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Synthesis of Salicylamide and Bipyridine Containing Ligands for Iron(II) and Iron(III) Coordination

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Abstract. The synthesis and characterization of potential iron sequestering agents is reported. Both *single-stranded* ligands incorporating salicylamides for chelation of iron(III) and bipyridines for iron(II) as well as tripodal systems have been synthesized.

INTRODUCTION

Iron is the most abundant transition element on earth's crust. Whether this fact alone explains the predominance of iron as transition metal in biological systems is not clear. Its use has created a dependence that has survived the appearance of dioxygen in the atmosphere ca. 2.5 billion years ago, with concomitant oxidation of ferrous to ferric ion and rust. Under physiological conditions, Fe(III) is mostly present as $Fe(OH)_3$, or FeO(OH), and is extremely insoluble. Nature thus has devised very efficient scavengers, siderophores, to collect this vital metal.[1]

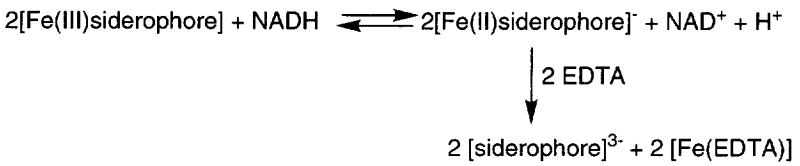
Most siderophores possess either tris-catechol or tris-hydroxamate binding sites and more than 200 naturally occurring iron scavengers have been isolated and characterized to date.[2] As both an iron deficiency and iron excess are detrimental to living organisms, understanding the iron uptake and iron storage mechanism is crucial.[3] Much effort has been invested in the synthesis of both natural and synthetic siderophores, eventually leading to the commercialization of desferrioxamine, administered in case of iron poisoning.[4]

To overcome the low solubility of iron hydroxides present in sea water from which contemporary organisms are thought to have evolved, the complexing agent must possess very high binding constants towards Fe(III), greater than the solubility product of $Fe(OH)_3$: $pK_{sp} = 36$. The naturally occurring tris-catechol enterobactin is the most powerful natural iron(III) chelator known with an overall stability constant of $\approx 10^{49}$. With such high affinity for Fe(III), the iron release mechanism remains to be solved.

Apart from its natural abundance, iron could well have been chosen because of its wide range of accessible oxidation states. A ferric ion is considered as an A class metal with a high affinity for hard donors like oxygen. A one-electron reduction suffices to dramatically change

the metal affinity: Fe(II) binds preferentially to softer donors such as nitrogen. Raymond has shown that for a series of macrobicyclic tris-catechols, the ratio of the formation constants of ferric to ferrous complexes ranges from $10^{28.1}$ to $10^{29.6}$.[5] Therefore, [Fe(III)(siderophore)]- reduction to the ferrous state favours liberation of the cation, which could then be incorporated in the cell. *In vitro* experiments show that, after reduction with NADH, EDTA can trap the reduced cations as shown in Scheme 1.[6]

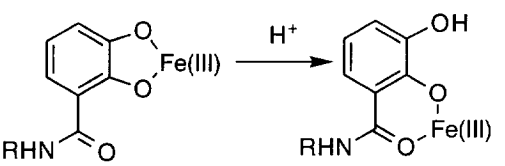
Scheme 1



We wish to test the above observation by synthesizing a ligand system which contains both a hard binding site for ferric cations as well as a softer site for ferrous ions. A single iron atom is expected to bind specifically to one or the other site, depending on its oxidation state. By modifying the oxidation state, the metal ion is expected to switch from one binding site to the other. Both the oxidation state, the spin state as well as the metal environment could be addressed and exploited by various techniques including UV-vis, IR and Mössbauer spectroscopy.

In the field of supramolecular chemistry, the synthesis of ligands with hard and soft donor sites has attracted considerable attention recently, e.g. polypyridine- and catechol-containing ligand systems.[7-9] However, catechols are easily oxidized. Therefore, we reasoned that such hard donors could not be incorporated into a redox-triggered switch containing an Fe(II)/Fe(III) couple. Upon attempted oxidation of the Fe(II) in the presence of free catechol, this latter may be oxidized, yielding undesired o-quinones. To overcome this, Pierre *et al.* reported a bis-phenol-based siderophore which is oxidation resistant.[10] More recently, Baret *et al.* have reported a tris-(8-hydroxyquinoline) siderophore with high affinity for both ferric and ferrous ions.[11]

Scheme 2



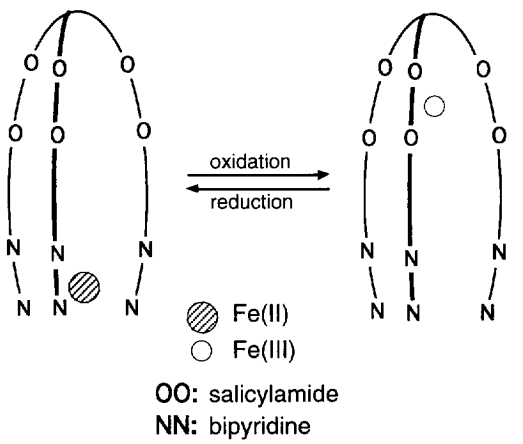
Upon acidification of the [Fe(III) tris-catecholate]$^{3-}$ moiety, it is believed that a phenolic function is protonated. Translocation of the iron to the so-called *salicylate* binding mode, depicted in Scheme 2, decreases the binding constant of the ferric ion to the siderophore, perhaps allowing iron release.[12,13] To the best of our knowledge, salicylamides have received

little attention as potential ligands for iron.[14,15] We wish to study the binding capabilities of these anionic amides towards iron. This will shed light on the iron release mechanism via the *salicylate* binding mode in tris-catechol siderophores.

