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Molecular Imprinting Inside Dendrimers

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Abstract: Synthetic hosts capable of binding porphyrins have been produced by a mixed-covalent-noncovalent imprinting process wherein a single binding site is created within cross-linked dendrimers. Two synthetic hosts were prepared, using as templates 5,10,15,20-tetrakis(4-hydroxyphenyl)porphyrin and 5,10,15,20-tetrakis(3,5-dihydroxyphenyl)porphyrin. These two templates were esterified with, respectively, fourth- and third-generation Fréchet-type dendrons containing homoallyl end-groups. The resulting tetra- and octadendron macromolecules underwent the ring-closing metathesis reaction using Grubbs' Type I catalyst, $RuCl_2(P(C_6H_5)_3)_2(CHCH_2C_6H_5)$, to give extensive interdendron cross-linking. Hydrolytic removal of the porphyrin cores afforded imprinted hosts whose ability to bind porphyrins with various peripheral substituents was investigated by UV−visible spectrophotometric titrations and size exclusion chromatography. The results indicate a high yield of imprinted sites that show high selectivity for binding of porphyrins capable of making at least four hydrogen bonds, but only a moderate degree of shape selectivity.

Introduction

Host−guest chemistry has emerged as a central paradigm within organic chemistry.[1] The design and synthesis of diverse host molecules that selectively and tightly complex many different classes of guest molecules have been notably successful. As effective as this approach has been, especially for small molecule hosts, the requirement to prepare hosts bond by bond through multistep synthetic routes has limited their widespread application. Furthermore, each new target guest typically requires an entirely new host design and development program.

Two strategies that have the potential to significantly extend the host−guest approach involve molding an organic receptor around the guest "template". The first, using molecularly imprinted polymers (MIP), was initially described in Wulff's seminal 1972 report,[2] in which a matrix was polymerized around the template molecules, followed by removal of the template; this leaves host cavities that, ideally, retain a shape and functional group complementarity to the guest-template. This early synthesis of a MIP is referred to as the covalent approach because the template is reversibly linked to the matrix by covalent bonds.[3] A noncovalent approach, in which one or more monomers complex the template, was pioneered by Mosbach and co-workers and is now the most commonly used method of MIP synthesis.[4] Subsequently, mixed covalent−noncovalent methods were developed[5] as well as numerous related approaches.[6,7] Indeed, molecularly imprinted polymers (MIPs) have been among the most extensively studied host−guest systems. MIPs have several drawbacks, however, including incomplete template removal and slow mass transfer;[6,7−9] their practical application is also severely limited by the heterogeneity of the binding sites for which a broad range of affinities are observed.[6,10]

A second strategy for rapid host construction has emerged more recently. It uses a dynamic combinatorial library (DCL) of hosts, in which one or more members are bound to and stabilized by the guest molecule.[11−13] The molding process in the DCL approach is different in two ways. First, the molding uses reversible reactions so that ineffective hosts may be sacrificed in favor of superior ones. The DCL approach is further distinguished in that the molded receptors each contain a single binding site so that individual receptors or classes of receptors can be separated, characterized, and studied in solution.

We recently described a "monomolecular imprinting" approach, which contains elements of both the DCL and the mixed-covalent-noncovalent imprinting approaches and pro-

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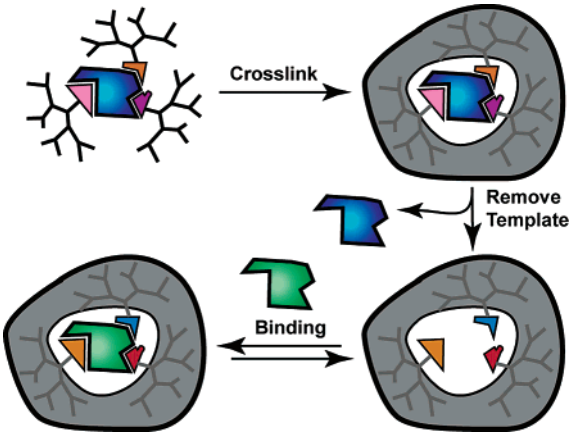

Figure 1. Schematic representation of the monomolecular imprinting process.

duces macromolecular hosts containing a single binding site.[14,15] Herein, full details of those studies are described, including binding kinetics and imprinting experiments using a different but related template.

Design of a Monomolecular Imprinting System

To make a selective MIP, each template should produce an effective binding site, and each binding site must originate from template-mediated imprinting. The approach chosen to test the basic strategy involves three distinct steps (Figure 1): (1) covalent attachment of functional dendrons to the template with cleavable bonds, (2) cross-linking of the dendron end-groups, and (3) removal of the template. In principle, a single binding site could be imprinted into virtually any macromolecule. Even though they often require multistep synthesis, dendrimers were attractive candidates for these early studies both because their homogeneity assists in purification and characterization and because the large number of end-groups should allow a significant degree of cross-linking.[16]

With respect to the cross-linking reaction, a reversible chemical process was desirable as a way to effect a dynamic molding that might result in a "best-fit" imprint for the template. Recent advances in the development of novel catalysts for olefin metathesis have made reversible, but robust, alkene cross-links easily accessible.[19,20] For example, the Grubbs' ruthenium benzylidene catalysts exhibit broad functional group tolerance and are relatively insensitive to water, oxygen, or other impurities.[20] The commercially available Type I catalyst (**2**) is particularly well studied and known to produce medium and large ring systems,[21] although the more recently reported Type II catalyst has certain advantages in this regard.[22] The Type I catalyst has also been used to covalently capture supramolecular assemblies.[23] Most appealing from the perspective of dynamic molding was the finding that the pendant alkene groups in 1,2-polybutadiene underwent extensive ring-closing metathesis (RCM) reactions and that undesirable ring closings were reopened, ultimately allowing nearly all adjacent alkenes to couple.[24] To demonstrate this concept of monomolecular imprinting, we decided to imprint a porphyrin within a Fréchet-type dendrimer[25] for multiple reasons. First, the dendrimer shell must be relatively nonpolar to permit hydrogen bond-mediated recognition in the core.[26] The Fréchet-type phenyl-benzyl ether-based dendrimers fulfill this requirement, and a range of other recognition processes have been shown to occur readily within the interior of these dendrimers.[17] Fréchet-type dendrimers are also chemically robust, which allows considerable latitude in the chemistry used to implement the imprinting process outlined in Figure 1. Furthermore, they possess an intermediate degree of flexibility in comparison to that of poly(propylene imine) or phenylacetylene based systems. Most importantly, we reported that, upon treatment with RCM catalyst **2**, dendrimer **1** underwent extensive cross-linking to give **3**, which subsequently afforded **4** upon core removal (Scheme 1).[27]

To our knowledge, porphyrins have not been used as templates for the synthesis of MIPs, although their incorporation into MIPs for recognition and sensing was reported by Takeuchi,[28] and porphyrins have been used extensively in molecular recognition, shape selective oxidation, and self-assembly studies.[29] In the current work, polyhydroxylated tetraphenylporphyrins were considered excellent candidates as templates because the multiple hydroxyl groups provide sites for dendron attachment. These, in turn, would produce an imprinted structure capable of multipoint recognition. Furthermore, the visible

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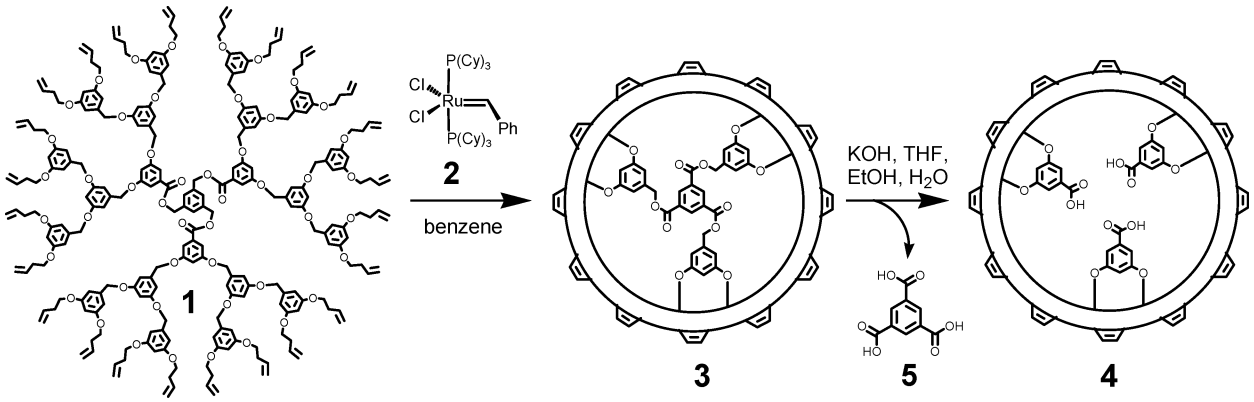
Scheme 1



absorption bands of the porphyrin chromophore are intense and sensitive to the local environment. Porphyrin-core dendrimers have been studied as synthetic models of heme proteins, and porphyrins have been shown to be excellent reporter groups in studies of the photochemical and electrochemical properties of dendrimers.[30]

Two synthetic hosts were prepared by imprinting 5,10,15,-20-tetrakis(3,5-dihydroxyphenyl)porphyrin (**6**) and 5,10,15,20-tetrakis(4-hydroxyphenyl)porphyrin (**22**) into octa- and tetradendron macromolecules, respectively. Extensive complexation studies with several potential porphyrin guests probed the structural requirements for binding. The results suggest that this strategy, wherein a single molecular template imprints a single binding site within a single macromolecule, is a promising one that merits further development.

Results and Discussion

Imprinting 5,10,15,20-Tetrakis(3,5-dihydroxyphenyl)porphyrin (6) Inside of a Dendrimer. As shown in Scheme 2, porphyrin-core dendrimer **7** was synthesized by DCC-mediated esterification using dendron **8** and 5,10,15,20-tetrakis(3,5-dihydroxyphenyl)porphyrin (**6**). Large-scale (ca. 40 g) preparation of dendron **8** was accomplished in six steps in 48% overall yield from commercially available methyl 3,5-dihydroxybenzoate and homoallyl alcohol. Because of poor solubility, the reaction was initially carried out in THF, but after partial esterification the solvent was replaced with methylene chloride. Typically, the esterification was partially incomplete with ca. 5% of the product containing only six or seven dendrons, as discussed in greater detail below.

Porphyrin-core dendrimer **7** was cross-linked in benzene (10^{-6} M) with 4 mol % Grubbs' catalyst (**2**) per alkene to produce the cross-linked dendrimer **9** in 88% yield, with less than 5% interhost cross-linking. The ^{1}H NMR spectrum of **9** showed the expected broadening of all of its signals, as well as the nearly complete loss of the alkene methine resonance at ca. 5.81 ppm and the appearance of a new alkene peak at 5.60 ppm corresponding to the disubstituted alkene group. Integration of these overlapping signals suggested that the average number of cross-links was about 29. Comparison of the MALDI-TOF mass spectra of **7** and **9** (Figure 2A and 2B, respectively) revealed a reduction in mass consistent with the formation of 28−32 cross-links, with the signal corresponding to 30 cross-links being the most intense (Table 1).

Dendrimers **7** and **9** were studied by size-exclusion chromatography (SEC). The apparent M_w of **7** as determined by SEC in toluene is 8200 Da, 26% below its actual M_w as measured by MALDI-TOF MS. This discrepancy is due to the globular shape of **7** being more compact than the linear polystyrene standards used for the M_w calibration. The SEC-determined apparent M_w of the cross-linked dendrimer **9** is 5500 Da, nearly 54% below its actual molecular weight observed by MALDI-TOF MS. This is consistent with the formation of an even more compact structure upon cross-linking.

Cross-linked dendrimer **9** was hydrolyzed using a 2.5 M aqueous KOH solution in THF to produce **10** in 43% yield. The ^{1}H NMR spectrum of the imprinted dendrimer **10** showed loss of the porphyrin signals at 9.21, 8.14, 7.74, and −2.86 ppm. Additionally, the aromatic protons ortho to the ester group and appearing at 7.53 ppm in **9** were replaced by a signal at 7.20 ppm, consistent with loss of the porphyrin core and ester to carboxylic acid conversion. Comparison of the MALDI-TOF mass spectra of **9** and **10** (Figure 2B and 2D, respectively) showed a difference of 605.4 Da corresponding to the loss of the porphyrin core ($C_{44}H_{22}N_4$: 606.7 Da).

