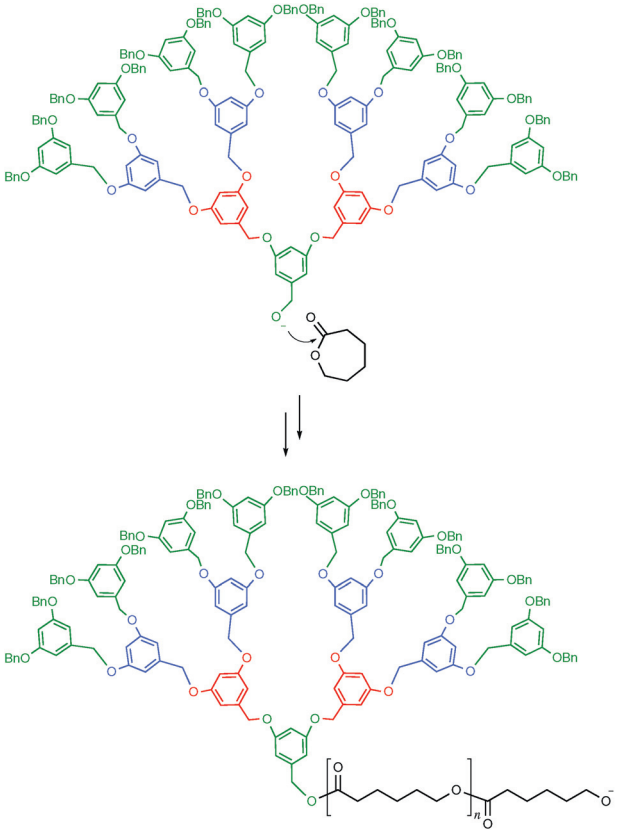


Fig. 11 The structure of Fréchet's fourth generation dendritic initiator used in the ring opening polymerization of ε-caprolactone.

Fréchet's group has been one of the most active within the area of dendritic catalysis. The first catalytic study by Fréchet and co-workers was published in 1994. In this work, benzyl ether based dendrimers with an alkoxy group located at the core were used as initiators for the anionic ring opening polymerization of ε-caprolactone.[30] In 1996, this work was followed up by the study of a similar system with a TEMPO-based initiator attached to the core. This initiator was used in radical polymerizations.[31] The two studies were very similar and only the original will be discussed here.

The structure of the dendrimer and the reaction are illustrated in Fig. 11. Prior to Fréchet's study, the polymerization initiated with non-dendritic alkali metal alcoholates had been examined. The products of this polymerization were low molecular weight polymers with broad molecular weight distributions. One of the main factors responsible for the high polydispersity was contamination with substantial amounts of cyclic oligomers. The formation of these oligomers resulted from intramolecular transesterifications that were competing with the propagation of the growing polymer chain. By introducing dendrons to the initiator, one of the hoped-for effects was to achieve control of this so-called *back-biting* side reaction.

A value of 1.07 for the ratio of weight to number-average molecular weights was obtained in Fréchet's dendritic system, which

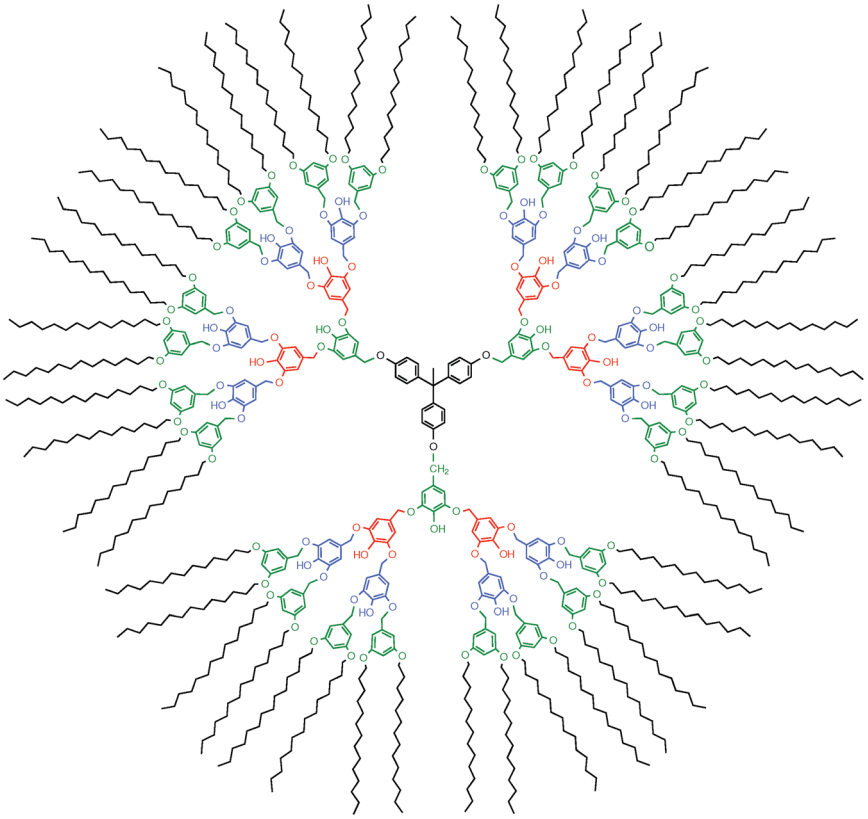


Fig. 12 The structure of Fréchet's dendritic catalyst for an E1 elimination and an S_N2 substitution.

was a significant lowering of the polydispersity. This improved result showed that the dendron provided the hoped-for protection of the ester functionalities of the growing polymeric chain. Due to the uniformity of the dendritic structures, this protection was constant in each dendritic catalyst, and in this way the monodispersity of the initiators was to some extend transferred to the generated polymer.

In addition to the improved polydispersity, Fréchet's system was also associated with a rate enhancing effect. In six minutes, a 99% yield of the polymer was isolated with the dendritic initiator present at a concentration of 0.097 M. This stands in contrast to only 9% yield after seven hours of reaction when potassium *tert*-butylate at a concentration of 5 M was used as initiator.

Later, Fréchet's group designed other systems whose dendritic interiors are used both to provide a protected reaction environment and to control mass transport through the dendrimer. In the first of these systems, dendrimers as illustrated in Fig. 12 were designed and synthesized.[32] The large number of electron-donating hydroxy groups and aromatic rings in the interior was planned to provide favorable conditions for reactions with positively or partly positively charged transition states. In E1 eliminations and certain types of S_N2 substitutions such transition states are expected, and hence these processes were chosen as the test reactions.

For the E1 reaction, tertiary alkyl halides were chosen as the substrates and $NaHCO_3$ was used to trap the acidic hydrogen halide byproduct. This reaction was tested both with and without the dendritic catalyst present. The control experiment without dendrimer showed little or no reaction whereas the dendritic studies showed essentially complete conversion even when less than 0.01 mol% dendrimer was used. The influence of the dendrimer generation was also tested. Going from generation four to three results in a 15–20% decrease in both reaction rate and turnover number, and this demonstrated a positive dendritic effect. A decrease in the same range was observed when the hydroxy groups in the interior of the dendritic system were changed to less polar ester groups.