Bipyridine, bpy, is an excellent ligand for the ferrous state. Upon oxidation, however, the [Fe(III)(bpy)$_3$] is unstable, and we expect the ferric ion to be released if a harder ligand can accommodate this latter.

Recently, Shanzer *et al.* have published an outstanding report on a molecular redox switch, based on the chemical triggering of iron translocation in triple helical complexes. The soft tris-bipyridine site is linked to a harder tris-hydroxamate site and the system acts as a switch upon oxidation or reduction of the single iron cation present in the helicate.[16,17] Related to redox switches is Sauvage's *et al.* contribution on an electrochemically triggered swinging of a polypyridine-[2]-catenane containing copper as redox-active center.[18]

Scheme 3



We have undertaken the synthesis of polydentate ligand systems incorporating both hard salicylamide donors as well as softer bipyridines, symbolized by **OO** and by **N N** respectively. Upon complexation, the ferric ion is expected to bind the **OO** site, and upon reduction, the ferrous ion should translocate to the **NN** site in a reversible process, scheme 3. We report here on the synthesis of *single-stranded*- as well as tripodal ligands containing hard- and soft donor sites.

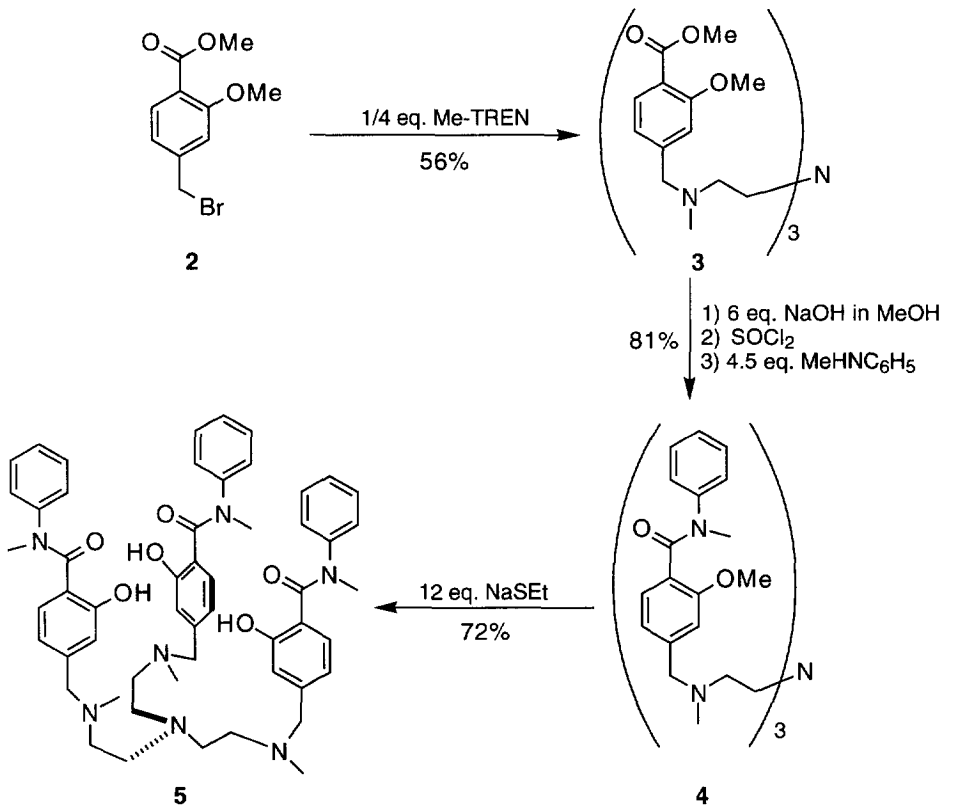
RESULTS AND DISCUSSION

For the Fe(II) binding site, the choice of 2,2'-bipyridyl-5,5'-bis(ethylcarboxylate) is obvious, in light of the straightforward monosaponification of a single ester function reported by Vögtle.[19] Eventually, the remaining ester can be functionalized either to form macrobicyclic ligand systems or longer *single-stranded* ligands. The commercially available 4-methylsalicylic

acid **1** offers an attractive starting material for the synthesis of a salicylate binding pocket. The presence of a methyl group in 4-position allows functionalization and capping to yield tripodal ligands.

To study the coordination properties of salicylamides, we synthesized the tripod **5** from bromo-ester **2**.[20] Nucleophilic substitution in DMF with 0.25 eq. of tris-(N-methylaminoethyl)-amine, Me-TREN,[21] in the presence of K_2CO_3 affords the methylated tripod **3**. Formation of the acid chloride and treatment with N-methylaniline yields the methylether-protected ligand **4**. Many methylether deprotection procedures were attempted unsuccessfully.[22] Eventually, treatment with NaSEt affords the desired synthetic siderophore **5** (Scheme 4).