The molecular weight of **10** could not be determined by SEC because this rather polar compound did not elute from the column. However, its octa-ethyl ester analogue **10-$(CO_2Et)_8$**, prepared by ethanolysis of **9**, had an apparent molecular weight of 4700 Da, 48% below its calculated molecular weight. In comparison to **9**, whose SEC-derived M_w was 5500, **10-$(CO_2Et)_8$** appears to be even more compact. This result suggests maintenance of a compact cross-linked dendrimer after the core removal with partial or full contraction of the carboxylic acid groups. It is not consistent with formation of a flexible, unfolded structure. Elemental analysis of **10** confirmed that no nitrogen was present, and, most significantly, the UV−visible spectrum of **10** showed no detectable absorbance (i.e., less than 0.01

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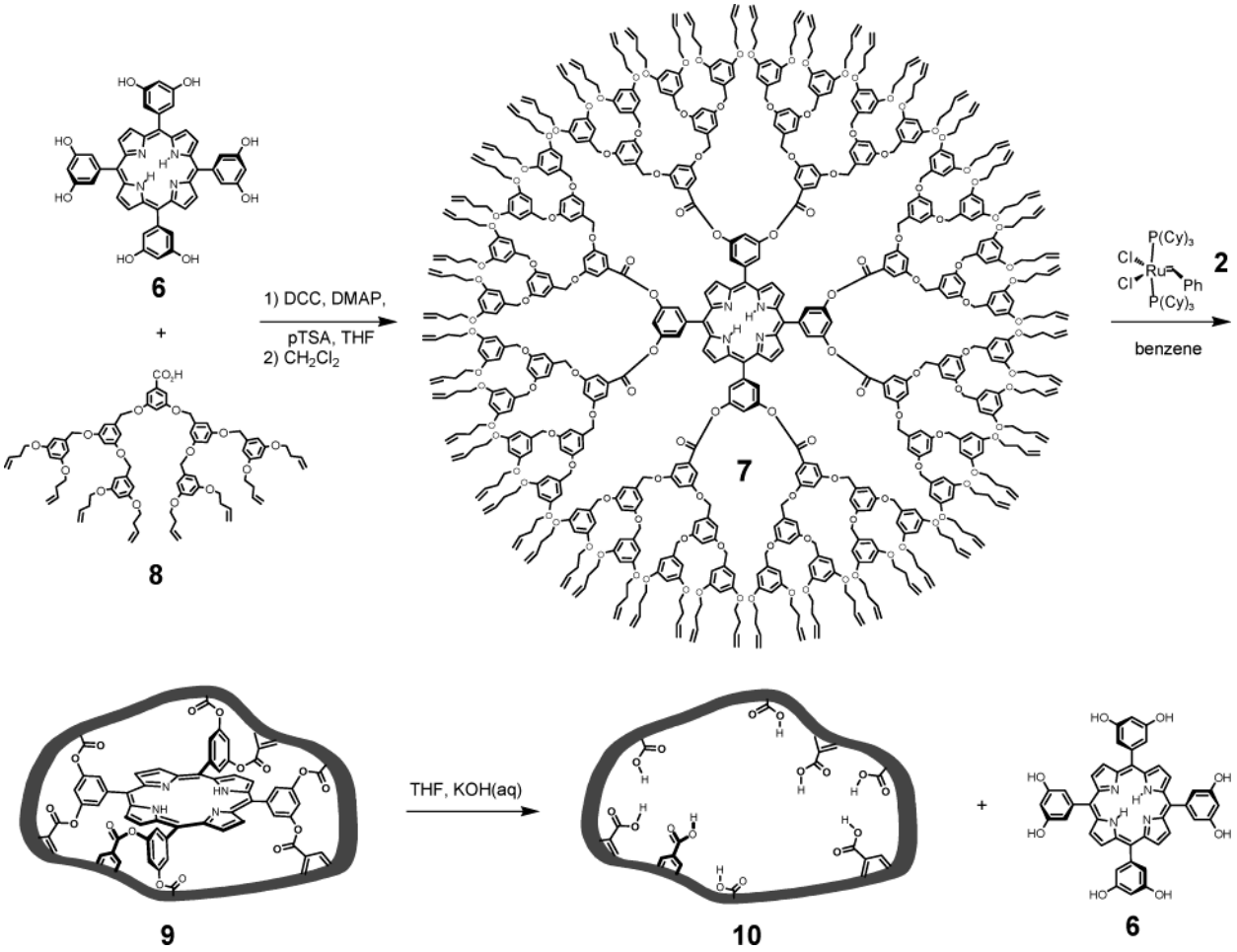
Scheme 2



absorbance, which is less than 0.1% of retained porphyrin) at 420 nm (Soret band). Thus, despite extensive cross-linking, the porphyrin template can be quantitatively removed.

Several aspects of the cross-linking reaction warrant additional comment. First, cross-links may form within or between dendritic wedges. As seen in Figure 3, there are two types of intrawedge cross-links, a−b and a−c, and two types of interwedge cross-links, a−d and a−e. Proximity likely promotes intrawedge links, whereas interwedge connections are favored statistically. Although none of the methods of characterization used is capable of directly distinguishing the cross-link isomers, if all were of type a−b and b−c, then the hydrolysis reaction of **9** to **10** would lead to fragmentation with loss of one or more cross-linked wedges. Neither the MALDI-TOF MS nor the SEC traces of the crude reaction mixture or purified **10** showed significant evidence of fragmentation. Thus, the cross-linking reaction produces at least seven cross-links between the eight dendritic wedges, seven interwedge cross-links being the minimum needed to hold the cored dendrimer together.

In the RCM reaction of **1**, it was estimated that nearly 1.7 million isomers are possible with just six cross-links. This number, which was determined by enumeration, took into account formation of both cis and trans alkenes, but neglected topological isomers and the many isomers that would be structurally untenable. Many more cross-link isomers are possible for **9** in comparison to **3**, but in both cases it is likely that only a subset of isomers is formed.

At issue are whether these isomers are kinetically or thermodynamically favored and by what mechanism is **9** able to become nearly fully cross-linked (i.e., 29−30 of 32 possible cross-links)? Molecular modeling experiments to be published elsewhere suggest that kinetic products are formed with several alkenes left dangling sufficiently far from one another that they cannot undergo the RCM reaction. Thus, a model is favored in which the reversibility of the RCM reaction allows the cross-linked dendrimer to dynamically mold itself around the porphyrin template.

Complexation Studies. In the noncovalent approach to MIPs, the ligand that is the ultimate target for binding is also used as the template in the imprinting reaction. In contrast, the target ligand for covalently synthesized MIPs may not be an appropriate template. For example, in the hydrolytic removal of template **6** from cross-linked dendrimer **9**, eight additional hydroxyl groups are added to the cored dendrimer, reducing the size of the binding cavity. Thus, as seen by the very simple analysis shown in Figure 4, a rigidly imprinted **10** would have a binding cavity too small to complex **6**, although the isomeric porphyrin **11** (Chart 1) could fit and potentially form multiple $CO_2H\cdots$ OH hydrogen bonds. The same analysis indicates that the covalent phenyl ester linkage is, to a good approximation, isosteric with a pyridine-carboxylic acid hydrogen bond (Figure 4). As a result, a series of porphyrins (**11**−**20**, Chart 1) was prepared and used to study the binding selectivity of imprinted dendrimer **10**.

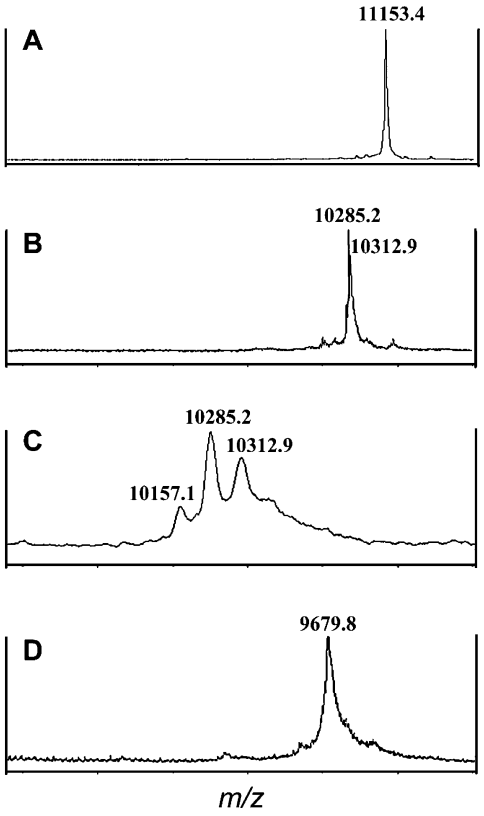


Figure 2. MALDI-TOF MS spectra of (A) porphyrin-core dendrimer **7**; (B) and (C) cross-linked dendrimer **9**; and (D) cored dendrimer **10**.

Table 1. A List of Observed Values, Peak Assignments, and Calculated Values for the Mass Spectra of **7**, **9**, and **10**

compound	observed value	peak assignment	calculated value
7	11 153	$M + H^+$	11 156.4
9	10 313	$M + H^+ - 30C_2H_4$	10 313.9
	10 285	$M + H^+ - 31C_2H_4$	10 285.9
	10 257	$M + H^+ - 32C_2H_4$	10 257.9
10	9680	$M + H^+ - 31C_2H_4 - C_{44}H_{22}N_4$	9679.2

A typical binding experiment consisted of titrating a dilute porphyrin solution with a concentrated imprinted dendrimer solution in toluene (5% EtOAc−toluene for **6** and **11**) by adding a 10^{-2} M solution of **10** to a 10^{-5} M solution of porphyrin and recording the absorbance of the Soret band region 10 min after each addition of imprinted dendrimer. Complexation of the porphyrin by the dendrimer host was signaled by a red shift of the λ_{max} of the Soret band. Factors that might produce such a red shift include a general polarity change in the environment, $\pi-\pi$ stacking, hydrogen bonding between the pyrrole nitrogen atoms and the carboxylic acid groups, and a complexation-induced deplanarization of the porphyrin ring.[31] Initial experiments using **11** indicated that the extent of the red shift was dependent both on the amount of **10** added and on the time elapsed. Similar observations were made for **12** and **14**−**16**, and in each case it appeared that the red shift occurred in two distinct phases, one fast (seconds/minutes) and one very slow (hours/days). The apparent biphasic binding kinetics is discussed in greater detail below, but the experiments described first focused on the fast binding component.

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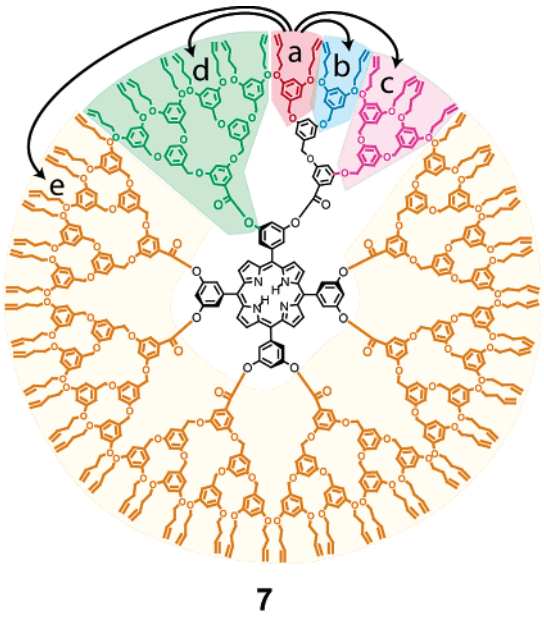


Figure 3. Dendrimer **7** with wedges and subwedges color-coded to show different types of cross-link isomers.

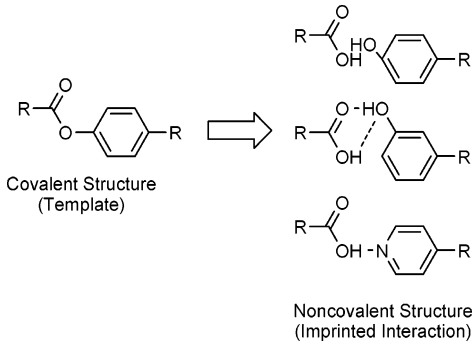
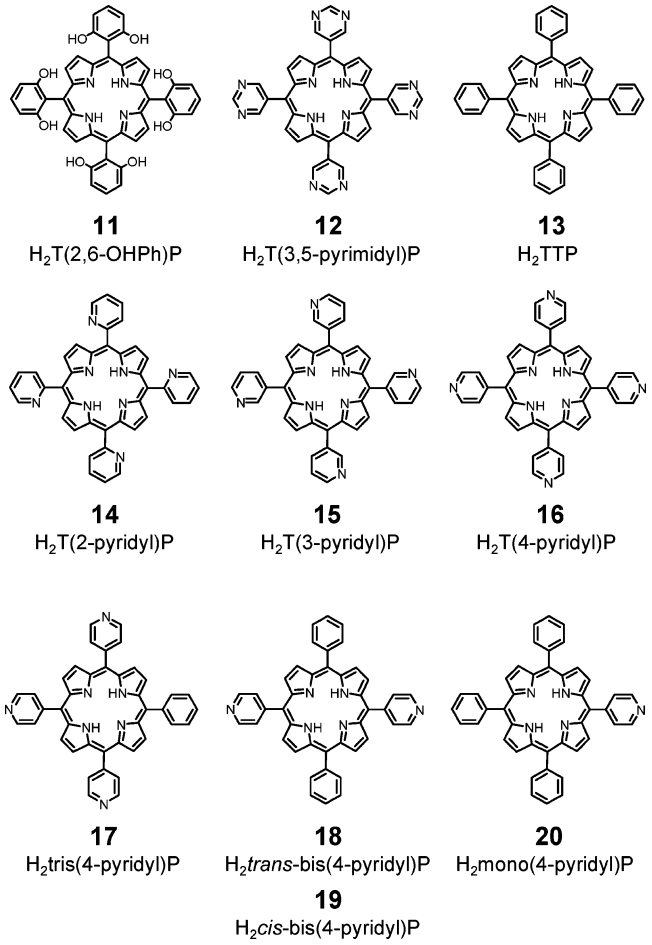


Figure 4. Schematic illustration of how covalent linkage between template and dendrimer scaffold impacts the ultimate binding interaction between imprinted dendrimer and ligand.

Several control experiments were performed that are consistent with reversible complexation of **11**, **12**, and **14**−**16** by hydrogen bonding. First, no red shift was observed with porphyrins lacking hydrogen bond donor−acceptor groups such as 5,10,15,20-tetraphenylporphyrin, **13**. The red shift observed upon addition of **10** to a solution of **11** could be fully reversed by increasing the EtOAc content from 5% to 15% (v/v) in toluene. Likewise, addition of **10** to a solution of **11** in 50% EtOAc did not produce a red shift. To demonstrate the importance of the carboxylic acid groups of **10** in the binding, the octa-ethyl ester dendrimer **10-($(CO_2Et)_8$)** was prepared by ethanolysis of **9** (K_2CO_3, toluene, ethanol, reflux). The structure of **10-($(CO_2Et)_8$)** was verified by SEC, ^{1}H NMR spectroscopy, MALDI-TOF MS, and UV−visible spectroscopy. The addition of approximately 60 equiv of **10-($(CO_2Et)_8$)** to H_2T(3-pyridyl)P (**15**) did not produce a red shift even over the course of 95 h. Likewise, addition of simple carboxylic acids did not cause a red shift of H_2T(3-pyridyl)P (**15**). Neither the addition of 640 equiv of dendron carboxylic acid **2** to a ca. 3 μM solution of H_2T(2,6-OHPh)P (**11**) in 5% EtOAc−toluene nor the addition of 2000 equiv of 4-*tert*-butyl benzoic acid to a ca. 3 μM solution of H_2T(3-pyridyl)P (**15**) in toluene led to any red shift. Finally, cored dendrimer **4** with three acid groups, which was imprinted

Chart 1



with 1,3,5-tris(hydroxymethyl)benzene, did not alter the position of the Soret band of a ca. 3 μM solution of **11** in toluene even upon addition of 49 equiv in 95 h.