For the S_N2 reaction, pyridine was used as the nucleophile and methyl iodide as the electrophile. As in the elimination studies, the higher generation dendrimers gave rise to the largest acceleration. However, there were differences between the two parts of the study. In contrast to the E1 reactions, a low concentration of dendrimer resulted in incomplete conversions for the S_N2 reaction. This was interpreted to occur as a consequence of differences in affinity between the dendritic interior and the two types of products. In the substitution, the generated pyridinium salt had a high affinity for the polar dendrimer. This caused accumulation of product in the interior, and this led to inhibition of the catalytic activity. In contrast, the nonpolar alkene product from the elimination was driven out of the polar interior, and thereby the active dendrimers were continuously reformed.

The catalysis of the E1 reaction illustrates the main ideas in several of Fréchet's studies. Initially, slightly polar substrates are drawn into the dendritic interior. The properties of this interior are designed to stabilize the transition state of the reaction, and this gives rise to the catalytic activity. Finally, the polarity difference between the interior and exterior provides the necessary

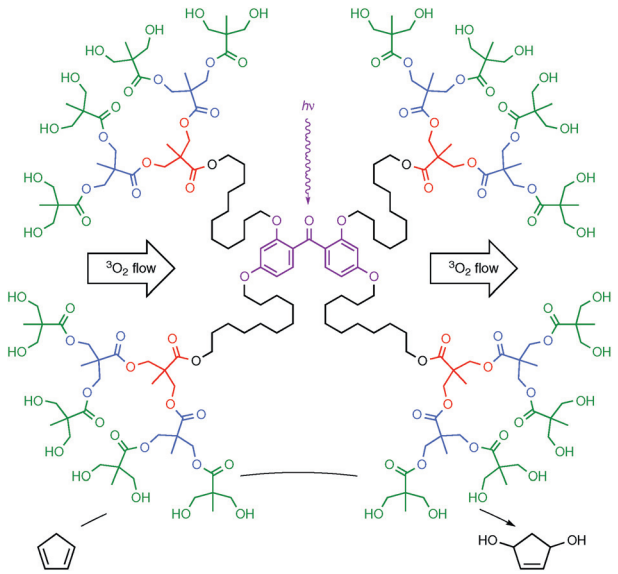


Fig. 13 The structure of Fréchet's dendritic photocatalyst for the [4 + 2] cycloaddition between singlet oxygen and cyclopentadiene.

driving force for product transport out of the dendrimer, and this leaves active dendrimers that can catalyze the next process. By this design, Fréchet's catalytic dendrimers can be thought of as *nanoreactors* wherein the driving force for pumping reagents through the dendrimer is a built-in part of the system.[33]

Fréchet's group has illustrated the possibilities of this idea in other systems, and in Fig. 13 one of these systems is shown.[34] This dendrimer has an nonpolar interior and hydrophilic surface functionalities. Thereby, the polarity gradient between interior and exterior is reversed relative to the original study. However, by the right choice of test reaction the principles controlling the reaction can still be the same.

The test reaction was a [4 + 2] cycloaddition between singlet oxygen and cyclopentadiene. The core of the dendrimer was a photosensitizer, and this part of the structure was used to generate the active singlet state of oxygen. Thereby, the dienophile was automatically concentrated in the dendritic interior. The polarity gradient between the interior and the exterior drove the nonpolar diene into the dendrimers, and thereby high local concentrations of both reagents was created and the cycloaddition was catalyzed. The endoperoxide product had a short lifetime and was opened to the corresponding diol by subsequent reaction with $(H_2N)_2$ CS which was used in excess. This final product is hydrophilic and was therefore transported out of the dendrimers leaving the space and possibility for further catalysis.

Although a detailed kinetic analysis was complicated by the inherent complexity of the system, a relative reactivity trend could be deduced. This trend showed that higher generation led to both faster reactions and higher conversions, and this illustrated a positive dendritic effect. The origin of this effect was proposed to be a combination of (*i*) higher ability to concentrate cyclopentadiene in the dendritic interior with higher generation, and (*ii*) longer lifetime of singlet oxygen in the dendrimers of higher generation.

All systems described to this point illustrate the importance of the dendritic interior for high catalytic activity. However, only few of the studies provide information about how changes in the reaction environment affect the efficiency of the systems. Such information is only obtainable if a given reaction is studied in different closely related dendrimers, but of the above examples, only Ford's studies and Morao and Cossío's work have been designed with this purpose. In recent years, Fréchet's group has also initiated studies to obtain a deeper understanding of how small variations in the dendritic structure change catalytic activity.

In the first study following this strategy, a dendronized polymer that contained pyrrolidinopyridine substituents for every 12th unit along the polymer backbone was examined.[35] Compounds with properties similar to these substituents are often used as nucleophilic catalysts, and in Fréchet's study the catalytic activity of the substituents was exploited in esterifications. This study showed that the dendronization improved the catalytic activity, and motivated by these results the work was followed up by studies of other esterifications in the two dendrimers shown in Fig. 14.[36] Both the core and the functionalization at the surface were identical in the two dendrimers. Only the branching structures were different and this provided basis for a comparative study.

In all test esterifications, the catalytic activities were highest for dendrimer **6**. The proposed explanation for these results was that dendrimer **6** had (*i*) a higher ability to accumulate substrates in close proximity to the catalytic active centers and (*ii*) a higher ability to pump out the product after reaction. The rationale behind this explanation lies in the compactness of the two dendrimers. In **6**, the distance between the branching points was small relative to the same distance in **7**. Presumably, this resulted in a more efficient encapsulation in **6**, and thereby this structure was associated with a higher degree of differentiation between outer and inner properties.

The authors also suggested other factors to play a part in the explanation. For instance, differences in transition state stabilization in the two dendrimers were proposed, but more experiments were needed to reach definitive answers about which factors were most important. Even though this uncertainty exists, Fréchet's study showed the very important result that small changes in the dendritic structure can have large effects on the catalytic activity.

A final topic to be covered in this section is enantioselective catalysis. In 2006 Zhao and co-workers studied catalysis of ketone reduction by a combination of borane and the chiral dendrimer shown in Fig. 15.[37] This work was followed up by additional studies of (*i*) epoxidation of conjugated enones,[38] and (*ii*) Michael-type addition of aldehydes to nitrostyrenes.[39] The dendrimers used in all studies were the same, and therefore only Zhao's original study will be described here.

The ketone reductions were carried out under conditions where the temperature, solvent, and catalyst loading were varied. In general, these parameters had little influence on yields and enantioselectivities which were both around 90% and above. The effect of the dendrimer generation was also tested and again almost no differences were observed. Despite this absence of a dendritic affect, the dendronization still entailed advantages. Due to the properties of the dendrimers, the catalysts could be precipitated by a solvent change and recovered by filtration. After five consecutive cycles of catalysis and recovery the efficiency stayed unchanged.

