Chiral Confined Space: Induction of Stereochemistry in a M_4L_4 Metallosupramolecular Container

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Abstract: A triangular triscatechol ligand with enantiomerically pure terminal amide groups is prepared and used for the diastereoselective self-assembly of enantiomerically pure metallosupramolecular M_4L_4 tetrahedra.

Key words: tetrahedron, chirality, coordination compound, self-assembly, catechol

Container molecules are of general interest due to their application as molecular flasks for the stabilization of reactive intermediates and for the promotion of unusual reactions. The self-assembly of such compounds from simple components can be achieved by utilization of noncovalent bonds (like hydrogen bonds) or by metal coordination.[1]

In order to investigate the chiral recognition properties of container molecules, it is important to prepare them in enantiomerically pure form. This was realized for M_4L_6 tetrahedra. The first example was described by Stack, who used ligands which contain chiral groups at the linker to stereospecifically prepare enantiomerically pure container compounds.[2] Later, Raymond reported the resolution of a container compound in the presence of *N*-methylnicotinium cations as templates. The cation can be substituted by tetraethylammonium to leave the enantiomerically pure complex, which due to the mechanical coupling of the coordination sites at the corners possesses an impressive configurational stability.[3] Recently, Ward used linear ligands bearing enantiomerically pure units at the termini, which induce the twist at the ligand and thus the chirality of the M_4L_6 cage.[4]

In 2003, we described the formation of big chiral, but racemic M_4L_4 tetrahedra. These show a pronounced host-guest chemistry. Thus, it is possible to substitute internally bound alkali metal cations by appropriate organic cationic species.[5]

A tetrahedron itself is not chiral. However, in the coordination compounds (M_4L_4 as well as M_4L_6) the overall tetrahedral structure is built up from chiral building blocks, like the octahedral complex units at the corners and helically twisted connecting moieties (e.g., phenyl groups). Those chiral units form in the interior of the compounds a chiral confined space. In order to use the chiral information, this 'space' has to be generated in an enantioenriched or enantiopure form. Therefore, we now present the preparation of a triscatecholimine ligand, which bears chiral amide units at the terminus of the ligand and in a diastereoselective assembly affords an enantiomerically pure tetrahedron.

The amide linkage was chosen as the connecting unit, because a hydrogen bond is formed towards the catecholate oxygen upon complexation, which forces the chiral unit close to the coordination site. Therefore it is effective in the induction of the configuration at this moiety (Figure 1).[6] This principle was already used to prepare enantiomerically pure mononuclear complexes (like siderophore analogues[6]) and triple stranded helicates.[7]

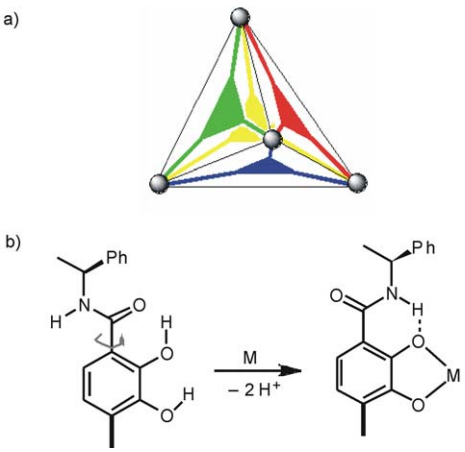

Figure 1 a) Schematic representation of a metallosupramolecular M_4L_4 tetrahedron with triangular ligands. b) Rotation of the amide unit at catechol occurs upon metal coordination and forces the chiral moiety close to the complex unit.

In the synthetic approach, 2,3-dimethoxybenzyl alcohol (**1**) is deprotonated twice (*n*-BuLi, TMEDA). The first deprotonation occurs at the OH group to generate an anion that prevents proton abstraction at the benzylic position. The second deprotonation takes place *ortho* to the methoxy group.[8] The dianion is quenched by addition of (*S*)-1-phenylethyl isocyanate (Scheme 1). The low yield of 17% for **2** is due to severe formation of side products and demanding purification steps. The alcohol unit of **2** is oxidized by Swern reaction to afford the aldehyde **3** (88%)

