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Synthesis of Metallomacrocyclophanes: Deduction of Structure from Electrospray Ionization Mass Spectroscopy and Molecular Mechanics Computations.

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Abstract: The synthesis of metallomacrocyclophanes **7-tos** and **8**, in which environmentally tunable ferric-catecholamide coordination bonds hold the cyclophane together, is described. UV-vis spectroscopic studies of **7-tos** and **8** display characteristics of ferric-tris(catecholamide) complexes, i.e. burgundy color (λ_{max}= ca. 490 nm)and high stability, at high pH, and 1:1 stoichiometry. Electrospray ionization mass spectra of **8** show prominent ions due to a monomeric 1:1 (ligand/metal) complex. Molecular mechanics calculations on **7** and **8** indicate that *out*-isomeric configurations predominate, leaving a void in the metallomacrocyclophane interiors.

INTRODUCTION

The development of design principles plays an important role in creating a comprehensive strategy for the construction of macrocyclophanes.[1] Recently, an "origami" approach, using metal assisted acetylene trimerization, has been implemented to prepare a covalently closed macrocyclophane (figure 1).[1a,2] This approach also applies to the synthesis of metallomacrocyclophanes, i.e. macrocyclophanes in which metal ligand coordination bonds take the place of covalent bonds in order to hold the cyclophane together.[3] Elaboration of a molecular keystone[1b] with linkers ending in metal-coordinating units provides the necessary open structure, and addition of an appropriate metal gathers the dangling ends into a well organized metallomacrocyclophane assembly.[3,4] Ferric-tris(catecholate) complexes are attractive metal-ligand complexes

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for such a study, because the stability of these complexes is pH sensitive. In basic aqueous solution, these complexes display a composite bond strength comparable to a weak covalent bond, however, in acidic solution the stability of the complex drops to the point that the equilibrium shifts in favor of the uncomplexed catechol.[5] The topology of molecules so equipped could therefore be manipulated by the pH of the solution. Herein, we report the synthesis of two 2,6,10-triaminotrioxatricornan keystones with appended catechol metal coordinating units, and characterization of their polycyclic metallomacrocyclophanes formed by complexation to ferric ions in aqueous and acetonitrile media.

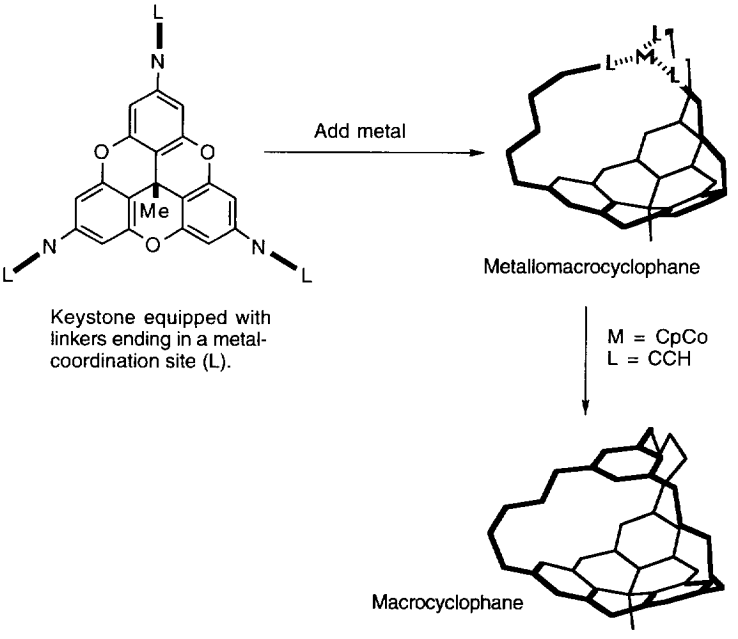
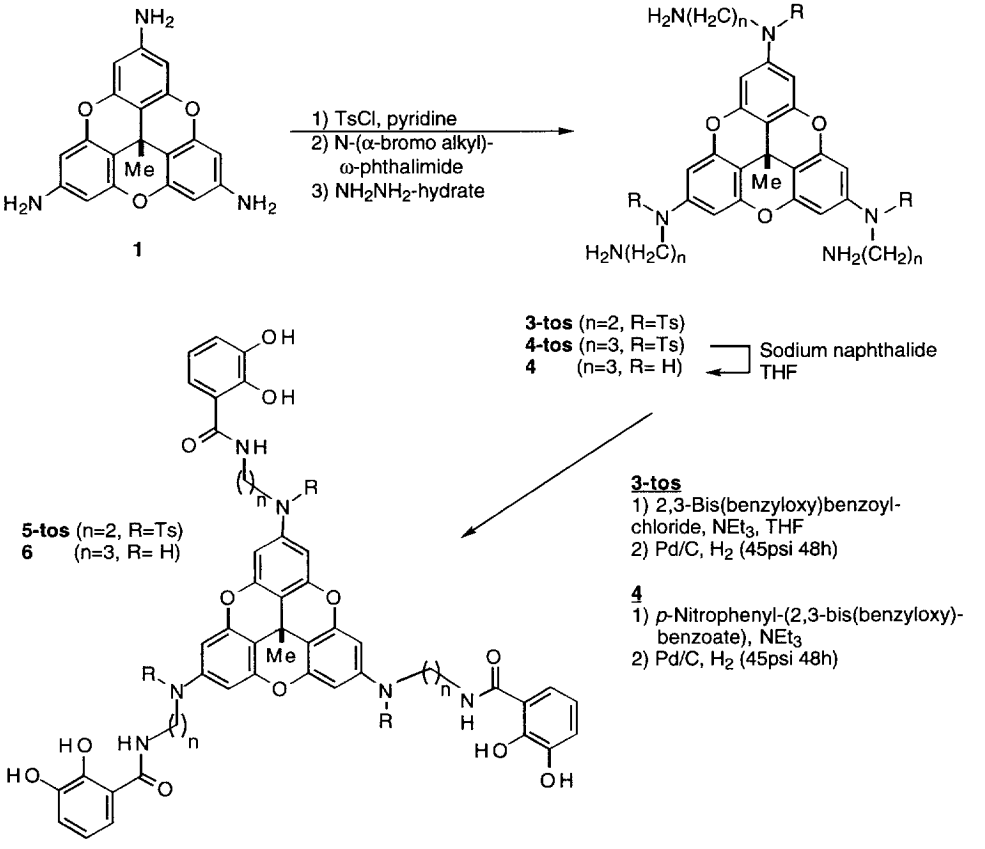


