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Catalytic Chameleon Dendrimers

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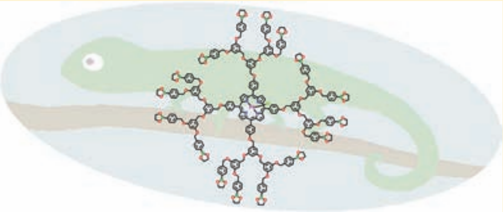
Ⓢ *Supporting Information*



ABSTRACT: Dendrimers with boronic ester end-groups and an iron porphyrin core were synthesized and characterized. The dendrimer termini were reversibly exchanged by the addition of appropriate diol molecules. According to molecular dynamics (MD) simulations, the exchange of termini may lead to changes in the conformational behavior of the dendrimer, specifically regarding the average position of the end groups relative to the core. The spatial steric disposition attained with different termini was shown to significantly affect epoxidation reaction activity and selectivity with various alkenes, thus allowing for an original way to control and adjust catalytic behavior under alternating environments.

INTRODUCTION

Changes in macromolecular structures induced by environmental stimuli are well-known and are the basis for many basic processes. For instance, most soluble polymers increase their hydrodynamic radii when a poor solvent is replaced by a good solvent.[1] An alternative mode for structural reorganization in macromolecules may be brought on by the binding of a substrate on a polymer. This type of modification may significantly affect the properties of the macromolecule; a ubiquitous example of this behavior is prevalent in many signal transduction cascades, where competitive binding of signaling molecules leads to triggering of enzymatic pathways. Inspired by this model, we propose that specific synthetic macromolecules equipped with catalytic centers and labile functional groups may exhibit "chameleonic" behavior, adapting their properties in response to the environment.[2] In a first approach to this catalytic "chameleon", we describe herein how a reversible exchange of termini in dendrimers noticeably influenced the reactivity and selectivity of a catalytic process.

Dendrimers may be divided into three main components: core, backbone, and termini. The relative spatial positioning of these components, i.e., the dendrimer's conformational behavior, may be greatly influenced by the type of functional groups that constitute the dendrimer.[3] Understanding the individual effect of dendrimer components on its overall properties may allow for the construction of novel macromolecules with smart functions. Molecular dynamics (MD) simulations are a fundamental tool to understand the behavior of dendrimer dynamics and terminal group influence on relevant conformations. Simulation studies have shown that changes in the branching motif[4] have fundamental consequences on the final properties of dendrimers[5] and dendrons.[6] The customization of the dendritic termini[7] may also play a pivotal role in the final behavior of these multivalent molecules. For instance, substitution of flexible spermine ligands with *N*,*N*-di-(3-aminopropyl)-*N*-(methyl)amine (DAPMA) surface groups induced consistent surface rigidity in Newkome-type dendrons, influencing the efficiency of DNA binding.[8] In this framework, atomistic simulation is the ideal technique to explore the effect of surface modifications on the dynamic behavior of dendrimers.

While comprising great potential due to their highly symmetric multivalent structures, dendrimers' expediency is limited by the stringent and trying synthetic requirements for their construction.[9] Notably, dendritic related catalysis,[10] drug delivery,[11] surface processes,[12] and light and energy transfer[13] are all strongly dependent on the terminal groups utilized. Consequently, the ability to replace dendritic termini without the necessity of a de novo synthesis stands out as an appealing goal.[14] Dynamic covalent chemistry[15] is based on the use of reversible reactions and may be conveniently applied for the specific goal of dendrimer termini exchange. A significant advantage of dynamic covalent systems is their enhanced stability (as compared to supramolecular ensembles), coupled with the prospective for self-assembly and dynamic behavior. However, in comparison to conventional synthetic chemistry, useful covalent reversible reactions are relatively scarce. Functional groups that may participate in dynamic covalent chemistry include disulfides,[16] hydrazones,[17] imines,[18] alkenes in olefin metathesis,[19] thioesters,[20] and acetals.[21] Curiously, to date, boronic ester formation has not been widely used for dynamic covalent chemistry,[22] even though ubiquitous diol substrates (ethylene glycol, pinacol, sugars, etc.) are ideal for reversible covalent binding with