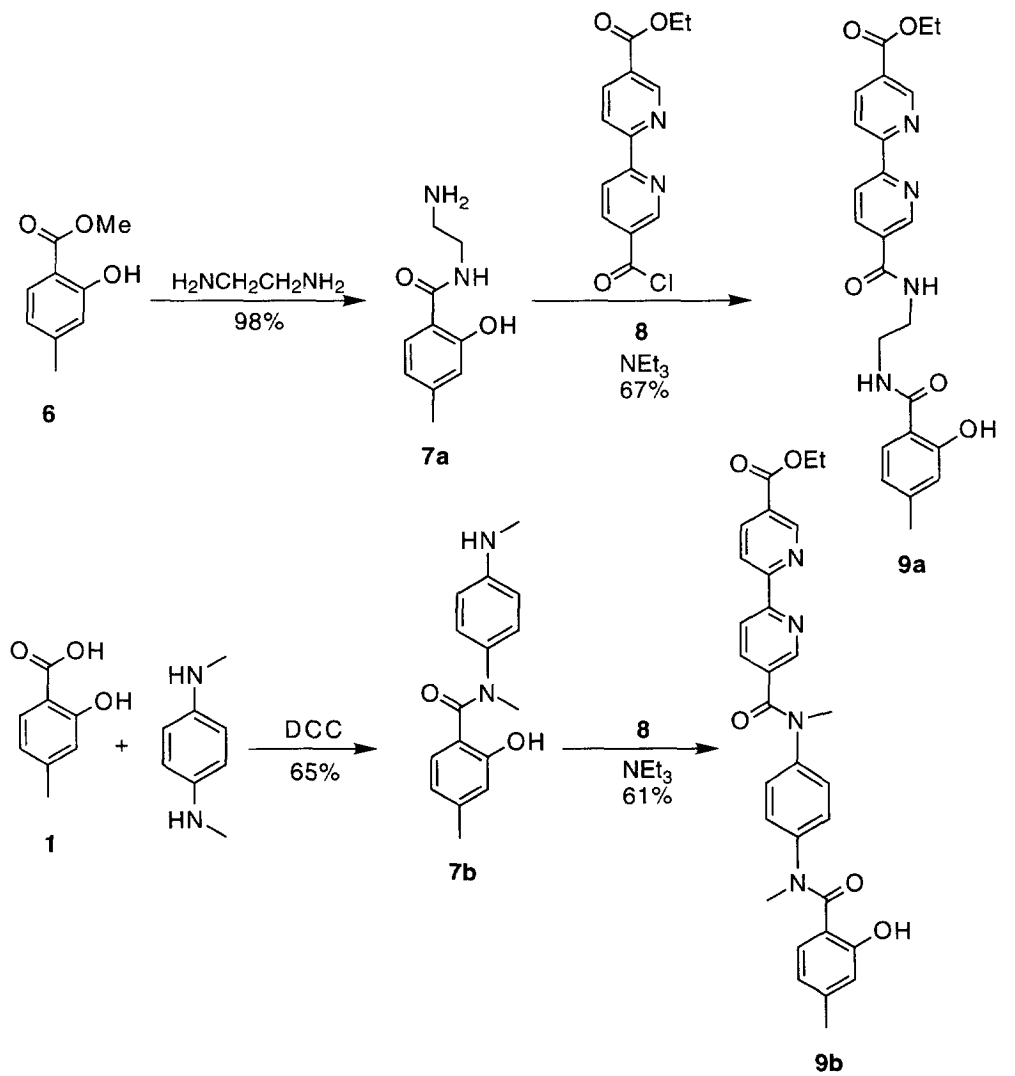
Scheme 4



Next we focused on the synthesis of *single-stranded* ligands incorporating both a soft bipyridine- as well as the salicylamide-moiety. Both aliphatic and aromatic spacers have been incorporated between the **OO**- and **NN**-binding sites, **9a** and **9b**, see Scheme 5. First attempts to form an amide from ester **6** in the presence of catalytic amounts of NaCN, yielded the desired amino-amide **7a** in nearly quantitative yield. Eventually, we found that, in neat ethylenediamine, the ester **6** reacts smoothly even without any catalyst. An aromatic spacer can

be introduced in the *single-stranded* ligand by means of a DCC coupling between methylsalicylic acid **1** and N,N'-dimethyl-*p*-phenylendiamine,[23] affording the amino-amide **7b**. Reaction of **7a** or **b** with acid chloride **8** affords the *single-stranded* ligands **9a** or **b** respectively. Under identical reaction conditions, it is possible to use *p*-phenylendiamine, yielding a *single-stranded* ligand with an aromatic secondary amide spacer. We are testing these ligands for the formation of heterobimetallic helicates.[24]

