Tripodal Dodecadentate Ligands with Salicylamide and Bipyridine Binding Sites for Iron(II) and Iron(III) Coordination

by **Andreas Lutz** and **Thomas R. Ward***

Chemistry and Biochemistry Department, University of Berne, Freiestrasse 3, CH-3012 Berne

The synthesis and characterization of tripodal dodecadentate ligands with salicylamide and bipyridine binding sites for iron(II) and iron(III) are presented.

1. Introduction. – Organisms had developed an addiction to iron long before the appearance of dioxygen on earth. Soon thereafter, the primordial soup was depleted of vital iron, as rust is highly insoluble. Eventually, these organisms released siderophores (iron-sequestering agents) capable of dissolving Fe_2O_3 to collect the essential metal ion [1].

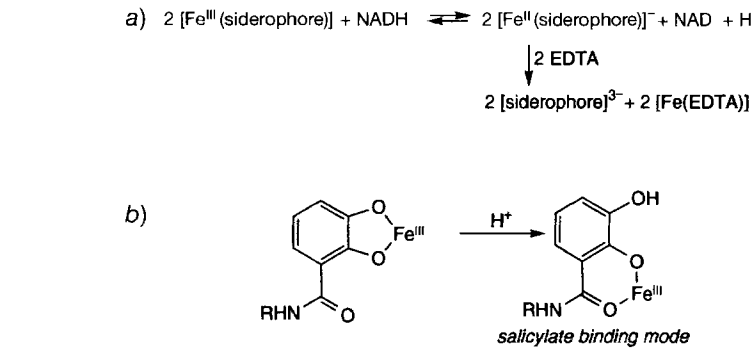
Most siderophores possess either tris-catechol or tris-hydroxamate binding sites, and more than 200 naturally occurring ferric-ion scavengers have been isolated and characterized to date [2]. Interestingly, *Baret et al.* have reported a tris(8-hydroxyquinoline) siderophore with high affinity for both ferric and ferrous ions [3][4].

As both an iron deficiency and iron excess are detrimental to living organisms, understanding the iron uptake and iron storage mechanisms is crucial [5]. 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 [6].

To overcome the low solubility of iron hydroxides present in sea water from which contemporary organisms are thought to have evolved, the siderophore 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 *ca.* 10^{49}. With such high affinity for Fe^{III}, the iron-release mechanism remains to be solved.

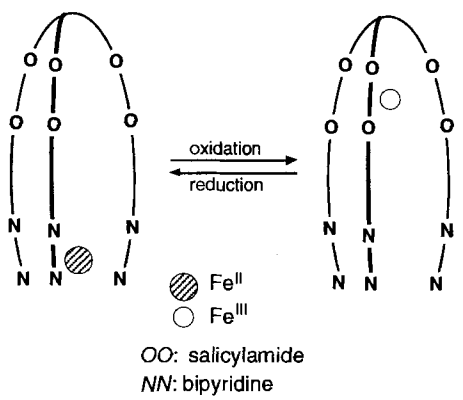
To date, there are three working hypotheses: *i*) Reduction of the Fe^{III} by NADH which yields a labile [Fe^{II}(siderophore)] complex: *Raymond* and coworkers have shown that for a series of macrobicyclic tris-catechols, the ratio fo the formation constants of ferric to ferrous complexes ranges from $10^{28.1}$ to $10^{29.6}$ [7]. Therefore, a [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 (ethylenediaminetetraacetic acid), can trap the reduced cations (*Scheme 1,a*) [8]. *ii*) Protonation of the [Fe^{III}(siderophore)], favouring its release: *Raymond* and coworkers have suggested that synthetic tris-catechol siderophores could be protonated at a phenol site with a concomitant change in coordination to a salicylate binding mode (*Scheme 1,b*). *iii*) Enzymatic degradation of the siderophore.

Scheme 1. *Possible Release Mechanism for Iron Siderophores:* a) *Reduction by NADH*; b) *Protonation*



To probe the iron-release mechanism, we set out to synthesize a dodecadentate tripodal ligand incorporating a hard tris-salicylate binding site as well as a softer tris-bipyridine cavity. A single iron ion is expected to bind specifically to one or the other site, depending on its oxidation state. By modifying the oxidation state, the metal ion should switch from one binding site to the other, eventually leading to the development of a redox-triggered molecular switch, as illustrated in *Scheme 2* [9–12].

Scheme 2. *An Iron-Based Molecular Switch*



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 [13–15]. Bipyridine (bpy) is a good ligand for the ferrous state. Upon oxidation, however, the $[Fe(bpy)_3]^{3+}$ is unstable, and we expect the ferric ion to be released if a harder ligand can accommodate this latter. To test the possible involvement of the salicylate binding mode, we planned to incorporate three salicylamides as hard donor sites for chelation of the ferric ion. Despite their biological relevance, salicylamides have received very little attention as potential ligands for iron [16][17].

Herein, we report on the synthesis and characterization of dodecadentate tripodal ligands incorporating both hard salicylamide donors as well as softer bipyridines, symbolized by *OO* and by *NN*, respectively.

2. Results and Discussion. – For the Fe^{II} binding site, the choice of diethyl [2,2′-bipyridyl]-5,5′-dicarboxylate is obvious, in the light of the straightforward monosaponification of a single ester function as reported by *Vögtle* and coworkers [18] (see *Fig.*). The remaining ester group can possibly be functionalized to form either macrobicyclic ligand systems or longer *single-stranded* ligands. Electron-deficient 2,2′-bipyridines, *i.e.*, bearing carboxylate groups in 5,5′-positions, should display weaker σ-donor properties and thus decrease the stability of the resulting complexes, possibly favouring iron release. The commercially available 4-methylsalicylic acid offers an attractive starting material for the synthesis of a salicylamide binding pocket (*Fig.*). The presence of a methyl group in 4-position allows functionalization and capping to yield tripodal ligands. All building blocks, *i.e.*, *NN* and *OO* binding units, tripodal anchors, and spacers used in this study are presented in the *Figure*. Both arene-based triamines and tris(2-aminoethyl)amine (tren) have been widely used as tripodal anchors in the synthesis of macrobicyclic compounds and artificial siderophores. The presence of secondary-amine groups in the anchors ensures enhanced solubility of the resulting *N,N*-disubstituded amide and amine moieties formed upon condensation and substitution, respectively. *Albrecht et al.* have recently shown that the spacer length between two octahedral binding sites can have a dramatic effect on the configuration of dinuclear triple helicates [19]. We thus synthesized dodecadentate ligands incorporating ethane-1,2-diamine and propane-1,3-diamine as spacers.