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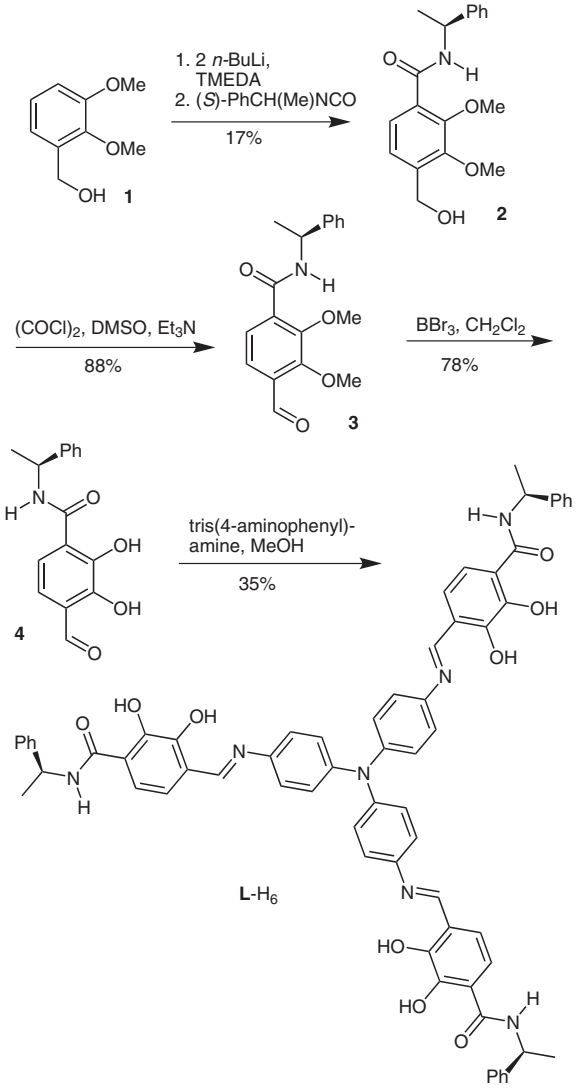
and the methoxy groups are finally cleaved by reaction with BBr_3. The catechol building block **4** is obtained in 78%. This is coupled to the triphenylamine backbone by triple imine condensation with tris(4-aminophenyl)amine in methanol. The ligand L-H_6 does not precepitate from this solvent and has to be purified by repeated recrystallization from dichloromethane–pentane (1:1), dichloromethane–cyclohexane (1:1) and dichloromethane–diethyl ether–cyclohexane (1:1:1). This intense purification procedure leads to a low yield of 35% for L-H_6 in the final step.



Scheme 1 Preparation of the enantiomerically pure triscatechol ligand L-H_6 (TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine).

L-H_6 shows in its ^{1}H NMR spectrum in $CDCl_3$ the singlet of the imine CH at δ = 8.56 (3 H). The aromatic units give rise to resonances at δ = 7.35–7.12 (m, 24 H), 7.12 (d, *J* = 8.8 Hz, 1 H), 7.08 (d, *J* = 8.5 Hz, 6 H), 6.87 (d, *J* = 8.5 Hz, 6 H). One OH proton is found at 10.60 ppm, while the other is hidden under aromatic signals at 7.35–7.25 ppm. The amide NH appears at δ = 7.01 (d, *J* = 7.4 Hz). As special spectroscopic probes act the methine (5.28 ppm, dq, *J* = 7.4, 6.9 Hz) as well as the methyl protons (1.57 ppm, d, *J* = 6.9 Hz) of the phenylethyl group.

Reaction of the ligand L-H_6 with titanoyl bisacetylacetonate and alkali metal carbonates in DMF afford tetranuclear titanium(IV) complexes $M_8[\mathbf{L}_4Ti_4]$ (M = Li, Na, K) in quantitative yield. The ^{1}H NMR spectrum of the sodium salt in DMSO-d_6 shows the amide proton which is hydrogen bonded to a catecholate oxygen at δ = 10.05 and the signal of the imine CH=N at δ = 8.88. The aromatic region is not well resolved. It reveals overlapping signals at δ = 7.4–6.8. As mentioned before, the NMR resonances of the ethyl group of the amide side chain are informative. They appear at δ = 5.20 (CH) and 1.30 (CH_3). The observation of one set of signals for this group indicates the presence of only one stereoisomer (or at least a dominating one).