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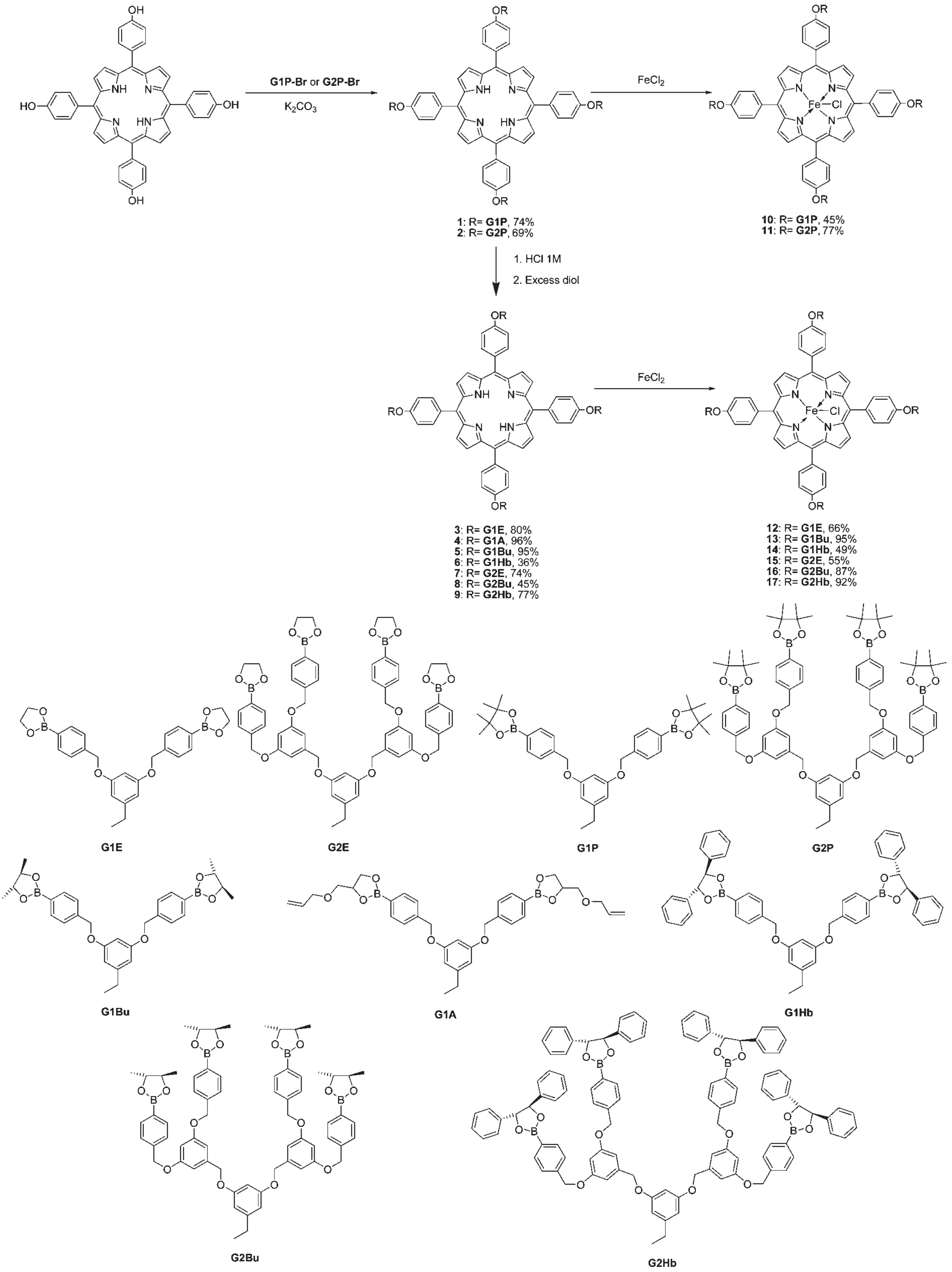
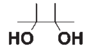
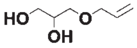
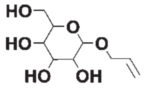
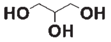
Scheme 1. Synthesis of Boronic Ester Terminated Dendrimers 1−17



boronic acids. The ability to reversibly modify dendrimers just by changing the surrounding molecular environment provides the opportunity to study the effect of terminal group "switchability" on several properties, such as catalytic selectivity and conformational behavior, and try out the catalytic chameleon dendrimer concept.

Table 1. Qualitative Dendrimer Termini Exchange Experiments with Selected Diols[a]

Diol/Dendrimer					
1	n.a.	-	-	-	-
3	+	n.a.	+	+	±
4	+	±	n.a.	±	±

[a] Exchange processes observed by MALDI-TOF after 24 h. Diol transesterifications were carried out by addition of 600-fold excess equivalents of the appropriate diol (rt) to a solution of the starting dendrimer in acetone/ethyl acetate (1:1). Legends indicate: +, full exchange; ±, partial exchange; −, no exchange.

Table 2. Epoxidation of Alkenes Catalyzed by 10−17[a]

generation	termini	compound	CST conversion (%)	CYO conversion (%)	LIM conversion (%)
0 (control)	none	Fe(TPP)Cl	53	63	61
first	pinacol	**10**	47	24	35[b]
first	ethylene glycol	**12**	21	5	32[b]
first	2,3-butanediol	**13**	38[b]	28[b]	36
first	hydrobenzoin	**14**	48	18[b]	36
second	pinacol	**11**	28	57	41
second	ethylene glycol	**15**	53	4	16[b]
second	2,3-butanediol	**16**	29	21[b]	26[b]
second	hydrobenzoin	**17**	4[b]	23[b]	24

[a] Conversion processes observed by GC-MS until no further progress in conversion could be observed (to 3 h). All reactions were run in triplicate (see the Supporting Information). [b] Duplicate repeats.

RESULTS AND DISCUSSION

Following the procedures presented in Scheme 1, Fréchet-type boronic ester terminated dendrimers of the first and second generation **1**−**17** were synthesized. Dendrimers **3**−**9** were readily formed within 2 h under mild conditions by full hydrolysis of dendrimers **1** or **2** and addition of the appropriate diols. All new dendrimers could be clearly characterized by both NMR and MALDI-TOF techniques (see the Supporting Information). Addition of ferrous chloride readily provided catalytically active metalated porphyrin dendrimers **10**−**17**.