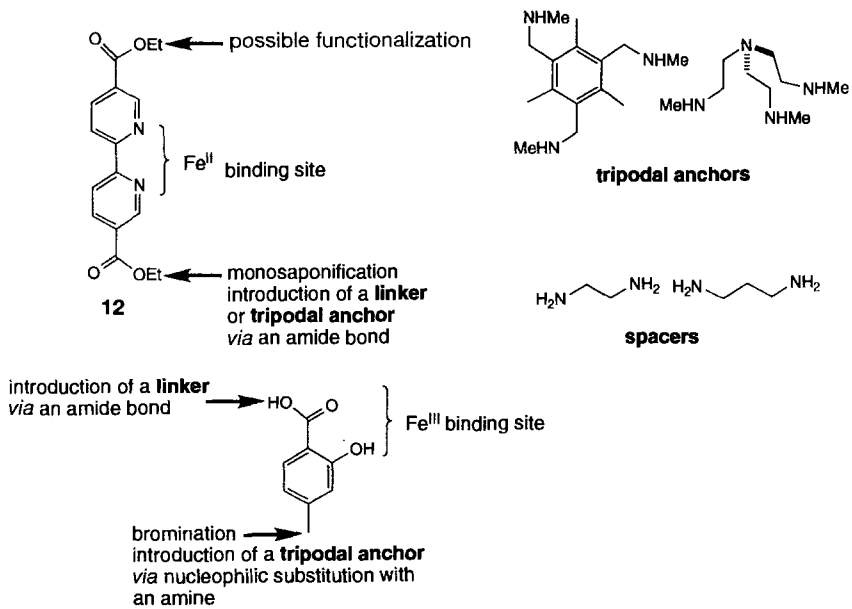
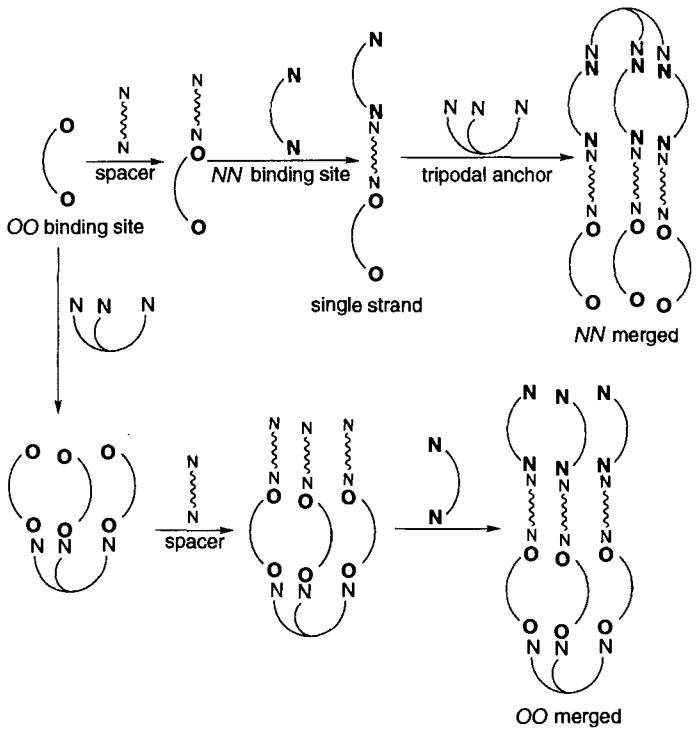


Figure. *Building blocks for tripodal dodecadentate ligands bearing hard salicylamide and soft bipyridine binding sites for Fe^{III} and Fe^{II}, respectively*

Two approaches for the synthesis of dodecadentate tripodal ligands are summarized in *Scheme 3*. The high-yielding and straightforward synthesis of the tetradentate single-stranded ligand **3** [20] encouraged us to attempt coupling of the bipyridine sites to a tripodal anchor, affording the dodecadentate ligand merged at the *NN* sites. Alternatively, nucleophilic substitution at the salicylate binding site with a triamine anchor, followed by introduction of a spacer and finally the bipyridine units, affords dodecadentate ligands merged at the *OO* sites.

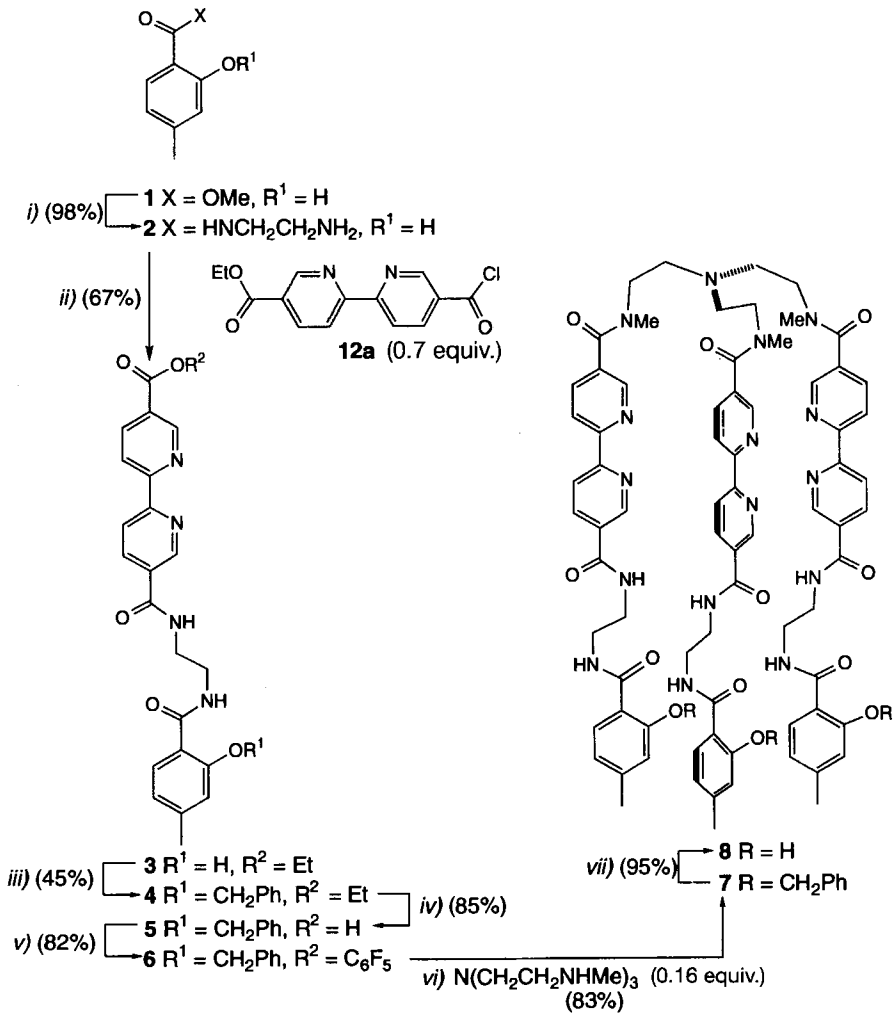
Scheme 3. *Two Approaches for the Synthesis of Tripodal Dodecadentate Ligands*



Both approaches require protection of the phenol functionality. Although methyl ethers have widely been used as protective groups in siderophore syntheses, we have had many problems to remove these, especially when amines are present in the molecule. We thus turned to benzyl ethers or alternatively methoxymethyl ethers (MOM) which resulted in more soluble compounds that could easily be cleaved under mild conditions. Thus, reaction of the single strand (obtained from **1** *via* **2** [20]) with benzyl bromide yielded the benzyl-proteced ligand **4** (*Scheme 4*). Saponification in EtOH in the presence of NaOH afforded, after acidic workup, the acid **5**. All attempts to transform this latter into the corresponding acyl chloride gave essentially insoluble material which failed to react with amines. Esterification with pentafluorophenol in the presence of EDC (EDC = 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride) and catalytic amounts of 4-(dimethylamino)pyridine (DMAP) yielded the activated pentafluorophenyl ester **6**

which was isolated and purified by chromatography. The latter reacted smoothly with the tripodal anchor Me_3tren (Me_3tren = tris[2-(methylamino)ethyl]amine) in DMF to afford the benzyl-protected dodecadentate ligand **7**. The protecting groups were hydrogenated at room temperature to give the unprotected *NN*-merged tripod **8** in 19% overall yield.