The composition of the $[\mathbf{L}_4Ti_4]^{8-}$ tetrahedron is confirmed by negative ESI FT-ICR MS. The sodium salt shows the corresponding peaks at *m*/*z* = 1550.1 ($[Na_5\mathbf{L}_4Ti_4]^{3-}$), 1543.1 ($[HNa_4\mathbf{L}_4Ti_4]^{3-}$), 1535.8 ($[H_2Na_3\mathbf{L}_4Ti_4]^{3-}$), 1156.8 ($[Na_4\mathbf{L}_4Ti_4]^{4-}$), 1151.6 ($[HNa_3\mathbf{L}_4Ti_4]^{4-}$), 1146.1 ($[H_2Na_2\mathbf{L}_4Ti_4]^{4-}$), 1140.6 ($[H_3Na\mathbf{L}_4Ti_4]^{4-}$), 920.9 ($[Na_3\mathbf{L}_4Ti_4]^{5-}$), 916.5 ($[HNa_2\mathbf{L}_4Ti_4]^{5-}$), 912.3 ($[H_2Na\mathbf{L}_4Ti_4]^{5-}$), 907.9 ($[H_3\mathbf{L}_4Ti_4]^{5-}$), 763.6 ($[Na_2\mathbf{L}_4Ti_4]^{6-}$), 759.9 ($[HNa\mathbf{L}_4Ti_4]^{6-}$), 756.4 ($[H_2\mathbf{L}_4Ti_4]^{6-}$). No species with a composition of the central complex unit other than $[\mathbf{L}_4Ti_4]^{8-}$ are observed.

It has not been possible to obtain X-ray quality crystals of $M_8[\mathbf{L}_4Ti_4]$. However, the solid state structure of the corresponding complex without the chiral amide substituents is known.[5a] Based on this we calculated the structure of the octaanion $[\mathbf{L}_4Ti_4]^{8-}$ by MMFF (molecular mechanics force field) methods.[9] The result of the modeling is shown in Figure 2a. Figure 2b depicts one of the 'corners' of the tetrahedron. The chiral amide substituents are bound 'on top' of the triscatechol titanium(IV) unit, forming hydrogen bonds to the catecholate oxygens. From investigations by Raymond, it is known that the (*S*)-phenylethylamide induces a Λ-configuration at the complex units as shown in the figure. He used mono-, di-, and tritopic ligands, which contain the (*S*)-phenylethylamide as terminal group bound to the catechol unit and prepared different complexes with iron(III) or gallium(III) cations, which adopted exclusively a Λ-configuration. Based on the solid state structure, Raymond could show that the preferred *trans* configuration of an amide proton to a methine proton in combination with the described hydrogen bonding promotes the interaction among the terminal chiral groups. The most favored aryl/aryl and methyl/aryl interaction leads to the stereospecific formation of the complexes. In the modeled structure, the amide substitutents adopt a conformation, which is related to the one in Raymond's complexes.[6] Therefore, we expect that the (*S*)-phenylethylamide induces a Λ-configuration at the metals which transfer the chiral information from the outside of the tetrahedron to the interior. The chirality might be enhanced by induction of the twisting of the triphenyl amine propeller.

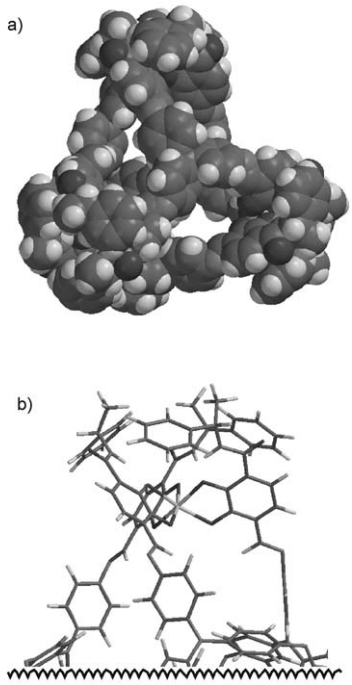


Figure 2 (a) Calculated model of the octaanion $[\mathbf{L}_4Ti_4]^{8-}$ (MMFF, Spartan O2). The structure of the central tetranuclear unit corresponds to the one found by X-ray crystal structure analysis. The orientation of the phenylethyl group is similar to the one observed in related mononuclear triscatcholate complexes. (b) Zoom-in of the structure, showing the coordination site at one titanium(IV) ion.