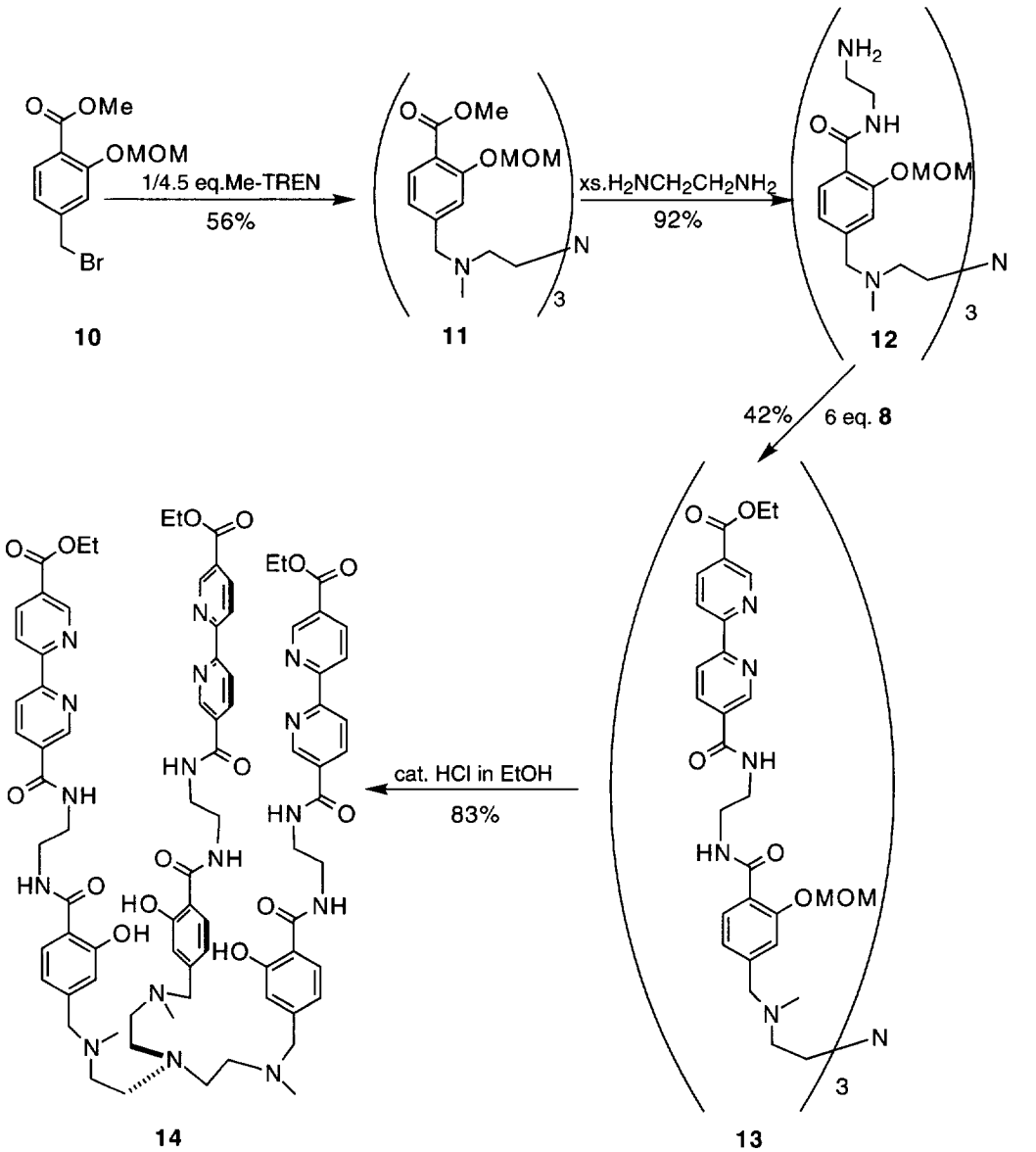
Scheme 5



This simple procedure circumvents a protection-deprotection sequence of the phenolic function, although some of the acid chloride reacts with the phenol, the yields speak in favour

of this straightforward synthetic route. However, for the tripodal analog **14**, the phenol-protection is unavoidable.

Scheme 6



For the synthesis of **14**, MOM-protected **10**[25] is reacted with Me-TREN. Heating the triester **11** in ethylenediamine affords the triamide **12**. Reaction of **12** in the presence of 6 eq. of acid chloride **8** yields the MOM-protected tripod **13**. The deprotection is best carried out in

ethanol in the presence of conc. HCl to afford the desired tripod **14** incorporating both hard and soft binding sites in 18% overall yield (Scheme 6).

CONCLUSION

The syntheses presented here allow access to gram quantities of both *single-stranded* and tripodal ligands incorporating hard salicylamide as well as softer bipyridine donors. Preliminary experiments show promising binding selectivities for both ferric and ferrous ions. We are currently actively working on the coordination chemistry of these systems.

EXPERIMENTAL SECTION

Compounds **2**,[20] **6**,[26] **8**,[19] **10**[25] and **Me-tren**[21] were prepared according to published procedures. All other starting materials were purchased from Fluka AG or Aldrich and were used without further purification. Column chromatography was carried out with Baker silica gel 40 μm. NMR characterization was carried out on a Bruker AM 300 (^{1}H 300 MHz, ^{13}C 75 MHz) or a Bruker DMX 500 (^{1}H 500 MHz, ^{13}C 125 MHz) and were referenced with residual solvent peaks. Chemical shifts δ (ppm), coupling constants J (Hz). Combustion analyses were carried out at Ciba Geigy AG, Basel. Mass Spectra were recorded on EI Varian MAT CH7A or on LSIMS (FAB) (Cs^+) VG Autospec.; only the molecular peak and the most intense peak are reported.

4,4',4''-[Nitrilotris[2,1-ethanediyl(methylimino)methylene]]tris[2-methoxy]-benzoic acid, tri-methyl ester 3. Me-TREN (3.30 g, 17.52 mmol) was dissolved in dimethylformamide (400 ml) and potassium carbonate (48.00 g, 0.34 mol) was added. The suspension was heated to 80°C and a solution of bromo-compound **2** (18.00 g, 69.47 mmol) in dimethylformamide was slowly added. The suspension was stirred at this temperature for 3 days, the solid was filtered, and the solvent concentrated under vacuum, yielding a brown oil. Chromatography (dichloromethane-methanol-ammonia solution in water (25%) 100: 5: 1) gives protected tris-salicylate **3** as a light brown oil (7.02 g, 56 %, 9.71 mmol). ^{1}H NMR ($CDCl_3$): 2.14 (s, 9H, NCH_3), 2.38-2.43 (m, 6H, CH_2), 2.57-2.61 (m, 6H, CH_2), 3.44 (s, 6H, NCH_2), 3.83 (s, 9H, OCH_3), 3.86 (s, 9H, CO_2CH_3), 6.86 (d, J= 8.1, 3H, aromatic H), 6.93 (s, 3H, aromatic H), 7.70 (d, J= 8.1, 3H, aromatic H); ^{13}C NMR ($CDCl_3$): 42.39 (NCH_3), 51.41 ($CO_2\underline{C}H_3$), 52.55 (CH_2), 54.98 (CH_2), 55.54 (OCH_3), 62.16 (NCH_2), 111.73, 118.06, 119.96, 131.16, 145.28, 158.87 (aromatic C), 166.06 (CO_2). MS (LSIMS): 723.40, 236.10. Anal. Calcd. for $C_{39}H_{54}N_4O_9$: C, 64.80; H, 7.53; N, 7.75. Found: C, 64.87; H, 7.50; N, 7.48.