Scheme 4. *Preparation of the* NN-*Merged Tripodal Ligand* **8** via *the Single-Strand Route*

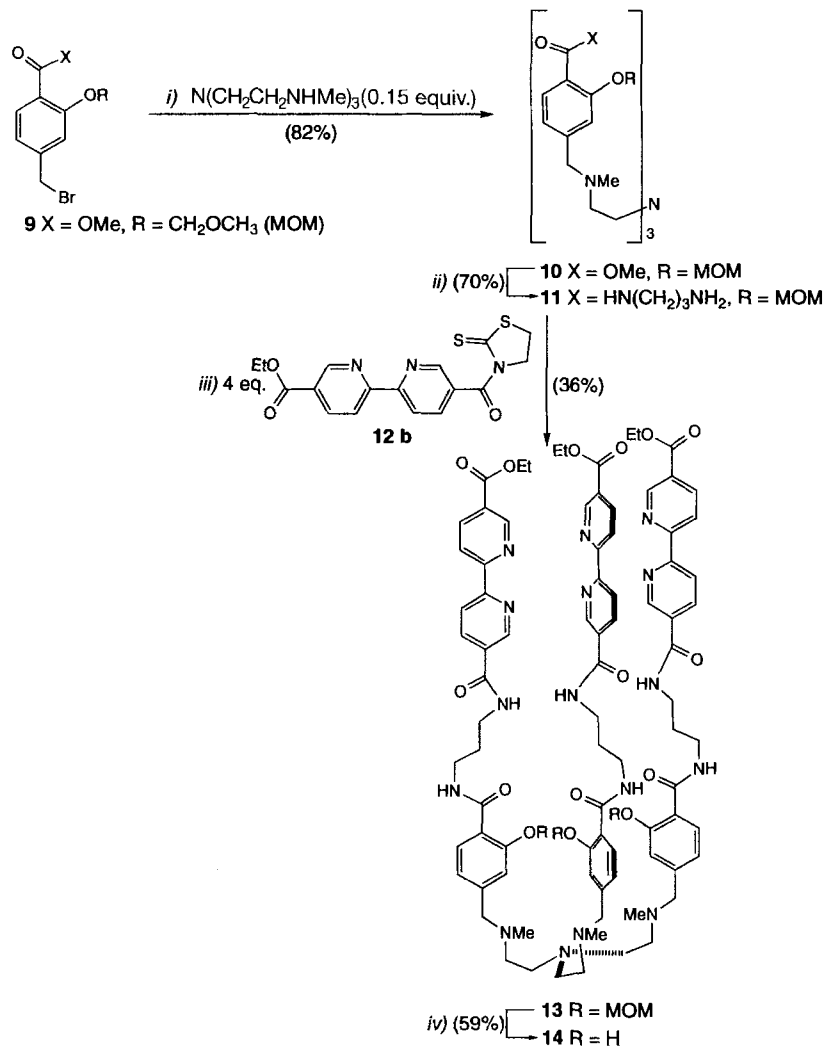


i) Neat $H_2NCH_2CH_2NH_2$, reflux. *ii*) Et_3N (2 equiv.), CH_2Cl_2, **12a** (0.7 equiv.). *iii*) $PhCH_2Br$ (1.5 equiv.), K_2CO_3 (21 equiv.), DMF reflux. *iv*) NaOH (1.5 equiv.), EtOH, reflux. *v*) C_6F_5OH (1.3 equiv.), EDC (1.3 equiv.), cat. DMAP, DMF, r.t. *vi*) Et_3N (2 equiv.), DMF, r.t. *vii*) Cat. Pd/C, H_2, AcOEt, r.t.

The bromomethyl compound **9** is a patented compound which is prepared in three straightforward steps from 4-methylsalicylic acid: esterification, MOM protection of the phenol followed by bromination afforded **9** [21] which reacted with Me_3tren to give

tripod **10** (*Scheme 5*). Heating **10** in neat propane-1,3-diamine yielded the amino-amide **11**, and reaction of the latter with the activated bipyridine ester **12b** gave the MOM-protected ligand **13**. Acetal cleavage in the presence of catalytic amounts of HCl in EtOH provided the *OO*-merged dodecadentate ligand **14** in 12% overall yield. It thus appears that both ethane-1,2-diamine [20] and propane-1,3-diamine smoothly react with methyl salicylates to afford the corresponding amino-amides. The acylation of amines with esters proceeds by a $B_{AC}2$ mechanism and involves two molecules of amine in the rate-determining step [22]. With ethane-1,2- and propane-1,3-diamine, this proton-abstraction step is probably intramolecular, and thus entropically favoured.

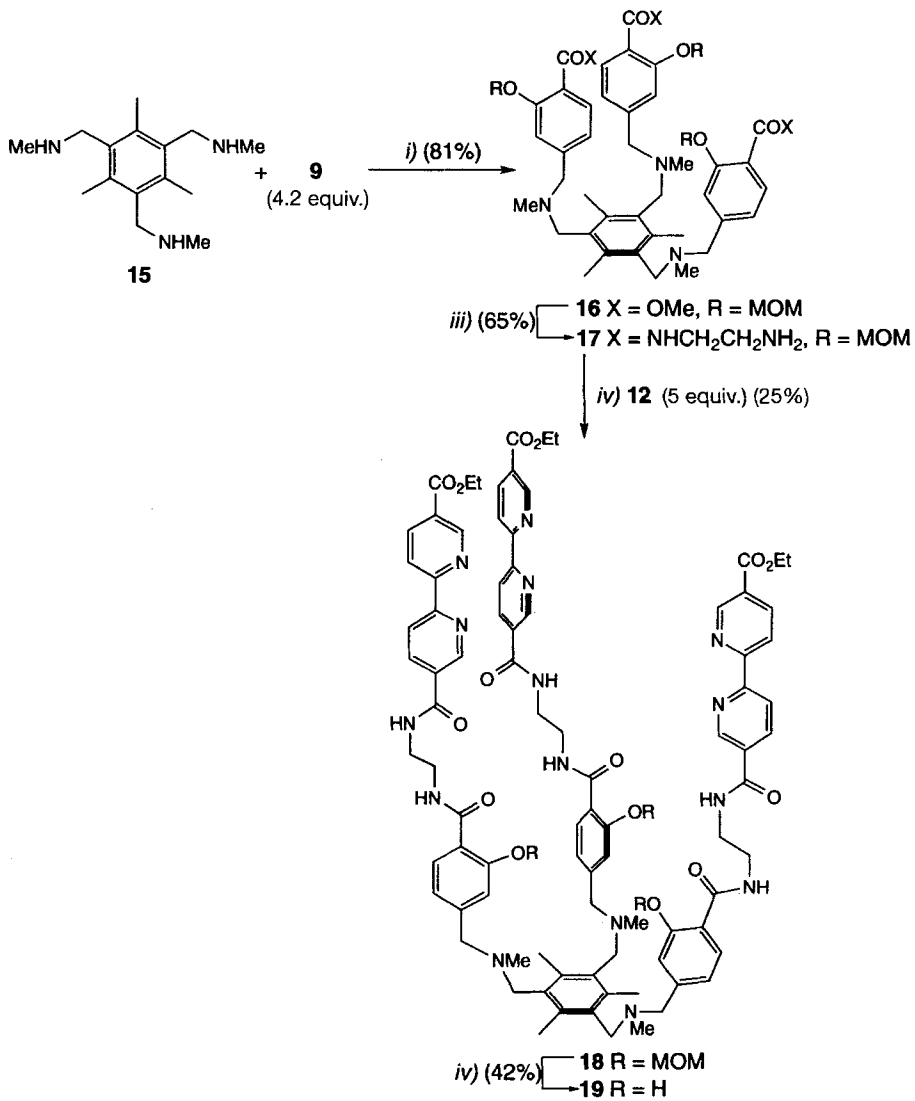
Scheme 5. *Preparation of the Tripodal Ligand* **14**



i) K_2CO_3, DMF, r.t. *ii*) Neat $H_2NCH_2CH_2CH_2NH_2$, 50°. *iii*) DMF, r.t. *iv*) Cat. HCl, EtOH, reflux.