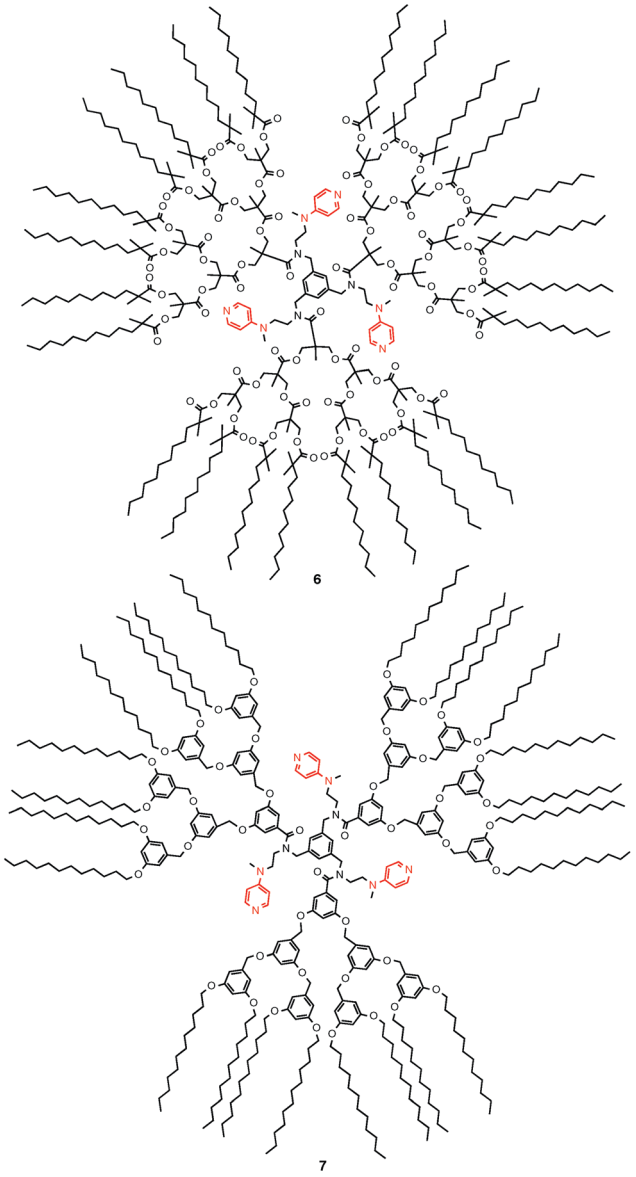


Fig. 14 The structure of Fréchet's two dendrimers used in comparison studies.

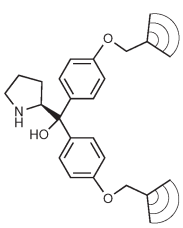


Fig. 15 The structure of Zhao's catalytic candidates with attached Fréchet-type dendrons of generation zero to three.

The possibility of catalyst recovery and reusability has also been one of the motivations behind the development of a dendritic catalyst for an asymmetric Morita–Baylis–Hillman reaction.[40] In this study, Liu and Shi catalyzed the reaction between methyl vinyl ketone and different *N*-tosylated aromatic imines with the chiral phosphine cored dendrimers illustrated in Fig. 16.

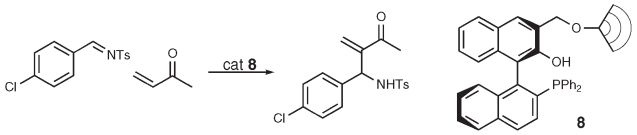


Fig. 16 The Morita–Baylis–Hillman reaction studied in Liu and Shi's work with the chiral phosphine core with attached Fréchet-type dendrons of generation zero to three.

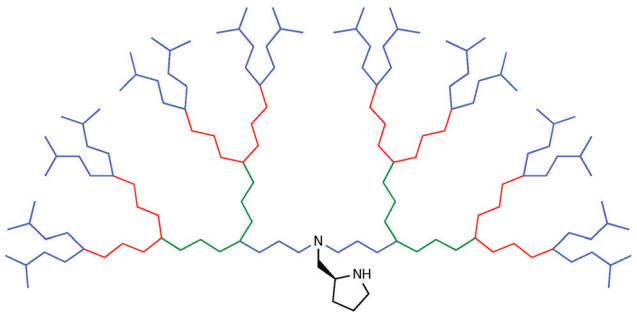


Fig. 17 The structure of the most efficient series of dendrimers used by Lo and Chow in the study of nitro Michael-type additions and aldol reactions.

The catalytic tests showed that all four dendrimers gave rise to ee's in the range 89–94% and also that no relation between enantioselectivity and generation could be deduced. The yields were high for the lower generation catalysts, but a sudden decrease to 67% was observed in the transition to the G3-dendrimer. If the combination of yield and enantioselectivity could be taken as the evaluation criterion, the second generation dendritic catalyst was superior, and in the further studies this dendrimer was used exclusively.

In these further studies, optimization tests showed that yields and selectivities could be tuned to 98% and 97%, respectively. In addition, the further studies included testing of possible recovery and reusability of the dendritic catalyst. By filtration, 75% of the catalyst could be recovered, and subsequent reuse showed remaining catalytic activity even though a decrease in both yield and selectivity of about 10% was observed.

The final example of catalytic dendrimers in this section brings the discussion back to the micellar starting point. This example was presented by Lo and Chow who studied catalysis with emulsions of the chiral dendrimers shown in Fig. 17.[41] The test reactions were (*i*) nitro Michael-type additions to β-nitrostyrenes with various types of substituents and (*ii*) aldol reactions to aromatic aldehydes. In both processes, the nucleophile was believed to be the enamine from cyclohexanone and the secondary amine in the core of the dendrimer.

In most cases, both the yields and enantioselectivity decreased when the generation of the dendrimers increased. However, in the Michael-type addition to β-nitrostyrene with a methoxy substituent in the *para*-position the yields were 61%, 68%, and 75%, when catalyzed by the first, second, and third generation dendrimer, respectively. For the same reaction the corresponding ee's were 71%, 87%, and 90%, and thereby catalysis of this particular reaction was associated with a positive dendritic effect with respect to both parameters.

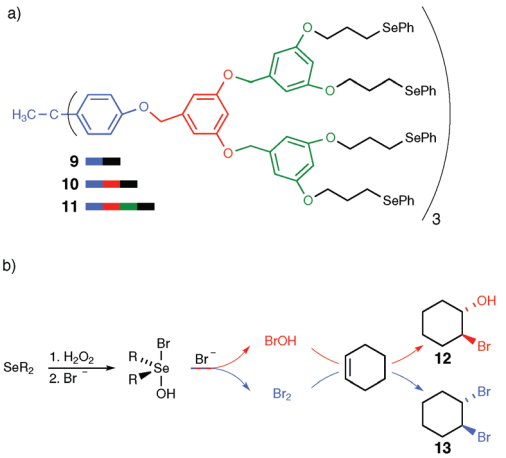


Fig. 18 (a) The structure of Detty's selenium based dendritic catalysts, and (b) the proposed path for the test reaction.

2.2 Organocatalysis near the surface

The development of catalysts for test reactions taking place near the surface of organocatalytic dendrimers has not evolved at the same speed as the development of the catalytic examples described above. In the examples that have been realized, the catalytic effects result from substituents at the surface, and the interior of the dendrimer is seemingly less important. Despite this connection between individual centers and catalytic activity, systems have been designed where the centers co-operate and create positive dendritic effects.