4,4',4''-[Nitrilotris[2,1-ethanediyl(methylimino)methylene]]tris[2-methoxy-N-methyl-N-phenyl]-benzamide 4. Compound **3** (855 mg, 1.18 mmol) was dissolved in methanol (50 ml) and sodium hydroxide (270 mg, 6.75 mmol) was added. The solution was refluxed overnight and concentrated under vacuum. The resulting solid was dried at 60°C under vacuum and suspended at -80°C in thionyl chloride (50 ml). The suspension was allowed to warm to RT

overnight. Solvents were evaporated and the light green oil was dried under vacuum for 3 h. The oil was dissolved in THF (100 ml) and a solution of N-methylaniline (0.58 ml, 5.30 mmol) and triethylamine (1.00 ml, 7.10 mmol) in THF (50 ml) was slowly added. After stirring overnight, the solution was concentrated under vacuum. Chromatography (dichloromethane-methanol-ammonia solution in water (25%) 100: 5: 1) afforded the methyl ether protected tris-chelate **4** as a colourless oil (910 mg, 0.69 mmol, 81%).^{1}H NMR ($CDCl_3$): 1.97 (s, 9H, NCH_3), 2.30-2.32 (m, 6H, CH_2), 2.46-2.48 (m, 6H, CH_2), 3.26 (s, 6H, NCH_2), 3.38 (s, 9H, $PhNCH_3$), 3.50 (s, 9H, OCH_3), 6.52 (brd s, 3H, aromatic H), 6.63 (brd s, 3H, aromatic H), 6.98 (brd m, 18H, aromatic H); ^{13}C NMR ($CDCl_3$): 28.67 (NCH_3), 42.31 (NCH_3), 52.68 (CH_2), 54.92 (OCH_3), 55.41 (CH_2), 62.34 (NCH_2), 110.75, 120.47, 125.07, 126.15, 126.27, 128.12, 128.54, 130.65, 141.64, 143.76, 155.05 (aromatic C), 168.94 (CO). MS (LSIMS): 948.40, 254.10. Anal. Calcd. for $C_{57}H_{69}N_7O_6$: C, 72.20; H, 7.33; N, 10.34. Found: C, 71.67; H, 7.55; N, 9.96.

4,4',4"-[Nitrilotris[2,1-ethanediyl(methylimino)methylene]]tris[2-hydroxy-N-methyl-N-phenyl]-benzamide 5. Tris-methyl ether **4** (1.20 g, 1.22 mmol) was dissolved in dimethylformamide (100 ml) and sodium thioethanolate (1.23 g, 15.00 mmol) was added. The solution was heated overnight at 130°C. After hydrolysis, the volatiles were evaporated under vacuum. Chromatography (dichloromethane-methanol-ammonia solution in water (25%) 100: 10: 1) yields the tris-salicylate tripod **5** as a colourless oil (0.80 g, 0.88 mmol, 72%). ^{1}H NMR ($CDCl_3$): 2.03 (s, 9H, NCH_3), 2.26-2.33 (m, 6H, CH_2), 2.49-2.53 (m, 6H, CH_2), 3.25 (s, 6H, NCH_2), 3.38 (s, 9H, $PhNCH_3$), 6.26 (d, J= 8.2, 3H, aromatic H), 6.51 (d, J= 8.2, 3H, aromatic H), 6.82 (s, 3H, aromatic H), 7.01 (d, J= 7.7, 6H, aromatic H), 7.13 - 7.27(m, 9H, aromatic H); ^{13}C NMR ($CDCl_3$): 29.69 (NCH_3), 42.60 (NCH_3), 52.93 (CH_2), 55.46 (CH_2), 62.12 (NCH_2), 117.97, 118.32, 126.72, 127.10, 129.65, 130.22, 145.49, 160.86 (aromatic C), 171.59 (CO). MS (LSIMS) : 906.40, 240.10. Anal. Calcd. for $C_{54}H_{63}N_7O_6*(H_2O)$: C, 70.18; H, 7.09; N, 10.61. Found: C, 70.34; H, 7.46; N, 10.54.

4-Methyl-2-hydroxy-N-2-aminoethyl-benzamide 7a. Methylester **6** (1.20 g, 7.22 mmol) was dissolved in neat ethylendiamine (20 ml) and refluxed for 3 h. The solution was concentrated under vacuum yielding a light brown oil. Chromatography (dichloromethane-methanol-solution of ammonia in water (25%) 100: 17: 1) or recrystallization from hot ethanol gives **7a** as a white crystalline powder (1.40 g, 7.10 mmol, 98%, mp 155-158°C). ^{1}H NMR (dmso-d_6): 2.23 (s, 3H, $PhCH_3$), 2.73 (t, J= 6.8, 2H, CH_2), 3.43 (t, J= 6.8, 2H, CH_2), 6.58 (d, J= 8.1, 1H, aromatic H), 6.67 (s, 1H, aromatic H), 7.72 (d, J= 8.1, 1H, aromatic H), 9.24 (brd s, 1H, OH). ^{13}C NMR (dmso-d_6): 21.09 ($PhCH_3$), 40.87, 41.60 (CH_2CH_2), 113.49, 117.98, 118.27, 128.10, 143.33, 161.43 (aromatic C), 168.84 (CO). MS (EI): 194.00, 135.00. Anal. Calcd. for $C_{10}H_{14}N_2O_2$: C, 61.84; H, 7.27; N, 14.42. Found: C, 61.77; H, 7.31; N, 14.40.