The results of two additional experiments indicated that porphyrins **11**, **12**, and **14**−**16** were complexed within **10** and that its binding sites arose from an imprinting process. First, complexation of H_2T(2,6-OHPh)P (**11**) by imprinted dendrimer **10** was observed by SEC. A 5% EtOAc−toluene solution containing a 5:1 molar ratio of **10** to **11** was analyzed by analytical SEC using 5% EtOAc−toluene as the eluent. Whereas porphyrin **11** absorbs to the SEC matrix and does not elute by itself, it coelutes with imprinted dendrimer **10** (as detected at λ_{max} = 417 nm Soret band). Thus, complexation within the dendrimer protects the polar porphyrin from SEC matrix absorption during the course of its elution. A second, key experiment involved adding **10** to template **6** in 5% EtOAc−toluene. No change in the Soret band was observed upon titration of **6** with **10**. This finding supports the model presented in Figure 4 and is inconsistent with **10** being a flexible octa-acid able to complex any guest with sufficient hydrogen bond donor and acceptor groups.

To determine more quantitatively the binding profile of **10**, the titration data for porphyrins **11**−**20** (Chart 1) were analyzed using a modified form of the Drago equation: [**10**] versus [**10**]/ΔA, where ΔA is the change in absorbance upon addition of **10**.[32] The reciprocal of the intercept of this plot gives the association constant (K_{assoc}). One advantage of this approach is that the K_{assoc} values can be determined without knowledge of the concentration of the free or complexed porphyrin. To examine the fast binding component, the titrations were completed within 1 h. All gave linear plots, which, by analogy to Scatchard-type plots, indicates formation of 1:1 complexes.

Table 2. Apparent Association Constants (K_{App}) for Complexes Formed between Imprinted Dendrimer **10** and Porphyrins

porphyrin	$\Delta\lambda_{max}$[a]	K_{app} ($\times 10^4$ M)[b]
H_2T(3,5-OHPh)P (**6**)	0	<0.1
H_2T(2,6-OHPh)P (**11**)	6.8	10
H_2T(3,5-pyrimidyl)P (**12**)	0.8	5
H_2TPP (**13**)	0	<0.1
H_2T(2-pyridyl)P (**14**)	3.0	5
H_2T(3-pyridyl)P (**15**)	5.8	14
H_2T(4-pyridyl)P (**16**)	5.4	13
H_2-tris(4-pyridyl)P (**17**)	0	<0.1
H_2-*trans*-bis(4-pyridyl)P (**18**)	0	<0.1
H_2-*cis*-bis(4-pyridyl)P (**19**)	0	<0.1
H_2-mono(4-pyridyl)P (**20**)	0	<0.1
CuT(3-pyridyl)P (**15a**)	4.6	11

[a] A value of $\Delta\lambda_{max} = 0$ indicates no observed change in the absorption spectrum. [b] Upper limits on solubility prevented a more accurate upper limit from being obtained.

The association constants, which are listed in Table 2, are denoted as K_{app} because of the likely heterogeneity in **10** and time dependency of the binding. As predicted by Figure 4, H_2T-(3,5-pyrimidyl)P (**12**) is bound by **10**, and its $K_{app} = 5 \times 10^4$ M^{-1} is of the same magnitude as the value determined for the **10·15** complex. The pyridyl porphyrins **14**−**16** bind equally well despite their capacity to make only half as many hydrogen bonds as **12**. This may indicate that all eight carboxylic acids are not involved in binding H_2T(3,5-pyrimidyl)P (**12**); however, the difference must at least partially originate in the 10^4-fold higher basicity of pyridine relative to pyrimidine (pK_a 5.23 vs 1.2).[33] The K_{app} for the **10·14** complex (2-pyridyl isomer) is approximately 2-fold lower than that for the 3- and 4-pyridyl isomers **15** and **16**. Thus, there is a small degree of shape selectivity in the imprint. No binding was detected for pyridyl porphyrins **17**−**20**, showing that a minimum of four binding contacts are necessary for complexation under the conditions used in this study.

Although the K_{app} values for several of the porphyrin guests are large, one might have expected them to be even larger given that a typical benzoic acid−pyridine complex in apolar organic solvents has a $K_{assoc} \approx 10^2$ M^{-1}.[34] Several factors may be responsible for lowering the absolute porphyrin affinity exhibited by **10**. Conformational reorganization may be necessary if the empty imprint relaxes into a lower energy structure; such a state might include partial collapse of the core site through internal carboxylic acid dimerization or the internal binding of multiple water molecules. The IR spectra of **10** were inconclusive with regard to the latter possibility, but the elemental analysis did reveal the presence of multiple water molecules, presumably solvating the polar carboxylic acid groups. In studies of adenine complexation by molecular tweezers with a single "active site" carboxylic acid group, we reported that added water in chloroform led to a measurable depression in the binding constant.[35]

(32) Collman, J. P.; Brauman, J. I.; Doxsee, K. M.; Halbert, T. R.; Hayes, S. E.; Suslick, K. S. *J. Am. Chem. Soc.* **1978**, *100*, 2761−2766.
(33) Stewart R. *The Proton: Applications to Organic Chemistry*; Academic Press: Orlando, FL, 1985.
(34) Dega-Szafran, Z.; Szafran, M. *Heterocycles* **1994**, *37*, 627−659.

Dendrimer Fractionation. The observation of slow and fast binding processes may be consistent with two limiting populations of imprinted dendrimers, one that is tightly cross-linked with a somewhat inaccessible core and another that is more flexible and open. The latter properties are exactly those which would be expected for an impurity of **10** missing one or more dendron segments, and, thus, attention was focused on the ca. 5% impurity in **10** containing just six and seven dendrons (vide supra). To determine if this imperfect component was responsible for the observed two-phase binding, two series of experiments were conducted. In the first, dendrimer **10** was synthesized using a large excess of dendron **8**. The new sample of **10** obtained in this way contained significantly less hexa- and heptadendritic material. The titration of **15** with this new sample of **10**, however, was essentially identical to that with the original (Table 2).

In the second set of experiments, the hexa- and heptadendrons associated with impurities in **10** were isolated and examined directly. Thus, **6**-**Zn** was found to be significantly less reactive in the Mitsunobu esterification reaction. Thus, treatment of **6**-**Zn** with 8 equiv of **8** under the same conditions used with **6** afforded **7**-**Zn** containing a significant amount of hexa- and heptadendron product. Cross-linking of **7**-**Zn** under standard conditions gave **9**-**Zn** whose MALDI-TOF spectrum is shown in Figure 5A. The material containing predominantly six and seven dendrons was separated from the dendrimers containing mainly eight dendrons by selective absorption on a diethylenetriamine-modified polystyrene resin in benzene. The material left in solution contained mostly seven and eight dendrons (Figure 5B), while the material "trapped" on the resin and removed with 5% pyridine contained mostly six and seven dendrons (Figure 5C). The selectivity in the absorption was explained by a stronger amino group ligation to the more accessible Zn(II) center in the imperfect dendritic macromolecules. The dendrimers with six and seven dendrons were cored, resulting in "imperfect" imprinted material. When added to a toluene solution of **15**, this material, which was noticeably less soluble than previous preparations of **10**, did not induce a red shift. Therefore, it was concluded that hexa- and heptadendritic structures do not participate in porphyrin binding to a measurable extent and that the origin of biphasic binding kinetics lies elsewhere.

Binding Site Heterogeneity, Complexation Kinetics, and Cu-T(3-pyridyl)P. The incomplete reaction between **6** and **8** led to one type of heterogeneity in imprinted dendrimer **10**. A second type originates in the RCM reaction of dendrimer **7**, which can produce **9** containing a very large number of cross-link isomers (vide supra). It is possible that the slow and fast binding kinetics indicate two populations of cross-link isomers. For example, it is likely that isomers containing cross-links primarily between dendrons will be more compact and rigid with slower binding kinetics than those isomers where intradendron cross-links predominate. To examine more systematically the kinetics of binding, six 3 μM solutions of H_2T(3-pyridyl)P (**15**) containing 0.0, 0.5, 1, 1.5, 2.0, and 5.0 equiv of **10** were monitored over a period of 408 h (17 days). Shown in

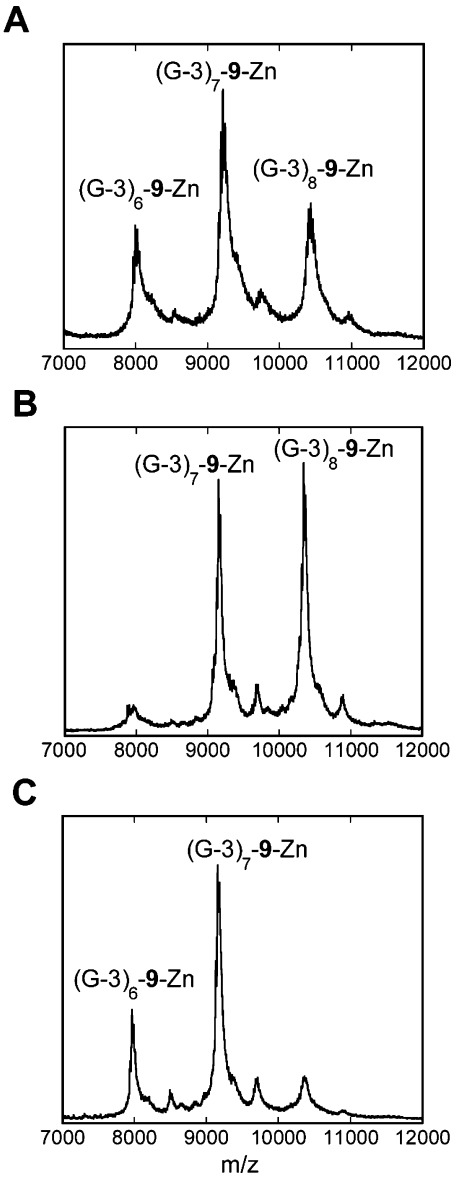


Figure 5. MALDI-TOF MS spectra of (A) a mixture of porphyrin-core dendrimer **9**-**Zn**; (B) dendrimers with mainly eight dendrons left in solution; and (C) dendrimers with mainly six and seven dendrons absorbed on the resin.

Figure 6A and B are overlaid spectra of the solutions taken at 1 and 408 h, respectively. The overlaid spectra at intermediate times similarly show an isosbestic point, whose position moves only slightly with time. These data indicate that (1) a single equivalent of **10** is able to complex most of H_2T(3-pyridyl)P, and (2) there are two classes of bound species. The former observation has important implications for the monomolecular imprinting approach in that it demonstrates that the chemistry shown schematically in Figure 1 and in detail in Scheme 2 produces **10** containing >95% effective imprinted binding sites.

To gain insight into the nature of the bound species, the 35 spectra described above (5 solutions at 0.17, 1, 3, 28, 116, 206, 408 h) were deconvoluted using model spectra for three species (Figure 6C): (1) free porphyrin (λ_{max} = 421 nm), (2) the fast forming complex (Complex I), and (3) the slow forming complex (Complex II). The model spectrum for Complex I (λ_{max} = 426 nm) was obtained 1 h after mixing 50 equiv of **10** and H_2T(3-pyridyl)P in toluene, conditions that led to >95% bound

(35) Zimmerman, S. C.; Wu, W.; Zeng, Z. *J. Am. Chem. Soc.* **1991**, *113*, 196−201. In a receptor using two carboxylic acid groups, Adrian and Wilcox reported an ca. 15% decrease in K_{assoc} and further showed a much larger, but compensating, effect on the complexation enthalpies and entropies of complexation: Adrian, J. C., Jr.; Wilcox, C. S. *J. Am. Chem. Soc.* **1991**, *113*, 678−680. It is possible with multiple carboxylic acids that the effect is cumulative.

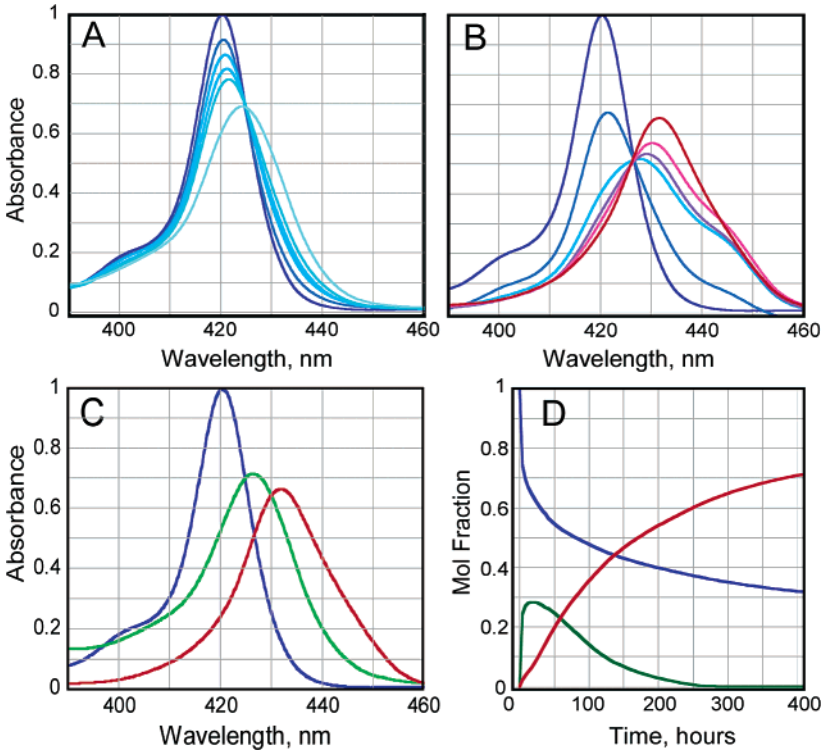


Figure 6. Overlaid spectra of the titration solutions taken at (A) 1 h and (B) 408 h; spectra of the model species (C) and the time course of the binding of the porphyrin **15** with 1 equiv of **10** (D); blue line, **15**; green line, Complex I; red line, Complex II.

porphyrin. The model spectrum for Complex II ($\lambda_{max} = 432$ nm) was that generated after equilibrating 5 equiv of **10** and H_2T(3-pyridyl)P in toluene for 408 min. The model spectra of Complexes I and II are broader than that of the free porphyrin, suggesting that each is a class of complexes that are similar in their stability, formation kinetics, and UV−visible spectra. Using the three model spectra, we deconvoluted each titration spectrum with an average deviation of 0.019 au. The apparent molar absorption coefficients determined for Complexes I and II are 2.07×10^5 and 1.92×10^5 mol^1 cm^{-1}, respectively.