Once the dendrimers were secured, the in situ exchange behavior of first-generation dendrimers **1**, **3**, and **4** with other diols (i.e., transesterification) was studied. The desired exchange reactions were carried out in the presence of a large excess of diols at room temperature in ethyl acetate/acetone solution (1:1) for enhanced solubility and for some cases also in methylene chloride or chloroform solution (see the Supporting Information). Reaction progress was monitored by MALDI-TOF mass spectrometry, ^{1}H NMR, and DOSY-NMR techniques—Table 1 qualitatively describes the results obtained. As expected, due to the more labile nature of ethylene boronic esters compared to their bulkier analogues,[23] the ethylene glycol terminal groups of dendrimer **3** were easily exchanged, while pinacol termini in dendrimer **1** could not be transesterified by any other diol under the neutral reaction conditions used. Allylglycerol terminated dendrimer **4** showed an intermediate behavior. These results indicate that labile diols may be readily exchanged in situ just by adding another diol, while a more vigorous hydrolysis reaction is needed to exchange diols such as pinacol.

After assessing the switchable character of the boronic ester termini, a known olefin epoxidation reaction catalyzed by a metalloporphyrin core dendrimer[24,25] was chosen to study the effect of terminal group switching on catalytic selectivity. Because pinacol and ethylene glycol possess dissimilar steric volumes, we presumed that dendrimers terminated with these groups could manifest different reactivity patterns. Intermediate size termini derived from 2,3-butanediol and hydrobenzoin were also tested. Table 2 shows the conversions for epoxidation of cyclooctene (CYO), *cis*-stilbene (CST), and limonene (LIM) with first-generation catalysts **10**, **12**, **13**, and **14** and second-generation catalysts **11**, **15**, **16**, and **17**. All reactions were also carried out with iron tetraphenylporphyrin chloride (Fe(TPP)Cl) as a control experiment and using iodosobenzene as oxidant, by the same method as previously detailed for this reaction.[24b,25]

The results showed that first-generation dendrimers **10**, **13**, and **14** were more efficient than **12** at catalyzing the oxidation of CST and CYO; this trend was not followed in the oxidation of LIM. Thus, even at the first generation, the features of the terminal group had a noticeable effect on catalyst efficiency. Second-generation dendrimers, possessing 16 terminal groups, presented even more prominent reactivity patterns. For instance, CYO was oxidized with 57% conversion using dendrimer **11**, compared to negligible catalytic activity with dendrimer **15**. On the other hand, catalyst **15** showed a 2-fold higher catalytic activity with CST as the substrate compared to dendrimer **11** (53% vs 28%, respectively).

These results effectively showed that dendrimer reactivity was significantly altered by exchanging terminal groups; moreover,

