Synthesis and Metal Binding Properties of Salicylate-, Catecholate-, and Hydroxypyridinonate-Functionalized Dendrimers

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Abstract: The synthesis, characterization, and metal-binding studies of chelate-functionalized dendrimers is reported. Salicylate, catecholate, and hydroxypyridinonate bidentate chelators have been coupled to the surface of both poly(propyleneimine) (Astramol) and poly(amidoamine) (Starburst, PAMAM) dendrimers up to the fifth generation (64 endgroups). A general method has been developed for the facile and high quality chromatographic purification of poly(propyleneimine) and poly(amidoamine) dendrimer derivatives. One- and two-dimensional (TOCSY) ^{1}H NMR experiments and electrospray ionization mass spectrometry (ESI-MS) have confirmed the exhaustive coupling of these chelators to the primary amine functionalities of the dendrimers. Spectrophotometric titrations were used to investigate the metal binding ability of these macrochelates. Spectral analysis shows that ferric iron binding to these ligands is localized to the chelating endgroups. The ability of these dendritic polymers to bind large numbers of metal ions may lead to applications as metal sequestering agents for waste remediation technologies.

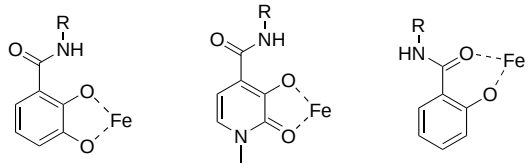
Keywords: dendrimers · iron · metal sequestration

Introduction

The synthesis of new dendrimers represents a rapidly growing field of chemistry and nanotechnology.[1, 2] Included in these investigations is the study of metal-containing dendrimers. Dendrimers have been prepared that contain metals at the core,[3–5] within the branches,[6] and at the periphery of the macromolecular structure.[7–10] These macromolecules have been pursued as challenging synthetic targets as well as for potential applications in various technologies.[1, 9, 11] Although many metal-modified dendrimers have been synthesized, only one report describes the use of dendrimers for the specific purpose of sequestering large amounts of metal ions from their environment.[12]

Catecholamides are powerful Lewis base chelators found in bacterial siderophores, sequestering agents for the hard Lewis acid Fe^{3+}. Chelators related to catecholamides including salicylamides,[13] 1,2- and 3,2-hydroxypyridinonamides (1,2-HOPO and 3,2-HOPO, respectively),[14] and 2,3-dihydroxyterephthalamides[15] are also good chelators for a variety of hard metal cations such as Fe^{3+}, Pu^{4+}, and Gd^{3+}.[16] The high stability of the metal complexes formed with catecholamides[17, 18] (and several catecholamide derivatives) promoted the investigation of these ligands in various applications including iron chelation therapy,[18] magnetic resonance imaging,[14] and waste remediation.[16]

Herein we describe the synthesis, characterization, and metal-sequestering properties of dendrimers substituted with salicylate, catecholate, and 3,2-hydroxypyridinonate chelators (Scheme 1). Two different types of commercially available dendrimers, poly(amidoamine) and poly(propyleneimine) polymers, have been functionalized with up to 64 bidentate chelators. A high quality and throughput purification was



Scheme 1. Diagram of the three binding units that were appended to poly(amidoamine) and poly(propyleneimine) dendrimers. Catecholamide (CAM, left), 3,2-hydroxypyridinonamide (HOPO, middle), and salicylamide (SAM, right) chelators.

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Supporting information for this article is available on the WWW under http://www.wiley-vch.de/home/chemistry/ or from the author. The information includes two-dimensional TOCSY ^{1}H NMR for Starburst(Bn3,2HOPO)$_{32}$, ^{1}H NMR for Astramol(Bn3,2HOPO)$_{32}$ (**11**) and Astramol(H3,2HOPO)$_{32}$ (**12**), experimental spectra of Astramol-(HSAM)$_{32}$ (**4**) and Astramol(CAM)$_{32}$ (**8**) titrated with $FeCl_3$, and plot of absorbance at 450 nm for Astramol(HSAM)$_{32}$ (**4**) and at 498 nm for Astramol(CAM)$_{32}$ (**8**) versus equivalents of Fe^{3+} per bidentate chelator.

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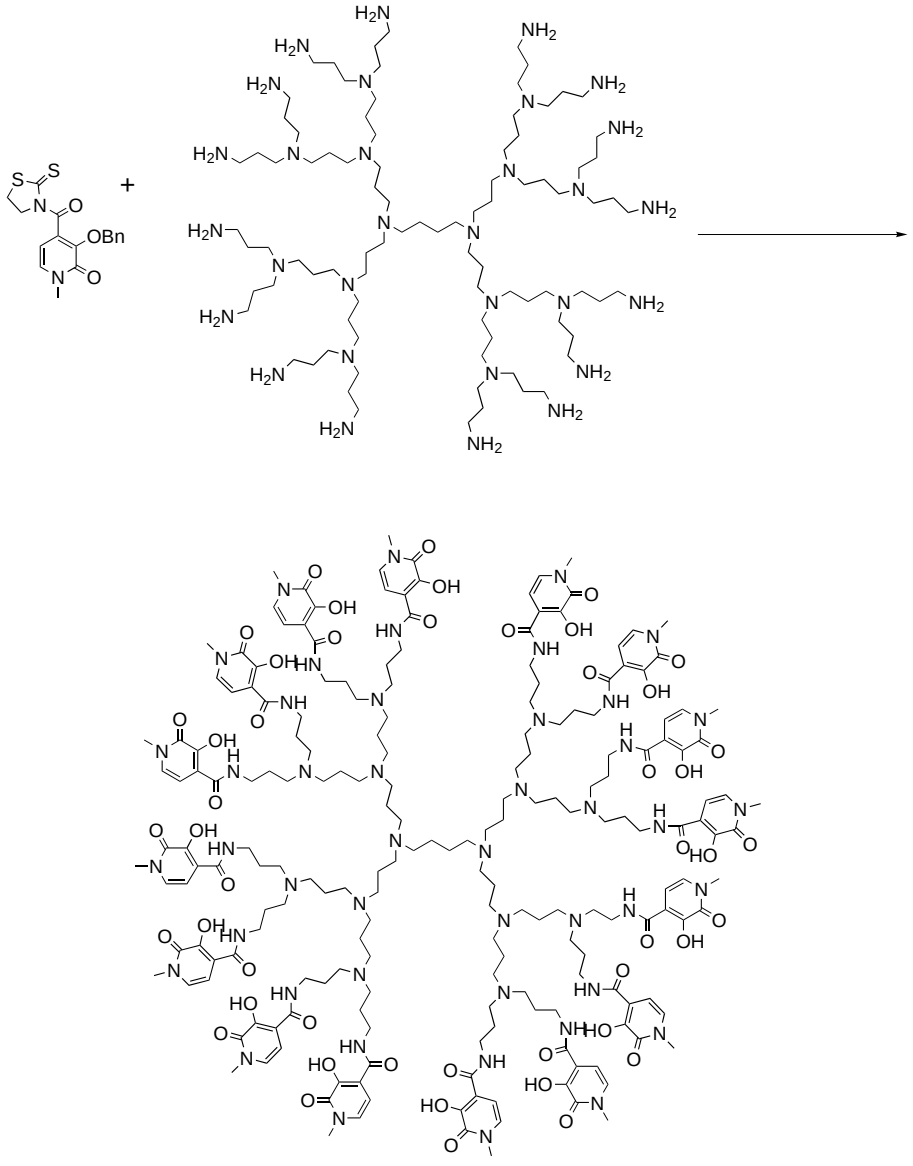
developed which should be applicable to many derivatives of these extensively studied, commercially available dendrimers. The coupling of the dendrimer surface was confirmed by total correlation spectroscopy (TOCSY) experiments and electrospray ionization mass spectrometry (ESI-MS). The ability of these dendrimers to bind Fe^{3+} was investigated using batch spectrophotometric titration methods. These dendrimer-based ligands, which incorporate strong metal chelators, may be useful in a number of metal ion sequestering applications.