The time course of the binding as revealed by the spectral deconvolution is shown in Figure 6D. Taken together, all of the results are consistent with the free porphyrin rapidly forming Complex I with an approximately 5 nm red shift. The deconvolution indicates a maximum of 30% of H_2T(3-pyridyl)P (at 10^{-5} M concentration of the porphyrin) is bound by a single equivalent of **10**, consistent with the amount expected given the $K_{app} = 1.4 \times 10^5$ M^{-1}. Over time, Complex I is replaced by Complex II whose K_{app} is about 10-fold higher, leading to 70% H_2T(3-pyridyl)P being bound. Although the two complexes may arise from heterogeneity in the imprint (i.e., separate isomers of **10**), the stronger binding, the additional 6 nm red shift observed for Complex II, and the evolution of the red shift seen in Figure 6D are particularly well explained by a slow conformational change to a tighter fitting complex.

Although there are several explanations for the observed fast and slow complex formation, a conformation change represents a likely candidate, and it is possible to speculate on its nature. Given that only four of the carboxylic acid groups of **10** are needed to complex H_2T(3-pyridyl)P, a free carboxylic acid group might hydrogen bond to an inner pyrrole nitrogen atom of the porphyrin guest. Such a significant conformational reorganization might take considerable time. Furthermore, the increased nonplanarity of the porphyrin nucleus required for the additional stabilizing hydrogen bond would explain the additional 6 nm red shift.[31] Direct support for such a mechanism is not available, but the use of CuT(3-pyridyl)P (**15-Cu**) which lacks a free pyrrole nitrogen atom completely eliminates the slow complexation process. The dramatic change in the binding course is clearly seen in the side-by-side comparison of the spectrophotometric titrations of H_2T(3-pyridyl)P and CuT(3-pyridyl)P with **10** (Figure 7). Whereas the Soret band of **15** continues to shift to longer wavelength after the initial rapid red shift, CuT(3-pyridyl)P gives $\Delta\lambda_{max} = 4.6$ nm in 10 min and then shows no additional shift. The K_{app} values determined for **10**·H_2T(3-pyridyl)P and **10**·CuT(3-pyridyl)P are quite similar (Table 2).

Imprinted Tetradendron Molecule. To examine whether a porphyrin template with only four attachment points could imprint an effective binding site containing four carboxylic acid groups, dendritic porphyrin **21** was synthesized from 5,10,15,-20-tetrakis(4-hydroxyphenyl)porphyrin and **23** (Scheme 3). Thus, **8** was treated with oxalyl chloride in THF to produce **23** in 64% yield, which was reacted directly with 5,10,15,20-tetrakis(4-hydroxyphenyl)porphyrin and DMAP in THF, affording porphyrin core dendrimer **21** in 90% yield. The cross-linking of **21** was accomplished in 79% yield using Grubbs' catalyst **2** and the same conditions described for **7**. Analysis by MALDI-TOF MS indicated an average of 15 out of 16 possible cross-links. However, upon core removal (same conditions as for **10**), MALDI-TOF mass spectra showed clear evidence of fragmentation as peaks corresponding to cross-linked dendrimers with only two and three dendrons were observed. The results suggested that the dendrons in **21** were too far apart to promote extensive interdendron cross-linking.

To favor interdendron cross-linking, the larger, fourth-generation dendron **24** was employed (Scheme 4). Dendron **24**

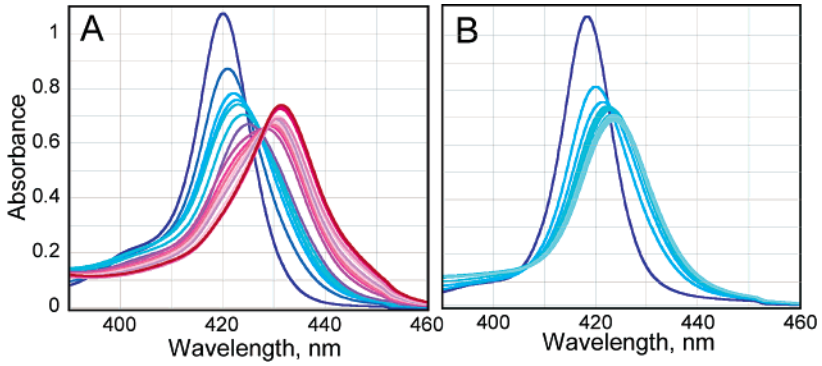
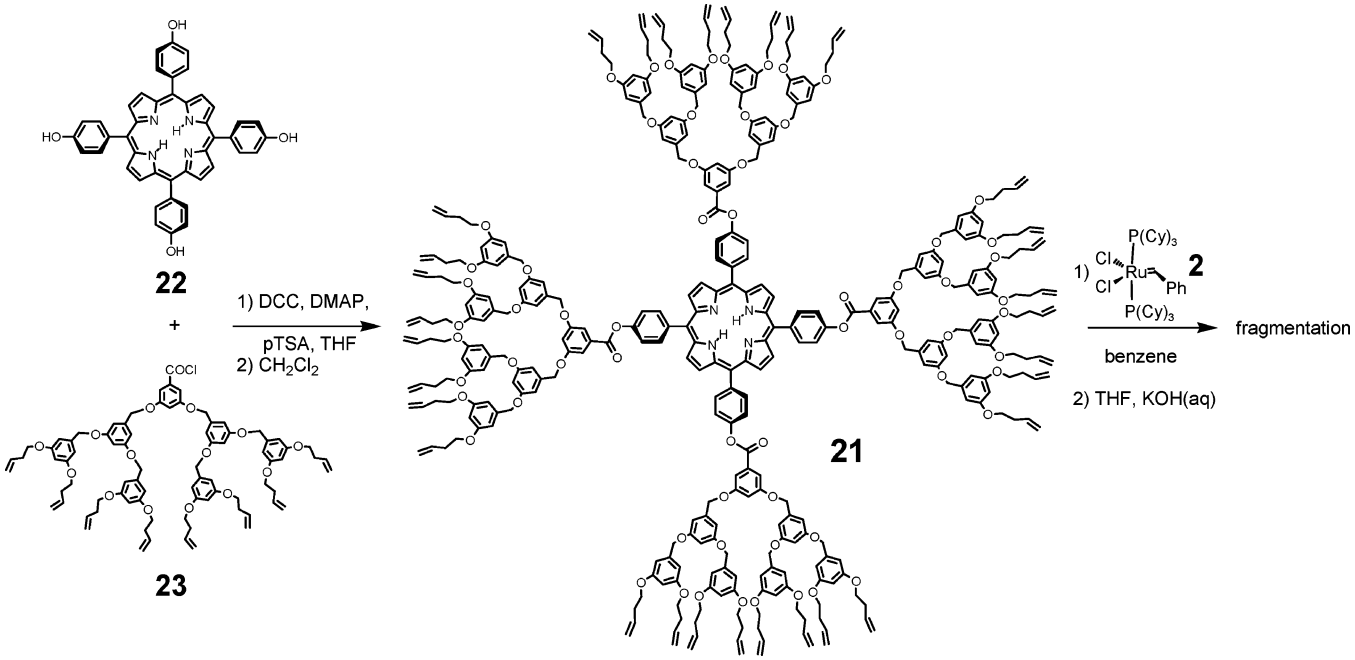


Figure 7. Overlaid spectra of the titration solutions for (A) H_2T(3-pyridyl)P and (B) Cu-T(3-pyridyl)P after 408 h; fast binding is shown in blue, and slow binding is shown in red.

Scheme 3



was prepared in 83% yield by basic hydrolysis of the corresponding methyl ester, which was prepared in 89% yield by reaction of methyl 3,5-dihydroxybenzoate with [G-3]-OH under Mitsunobu conditions. Porphyrin-core dendrimer **25** was synthesized in 46% yield by coupling **22** to **24** in THF with DPTS and DCC (same conditions as for **7**). Dendrimer **25** was cross-linked in benzene using 5 mol % Grubbs' catalyst per alkene to afford the cross-linked dendrimer **26** in 88% yield, which was hydrolyzed to produce the imprinted dendrimer **27** in 48% yield.

As in the **7** → **9** → **10** conversion, the MALDI-TOF mass spectra provide the most conclusive evidence for the success of the cross-linking and coring reactions. The observed and calculated values for the MALDI-TOF mass spectra peaks, as well as the corresponding peak assignments for **25**, **26**, and **27**, are listed in Table 3. The data indicate an average of 31 of 32 cross-links for **26**. Evidence of the removal of the porphyrin core was obtained by comparing the MALDI-TOF mass spectra of **26** and **27**. No peak corresponding to **26** was observed in the spectrum of **27**, but a new peak was present consistent with a loss of ca. 607 Da. The loss in mass was within experimental error of that expected for loss of the core ($C_{44}H_{28}N_4$, 614.7). The mass spectrum of **27** also showed that, in contrast to the cross-linked and cored product from **21**, little if any of **26** fragmented upon coring.

The pyridyl porphyrins **14**−**16** were titrated with imprinted dendrimer **27** in toluene, and their binding constants were determined (Table 4). The decrease in binding constants in the series **14**−**16** may result from a combination of the shape-selective binding and decreasing basicity of the pyridyl groups. The plots used to calculate binding constants for the complexes formed between porphyrins **14**−**16** and **27** were linear, indicating the stoichiometry of these complexes was 1:1. A control study was performed by titrating tetraphenylporphyrin (**13**) with imprinted dendrimer **27**, and no change in the Soret band position of **13** was observed even upon the addition of 66 equiv of **27**, confirming that hydrogen-bonding to the imprinted dendrimer is the cause for the red shift observed for the pyridyl porphyrins. The titration solutions of **14** and **15** with **27** were injected onto an analytical SEC column and eluted with toluene. Porphyrins **14** and **15** coeluted with the imprinted dendrimer **27**. When toluene was removed from the solution of **15** and **27** and the mixture redissolved in THF was injected into the SEC

Scheme 4

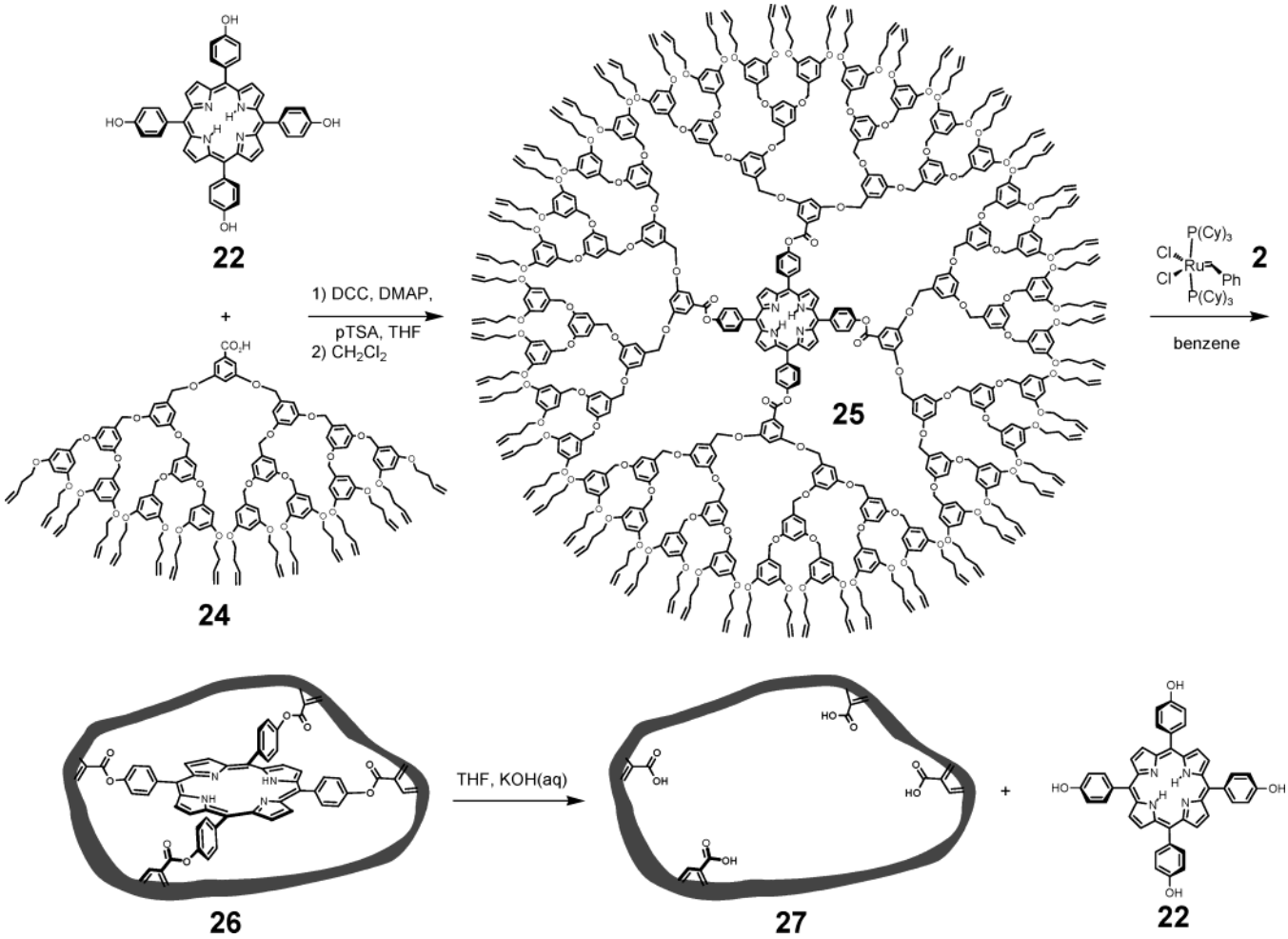


Table 3. A List of Observed Values, Peak Assignments, and Calculated Values for the Mass Spectra of **25**, **26**, and **27**

compound	observed value	peak assignment	calculated value
25	11 526	$M + H^+$	11 525.0
26	10 624	$M + H^+ - 32C_2H_4$	10 627.2
	10 653	$M + H^+ - 31C_2H_4$	10 655.3
27	10 041	$M + Na^+ - 32C_2H_4 - C_{44}H_{28}N_4$	10 034.5
	10 069	$M + Na^+ - 31C_2H_4 - C_{44}H_{28}N_4$	10 062.6

Table 4. Apparent Association Constants (K_{App}) for Complexes Formed between Imprinted Dendrimer **27** and Porphyrins

porphyrin	$\Delta\lambda_{max}$	K_{app} ($\times 10^4$ M)
H_2T(2-pyridyl)P (**14**)	1.0	3.3
H_2T(3-pyridyl)P (**15**)	2.8	1.6
H_2T(4-pyridyl)P (**16**)	1.6	0.9

column, the porphyrin **15** eluted significantly later than the imprinted dendrimer **27**.