Raymond and coworkers have used hexasubstituted triamino-arene derivatives as anchors for enterobactin analogs [25]. The steric predisposition of the anchor yields higher binding constants than for the trisubstituted arene. We thus synthesized triamine **15** from the corresponding tribromide by nucleophilic substitution with NaN_3, reduction with $LiAlH_4$, followed by *N*-alkylation. Nucleophilic substitution with the bromo-salicylate **9** provided the tripod **16** which smoothly reacted in neat ethane-1,2-diamine to give amino-amide **17** (*Scheme 6*). Reaction with the activated bipyridine diester **12**

Scheme 6. *Preparation of Tripodal Ligand* **19**



i) K_2CO_3 (19 equiv.), DMF, r.t. *ii*) neat $H_2NCH_2CH_2NH_2$, 50°. *iii*) DMF, r.t. *iv*) Cat. HCl, EtOH, reflux.

afforded the MOM-protected ligand **18** which was transacetalized in EtOH to the dodecadentate tripodal ligand **19** (8% overall yield).

The modular approach presented herein is widely applicable for the synthesis of tripodal ligands incorporating both hard and soft donor sites. We find that the protection and deprotection of phenols with benzyl ethers is most convenient and high yielding. The pentafluorophenyl ester (in conjunction with ECD and DMAP) gives the highest yields for the amide formation and should preferentially be used.

3. Conclusion. – The synthesis and characterization of tripodal dodecadentate ligands is reported. Both *NN*- and *OO*-merged ligands are presented. Findings observed in our laboratory suggest that $[Fe^{II}('bpy')_3]^{2+}$ ('bpy' unsymmetrically substituted 2,2′-bipyridine) forms both *facial* and *meridional* diastereoisomers [14][23]. The *NN*-merged tripod is expected to afford exclusively the *facial* isomer. All three ligands present good solubility properties and can be prepared in gram quantities. We are currently actively working on the coordination properties of these tripodal systems, and the results will be published in due course.

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Experimental Part

General. Abbreviations: Me_3tren, tris[2-(methylamino)ethyl]amine; EDC, 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride. Compounds **1**–**3** and **10** [20], **12a** [18], **9** [21], Me_3tren [24], and 2,4,6-trimethylbenzene-1,3,5-trimethanamine [25] were prepared according to published procedures. All other starting materials were purchased from *Fluka AG* or *Aldrich* and were used without further purification. All solvents were dried using standard procedures and distilled under N_2. Column chromatography (CC): *Baker* silica gel 40 μm; addition of 25% aq. NH_3 soln. to the eluent had a beneficial effect on the separations. NMR Spectra: *Bruker-AM-300* (^{1}H 300 MHz, ^{13}C 75 MHz) or *Bruker-DMX-500* (^{1}H 500 MHz, ^{13}C 125 MHz) spectrometer; chemical shifts δ in ppm rel. to residual solvent peaks, coupling constants J in Hz. Mass spectra: *EI Varian MAT CH7A* or *LSIMS* (FAB; Cs^+) *VG Autospec.*; LSI = liquid secondary ionization, FAB = fast-atom bombardment; only molecular peak (rel. %) and the most intense peak. Combustion analyses were carried out at *Novartis*, Basel. The *Chemical Abstracts Registry Service* provided the names for **3**, **7**, **13**, **16**, and **18**. Names for the other tripodal compounds were derived from these.

5′-{{{2-{[2-(Phenylmethoxy)-4-methylbenzoyl]amino}ethyl}amino}carbonyl}[2,2′-bipyridine]-5-carboxylic Acid Ethyl Ester (**4**). To a soln. of **3** (641.40 mg, 1.43 mmol) in DMF (100 ml), K_2CO_3 (3.95 g, 0.03 mol)) and benzyl bromide (0.25 ml, 2.15 mmol) were added, and the suspension was refluxed overnight. After filtration and evaporation of the filtrate, the resulting oil was chromatographed (CH_2Cl_2/MeOH/25% NH_3 soln. 1000:10:1): **4** (344.00 mg, 45%). Colourless foam. ^{1}H-NMR ($CDCl_3$): 1.45 (*t*, *J* = 7.2, $MeCH_2$); 2.40 (*s*, MeC_6H_3); 3.57–3.62 (*m*, CH_2CH_2); 4.45 (*q*, $MeCH_2$); 5.20 (*s*, $PhCH_2$); 6.88 (*s*, 1 arom. H); 6.95 (*d*, *J* = 8.1, 1 arom. H); 7.38–7.45 (*m*, Ph); 8.16 (*d*, *J* = 8.1, 1 arom. H); 8.22 (*m*, NH); 8.27 (*dd*, *J* = 8.4, 2.2, 1 'bpy' H); 8.43 (*dd*, *J* = 8.4, 2.2, 1 'bpy'); 8.50 (*dd*, *J* = 8.4, 0.8, 1 'bpy' H); 8.56 (*dd*, *J* = 8.4, 0.8, 1 'bpy' H); 9.16 (*dd*, *J* = 2.2, 0.8, 1 'bpy' H); 9.29 (*dd*, *J* = 2.2, 0.8, 1 'bpy' H). ^{13}C-NMR ($CDCl_3$): 14.5 ($MeCH_2$); 22.0 (MeC_6H_3); 39.2, 43.3 (CH_2CH_2); 61.7 ($MeCH_2$); 71.8 ($PhCH_2$); 113.8, 118.5, 121.2, 121.6, 127.9, 129.1, 132.5, 135.8, 144.6, 158.8 (arom. C); 122.9, 126.5, 129.3, 130.2, 136.1, 138.2, 148.7, 150.8, 157.2, 157.3 ('bpy' C); 165.6 (2 CO); 168.2 (CO). EI-MS: 538.00. Anal. calc. for $C_{31}H_{30}N_4O_5$: C 69.13, H 5.61, N 10.40; found: C 69.06, H 5.71, N 10.14.