5'-[[[2-[(2-Hydroxy-4-methylbenzoyl)amino]ethyl]amino]-carbonyl]-[2,2'-bipyridine]-5-carboxylic acid ethyl ester 9a. A suspension of acid chloride **8** (320 mg, 1.10 mmol) in dichloromethane (50 ml) was added to a solution of amine **7a** (322 mg, 1.66 mmol) containing 0.50 ml triethylamine (3.32 mmol) in dichloromethane (50 ml). A white precipitate formed

immediately. The suspension was stirred overnight at RT and was concentrated under vacuum to give a light brown powder. The single strand **9a** was purified either by recrystallization from hot ethanol or by chromatography (toluene-acetone-ammonia solution in water (25%) 100: 12: 1) (312 mg, 0.74 mmol, 67%, mp 248-250°C). ^{1}H NMR (dmso-d_6): 1.49 (t, J= 7.0, 3H, $CH_2\underline{CH}_3$), 2.39 (s, 3H, $PhCH_3$), 3.64 (brd s, 4H, CH_2CH_2), 4.52 (q, J= 7.0, 2H, $CO_2\underline{CH}_2$), 6.81 (d, J= 7.9, 1H, aromatic H), 6.82 (s, 1H, aromatic H), 7.82 (d, J= 7.9, 1H, aromatic H), 8.47 (dd, J= 2.2, J= 8.2, 1H, bipy H), 8.56 (dd, J= 2.2, J= 8.2, 1H, bipy H), 8.63 (dd, J= 0.8, J= 8.2, 1H, bipy H), 8.67 (dd, J= 0.8, J= 8.2, 1H, bipy H), 8.89 (brd s, 2H, NH), 9.24 (d, J= 0.8, 1H, bipy H), 9.31 (dd, J= 0.8, J= 2.2, 1H, bipy H), 12.52 (s, 1H, OH); ^{13}C NMR (dmso-d_6): 14.09 ($CH_2\underline{C}H_3$), 21.04 ($PhCH_3$), 38.76, 39.07 (CH_2CH_2), 61.26 ($\underline{C}H_2CH_3$), 117.53, 119.49, 127.55, 144.06, 148.53, 160.35, (aromatic C), 120.87, 120.94, 126.25, 130.78, 136.35, 138.12, 148.53, 149.99, 156.08, 158.00 (bipy C), 164.55, 164.87, 169.58 (CO). Anal. Calcd. for $C_{24}H_{24}N_4O_5$: C, 64.28; H, 5.39; N, 12.49. Found: C, 63.71; H, 5.50; N, 12.36.

4-Methyl-2-hydroxy-N-4'-methylaminophenyl-N-methyl-benzamide 7b. 1,4-N,N'-Dimethylphenylendiamine (54 mg, 0.39 mmol) and N, N'-dicyclohexylcarbodiimide (102 mg, 0.49 mmol) were dissolved in dichloromethane (40 ml). A solution of methylsalicylic acid **1** (50 mg, 0.33 mmol) in dichloromethane (10 ml) was added slowly. The resulting suspension was stirred for 20 h at RT, the precipitate filtered off and the solution concentrated under vacuum. Chromatography (toluene-acetone 30: 1) gives pure amino-amide **7b** as a colourless oil which can be recrystallized from hot hexane (58 mg, 0.22 mmol, 65%, mp. 110°C). ^{1}H NMR ($CDCl_3$): 1.26 (s, 1H, NH), 2.21 (s, 3H, $PhCH_3$), 2.84 (s, 3H, NCH_3), 3.45 (s, 3H, $(O)CNCH_3$), 6.24 (d, J= 8.1, 1H, aromatic H), 6.54 (d, J= 8.8, 2H, aromatic H), 6.64 (d, J= 8.1, 1H, aromatic H), 6.73 (brd s, 1H, aromatic H), 6.93 (d, J= 8.8, 2H, aromatic H), 12.14 (s, 1H, OH); ^{13}C NMR ($CDCl_3$): 21.44 ($PhCH_3$), 30.65 (NCH_3), 39.69 ($(O)CNCH_3$), 112.83, 113.36, 117.95, 118.78, 127.50, 130.33, 134.89, 143.26, 148.23, 161.11 (aromatic C), 171.38 (CO). MS (EI) : 270.00, 136.00. Anal. Calcd. for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.36. Found: C, 71.27; H, 6.68; N, 9.92.