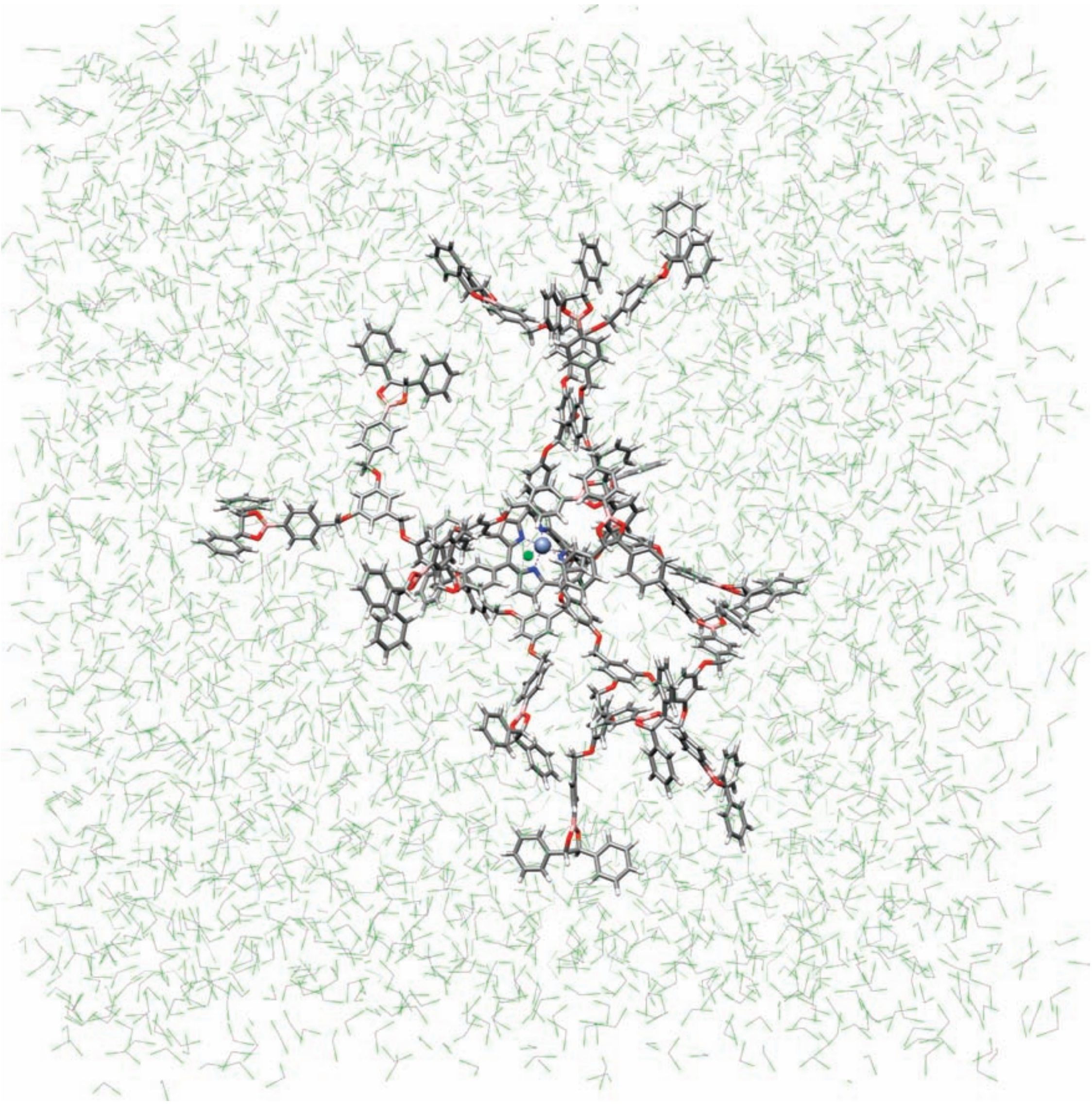


Figure 1. Starting conformation of **17** with explicit solvent molecules. The dendrimer and CH_2Cl_2 are colored per atom (C, gray; H, white; O, red; N, blue; Fe, purple; Cl, green; and B, pink). CH_2Cl_2 molecules are shadowed, and hydrogen atoms are not shown for clarity.

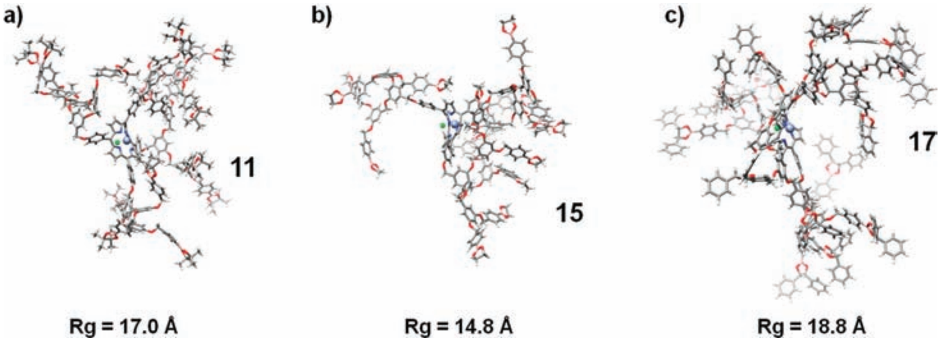


Figure 2. Equilibrated snapshots taken from the MD solution-phase simulation of the dendrimers **11** (a), **15** (b), and **17** (c) (and respective radii of gyration, Rg). CH_2Cl_2 molecules and hydrogen atoms are not shown for clarity; dendrimers are colored per atom.

the use of higher dendrimer generations led to specific selectivities not observed with the lower generations. We hypothesized that this behavior could be due to the conformational arrangements found in the higher-generation dendrimers. To pursue this assumption, we carried out MD simulations on model systems.

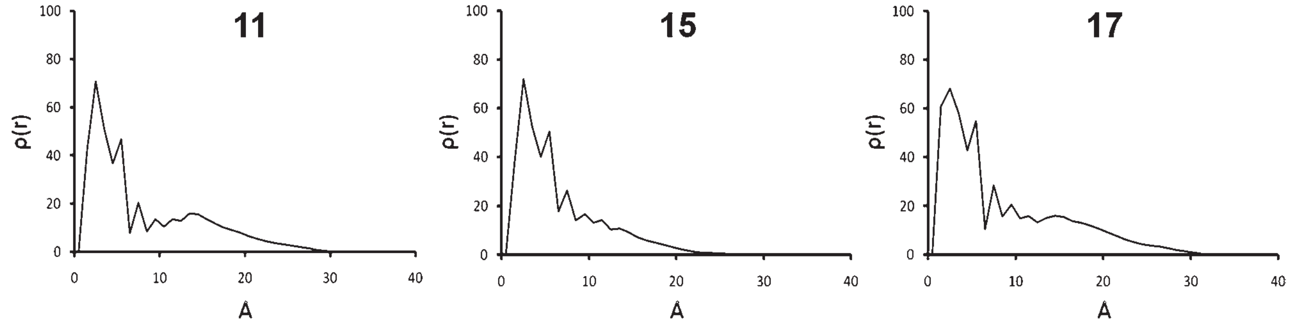


Figure 3. Radial distribution function (RDF) profiles of atoms of **11**, **15**, and **17** calculated with respect to the Fe atom. The unit value for $\rho(r)$ is expressed in atoms/Å^3.