Conclusions

Described herein is a new strategy to make synthetic hosts that combines elements of the traditional polymer imprinting and dynamic combinatorial library approaches. There are several appealing features of this monomolecular imprinting strategy. The first is the use of the RCM reaction, which forms robust carbon−carbon double-bond cross-links but is nonetheless reversible. The ability to equilibrate cross-link isomers potentially allows the dendritic framework to reach a lowest-energy "mold" around the template. Perhaps more importantly this strategy produces soluble and sizable macromolecular hosts ($M_w \approx 10$ kDa) but with a single imprinted site per molecule. Although there was no strong evidence of binding site heterogeneity in the present system, in cases where mixed imprints do arise, the potential exists for fractionation. In this regard, the ability to select hosts based on binding kinetics, selectivity, or affinity would be quite powerful.

In conventional polymer imprinting, removing the template remains a challenge. Retained template has been shown to be a serious obstacle to trace analysis applications[36] and to be involved in apparent chiral recognition exhibited by imprinted polymers.[8] In the two cases described here, the template was quantitatively removed. Another significant finding is that 1 equiv of H_2T(3-pyridyl)P, **15**, was nearly fully complexed by a single equivalent of **10**, indicating that almost all of the imprints were effective. Improvements in affinity and shape selectivity are clearly needed but will come as the structure of the dendron is tuned to provide a greater degree of rigidity. In this respect, there are limitless variations possible, and one can even envision highly rigid imprints with entry and exit channels designed into the system.

(36) Venn, R. F.; Goody, R. J. In *Drug Development Assay Approaches Including Molecular Imprinting and Biomarkers*; Reid, E., Hill, H. M., Wilson, I. D., Eds.; Royal Society of Chemistry: Cambridge, U.K., 1998; pp 13−20.

The cross-linking of **7** and **25** was performed under high dilution conditions that favored intramolecular cross-linking but made it difficult to scale-up the preparations and obtain significant quantities of the imprinted hosts. It is possible to overcome this limitation given the recent finding that alkene groups within the branching units of a dendrimer can avoid intermolecular cross-linking at significantly higher concentrations.[37] One of the advantages of using dendrimers for imprinting is in their monodispersity, which facilitates characterization. For example, in the current work, this allowed the number of cross-links to be determined. Ultimately, more rapid dendrimer syntheses,[38] or even hyperbranched polymerizations[39] or single-step syntheses of related macromolecules, might be applied. Along with efforts in these areas, our current attention is focused on expanding the types of binding contacts used, developing new dendrons, and integrating reporter groups into the binding site.

Experimental Section

General. All of the reactions described below were run under a dry nitrogen atmosphere, and all temperatures reported as reaction or drying conditions were the temperatures of the heating medium. All solvents and reagents were of reagent quality, purchased commercially, and used without further purification, except as noted below. The following solvents were freshly distilled prior to use: diethyl ether (Et_2O) and tetrahydrofuran (THF) from sodium-benzophenone; ethyl acetate (EtOAc), methylene chloride (CH_2Cl_2), and toluene from calcium hydride; benzene from sodium; and methanol (MeOH) from calcium sulfate. Acetone and *N*,*N*-dimethylformamide (DMF) were stored over 4 Å molecular sieves. 3,5-Dihydroxybenzoic acid methyl ester,[40] 5,-10,15,20-tetrakis(3′,5′-dihydroxyphenyl)porphyrin (**6**),[41] 5,10,15,20-tetrakis(2′,6′-dihydroxyphenyl) porphyrin (**11**),[42] 5,10,15,20-tetrakis(2′-pyridyl)porphyrin (**14**),[43] 5,10,15,20-tetrakis(3′-pyridyl)porphyrin (**15**),[43] pyrimidine-5-carboxaldehyde,[44] and 5,10,15,20-tetrakis(phenyl)porphyrin (**13**)[45] were synthesized according to published procedures.

Thin-layer chromatography was performed on 0.2 mm silica 60 coated plastic sheets (EM Science) with F_{254} indicator. Flash chromatography was performed on Merck 40−63 μm silica gel. Solvent ratios for the purification of compounds by flash chromatography are reported as percent volume (v/v). Dimensions of the columns used for the flash chromatography are reported as (width × height).

All nuclear magnetic resonance (NMR) spectra were acquired in the Varian-Oxford Center for Excellence in NMR Spectroscopy (VOICE) laboratory at the University of Illinois, Urbana-Champaign. All ^{1}H and ^{13}C NMR spectra were recorded on a Varian Unity 500 spectrometer (^{1}H, 500 MHz; ^{13}C, 125.7 MHz). Heteronuclear multiple quantum coherence (HMQC) and heteronuclear multiple bond correlation (HMBC) NMR experiments were performed on a Varian Unity Inova 500NB spectrometer (^{1}H, 500 MHz; ^{13}C, 125.7 MHz). ^{1}H NMR coupling constants are reported in hertz (Hz). The ^{1}H NMR chemical shifts were referenced to the residual protio solvent peak at 7.26 ppm in chloroform-*d* ($CDCl_3$), 5.32 ppm in methylene chloride-d_2 (CD_2Cl_2), and 2.09 in toluene-d_8. The ^{13}C NMR chemical shifts were referenced to the solvent peak at 77.0 ppm in $CDCl_3$ and 53.8 ppm in CD_2Cl_2. Unless stated otherwise, the ^{1}H and ^{13}C NMR spectra were acquired in $CDCl_3$.

All mass spectra were obtained in the Mass Spectrometry Laboratory, School of Chemical Sciences, University of Illinois, Urbana-Champaign. Mass spectra were measured by the technique of field desorption (FD) and field ionization (FI) on a Finnigan-MAT 731 spectrometer, chemical ionization (CI) and electron impact (EI) on a VG 70-VSE spectrometer, and fast atom bombardment (FAB) on a VG ZAB-SE spectrometer. Mass spectra were measured by matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) on a PerSeptive Biosystems Voyager DE-STR spectrometer; 2-(4-hydroxyphenylazo)benzoic acid was used as the matrix to obtain the MALDI-TOF mass spectrum.

Infrared spectra were recorded on a Mattson Galaxy Series FTIR 5000 spectrometer and are reported in cm^{-1}. Ultraviolet/visible (UV/vis) absorbance spectra were recorded on a Hitachi U-3300 spectrophotometer using a tungsten lamp light source, and λ_{max} are reported in nanometers. Elemental analyses were performed at the Microanalysis Laboratory, School of Chemical Sciences, University of Illinois, Urbana-Champaign.

Analytical size-exclusion chromatography (SEC) was performed on a Waters Styragel HR3 column (molecular weight range 500−30 000) coupled with a Water 410 differential refractometer and PD2000 dual angle laser light scattering detectors or with an Hitachi L-4000H UV detector using an Hitachi L-6000 pump. Molecular weights (M_w) calculated from SEC were based on using polystyrene standards. Preparative SEC was carried out on Bio-Beads S-X1 Beads gel permeation gel 200−400 mesh (Bio-Rad Laboratories), which has exclusion limits from 400 to 14 000.

In addition to a compound name, dendrons and dendrimers are designated using the notation [G-*x*]-core, where [G-*x*] refers to the generation number ($x = 1$, 2, 3, or 4), and core refers to the functional group at the focal point of the dendron or the molecule used as the core to make the dendrimer. Because of the complexity of structure, the cross-linked and cored dendrimers are named with the word cross-linked or cored preceding the shorthand name for that compound. This shorthand notation is used throughout the text to refer to these compounds.

The titration data were analyzed by plotting [ID] versus [ID]/ΔA, where [ID] is the imprinted dendrimer concentration and ΔA is the change in absorbance upon addition of **10** or **27**. This method allows association constants to be determined by finding the line intercept that gives $1/K_{app}$ and does not require knowledge of the concentration of the free or complexed porphyrin. The titrations were all completed within 1 h and all gave linear plots. As with other Scatchard-type plots, linearity indicates the formation of 1:1 complexes.

3,5-Bis(3-buten-1-oxy)benzoic Acid Methyl Ester ([G-1]-CO_2Me). To a mixture of 75.0 g (1.04 mol) of 3-buten-1-ol, 79.4 g (472 mmol) of 3,5-dihydroxybenzoic acid methyl ester, and 310.0 g (1.18 mol) of triphenylphosphine (PPh_3) in 1.0 L of THF cooled to 0 °C with an ice/water bath was added dropwise a solution of 262.2 g (1.51 mol) of diethyl azodicarboxylate (DEAD) in 3.0 L of THF. The reaction was allowed to warm to room temperature and stirred until the reaction was complete as indicated by TLC. The reaction was stopped by adding 700 mL of water and removing the THF under reduced pressure. The resulting aqueous layer was extracted with Et_2O (3 × 2 L). The organic layers were combined and washed with an equal volume of 2.5 M aqueous potassium hydroxide (KOH) and an equal volume of water. The organic layers were dried over sodium sulfate and filtered. The filtrate was reduced to one-third of its volume and placed in the freezer (−17 °C) overnight. A white precipitate (triphenylphosphine oxide) was filtered off and washed with cold Et_2O. The resulting filtrate was concentrated under reduced pressure. Approximately 25−30 g of the

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crude product was purified at a time by column chromatography. The crude product was loaded onto a silica gel plug (8 × 12 cm) and eluted with 1.5 L of petroleum ether (PE), 2.0 L of 5% EtOAc/95% PE, and 1.0 L of 10% EtOAc/90% PE. The product was dried under vacuum (0.1 mmHg, 45 °C) overnight to afford 109.9 g (84%) of [G-1]-CO_2-Me as a clear, colorless oil. ^{1}H NMR: δ 7.16 (d, 2H, J = 2.4), 6.64 (t, 1H, J = 2.4), 5.88 (ddt, 2H, J = 17.2, 10.3, 6.8), 5.16 (ddt, 2H, J = 17.2, J = 1.8, 1.5), 5.11 (ddt, 2H, J = 10.3, J = 1.8, 1.3), 4.01 (t, 4H, J = 6.6), 3.88 (s, 3H), 2.52 (dtdd, 4H, J = 6.8, 6.6, 1.5, 1.3). ^{13}C NMR: 166.8, 159.9, 134.3, 131.9, 117.1, 107.8, 106.7, 67.4, 52.2, 33.5. IR (neat): 3070, 2980, 1724, 1642, 1597, 1169, 1057, 996, 918. MS (FAB): m/z 277.1 (M + H$^+$). Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.55; H, 7.30. Found: C, 69.41; H, 7.12.

3,5-Bis(3-buten-1-oxy)benzyl Alcohol ([G-1]-OH). To a suspension of 24.6 g (649 mmol) of lithium aluminum hydride (LAH) in 500 mL of THF cooled to 0 °C with an ice/water bath was added dropwise a solution of 109.8 g (397 mmol) of [G-1]-CO_2Me in 1.5 L of THF. The suspension was allowed to warm to room temperature and stirred until no starting material remained by TLC. The reaction was stopped by quenching the excess hydride with 200 mL of water and neutralizing the pH with 200 mL of 3 M aqueous hydrochloric acid (HCl). The THF was removed under reduced pressure, and the resulting aqueous layer was extracted with Et_2O (4 × 750 mL). The combined organic layers were washed with water, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The product was purified by vacuum distillation (140−150 °C, 0.2 mmHg) to afford 96.4 g (98%) of [G-1]-OH as a clear, colorless oil. ^{1}H NMR: δ 6.51 (d, 2H, J = 2.2), 6.38 (t, 1H, J = 2.2), 5.89 (ddt, 2H, J = 17.2, 10.3, 6.8), 5.17 (ddt, 2H, J = 17.2, 1.8, 1.5), 5.10 (ddt, 2H, J = 10.3, 1.8, 1.3), 4.60 (s, 2H), 3.99 (t, 4H, J = 6.6), 2.53 (dtdd, 4H, J = 6.8, 6.6, 1.5, 1.3), 1.87 (bs, 1H). ^{13}C NMR: 160.3, 143.3, 134.4, 117.1, 105.3, 100.7, 67.2, 65.3, 33.6. IR (neat): 3370 (bs), 3077, 1642, 1597, 1167, 1057, 992, 917. MS (FAB): m/z 249.2 (M + H$^+$). Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.27; H, 8.35.

3,5-Bis[3,5-bis(3-buten-1-oxy)benzyloxy]benzoic Acid Methyl Ester ([G-2]-CO_2Me). To a mixture of 96.0 g (387 mmol) of [G-1]-OH, 29.6 g (176 mmol) of 3,5-dihydroxybenzoic acid methyl ester, and 115.6 g (441 mmol) of PPh_3 in 500 mL of THF cooled to 0 °C with an ice/water bath was added dropwise a solution of 99.6 g (572 mmol) of DEAD in 1.5 L of THF. The reaction was allowed to warm to room temperature and stirred until the reaction was complete as indicated by TLC. The reaction was stopped by adding 500 mL of water and removing the THF under reduced pressure. The resulting aqueous layer was extracted with Et_2O (4 × 750 mL). The combined organic layers were washed with an equal volume of 2.5 M aqueous KOH and an equal volume of water. The organic layers were dried over sodium sulfate and filtered. The filtrate was reduced to one-third its volume and placed in the freezer (−17 °C) overnight. A white precipitate (triphenylphosphine oxide) was filtered off and washed with cold Et_2O. The resulting filtrate was concentrated under reduced pressure. Approximately 25−30 g of the crude product was purified at a time by column chromatography. The crude product was loaded onto a silica gel plug (8 × 12 cm) and eluted with 1.0 L of PE, 3.0 L of 5% EtOAc/95% PE, and 3.0 L of 10% EtOAc/90% PE. The product was dried under vacuum (0.15 mmHg, 68 °C) overnight to afford 94.0 g (85%) of [G-2]-CO_2Me as a clear, colorless oil. ^{1}H NMR: δ 7.29 (d, 2H, J = 2.4), 6.79 (t, 1H, J = 2.4), 6.58 (d, 4H, J = 2.2), 6.43 (t, 2H, J = 2.2), 5.90 (ddt, 4H, J = 17.2, 10.3, 6.8), 5.18 (ddt, 4H, J = 17.2, 1.8, 1.5), 5.11 (ddt, 4H, J = 10.3, 1.8, 1.3), 4.99 (s, 4H), 4.01 (t, 8H, J = 6.6), 3.91 (s, 3H), 2.54 (dtdd, 8H, J = 6.8, 6.6, 1.5, 1.3). ^{13}C NMR: 166.8, 160.3, 159.7, 138.7, 134.4, 132.0, 117.1, 108.4, 107.2, 105.9, 101.1, 70.2, 67.3, 52.3, 33.6. IR (neat): 3094, 2980, 1734, 1656, 1597, 1174, 1062, 997, 924. MS (FD): m/z 628.3 (M$^+$). Anal. Calcd for $C_{38}H_{44}O_8$: C, 72.59; H, 7.05. Found: C, 72.64; H, 6.84.