Figure 1. An Origami approach to the synthesis of (metallo)macrocyclophanes. Computer drawings of the metallomacrocyclophane and macrocyclophane were generated in MacMoMo, with oxygen and nitrogen atom labels omitted for clarity.

SYNTHESIS

The bowl-shaped 2,6,10-triaminotrioxatricornan (**1**) serves as the supporting keystone for our constructions of polycyclic metallomacrocyclophanes (scheme 1).[1a,b] Tosylation of the radial amino groups of **1** allows the nitrogens to be alkylated with a "Gabriel" protected α,ω-aminohaloalkane. Deprotection with hydrazine hydrate yields keystones with terminal ethyl (**3-tos**) and propyl (**4-tos**) amines appended in good to moderate yield. Acylation of **3-tos** with 2,3-bis(benzyloxy)benzoylchloride[6] followed by hydrogenolysis of the benzyloxy groups with palladium on charcoal produces the ethylene linked keystone/catechol composite **5-tos** in 67% yield (2 steps).

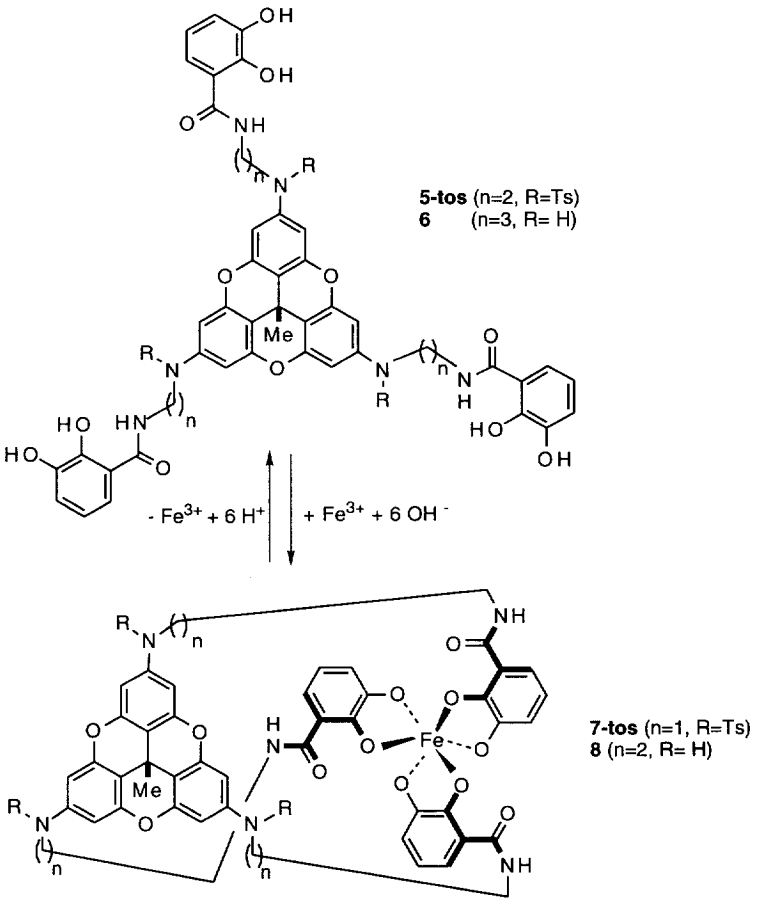
Scheme 1



Removal of the tosyl groups is best achieved prior to formation of the catecholamide. For example, treatment of **4-tos** with sodium naphthalide cleanly produces the hexa-amine **4** (66%). Reaction of **4** with *p*-nitrophenyl-2,3-bis(benzyloxy)benzoate selectively acylates the primary amines,[7] and debenzylation unveils the propylene linked keystone/catechol composite **6**.