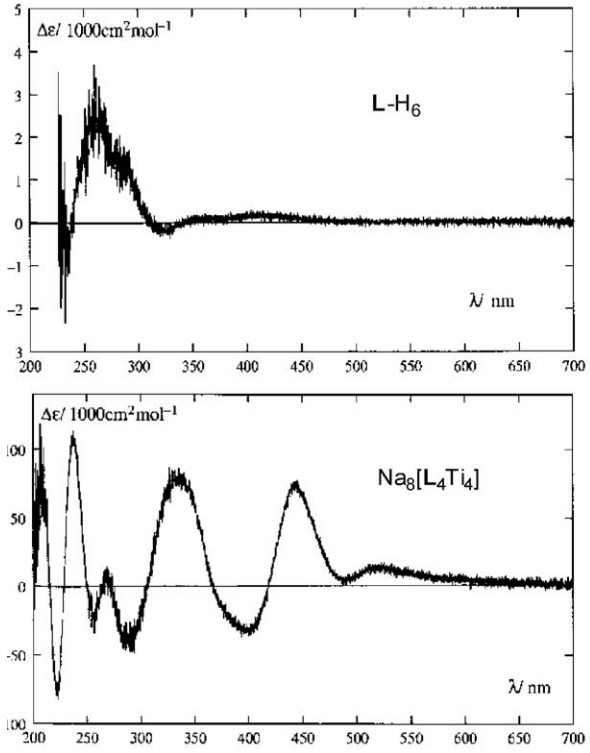


Figure 3 Top: CD spectrum of the ligand L-H_6 in methanol. Bottom: CD-spectrum of $Na_8[\mathbf{L}_4Ti_4]$ in methanol.

In order to support our stereochemical considerations, we performed CD-measurements in methanol at room temperature. The ligand L-H_6 shows only a slight Cotton effect at 260 nm (probably $\pi \rightarrow \pi^*$ transition) (Figure 3). The complexes $M_8[\mathbf{L}_4Ti_4]$ (M = Li, Na) lead to more pronounced spectra, which are both similar to each other. The region of LMCT bands is especially informative. Following earlier investigations, the band around 450 nm (positive Cotton effect) might be assigned to the $\pi \rightarrow Ti(d_x2_{-y}2, d_{xy})$ transition and the band around 400 nm (negative Cotton effect) to the $\pi \rightarrow Ti(d_x2_{-y}2, d_{xy}, d_z2)$ transition. According to the results of the earlier theoretical investigations, the signs of the observed Cotton effects support the conclusion that the metal complex moieties are Λ-configured.[10]

In summary, we have reported the preparation of an enantiomerically pure triangular ligand, which forms the first enantiomerically pure M_4L_4 tetrahedron. Due to our rationalization considering earlier results by us and others and to CD spectroscopic investigations the most probable conformation at the metal complex units is Λ. In future studies chiral organic cations will be introduced and it will be investigated if our chiral cavity is able to discriminate between different stereoisomers.

NMR spectra were recorded on a Varian Mercury 300 or Inova 400 spectrometer. FT-IR spectra were recorded on a Bruker IFS spectrometer. ESI FT-ICR mass spectra were measured on a Bruker APEX IV Fourier-transform ion cyclotron resonance (FT-ICR) mass spectrometer with an Apollo electrospray ion source. Elemental analyses were obtained with a Heraeus CHN-O-Rapid analyzer. Melting points: Büchi B-540 apparatus (uncorrected).

(*S*)-4-(Hydroxymethyl)-2,3-dimethoxy-*N*-(1-phenylethyl)benzamide (2)

2,3-Dimethoxybenzylic alcohol (**1**; 1.00 g, 5.92 mmol) was dissolved in anhyd hexane (60 mL) under N_2. TMEDA (2.06 g, 17.8 mmol) and *n*-BuLi (1.6 n in hexane, 11.2 mL, 17.8 mmol) were added and the mixture was stirred for 4 h at r.t. At 0 °C, (*S*)-1-phenylethyl isocyanate (1.99 g, 11.8 mmol) was added and the mixture was stirred for 2 h at this temperature before it was allowed to warm to r.t. and stirred overnight. The solvent was removed and aq 2 N HCl (1 mL) and brine (10 mL) were added. The mixture was extracted with Et_2O (3 × 20 mL) and the combined organic phases were dried (Na_2SO_4). The solvent was removed in vacuum and the residue purified by column chromatography on silica gel (pentane–EtOAc, 2:3) to obtain a yellow oil; yield: 0.320 g (17%).