An example that illustrates this has been presented by Detty and co-workers.[42] The system was based on a Fréchet-type branching structure with phenylselenium functionalities attached to the surface (Fig. 18). The test reaction was the combined addition of bromine and hypobromous acid to the double bond in cyclohexene, and the reagents were NaBr and H_2O_2. Prior to Detty's work, non-dendritic catalytic studies of this test reaction by dialkylselenides had been carried out, and from these studies the reaction path shown in Fig. 18b had been proposed.

In Detty's work, initial reaction rates were calculated from the sum of the two adducts **12** and **13** when the process was catalyzed both by the three dendritic catalysts in Fig. 18 and the non-dendritic reference catalyst 3-phenoxypropylphenylselenide **14**. When the different number of selenium moieties was taken into account, the relative rates for **14**, **9**, **10**, and **11** were 1, 3.2, 21, and 53, respectively. Hence, the system was associated with a positive dendritic effect.

The work was followed up by studies of similar dendritic systems with sulfur and tellurium instead of selenium.[43] As expected from earlier non-dendritic studies, the dendritic tellurium analogues also displayed catalytic activity. However, the dendritic effect from the selenium study was absent in the tellurium system. This difference initiated additional mechanistic studies.[44] These studies indicated that the two types of catalysts proceed *via* different mechanisms, and only the reaction catalyzed by the tellurium dendrimers followed the path in Fig. 18b.

For the selenium system, the initial oxidation of the selenium centers was instead proposed to result from reaction with Br_2 and BrOH, and not as originally thought by H_2O_2. A comparison

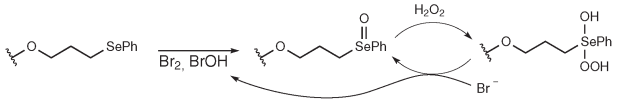


Fig. 19 Corrected reaction path for the generation of the active electrophiles in the selenium catalyzed reaction.

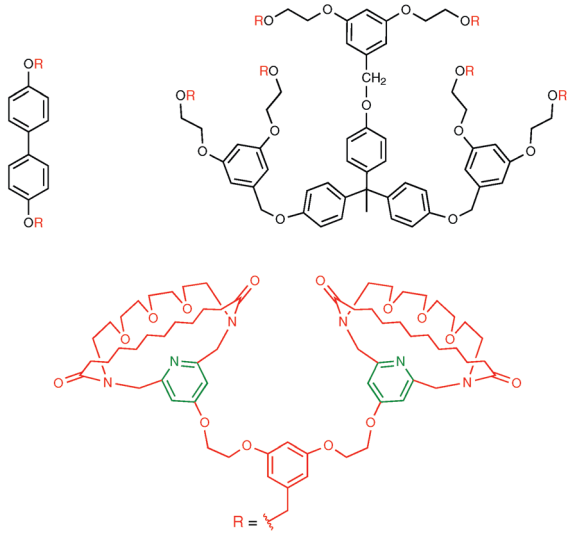


Fig. 20 The structure of Lüning's catalytic dendrimers with bicyclic surface groups that contain pyridine.

of the rate profiles for the catalyzed and non-catalyzed reactions indicated that the necessary starting amount of the two oxidants resulted from the non-catalyzed background reaction. After the initial oxidation, the selenium centers reacted with H_2O_2 and bromide to generate additional Br_2 and BrOH as shown in Fig. 19. A part of these species participated as electrophiles in the addition to cyclohexene, and the rest worked as oxidants that activated new selenium centers. This activation accelerated the generation of electrophiles/oxidants, and thereby the selenium system was autocatalytic.

Based on these mechanistic findings, the positive dendritic effect associated with the selenium dendrimers was rationalized. Due to the continuously reduced distance between the surface functionalities with increasing generation, the local concentration of Br_2 and BrOH around non-activated selenium centers increased. Thereby, the fraction of the oxidants/electrophiles that participated in activation also increased, and this enhanced the effect of the autocatalysis.

Fréchet-type dendrimers with organocatalytic moieties at the surface other than in Detty's work have also been studied. For example, Lüning and co-workers used the dendrimers in Fig. 20 as size selective catalysts for the esterification of primary, secondary and tertiary alcohols with diphenylketene.[45] Earlier non-dendritic studies of the surface groups had shown that the pyridine moieties highlighted in green acted as general base catalysts.[46]

The catalytic activity of these groups was transferable to the surface of the dendritic catalysts, and both structures exhibited the same selectivity. No reaction was observed with *tert*-butanol, and the reaction with the ethanol was 11–12 times more

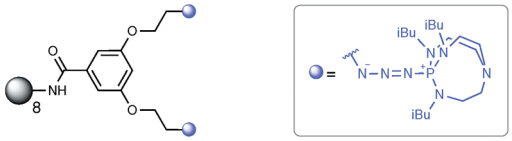


Fig. 21 The structure of Verkade's PPI dendrimers with basic azido-phosphine functionalities attached to the surface.

favorable than with isopropanol. These results were analogous to the obtained selectivity in the non-dendritic studies, and this showed that each catalytic unit operated individually.

Lüning's example illustrated general base catalysis at the dendrimer surface. In addition to this work, dendrimers with surface functionalities that allow specific base catalysis have also been prepared. For example, Verkade and co-workers have exploited the base properties of the dendrimer in Fig. 21 in catalysis of Michael additions and Henry reactions, and the nucleophilic properties of the same surface groups in catalysis of isocyanate trimerizations.[47]

Only the second generation dendrimer was tested, and therefore no information about variations in activity with the size of the dendrimer is available. However, there were indications that the dendritic catalyst enhanced the catalytic properties of the azido-phosphine functionalities. These indications came from a comparison of the activities for the catalytic dendrimer and for the surface moiety in its monomeric form, and this comparison showed a significantly lower needed catalyst loading in the dendritic case.

The primary amino end-groups of unfunctionalized PAMAM dendrimers have also been used as base catalysts.[48] In this study, the catalytic activity of the first and second generation dendrimers were tested in the Knoevenagel reaction and in the Mannich reaction. For both processes, the second generation dendrimer gave the highest yield.

A very similar study has been carried out by Kapoor and co-workers.[49] Instead of using 'free' dendrimers, catalytic activity of polymer supported PAMAM dendrons were tested in the Knoevenagel reaction between benzaldehyde and malononitrile. The used polymeric supports were (*i*) mesoporous silica, and (*ii*) periodic mesoporous 'benzene-silica', and in the pore channels of these polymers the dendritic structure was attached as shown in Fig. 22.

Turnover frequencies (mol product per mmol NH_2 per hour) were calculated for both types of support. In the silica support these frequencies for generation zero, one, and two were 21.7, 26.6, and 45.3 respectively, and the similar results with the other support were 42.6, 55.4, and 124.1. As in the non-supported study, a positive dendritic effect was evident.