Characterization of **5-tos** and **6** follows from their ^{1}H and ^{13}C NMR spectra, which manifest the three-fold symmetry of the molecules. Furthermore, FABMS spectra for **5-tos** and **6** show the expected $[M+H]^+$ ions at m/z 1345 and 925 respectively. Addition of ferric ion to **5-tos** and **6** creates the corresponding metallomacrocyclophanes **7-tos** and **8** (scheme 2), as demonstrated by the appearance of the characteristic UV-vis absorption of ferric tris(catecholamide) complexes, and by molecular weight determinations (vide infra).

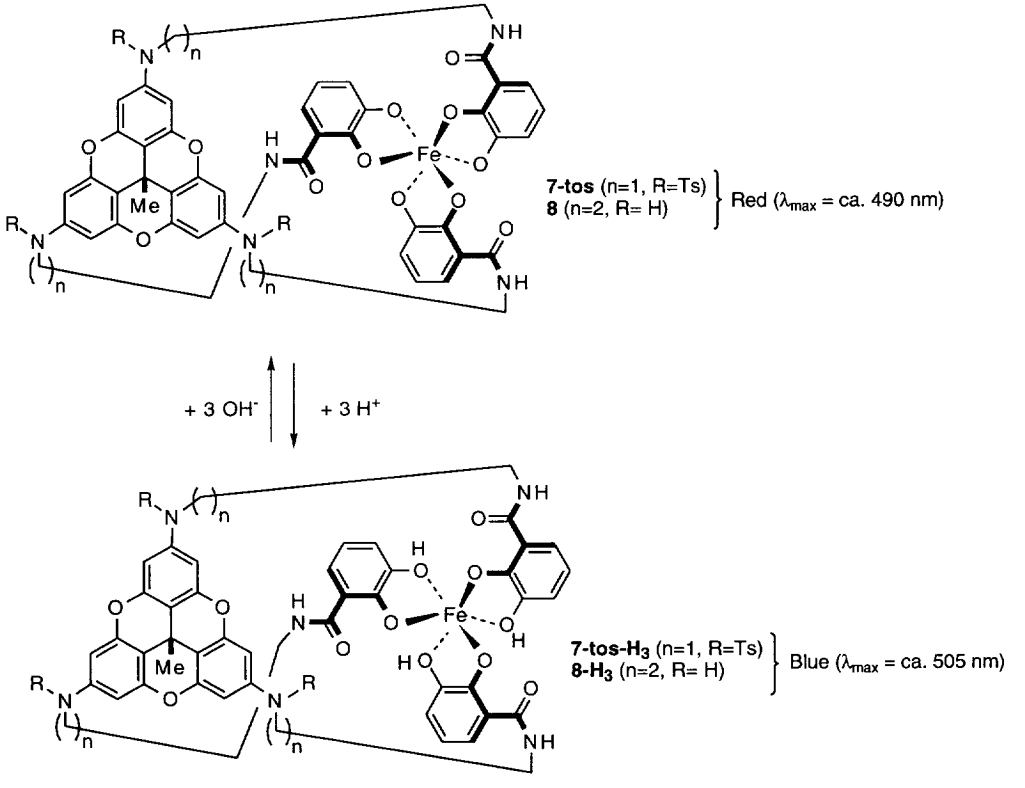
Scheme 2



CHARACTERIZATION OF METALLOMACROCYCLOPHANES 7-TOS AND 8.

A classic feature of ferric tris(catecholamide) complexes is the shift from the red color of their trianionic form to a blue/purple color upon protonation.[8] Addition of a ferric chloride solution to **5-tos** in aqueous base causes the formation of a red soluble complex (λ_{max}=491 nm, ε_{491}=4900 $M^{-1}cm^{-1}$) **7-tos**.[9] Lowering the pH results in a continuous blue shift of the ligand-to-metal charge-transfer (LMCT) absorption, and at pH less than 7 the blue neutral complex **7-tos-H_3** precipitates.[10] The blue shifted absorption band is also seen for the neutral complex **8-H_3**, which is prepared from **6** in an acetonitrile solution using ferric(acac)$_3$ (λ_{max}=505 nm, ε_{490}=4352 $M^{-1}cm^{-1}$).[11] Addition of excess tetramethyl ammonium hydroxide to the neutral **8-H_3** in acetonitrile produces the corresponding deprotonated trianionic red form **8** (λ_{max}=490 nm, ε_{490}=5833 $M^{-1}cm^{-1}$) (scheme 3).

Scheme 3



In order to establish the Fe^{3+} to **5**-tos ratio in the metallomacrocyclophane **7-tos**, a basic aqueous solution of **5**-tos was titrated with an aqueous ferric chloride solution and the absorbance at 492 nm was monitored.[12] The titration experiment showed that addition of ferric ion beyond 1 equivalent causes no further increase in the absorbance at 492 nm establishing the expected 1:1 stoichiometry (**5-tos**/Fe^{3+}).