Results and Discussion

Synthesis: The synthesis of the dendrimer ligands followed essentially the same protocol regardless of whether salicylate, catecholate, or 3,2-hydroxypyridinonate chelates were attached to either poly(propyleneimine) or poly(amidoamine) dendrimers (Scheme 2). An activated ester of the chelate[14, 19] was added to a solution of the dendrimer dissolved in a minimum amount of CH_2Cl_2 (poly(propyleneimine)) or CH_2Cl_2/MeOH (poly(amidoamine)). The mixtures were monitored by TLC and typically allowed to react for about 18 h. A variety of purification methods were investigated including dialysis, extractions, and silica flash chromatography. Ultimately, purification by using flash chromatography on deactivated alumina was found to be effective. An alumina slurry with CH_2Cl_2 was prepared with 3–15% (by weight) of water. The evaporated reaction mixture was redissolved in a minimum amount of CH_2Cl_2 and was loaded onto the column. The side products were removed by elution with CH_2Cl_2 and the protected dendrimer chelate was eluted with 5–20% MeOH in CH_2Cl_2. This chromatographic method could be performed rapidly (15 min), and consistently gave pure products with dendrimers as large as the fourth and fifth generations (32 and 64 terminal groups, respectively). The benzyl protecting groups of the chelators were then quantitatively removed by using 1:1 glacial acetic acid/concentrated HCl to give the macrochelates as polyhydrochoride salts.



Scheme 2. Synthesis of the dendrimers.

NMR spectroscopy: The purity of these dendrimers could not be consistently characterized with elemental analysis, as the benzyl-protected dendrimers trapped organic solvents (e. g. CH_2Cl_2, MeOH), while the deprotected dendrimers were extremely hygroscopic (due to the fact that they were isolated as polyhydrochloride salts). The use of NMR spectroscopy in characterizing these dendrimer–chelates was critical for three primary reasons. First, simple ^1H and ^{13}C NMR spectra provided strong qualitative evidence for the purity of these compounds.[6] Second, two-dimensional total correlation spectroscopy (TOCSY) NMR experiments were used to confirm that coupling of the surface amines with the desired chelates was exhaustive within the limits of the NMR experiment (ca. 95%).[20] Finally, NMR spectra demonstrated that the removal of the benzyl protecting groups, using glacial acetic acid/concentrated HCl, was nearly quantitative.

The ^1H and ^{13}C NMR spectra of the protected ligands confirmed the effectiveness of the synthesis and purification procedures. The resonance signals

for the chelator and dendrimer protons could be easily distinguished with no evidence of any major impurities. The total loss of the aromatic and methylene resonances assigned to the benzyl protecting groups in the deprotected dendrimers, as evidenced by the ^{1}H and ^{13}C NMR spectra, suggests that the reaction was nearly quantitative under the conditions described (see Supporting Information). The spectra clearly show that all the resonances of the benzyl protecting groups disappear and only the aromatic and amide resonances remain in the downfield region.

^{1}H NMR peak integration has been previously used to evaluate the completeness of reaction of dendrimer terminal groups.[21] However, few details have been reported on how these integrations were performed and which dendrimer resonances were used as an integration reference. Because of the large number of protons associated with the dendrimer structure, we sought to determine a specific set of dendrimer resonances that could be used as a standard for integration. The well resolved ^{1}H NMR spectra of the benzyl-protected dendrimer–chelates prompted the use of total correlation spectroscopy (TOCSY) as a means by which to determine a set of reference resonances. TOCSY experiments demonstrated that the terminal dendrimer methylene (methylene group adjacent to the terminal amide group) of both the poly(propyleneimine) and poly(amidoamine) dendrimers could be easily assigned as shown in Figure 1. Because TOCSY correlates adjacent protons, the terminal methylene group produces a cross-peak with the aromatic amide proton. This cross-peak was used to assign the terminal methylene resonances of the dendrimer. In the poly(propyleneimine) dendrimers this resonance is very well separated from any other signals, therefore allowing for a straightforward comparison of peak areas to determine the degree of coupling. Comparison of protons associated with the chelating groups and those of the dendrimer terminal methylene protons (which is equal to two times the number of dendrimer arms) confirmed that the dendrimer surface amines reacted with the desired chelator to at least 95% completion. Similar analyses were performed for the poly(amidoamine) derivatives. Although the terminal methylene groups in the PAMAM dendrimers are not as cleanly separated, peak integration also indicated essentially complete coupling (see Supporting Information). Both dendritic polymers, when subjected to identical synthetic and purification methodologies provided clean, low dispersity polydentate ligand systems.

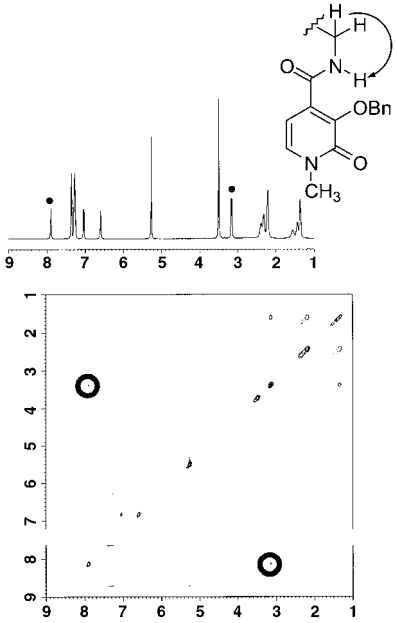


Figure 1. One-dimensional ^{1}H NMR (top) and two-dimensional total correlation spectroscopy (TOCSY, bottom) of Astramol(Bn3,2HOPO)$_{32}$. Cross-peaks are observed in the TOCSY spectrum between the aromatic amide proton and the terminal methylene protons of the dendrimer (inset). This assignment allowed for precise determination of the coupling efficiency. Amide bond formation was found to be complete in all of the compounds prepared.

Mass spectrometry: Matrix-assisted laser desorption time-of-flight (MALDI-TOF) mass spectrometry has been the technique of choice for characterizing various dendrimers.[20, 22, 23] MALDI-TOF has been used because this ionization technique produces ions of low internal energy that minimizes the fragmentation of the analyte, allowing detection of the product ion peak. MALDI-TOF predominantly produces singly charged ions, and therefore in the case of macromolecules, requires detection systems with very high mass ranges. An alternative method, electrospray ionization mass spectrometry (ESI-MS), has recently become an extremely powerful tool for studying supramolecular and macromolecular structures.[24–29] Like MALDI-TOF experiments, ESI-MS is also a very gentle ionization method that minimizes the fragmentation of the analyte molecules. However, unlike MALDI-TOF that produces mostly singly charged ions, ESI-MS produces multiply charged ions providing several peaks of different charge states for the same macromolecular system.[4, 30, 31] Because the mass-to-charge ratio is reduced by the production of multiply charged ions, ESI-MS requires relatively low mass range detectors which provides for improved mass resolution.

Good mass spectra were obtained for the poly(propyleneimine) dendrimers following addition of approximately 10% formic acid to the analyte (Figure 2). The addition of acid appeared to improve the mass spectra regardless of whether the dendrimer endgroups were hydrophobic (benzyl-protected chelates) or hydrophilic (deprotected chelates) in nature, suggesting that signal enhancement may have been due to increased protonation of the internal tertiary dendrimer amines.[32] The high molecular weight of these dendrimers does not permit direct observation of the molecular ion peak by ESI-MS. Therefore, to confirm the deconvolution results of these experiments, a complementary MALDI-TOF experiment was also performed. Astramol(H3,2HOPO)$_{32}$ (**12**) gave the expected molecular ion peak (as determined by the ESI-MS experiments) in the MALDI-TOF analysis (see Experimental Section). The advantage of ESI-MS in these systems was further illustrated by the fact that the MALDI-TOF data could not be obtained for several of the dendrimer–chelates that were successfully measured by electrospray methods. Only a few dendrimers with poly(propyleneimine) cores could not be analyzed by electrospray mass spectrometry. In general, the compounds that were difficult to analyze by ESI-

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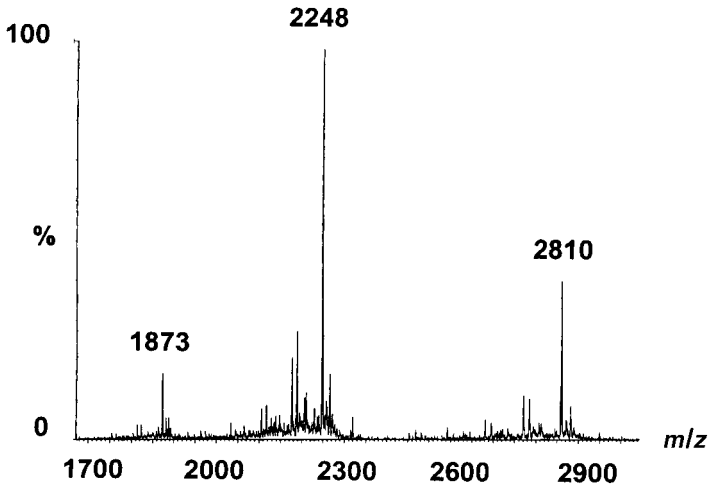

Figure 2. Electrospray ionization mass spectrum of Astramol(Bn3,2HOPO)$_{32}$. Several multiply charged peaks (m/z 2810 [M^{4+}+4H], 2248 [M^{5+}+5H], 1873 [M^{6+}+6H]) are observed corresponding to a molecular weight of 11234.31 ± 0.50.