5'-[[[4-[(2-Hydroxy-4-methylbenzoyl)methylimino]-phenylene]-methylimino]-carbonyl]-[2,2'-bipyridine]-5-carboxylic acid ethyl ester 9b. Amino-amide **7b** (353 mg, 1.31 mmol) and triethylamine (0.37 ml, 2.62 mmol) were dissolved in dichloromethane (50 ml) and a suspension of acid chloride **8** (381 mg, 1.31 mmol) in dichloromethane (50 ml) was added slowly. The solution was stirred overnight at RT. After evaporation, a colourless foam was obtained. Chromatography (toluene-acetone-ammonia solution in water (25%) 100: 10: 1) affords pure *single-stranded* ligand **9b** as a colourless foam (418 mg, 0.80 mmol, 61%). ^{1}H NMR ($CDCl_3$): 1.43 (t, J= 7.2, 3H, $CH_2C\underline{H}_3$), 2.05 (s, 3H, $PhCH_3$), 3.49 (s, 3H, NCH_3), 3.52 (s, 3H, NCH_3), 4.44 (q, J= 7.2, 2H, $C\underline{H}_2CH_3$), 6.28 (dd, J= 8.3, J= 1.5, 1H, aromatic H), 6.42 (d, J= 8.3, 1H, aromatic H), 6.69 (d, J= 1.5, 1H, aromatic H), 7.05-7.09 (m, 4H, aromatic H), 7.81 (dd, J= 8.1, J= 2.2, 1H, bipy H), 8.38-8.42 (m, 2H, bipy H), 8.49 (dd, J= 8.1, J= 0.9, 1H, bipy H), 8.59 (dd, J= 2.2, J= 0.7, 1H, bipy H), 9.27 (dd, J= 2.2, J= 0.7, 1H, bipy H), 10.86 (s, 1H, OH); ^{13}C NMR ($CDCl_3$): 14.75 ($CH_2\underline{C}H_3$), 21.76 ($PhCH_3$), 38.90 (NCH_3), 39.50 (NCH_3), 62.01 ($\underline{C}H_2CH_3$), 113.14, 118.69, 119.41, 128.15, 132.38, 143.14, 144.64, 144.77, 161.27 (aromatic C), 121.28, 121.37, 126.90, 128.68, 130.63, 137.93, 138.52, 149.82,

151.05, 158.68, (bipy C), 165.59, 168.31, 172.03 (CO). MS (EI) : 524.00, 135.00. Anal. calcd. for $C_{30}H_{28}N_4O_5$: C, 68.69; H,5.38; N, 10.68. Found: C, 68.75; H, 5.67; N, 10.10.

4,4',4''-[Nitrilotris[2,1-ethanediyl(methylimino)methylene]]tris[2-methoxymethoxy]-benzoic acid trimethyl ester 11. Me-TREN (500 mg, 2.66 mmol) was dissolved in dimethylformamide (80 ml) and potassium carbonate (7.19 g, 52.02 mmol) was added. A solution of **10** (3.45 g, 12.00 mmol) in dimethylformamide (20 ml) was added to this suspension. After stirring overnight at RT, the solution was filtered and concentrated under vacuum. Chromatography (dichloromethane-methanol-ammonia solution in water (25%) 100: 10: 1) yields the tripod **11** as a light brown oil (1.20 g, 1.48 mmol, 56%). ^{1}H NMR ($CDCl_3$): 2.14 (s, 9H, NCH_3), 2.41-2.44 (m, 6H, CH_2CH_2), 2.57-2.62 (m, 6H, CH_2CH_2), 3.45 (s, 6H, NCH_2), 3.49 (s, 9H, OCH_3), 3.85 (s, 9H, CO_2CH_3), 5,23 (s, 6H, OCH_2), 6.96 (d, J= 8.0, 3H, aromatic H), 7.10 (s, 3H, aromatic H), 7.70 (d, J= 8.0, 3H, aromatic H); ^{13}C NMR ($CDCl_3$): 42.75 (NCH_3), 51.87 ($CO_2\underline{C}H_3$), 53.04, 55.55 (CH_2CH_2), 56.36 (OCH_3), 62.44 (NCH_2), 95.09 (OCH_2), 116.54, 119.83, 121,86, 131.36, 145.65, 156.76 (aromatic C), 166.45 (CO_2). MS (LSIMS) : 813.20, 132.90. Anal. Calcd. for $C_{42}H_{60}N_4O_{12}$: C, 62.05; H, 7.44; N, 6.89. Found: C, 61.91; H, 7.38; N, 6.77.

4,4',4''-[Nitrilotris[2,1-ethanediyl(methylimino)methylene]]tris[2-methoxymethoxy-N-aminoethyl]-benzamide 12. Compound **11** (988 mg, 1.22 mmol) was dissolved in neat ethylendiamine (40 ml) and stirred overnight at 50°C. After evaporation of the volatiles, the orange oil was subjected to chromatography using methanol-ammonia solution in water (25%) 10: 1 as eluent, yielding pure tris-amine **12** as a light yellow oil (1.01 g, 1.13 mmol, 92%). ^{1}H NMR (CD_3OD): 2.09 (s, 9H, NCH_3), 2.34-2.37 (m, 6H, CH_2CH_2), 2.52-2.55 (m, 6H, CH_2CH_2), 2.75 (t, J= 4.9, 6H, (O)$CNCH_2C\underline{H}_2$), 3.38 (s, 6H, NCH_2), 3.39 (m, 6H, (O)$CNC\underline{H}_2CH_2$), 3.40 (s, 9H, OCH_3), 5.25 (s, 6H, OCH_2), 6.94 (d, J= 7.7, 3H, aromatic H), 7.14 (s, 3H, aromatic H), 7.68 (d, J= 7.7, 3H, aromatic H); ^{13}C NMR (CD_3OD): 42.32 (CH_2), 43.45 (NCH_3), 43.70 (CH_2), 53.93, 56.17 (CH_2CH_2), 57.29 (OCH_3), 63.49 (NCH_2), 96.58 (OCH_2), 117.18, 124.02, 131.98, 145.51, 156.82 (aromatic C), 168.84 (CO). MS (LSIMS) : 897.60, 132.90. Anal. Calcd. for $C_{45}H_{72}N_{10}O_9$*5(H_2O): C, 54.75; H, 8.37; N, 14.19. Found: C, 54.98; H, 8.42; N, 14.32.