The high stability of the iron complex in **7-tos** and **8**, indicated by the titration curve, was also demonstrated by a competition experiment between **5-tos** and ethylenediaminetetraacetic acid (EDTA). Addition of EDTA (700 equivalents) to a pH 12 solution of **7-tos** resulted in no changed in absorbance at 492 nm. On the basis of this result and the known binding constant for iron-EDTA, a lower limit for the formation constant of the metal complexation was calculated.[13,14]

Contrary to the naturally occurring ferric complexing agent enterobactin,[8] which is structurally preorganized for binding ferric ion, the open keystone/catechol composites **5**-tos and **6** are not preorganized for ferric ion binding. In these studies, the inherent strength of the catechol metal interaction[5,8] is exploited to organize a flexible organic ligand into an ordered polycyclic structure. Due to this lack of preorganization there is some concern that addition of ferric ion to **5**-tos or **6** would result in formation of polymeric complexes with UV-vis spectral properties accidentally similar to the monomeric complexes and displaying metal/ligand ratios close to 1:1 (i.e. 3 catecholamides to 1 iron).[15] To probe this question the solution molecular weight of the metallomacrocyclophane **8**-H_3 was obtained by electrospray ionization mass spectroscopy (ESI-MS)[16] and that of **7-tos** was probed by ultrafiltration techniques.[17]

The recent advent of ESI-MS makes it possible to obtain molecular weights of low volatile species such as proteins, polymers and transition metal complexes.[18,19] ESI-MS on samples of neutral **8**-H_3 prepared in acetonitrile shows a molecular ion corresponding to intact monomeric metallomacrocyclophanes with a prominent $[M-H]^-$ peak at m/z 976, and a doubly charged $[M-2H]^{2-}$ ion at m/z 487 (figure 2).[20] Ultrafiltration experiments on acetonitrile solutions of **7-tos-H3** indicate that the molecular weight is significantly less than 10 KD, ruling out polymer formation and corroborating the ESI-MS results for **8**-H_3.[21,22] The low abundance of peaks from any impurity ions in the ESI-MS spectra demonstrates the success of the synthetic methodology utilized herein for assembly of metallomacrocyclophanes, especially in light of that no purification was performed after incorporation of the metal atom.

STRUCTURE OF THE METALLOMACROCYCLOPHANES.

Construction of CPK models of the ethylene (**7**) and propylene (**8**) linked metallomacrocyclophanes reveals two classes of molecular geometries: One in which the central methyl group on the keystone is located outside (*out*-isomer), and one in which it is located inside (*in*-isomer) the cyclophane cavity.[23] The *out*-isomers have internal void dimensions that would allow for incorporation of organic molecules such as benzene,[24] however, most of the internal space in the *in*-isomers is occupied by the *in* oriented methyl group.

In order to probe the dimensions of the interior voids more accurately and to estimate the energetic difference between the *in*- and *out*-isomers, energy minimized structures were obtained by empirical force field (EFF) calculations.[25,26,27] EFF calculations on the keystone portion alone and cyclophanes constructed from it have previously been shown to agree well with crystal structures and higher level calculations.[1a,4,28]

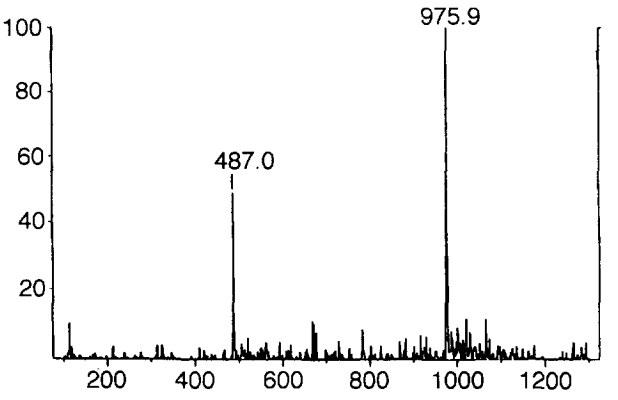


Figure 2. Electrospray generated negative ion mass spectrum of metallomacrocyclophane **8-H_3**, showing a prominent $[M-H]^-$ ion at 976 and a doubly charged $[M-2H]^{2-}$ ion at 487. The electrospray ion source was operated at atmospheric pressure at 2000 V. The samples were dissolved in 50/50 DMSO:MilliQ water infused at 2 mL/min with an analyte concentration of 30 pm/mL.