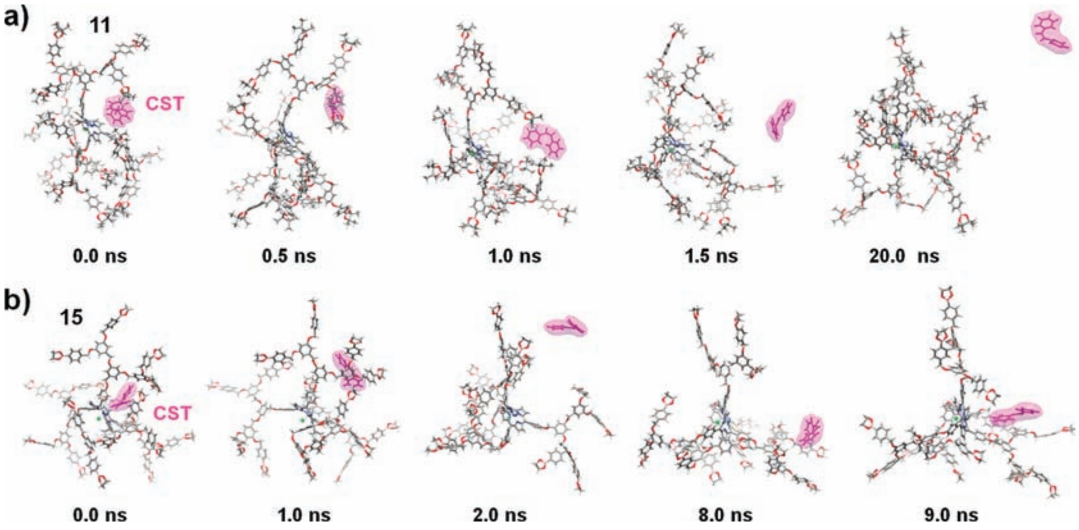


Figure 4. Snapshots taken from the MD simulations of (a) **11** + CST and (b) **15** + CST. CH_2Cl_2 is omitted for clarity, and CST is highlighted in pink.

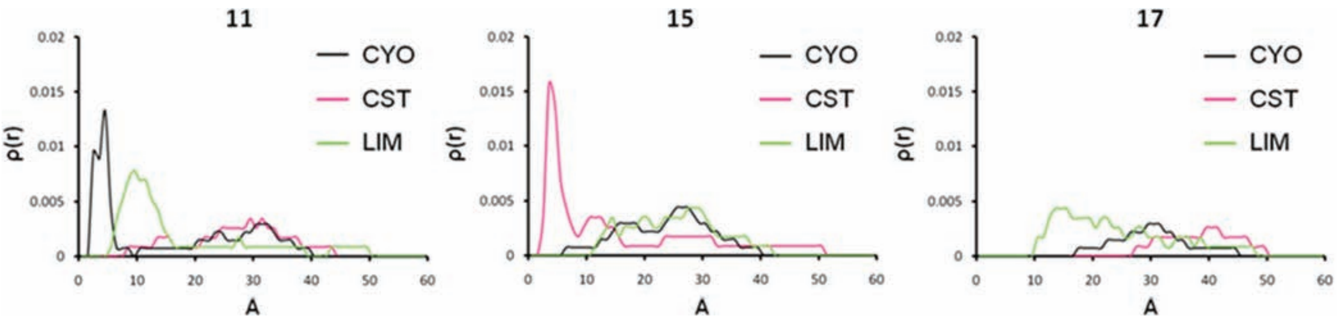


Figure 5. RDF plots for CST, CYO, and LIM atoms with respect to the central Fe atom of dendrimers **11**, **15**, and **17**. The unit value for $\rho(r)$ is expressed in atoms/Å^3.

Theoretical Calculations. Dendrimers **11**, **15**, and **17** were constructed as composed by three different residues according to previous studies on the simulation of dendrons[26] and dendrimers:[27] the porphyrin core (COR), the branched repetitive units (REP), and the surface boronic ester end groups (END, different for **11**, **15**, and **17**). Atomistic simulation was used to understand the conformation assumed by the different dendrimers in CH_2Cl_2 solution. With this aim, **11**, **15**, and **17** (Figure 1) were immersed in a periodic box containing explicit CH_2Cl_2 molecules, and the solution-phase systems were simulated by running 10 ns molecular dynamics (MD) runs. During this time all dendrimers converged to the equilibrium with good stability. All MD simulations conducted in this study were carried out in NPT conditions at 300 K and 1 atm of pressure using the AMBER 11 suite of programs.[28] The MD equilibrated trajectories of the **11**, **15**, and **17** solution-phase systems were thus processed to obtain structural information about the equilibrated conformations assumed by dendrimers with different termini. Extensive details on the computational procedure adopted for simulations and data analysis are available in the Supporting Information.

The radius of gyration (Rg) of **11**, **15**, and **17** was calculated over the last 2 ns taken from the equilibrated phase of the molecular dynamic trajectories to determine the final size of the three dendrimers in solution. Rg values in Figure 2 verify that all dendrimers undergo an expected structural rearrangement in CH_2Cl_2 solution, shrinking with respect to their starting conformations.