5',5''',5''''-[Nitrilotris[2,1-ethanediyl(methylimino)methylene[2-(methoxymethoxy)-4,1-phenylene]carbonylimino-2,1-ethanediyliminocarbonyl]]tris[2,2'-bipyridine]-5-carboxylic acid triethyl ester 13. Tris-amine **12** (1.37 g, 1.53 mmol) and triethylamine (2.18 ml, 16.00 mmol) in dimethylacetamide (10 ml) were slowly added to a suspension of acid chloride **8** (2.67 g, 9.18 mmol) in dimethylacetamide (50 ml). After stirring overnight at RT and evaporation of the volatiles under vacuum, the solid was purified by chromatography (dichloromethane-methanol-ammonia solution in water (25%) 100: 10: 1), yielding pure MOM-protected tripod **13** as a white crystalline powder (1.06 g, 0.64 mmol, 42%). ^{1}H NMR (dmso-d_6): 1.35 (t, J= 7.1, 9H, $CH_2C\underline{H}_3$), 2.08 (s, 9H, NCH_3), 2.29-2.31 (m, 6H, CH_2CH_2), 2.48-2.52 (m, 6H, CH_2CH_2), 3.34 (s, 9H, OCH_3) 3.38 (s, 6H, NCH_2), 3.50 (brd s, 12H, (O)$CNCH_2CH_2CN(O)$), 4.36 (q, J= 7.1, 6H, $C\underline{H}_2CH_3$), 5.24 (s, 6H, OCH_2), 6.93 (d, J= 7.9, 3H, aromatic H), 7.10 (s, 3H, aromatic H), 7.68 (d, J= 7.9, 3H,

aromatic H), 8.36 (dd, J= 8.3, J= 2.2, 3H, bipy H), 8.41 (dd, J= 8.3, J= 2.2, 3H, bipy H), 8.48-8.54 (m, 6H, bipy H), 8.91 (brd s, 3H, NH), 9.12 (dd, J= 2.2, J= 0.8, 3H, bipy H), 9.16 (dd, J= 2.2, J= 0.8, 3H, bipy H) ^{13}C NMR (dmso-d_6): 14.08 ($CH_2\underline{C}H_3$), 39.05, 39.12 (CH_2CH_2), 42.36 (NCH_3), 52.31, 54.83 (CH_2CH_2), 55.87 (OCH_3), 61.23 ($\underline{C}H_2CH_3$), 61.43 (NCH_2), 94.32 (OCH_2), 114.84, 122.55, 130.23, 130.45, 143.90, 155.86 (aromatic C), 120.80, 120.85, 121.56, 126.04, 136.35, 138.16, 148.48, 149.96, 154.54, 157.73 (bipy C) 164.40, 164.62, 165.16 (CO). MS (LSIMS) : 1660.70, 613.70. Anal. Calcd. for $C_{87}H_{102}N_{16}O_{18}$*2($H_2O$): C, 61.62; H, 6.30; N, 13.22. Found: C, 61.64; H, 6.51; N, 13.13.

5',5''',5'''''-[Nitrilotris[2,1-ethanediyl(methylimino)methylene[2-(hydroxy)-4,1-phenylene]carbonylimino-2,1-ethanediyliminocarbonyl]]tris[2,2'-bipyridine]-5-carboxylic acid triethyl ester 14. The MOM-protected tris-chelate **13** (1.00 g, 0.61 mmol) was dissolved in ethanol (200 ml) and a few drops of conc. HCl were added. The solution was refluxed for 2 h and neutralized with a saturated sodium bicarbonate solution. After evaporation of the volatiles, the product was purified by chromatography (dichloromethane-methanol-ammonia solution in water (25%) 100: 20: 1) affording pure tripod **14** (770 mg, 0.50 mmol, 83%). ^{1}H NMR (dmso-d_6): 1.36 (t, J= 7.1, 9H, CH_3), 2.06 (s, 9H, NCH_3), 2.33-2.36 (m, 6H, CH_2CH_2), 2.52-2.55 (m, 6H, CH_2CH_2), 3.37 (s, 6H, NCH_2), 3.49 (brd s, 12H, (O)CNCH_2CH_2CN(O)), 4.37 (q, J= 7.1, 6H, CO_2CH_2), 6.77 (d, J= 8.5, 3H, aromatic H), 6.80 (s, 3H, aromatic H), 7.76 (d, J= 8.5, 3H, aromatic H), 8.34 (dd, J= 8.2, J= 2.2, 3H, bipy H), 8.42 (dd, J= 8.2, J= 2.2, 3H, bipy H), 8.49 (d, J= 8.2, 3H, bipy H), 8.53 (d, J= 8.2, 3H, bipy H), 8.92 (brd s, 6H, NH), 9.11 (d, J= 2.2, 3H, bipy H), 9.17 (d, J= 2.2, 3H, bipy H), 12.62 (s, 3H, OH); ^{13}C NMR (dmso-d_6): 14.06 ($CH_2\underline{C}H_3$), 38.54, 38.87 (CH_2CH_2), 42.36 (NCH_3), 52.31, 54.84 (CH_2CH_2), 61.26 ($\underline{C}H_2CH_3$), 61.38 (NCH_2), 117.01, 120.78, 120.84, 130.51, 145.70, 155.83 (aromatic C), 113.70, 118.60, 126.01, 127.49, 136.36, 138.13, 148.47, 149.94, 157.74, 160.28 (bipy C) 164.44, 164.65, 169.26 (CO). MS (LSIMS) : 1528.30, 613.70. Anal. Calcd. for $C_{81}H_{90}N_{16}O_{15}$: C, 63.68; H, 5.94; N, 14.67. Found: C, 63.09; H, 6.00; N, 14.50.

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