3,5-Bis[3,5-bis(3-buten-1-oxy)benzyloxy]benzyl Alcohol ([G-2]-OH). To a suspension of 6.29 g (166 mmol) of LAH in 250 mL of THF cooled to 0 °C with an ice/water bath was added dropwise a solution of 64.5 g (103 mmol) of [G-2]-CO_2Me in 750 mL of THF. The suspension was allowed to warm to room temperature and stirred until no starting material remained by TLC. The reaction was stopped by quenching the excess hydride with 150 mL of water and neutralizing the pH with 130 mL of 1 M aqueous HCl. The THF was removed under reduced pressure, and the resulting aqueous layer was extracted with Et_2O (3 × 1.5 L). The combined organic layers were washed with water, dried over sodium sulfate, filtered, and concentrated under reduced pressure. Approximately 20 g of the crude product was purified at a time by column chromatography. The crude product was loaded onto a silica gel column (8 × 26 cm) and eluted with 20% EtOAc/80% PE. The product was dried under high vacuum (0.2 mmHg, 75 °C) overnight to afford 54.8 g (89%) of [G-2]-OH as a clear, colorless oil. ^{1}H NMR: δ 6.61 (d, 2H, J = 2.2), 6.57 (d, 4H, J = 2.2), 6.53 (t, 1H, J = 2.2), 6.41 (t, 2H, J = 2.2), 5.90 (ddt, 4H, J = 17.2, 10.3, 6.8), 5.17 (ddt, 4H, J = 17.2, 1.8, 1.5), 5.11 (ddt, 4H, J = 10.3, 1.8, 1.3), 4.96 (s, 4H), 4.63 (d, 2H, J = 6.2), 4.00 (t, 8H, J = 6.6), 2.53 (dtdd, 8H, J = 6.8, 6.6, 1.5, 1.3), 1.57 (t, 1H, J = 6.2). ^{13}C NMR: 160.3, 160.1, 143.5, 139.1, 134.4, 117.1, 105.9, 105.7, 101.3, 101.0, 70.0, 67.3, 65.3, 33.6. IR (neat): 3425 (bs), 3077, 2979, 1641, 1599, 1166, 1054, 993, 918. MS (FD): m/z 600.3 (M$^+$). Anal. Calcd for $C_{37}H_{44}O_7$: C, 73.98; H, 7.38. Found: C, 73.92; H, 7.18.

3,5-Bis{3,5-bis[3,5-bis(3-buten-1-oxy)benzyloxy]benzyloxy}-benzoic Acid Methyl Ester ([G-3]-CO_2Me). To a mixture of 49.3 g (82.1 mmol) of [G-2]-OH, 6.28 g (37.3 mmol) of 3,5-dihydroxybenzoic acid methyl ester, and 24.5 g (93.5 mmol) of PPh_3 in 200 mL of THF cooled to 0 °C with an ice/water bath was added dropwise a solution of 20.2 g (116 mmol) of DEAD in 300 mL of THF. The reaction was allowed to warm to room temperature and stirred until the reaction was complete as indicated by TLC. The reaction was stopped by adding 150 mL of water and removing the THF under reduced pressure. The resulting aqueous layer was extracted with Et_2O (3 × 500 mL). The combined organic layers were washed with an equal volume of 2.5 M aqueous KOH and an equal volume of water. The organic layers were dried over sodium sulfate and filtered. The filtrate was reduced to one-third its volume and placed in the freezer (−17 °C) overnight. A white precipitate (triphenylphosphine oxide) was filtered off and washed with cold Et_2O. The resulting filtrate was concentrated under reduced pressure. Approximately 40 g of the crude product was purified at a time by column chromatography. The crude product was loaded onto a silica gel column (10 × 25 cm) and eluted with 7.0 L of 20% EtOAc/80% PE and 3.0 L of 30% EtOAc/70% PE. The product was dried under vacuum (0.1 mmHg, 75 °C) overnight to afford 44.7 g (90%) of [G-3]-CO_2Me as a clear, colorless oil. ^{1}H NMR: δ 7.29 (d, 2H, J = 2.4), 6.80 (t, 1H, J = 2.4), 6.68 (d, 4H, J = 2.20), 6.58 (d, 8H, J = 2.4), 6.57 (t, 2H, J = 2.2), 6.42 (t, 4H, J = 2.4), 5.90 (ddt, 8H, J = 17.2, 10.3, 6.6), 5.16 (ddt, 8H, J = 17.2, 1.8, 1.5), 5.10 (ddt, 8H, J = 10.3, 1.8, 1.3), 5.01 (s, 4H), 4.96 (s, 8H), 4.00 (t, 16H, J = 6.8), 3.91 (s, 3H), 2.53 (tddd, 16H, J = 6.8, 6.6, 1.5, 1.3). ^{13}C NMR: 166.8, 160.3, 160.2, 159.7, 139.0, 138.8, 134.4, 132.1, 117.1, 108.4, 107.2, 106.4, 105.9, 101.7, 101.0, 70.2, 70.1, 67.3, 52.3, 33.6. IR (neat): 3078, 2979, 1721, 1641, 1597, 1166, 1054, 994, 917. MS (MALDI-TOF): m/z 1355.0 (M + Na$^+$). SEC (toluene) Calcd M_w = 1338. Anal. Calcd for $C_{82}H_{92}O_{16}$: C, 73.85; H, 6.95. Found: C, 74.16; H, 7.08.

3,5-Bis-{3,5-bis[3,5-bis(3-buten-1-oxy)benzyloxy]benzyloxy}-benzoic Acid ([G-3]-CO_2H) (8). A 40% (w/w) aqueous KOH solution was made by dissolving 2.48 g (38.0 mmol) of KOH in 4 mL of water. This solution was added to a solution of 4.85 g (3.64 mmol) of [G-3]-CO_2Me dissolved in 25 mL of THF. Ethanol (20 mL) was added to make the reaction mixture homogeneous. The reaction was stirred at reflux until no starting material remained by TLC. The reaction was stopped by adding concentrated aqueous HCl to make the reaction mixture acidic (pH < 3). The solvents were removed under reduced pressure. The remaining residue was partitioned between 100 mL of water and 100 mL of CH_2Cl_2. The aqueous layer was extracted with

CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with water, dried over sodium sulfate, and filtered. The resulting filtrate was concentrated under reduced pressure. The product was loaded onto a silica gel column (10 × 12 cm) and eluted with 1% acetic acid/30% EtOAc/69% PE. The product was dried under vacuum (0.15 mmHg, 100 °C) overnight to afford 4.08 g (85%) of **8** as a beige oil. ^{1}H NMR: δ 7.35 (d, 2H, J = 2.4), 6.84 (t, 1H, J = 2.4), 6.68 (d, 4H, J = 2.2), 6.57 (d, 8H, J = 2.2), 6.56 (t, 2H, J = 2.2), 6.42 (t, 4H, J = 2.2), 5.89 (ddt, 8H, J = 17.2, 10.3, 6.6), 5.16 (ddt, 8H, J = 17.2, 1.8, 1.5), 5.10 (ddt, 8H, J = 10.3, 1.8, 1.3), 5.01 (s, 4H), 4.96 (s, 8H), 4.00 (t, 16H, J = 6.8), 2.52 (tddd, 16H, J = 6.8, 6.6, 1.5, 1.3). ^{13}C NMR: 171.2, 160.3, 160.2, 159.8, 139.0, 138.7, 134.4, 131.1, 117.1, 108.9, 108.0, 106.5, 105.9, 101.8, 101.0, 70.2, 70.1, 67.3, 33.6. IR (neat): 3196, 3078, 2977, 1692, 1642, 1594, 1163, 1055, 993, 917. MS (MALDI-TOF): m/z 1342.7 ($M + Na^+$). Anal. Calcd for $C_{81}H_{90}O_{16}$: C, 73.73; H, 6.87. Found: C, 73.86; H, 6.80.

5,10,15,20-Tetrakis{3,5-bis[3,5-bis(3,5-bis(3,5-bis(3-buten-1-oxy)-benzyloxy)benzyloxy)benzoyloxy]phenyl}porphyrin ([G-3]$_8$-T(3,5-OHPh)P) (7). [G-3]-CO_2H (**8**) (283 mg, 215 μmol), 13.2 mg (17.8 μmol) of 5,10,15,20-tetrakis(3′,5′-dihydroxyphenyl)porphyrin (H_2T(3,5-OHPh)P) **6**, 519 mg (2.5 mmol) of DCC, 78.6 mg (643 μmol) of DMAP, and 118 mg (621 μmol) of *p*-toluenesulfonic acid were dissolved in 15 mL of THF. The reaction was stirred overnight at room temperature. The reaction mixture was vacuum filtered to remove the DCU formed. The filtrate was concentrated under reduced pressure and dissolved in 15 mL of CH_2Cl_2. To this solution, 510 mg (2.5 mmol) of DCC, 75.8 mg (620 μmol) of DMAP, and 117 mg (615 μmol) of *p*-toluenesulfonic acid were added. This solution was stirred at room temperature and monitored by TLC and SEC. The reaction was determined to be complete after 3 days. The reaction mixture was vacuum filtered to remove the DCU, and the resulting filtrate was concentrated under reduced pressure. The remaining residue was loaded onto a silica gel column (4 × 15 cm) and eluted with 30% EtOAc/PE. The product was further purified by loading it onto a SEC column and eluting it with toluene. The product was dried overnight under vacuum (1.0 mmHg, 98 °C) to afford 107 mg (54%) of **7** as a deep red oil. ^{1}H NMR (CD_2Cl_2): δ 9.22 (s, 8H), 8.15 (d, 8H, J = 2.1), 7.75 (t, 4H, J = 2.1), 7.54 (d, 16H, J = 2.1), 6.81 (t, 8H, J = 2.1), 6.64 (d, 32H, J = 2.1), 6.48 (m, 80H), 6.31 (t, 32H, J = 2.1), 5.81 (ddt, 64H, J = 17.2, 10.2, 6.7), 5.07 (ddt, 64H, J = 17.2, 1.8, 1.5), 5.01 (ddt, 64H, J = 10.2, 1.8, 1.2), 4.98 (s, 32H), 4.87 (s, 64H), 3.88 (t, 128H, J = 6.7), 2.42 (tddd, 128H, J = 6.7, 6.7, 1.5, 1.2), −2.86 (s, 2H). ^{13}C NMR (CD_2Cl_2): 165.1, 160.7, 160.5, 160.4, 150.3, 144.2, 139.6, 139.3, 135.0, 131.6, 126.3, 18.9, 17.0, 109.3, 108.1, 106.7, 106.2, 101.9, 101.0, 70.5, 70.3, 67.6, 33.9. MS (MALDI-TOF): m/z 1153.4 ($M + H^+$). SEC (toluene) Calcd M_w = 8155. UV/vis (CH_2Cl_2) λ_{max} = 275.0, 420.5 (Soret). Anal. Calcd for $C_{692}H_{734}N_4O_{128}$: C, 74.51; H, 6.63; N, 0.50. Found: C, 74.56; H, 6.41; N, 0.48.

Cross-linked [G-3]$_8$-T(3,5-OHPh)P (9). To a solution of 497 mg (44.6 μmol) of **7** in 4.4 L of benzene was added 99.6 mg (120 μmol) of the Grubbs' catalyst **2**. The reaction was stirred at room temperature for 22 h. The benzene was removed under reduced pressure. The crude product was loaded onto a silica gel plug (4 × 6 cm) and eluted with 400 mL of 50% PE/50% CH_2Cl_2 and 400 mL of 5% EtOAc/CH_2Cl_2. The EtOAc/CH_2Cl_2 solution was concentrated under reduced pressure. The product was dried overnight under vacuum (2 mmHg, 85 °C) to afford 409 mg (89%) of **9** as a dark red powder. ^{1}H NMR (d_8-toluene): δ 9.17 (bs, 8H), 8.15 (bs, 8H), 7.70 (bs, 20H), 6.59 (bs, 152H), 5.78 (bs, ∼4H), 5.51 (bs, ∼60H), 5.04 (bs, ∼8H), 4.82 (bs, 96H), 3.70 (bs, 128H), 2.33 (bs, 128H). MS (MALDI-TOF): m/z 10 257.1 ($M + H^+ - 32C_2H_4$), 10 285.2 ($M + H^+ - 31C_2H_4$), 10 312.3 ($M + H^+ - 30C_2H_4$). SEC (toluene) Calcd M_w = 5509. UV/vis (CH_2Cl_2) λ_{max} = 276.0, 421.0 (Soret).