The Rg provides general information about the size of dendrimers in solution. However, to gain a clear comprehension of the structural consequences of the terminal group exchange, the radial distribution function (RDF) profiles of the atoms of **11**, **15**, and **17** were also calculated (Figure 3). This function represents the density and the distribution of atoms in space with respect to the Fe atom in the porphyrin core of each dendrimer. RDF plots were reported as the average over the equilibrated phase of the dynamic trajectories, giving information also on the dynamics of the system and providing an indication on the time period in which a certain atom is present in a certain area in the dendritic volume (dynamic density). Thus, high and narrow peaks in a small area of these graphs identify not only high density of atoms in a certain zone but also high localization and low mobility of these atoms. On the other hand, broad and low intensity peaks indicate low density and high atomic vibrations.

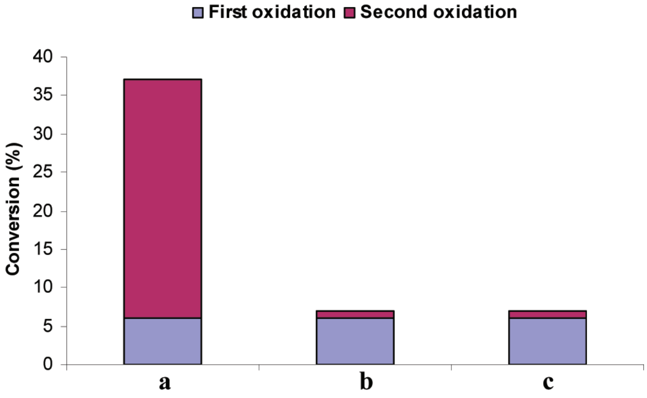


Figure 6. CYO epoxidation starting with catalyst **15**. (a) First oxidation: iodosobenzene (10 μmol), dendrimer **15** (1 μmol), cyclooctene (28.8 μmol), and internal standard (mesitylene) in 1.5 mL of dry CH_2Cl_2. The second oxidation was performed after 3 h: fresh iodosobenzene (10 μmol) and pinacol (33.3 μmol) were added. (b) Iodosobenzene (10 μmol), dendrimer **15** (1 μmol), cyclooctene (28.8 μmol), and internal standard (mesitylene) in 1.5 mL of dry CH_2Cl_2. The second oxidation was performed after 3 h: fresh iodosobenzene (10 μmol) was added. (c) Iodosobenzene (10 μmol), dendrimer **15** (1 μmol), cyclooctene (28.8 μmol), and internal standard (mesitylene) in 1.5 mL of dry CH_2Cl_2. The second oxidation was performed after 3 h: fresh iodosobenzene (10 μmol) and ethylene glycol (33.3 μmol) were added.

Plots in Figure 3 indicate that the smaller dimensions of the termini of **15** (ethylene glycol) result in a higher degree of backfolding in the equilibrated molecule. The RDF profile of **15** is characterized by a dense core and by a uniformly decreasing density going from the center to the surface of the dendrimer. On the other hand, **11** and **17** show a less dense core than **15** and consistent density at the surface. The peak present in the RDF plots of **11** and **17** at the distance of ~15 Å identifies a region of greater surface rigidity commonly seen in some dendrimers (i.e., PAMAM) at low pH conditions[29] or at higher generations.[30] Data suggest that indeed surface modification can play an important role in the structural and dynamic behavior of these catalytic dendrimers. To explore the effect of the conformations assumed by **11**, **15**, and **17** on the accessibility of the olefin substrates to the porphyrin core, simulations were run on systems containing both dendrimer and alkene in solution. A single substrate molecule (CYO, CST, and LIM) was put in close proximity to the center of **11**, **15**, and **17** (*trans* to the chloride ligand), and MD simulations were run for 20 ns (Figure 4). In addition, we considered that the oxidation of the porphyrin core by iodosobenzene should not significantly influence the olefin penetration of the dendritic scaffold.

Even though a computational approach based on classical molecular dynamics does not allow the study of any explicit reaction, the ability of the substrates to access the porphyrin core is a fundamental requirement of the catalytic reaction. The simulations show that CST cannot penetrate **11** once it leaves the core's proximity (after ~1.5 ns; Figure 4a). On the contrary, the substrate in **15** is able to return to the interior of the dendrimer during the 20 ns of MD simulation (Figure 4b).

Interestingly, the MD simulations show the opposite behavior for the CYO ensembles. In the case of *cis*-cyclooctene, penetration is more efficient in dendrimer **11** when compared to dendrimer **15**. In addition, the consistent surface crowding present in **17** prevents close proximity to the porphyrin core for all of the three substrates after the initial separation (snapshots related to these additional simulations are available in the