MSwere of higher molecular weight (>15000 amu). High quality ^{1}H NMR (one- and two-dimensional), ^{13}C NMR, and IR were used to characterize these large dendrimers. Because all the dendrimers were synthesized and purified using identical methods the spectroscopic data for the higher molecular weight dendrimers was presumed sufficient for their characterization for use in metal-binding experiments.

The poly(amidoamine) dendrimers, which possess the same endgroups as the poly(propyleneimine) dendrimers, gave poor ESI-MS results. No conditions were found that provided acceptable spectra for any dendrimer with a poly(amidoamine) core, only broad irresolvable signals were obtained for these compounds. No difference in the spectral quality were seen between protected ligands (hydrophobic) and deprotected ligands (hydrophilic). Addition of formic acid also did not improve spectral results. Ultimately, the characterization of poly(amidoamine) dendrimer–chelates relied on the high-resolution ^{1}H NMR (one- and two-dimensional), ^{13}C NMR, and IR data. Again, considering that the poly(amidoamine) and poly(propyleneimine) dendrimers were synthesized and purified using identical methods the spectroscopic data for the poly(amidoamine) derived compounds provided satisfactory characterization of these ligands. In addition, the similar metal-binding behavior of the poly(amidoamine) dendrimers and the poly(propyleneimine) dendrimers suggests that the quality of the poly(amidoamine) compounds were sufficient for investigating their metal-sequestering properties.

Metal-binding properties: In order to evaluate the Fe^{3+} binding properties of these dendrimers, UV/Vis spectrophotometric titrations were performed by addition of up to 50 equivalents of anhydrous $FeCl_3$ to basic solutions of the dendrimers in anhydrous DMSO. Batch titrations were executed on samples that were incubated at 37 °C for 15 h before spectral acquisition (to avoid kinetic effects). Five dendrimers were investigated in order to evaluate the different binding groups (salicylamide, catecholamide, and 3,2-hydroxypyridinonamide), dendrimer generations (16 and 32 branches), and dendrimer structures (poly(amidoamine) and poly(propyleneimine)) that were synthesized. The ligand-to-metal charge transfer (LMCT) band of the Fe^{3+} complexes formed with the 3,2-hydroxypyridinonamide dendrimers appears at lower energy and is more distinct from the $\pi \rightarrow \pi^*$ bands centered on the ligand (compared to the corresponding complexes formed with salicylamide and catecholamide groups). Therefore, 3,2-hydroxypyridinonate dendrimers were studied to evaluate the metal-binding effects of different dendrimer sizes and core structures by titrating Astramol(H3,2HOPO)$_{16}$, Astramol(H3,2HOPO)$_{32}$, and Starburst(H3,2HOPO)$_{32}$. The salicylamide and catecholamide binding properties were analyzed by using the dendrimers Astramol(HSAM)$_{32}$ and Astramol(H_2CAM)$_{32}$, respectively.

Titrations of the hydroxypyridinonate dendrimers, Astramol(H3,2HOPO)$_{16}$, Astramol(H3,2HOPO)$_{32}$, and Starburst(H3,2HOPO)$_{32}$ with Fe^{3+} displayed similar spectral behavior. Addition of a small amount iron to the dendrimer solutions produced a purple-red color. The color of these solutions arises from the formation of tris-bidentate complexes that possess a LMCT band with maxima at approximately 430 and 538 nm (Figure 3). The large number of intermediate iron species formed between the chelating groups of the dendrimer prevents rigorous determination of the formation constants of the resulting complexes by analysis of the experimental spectra.[33–36] However, plots of absorbance versus equivalents of Fe^{3+} were used as a qualitative assessment of these systems.[37] The intensity of the LMCT bands increase until a 1:3 ratio of iron to bidentate chelator is obtained in each titration (e. g. ca. 10 equivalents for Astramol(H3,2HOPO)$_{32}$ and Starburst(H3,2HOPO)$_{32}$ and ca. 5 equivalents for Astramol(H3,2HOPO)$_{16}$). At these stoichiometries the dendrimers show a break in absorbance as evidenced in Figure 3. These data suggest that the HOPO-functionalized dendrimers bind Fe^{3+} in a tris-bidentate fashion and that the dendrimer architecture is sufficiently flexible to permit the formation coordinatively saturated metal complexes. These experiments show that the different dendrimer sizes and structures (e.g. poly(amidoamine) and poly(propyleneimine)) do not strongly influence the metal binding properties of the chelating endgroups.

Addition of Fe^{3+} to Astramol(H_2CAM)$_{32}$ results in a pink-red solution due to a strong LMCT band centered at 498 nm (see Supporting Information). A plot of absorbance versus equivalents of Fe^{3+} for Astramol(H_2CAM)$_{32}$ showed a different result to that found for Astramol(HHOPO)$_{32}$. The present titrations and dendrimer purity introduce some uncertainty in determining the binding stochiometry. Changes in the absorption at 498 nm increase linearly up to approximately 0.3 equivalents of Fe^{3+} per chelator, after which the absorbance at the LMCT remains essentially constant (see Supporting Information). This implies the formation of the tris-bidentate complex as seen in the HOPO-derivatized dendrimer. However, unlike the HOPO systems, no plateau in absorbance is observed during the titration. After 0.3 equivalents of Fe^{3+} the Astramol(H_2CAM)$_{32}$ dendrimer has an insufficient number of chelators to bind all ferric ions in an exclusively tris-bidentate fashion. Therefore, the ligand can