In the above examples, base catalytic properties at the dendrimer surface were exploited. Piers and co-workers have taken the opposite approach and attached end groups with Lewis acidic properties to the dendrimers shown in Fig. 23.[50] The test reaction was the hydrosilylation of acetophenone, and at room temperature all dendritic catalysts gave essentially quantitative yields within minutes at 5% catalyst loading. At lower temperatures, the reactions could be followed, and this part of the study showed that increased generation lowered the catalytic efficiency.

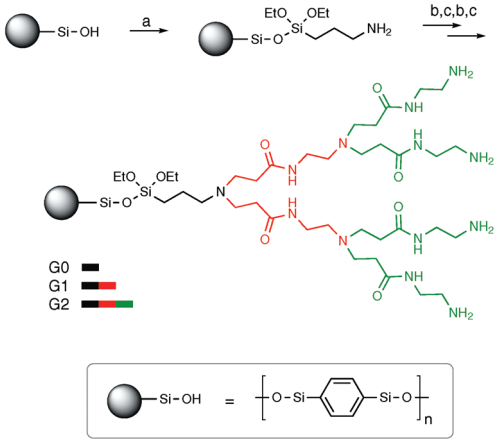


Fig. 22 The synthetic route to benzene-silica supported PAMAM dendrons. *Reagents*: (a) $(EtO)_3SiCH_2CH_2NH_2$, (b) $H_2C{=}CHCOOMe$, and (c) $NH_2CH_2CH_2NH_2$.

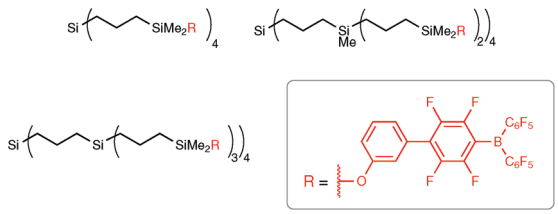


Fig. 23 The structures of Pier's Lewis acid terminated dendrimers.

Another approach to dendritic catalysis was demonstrated by Lacour *et al.* in 2008.[51] In this study, the catalytic activity of phosphorus based G0 and G1 dendrimers with bis(phosphoranylidene)ammonium $(PNP)^+$ salts attached to the surface was examined in the aromatic nucleophilic substitution on 4-chloronitrobenzene by fluoride ions. Due to low solubilities of metal fluorides in organic solvents, the test reaction normally requires harsh condition, but with phase transfer catalysts such as $(PNP)^+$ salts the reaction temperature can be lowered. This effect was illustrated at reaction temperatures about 100 °C below normal with yields of 100%, 63%, and 9% in the G0-, G1-catalyzed, and uncatalyzed reactions, respectively.

As for the interior-based dendritic catalysts, stereoselective catalysis has also been an area of interest for the surface-based analogues. In 2005 Kokotos and co-workers studied the catalysis of the aldol reaction with the proline terminated PPI dendrimer (Fig. 24a).[52] The nucleophile in the reaction was the enamine from acetone and the secondary amine of the proline end-groups. The stereoselectivity was proposed to be controlled by a hydrogen bond from the proline carboxylic acid to the electrophile as shown in Fig. 24b. Besides providing preorganisation and hence stereocontrol, the proline units activated both reagents and enhanced the rate of reaction.

Dendrimers with generations ranging from one to five were tested, and all structures gave yields that were comparable to what was obtainable by a non-dendritic reference catalyst. However, for the generations two, three, four, and five, these yields were achievable at reduced catalyst loading, and hence the system was associated with a positive dendritic effect. Besides

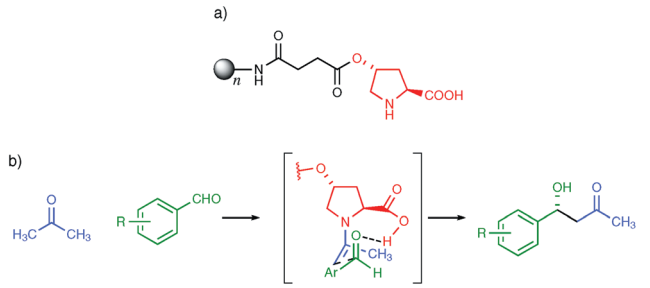


Fig. 24 (a) The structure of Kokotos's stereoselective catalytic PPI dendrimers, and (b) the studied aldol reaction.

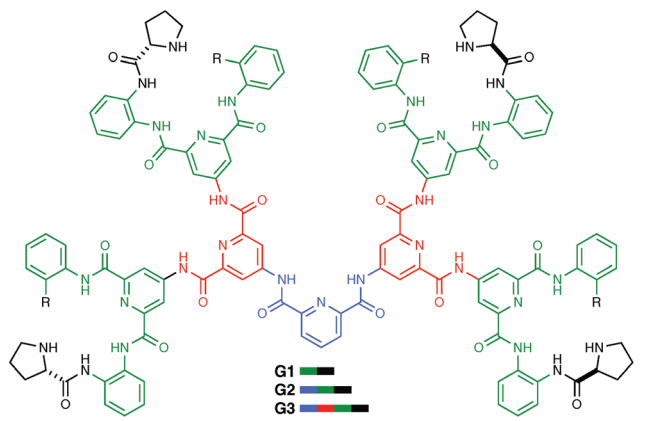


Fig. 25 The structures of two series of Parquettes' proline terminated (R = H or prolinamide).

for the second generation dendrimer, stereoselectivity decreased in the transition from the non-dendritic reference catalyst to the dendrimers. The G2 dendrimer stands out with both high catalytic activity *and* selectivity.

Proline-based dendritic catalysis of the aldol reaction has also been studied by Parquette and co-workers with the dendrimers illustrated in Fig. 25.[53] The results in this study were completely opposite of what Kokotos observed. Here, an increase in generation reduced the yields and enhanced the selectivities. A combination of calculations and circular dichroic tests suggested that an increased tendency for the higher generation dendrimers to adopt a helical overall structure was the reason for the enhanced stereoselectivity.

Besides Kokotos's PPI dendrimers and Parquettes's polyamide dendrimers, polymer supported dendrons with terminal proline moieties have been used to catalyze the aldol reaction.[54] This study was carried out by Portnoy and co-workers and the used catalysts are shown in Fig. 26.

The catalytic tests showed that both conversion and selectivity increased when the generation was raised. For example, the yields of the aldol adduct when the reaction was catalyzed by the zeroth, first, and second generation dendrons were 42%, 73%, and 100%, respectively, and the corresponding ee's were 27%, 68%, and 68%. For both parameters, this illustrated a positive dendritic effect. The origin of this effect was not entirely understood, but additional studies with systematic variations in the dendritic structure showed that a close proximity of the

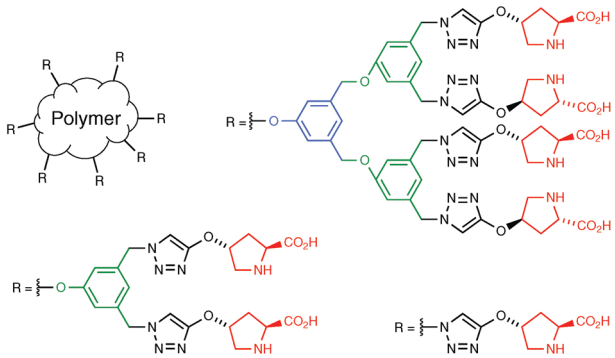


Fig. 26 The structure of Portnoy's polystyrene supported proline decorated dendrons that were used as catalysts in the aldol reaction.

proline moieties was crucial for achieving the high yields and enantioselectivities.[55]

In 2010 Portnoy's group followed their catalytic studies up with examinations of the Morita–Baylis–Hillman reaction.[56] The three types of dendrimers used were also polymer supported with an overall similar structure to the ones from the earlier work but with histidine end groups instead of terminal prolines. The specific reactions studied were between methyl vinyl ketone and different aromatic aldehydes and the catalytic activity of three generations were tested within each type of dendrimer.