IR ($CHCl_3$): 3368, 3061, 3028, 2974, 2936, 2869, 1735, 1644, 1528, 1453, 1407, 1266, 1016, 839, 762, 702 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.18 (d, *J* = 7.4 Hz, 1 H, NH), 7.80 (d, *J* = 8.1 Hz, 1 H_{arom}), 7.35–7.20 (m, 5 H_{arom}), 7.13 (d, *J* = 8.1 Hz, 1 H_{arom}), 5.29 (quint, *J* = 7.0 Hz, 1 H, CH), 4.65 (s, 1 H, OH), 3.84 (s, 3 H, OCH_3), 3.79 (s, 3 H, OCH_3), 1.54 (d, *J* = 7.0 Hz, 3 H, CH_3).

MS (EI): *m*/*z* = 315.2 (M^+), 316.2 (M + H^+).

Anal. Calcd for $C_{18}H_{21}NO_4$ (315.36): C, 68.55; H, 6.71; N, 4.44. Found: C, 68.02; H, 6.93; N, 4.96.

(*S*)-2,3-Dimethoxy-*N*-(1-phenylethyl)benzamide-4-carbaldehyde (3)

At –78 °C, DMSO (3.61 g, 46.1 mmol) was added to oxalyl chloride (4.10 g, 32.3 mmol) in anhyd CH_2Cl_2. After 5 min, compound **2**

(1.46 g, 4.60 mmol) in CH_2Cl_2 (80 mL) was added, followed by DIPEA (5.96 g, 46.1 mmol) after another 5 min. After warming to r.t., the mixture was filtered over silica gel and the residue was washed with CH_2Cl_2 (50 mL) and pentane–Et_2O (1:1, 50 mL). The solvent was removed, the residue dissolved in H_2O (100 mL) and extracted with EtOAc (2 × 30 mL). Drying (Na_2SO_4) and removal of the solvent afforded a yellow oil; yield: 1.34 g (93%).

IR ($CHCl_3$): 3368, 2977, 2939, 1692, 1650, 1530, 1455, 1408, 1386, 1256, 1107, 1039, 1011, 910, 828, 766, 733, 701 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 12.16 (s, 1 H, CHO), 8.12 (d, *J* = 7.7 Hz, 1 H, NH), 7.78 (dd, *J* = 8.2, 0.7 Hz, 1 H_{arom}), 7.51 (dd, *J* = 8.2 Hz, 1 H_{arom}), 7.34–7.14 (m, 5 H_{arom}), 5.25 (dq, *J* = 7.7, 6.9 Hz, 1 H, CH), 4.65 (s, 2 H, CH_2), 3.91 (s, 3H, OCH_3), 3.80 (s, 3 H, OCH_3), 1.52 (d, *J* = 6.9 Hz, 3 H, CH_3).

MS (EI): *m*/*z* = 313.0 (M^+), 314.0 (M + H^+).

Anal. Calcd for $C_{18}H_{19}NO_4 \cdot H_2O$ (331.4): C, 65.24; H, 6.39; N, 4.23. Found: C, 65.79; H, 6.62; N, 4.70.

(*S*)-2,3-Dihydroxy-*N*-(1-phenylethyl)benzamide-4-carbaldehyde (4)

BBr_3 (2 mL, 5.12 g, 20.4 mmol) was slowly added to the protected compound **3** (0.80 g, 2.6 mmol) in CH_2Cl_2 (50 mL) at –78 °C. After 12 h, MeOH (5 mL) was added and the solution was concentrated in vacuum. The oily residue was dissolved in EtOAc (50 mL) and washed with acidified H_2O (pH 4–5, 30 mL). The solvent was removed and the residue dissolved in CH_2Cl_2 (50 mL). On addition of pentane, the product precipitated as an orange oil; yield: 0.61 g (83%).