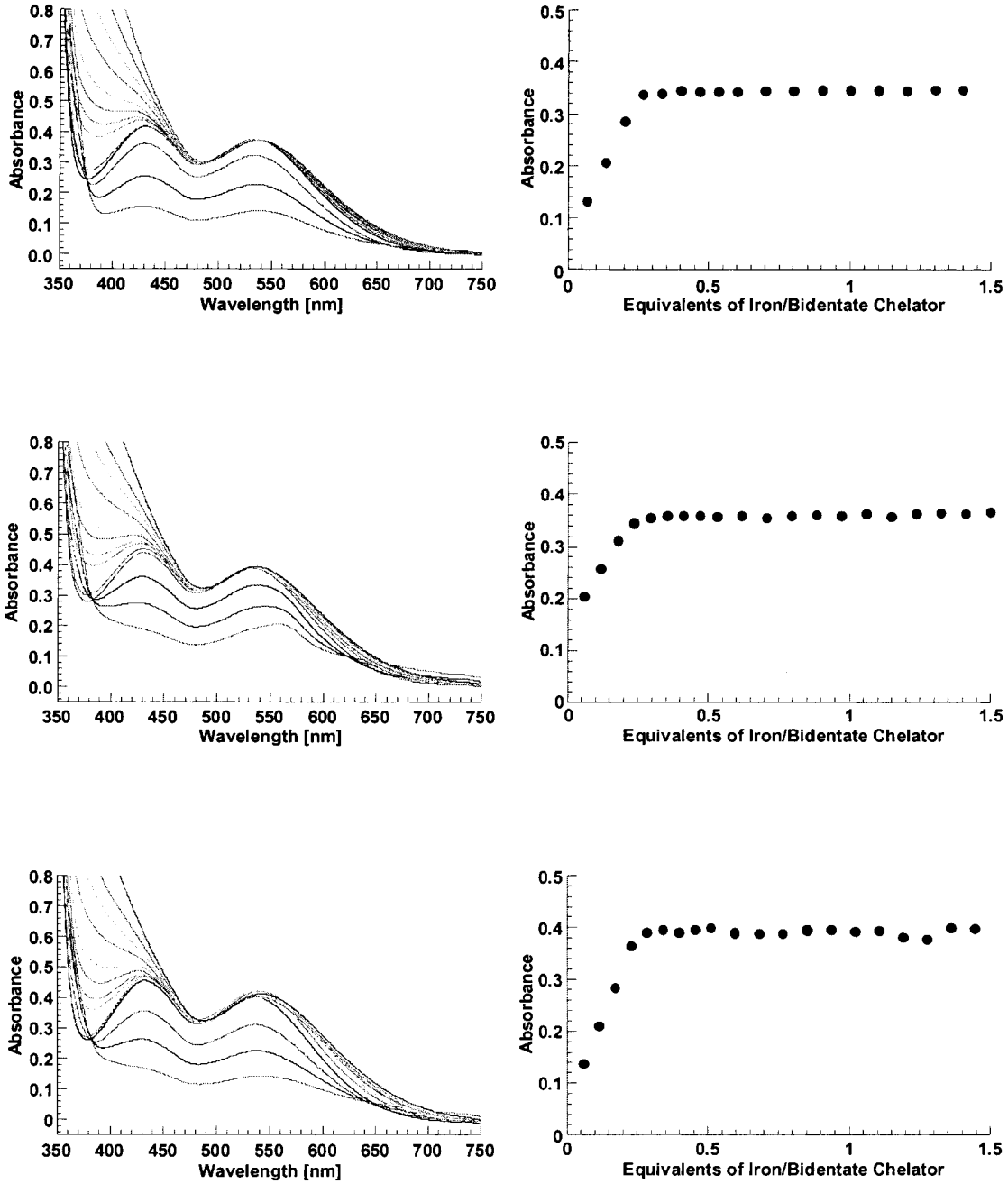

Figure 3. Intense ligand-to-metal charge transfer (LMCT) bands are observed upon metal complexation by chelate-substituted dendrimers. Experimental spectra of Astramol(H3,2HOPO)$_{16}$ (top left), Astramol(H3,2HOPO)$_{32}$ (middle left), and Starburst(H3,2HOPO)$_{32}$ (bottom left) with $FeCl_3$ in anhydrous DMSO. Changes in absorption demonstrate formation of tris-bidentate metal complexes. Plot of absorbance at 558 nm versus equivalents of Fe^{3+} per bidentate chelator (dendrimer endgroup) for the titration with Astramol(H3,2HOPO)$_{16}$ (top right), Astramol(H3,2HOPO)$_{32}$ (middle right), and Starburst(H3,2HOPO)$_{32}$ (bottom right).

either 1) form only tris-bidentate complexes and leave excess metal ion in solution (as observed for the HOPO-based dendrimers), or 2) form coordinately unsaturated mixtures of tris-, bis-, and mono-bidentate complexes, thereby sequestering as much iron as possible. The second model was supported by two essential observations. First, the continued increase in the LMCT band after 0.3 equivalents of iron indicates that the dendrimer is binding more Fe^{3+} than could be accommodated by only tris-bidentate complexes. If the dendrimer only formed tris-bidentate complexes complete saturation would be observed at 0.3 equivalents of iron per chelator (vide supra). Second, direct visual inspection showed the formation of unsaturated (mono- and bis-bidentate) iron complexes. Solutions of Astramol$(H_2CAM)_{32}$ with iron displayed a remarkable color change with increasing iron concentration. At less than 10 equivalents of iron per dendrimer (which corresponds to less than 0.3 equivalents of iron per chelator) the solutions appeared pink-red in color. At greater than 10 equivalents of iron the solutions became purple. Finally, at greater than about 32 equivalents of iron, where more than one equivalent of iron is present for every catecholamide, the solutions turned pale green. These color changes correspond-

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ed to a 59 nm shift in the absorbance maximum of the LMCT band of the metal complexes from 498 to 557 nm. This change in color is consistent with the known colors of the previously reported tris-, bis-, and mono-catecholamide iron complexes, which are typically red, purple, and green in color, respectively.[35, 36] The lack of saturation behavior in the catecholamide dendrimers may be the consequence of competition with protons. Unlike the HOPO dendrimers (pK_a 6.12), the catecholamide ligands are much more basic (pK_a values of 8.42 and 12.1).[38] In Astramol$(H_2CAM)_{32}$ the pyridine base is not sufficient to completely deprotonate all of the catecholamide ligands, resulting in the formation of lower denticity complexes.

Addition of Fe^{3+} to a solution of Astramol$(HSAM)_{32}$ immediately caused the solution to become bright orange due to formation of a LMCT band (see Supporting Information). This band shows a maximum at 450 nm as expected for a ferric tris-salicylate complex.[13] Monitoring changes in the LMCT absorption at 450 nm showed the formation of the tris-bidentate species, with a clear break from linear absorbance behavior at 0.3 equivalents of Fe^{3+} per bidentate chelator (see Supporting Information). This change, at a ratio of ten equivalents of Fe^{3+} for one equivalent of Astramol$(HSAM)_{32}$, correlates well with the ligand stoichiometry, since Astramol$(HSAM)_{32}$ has 32 chelating units and can bind a maximum of ten Fe^{3+} atoms in a tris-bidentate fashion. However, unlike the discrete saturation behavior observed in the HOPO-functionalized systems, the salicylate system shows evidence for further reaction with added Fe^{3+}, in a manner similar to that seen in the titration of Astramol$(H_2CAM)_{32}$. The intensity of the LMCT band continues to gradually increase with increasing iron concentration. The LMCT band also shifts approximately 20 nm to lower energy by the end of the titration (determination of the final λ_{max} is obscured from strong ligand absorbances at high energy, see Supporting Information). Complete saturation is not obtained with as much as 45 equivalents of iron per dendrimer, suggesting that Astramol$(HSAM)_{32}$ switches from tris- bidentate to a mixture of bis- and mono-bidentate complexes with increasing iron concentration. As in the HOPO systems, the salicylate chelates form neutral tris-bidentate complexes with Fe^{3+}. However, the salicylate dendrimers also form lower denticity complexes in contrast to the HOPO compounds. This difference in complexation behavior can also be attributed to the differences in pK_a for salicylate and hydroxypyridinonate tris-bidentate complexes. Salicylamide ligands are more basic (pK_a 8.03)[13] than the corresponding HOPO chelators and therefore will be more effectively competed for by protons to form lower denticity complexes.[13, 39]

In summary, these dendrimer ligands demonstrate linear changes in absorbance at concentrations corresponding to the formation of tris-bidentate ferric complexes. It is possible that intermolecular complexation reactions occurred during the titrations, forming cross-linked, polymeric materials. However, the high solubility of these systems throughout the titrations strongly suggets that metal chelation was predominantly intramolecular, although the possibility of low levels of cross-linking cannot be excluded. The titrations of Astramol$(H3,2HOPO)_{32}$, Starburst$(H3,2HOPO)_{32}$, and Astramol$(H3,2HOPO)_{16}$ with Fe^{3+} showed that the metal binding behavior is essentially independent of the size and structure of the dendrimer polymer, but rather is governed by the nature of the chelating groups. The analyses performed by monitoring the LMCT transitions show that the HOPO-based dendrimers exhibit saturation behavior, forming only tris-bidentate complexes upon addition of iron. However, the more basic salicylamide- and catecholamide-based dendrimers appear to form lower denticity complexes. The absorption data are consistent with highly localized metal binding at the chelator endgroups appended to the dendrimer scaffold.