The specific yields were found to be very solvent dependent, but regardless of the reaction medium, positive dendritic effects were evident in all cases. Earlier mechanistic studies of the Morita–Baylis–Hillman had demonstrated that the proton exchange taking place after C–C bond formation is the rate-limiting step in the reaction sequence, and based on these findings the positive dendritic effect was rationalized. Activation of methyl vinyl ketone and coupling to the aromatic aldehyde requires attack from one histidine, and afterward a second histidine end group was proposed to catalyze the rate-determining proton transfer. With increasing generation, the local concentration of the second histidine moiety increases, and hence the positive effect.

The last studies to be reviewed in this section aim at the construction of artificial enzymes. Reymond and co-workers have been very active in the search for enzyme-mimicking peptide dendrimers. The overall idea in this search has been to use the branching pattern in dendrimers to overcome the difficulty in predicting protein folding in linearly constructed artificial peptides.[57]

As shown in Fig. 27, the dendrimers used in Reymond's initial studies were constructed by alternating couplings of amino acids (highlighted in blue) and branching units (highlighted in red). Due to their presence in most esterases and lipases, the amino acids aspartate, histidine, and serine were chosen as building blocks for solid phase syntheses of all six possible dendrons with the amino acids permuted.[58] These dendrons were subsequently bridged *via* the two cysteine units (highlighted in green) and this gave rise to a family of twenty-one dimeric structures.

The esterase activity of this family of dendrimers was studied with a series of *N*-methylquinolium ester substrates. The dendrimers bearing histidine moieties at the surface all catalyzed the

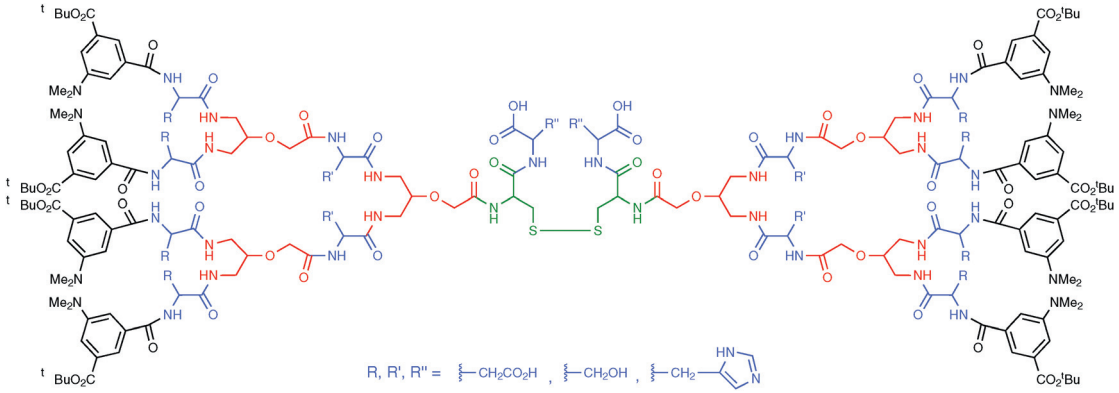


Fig. 27 The structure of Reymond's original studied family of peptide dendrimers.

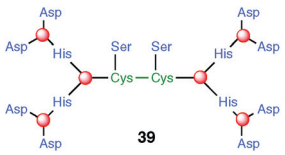


Fig. 28 The structure of the most active catalyst with histidine moieties located in the interior.

hydrolysis, and the reaction displayed Michaelis–Menten kinetics with K_M 100–200 μm and with $k_{cat}/k_{uncat} \approx 103$. Enantiomerically pure ester substrates were also tested, but these tests showed that all dendrimers only gave rise to very modest enantioselectivities.

This work was followed up by studies of new families of peptide dendrimers with changes in the branching units,[59] and the amino acids.[60] In analogy with the original work, these studies showed that the most efficient catalysts contained histidines at the surface and no useful enantioselectivity was obtainable. These results suggested (*i*) that the histidines were crucial for high activity, and (*ii*) that access to these amino acids only was possible when they were positioned at the surface. In order to make the interior amino acids more accessible, rigid branching units were incorporated into the structures.[61] Thereby, the trends from the initial studies changed, and the most active catalyst now became the dendrimer shown in Fig. 28 with the histidines in the interior.

Besides increasing the catalytic activity, the movement of the histidines to the interior also gave rise to enantioselectivity. For example, catalysis of the hydrolysis of a chiral 2-phenylpropionate ester with the dendrimer in Fig. 28 gave an enantiomeric ratio $E = (k_{cat,S}/k_{M,S})/(k_{cat,R}/k_{M,R}) = 2.8$. The kinetics behind this reaction showed that this selectivity mainly resulted from a lower K_M-value for *S*-enantiomer.

In the further work, Reymond turned to dendrimers of a different type that only contained histidine and serine.[62] The new dendrimers are shown in Fig. 29, and the change in these structures allowed catalytic activity to be related to the dendrimer generation. All dendrimers were potent catalysts for ester hydrolysis, and the catalytic activity increased with increasing generation. Relative to the reference catalyst 4-methylimidazole, the fourth generation dendrimer was 140 000 times more efficient, corresponding to a factor 4500 per histidine side chain.

The positive dendritic effect was proposed to result from a combination of (*i*) increased affinity between dendrimer and substrate with increasing generation, and (*ii*) increased co-operation between histidine side chains with increasing generation.[63] The second part of this explanation was rationalized by a mechanism that involved two histidine sides chains. One of these was believed to work as a nucleophilic catalyst that attacked the ester and formed a tetrahedral intermediate, and the other one in its protonated form was believed to stabilize this intermediate. With increasing generation, these side chains moved closer together and this was believed to ease their co-operation.

In Reymond's studies to this point, catalytic screening studies were carried out on dendritic libraries where each candidate of the library was synthesized and isolated. This is a time demanding strategy and only a relative small number of catalytic candidates were examined. In order to overcome these drawbacks, the group initiated studies where the so-called split-and-mix technique was used to construct combinatorial libraries with as many as 65 536 different dendrimers.[64] The catalytic screening studies were carried out on this library, and the active candidates were separated from the rest, analyzed and finally resynthesized. By this technique the group found different dendritic aldolases,[65] and other types of esterases.[66,67]

Ester hydrolysis and aldol type reactions were also some of the target processes in one of the most recent studies from 2011 by the Reymond group.[68] In this study, two 6750-membered third generation dendritic peptide libraries were screened for catalytic activity. No hits were identified in the studies regarding the aldol type reactions, whereas several esterases were identified. Analysis of the content of the different amino acids in the active catalysts showed, as observed in the earlier studies, that peripheral histidines were crucial for high activity.