IR ($CHCl_3$): 3372, 3022, 2977, 2932, 1657, 1610, 1539, 1447, 1390, 1292, 1217, 1104, 833, 757, 700, 666 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 11.41 (s, 1 H, OH), 10.68 (s, 1 H, OH), 9.88 (s, 1 H, CHO), 7.31–7.23 (m, 5 H_{arom}), 7.10 (d, *J* = 8.4 Hz, 1 H, NH), 7.02 (d, *J* = 8.4 Hz, 1 H_{arom}), 6.93 (m, 1 H_{arom}), 5.25 (dq, *J* = 7.3, 6.9 Hz, 1 H, CH), 1.56 (d, *J* = 6.9 Hz, 3 H, CH_3).

ESI-MS (positive, MeOH): *m*/*z* = 286.3 (MH^+), 331.9 ($C_{18}H_{21}NO_5H^+$ dimethoxyacetal of **4**).

Anal. Calcd for $C_{16}H_{15}NO_4 \cdot 2/3\ H_2O$ (297.30): C, 64.64; H, 5.54; N, 4.71. Found: C, 64.17; H, 5.03; N, 4.11.

4,4′,4″-(1*E*,1′*E*,1″*E*)-[4,4′,4″-Nitrilotris(4,1-phenylene)tris(azan-1-yl-1-ylidene)]tris(methan-1-yl-1-ylidene)tris(2,3-dihydroxy-*N*-[(*S*)-1-phenylethyl]benzamide) (L-H_6)

N^1,N^1-Bis(4-aminophenyl)phenylene-1,4-diamine (0.058 g, 0.2 mmol) and **4** (0.22 g, 0.8 mmol) were dissolved in MeOH (20 mL) and stirred overnight at r.t. The solvent was removed and the residue dissolved in CH_2Cl_2 (40 mL), and filtered. The product obtained after evaporation of the solvent was repeatedly recrystallized from CH_2Cl_2–pentane (1:1), CH_2Cl_2–cyclohexane (1:1), and CH_2Cl_2–Et_2O–cyclohexane (1:1:1). The product was obtained as a red solid; yield: 0.081 g (37%).

IR (KBr): 3389, 1613, 1535, 1502, 1445, 1293, 1206, 832, 700, 539 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 10.60 (s, 3 H, 3 × OH), 8.56 (s, 3 H, 3 × N=CH), 7.35–7.12 (m, 24 H, 3 × OH + 21 H_{arom}), 7.08 (d, *J* = 8.5 Hz, 6 H_{arom}), 7.01 (d, *J* = 7.4 Hz, 3 H, 3 × NH), 6.87 (d, *J* = 8.5 Hz, 6 H_{arom}), 5.28 (dq, *J* = 7.4, 6.9 Hz, 3 H, 3 × CH), 1.57 (d, *J* = 6.9 Hz, 9 H, 3 × CH_3).

ESI-MS (positive, MeOH): *m*/*z* = 1092.3 (M + H^+), 825.4 ($C_{50}H_{44}N_6O_6H^+$), 558.4 ($C_{34}H_{31}N_5O_3H^+$).

ESI-MS (negative, MeOH): *m*/*z* = 1090.8 (M – H^-), 823.9 ($C_{50}H_{43}N_6O_6^-$).

Anal. Calcd for $C_{66}H_{57}N_7O_9 \cdot 3.5\ H_2O$ (1155.3): C, 68.62; H, 5.58; N, 8.49. Found: C, 68.25; H, 5.32; N, 8.81.

Metal Complexes with L-H_6; General Procedure

L-H_6 (0.025 g, 0.023 mmol), $TiOacac_2$ (6.0 mg, 0.023 mmol) and the respective alkali metal carbonate (0.023 mmol) were dissolved in DMF (40 mL) and the mixture stirred overnight at r.t. The solvent was distilled off and the residue dried in vacuum. An orange solid was obtained as the product. Elemental analyses show a high content of solvent in the crystal, which probably fills up the cavity of the tetrahedron and the pores in the structure as it was observed earlier for a related complex by X-ray diffraction.[5a]

$Li_4[L_6Ti_4]$

Yield: 0.038 g (quant).