5′-{{{2-{[2-(Phenylmethoxy)-4-methylbenzoyl]amino}ethyl}amino}carbonyl}[2,2′-bipyridine]-5-carboxylic Acid (**5**). To a soln. of **4** (293.00 mg, 0.54 mmol) in EtOH (100 ml), NaOH (32.64 mg, 0.82 mmol) was added. After refluxing overnight followed by evaporation, the resulting solid was dissolved in H_2O, the pH adjusted to 6 with 1M HCl, and the precipitate filtered off and dried *in vacuo*: anal. pure **5** (235.60 mg, 85%). ^{1}H-NMR ((D$_6$)DMSO): 2.27 (*s*, MeC_6H_3); 3.43 (*m*, CH_2CH_2); 5.22 (*s*, $PhCH_2$); 6.81 (*d*, *J* = 7.7, 1 arom. H); 6.99

(*s*, 1 arom. H); 7.22–7.37 (*m*, 3 H, Ph); 7.41 (*d*, *J* = 7.2, 2 H, Ph); 7.65 (*d*, *J* = 7.7, 1 arom. H); 8.29–8.31 (*m*, 1 'bpy' H); 8.40 (*dd*, *J* = 8.2, 2.0, 1 'bpy' H); 8.47 (*d*, *J* = 8.2, 1 'bpy' H); 8.50 (*d*, *J* = 8.2, 1 'bpy' H); 8.84 (br. *s*, NH); 9.07 (*d*, *J* = 2.0, 1 'bpy' H); 9.15 (*d*, *J* = 1.2, 1 'bpy' H). ^{13}C-NMR ((D$_6$)DMSO): 21.6 (*Me*C$_6$H$_3$); 39.3, 39.6 (CH$_2$CH$_2$); 70.2 (PhCH$_2$); 114.5, 121.2, 121.9, 127.7, 128.8, 130.9, 136.8, 138.8, 142.7, 156.4 (arom. C); 121.1, 121.2, 127.7, 130.8, 136.8, 137.1, 148.9, 150.7, 156.3, 158.0 ('bpy' C); 165.0, 165.7, 166.4 (CO). LSI-MS: 511.30. Anal. calc. for C$_{29}$H$_{26}$N$_4$O$_5$ · H$_2$O: C 65.90, H 5.34, N 10.60; found: C 65.24, H 5.46, N 10.14.

5'-{{{2-{[2-(Phenylmethoxy)-4-methylbenzoyl]amino}ethyl}amino}carbonyl}[2,2'-bipyridine]-5-carboxylic Acid Pentafluorophenyl Ester [**6**]. To a suspension of **5** (201.30 mg, 0.39 mmol) in DMF (3 ml), a DMF soln. (2 ml) of pentafluorophenol (94.35 mg, 0.51 mmol) was added in one portion. EDC (98.34 mg, 0.51 mmol) and a spatula tip of DMAP were added as solids to the soln. After stirring for 1 h at r.t., the suspension was filtered and the filtrate evaporated. The resulting solid was chromatographed (CH$_2$Cl$_2$/MeOH 40:1): **6** (228.00 mg, 82%). Colourless solid. ^{1}H-NMR (CDCl$_3$): 2.40 (*s*, *Me*C$_6$H$_3$); 3.57–3.64 (*m*, CH$_2$CH$_2$); 5.20 (*s*, PhC*H*$_2$); 6.89 (*s*, 1 arom. H); 6.94 (*dd*, *J* = 7.7, 1.0, 1 arom. H); 7.38–7.45 (*m*, Ph); 8.16 (*d*, *J* = 7.7, 1 arom. H); 8.28 (*m*, NH); 8.29 (*dd*, *J* = 8.2, 2.2, 1 'bpy' H); 8.43–8.47 (*m*, NH); 8.57 (*dd*, *J* = 8.2, 2.2, 1 'bpy' H); 8.58 (*dd*, *J* = 8.2, 0.7, 1 'bpy' H); 8.68 (*dd*, *J* = 8.2, 0.7, 1 'bpy' H); 9.18 (*d*, *J* = 2.2, 1 'bpy' H); 9.44 (*d*, *J* = 0.7, 1 'bpy' H). ^{13}C-NMR (CDCl$_3$): 21.8 (*Me*C$_6$H$_3$); 39.0, 43.5 (CH$_2$CH$_2$); 71.6 (PhC*H*$_2$); 113.7, 118.2, 122.8, 123.1, 129.0, 129.1, 130.4, 132.3, 135.6, 139.1, 144.6, 160.2 (arom. C); 121.5, 121.8, 127.8, 130.4, 136.0, 138.1, 148.6, 151.4, 156.5, 157.0 ('bpy' C); 161.5, 165.3, 168.2 (CO). LSI-MS: 677.10. Anal. calc. for C$_{35}$H$_{25}$F$_5$N$_4$O$_5$ · H$_2$O: C 60.52, H 3.92, N 8.07; found: C 60.20, H 3.62, N 8.07.

N,N'',N''''-*(Nitrilotriethane-2,1-diyl)tris{*N-*methyl*-N'-*{2-{[4-methyl-2-(phenylmethoxy)benzoyl]amino}ethyl}[2,2'-bipyridine]-5,5'-dicarboxamide}* (**7**). To a soln. of **6** (218.00 mg, 0.31 mmol) in DMF (5 ml), a DMF soln. (5 ml) of Me$_3$tren (9.70 mg, 0.05 mmol) was added dropwise, followed by Et$_3$N (86 µl, 0.62 mmol). The resulting soln. was stirred overnight at r.t. Evaporation and CC (CH$_2$Cl$_2$/MeOH/25% NH$_3$ soln. 100:7:1) yielded 7 (71.20 mg, 83%). Colourless solid. ^{1}H-NMR ((D$_6$)DMSO): 2.27 (*s*, 3 *Me*C$_6$H$_3$); 3.41–3.45 (*m*, 21 H, CH$_2$CH$_2$, MeN); 5.20 (*s*, 3 PhC*H*$_2$); 6.80 (*d*, *J* = 7.7, 3 arom. H); 6.98 (*s*, 3 arom. H); 7.25–7.27 (*m*, 9 H, Ph); 7.40 (*d*, *J* = 7.0, 6 H, Ph); 7.65 (*d*, *J* = 7.7, 3 arom. H); 8.19–8.25 (*m*, 9 'bpy' H); 8.36–8.38 (*m*, 6 'bpy' H); 8.66 (br. *s*, 6 NH); 9.03 (br. *s*, 3 'bpy' H). ^{13}C-NMR ((D$_6$)DMSO): 20.4 (MeN); 21.6 (*Me*C$_6$H$_3$); 39.0, 43.3 (NCH$_2$CH$_2$N); 47.1, 59.5 (NCH$_2$CH$_2$NMe); 71.6 (PhCH$_2$); 114.4, 115.0, 120.6, 121.1, 128.2, 128.8, 130.4, 137.0, 143.2, 156.7 (arom. C); 120.9, 127.7, 127.8, 130.9, 142.7, 147.9, 148.8, 155.2, 155.3, 156.3 ('bpy' C); 165.1, 165.7, 167.4 (CO). LSI-MS: 1666.50 (60), 550.30. Anal. calc. for C$_{96}$H$_{96}$N$_{16}$O$_{12}$ · 10 CH$_3$OH: C 64.09, H 6.90, N 11.28; found: C 64.06, H 6.63, N 11.35.