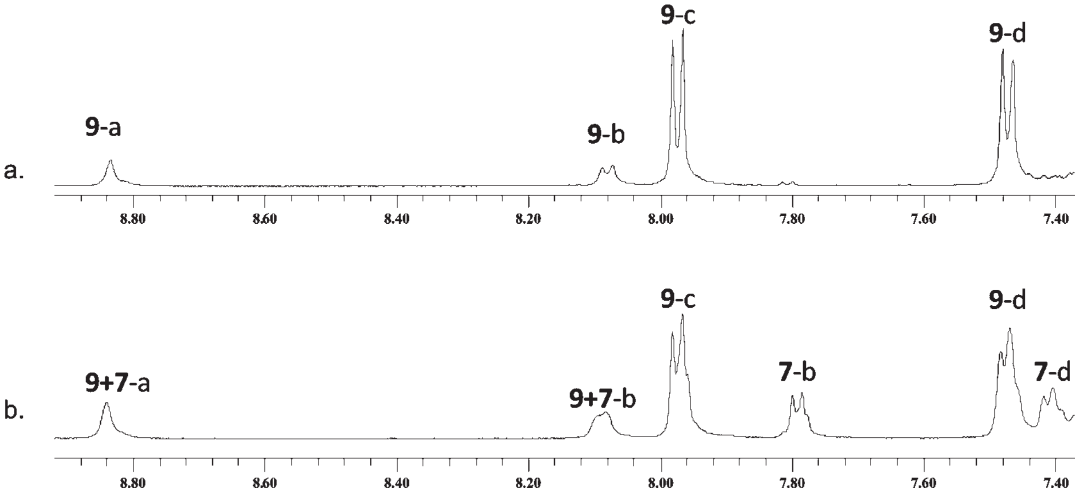


Figure 7. (a) ^{1}H NMR (500 MHz) of dendrimer **9**. (b) 3 h after adding 24 equiv of ethylene glycol.

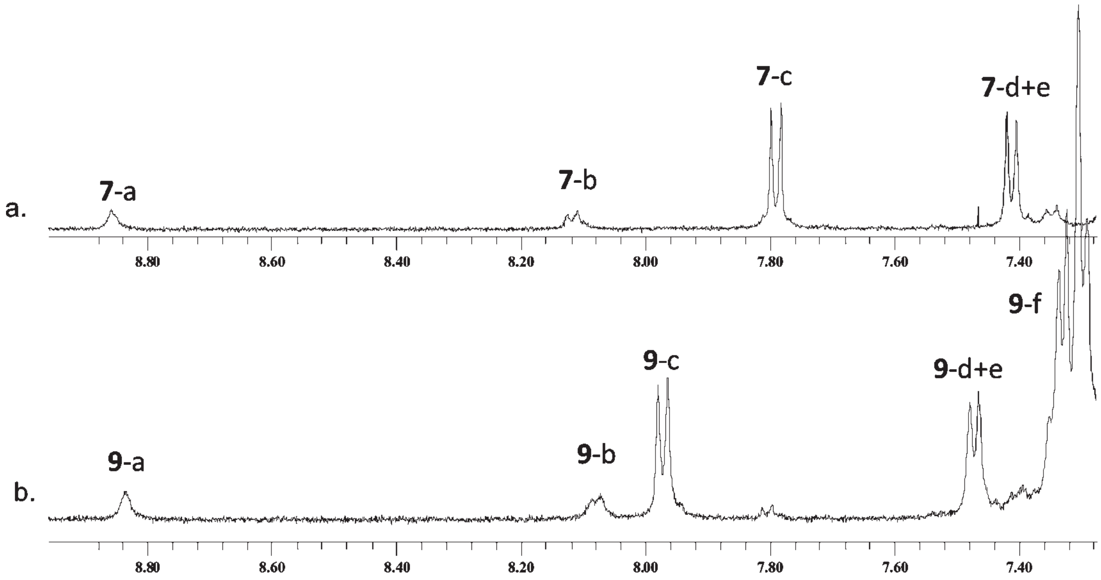


Figure 8. (a) ^{1}H NMR (500 MHz) of dendrimer 7. (b) 5 min after adding 24 equiv of hydrobenzoin.