Conclusion

A novel series of metal-chelating dendrimers has been synthesized by using a variety of catecholamide-derived bidentate ligands. These polydentate chelators have been characterized by one- and two-dimensional ^1H NMR, ^{13}C NMR, and IR spectroscopy, and electrospray ionization mass spectrometry (ESI-MS). The metal-binding properties of these hyperbranched polymers have been investigated by using batch spectrophotometric titrations. Tris-bidentate and lower denticity modes of metal binding were identified. Metal binding is specifically localized to the chelating endgroups, with complexation halting at the formation of tris-bidentate complexes in the HOPO-based systems. These materials are a new metal-sequestering motif with a high loading capacity that may find use in metal separation technologies.[12]

Experimental Section

General: Unless otherwise noted, starting materials were obtained from commercial suppliers and used without further purification. Flash silica gel chromatography was performed using Merck silica gel 40–70 mesh. Flash alumina gel chromatography was performed using Fluka Basic Brockman Activity I Alumina 60–325 mesh. Mass spectra were recorded at the Mass Spectrometry Laboratory, College of Chemistry, University of California, Berkeley. Electrospray ionization mass spectrometry (ESI-MS) was performed on a VG-BIOQ (Micromass) triple quadrapole mass spectrometer. ^1H and ^{13}C NMR spectra were recorded on an AMX 300 or AMX 400 Bruker superconducting Fourier transform spectrometer or a DRX 500 Brucker superconducting digital spectrometer. Infrared spectra were measured using a Nicolet Magna IR 550 Fourier transform spectrometer.

Spectrophotometric titrations: Batch spectrophotometric titrations were performed by using a Perkins-Elmer Lambda 9 spectrophotometer scanning from 260 to 800 nm in a 1.0 cm quartz Suprasil cell. Titrations were performed in anhydrous DMSO (Aldrich) as some of the metal complexes precipitated from water during equilibration. Dendrimer solutions were prepared in anhydrous DMSO (Aldrich) with a stock $FeCl_3$ solution (also in anhydrous DMSO) and an excess of pyridine (0.490 mL) as base to a total volume of 3.0 mL. The final dendrimer concentrations were between 1.4×10^{-5} and 8.9×10^{-6} M. The exact concentration of the $FeCl_3$ stock solution was determined by atomic absorption analysis. All samples were equilibrated by incubation in a thermostatic shaker at 37 °C for at least 15 h.

Representative synthesis of dendrimer–chelate conjugates: Astramol third-generation (16 terminal amines) dendrimer (0.15 mmol) was dissolved in CH_2Cl_2 (10 mL). To this solution was added 3-benzoxy-1-methyl-4-(2-thioxothiazolidin-1-yl)carbonyl-2-pyridinone[14] (2.5 mmol) in CH_2Cl_2 (2 mL). The solution was protected from light and stirred for about 18 h. The mixture was evaporated to dryness and the remaining pale yellow residue was purified by flash alumina column chromatography (30 g, deactivated with 1.5 mL of water; elution with CH_2Cl_2 followed by 5–20 %

MeOH in CH_2Cl_2). Removal of solvent and oven drying gave a colorless oil. The product was extremely pure according to ^1H and ^{13}C NMR spectra. Reported yields (vide infra) were calculated from the initial quantities of unfunctionalized dendrimer starting materials (the chelators were added in slight excess).

Representative deprotection of dendrimer–chelate conjugates: Astramol(Bn3,2HOPO)$_{16}$ (0.11 mmol) was dissolved in a 1:1 mixture of concentrated HCl and glacial acetic acid (30 mL). The mixture was sealed and stirred for about 48 h. The reaction mixture was evaporated to dryness and the remaining residue coevaporated with MeOH (5 × 30 mL) to give a beige foam which was dried in a vacuum oven. If required, the foam could be passed through a Sephadex LH-20 column (MeOH eluant) to remove excess HCl. Yields of greater than 80% were obtained for the deprotection reactions, based on products where all tertiary amines are protonated and the dendrimers are isolated as polyhydrochloride salts.

Astramol(BnSAM)$_{16}$ (1): Colorless oil. Yield: 90%. IR (film from $CDCl_3$): $\tilde{\nu}$ = 1652, 2807, 2869, 2944, 3034, 3399 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.38–1.51 (brs, 60H; CH_2), 2.16/2.27 (brs, 84H; CH_2), 3.25 (brd, 32H; CONHCH_2), 5.03 (s, 32H; OCH_2), 6.90 (d, J = 8.3 Hz, 16H; ArH), 6.98 (t, J = 7.5 Hz, 16H; ArH), 7.31 (brm, 96H; ArH), 7.86 (brt, 16H; CONHCH$_2$), 8.11 (d, J = 7.7 Hz, 16H; ArH); ^{13}C NMR (400 MHz, $CDCl_3$, 25 °C): δ = 24.4 (CH_2), 26.8 (CH_2), 38.0 (CH_2), 51.2 (CH_2), 52.1 (CH_2), 71.2 (CH_2-O), 112.7 (ArC), 121.4 (ArC), 122.3 (ArC), 127.8 (ArC), 128.6 (ArC), 128.9 (ArC), 132.1 (ArC), 132.4 (ArC), 135.7 (ArC), 156.7 (ArC), 165.1 (C=O); (+)-ESI-MS: m/z: 1685 [M^{3+}+3H], 1264 [M^{4+}+4H], 1011 [M^{5+}+5H].

Astramol(HSAM)$_{16}$·14HCl (2): Beige foam. ^1H NMR (500 MHz, [D$_6$]DMSO, 25 °C): δ = 2.03/2.27 (brs, 60H; CH_2), 3.20/3.37 (brs, 116H; CH_2), 6.81 (t, J = 7.4 Hz, 16H; ArH), 6.88 (d, J = 8.2 Hz, 16H; ArH), 7.32 (t, J = 7.4 Hz, 16H; ArH), 7.97 (d, J = 7.8 Hz, 16H; ArH), 9.12 (brs, 16H; CONHCH$_2$), 10.79 (brs, 8H; ArOH), 11.11 (brs, 8H; ArOH); ^{13}C NMR (500 MHz, [D$_6$]DMSO, 25 °C): δ = 18.1 (CH_2), 23.5 (CH_2), 36.7 (CH_2), 49.2 (CH_2), 50.4 (CH_2), 115.6 (ArC), 117.7 (ArC), 118.9 (ArC), 128.4 (ArC), 134.0 (ArC), 160.4 (ArC), 169.6 (C=O); (+)-ESI-MS: m/z: 1204 [M^{3+}+3H], 903 [M^{4+}+4H], 723 [M^{5+}+5H], 603 [M^{6+}+6H].

Astramol(BnSAM)$_{32}$ (3): Colorless foam. Yield: 64%. IR (film from CH_2Cl_2): $\tilde{\nu}$ = 1652, 2808, 2869, 2943, 3033, 3398 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 1.36/1.52 (brs, 124H; CH_2), 2.13/2.26/2.36 (brs, 180H; CH_2), 3.22 (brs, 64H; CONHCH_2), 4.98 (s, 64H; OCH_2), 6.86 (brd, 32H; ArH), 6.93 (brt, 32H; ArH), 7.28 (brs, 192H; ArH), 7.84 (brs, 32H; CONHCH$_2$), 8.06 (brd, 32H; ArH); ^{13}C NMR (500 MHz, $CDCl_3$, 25 °C): δ = 24.3 (CH_2), 26.7 (CH_2), 38.0 (CH_2), 51.1 (CH_2), 51.8 (CH_2), 52.0 (CH_2), 71.0 (CH_2-O), 112.7 (ArC), 121.3 (ArC), 122.2 (ArC), 127.7 (ArC), 128.5 (ArC), 128.8 (ArC), 131.9 (ArC), 132.3 (ArC), 135.7 (ArC), 156.6 (ArC), 165.0 (C=O); (+)-ESI-MS: m/z: 3414 [M^{3+}+3H], 2562 [M^{4+}+4H], 2049 [M^{5+}+5H], 1708 [M^{6+}+6H].