Imprinted [G-3]$_8$-T(3,5-OHPh)P (10). To a solution of 102 mg (9.88 μmol) of **9** dissolved in 15 mL of THF was added 10 mL of 2.5 M aqueous KOH. The reaction was stirred vigorously at reflux until the reaction was complete by TLC. The reaction was stopped by removing the THF under reduced pressure. The resulting aqueous layer was extracted with $CHCl_3$ (3 × 25 mL). The combined organic layers were washed with 1 M aqueous HCl, washed with water, and concentrated under reduced pressure. The product was dried under vacuum (0.2 mmHg, 70 °C) to afford 41.5 mg (43%) of **10** as a beige powder. ^{1}H NMR: δ 7.23 (bs, 16H), 6.51 (bs, 152H), 5.86 (bs, ∼4H), 5.60 (bs, ∼60H), 5.12 (bs, ∼8H), 4.86 (bs, 96H), 3.92 (bs, 128H), 2.45 (bs, 128H). MS (MALDI-TOF): m/z 9679.8 ($M + H^+ - 31C_2H_4 - C_{44}H_{22}N_4$). SEC (toluene) Calcd M_w = 4656. Anal. Calcd for $C_{588}H_{600}O_{128}$: C, 72.70; H, 6.22; N, 0.00; Ru, 0.00. Found: C, 70.83; H, 6.19; N, 0.00; Ru, 0.00.

5,10,15,20-Tetrakis(3′,5′-pyrimidyl)porphyrin (12). Pyrimidine-5-carboxaldehyde (245 mg, 2.27 mmol) and 160 μL (2.31 mmol) of freshly distilled pyrrole were added to 12 mL of refluxing propionic acid. The solution quickly turned black and was maintained at reflux for 1 h. The reaction mixture was cooled, and the propionic acid was removed under reduced pressure to give a tarry residue. The resulting residue was partitioned between water and $CHCl_3$. The aqueous layer was extracted with $CHCl_3$. The organic layers were combined and concentrated under reduced pressure. The resulting residue was loaded onto a silica gel column and eluted with 50% $CHCl_3$/50% acetone. The second, more intense band was collected and concentrated under reduced pressure. The product was dried under vacuum to afford 2.8 mg (1%) of **12** as a purple solid. ^{1}H NMR: δ 9.72 (s, 4H), 9.59 (s, 8H), 8.94 (s, 8H), −2.87 (s, 2H). MS (FAB): m/z 623.4 ($M + H^+$). UV/vis (chloroform) λ_{max} = 420.0 (Soret), 515.5, 549.5, 590.5, 646.0.

Mixed Porphyrin Condensation. Pyrrole (12.5 mL, 180 mmol) was added dropwise to a refluxing solution of benzaldehyde (14.0 mL, 138 mmol) and pyridine-4-carboxaldehyde (6.0 mL, 63.0 mmol) in propionic acid (500 mL). The solution quickly changed color from yellow to black. The solution was stirred at reflux for 1.5 h. The reaction flask was cooled in an ice/water bath. Diethylene glycol (350 mL) was added to the cooled reaction solution. The solution was refrigerated overnight. The purple precipitate that formed was isolated by vacuum filtration. The solid was washed with MeOH. The crude product mixture (1.25 g) was loaded on a silica gel column and eluted with $CHCl_3$. The following compounds were isolated from the column in this order: 5,10,15,20-tetrakis(phenyl)porphyrin (**13**), 5-(4′-pyridyl)-10,15,20-tris-(phenyl)porphyrin (**20**), *cis*-5,10-bis(4′-pyridyl)-15,20-bis(phenyl)porphyrin (**19**), *trans*-5,15-bis(4′-pyridyl)-10,20-bis(phenyl)porphyrin (**18**), and a mixture of 5,10,15-tris(4′-pyridyl)-20-(phenyl)porphyrin (**17**) and 5,10,15,20-tetrakis(4′-pyridyl)porphyrin (**16**). Porphyrins **16** and **17** were isolated by loading the mixture of the two from the first column onto a second silica gel column. The column was eluted with 2% MeOH/98% $CHCl_3$ with **17** eluting from the column first.

5,10,15-Tris(4′-pyridyl)-20-(phenyl)porphyrin (17). Compound **17** was isolated in 2.3% yield from the mixed porphyrin condensation reaction as a reddish-purple solid. ^{1}H NMR ($CDCl_3$): δ 9.08 (m, 6H), 8.94 (d, 2H, J = 4.8), 8.88 (s, 4H), 8.84 (d, 2H, J = 4.8), 8.23 (m, 2H), 8.18 (m, 6H), 7.81 (m, 3H), −2.86 (s, 2H). MS (high-resolution FAB): m/z 618.24 ($M + H^+$). UV/vis ($CHCl_3$) λ_{max} = 417.5 (Soret), 513.5, 548.0, 589.0, 645.0.

***trans*-5,15-Bis(4′-pyridyl)-10,20-bis(phenyl)porphyrin (18).** Compound **18** was isolated in 0.7% yield from the mixed porphyrin condensation reaction as a reddish-purple solid. ^{1}H NMR ($CDCl_3$): δ 9.04 (m, 4H), 8.91 (d, 4H, J = 4.6), 8.81 (d, 4H, J = 4.6) 8.22 (m, 4H), 8.17 (m, 4H), 7.78 (m, 6H), −2.85 (s, 2H). MS (high-resolution FAB): m/z 617.24 ($M + H^+$). UV/vis ($CHCl_3$) λ_{max} = 418.0 (Soret), 514.0, 548.5, 590.5, 645.0.

***cis*-5,10-Bis(4′-pyridyl)-15,20-bis(phenyl)porphyrin (19).** Compound **19** was isolated in 1.2% yield from the mixed porphyrin condensation reaction as a reddish-purple solid. ^{1}H NMR ($CDCl_3$): δ 9.05 (m, 4H), 8.91 (d, 2H, J = 4.9), 8.87 (s, 2H), 8.84 (s, 2H), 8.81 (d, 2H, J = 4.9), 8.22 (m, 4H), 8.17 (m, 4H), 7.77 (m, 6H), −2.85 (s,

2H). MS (high-resolution FAB); *m*/*z* 617.24 ($M + H^+$). UV/vis ($CHCl_3$) $\lambda_{max} = 418.0$ (Soret), 514.0, 549.0, 590.0, 645.0.

5-(4′-Pyridyl)-10,15,20-tris(phenyl)porphyrin (20). Compound **20** was isolated in 2.9% yield from the mixed porphyrin condensation reaction as a reddish-purple solid. ^{1}H NMR ($CDCl_3$): δ 9.04 (m, 2H), 8.90 (d, 2H, $J = 4.9$), 8.87 (s, 4H), 8.80 (d, 2H, $J = 4.9$), 8.22 (m, 6H), 8.17 (m, 2H), 7.77 (m, 9H), −2.80 (s, 2H). MS (FAB): *m*/*z* 616.3 ($M + H^+$). UV/vis ($CHCl_3$) $\lambda_{max} = 418.0$ (Soret), 515.0, 549.0, 589.5, 645.0. Anal. Calcd for $C_{43}H_{29}N_5$: C, 83.88; H, 4.75; N, 11.37. Found: C, 83.13; H, 4.57; N, 11.13.

Imprinted Octakis(ethyl ester) [G-3]$_8$-T(3,5-OHPh)P (10-(CO_2Et)$_8$). To a solution of 409 mg (39.7 μmol) of cross-linked [G-3]$_8$-T(3,5-OHPh)P dendrimer (**9**) in 10 mL of toluene were added 2.0 mL of EtOH and 88.0 mg (637 μmol) of potassium carbonate. The suspension was stirred at reflux until the reaction was complete by TLC. The toluene and EtOH were removed under reduced pressure. The resulting residue was partitioned between 100 mL of EtOAc and 30 mL of water. The pH was brought to 7 by adding 1 M aqueous HCl. The aqueous layer was further extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with an equal volume of water, dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The crude product was loaded onto a silica gel plug (4 × 6 cm) and eluted with 5% EtOAc/95% CH_2Cl_2. The EtOAc/CH_2Cl_2 solution was concentrated under reduced pressure. The product was dried overnight under vacuum (0.2 mmHg, 75 °C) to afford 116 mg (30%) of **10-(CO_2Et)$_8$** as a beige powder. ^{1}H NMR (toluene-d_8): δ 7.47 (bs, 16H), 6.62 (bs, 152H), 5.75 (bs, ∼4H), 5.48 (bs, ∼60H), 5.03 (bs, ∼8H), 4.78 (bs, 96H), 4.17 (bs, 16H), 3.67 (bs, 128H), 2.31 (bs, 128H), 1.12 (bs, 24H). MS (MALDI-TOF): *m*/*z* 9906.8 ($M + Na^+ - 32C_2H_4 - C_{28}H_{18}N_4$), 9934.6 ($M + Na^+ - 31C_2H_4 - C_{28}H_{18}N_4$), 9963.2 ($M + Na^+ - 30C_2H_4 - C_{28}H_{18}N_4$), 9990.1 ($M + Na^+ - 29C_2H_4 - C_{28}H_{18}N_4$). SEC (toluene) Calcd $M_w = 4656$.

3,5-Bis{3,5-bis[3,5-bis(3-buten-1-oxy)benzyloxy]benzyloxy}-benzoyl Chloride ([G-3]-COCl) (23). [G-3]-CO_2H (**8**) (351 mg, 266 μmol) was dissolved in 10 mL of THF. To this solution were added 10 μL (129 μmol) of DMF and 50 μL (537 μmol) of oxalyl chloride. The reaction mixture was stirred at room temperature for 30 min. The reaction mixture was heated to 50 °C and stirred at this elevated temperature for 15 min. An aliquot of the reaction mixture was placed in dry MeOH (to form the methyl ester), and TLC of this solution showed that the starting material has disappeared. The reaction was stopped by removing the solvent (and the HCl formed) under reduced pressure. The crude material was loaded onto a silica gel column (2.5 × 20 cm) and eluted with 30% EtOAc/70% PE. This afforded 227 mg (64%) of **23** as clear, colorless oil. It was discovered that the product partially hydrolyzed on silica gel as the remainder of the material was isolated as the starting material. Subsequent formation of acyl chloride dendrons followed this procedure with the modification that once the reaction was determined to be complete by TLC, the solvent was removed under reduced pressure, and the resulting material was dried gently with heat under vacuum until it was considered dry and the excess HCl was removed. ^{1}H NMR: δ 7.34 (d, 2H, $J = 2.2$), 6.88 (t, 1H, $J = 2.2$), 6.67 (d, 4H, $J = 2.2$), 6.59 (t, 2H, $J = 2.2$), 6.58 (d, 8H, $J = 2.2$), 6.43 (t, 4H, $J = 2.2$), 5.90 (ddt, 8H, $J = 17.2$, 10.3, 6.6), 5.17 (ddt, 8H, $J = 17.2$, 1.8, 1.5), 5.11 (ddt, 8H, $J = 10.3$, 1.8, 1.3), 5.01 (s, 4H), 4.97 (s, 8H), 4.00 (t, 16H, $J = 6.8$), 2.54 (tddd, 16H, $J = 6.8$, 6.6, 1.5, 1.3). IR (neat): 3078, 2980, 1760, 1642, 1593, 1163, 1055, 992, 919.

5,10,15,20-Tetrakis{4-[3,5-bis(3,5-bis(3,5-bis(3-buten-1-oxy)-benzyloxy)benzyloxy)benzoyloxy]phenyl}porphyrin ([G-3]-T(4-OHPh)P) (21). [G-3]-COCl (**23**) (684 mg, 511 μmol) was dissolved in 15 mL of THF and added to a flask containing 57.8 mg (85.2 μmol) of H_2T(4-OHPh)P (**22**) and 251 mg (2.05 mmol) of DMAP in 10 mL of THF. The reaction was stirred at reflux for 17 h. TLC showed the reaction was progressing very slowly. Additional DMAP (252 mg, 2.07 mmol) was added to the reaction mixture. The reaction mixture was stirred at reflux until complete as indicated by TLC. The reaction was stopped by removing the THF under reduced pressure. The resulting residue was loaded onto a silica gel column (3 × 17 cm) and eluted with 1% acetic acid/30% EtOAc/69% PE. The product was further purified by loading it onto a series of preparatory SEC columns and eluting it with toluene. The product was dried overnight under vacuum (0.2 mmHg, 75 °C) to afford 450 mg (90%) of **21** as a dark red oil. ^{1}H NMR (CD_2Cl_2): δ 8.97 (s, 8H), 8.31 (m, 8H), 7.69 (m, 8H), 7.62 (d, 8H, $J = 2.3$), 6.95 (t, 4H, $J = 2.3$), 6.76 (d, 16H, $J = 2.3$), 6.59 (t, 8H, $J = 2.3$), 6.58 (d, 32H, $J = 2.3$), 6.39 (t, 16H, $J = 2.3$), 5.88 (ddt, 32H, $J = 17.1$, 10.4, 6.7), 5.13 (m, 48H), 5.07 (ddt, 32H, $J = 10.4$, 1.8, 1.2), 5.01 (s, 32H), 3.99 (t, 64H, $J = 6.7$), 2.50 (tddd, 64H, $J = 6.7$, 6.7, 1.8, 1.2), −2.80 (s, 2H). MS (MALDI-TOF): *m*/*z* 5884.0 ($M + H^+$).

Cross-linking and Hydrolysis of [G-3]-T(4-OHPh)P. To a solution of 50.0 mg (8.49 μmol) of **21** in 1.15 L of benzene was added 8.87 mg (10.8 μmol) of the Grubbs' catalyst. The reaction was stirred at room temperature for 18 h. The benzene was removed under reduced pressure. The crude product was loaded onto a silica gel plug (4 × 6 cm) and eluted with 250 mL of 50% PE/50% CH_2Cl_2 and 300 mL of 5% EtOAc/95% CH_2Cl_2. The EtOAc/CH_2Cl_2 solution was concentrated under reduced pressure. The product was dried overnight under vacuum (0.2 mmHg, 80 °C) to afford 36.5 mg (79%) of a dark red powder. ^{1}H NMR (CD_2Cl_2): δ 8.98 (bs, 8H), 8.30 (bs, 8H), 7.60 (bs, 16H), 6.96 (bs, 4H), 6.45 (bs, 72H), 5.87 (bs, ∼2H), 5.65 (bs, ∼30H), 5.04 (bs, ∼52H), 3.99 (bs, 64H), 2.45 (bs, 64H), −2.74 (bs, 2H). MS (MALDI-TOF): *m*/*z* 5440.9 ($M + H^+ - 16C_2H_4$), 5468.9 ($M + H^+ - 15C_2H_4$), 5498.2 ($M + H^+ - 14C_2H_4$).