N,N'',N''''-*(Nitrilotriethane-2,1-diyl)tris{*N-*methyl*-N'-*{2-[(4-methyl-2-hydroxybenzoyl)amino]ethyl}[2,2'-bipyridine]-5,5'-dicarboxamide}* (**8**). To a soln. of **7** (40.90 mg, 0.025 mmol) in DMF (6 ml), a few drops of AcOEt were added, followed by a spatula of Pd/C. The suspension was stirred for 2 days at r.t. under H$_2$. After filtration and evaporation of the filtrate, the solid was purified by CC (CH$_2$Cl$_2$/MeOH/25% NH$_3$ soln. 100:7:1): **8** (32.55 mg, 95%). Colourless solid. ^{1}H-NMR ((D$_6$)DMSO): 2.23 (*s*, 3 MeC$_6$H$_3$); 3.41–3.55 (*m*, 21 H, CH$_2$CH$_2$, MeN); 6.64 (*s*, 3 arom. H); 6.66 (*s*, 3 arom. H); 7.67 (*d*, *J* = 8.1, 3 arom. H); 8.27–8.29 (*m*, 9 'bpy' H); 8.37–8.40 (*m*, 6 'bpy' H); 8.74 (br. *s*, 6 NH); 9.05 (br. *s*, 3 'bpy' H). ^{13}C-NMR ((D$_6$)DMSO): 20.3 (MeN); 21.4 (*Me*C$_6$H$_3$); 39.2, 39.4 (NCH$_2$CH$_2$N); 67.7, 67.8 (NCH$_2$CH$_2$NMe); 113.1, 115.0, 117.9, 120.6, 136.6, 144.5 (arom. C); 119.9, 121.0, 127.9, 128.0, 130.7, 143.7, 147.7, 148.8, 155.3, 156.8 ('bpy' C); 165.3, 169.9, 175.9 (CO). LSI-MS: 1394.60 (1), 307.00. Anal. calc. for C$_{75}$H$_{78}$N$_{16}$O$_{12}$ · 7 CH$_3$OH: C 60.80, H 6.59, N 13.84; found: C 60.89, H 6.19, N 13.65.

4,4',4''-{Nitrilotris[ethane-2,1-diyl(methylimino)methylene]}tris[2-(methoxymethoxy)-N-*(3-aminopropyl)benzamide]* (**11**). A soln. of **10** (254.30 mg, 0.31 mmol) in neat propane-1,3-diamine (50 ml) was stirred overnight at 50°. The excess propane-1,3-diamine was evaporated. After drying the oil for 1 day under high vacuum at r.t., the product was purified by CC (MeOH/25% NH$_3$ soln. 5:1): **11** (204.50 mg, 70%). Yellowish oil. ^{1}H-NMR (CD$_3$OD): 1.70 (*t*, *J* = 6.8, 6 H, CH$_2$); 2.10 (*s*, 3 MeN); 2.34–2.37 (*m*, 6 H, CH$_2$); 2.53–2.57 (*m*, 6 H, CH$_2$); 2.68 (*t*, *J* = 6.8, 6 H, CH$_2$); 3.40 (*s*, 3 MeO); 3.40–3.41 (*m*, 6 H, CH$_2$); 5.26 (*s*, 3 CH$_2$O); 6.95 (*d*, *J* = 8.2, 3 arom. H); 7.15 (*m*, 3 arom. H); 7.69 (*d*, 3 arom. H). ^{13}C-NMR (CD$_3$OD): 31.7 (CH$_2$); 36.5 (CH$_2$); 38.1 (CH$_2$); 41.8 (MeN); 52.2 (CH$_2$); 54.4 (CH$_2$); 55.6 (MeO); 61.8 (CH$_2$); 94.7 (CH$_2$O); 116.9, 123.5, 123.7, 131.7, 145.2, 156.5 (arom. C); 168.4 (CO). LSI-MS: 961.50 (2, [*M* + Na]$^+$), 939.50. Anal. calc. for C$_{48}$H$_{78}$N$_{10}$O$_9$ · 3.5 H$_2$O: C 57.53, H 8.55, N 13.98; found: C 57.46, H 8.51, N 14.28.

5'-[(2-Thioxothiazolidin-3-yl)carbonyl][2,2'-bipyridyl]-5-carboxylic Acid Ethyl Ester (**12b**). To an NaH suspension (116.40 mg, 4.85 mmol) in THF (50 ml), 4,5-dihydrothiazol-2-thiol (578.00 mg, 4.85 mmol) was added at 0°. After the evolution of H$_2$ had ceased, the soln. was reverse-filtered by means of a cannula into a THF soln. (100 ml) of 5'-(chlorocarbonyl)[2,2'-bipyridyl]-5-carboxylic acid ethyl ester (**12a**; 1.17 g, 4.04 mmol). The resulting bright yellow soln. was stirred overnight at r.t. After evaporation, the product was purified by recrystallization

in CH_2Cl_2: **12b** (766.00 mg, 51%). Yellow crystals. ^{1}H-NMR ((D$_6$)acetone): 1.42 (*t*, *J* = 7.0, *Me*CH$_2$); 3.73 (*t*, *J* = 7.2, 2 H, CH$_2$CH$_2$); 4.43 (*q*, MeC*H*$_2$); 4.69 (*t*, *J* = 7.2, 2 H, CH$_2$CH$_2$); 8.27 (*m*, 1 'bpy' H); 8.54 (*m*, 1 'bpy' H); 8.70 (*m*, 2 'bpy' H); 9.00 (*m*, 1 'bpy' H); 9.26 (*m*, 1 'bpy' H). ^{13}C-NMR ((D$_6$)acetone): 13.6 (*Me*CH$_2$); 29.9 (*C*H$_2$CH$_2$); 56.8 (CH$_2$*C*H$_2$); 61.3 (MeCH$_2$); 120.9, 121.2, 126.8, 131.3, 138.0, 138.2, 149.6, 150.1 (2×), 151.4 ('bpy' C); 157.8 (CS); 164.5; 169.2 (CO). EI-MS: 373.00 (4), 290.00. Anal. calc. for $C_{17}H_{15}N_3O_3S_2 \cdot H_2O$: C 52.16, H 4.38, N 10.73; found: C 52.88, H 4.06, N 10.63.

5′,5‴,5⁗,5⁗′-{Nitrilotris{ethane-2,1-diyl(methylimino)methylene[2-(methoxymethoxy)-4,1-phenylene]carbonyliminopropanene-3,1-diyliminocarbonyl}}tris{[2,2′-bipyridine]-5-carboxylic Acid} Triethyl Ester (**13**). A soln. of **12b** (124.21 mg, 0.33 mmol) in DMF (10 ml) was slowly added to a DMF soln. (10 ml) of **11** (78.10 mg, 0.08 mmol). After stirring for 2 days at r.t. the soln. was evaporated and the solid submitted to CC (CH_2Cl_2/MeOH/25% NH_3 soln. 100:7:1): (50.70 mg, 36%). Colourless foam. ^{1}H-NMR (CD$_3$OD): 1.37 (*t*, *J* = 7.1, 3 *Me*CH$_2$); 1.80–1.84 (*m*, 6 H, CH$_2$); 2.12 (*s*, 3 MeN); 2.38–2.41 (*m*, 6 H, CH$_2$); 2.49–2.50 (*m*, 6 H, CH$_2$); 2.56–2.58 (*m*, 6 H, CH$_2$); 3.37–3.45 (*m*, 21 H, 2 CH$_2$, MeO); 4.39 (*q*, 3 MeC*H*$_2$); 5.30 (*s*, 3 CH$_2$O); 6.97 (*d*, *J* = 7.5, 3 arom. H); 7.12 (*s*, 3 arom. H); 7.68 (*d*, 3 arom. H); 8.13–8.15 (*m*, 3 'bpy' H); 8.35 (*dd*, *J* = 8.3, 2.1, 3 'bpy' H); 8.42 (*dd*, *J* = 8.3, *J* = 2.1, 3 'bpy' H); 8.48 (*d*, *J* = 8.2, 3 'bpy' H); 8.53 (*d*, *J* = 8.2, 3 'bpy' H); 8.61–8.67 (*m*, 6 NH); 9.12–9.18 (*m*, 3 'bpy' H). ^{13}C-NMR (CD$_3$OD): 13.9 (*Me*CH$_2$); 29.4, 36.8, 37.1 (CH$_2$); 42.4 (MeN); 52.6, 55.2 (CH$_2$); 56.1 (MeO); 61.6 (MeCH$_2$); 61.5 (CH$_2$); 95.0 (CH$_2$O); 115.1, 120.7, 123.0, 130.6, 143.7, 155.9 (arom. C); 120.7, 121.6, 126.0, 130.0, 136.0, 137.9, 148.3, 149.8, 154.4, 157.8 ('bpy' C); 164.4, 164.5, 164.9 (CO). LSI-MS: 1702.10 (4), 309.00 (42), 154.00. Anal. calc. for $C_{90}H_{108}N_{16}O_{18} \cdot 2 H_2O$: C 62.20, H 6.49, N 12.89; found: C 62.09, H 6.61, N 12.84.

