Dendritic Polymers: From Efficient Catalysis to Drug Delivery

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Summary: Dendritic polymers constitute an intriguing class of macromolecules that offer tremendous potential in designing new materaisl for applications in areas such as catalysis and small molecule loading and delivery. Synthesis of a variety of dendritic polymers using a simple and highly versatile synthetic methodology has enabled us to carry out a detailed investigation of dendritic effects in transition metal catalyzed organic transformations. Small dye molecules such as *p*-nitroaninline and DR1 could be loaded into the intrinsic cavities of the backbone of 3,5-dihydroxybenzyl alcohol based dendrimers, leading to a change in physical properties of both the dye and the dendrimer. We are also exploring the use of dendrimers as templates to prepare network carriers containing cavities of predetermined size and disposition.

Keywords: catalysis; dendritic networks; olefin hydrogenation; organometallic dendrimers; small molecule loading

Introduction

Dendrimers constitute an intriguing class of macromolecules with a unique set of properties which can be related to their monodisperse nature and a well-defined three-dimensional structure. The potential offered by these systems of nanoscopic dimensions for applications in significant areas such as recoverable catalysts and medicinal chemistry, continues to provoke intense interest in their syntheses and a detailed understanding of their physical characterisitics.[1] Divergent (inside out) and convergent (outside in) are two common methodologies that have been extensively used to prepare a variety of dendrimers with varied backbone architecture. In principle, divergent build-up of dendrimers could lead to inherent defects in generation-by-generation build-up of dendrimers. However, it is an easy synthetic route to prepare large macromolecules with an overall high structural integrity.

Metallodendrimers, a much more recent addition to the dendrimer family, provide a good platform to address key issues related to recoverable catalysts.[2] The latter class of dendrimers

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can be divided into two categories, the more common organic backbone dendrimers that are periphery functionalized with organometallic fragments, and those in which organometallic moieties are distributed throughout the backbone. A large variety of organometallic dendrimers have now been prepared,[3] however, key issues related to the effect of dendritic shape and the location of functional groups in the dendritic architecture in catalysis, still remain. In addition, the advantages of using multistep build-up of dendrimers which is an arduous task, compared with their hyperbranched analogs prepared using simple one-pot reaction chemistry, are not clearly defined. It is understood that dendrimers have a perfect structure compared to hyperbranched polymers, but the role of defects in altering catalytic efficiency, needs to be elaborated. A detailed investigation of the behavior of similar organometallic dendritic polymers under catalytic conditions will address these important concerns.

Efficient loading and delivery of small molecules are two noteworthy goals in drug design[4] To achieve these, one needs to construct backbone structures with tailorable nanosized cavities and well-defined structures. There is intense research activity in this area and several strategies to develop such nanostructures have been proposed. These include conjugated proteins,[5] liposomes,[6] antibodies,[7] and foldamers.[8] More recently there has been much interest in exploiting the intriguing properties of dendrimers including a well-defined molecular architecture for applications in drug delivery.[9-11] Despite extensive efforts in this area, synthesizing materials with holes of tunable sizes and distribution has alluded us. Dendrimers offer another unexplored venue in developing nanomaterials with pre-determined physical properties i.e., size and distribution of nanocavities. We are exploring a novel strategy that involves dendrimer templated sol-gel synthesis. The dendrimer generation helps control the size of the sphere from which sol-gel process is affected, leading to a well-defined architecture with precisely defined distribution of dendrimers in the matrix. The dendrimer fractions could then be removed from the backbone using simple hydrolysis, yielding desired nanomaterials.

Results and Discussion

Dendrimers in Catalysis: The synthetic methodology to construct dendrimers is based on a general acid-base hydrolysis strategy developed in our laboratory to prepare a variety of new materials ranging from simple monolayers to complex functionalized polymers and networks.[12] In order to evaluate dendritic effects in catalysis, a detailed study should involve the construction of dendrimers i) in which the transition metal centers are distributed throughout the backbone; ii) the transition metal fragments are attached at the periphery; iii) dendrimers in which the overall shape of the macromolecule is non-spherical; and iv) synthesis of hyperbranched polymers containing transition metals in the backbone or at the periphery. In order to prepare dendrimers containing transition metal centers distributed throughout the backbone, we developed a new divergent synthetic methodology to phosphorus containing dendrimers.[13] It involved the reaction of a trifunctional phosphine ($[HO(CH_2)_3]_3P$) with bis(dimethylamino)silane in an iterative sequence as shown in Scheme **1**. Using this methodology, dendrimers upto fourth generation containing phosphorus donor centers distributed throughout the backbone were prepared. The latter could be easily functionalized with Rh(I) fragments via a bridge splitting reaction with Rh(I) dimer $[Rh(COD)Cl]_2$. In order to ascertain that the metal centers are bound to each phosphine unit in the dendrimers, phosphine monomer ($[HO(CH_2)_3]_3P$) was first ligated with rhodium before being employed in the build-up of the dendrimer.