Astramol(HSAM)$_{32}$·30HCl (4): Off-white powder. ^1H NMR (500 MHz, [D$_6$]DMSO, 25 °C): δ = 2.02/2.28 (brs, 124H; CH_2), 3.20/3.36 (brs, 244H; CH_2), 6.80 (brs, 32H; ArH), 6.86 (brd, J = 7.0 Hz, 32H; ArH), 7.31 (brs, 32H; ArH), 7.93 (brs, 32H; ArH), 9.07 (brs, 32H; CONHCH$_2$), 10.70 (brs, 16H; ArOH), 11.09 (brs, 16H; ArOH); ^{13}C NMR (500 MHz, [D$_6$]DMSO, 25 °C): δ = 18.0 (CH_2), 23.6 (CH_2), 36.7 (CH_2), 49.2 (CH_2), 50.4 (CH_2), 115.6 (ArC), 117.7 (ArC), 118.9 (ArC), 128.4 (ArC), 134.0 (ArC), 160.3 (ArC), 169.6 (C=O); (+)-ESI-MS m/z 1840 [M^{4+}+4H], 1472 [M^{5+}+5H], 1227 [M^{6+}+6H], 1052 [M^{7+}+7H].

Astramol(Bn$_2$CAM)$_{16}$ (5): Colorless glass. Yield: 83%. IR (film from $CDCl_3$): $\tilde{\nu}$ = 1653, 2806, 2868, 2944, 3032, 3384 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.41–1.56 (brs, 60H; CH_2), 2.22/2.32 (brs, 84H; CH_2), 3.22 (brs, 32H; CONHCH_2), 4.99 (s, 32H; OCH_2), 5.03 (s, 32H; OCH_2), 7.03 (brs, 32H; ArH), 7.33 (brm, 160H; ArH), 7.60 (brs, 16H; ArH), 7.91 (brs, 16H; CONHCH$_2$); ^{13}C NMR (400 MHz, $CDCl_3$, 25 °C): δ = 24.2 (CH_2), 26.8 (CH_2), 38.2 (CH_2), 51.4 (CH_2), 52.1 (CH_2), 71.2 (CH_2-O), 76.3 (O-CH_2), 116.7 (ArC), 123.1 (ArC), 124.3 (ArC), 127.6 (ArC), 128.2 (ArC), 128.6 (ArC), 128.7 (ArC), 136.5 (ArC), 146.7 (ArC), 151.7 (ArC), 165.2 (C=O); (+)-ESI-MS m/z 2250 [M^{3+}+3H], 1688 [M^{4+}+4H], 1350 [M^{5+}+5H].

Astramol(H$_2$CAM)$_{16}$·14HCl (6): Amber foam. ^1H NMR (300 MHz, [D$_6$]DMSO, 25 °C): δ = 1.97 (brs, 60H; CH_2), 3.12 (brs, 116H; CH_2), 6.61 (brt, 16H; ArH), 6.88 (brd, 16H; ArH), 7.15 (brt, 16H; CONHCH$_2$), 7.37 (brd, 16H; ArH), 9.01 (brs, 16H; ArOH), 9.18 (brs, 16H; ArOH); ^{13}C NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 23.7 (CH_2), 36.8 (CH_2), 50.5 (CH_2), 115.5 (ArC), 117.9 (ArC), 118.4 (ArC), 119.4 (ArC), 146.6 (ArC), 150.0 (ArC), 170.4 (C=O); (+)-ESI-MS: m/z: 1289 [M^{3+}+3H], 967 [M^{4+}+4H], 774 [M^{5+}+5H], 645 [M^{6+}+6H].

Astramol(Bn$_2$CAM)$_{32}$ (7): Colorless glass. Yield: 25%. IR (film from $CDCl_3$): $\tilde{\nu}$ = 1653, 2811, 2868, 2946, 3032, 3386 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.35–1.55 (brs, 124H; CH_2), 2.17/2.29/2.38 (brs, 180H; CH_2), 3.16 (brs, 64H; CONHCH_2), 4.93 (s, 64H; OCH_2), 4.98 (s, 64H; OCH_2), 6.96 (brs, 64H; ArH), 7.20/7.28/7.33 (brs, 320H; ArH), 7.51 (brs, 32H; ArH), 7.85 (brs, 32H; CONHCH$_2$); ^{13}C NMR (500 MHz, $CDCl_3$, 25 °C): δ = 24.1 (CH_2), 26.7 (CH_2), 38.1 (CH_2), 51.2 (CH_2), 52.0 (CH_2), 71.0 (O-CH_2), 76.1 (CH_2-O), 116.5 (ArC), 122.9 (ArC), 124.2 (ArC), 127.5 (ArC), 128.0 (ArC), 128.5 (ArC), 128.6 (ArC), 136.5 (ArC), 146.5 (ArC), 151.6 (ArC), 165.1 (C=O).

Astramol(H$_2$CAM)$_{32}$·30HCl (8): Off-white powder. ^1H NMR (300 MHz, [D$_6$]DMSO, 25 °C): δ = 1.96/2.25 (brs, 124H; CH_2), 3.24/3.39 (brs, 244H; CH_2), 6.61 (brt, 32H; ArH), 6.88 (brd, 32H; ArH), 7.13 (brt, 32H; CONHCH$_2$), 7.33 (brd, 32H; ArH), 8.98 (brs, 32H; ArOH), 9.18 (brs, 32H; ArOH); ^{13}C NMR (500 MHz, [D$_6$]DMSO, 25 °C): δ = 18.0 (CH_2), 23.6 (CH_2), 36.8 (CH_2), 37.3 (N-CH_3), 49.3 (CH_2), 50.5 (CH_2), 115.5 (ArC), 117.9 (ArC), 118.4 (ArC), 119.3 (ArC), 146.5 (ArC), 149.9 (ArC), 170.3 (C=O).

Astramol(Bn3,2HOPO)$_{16}$ (9): Colorless oil. Yield: 84%. IR (film from $CDCl_3$): $\tilde{\nu}$ = 1601, 1647, 2870, 2948, 3065, 3381 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 1.37–1.44 (brs, 60H; CH_2), 2.22/2.31 (brs, 84H; CH_2), 3.16 (d, J = 6.2 Hz, 32H; CONHCH_2), 3.53 (s, 48H; NCH_3), 5.29 (s, 32H; OCH_2), 6.64 (d, J = 7.1 Hz, 16H; ArH), 7.05 (d, J = 7.1 Hz, 16H; ArH), 7.29 (d, J = 7.3 Hz, 48H; ArH), 7.37 (d, J = 6.5 Hz, 32H; ArH), 7.89 (brs, 16H; CONHCH$_2$); ^{13}C NMR (400 MHz, $CDCl_3$, 25 °C): δ = 24.1 (CH_2), 26.6 (CH_2), 37.6 (N-CH_3), 38.1 (CH_2), 51.2 (CH_2), 52.0 (CH_2), 74.7 (O-CH_2), 104.8 (ArC), 128.7 (ArC), 129.0 (ArC), 131.1 (ArC), 132.2 (ArC), 136.3 (ArC), 146.1 (ArC), 159.5 (ArC=O), 163.2 (C=O); (+)-ESI-MS: m/z: 2775 [M^{2+}+2H], 1850 [M^{3+}+3H], 1388 [M^{4+}+4H].

Astramol(H3,2HOPO)$_{16}$·14HCl (10): Beige foam. ^1H NMR (500 MHz, [D$_6$]DMSO, 25 °C): δ = 1.98/2.25 (brs, 60H; CH_2), 3.17/3.34 (brs, 116H; CH_2), 3.42 (s, 48H; NCH_3), 6.54 (d, J = 6.8 Hz, 16H; ArH), 7.12 (d, J = 6.8 Hz, 16H; ArH), 8.70 (brs, 16H; CONHCH$_2$), 10.76 (brs, 8H; ArOH), 11.10 (brs, 8H; ArOH); ^{13}C NMR (500 MHz, [D$_6$]DMSO, 25 °C): δ = 18.0 (CH_2), 23.5 (CH_2), 36.9 (CH_2), 37.3 (N-CH_3), 49.2 (CH_2), 50.2 (CH_2), 102.8 (ArC), 117.3 (ArC), 128.1 (ArC), 148.5 (ArC), 158.3 (ArC=O), 166.6 (C=O); (+)-ESI-MS: m/z: 2053 [M^{2+}+2H], 1369 [M^{3+}+3H], 1027 [M^{4+}+4H].