5′,5‴,5⁗,5⁗′-{Nitrilotris{ethane-2,1-diyl(methylimino)methylene[2-hydroxy-4,1-phenylene]carbonyliminopropane-3,1-diyliminocarbonyl}}tris{[2,2′-bipyridine]-5-carboxylic Acid} Triethyl Ester (**14**). To a soln. of **13** (41.40 mg, 0.02 mmol) in EtOH (100 ml), a few drops of 37% HCl soln. (0.05 ml) were added. After refluxing overnight, the soln. was cooled to r.t. and a sat. $NaHCO_3$ soln. was carefully added. Solvent removal and CC (CH_2Cl_2/MeOH/25% NH_3 soln. 100:12.5:1) gave **14** (22.60 mg, 59%). Colourless solid. ^{1}H-NMR ((D$_6$)DMSO): 1.35 (*t*, *J* = 7.1, 3 *Me*CH$_2$); 1.80–1.82 (*m*, 6 H, CH$_2$); 2.06 (*s*, 3 MeN); 2.32–2.35 (*m*, 6 H, CH$_2$); 2.51–2.62 (*m*, 6 H, CH$_2$); 3.34–3.36 (*m*, 18 H, 3 CH$_2$); 4.37 (*q*, 3 MeC*H*$_2$); 6.75 (*d*, *J* = 7.5, 3 arom. H); 6.79 (*s*, 3 arom. H); 7.74 (*d*, 3 arom. H); 8.33 (*dd*, *J* = 8.2, 2.1, 3 'bpy' H); 8.42 (*dd*, *J* = 8.2, 2.1, 3 'bpy' H); 8.48 (*d*, *J* = 8.2, 3 'bpy' H); 8.53 (*d*, *J* = 8.2, 3 'bpy' H); 8.78 (*t*, *J* = 5.5, 6 NH); 9.09 (*d*, *J* = 2.2, 3 'bpy' H); 9.16 (*d*, *J* = 2.2, 3 'bpy' H); 12.61 (br. *s*, 3 OH). ^{13}C-NMR ((D$_6$)DMSO): 14.5 (*Me*CH$_2$); 37.2, 37.6 (CH$_2$); 42.8 (MeN); 52.8, 55.3 (CH$_2$); 61.7 (MeCH$_2$); 61.8 (CH$_2$); 110.1, 114.9, 117.5, 121.2, 138.6, 156.2 (arom. C); 120.3, 121.3, 126.4, 131.0, 136.7 (2×), 148.9 (2×), 150.4, 158.2 ('bpy' C); 164.8 (2×CO); 164.9 (CO). LSI-MS: 1569.10 (11), 134.00. Anal. calc. for $C_{84}H_{96}N_{16}O_{15} \cdot 2 H_2O$: C 62.83, H 6.28, N 13.96; found: C 62.70, H 6.27; N 13.81.

N,N′,N″,2,4,6-Hexamethylbenzene-1,3,5-trimethanamine (**15**). A CH_2Cl_2 soln. (100 ml) Et_3N (3.74 ml, 26.83 mmol) and ethyl carbonochloridate (1.54 ml, 16.00 mmol) was slowly added at 0° to a CH_2Cl_2 soln. (100 ml) of 2,4,6-trimethylbenzene-1,3,5-trimethanamine (926.00 mg, 4.47 mmol). After stirring overnight at r.t., the mixture was filtered and the filtrate washed with 0.5M HCl, sat. $NaHCO_3$ soln., and brine and evaporated. The crude solid was dissolved in THF (200 ml), the soln. cooled to 0°, and solid $LiAlH_4$ (2.66 g, 0.07 mol) added. The resulting suspension was refluxed overnight, and then filtered through a *Celite* pad. The filtrate was evaporated and the product purified by CC (CH_2Cl_2/MeOH/25% NH_3 soln.): **15** (293.30 mg, 26%). Colourless solid. ^{1}H-NMR ($CDCl_3$): 1.52 (br. *s*, 3 NH); 2.42 (*s*, 3 MeC); 2.52 (*s*, 3 MeN); 3.73 (*s*, 6 H, CH$_2$). ^{13}C-NMR ($CDCl_3$): 15.5 (*Me*C); 36.8 (MeN); 50.7 (CH$_2$); 134.8, 135.2 (arom. C). EI-MS: 249.00 (50), 203.00.

4,4′,4″-{(2,4,6-Trimethylbenzene-1,3,5-triyl)tris[methylene(methylimino)methylene]}tris[2-(methoxymethoxy)benzoic Acid] Trimethyl Ester (**16**). To a soln. of **15** (293.90 mg, 1.18 mmol) in DMF (100 ml), K_2CO_3 (3.04 g, 22 mmol) was added. Then **9** (1.43 g, 4.94 mmol) in DMF (100 ml) was slowly added to the suspension. The mixture was stirred for 1 day at r.t. and then evaporated. Purification by CC (CH_2Cl_2/MeOH/25% NH_3 soln. 100:3.3:1) yielded **16** (774.70 mg, 81%). Colourless foam. ^{1}H-NMR ($CDCl_3$): 2.10 (*s*, 3 MeC); 2.47 (*s*, 3 MeN); 3.47 (*s*, 6 H, CH$_2$N); 3.49 (*s*, 3 MeO); 3.64 (*s*, 6 H, CH$_2$N); 3.86 (*s*, 3 CO$_2$Me); 5.21 (*s*, 3 CH$_2$O); 6.94 (*dd*, *J* = 1.4, 8.0, 3 arom. H); 7.11 (*d*, *J* = 1.4, 3 arom. H); 7.67 (*d*, *J* = 8.0, 3 arom. H). ^{13}C-NMR ($CDCl_3$): 16.7 (*Me*C); 41.4 (MeN); 51.9 (CO$_2$*Me*); 56.1 (CH$_2$N); 56.3 (MeO); 60.9 (CH$_2$N); 95.1 (CH$_2$O); 116.6, 119.6, 121.9, 131.3, 133.2, 137.6, 146.5, 156.8 (arom. C); 166.5 (CO). LSI-MS: 872.20 (60), 157.00. Anal. calc. for $C_{48}H_{63}N_3O_{12}$: C 65.96, H 7.27, N 4.81; found: C 66.04, H 7.19, N 5.03.