Characterization of the dendrimer structure is an important step in understanding dendritic effects in catalysis. In addition to ^{1}H and ^{13}C NMR spectra, MALDI-TOF mass spec and elemental analyses, ^{31}P NMR spectra provided useful information about the evolving structure of these dendrimers. The phosphorus centers in each generation were found to be chemical shift distinct, and the appearance of a new singlet upon each addition of a new layer was observed.[14] Upon Rh(I) complexation, coupling of phosphorus and rhodium nuclei led a doublet in the ^{31}P NMR spectra with a coupling constat of ~145Hz (Table **1**).

These Rh(I) organometallic dendrimers were found to be active in the hydrogenation of decene. In a typical run, the organic substrate to metal in a ratio of 200:1 were mixed in benzene and allowed to react at room temperature for 30 minutes under 20 bars of hydrogen pressure.

Scheme 1

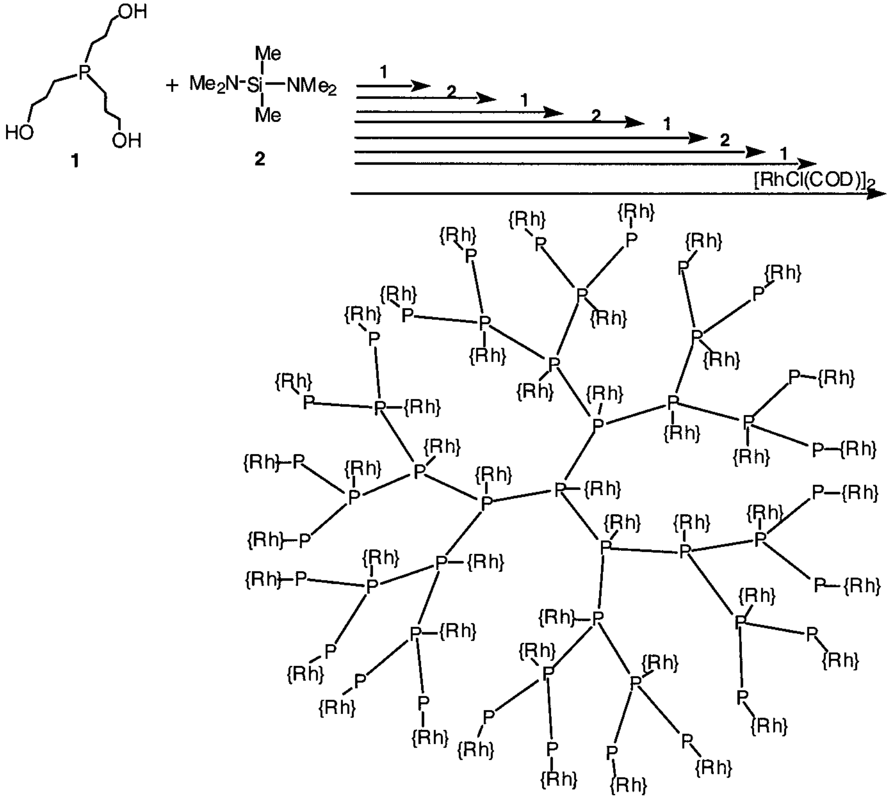


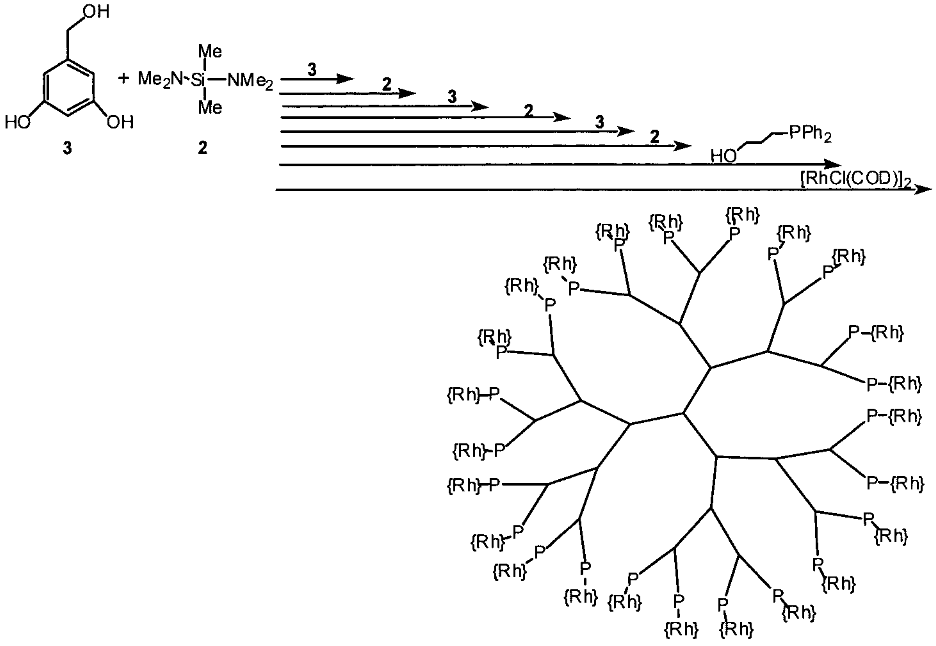
Table **1**

Compound	**$^{31}P\{^1H\}$ NMR** **δ ppm**	**Conversion** **%**	**TOF** **(h^{-1})**
RhP_1, $CODRhClP[(CH_2)_3OH]_3$	11.26 (d)	97.3	413
Rh_4P_4	15.4 (d), 18.7 (d)	100	399
$Rh_{10}P_{10}$	8.62 (d), 14.53 (d), 18.4 (d)	98.7	401
$Rh_{22}P_{22}$	8.73 (d), 10.89 (d), 14.55 (d), 18.39 (d)	99.2	400
$Rh_{46}P_{46}$	9.36 (d), 11.18 (d), 12.04 (d), 14.62 (d), 18.36 (d)	98.3 93.5 (Recycle)	393 374 (Recycle)

A conversion efficiency of 97-100% was observed with generations 0-4 (Table **1**). The catalyst was easily separated from the reaction mixture by crystallization from THF/hexanes mixture, and upon recycling showed efficiency that was only slighly lowered from the original run.[14]

The synthesis of dendrimers in which the peripheries could be functionalized with organometallic fragments was achieved by reacting 3,5-dihydroxybenzylalcohol with bis(dimethylamino)silane in a step-by-step build-up of generations 1-3.[15] These dendrimers contain 6-24 terminal OH groups which were used to anchor phosphine donor ligands by reacting them with bis(dimethylamino)silane and $Ph_2P(CH_2)_3OH$ in seqeunce. The latter were then reacted with Rh(I) dimer $[Rh(COD)Cl]_2$ to yield dendrimers containing 6-24 organometallic centers at the periphery (Scheme **2**).[15]