Minimizations from idealized C_3 symmetric and extended alkyl chain input geometries leads to the four structures **7**-*out*, **7**-*in*, **8**-*out*, and **8**-*in*. (figure 3)[29] The calculated distance from the ferric ion to the best plane formed by the radial carbons (2,6,10) of the keystones for the ethylene linked **7**-*out* is ca. 6 Å and for the propylene-linked **8**-*out* is ca. 8 Å. The distance from the methyl group carbon to the metal in the **7**-*in*-isomer is only ca. 3 Å and for the propylene-linked **8**-*in* is ca. 4.5 Å. The geometries at the metal coordination sites in **7**-*out*, **7**-*in*, **8**-*out*, and **8**-*in* obtained from the EFF calculations agree reasonably well with those obtained from crystal structures.[30,31]

The EFF calculations show that for both linker lengths the *out*-isomers are more stable than the corresponding *in*-isomers, indicating that under thermodynamic control the *out*-isomeric configurations should predominate.[32] The relative instability of the *in*-isomer is explained by a steric repulsion between the *o*-oxygens (at C-2) of the catecholamides and the inward turned methyl groups. To minimize this repulsion the twist angle of the octahedral complex increases and the keystone flattens out.

CONCLUSION

We have demonstrated a novel synthetic approach for assembly of macrocyclophanes in which a final metal coordination affects its formation. The metallomacrocyclophanes show LMCT bands similar to simple analogs such as ferric tris(*N,N*-dimethyl-2,3-dihydroxybenzamide) and 1:1 stoichiometry with formation constants in excess of 10^{27}. ESI-MS as well as ultrafiltration techniques support monomer formation. The

ESI-MS also demonstrates the homogeneity of the metallomacrocyclophane preparations. Molecular mechanics calculations indicate that under thermodynamic control the *out*-isomeric configurations will predominate.

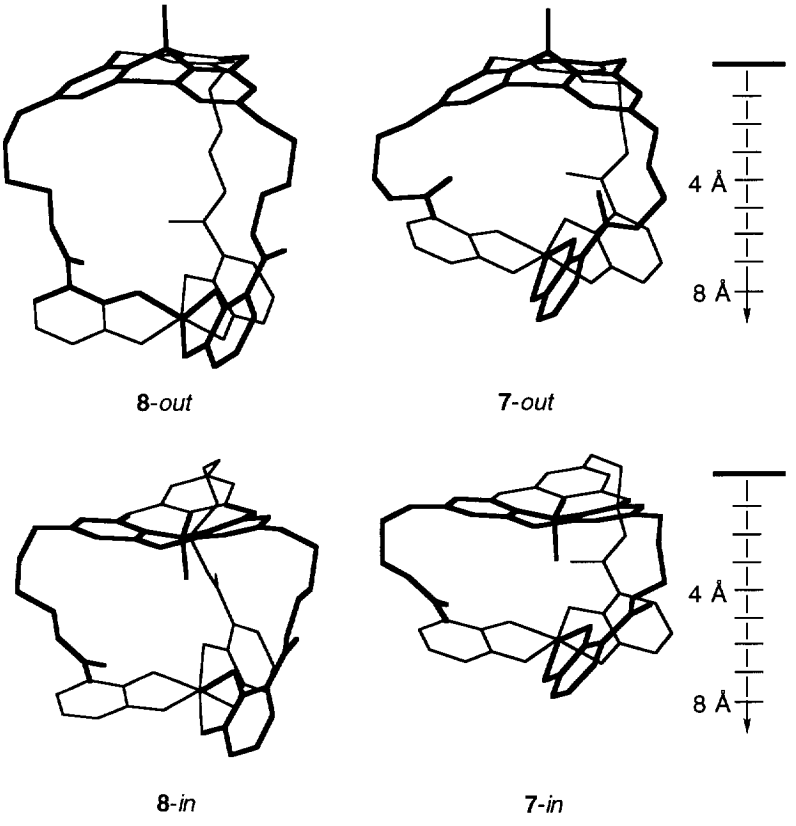


Figure 3 MacMoMo generated drawing of the EFF-calculated structures **7**-*in*, **7**-*out*, **8**-*in* and **8**-*out*. All atom labels omitted for clarity.

EXPERIMENTAL SECTION

General Data. Proton NMR spectra were recorded on a ^{1}H NMR spectrometer equipped with a Nicolet 1180E computer interfaced to an Oxford magnet operating at 360 MHz or on a Varian 500 MHz Unity spectrometer. Carbon NMR were recorded on a Nicolet NT200 spectrometer operating at 50 MHz or on a Varian 500 Unity spectrometer operating at 125 MHz. ESI-MS was recorded on a Finnigan SSQ 710 quadrupole mass spectrometer with ESI interface from Analytica of Branford. Infrared spectra were recorded on a Perkin-Elmer

1420 IR spectrometer. UV-vis spectra were recorded on a Perkin-Elmer 6 UV spectrometer. Unless otherwise stated, commercial chemicals were used as supplied.