4,4′,4″-{(2,4,6-Trimethylbenzene-1,3,5-triyl)tris[methylene(methylimino)methylene]}tris[2-(methoxymethoxy)-N-(2-aminoethyl)benzamide] (**17**). A soln. of **16** (150.30 mg, 0.17 mmol) in neat ethane-1,2-diamine (200 ml) was heated for 2 days at 50°. After evaporation and drying under high vacuum for 1 day at r.t., the viscous oil was chromatographed (MeOH/25% NH_3 soln. 5:1): pure **17** (106.90 mg, 65%). Pale yellow oil. ^{1}H-NMR

((D$_6$)DMSO): 2.00 (*s*, 3 MeC); 2.41 (*s*, 3 MeN); 2.63–2.66 (*m*, 6 H, CH_2CH_2); 3.16–3.34 (*m*, 6 H, CH_2CH_2); 3.34 (*s*, 3 MeO); 3.43 (*s*, 6 H, CH_2N); 3.59 (*s*, 6 H, CH_2N); 6.90 (*d*, *J* = 7.8, 3 arom. H); 7.07 (*s*, 3 arom. H); 7.58 (*d*, *J* = 7.8, 3 arom. H); 8.18 (*m*, 3 CONH). ^{13}C-NMR ((D$_6$)DMSO): 16.8 (*MeC*); 41.4 (MeN); 41.6, 42.9 (CH_2CH_2); 55.8 (CH_2N); 56.5 (MeO); 60.6 (CH_2N); 95.0 (CH_2O); 115.6, 122.1, 123.7, 130.5, 133.3, 137.5, 144.3, 154.8 (arom. C); 165.4 (CO). LSI-MS: 958.50 (53), 186.10. Anal. calc. for $C_{51}H_{75}N_9O_9 \cdot 2.5\,H_2O$: C 61.06, H 8.03, N 12.57; found: C 60.87, H 7.70, N 13.30.

5′,5‴,5⁗-{(2,4,6-Trimethylbenzene-1,3,5-triyl)tris{methylene(methylimino)methylene[2-(methoxymethoxy)-4,1-phenylenene]carbonyliminoethane-2,1-diyliminocarbonyl}}tris{[2,2′-bipyridine]-5-carboxylic Acid} Triethyl Ester (**18**). To a soln. of **17** (95.60 mg, 0.10 mmol) in DMF (10 ml), a soln. of **12b** (167.66 mg, 0.50 mmol) in DMF (5 ml) was added dropwise. The mixture was stirred for 2 days at r.t. and then evaporated. The solid was chromatographed (CH_2Cl_2/MeOH/25% NH_3 soln. 100:5:1): pure **18** (42.50 mg, 25%). ^{1}H-NMR ((D$_6$)DMSO): 1.34 (*t*, *J* = 7.1, 3 *Me*CH_2); 1.99 (*s*, 3 MeC); 2.39 (*s*, 3 MeN); 3.29 (*s*, 3 MeO); 3.41 (*s*, 6 H, CH_2N); 3.49 (*m*, 12 H, CH_2CH_2); 3.57 (*s*, 6 H, CH_2N); 4.36 (*q*, 3 MeCH_2); 6.89 (*d*, *J* = 7.9, 3 arom. H); 7.07 (*s*, 3 arom. H); 7.62 (*d*, 3 arom. H); 8.32 (*m*, 3 NH); 8.35 (*dd*, *J* = 8.3, 2.1, 3 'bpy' H); 8.41 (*dd*, *J* = 8.3, 2.1, 3 'bpy' H); 8.47 (*d*, *J* = 8.3, 3 'bpy' H); 8.51 (*d*, *J* = 8.3, 3 'bpy' H); 8.88 (*m*, 3 NH); 9.10 (*dd*, *J* = 2.1, 0.9, 3 'bpy' H); 9.15 (*dd*, *J* = 2.1, 0.9, 3 'bpy' H). ^{13}C-NMR ((D$_6$)DMSO): 14.1 (*Me*CH_2); 16.3 (*Me*C); 39.0, 39.1 (CH_2CH_2); 40.9 (MeN); 55.3 (CH_2N); 55.8 (MeO); 60.2 (CH_2N); 61.3 (MeCH_2); 94.4 (CH_2O); 115.1, 120.8, 122.7, 130.1, 130.5, 137.0, 144.1, 154.5 (arom. C); 120.9, 121.6, 126.0, 132.8, 136.4, 138.2, 148.5, 150.0, 155.9, 157.7 ('bpy' C); 164.5, 164.7, 165.2 (CO). LSI-MS: 1721.00 (25), 309.00. Anal. calc. for $C_{93}H_{105}N_{15}O_{18} \cdot H_2O$: C 64.24, H 6.20, N 12.08; found: C 64.42, H 6.29, N 11.79.

5′,5‴,5⁗-{(2,4,6-Trimethylbenzene-1,3,5-tryil)tris[methylene(methylimino)methylene(2-hydroxy-4,1-phenylenene)carbonyliminoethane-2,1-diyliminocarbonyl]}tris{[2,2′-bipyridine]-5-carboxylic Acid} Triethyl Ester (**19**). To a soln. of **18** (60.00 mg, 0.035 mmol) in EtOH (100 ml), a few drops of 37% HCl soln. (0.05 ml) were added. The soln. was heated overnight under reflux. After coolig to 0°, the soln. was carefully neutralized with a sat. $NaHCO_3$ soln. After evaporation, the solid was chromatographed (CH_2Cl_2/MeOH/25% NH_3 soln. 100:7:1): pure **19** (23.50 mg, 42%). ^{1}H-NMR ((D$_6$)DMSO): 1.35 (*t*, *J* = 7.1, 3 *Me*CH_2); 1.98 (*s*, 3 MeC); 2.42 (*s*, 3 MeN); 3.39 (*s*, 6 H, CH_2N); 3.48 (*m*, 12 H, CH_2CH_2); 3.60 (*s*, 6 H, CH_2N); 4.37 (*q*, 3 MeCH_2); 6.72 (*d*, *J* = 8.1, 3 arom. H); 6.76 (*s*, 3 arom. H); 7.71 (*d*, 3 arom. H); 8.33 (*d*, *J* = 8.1, 3 'bpy' H); 8.42 (*dd*, *J* = 8.2, 2.0, 3 'bpy' H); 8.48 (*d*, *J* = 8.2, 3 'bpy' H); 8.51 (*d*, *J* = 8.1, 3 'bpy' H); 8.88–8.97 (*m*, 6 NH); 9.09 (br. *s*, 3 'bpy' H); 9.15 (*d*, *J* = 2.0, 3 'bpy' H); 12.54 (br. *s*, 3 OH). ^{13}C-NMR ((D$_6$)DMSO): 14.1 (*Me*CH_2); 16.4 (*Me*C); 38.7, 38.8 (CH_2CH_2); 40.8 (MeN); 60.1 (CH_2N); 61.3 (MeCH_2, CH_2N); 113.7, 120.7, 120.8, 130.5, 136.4, 137.0, 138.2, 146.0 (arom. C); 120.8, 120.9, 126.1, 130.5, 136.3, 138.1, 148.4, 150.0, 155.9, 157.7 ('bpy' C); 160.1, 164.5, 164.7 (CO). LSI-MS: 1589.50 (6), 309.00. Anal. calc. for $C_{87}H_{93}N_{15}O_{15} \cdot 3\,H_2O$: C 63.61, H 6.07, N 12.79; found: C 63.27, H 6.04, N 12.37.

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