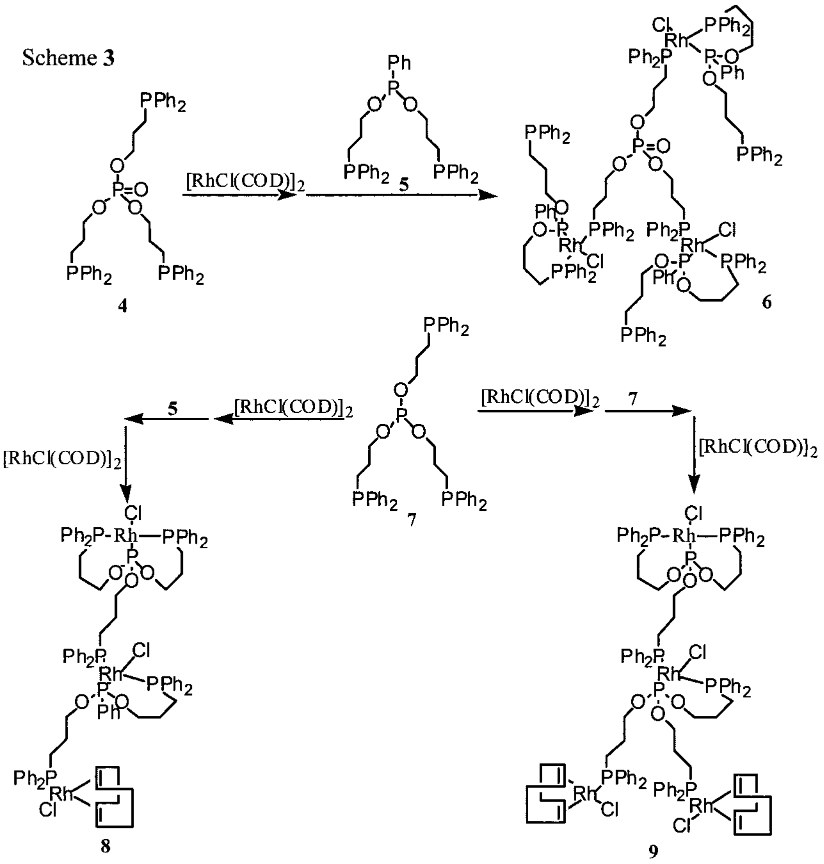
Scheme **2**



The catalytic efficiency of these dendrimers was examined under similar conditions as those used above (200:1 decene to metal ratio; 20 bars H_2 pressure, room temperature). The hydrogenation efficiency was found to be dependent on dendrimer generation and reaction time.[15] It increased upon an increase in generation number and reaction time. Dendrimer generation 3 functionalized with Rh(I) showed maximum conversion in 2h while generations 1-2 showed maximum conversion only after 5 h of reaction time. The dendrimer supported catalysts could be easily recovered and recycled with retention of catalyst activity.

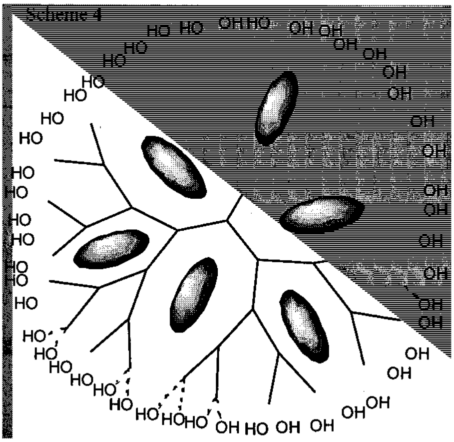
In order to examine the role of dendrimer shape on catalyst efficiency, we then prepared organometallic dendrimers in which the overall dendrimer structure was dictated by the complexation environments of phosphorus ligands.[16] Tripodal polyphosphorus ligand $O{=}P[O(CH_2)_3PPh_2]_3$ in which the phosphorus at the core is unable to coordinate to the transition metals, carries out typical bridge-splitting reaction of the terminal phosphine units with the rhodium dimer $[(\mu\text{-}Cl)(1,5\text{-}C_8H_{12})Rh]_2$. The latter upon further reaction in sequence first with $PhP[O(CH_2)_3PPh_2]_3$ and then the rhodium dimer yields, typical spherical multimetallic complexes (Scheme **3**).[16,17] On the other hand, treatment of tripodal polyphosphorus ligands such as $PhP[O(CH_2)_3PPh_2]_2$ and $P[O(CH_2)_3PPh_2]_3$ with the rhodium dimer $[(\mu\text{-}Cl)(1,5\text{-}C_8H_{12})Rh]_2$ leads to complexation with rhodium at the bridgehead phosphite group first, and then replacement of the 1,5-cyclooctadiene ligand with two terminal phosphines. Continuation of the dendrimer build-up process using $PhP[O(CH_2)_3PPh_2]_2$ or $P[O(CH_2)_3PPh_2]_3$ and the rhodium dimer $[(\mu\text{-}Cl)(1,5\text{-}C_8H_{12})Rh]_2$ in sequence, leads to organometallic dendrimers with atypical spherical structures.