IR (KBr): 3797, 3679, 3419, 2966, 2929, 2873, 2374, 2345, 1658, 1499, 1430, 1384, 1321, 1214, 1102, 1026, 831, 776, 686, 540, 501 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 10.2–10.0 (m, 12 H, 12 × NH), 8.82 (s, 12 H, 12 × N=CH), 7.4–6.8 (m, 132 H_{arom}), 5.2–5.0 (m, 12 H, 12 × CH), 1.5–1.2 (m, ^3J = 7.4 Hz, 36 H, 12 × CH_3).

ESI-MS (negative): *m*/*z* = 1140.9 (M – 4 Li^{4-}), 911.3 (M – 5 Li^{5-}), 758.4 (M – 6 Li^{6-}).

Anal. Calcd for $C_{264}H_{204}Li_8N_{28}O_{36}Ti_4 \cdot 42\ H_2O \cdot 17$ DMF (6590.85): C, 57.40; H, 6.22; N, 9.56. Found: C, 57.44; H, 6.24; N, 9.36.

$Na_4[L_6Ti_4]$

Yield: 0.041 g (quant).

IR (KBr): 3430, 3269, 3056, 2968, 2927, 2864, 2345, 1664, 1543, 1500, 1427, 1383, 1321, 1288, 1205, 1096, 1034, 830, 781, 699, 666, 500 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 10.1–10.0 (m, 12 H, 12 × NH), 8.88 (s, 12 H, 12 × N=CH), 7.4–6.8 (m, 132 H_{arom}), 5.3–5.1 (m, 12 H, 12 × CH), 1.4–1.2 (m, ^3J = 7.4 Hz, 36 H, 12 × CH_3).

ESI-MS (negative): *m*/*z* = 1550.1 (M – 3 Na^{3-}), 1543.1 (M – 4 Na + H^{3-}), 1535.8 (M – 5 Na + 2 H^{3-}), 1156.8 (M – 4 Na^{4-}), 1151.6 (M – 5 Na + H^{4-}), 1146.1 (M – 6 Na + 2 H^{4-}), 1140.6 (M – 7 Na + 3 H^{4-}), 920.9 (M – 5 Na^{5-}), 916.5 (M – 6 Na + H^{5-}), 912.3 (M – 7 Na + 2 H^{5-}), 907.9 (M – 8 Na + 3 H^{5-}), 763.6 (M – 6 Na^{6-}), 759.9 (M – 7 Na + H^{6-}), 756.4 (M – 8 Na + 2 H^{6-}).

Anal. Calcd for $C_{264}H_{204}N_{28}Na_8O_{36}Ti_4 \cdot 36\ H_2O \cdot 25$ DMF (7194.89): C, 56.58; H, 6.32; N, 10.32. Found: C, 56.65; H, 6.37; N, 10.21.

$K_4[L_6Ti_4]$

Yield: 0.039 g (quant).

IR (KBr): 3273, 1642, 1535, 1504, 1462, 1322, 1286, 1241, 1207, 971, 832, 783, 700, 673, 539 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 9.9–9.7 (m, 12 H, 12 × NH), 8.92 (s, 12 H, 12 × N=CH), 7.6–7.0 (m, 132 H_{arom}), 5.3–5.1 (m, 12 H, 12 × CH), 1.4–1.2 (m, ^3J = 7.4 Hz, 36 H, 12 × CH_3).

ESI-MS (negative): *m*/*z* = 1552.7 (M – 6 K + Na + 2 H^{3-}), 1539.8 (M – 8 K + 3 Na + 2 Li^{3-}), 1527.4 (M – 8 K + 2 Na + 3 H^{3-}), 1513.4 (M – 8 K + 5 H^{3-}), 1154.1 (M – 6 K + 2 H^{4-}), 1144.6 (M – 7 K + 3 H^{4-}), 1138.8 (M – 8 K + 4 H + H_2O^{4-}), 1135.1 (M – 8 K + 4 H^{4-}), 907.9 (M – 8 K + 3 H^{5-}).

Anal. Calcd for $C_{264}H_{204}K_8N_{28}O_{36}Ti_4 \cdot 52\ H_2O \cdot 13$ DMF (6735.9): C, 54.03; H, 5.97; N, 8.53. Found: C, 54.06; H, 5.98; N, 8.41.

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