A 25% (w/w) aqueous KOH solution was made by dissolving 48.3 mg (740 μmol) of KOH in 145 μL of water. This solution was added to a solution of 36.5 mg (6.68 μmol) of cross-linked [G-3]-T(4-OHPh)P dissolved in 2.0 mL of THF. Ethanol (145 μL) was added to make the reaction mixture homogeneous. The reaction was stirred at 85 °C until no starting material remained by TLC. The reaction mixture was allowed to settle such that two layers formed. The organic layer was decanted off, and the remaining aqueous layer was washed two more times with THF. The THF extracts were combined and concentrated under reduced pressure. The remaining residue was partitioned between 5.0 mL of 2.5 M aqueous KOH and 5.0 mL of CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The organic layers were combined and washed with 2.5 M aqueous KOH, 1 M aqueous HCl (twice), and water. The organic layer was dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure and dried under vacuum (0.1 mmHg, 75 °C) overnight to afford 24.0 mg of a beige powder. ^{1}H NMR (CD_2Cl_2): δ 7.23 (bs, 8H), 6.74 (bs, 4H), 6.45 (bs, 72H), 5.85 (bs, ∼2H), 5.64 (bs, ∼30H), 5.10 (bs, ∼4H), 4.99 (bs, 48H), 3.99 (bs, 64H), 2.45 (bs, 64H). MS (MALDI-TOF): *m*/*z* 4855.9 ($M + Na^+ - 16C_2H_4 - C_{44}H_{22}N_4$), 4883.3 ($M + Na^+ - 15C_2H_4 - C_{44}H_{22}N_4$), 4911.3 ($M + Na^+ - 14C_2H_4 - C_{44}H_{22}N_4$), and peaks corresponding to the loss of one and two dendrons.

3,5-Bis{3,5-bis[3,5-bis(3-buten-1-oxy)benzyloxy]benzyloxy}-benzyl Alcohol ([G-3]-OH). To a suspension of 886 mg (23.4 mmol) of LAH in 50 mL of THF cooled to 0 °C with an ice/water bath was added dropwise a solution of 18.4 g (13.8 mmol) of [G-3]-CO_2Me in 150 mL of THF. The suspension was allowed to warm to room temperature and stirred until no starting material remained by TLC. The reaction was stopped by quenching the excess hydride with 100 mL of water and neutralizing the pH with 20 mL of 1 M aqueous HCl. The THF was removed under reduced pressure, and the resulting aqueous layer was extracted with Et_2O (3 × 400 mL). The combined organic layers were washed with water, dried over sodium sulfate, filtered, and concentrated under reduced pressure. Half of the crude product was purified at a time by column chromatography. The crude product was loaded onto a silica gel column (10 × 20 cm) and eluted with 30% EtOAc/70% PE. The product was dried under vacuum (0.02 mmHg, 75 °C) overnight to afford 16.3 g (90%) of [G-3]-OH as a

clear, colorless oil. ^{1}H NMR: δ 6.66 (d, 4H, J = 2.20), 6.60 (d, 2H, J = 2.2), 6.56 (d, 8H, J = 2.2), 6.54 (t, 2H, J = 2.2), 6.52 (t, 1H, J = 2.2), 6.41 (t, 4H, J = 2.2), 5.89 (ddt, 8H, J = 17.2, 10.3, 6.6), 5.16 (ddt, 8H, J = 17.2, 1.8, 1.5), 5.10 (ddt, 8H, J = 10.3, 1.8, 1.3), 4.97 (s, 4H), 4.95 (s, 8H), 4.62 (d, 2H, J = 6.0), 3.93 (t, 16H, J = 6.8), 2.52 (tddd, 16H, J = 6.8, 6.6, 1.5, 1.3), 1.72 (t, 1H, J = 6.0). ^{13}C NMR: 160.3, 160.1, 160.0, 143.5, 139.3, 139.1, 134.4, 117.1, 106.3, 105.9, 105.7, 101.6, 101.3, 101.0, 70.1, 70.0, 67.3, 65.3, 33.6. IR (neat): 3531 (bs), 3077, 2979, 1641, 1591, 1140, 1058, 994, 916. MS (MALDI-TOF): m/z 1328.3 (M + Na$^+$). SEC (toluene) Calcd M_w = 1324. Anal. Calcd for $C_{81}H_{92}O_{15}$: C, 74.52; H, 7.10. Found: C, 74.52; H, 7.05.

3,5-Bis{3,5-bis[3,5-bis(3,5-bis(3-buten-1-oxy)benzyloxy)benzyloxy]-benzyloxy} Benzoic Acid Methyl Ester ([G-4]-CO$_2$Me). To a mixture of 1.13 g (862 μmol) of [G-3]-OH, 61.6 mg (366 μmol) of methyl-3,5-dihydroxybenzoate, and 241 mg (920 μmol) of PPh_3 in 10 mL of THF cooled to 0 °C with an ice/water bath was added dropwise a solution of 197 mg (1.13 mmol) of DEAD in 10 mL of THF. The reaction was allowed to warm to room temperature and stirred until the reaction was complete as indicated by TLC. The reaction was stopped by adding 20 mL of water and removing the THF under reduced pressure. The resulting aqueous layer was extracted with Et_2O (3 × 75 mL). The combined organic layers were washed water, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was loaded onto a silica gel column (4 × 20 cm) and eluted with 30% EtOAc/70% PE. The product was dried under vacuum (0.05 mmHg, 80 °C) overnight to afford 889 mg (89%) of [G-4]-CO$_2$-Me as a clear, colorless oil. ^{1}H NMR: δ 7.30 (d, 2H, $J_{2,4}$ = 2.0), 6.81 (t, 1H, J = 2.0), 6.68 (m, 12H), 6.57 (d, 16H, J = 2.0), 6.56 (m, 6H), 6.42 (t, 8H, J = 2.0), 5.89 (ddt, 16H, J = 17.2, 10.3, 6.6), 5.16 (ddt, 16H, J = 17.2, 1.8, 1.5), 5.10 (ddt, 16H, J = 10.3, 1.8, 1.3), 5.01 (s, 4H), 4.97 (s, 8H), 4.95 (s, 16H), 3.99 (t, 32H, J = 6.8), 3.90 (s, 3H), 2.52 (tddd, 32H, J = 6.8, 6.6, 1.5 1.3). ^{13}C NMR: 166.7, 160.3, 160.1, 159.8, 139.2, 139.1, 138.9, 134.4, 132.1, 117.1, 108.5, 107.1, 106.4, 106.0, 101.7, 101.6, 101.0, 70.2, 70.1, 67.3, 52.3, 33.6. IR (neat): 3077, 2976, 1723, 1642, 1595, 1164, 1052, 992, 916. MS (MALDI-TOF): m/z 2766.7 (M + Na$^+$). SEC (toluene) Calcd M_w = 2699. Anal. Calcd for $C_{170}H_{188}O_{32}$: C, 74.43; H, 6.91. Found: C, 74.46; H, 6.82.

3,5-Bis{3,5-bis[3,5-bis(3,5-bis(3-buten-1-oxy)benzyloxy)benzyloxy]-benzyloxy} Benzoic Acid ([G-4]-CO$_2$H) (24). A 40% (w/w) aqueous KOH solution was made by dissolving 1.20 g (18.4 mmol) of KOH in 1.8 mL of water. This solution was added to a solution of 4.81 g (1.75 mmol) of [G-4]-CO$_2$Me dissolved in 25 mL of THF. Ethanol (13 mL) was added to make the reaction mixture homogeneous. The reaction was stirred at reflux until no starting material remained by TLC. The reaction flask was removed from the heat and cooled to 0 °C in an ice/water bath. Water (5 mL) was added to the reaction mixture. The reaction was stopped by adding 1 M aqueous HCl until the reaction mixture was acidic (pH < 3). The solvents were removed under reduced pressure. The remaining residue was partitioned between 60 mL of water and 100 mL of CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with water, dried over sodium sulfate, and filtered. The resulting filtrate was concentrated under reduced pressure. The remaining residue was loaded onto a silica gel column (8 × 30 cm) and eluted with 3.0 L of 5% EtOAc/95% CH_2Cl_2 and 2.0 L of 10% EtOAc/90% CH_2Cl_2. The product was dried under vacuum (0.05 mmHg, 70 °C) overnight to afford 3.99 g (83%) of **24** as a beige oil. ^{1}H NMR: δ 7.38 (d, 2H, J = 2.4), 6.87 (t, 1H, J = 2.4), 6.71 (d, 4H, J' = 2.1), 6.70 (d, 8H, J = 2.1), 6.60 (t, 2H, J = 2.1), 6.59 (d, 16H, J = 2.1), 6.57 (t, 4H, J = 2.1), 6.43 (t, 8H, J = 2.1), 5.90 (ddt, 16H, J = 17.2, 10.3, 6.7), 5.18 (ddt, 16H, J = 17.2, 1.7, 1.5), 5.12 (ddt, 16H, J = 10.3, 1.7, 1.3), 5.03 (s, 4H), 4.99 (s, 8H), 4.96 (s, 16H), 4.00 (t, 32H, J = 6.7), 2.54 (tddd, 32H, J = 6.7, 6.7, 1.5, 1.3). ^{13}C NMR: 171.4, 160.5, 160.4, 160.1, 139.4, 139.3, 139.1, 134.7, 131.4, 117.3, 109.2, 108.2, 106.8, 106.7, 106.2, 102.0, 101.9, 101.2, 70.5, 70.3, 67.5, 33.8. MS (MALDI-TOF): m/z 2753.6 (M + Na$^+$). Anal. Calcd for $C_{169}H_{186}O_{32}$: C, 74.37; H, 6.87. Found: C, 74.45; H, 6.86.

5,10,15,20-Tetrakis{4-[3,5-bis(3,5-bis(3,5-bis(3,5-bis(3-buten-1-oxy)benzyloxy)benzyloxy)benzyloxy)benzoyloxy]phenyl}porphyrin ([G-4]-T(4-OHPh)P) (25). [G-4]-CO$_2$H (**24**) (296 mg, 109 μmol), 11.8 mg (17.4 μmol) of H_2T(4-OHPh)P (**22**), 13.4 mg (110 μmol) of DMAP, and 20.3 mg (107 μmol) of *p*-toluenesulfonic acid were dissolved in 10 mL of THF. In a separate flask, 86.5 mg (419 μmol) of DCC was dissolved in 5 mL of THF. This solution was added to the reaction mixture. The reaction was stirred overnight at room temperature. The reaction mixture was vacuum filtered to remove the DCU formed. The filtrate was concentrated under reduced pressure and redissolved in 10 mL of CH_2Cl_2. To this solution were added 286 mg (105 μmol) of **24**, 13.2 mg (108 μmol) of DMAP, and 20.2 mg (106 μmol) of *p*-toluenesulfonic acid. In a separate flask, 85.5 mg (414 μmol) of DCC was dissolved in 5 mL of CH_2Cl_2. This solution was added to the reaction mixture. The reaction mixture was stirred at room temperature until complete as indicated by both TLC and SEC. The reaction was stopped by vacuum filtering the mixture and condensing the filtrate under reduced pressure. The resulting residue was loaded onto a silica gel column (4 × 17 cm) and eluted with 5% EtOAc/95% CH_2Cl_2. The crude product was further purified by loading it onto a large preparatory (7 × 120 cm) SEC column and eluting it with toluene. The product was dried under vacuum (0.2 mmHg, 75 °C) overnight to afford 92.1 mg (46%) of **25** as a deep red oil. ^{1}H NMR (CD_2Cl_2): δ 9.01 (s, 8H), 8.34 (m, 8H), 7.73 (m, 8H), 7.68 (d, 8H, J = 2.1), 7.02 (t, 4H, J = 2.1), 6.80 (d, 16H, J = 2.1), 6.73 (d, 32H, J = 2.3), 6.64 (t, 8H, J = 2.1), 6.58 (d, 64H, J = 2.3), 6.57 (t, 16H, J = 2.3), 6.41 (t, 32H, J = 2.3), 5.90 (ddt, 64H, J = 17.2, 10.4, 6.7), 5.16 (ddt, 64H, J = 17.2, 1.8, 1.5), 5.09 (ddt, 64H, J = 10.4, 1.8, 1.2), 5.05 (s, 32H), 4.99 (s, 16H), 4.98 (s, 64H), 3.98 (t, 128H, J = 6.7), 2.51 (tddd, 128H, J = 6.7, 6.7, 1.5, 1.2), −2.78 (s, 2H). MS (MALDI-TOF): m/z 11 546.3 (M + Na$^+$). SEC (toluene) Calcd M_w = 10 793.

Cross-linked [G-4]-T(4-OHPh)P (26). To a solution of 90.0 mg (7.81 μmol) of 81 in 2.0 L of benzene was added 20.5 mg (24.9 μmol) of the Grubbs' catalyst. The reaction was stirred at room temperature for 20 h. The benzene was removed under reduced pressure. The crude product was loaded onto a silica gel plug (4 × 5 cm) and eluted with 250 mL of 50% PE/50% CH_2Cl_2 and 250 mL of 5% EtOAc/95% CH_2Cl_2. The EtOAc/CH_2Cl_2 solution was concentrated under reduced pressure. The product was dried under vacuum (0.05 mmHg, 65 °C) overnight to afford 73.2 mg (88%) of **26** as a dark red powder. MS (MALDI-TOF): m/z 10 624.4 (M + H$^+$ − 32C_2H_4), 10 652.7 (M + H$^+$ − 31C_2H_4).

Imprinted [G-4]-T(4-OHPh)P (27). To a solution of 73.2 mg (6.87 μmol) of cross-linked [G-4]-T(4-OHPh)P (**26**) dissolved in 100 mL of THF was added 25 mL of 2.5 M aqueous KOH. The reaction was stirred vigorously at reflux until the reaction was complete by TLC. The reaction was stopped by removing the THF under reduced pressure. The resulting aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The organic layers were combined and washed with an equal volume of 2.5 M aqueous KOH and water. The organic layer was stirred vigorously with an equal volume of 1 M aqueous HCl for 3 h at room temperature. The organic layer was concentrated under reduced pressure. The product was dried under vacuum (0.2 mmHg, 75 °C) overnight to afford 33.2 mg (48%) of **27** as a beige powder. MS (MALDI-TOF): m/z 10 040.9 (M + Na$^+$ − 32C_2H_4 − $C_{44}H_{22}N_4$), 10 069.1 (M + Na$^+$ − 31C_2H_4 − $C_{44}H_{22}N_4$).

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