2,6,10-Tris[*N*-(3-aminoethyl)tosylamino]-12c-methyl-4,8,12-trioxatricornan (3-tos): **2,6,10-Tris(tosylamino)-12c-methyl-4,8,12-trioxatricornan**[1a] (1.00 g, 1.24 mmol) was dissolved in 20 mL of dimethylformamide (distilled from calcium hydride). To this solution was added *N*-(2-bromoethyl)phthalimide (2.83 g, 11.1 mmol) and potassium carbonate (4.63 g, 33.5 mmol). The solution was heated at 75 °C for 24 h, after which the solvent was removed under reduced pressure. The residue was dissolved in tetrahydrofuran/diethyl ether and was extracted first with 0.1 M HCl then with brine. The organic phase was collected, dried with sodium sulphate and concentrated under reduced pressure to yield an oil. The crude product was purified by flash chromatography on silica gel (100-200 Mesh) eluting with 3% methanol/dichloromethane to give **phthalimide protected 3-tos** (1.22 g, 76 %) as a white solid (mp: 240-250 °C). **Phthalimide protected 3-tos** (800 mg, 0.61 mmol) and hydrazine hydrate (950 mg, 16 mmol) were dissolved in 40 mL of tetrahydrofuran. The clear solution was refluxed for 5 h resulting in formation of a white solid material. The solution was diluted with 100 mL of tetrahydrofuran and extracted twice with a 0.5 M sodium hydroxide solution. The organic phase was collected, dried with sodium sulphate and concentrated under reduced pressure to yield **3-tos** (520 mg, 90 %) as a white solid. ^{1}H NMR ($CDCl_3$) δ 7.56 (6 H, d, J= 8.1 Hz), 7.31 (6 H, d, J= 8.1 Hz), 6.70, (6 H, s), 3.55 (6 H, t, J= 6.0 Hz), 2.76 (6 H, t, J= 6.0 Hz), 2.46 (9 H, s), 1.54 (3 H, s); ^{13}C{^{1}H} NMR ($CDCl_3$) δ 151.7, 143.9, 139.5, 134.9, 129.7, 127.6, 113.7, 112.4, 53.98, 40.17, 31.82, 24.12, 21.64; IR (KBr) 3385, 1618, 1163 cm^{-1}; FABMS (high resolution) found 937.2739 (calcd for $C_{47}H_{49}N_6O_9S_3$ 937.2723 (MH+)).

2,6,10-Tris[*N*-(3-aminopropyl)amino]-12c-methyl-4,8,12-trioxatricornan (4): **2,6,10-Tris(tosylamino)-12c-methyl-4,8,12-trioxatricornan**[1a] (2.10 g, 2.6 mmol) was dissolved in 200 mL of acetone. To this solution was added *N*-(3-bromopropyl)phthalimide (6.27 g, 23.4 mmol) and potassium carbonate (4.31 g, 31.2 mmol). The solution was refluxed for 20 h, after which the acetone was evaporated under reduced pressure. The solid residue was dissolved in tetrahydrofuran/diethyl ether and extracted with first 0.1 M HCl followed by water. The organic solution was collected, dried with magnesium sulphate and concentrated under reduced pressure to yield an oil. The crude product was purified by flash chromatography on silica gel (230-450 Mesh) eluting with 60% ethylacetate:hexanes (r_f=0.27) to give **phthalimide protected 4-tos** (2.1 g, 59%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.80 (6 H, m), 7.68 (6 H, m), 7.55 (6 H, d, J= 8.2 Hz), 7.32 (6 H, d, J= 8.2 Hz), 6.71 (6 H, s), 3.74 (6 H, t, J= 7.2 Hz), 3.58 (6 H, t, J= 6.9 Hz), 2.46 (9 H, s), 1.86 (6 H, m), 1.53 (3 H, s). **Phthalimide protected 4-tos** (2.1 g, 1.53 mmol) was dissolved in 150 mL of tetrahydrofuran. Hydrazine hydrate (2.38 g, 40 mmol) was added and the solution was refluxed for 4 h during which a white solid formed. To the cooled solution was added 200 mL of diethyl ether and the solution was extracted with 300 mL of a 0.5 M potassium hydroxide solution. The organic phase was collected, dried with sodium sulphate and concentrated under reduced pressure to give **4-tos** (1.46 g, 97%) as a white solid. **4-tos** (1.46, 1.49 mmol) was dissolved in 50 mL of dry tetrahydrofuran. Freshly prepared sodium naphthalide 0.3 M in dry tetrahydrofuran solution was then added, via syringe, until a green

color persisted. After addition the solution was stirred at ambient temperature for another 30 min. Excess sodium naphthalide was quenched by addition of 5 mL of water followed by 200 mL of 5% aqueous HCl. The naphthalene was removed by extracting the acidic aqueous phase containing **4-tos** with two portions (100 mL) of diethyl ether. The aqueous phase was neutralized by addition of solid sodium hydroxide and extracted twice with tetrahydrofuran. The organic layer was collected, dried with sodium sulphate and concentrated under reduced pressure to give **4** (511 mg, 66 %) as an amorphous unstable solid. ^{1}H NMR ($CDCl_3$) δ 6.16 (6 H, s), 3.18 (6 H, t, J= 6.7 Hz), 2.84 (6 H, t, J=6.7 Hz), 1.76 (6 H, m), 1.41 (3 H, s); ^{13}C{^{1}H} NMR ($CDCl_3$) δ 152.6, 149.5, 103.3, 94.64, 41.23, 34.33, 32.20, 29.79, 21.58; IR (KBr) 3340 (broad), 1615, 1160 cm^{-1}; We were unable to obtain a molecular ion using FABMS technique.