Astramol(Bn3,2HOPO)$_{32}$ (11): Amber foam. Yield: 79%. IR (film from $CDCl_3$): $\tilde{\nu}$ = 1602, 1652, 2869, 2948, 3065, 3384 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 1.37/1.44/1.56 (brs, 124H; CH_2), 2.21/2.32/2.39 (brs, 180H; CH_2), 3.16 (d, J = 5.6 Hz, 64H; CONHCH_2), 3.50 (s, 96H; NCH_3), 5.27 (s, 64H; OCH_2), 6.59 (d, J = 7.0 Hz, 32H; ArH), 7.03 (d, J = 6.9 Hz, 32H; ArH), 7.27 (d, J = 7.4 Hz, 96H; ArH), 7.36 (d, J = 6.6 Hz, 64H; ArH), 7.89 (brs, 32H; CONHCH$_2$); ^{13}C NMR (500 MHz, $CDCl_3$, 25 °C): δ = 24.1 (CH_2), 26.6 (CH_2), 37.5 (N-CH_3), 38.1 (CH_2), 51.1 (CH_2), 51.8 (CH_2), 52.0 (CH_2), 74.5 (O-CH_2), 104.7 (ArC), 128.5 (ArC), 128.6 (ArC), 128.9 (ArC), 131.1 (ArC), 132.2 (ArC), 136.2 (ArC), 145.9 (ArC), 159.4 (ArC=O), 163.1 (C=O); (+)-ESI-MS: m/z: 2810 [M^{4+}+4H], 2248 [M^{5+}+5H], 1873 [M^{6+}+6H].

Astramol(H3,2HOPO)$_{32}$·30HCl (12): Pale yellow foam. ^1H NMR (500 MHz, [D$_6$]DMSO, 25 °C): δ = 1.99/2.29 (brs, 124H; CH_2), 3.20/3.34 (brs, 244H; CH_2), 3.41 (s, 96H; NCH_3), 6.52 (brd, 32H; ArH), 7.11 (brd, 32H; ArH), 8.69 (brs, 32H; CONHCH$_2$), 10.72 (brs, 16H; ArOH), 11.10 (brs, 16H; ArOH); ^{13}C NMR (500 MHz, [D$_6$]DMSO, 25 °C): δ = 17.9 (CH_2), 23.5 (CH_2), 36.9 (CH_2), 37.3 (NCH_3), 49.2 (CH_2), 50.3 (CH_2), 102.7 (ArC), 117.0 (ArC), 128.1 (ArC), 148.7 (ArC), 158.3 (ArC=O), 166.8 (C=O); (+)-ESI-MS: m/z: 2088 [M^{4+}+4H], 1671 [M^{5+}+5H], 1392 [M^{6+}+6H], 1194 [M^{7+}+7H], 1045 [M^{8+}+8H]; (+)-MALDI-TOF: m/z: 8350 [M^++H].

Astramol(Bn3,2HOPO)$_{64}$ (13): White oil. Yield: 52%. IR (film from $CDCl_3$): ν = 1602, 1653, 2870, 2947, 3065, 3383 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 1.34/1.42/1.57 (brs, 188H; CH_2), 2.18–2.54 (brs, 372H; CH_2), 3.13 (brs, 128H; CONHCH_2), 3.44 (s, 192H; NCH_3), 5.20 (s, 128H; OCH_2), 6.50 (brs, 64H; ArH), 6.99 (brs, 64H; ArH), 7.23/7.32 (brm, 320H; ArH), 7.86 (brs, 64H; CONHCH$_2$); ^{13}C NMR (500 MHz, $CDCl_3$, 25 °C): δ = 24.2 (CH_2), 26.6 (CH_2), 37.5 (NCH_3), 38.0 (CH_2), 51.1 (CH_2), 51.5 (CH_2),

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52.0 (CH_2), 74.4 (OCH_2), 104.6 (ArC), 128.6 (ArC), 128.9 (ArC), 131.3 (ArC), 132.3 (ArC), 136.3 (ArC), 145.8 (ArC), 159.4 (ArC=O), 163.2 (C=O).

Astramol(3,2HOPO)$_{64}$·62 HCl (14): Pale amber foam. ^{1}H NMR (500 MHz, [D$_6$]DMSO, 25 °C): $\delta = 1.98$ (brs, 254 H; CH_2), 3.41 (brs, 498 H; CH_2), 3.45 (brs, 192 H; NCH_3), 6.54 (brs, 64 H; ArH), 7.15 (brs, 64 H; ArH), 8.70 (brs, 64 H; CON*H*CH$_2$); ^{13}C NMR (500 MHz, [D$_6$]DMSO, 25 °C): $\delta = 23.5$ (CH_2), 36.9 (CH_2), 37.2 (NCH_3), 50.3 (CH_2), 102.7 (ArC), 117.0 (ArC), 128.9 (ArC), 148.7 (ArC), 158.2 (ArC=O), 166.8 (C=O).

Starburst(Bn$_2$CAM)$_{32}$ (15): Beige foam. Yield: 51 %. IR (film from $CDCl_3$): $\tilde{\nu} = 1558$, 1653, 2831, 2940, 3066, 3300 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta = 2.16/2.24/2.39/2.56/2.64$ (brs, 292 H; C*H*$_2$), 3.18 (brs, 128 H; C*H*$_2$), 3.29 (s, 64 H; CONHC*H*$_2$), 4.99/5.02 (brs, 128 H; OCH_2), 7.01 (brs, 64 H; ArH), 7.30 (brm, 352 H; ArH), 7.64 (brs, 60 H; N*H*), 8.13 (brs, 32 H; CON*H*CH$_2$); ^{13}C NMR (400 MHz, $CDCl_3$, 25 °C): $\delta = 33.9$ (CH_2), 39.4 (CH_2), 50.2 (CH_2), 71.1 (OCH_2), 76.2 (OCH_2), 116.9 (ArC), 122.5 (ArC), 124.4 (ArC), 127.7 (ArC), 128.2 (ArC), 128.6 (ArC), 128.8 (ArC), 136.4 (ArC), 146.5 (ArC), 151.8 (ArC), 166.4 (C=O), 173.1 (C=O), 173.3 (C=O).

Starburst(H$_2$CAM)$_{32}$·30 HCl (16): Off-white foam. ^{1}H NMR (500 MHz, [D$_6$]DMSO, 25 °C): $\delta = 2.67$ (brs, 128 H; CH_2), 3.24/3.35 (brs, 388 H; CH_2), 6.92 (s, 32 H; ArH), 7.24 (d, $^3J = 7.5$ Hz, 32 H; ArH), 7.35 (d, $^3J = 6.5$ Hz, 32 H; ArH), 8.47/8.60 (brs, 60 H; NH), 8.98 (brs, 32 H; CON*H*CH$_2$), 10.38 (brs, 64 H; ArOH); ^{13}C NMR (500 MHz, [D$_6$]DMSO, 25 °C): $\delta = 34.9$ (CH_2), 38.9 (CH_2), 50.0 (CH_2), 115.3 (ArC), 117.8 (ArC), 118.3 (ArC), 119.3 (ArC), 146.5 (ArC), 150.0 (ArC), 169.6 (C=O), 170.4 (C=O).

Starburst(Bn3,2HOPO)$_{32}$ (17): White oily solid. Yield: 57 %. IR (film from $CDCl_3$): $\tilde{\nu} = 1542$, 1652, 2830, 2942, 3086, 3298 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): $\delta = 2.20/2.42/2.61/2.66$ (brs, 292 H; CH_2), 3.14/3.23 (brs, 128 H; CH_2), 3.31 (s, 64 H; CONHC*H*$_2$), 3.51 (s, 96 H; NCH_3), 5.30 (s, 64 H; OCH_2), 6.54 (brd, 32 H; ArH), 7.09 (d, $J = 7.0$ Hz, 32 H; ArH), 7.31/7.37 (m, 160 H; ArH), 7.58/7.78 (brs, 60 H; N*H*), 8.15 (brs, 32 H; CON*H*CH$_2$); ^{13}C NMR (400 MHz, $CDCl_3$, 25 °C): $\delta = 33.8$ (CH_2), 37.6 (NCH_3), 38.9 (CH_2), 39.6 (CH_2), 50.0 (CH_2), 52.3 (CH_2), 74.5 (OCH_2), 104.4 (ArC), 128.7 (ArC), 128.9 (ArC), 129.0 (ArC), 131.2 (ArC), 132.6 (ArC), 136.2 (ArC), 145.9 (ArC), 159.5 (ArC=O), 164.0 (C=O), 172.5 (C=O), 172.9 (C=O).