Several of these histidine-containing dendrimers were resynthesized and studied further. This part of the work showed that the remaining amino acids in the dendritic peptides could be used to control substrate selectivity. The hydrolyses of different esters were studied, and it was illustrated how a high concentration of hydrophobic amino acids like phenyl alanine and leucine in the dendritic interior tuned the activity towards lipophilic esters.

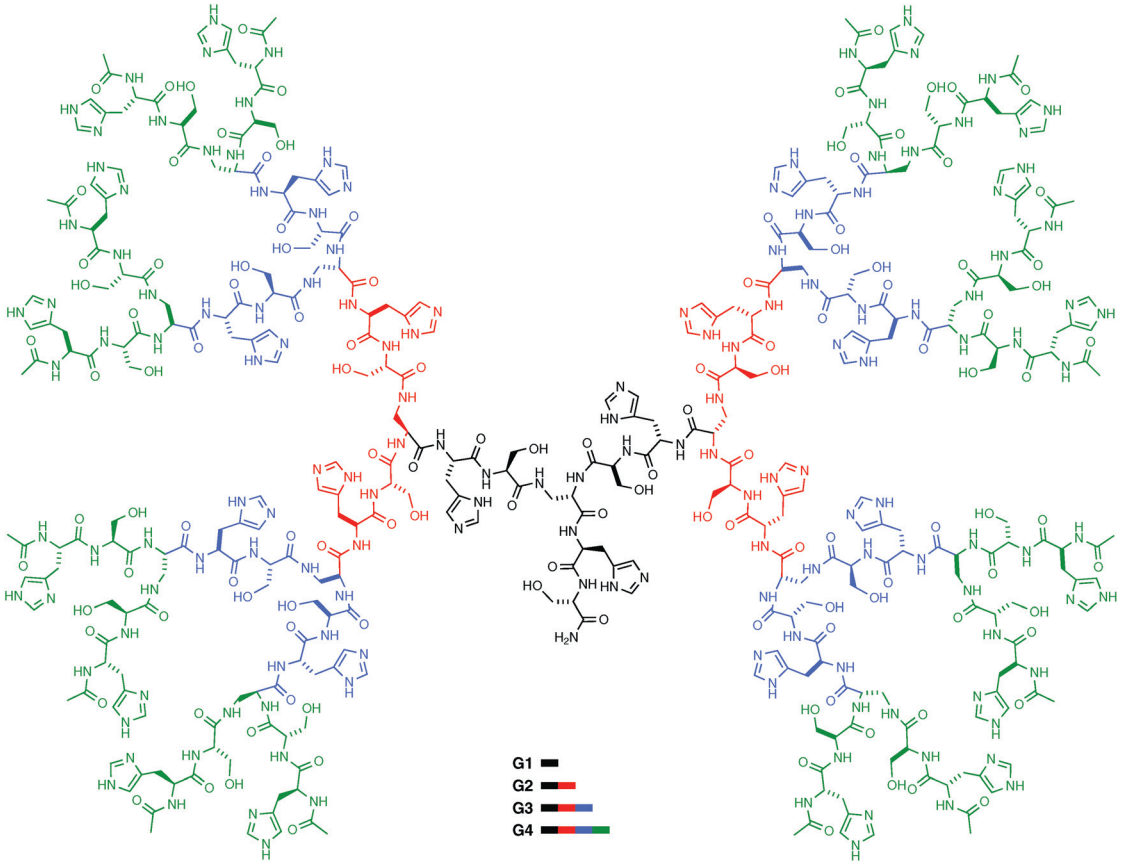


Fig. 29 The structure of the different generations in Reymond's peptide dendrimer that exclusively contains the amino acids histidine and serine.

3. Conclusions

In this review advances made in the area of organocatalysis with dendrimers have been outlined. In both the interior- and surface-based examples, the catalysis of reactions ranging from functional group interconversion and C–C bond forming reactions to enzyme mimicking processes have been covered.

References

1 D. A. Tomalia and J. M. J. Fréchet, *J. Polym. Sci., Part A: Polym. Chem.*, 2002, **40**, 2719–2728.
2 G. R. Newcome, C. N. Moorefield and F. Vögtle, *Dendrimers and Dendrons – Concepts, Syntheses, Applications*, Wiley, Weinheim, 2001.
3 D. Astruc and F. Chardac, *Chem. Rev.*, 2001, **101**, 2991–3023.
4 R. van Heerbeek, P. C. J. Kamer, P. W. N. M. van Leeuwen and J. N. H. Reek, *Chem. Rev.*, 2002, **102**, 3717–3756.
5 B. Helms and J. M. J. Fréchet, *Adv. Synth. Catal.*, 2006, **348**, 1125–1148.
6 X. Peng, Q. Pan and G. L. Rempel, *Chem. Soc. Rev.*, 2008, **37**, 1619–1628.
7 A.-M. Caminade, P. Servin, R. Laurent and J.-P. Majoral, *Chem. Soc. Rev.*, 2008, **37**, 56–67.
8 U. Boas, J. B. Christensen and P. M. H. Heegaard, *Dendrimers in Medicine and Biotechnology – New Molecular Tools*, RSC Publishing, Cambridge, 2006.
9 D. C. Tully and J. M. J. Fréchet, *Chem. Commun.*, 2001, 1229–1239.
10 A. Adronov and J. M. J. Fréchet, *Chem. Commun.*, 2000, 1701–1710.
11 P. I. Dalko and L. Moisan, *Angew. Chem., Int. Ed.*, 2004, **43**, 5138–5175.
12 S. Bertelsen and K. A. Jørgensen, *Chem. Soc. Rev.*, 2009, **38**, 2178–2189.
13 D. Monti, P. Tagliatesta, G. Mancini and T. Boschi, *Angew. Chem., Int. Ed.*, 1998, **37**, 1131–1133.
14 C. Siswanto, T. Battal, O. E. Schuss and J. F. Rathman, *Langmuir*, 1997, **13**, 6047–6052.
15 D. van Mersbergen, J. W. Wijnen and J. B. F. N. Engberts, *J. Org. Chem.*, 1998, **63**, 8801–8805.
16 J.-J. Lee, W. T. Ford, J. A. Moore and Y. Li, *Macromolecules*, 1994, **27**, 4632–4634.
17 Y. Pan and W. T. Ford, *Macromolecules*, 2000, **33**, 3731–3738.
18 J. L. Kreider and W. T. Ford, *J. Polym. Sci., Part A: Polym. Chem.*, 2001, **39**, 821–832.
19 E. Murugan, R. L. Sherman Jr., H. O. Spivey and W. T. Ford, *Langmuir*, 2004, **20**, 8307–8312.
20 T. Mizugaki, C. E. Hetrick, M. Murata, K. Ebitani, M. D. Amiridis and K. Kaneda, *Chem. Lett.*, 2005, **34**, 420–421.
21 X. Zhang, H. Xu, Z. Dong, Y. Wang, J. Liu and J. Shen, *J. Am. Chem. Soc.*, 2004, **126**, 10556–10557.
22 L. Liu and R. Breslow, *J. Am. Chem. Soc.*, 2003, **125**, 12110–12111.
23 L. Liu and R. Breslow, *Bioorg. Med. Chem.*, 2004, **12**, 3277–3287.
24 T. Habicher, F. Diederich and V. Gramlich, *Helv. Chim. Acta*, 1999, **82**, 1066–1095.
25 S. S. Agasti, S. T. Caldwell, G. Cooke, B. J. Jordan, A. Kennedy, N. Kryvokhyzha, G. Rabani, S. Rana, A. Sanyal and V. M. Rotello, *Chem. Commun.*, 2008, 4123–4125.
26 A. V. Davis, M. Driffield and D. K. Smith, *Org. Lett.*, 2001, **3**, 3075–3078.
27 I. Morao and F. P. Cossío, *Tetrahedron Lett.*, 1997, **38**, 6461–6464.
28 A. Zubia, F. P. Cossío, I. Morao, M. Rieumont and X. Lopez, *J. Am. Chem. Soc.*, 2004, **126**, 5243–5252.
29 E. L. V. Goetheer, M. W. P. L. Baars, L. J. P. van den Broeke, E. W. Meijer and J. T. F. Keurentjes, *Ind. Eng. Chem. Res.*, 2000, **39**, 4634–4640.
30 I. Gitsov, P. T. Ivanova and J. M. J. Fréchet, *Macromol. Rapid Commun.*, 1994, **15**, 387–393.