[16,17] The structures of the multimetallic compounds were also controlled by using phosphines with longer alkyl arms. For example, in contrast to the phosphines, $PhP[O(CH_2)_3PPh_2]_2$ or $P[O(CH_2)_3PPh_2]_3$, $PhP[O(CH_2)_{10}PPh_2]_2$ and $P[O(CH_2)_{10}PPh_2]_3$ react with the rhodium dimer in a typical bridge splitting reaction without displacement of the 1,5-cyclooctadiene ligand.[16] The catalytic activity of the multimetallic compounds with a typical spherical structures for hydrogenation of decene (1:200 metal to substrate ratio, 20 bar H_2 pressure, room temperature) was found to be lower than similar non-spherical compounds under similar conditions.

Scheme 3



Dendrimers as Hosts: Small molecule loading and its efficient delivery consitute a topical area of research, and dendrimers offer a unique opportunity to achieve these goals. Due to a layer-by-layer build-up that includes adding branching units in each generation, dendrimers contain a densely packed periphery but a hollow interior. Suitable functional groups ideally located at the periphery can also lead to aggregation using weak intermolecular interactions such as hydrogen bonding. 3,5-dihydroxybenzyl alcohol based dendrimers containing terminal OH groups have been demonstrated to yield aggregates of 130-180 nm in diameter depending on the concentration and dendrimer generation.[15] The aggregation phenomenon is reversible, and offers potential in encapsulating small molecules of interest in hollow interiors of these dendrimers at higher dilutions, followed by their assembly at above critical micellar concentrations. We have studied this behavior of dendrimers with a 3,5-dihydroxybenzyl alcohol backbone using the commercially available reagents such as *p*-nitroaniline and the dye DR1.[18] Encapsulation of DR1 (Scheme **4**) leads to changes in the physical properties of the dendrimer and the dye. For example, the solubility of the third-generation dendrimer is significantly enhanced upon loading with DR1. The UV-Vis absorption spectrum of DR1 is blue shifted upon trapping in the dendrimer interior. Upon loading of small molecules, the dendrimer could be easily zipped by reacting the peripheral OH groups withMe_3SiNEt_2 that leads to complete entrapment of the dye molecules.