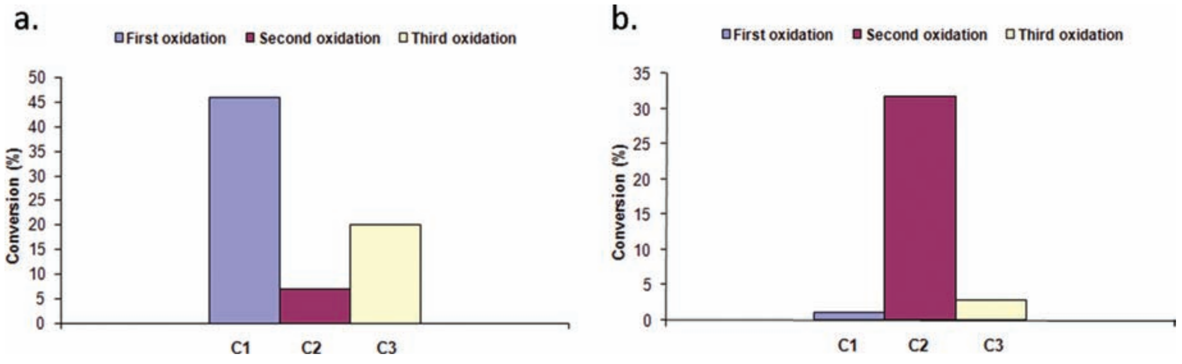


Figure 9. (a) CST epoxidation starting with catalyst **15**. C1) First oxidation: iodosobenzene (10 μmol), **15** (1 μmol), CST (28.8 μmol), and internal standard (mesitylene) in 1.5 mL of dry CH_2Cl_2. C2) Second oxidation: addition of (0.05 mmol) *R*,*R*-(+)-hydrobenzoin and iodosobenzene (10 μmol). C3) Third oxidation: addition of (1.09 mmol) ethylene glycol and iodosobenzene (10 μmol). (b) CST epoxidation starting with catalyst **17**. C1) First oxidation: iodosobenzene (10 μmol), **17** (1 μmol), CST (28.8 μmol), and internal standard (mesitylene) in 1.5 mL of dry CH_2Cl_2. C2) Second oxidation: addition of (1.09 mmol) ethylene glycol and iodosobenzene (10 μmol). C3) Third oxidation: addition of (0.05 mmol) *R*,*R*-(+)-hydrobenzoin and iodosobenzene (10 μmol).

Supporting Information). A more quantitative picture of these events can be seen in the RDF plots for all alkenes during simulations with dendrimers **11**, **15**, and **17** (Figure 5). These results are soundly consistent with the actual experimental activity profiles observed (Table 2), suggesting that the selectivity observed is directly related to the dynamic behavior of the different dendrimers that hinders subtrate approach to the catalytic core.

In Situ Exchange. Having shown that catalytic dendrimers with different terminal groups present different reactivities, we were interested in determining whether termini exchange and reactivity could be coupled in situ. As shown in Table 2, catalyst **11** was much more efficient than **15** in the epoxidation of CYO. Thus, a simple one-pot experiment was devised to test the effect of termini exchange during the course of the reaction. First, the oxidation of CYO with **15** was repeated in three separate vials until no further progress in conversion could be discerned. Subsequently, all vials were supplied with a further amount of fresh oxidant to promote additional oxidation. To the first and the second vial was added an additional amount of pinacol or ethylene glycol, respectively, while no diol was added to the third vial. Even though the overall activity was slightly depressed in the second oxidation (as expected due to catalyst decomposition), the in situ formation of **11** significantly increased the conversion of the reaction in the vial with added pinacol (Figure 6). A related experiment with first-generation catalysts afforded similar results, supporting the hypothesis that in situ formation of a more reactive dendrimer affects the catalytic activity (see the Supporting Information).

After assessing the effect of in situ exchange of termini, the reversibility properties of the chameleon dendrimers were explored by a series of CST oxidation reactions catalyzed by **15** and **17**. ^{1}H NMR experiments on dendrimers **9** and **7** with the addition of the corresponding diols confirmed the exchange of ethylene glycol by hydrobenzoin and vice versa (Figures 7 and 8), although, as expected, the addition of ethylene glycol to dendrimer **9** led only to partial transesterification (see the Supporting Information for full details and peak assignment).

As shown in Table 2, the second-generation ethylene glycol terminated Fe-dendrimer **15** efficiently catalyzed the oxidation of CST; on the other hand, when the termini are *R*,*R*-hydrobenzoin (Fe-dendrimer **17**), almost no reaction was observed. These two extreme behaviors present themselves as ideal to check the chameleonic reversible properties of the system. Thus, oxidation of CST catalyzed by **15** was followed by an additional epoxidation in the presence of hydrobenzoin (in situ formation of **17**) and subsequently followed by an additional oxidation with addition of excess ethylene glycol (partial restoration of catalyst **15**). The same oxidation reaction with reversible exchange was carried out starting with **17** and adding first ethylene glycol and then hydrobenzoin to restore **17**. As shown in Figure 9, the addition of ethylene glycol significantly increased the oxidation conversion, while addition of hydrobenzoin arrested the oxidation, as expected for a reaction catalyzed by a dendrimer with this terminal group. These series of experiments confirm that an in situ exchange of the dendrimers' termini can affect the catalytic selectivity and that a reversible chameleonic behavior can be obtained in the presence of suitable background molecules.

CONCLUSIONS

In conclusion, we have designed and synthesized novel boronic ester terminated dendrimers with iron porphyrin cores. These chameleon dendrimers readily exchange their surface by a dynamic covalent chemistry process on addition of excess diol. Alkene epoxidation reactions demonstrated that termini exchange strongly affects the dendrimers' catalytic activity, even at low generations. Moreover, we found that different substrates may have dissimilar and even opposite reactivity trends when dendrimer termini are modified. MD studies supported nicely our experimental findings suggesting that the differrent terminal groups affect the conformation assumed by the dendrimers in dichloromethane solution. We also demonstrated the possibility to reversibly change the catalytic behavior of chameleon dendrimers in situ if a suitable diol able to promote surface modification is added to the solution. This study presents a new concept in catalytic dendrimers where the reactivity and selectivity of a catalyst can be tuned by a simple exchange of the peripheral surface groups. Our current efforts are geared toward expanding this model and studying the effects of connecting termini and substrates.

ASSOCIATED CONTENT

Ⓢ **Supporting Information.** Synthetic procedures, MALDI-TOF MS and NMR spectroscopy characterizations, experimental details for exchange and epoxidation reactions, and extensive details about the parametrization and simulation procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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