Benzyl protected siderophore 5-tos (ethylene connected). **3-tos** (525 mg, 0.56 mmol) and triethylamine (187 mg, 2.78 mmol) were dissolved in 30 mL of dry tetrahydrofuran. 2,3-Bis(benzyloxy)benzoylchloride (790 mg, 2.24 mmol) dissolved in 8 mL of dry tetrahydrofuran was added over 30 min. After addition the solution was stirred for an additional hour and then diluted with 100 mL of tetrahydrofuran. The solution was extracted twice with a saturated sodium bicarbonate solution followed by water. The collected organic layer was dried with sodium sulfate and concentrated under reduced pressure to give a solid residue. The crude product was purified by flash chromatography on silica gel (100-200 Mesh) eluting with 65 % ethyl acetate/hexanes to give **benzyl protected siderophore 5-tos** (710 mg, 67 %) as a white solid. ^{1}H NMR ($CDCl_3$) δ 8.10 (3 H, t), 7.63 (3 H, dd, J= 6.0 Hz and J= 2.2 Hz), 7.50 (6 H, d, J= 8.3 Hz), 7.47-7.30 (m), 7.24 (6 H, d, J= 8.3 Hz), 7.14-7.06 (6 H, m), 6.61 (6 H, s), 5.15 (12 H, s), 3.54 (6 H, t, J= 6.4 Hz), 3.34 (6 H, m), 2.40 (9 H, s), 1.38 (3 H, s); ^{13}C{^{1}H} NMR ($CDCl_3$) δ 165.3, 151.6, 146.8, 143.8, 139.6, 136.3, 134.9, 129.6, 128.7, 128.2, 127.6, 126.8, 124.2, 123.1, 117.1, 113.6, 112.4, 71.22, 49.86, 38.64, 31.73, 23.98, 21.61

Benzyl protected 6 (propylene connected). **4** (400 mg, 0.77 mmol) and triethylamine (313 mg, 3.1 mmol) were dissolved in 20 mL of dimethylformamide. *p*-Nitrophenyl-2,3-bis(benzyloxy)benzoate (1.41 g, 3.1 mmol) dissolved in 20 mL of tetrahydrofuran was added over 30 min. The solution was stirred overnight after which the solvent was removed under reduced pressure. To the residual oil was added 100 mL of water resulting in dissolution of *p*-nitrophenol and crystallization of **benzyl protected 6**. The gummy solid was isolated and then purified by flash chromatography on silica gel (230-450 Mesh) eluting with first 50% ethylacetate:hexanes, followed by 75 % ethylacetate:hexanes. Fractions collected during elution with the more polar eluent contained **benzyl protected 6.** ^{1}H NMR ($CDCl_3$) δ 8.03 (3 H, t, J= 5.8 Hz), 7.75 (3 H, m) 7.50-7.15 (36 H, m), 6.10 (6 H, s) 4.05 (3 H, s), 3.35 (6 H, m), 3.02 (6 H, t, J= 6.3 Hz), 1.59 (6 H, m), 1.39 (3 H, s); ^{13}C{^{1}H} NMR ($CDCl_3$) δ 165.4, 153.2, 151.7, 148.3, 146.9, 136.4, 128.7, 128.7, 128.7, 128.2, 127.6, 127.1, 124.4, 123.3, 117.1, 105.4, 96.00, 76.42, 71.32, 41.20, 37.01, 31.85, 28.65, 22.46; IR (KBr) 3360, 1620, 1170 cm^{-1}; FABMS found 1467 (calcd for $C_{92}H_{85}N_6O_{12}$ 1467 (MH+)).

Siderophore 5-tos. **Benzyl protected 5-tos** (620 mg, 0.33 mmol) was dissolved in 20 mL of tetrahydrofuran and 10 mL of glacial acetic acid. Palladium on charcoal (10 %, 170 mg) was added to the

solution and the mixture was shaken in a Parr apparatus under 45 psi of hydrogen for 48 h. The catalyst was then removed by filtration and the solvent evaporated under reduced pressure to give **5-tos** (0.45 g, 100 %) as an off-white solid. ^{1}H NMR (acetone-d_6) δ 12.78 (3 H, s), 8.20 (3 H, t, 5 Hz), 7.63 (6 H, d, J= 8.2 Hz), 7.52 (3 H, s), 7.39 (6 H, d, J= 8.2 Hz), 7.06 (3 H, d, J= 7.5 Hz), 6,85 (6 H, s), 6.78 (3 H, d, J= 7.6 Hz), 6.51 (3 H, t, J= 7.9 Hz), 3.98 (6 H, t, J= 5.7 Hz), 3.63 (6 H, t), 2.43 (9 H, s), 1.25 (3 H, s); ^{13}C{^{1}H} NMR (acetone-d_6) δ 171.3, 152.0, 150.4, 146.9, 144.7, 141.4, 136.4, 130.4, 128.3, 118.9, 118.7, 117.3, 114.7, 113.8, 113.1, 50.14, 39.87, 34.87, 31.35, 24.30, 21.36; IR (KBr) 3400, 1640, 1615, 1160 cm^{-1}; FABMS found 1345 (calcd for $C_{68}H_{61}N_6O_{18}S_3$ 1345 (MH+)).