31 K. Matyjaszewski, T. Shigemoto, J. M. J. Fréchet and M. Leduc, *Macromolecules*, 1996, **29**, 4167–4171.
32 M. E. Piotti, F. Rivera Jr., R. Bond, C. J. Hawker and J. M. J. Fréchet, *J. Am. Chem. Soc.*, 1999, **121**, 9471–9472.
33 J. M. J. Fréchet, *Science*, 2002, **99**, 4782–4787.
34 S. Hecht and J. M. J. Fréchet, *J. Am. Chem. Soc.*, 2001, **123**, 6959–6960.
35 C. O. Liang, B. Helms, C. J. Hawker and J. M. J. Fréchet, *Chem. Commun.*, 2003, 2524–2525.
36 B. Helms, C. O. Liang, C. J. Hawker and J. M. J. Fréchet, *Macromolecules*, 2005, **38**, 5411–5415.
37 G.-Y. Wang, X.-Y. Liu and G. Zhao, *Synlett*, 2006, 1150–1154.
38 X.-Y. Liu, Y. Li, Z. Chai, Y.-Y. Wu and G. Zhao, *Tetrahedron: Asymmetry*, 2006, **17**, 750–755.
39 Y. Li, X.-Y. Liu and G. Zhao, *Tetrahedron: Asymmetry*, 2006, **17**, 2034–2039.
40 Y.-H. Liu and M. Shi, *Adv. Synth. Catal.*, 2008, **350**, 122–128.
41 C.-M. Lo and H.-F. Chow, *J. Org. Chem.*, 2009, **74**, 5181–5191.
42 C. Francavilla, F. V. Bright and M. R. Detty, *Org. Lett.*, 1999, **1**, 1043–1046.
43 C. Francavilla, M. D. Drake, F. V. Bright and M. R. Detty, *J. Am. Chem. Soc.*, 2001, **123**, 57–67.
44 M. D. Drake, F. V. Bright and M. R. Detty, *J. Am. Chem. Soc.*, 2003, **125**, 12558–12566.
45 T. Marquardt and U. Lüning, *Chem. Commun.*, 1997, 1681–1682.
46 W. Schyja, S. Petersen and U. Lüning, *Liebigs Ann.*, 1996, 2099–2105.
47 A. Sarkar, P. Ilankumaran, P. Kisanga and J. G. Verkade, *Adv. Synth. Catal.*, 2004, **346**, 1093–1096.
48 G. R. Krishnan, J. Thomas and K. Sreekumar, *ARKIVOC*, 2009, **Part X**, 106–120.
49 M. P. Kapoor, Y. Kasama, T. Yokoyama, M. Yanagi, S. Inagaki, H. Nanbu and L. R. Juneja, *J. Mater. Chem.*, 2006, **16**, 4714–4722.
50 R. Roesler, B. J. N. Har and W. E. Piers, *Organometallics*, 2002, **21**, 4300–4302.
51 M.-A. Lacour, M. Zablocka, C. Duhayon, J.-P. Majoral and M. Taillefer, *Adv. Synth. Catal.*, 2008, **350**, 2677–2682.
52 E. Bellis and G. Kokotos, *J. Mol. Catal. A: Chem.*, 2005, **241**, 166–174.
53 K. Mitsui, S. A. Hyatt, D. A. Turner, C. M. Hadad and J. R. Parquette, *Chem. Commun.*, 2009, 3261–3263.
54 T. Kehat and M. Portnoy, *Chem. Commun.*, 2007, 2823–2825.
55 K. Goren, T. Kehat and M. Portnoy, *Adv. Synth. Catal.*, 2009, **351**, 59–65.
56 K. Goren and M. Portnoy, *Chem. Commun.*, 2010, **46**, 1965–1967.
57 A. Esposito, E. Delort, D. Lagnoux, F. Djojo and J.-L. Reymond, *Angew. Chem., Int. Ed.*, 2003, **42**, 1381–1383.
58 T. Darbre and J.-L. Reymond, *Acc. Chem. Res.*, 2006, **39**, 925–934.
59 D. Lagnoux, E. Delort, C. Douat-Casassus, A. Esposito and J.-L. Reymond, *Chem.–Eur. J.*, 2004, **10**, 1215–1226.
60 A. Clouet, T. Darbre and J.-L. Reymond, *Adv. Synth. Catal.*, 2004, **346**, 1195–1204.
61 C. Douat-Casassus, T. Darbre and J.-L. Reymond, *J. Am. Chem. Soc.*, 2004, **126**, 7817–7826.
62 E. Delort, T. Darbre and J.-L. Reymond, *J. Am. Chem. Soc.*, 2004, **126**, 15642–15643.
63 E. Delort, N.-Q. Nguyen-Trung, T. Darbre and J.-L. Reymond, *J. Org. Chem.*, 2006, **71**, 4468–4480.
64 A. Clouet, T. Darbre and J.-L. Reymond, *Biopolymers*, 2006, **84**, 114–123.
65 J. Kofoed, T. Darbre and J.-L. Reymond, *Org. Biomol. Chem.*, 2006, **4**, 3268–3281.
66 S. Javor, E. Delort, T. Dabre and J.-L. Reymond, *J. Am. Chem. Soc.*, 2007, **129**, 13238–13246.
67 R. Biswas, N. Maillard, J. Kofoed and J.-L. Reymond, *Chem. Commun.*, 2010, **46**, 8746–8748.
68 N. Maillard, R. Biswas, T. Dabre and J.-L. Reymond, *ACS Comb. Sci.*, 2011, **13**, 310–320.