Starburst(H3,2HOPO)$_{32}$·30 HCl (18): Pale yellow solid. ^{1}H NMR (500 MHz, [D$_6$]DMSO, 25 °C): $\delta = 2.67$ (brs, 128 H; CH_2), 3.21/3.34 (brs, 388 H; CH_2), 3.43 (s, 96 H; NCH_3), 6.57 (d, $J = 7.0$ Hz, 32 H; ArH), 7.15 (d, $J = 5.5$ Hz, 32 H; ArH), 8.44 (brs, 32 H; CON*H*CH$_2$), 8.61/8.68 (brs, 60 H; NH), 10.39 (brs, 32 H; ArOH); ^{13}C NMR (500 MHz, [D$_6$]DMSO, 25 °C): $\delta = 29.3$ (CH_2), 37.3 (NCH_3), 39.1 (CH_2), 39.4 (CH_2), 49.0 (CH_2), 52.0 (CH_2), 102.8 (ArC), 117.0 (ArC), 128.1 (ArC), 148.8 (ArC), 158.3 (ArC=O), 166.8 (C=O), 169.6 (C=O), 170.5 (C=O).

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[1] a) M. Fischer, F. Vögtle, *Angew. Chem.* **1999**, *111*, 934–955; *Angew. Chem. Int. Ed.* **1999**, *38*, 884–905; b) A. W. Bosman, H. M. Janssen, E. W. Meijer, *Chem. Rev.* **1999**, *99*, 1665–1688; c) G. R. Newkome, E. He, C. N. Moorefield, *Chem. Rev.* **1999**, *99*, 1689–1746.
[2] D. K. Smith, F. Diederich, *Chem. Eur. J.* **1998**, *4*, 1353.
[3] C. B. Gorman, B. L. Parkhurst, W. Y. Su, K.-Y. Chen, *J. Am. Chem. Soc.* **1997**, *119*, 1141.
[4] B. Hong, T. P. S. Thoms, H. J. Murfee, M. J. Lebrun, *Inorg. Chem.* **1997**, *36*, 6146.
[5] R. Wang, Z. Zheng, *J. Am. Chem. Soc.* **1999**, *121*, 3349.
[6] G. R. Newkome, *J. Heterocyclic Chem.* **1996**, *33*, 1445.
[7] G. D. Storrier, K. Takada, H. D. Abruna, *Langmuir* **1999**, *15*, 872.
[8] Q. J. McCubbin, F. J. Stoddart, T. Welton, A. J. P. White, D. J. Williams, *Inorg. Chem.* **1998**, *37*, 3753.
[9] V. Balzani, S. Campagna, G. Denti, A. Juris, S. Serroni, M. Venturi, *Acc. Chem. Res.* **1998**, *31*, 26.
[10] G. R. Newkome, C. N. Moorefield, F. Votgle, *Dendritic Molecules. Concepts-Syntheses-Perspectives*, Springer, New York, **1996**.
[11] G. R. Newkome, *Dendrimers*, Springer, New York **1998**.
[12] M. S. Diallo, L. Balogh, A. Shafagati, J. H. Johnson Jr., W. A. Goddard III, D. A. Tomalia, *Envi. Sci. Tech.* **1999**, *33*, 820.
[13] S. M. Cohen, M. Meyer, K. N. Raymond, *J. Am. Chem. Soc.* **1998**, *120*, 6277.
[14] J. Xu, S. J. Frankin, D. W. Whisenhunt Jr., K. N. Raymond, *J. Am. Chem. Soc.* **1995**, *117*, 7245.
[15] J. Xu, T. D. P. Stack, K. N. Raymond, *Inorg. Chem.* **1992**, *31*, 4903.
[16] K. N. Raymond, M. E. Cass, S. L. Evans, *Pure Appl. Chem.* **1987**, *59*, 771.
[17] L. D. Loomis, K. N. Raymond, *Inorg. Chem.* **1991**, *30*, 906.
[18] J. R. Telford, K. N. Raymond in *Comprehensive Supramolecular Chemistry, Vol. 1* (Eds: J. L. Atwood, J. E. D. Davies, D. D. MacNicol, F. Vogtle), Elsevier, Oxford, **1996**, p. 245.
[19] S. M. Cohen, K. N. Raymond, unpublished results .
[20] Z. Xu, M. Kahr, K. L. Walker, C. L. Wilkins, J. S. Moore, *J. Am. Chem. Soc.* **1994**, *116*, 4537.
[21] E. C. Wiener, M. W. Brechbiel, H. Brothers, R. L. Magin, O. A. Gansow, D. A. Tomalia, P. C. Lauterbur, *Magn. Reson. Med.* **1994**, *31*, 1.
[22] K. L. Walker, M. S. Kahr, C. L. Wilkins, Z. Xu, J. S. Moore, *J. Am. Soc. Mass Spectrom.* **1994**, *5*, 731.
[23] T. Kawaguchi, K. L. Walker, C. L. Wilkins, J. S. Moore, *J. Am. Chem. Soc.* **1995**, *117*, 2159.
[24] B. Olenyuk, J. A. Whiteford, A. Fechtenkotter, P. J. Stang, *Nature* **1999**, *398*, 796.
[25] G. J. Kallos, D. A. Tomalia, D. M. Hedstrand, S. Lewis, J. Zhou, *Rapid Commun. Mass Spectrom.* **1991**, *5*, 383.
[26] B. L. Schwartz, A. L. Rockwood, R. D. Smith, D. A. Tomalia, R. Spindler, *Rapid Commun. Mass Spectrom.* **1995**, *9*, 1552.
[27] M. Yamashita, J. B. Fenn, *J. Phys. Chem.* **1984**, *88*, 4451.
[28] M. Yamashita, J. B. Fenn, *J. Phys. Chem.* **1984**, *88*, 4671.
[29] L. P. Tolic, G. A. Anderson, R. D. Smith, H. M. Brothers, R. Spindler, D. A. Tomalia, *Int. J. Mass Spectrom. Ion Proc.* **1997**, *165*, 405.
[30] M. Przybylski, M. O. Glocker, *Angew. Chem.* **1996**, *108*, 878–899; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 806–826.
[31] J. C. M. Van Hest, D. A. P. Delnoye, M. W. P. L. Baars, C. Elissen-Roman, M. H. P. van Genderen, E. W. Meijer, *Chem. Eur. J.* **1996**, *2*, 1616.
[32] G. L. M. Koper, M. H. P. van Genderen, C. Elissen-Roman, M. W. P. L. Baars, E. W. Meijer, M. Borkovec, *J. Am. Chem. Soc.* **1997**, *119*, 6512.
[33] It has been previously observed that simple, bidentate salicylamide, catecholamide, and hydroxypyridinonamide chelators bind ferric ion by forming the successive species ML, ML_2, and ML_3. The assumption that the three major iron species formed in solution during the dendrimer titration are the well-defined mono-bidentate (analogous to ML complex), bis-bidentate (ML_2), and tris-bidentate complexes (ML_3) does not facilitate rigorous fitting of the data. This is because the large number of intermediates species that adopt mixed binding modes (i. e., combinations of mono-, bis-, and tris-bidentate complexes) within a single dendrimer molecule prevent the use of any model for the mathematical treatment of the data.
[34] E. T. Clarke, A. E. Martell, *Inorg. Chim. Acta* **1992**, *191*, 57.
[35] W. R. Harris, C. J. Carrano, K. N. Raymond, *J. Am. Chem. Soc.* **1979**, *101*, 2213.
[36] F. L. Weitl, W. R. Harris, K. N. Raymond, *J. Med. Chem.* **1979**, *22*, 1281.
[37] P. D. Beer, D. Gao, *Chem. Commun.* **2000**, 443.
[38] T. M. Garrett, P. W. Miller, K. N. Raymond, *Inorg. Chem.* **1989**, *28*, 128.
[39] J. Xu, K. N. Raymond, unpublished results.

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