Siderophore 6 (propylene connected). Benzyl protected 6 (200 mg, 0.136 mmol) was dissolved in 3 mL of tetrahydrofuran. Absolute ethanol was added until the solution started to turn cloudy after which palladium on carbon (10 %) (50 mg) was added. The mixture was shaken in a Parr apparatus under 45 psi of hydrogen for 48 h. The catalyst was then removed by filtration and the solvent evaporated under reduced pressure, to give **6** (116 mg, 92 %) as an off-white solid. ^{1}H NMR (DMSO-d_6) δ 8.85 (3 H, t), 7.28 (3 H, d, J= 8.0 Hz), 6.89 (3 H, d, J= 8.2 Hz), 6.66 (3 H, t, J= 8.0 Hz), 6.13 (6 H, s), 5.86 (3 H, s), 3.06 (6 H, m), 1.80 (6 H, m), 1.29 (3 H, s); ^{13}C{^{1}H} NMR (DMSO-d_6) δ 169.8, 152.6, 149.8, 149.3, 146.2, 118.6, 117.7, 117.2, 115.0, 103.5, 94.82, 40.67, 37.03, 32.22, 28.30, 21.59; IR (KBr) 3390, 1620, 1165 cm^{-1}; FABMS (high resolution) found 925.3380 (calcd for $C_{50}H_{49}N_6O_{12}$ 925.3408 (MH+)).

Preparation of the ferric complexes 8 and 8-H$_3$ in acetonitrile. **6** (10 mg, 0.011 mmol) was dissolved in 10 mL of acetonitrile (freshly distilled from calcium hydride and degassed). The solution was stirred under a blanket of argon and ferric acetylacetonate (108 ul, 0.10 M) dissolved in acetonitrile was added. After stirring overnight a deep blue solution characteristic of **8** was formed. UV (MeCN) λ_{max} 505 nm ($\varepsilon_{(505\ nm)}$= 4352 M^{-1}cm^{-1}); ESI-MS found 976 (calcd for $C_{50}H_{44}N_6O_{12}Fe$ 976 (M-H)$^-$). (Ultrafiltration of a 0.3 mM acetonitrile solution of **7-tos-H$_3$**, prepared as described for **8-H$_3$**, using an AMICON (MW 10 KD cutoff) shows a solution molecular weight of less than 10 KD). To **8-H$_3$** (2.0 mL, 0.11 mM) was added tetramethylammonium hydroxide (0.1 M, 20 ul) dissolved in water, immediately producing the characteristic red color of the trianionic [ferric-tris(catecholamide)]$^{3-}$ complex **8**. UV (2 % H_2O/MeCN) λ_{max} 490 nm (ε_{490} = 5833 M^{-1}cm^{-1})

Preparation of the ferric complexes 7-tos-H3 and 7-tos in water. To 20 mL of a degassed aqueous sodium hydroxide solution (60 mM) was added **5-tos** (10.0 mg, 0.0074 mmol) dissolved in 2 mL of degassed methanol. The resulting cloudy mixture was stirred under a static blanket of argon, and an aqueous ferric chloride solution (80 ul, 0.1 M) was added via syringe, immediately producing the burgundy red solution of aqueous **7-tos**. UV (9% MeOH/H_2O) λ_{max} 491 nm (ε_{491} = 4900 M^{-1}cm^{-1}); Ultrafiltration of an aqueous 0.7 mM solution of **7-tos** using AMICON (10 KD) shows a solution molecular weight in excess of 10 KD, indicating that aggregation occurs at this concentration. The **7-tos** solution was acidified to pH 5 by addition of 1 M hydrochloric acid resulting in precipitation of the neutral complex, **7-tos-H3**. The solution was centrifuged and the supernatant was removed leaving a dark-blue solid, which is soluble in DMSO.

FABMS((-), nitrobenzyl alcohol matrix) found 1396 (calcd for $C_{68}H_{56}N_6O_{18}S_3Fe$ 1396 $(M\text{-}H)^-$); FABMS((+), nitrobenzyl alcohol matrix)) found 1398 (calcd for $C_{68}H_{58}N_6O_{18}S_3Fe$ 1398 $(M+H)^+$).

Stoichiometry determination: To **5-tos** (17 mg, 13.0 μmol) dissolved in 1.00 mL of acetone were added 9.00 mL of degassed phosphate buffer (0.05 M, pH 11.4) and EDTA (5 mmol). In the absence of EDTA excess ferric ion precipitates, which causes light scattering. The solution was titrated by addition of 0.1 mole-eq portions of aqueous ferric chloride and after each addition the solution was stirred for five min after which an aliquot was taken out and the absorbance at 492 nm was recorded.

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32. These empirical methods can give acceptable geometries but detailed quantitative analysis of the energies is unwarranted. As such, we restrict our discussion to a qualitative ranking.

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