Dendrimers as Templates: Some of the key issues in the design of carriers include, control on the size of the internal cavities into which designed molecules could be trapped, and their regular distribution in the backbone. We are studying a novel technique to achieve these goals by creating a merger of dendrimer chemistry with our newly developed sol-gel methodology.[19] The globular macromolecules of nanodimensions that have reactive groups at the periphery can be used to build network structures from which dendrimer fractions are finally removed. The terminal OH groups of different generations of 3,5-dihdroxybenzylalcohol based dendrimers are first reacted with $Si(NMe_2)_4$, followed by slow hydrolysis and condensation.[20] The dendrimer fractions are then removed from the network material by acid hydrolysis. Such an approach provides the desired control in tailoring the size and distribution of cavities that can be fine tuned to the specific needs of the host molecules. The latter can be physically trapped in the hollow spaces or chemically bound using residual Si-OH groups.


Scheme 4

Hyperbranched Polymers: We have also used our acid-base hydrolytic chemistry route to prepare hyperbranched polymers in which the organometallic fragments can be added throughout the backbone or are attached at the periphery.[3,15] To prepare the former type, uncontrolled reaction of ($[HO(CH_2)_3]_3P$) with bis(dimethylamino)silane was carried out in a one pot reaction of these building blocks in a 2:3 molar ratio. It led to the formation of a white viscous liquid that showed broad peaks in its ^1H NMR spectra, and three singlets in its $^{31}P\{^1H\}$ NMR spectra. The MALDI-TOF mass spectrum of the polymer showed a maximum mass corresponding to that of a second generation dendrimer. The data confirmed the polymeric and hyperbranched nature of these compounds. The phosphine backboned polymer was easily metallated upon reacting with $[Rh(COD)Cl]_2$ with the appearance of a doublet in the $^{31}P\{^1H\}$ NMR spectra ($J_{Rh\text{-}P}$ = 140 Hz) with no residual free phosphine.[14]

To prepare hyperbranched polymers containing phosphine donors at the periphery, 3,5-dihydroxybenzyl alcohol was reacted with bis(dimethylamino)silane in a manner typical of dendrimer construction (stepwise addition) but without any control on reaction conditions. It led to the formation of a hyperbranched polymer with a dendritic type growth but with more defects, as expected.[15] The peripheries of these polymers could be easily functionalized with donor phosphine ligands by reacting them first with $Me_2Si(NMe_2)_2$ and then with $Ph_2P(CH_2)_3OH$.[21] The latter were then reacted with $[Rh(COD)Cl]_2$ that yielded hyperbranched polymers functionalized with organometallic fragments at the periphery. A detailed investigation of the catalytic properties of these hyperbranched polymers containing active metallic sites in the backbone or at the periphery is currently in progress.

Conclusions

Acid-base hydrolytic chemistry of molecules containing multisite OH groups with aminosilanes is a useful approach to construct a variety of dendritic structures. The position of donor groups in these globular structures can be tailored to include them throughout the backbone or exclusively at the periphery. Upon metallation with rhodium, the resulting organometallic dendrimers are found to be efficient and recyclable catalysts for olefin hydrogenation. The dendrimers containing rhodium centers distributed throughout the cascade structures are more efficient in catalysis while the efficiency of periphery functionalized dendrimers is dependent on the generation number and temperature. We have also developed a methodology to build organometallic dendrimers in which their overall shape can be tailored by controlling the type of polyphosphorus ligands at the core. The latter is helping us evaluate the effect of dendrimer shape in catalysis. The hollow interiors of these dendrimers can be used as hosts for small molecules as evidenced by the successful entrapment of *p*-nitroaniline and the dye DR1. Using dendrimers as templates for building network materials using mild sol-gel processing affords structures with cavities of tailorable size and distribution. A detailed investigation of the latter materials is currently being pursued.

Acknowledgment

We would like to thank NSERC (Canada) and FCAR (Quebec, Canada) for financial support.

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