Quantification of solvent effects on molecular recognition in polyhedral coordination cage hosts

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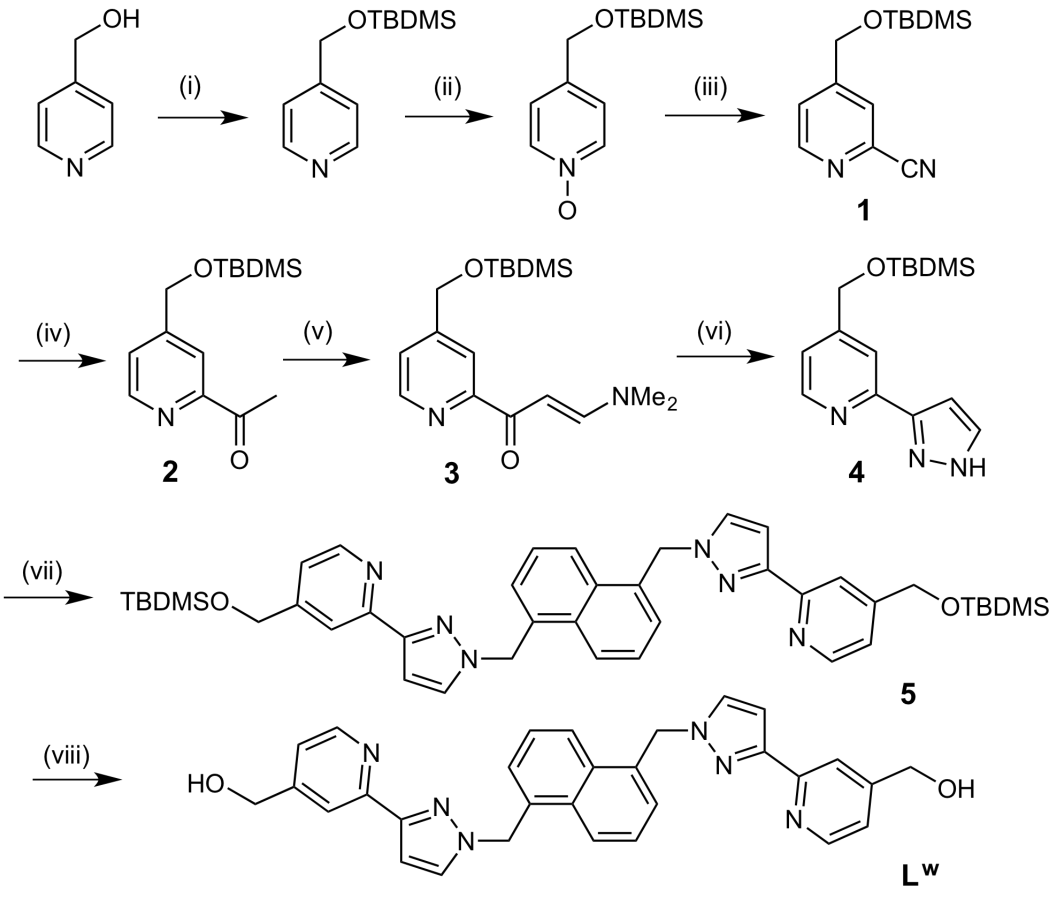
Experimental

Synthesis of the ligand ***L****ʷ.* The following compounds were prepared using previously published methods: 4-[(*tert*-butyldimethylsilyloxy)methyl]pyridine,[1] 4-[(*tert*-butyldimethylsilyloxy)methyl]pyridine *N*-oxide,[1] and 1,5-bis(bromomethyl)-naphthalene.[2] The metal salts and organic reagents used for all synthetic work were purchased from Sigma-Aldrich and used as received. The reaction sequence used to prepare **L**^{w} is below in Scheme S1.



Scheme S1: Preparation of L^{w}**.** (i) TBDMS-Cl, imidazole, DMF (see ref. S1); (ii) mCPBA, CH_2Cl_2 (see ref. S1); (iii) Me_3SiCN, Me_2NCOCl, CH_2Cl_2; (iv) MeMgBr, Et_2O; (v) *N,N*-Dimethylformamide-dimethylacetal; (vi) hydrazine hydrate, EtOH; (vii) 1,5-Bis(bromomethyl)naphthalene, NaH, thf; (viii) Bu_4NF, thf.

4-[(*tert*-Butyldimethylsilyloxy)methyl]picolinonitrile (**1**). To a stirred solution of 4-[(*tert*-butyldimethylsilyloxy)methyl]pyridine-*N*-oxide (28.7 g, 120 mmol) in dry CH_2Cl_2

(300 cm^3) was slowly added Me_3SiCN (14.9 g, 150 mmol); the mixture was stirred for a further 10 minutes at room temperature. Dimethylcarbamoyl chloride (16.1 g, 150 mmol) was added slowly and left to stir overnight. After 16 hours, saturated aqueous K_2CO_3 (200 cm^3) was added slowly and the mixture was left to stir for 10 minutes. The mixture was extracted with CH_2Cl_2 (3 x 250 cm^3) and the solvent evaporated, after which water (250 cm^3) was added to the residue and the mixture stirred for 1 hour to remove any remaining water-soluble impurities. The crude mixture was again extracted with CH_2Cl_2 (3 x 250 cm^3) and the solvent evaporated to yield a dark brown oil. The crude product was purified by column chromatography (silica, hexane/EtOAc, 9:1) to yield the product as a yellow oil (23.4 g, 77 %). ^1H NMR (400 MHz, $CDCl_3$): δ 8.67 (1H, d), 7.70 (1H, s), 7.48 (1H, d), 4.80 (2H, s), 0.94 (9H, s), 0.09 (6H, s). ESMS: *m/z* 249.1 [*M* + H]$^+$.

4-[(*tert*-Butyldimethylsilyloxy)methyl]-2-acetylpyridine (**2**). Compound **1** (3.0 g, 12.1 mmol) was dissolved in dry Et_2O (30 cm^3) cooled to 0 °C under N_2. MeMgBr (3M solution; 14 cm^3, 42 mmol) was added slowly and the mixture then stirred for 3 hours at room temperature. After this time, saturated aqueous NH_4Cl (50 cm^3) was added and the reaction mixture stirred vigorously for 2 minutes. The organic layer was separated and retained, and the aqueous layer was further extracted with CH_2Cl_2 (3 x 50 cm^3). The combined organic layers were dried ($MgSO_4$), and evaporation of the solvent afforded a brown crude product. This product was isolated following column chromatography (silica; CH_2Cl_2/MeO, 98:2) as a brown oil (0.62 g, 19%). ^1H NMR (250 MHz, $CDCl_3$): δ 8.63 (1H, d), 7.97 (1H, s), 7.51 (1H, d), 4.81 (2H, s), 2.75 (3H, s), 0.97 (9H, s), 0.14 (6H, s). ESMS: *m/z* 266.1 [*M* + H]$^+$.

Compound (3). A solution of compound **2** (3.31 g, 12.5 mmol) in *N,N*-dimethylformamide-dimethylacetal (2.67 g, 22.4 mmol) was stirred at 110 °C overnight. Concentration *in vacuo* afforded a brown oil which was purified by column chromatography (silica; CH_2Cl_2/MeOH, 9:1) to give **3** as a brown solid (3.70 g, 93%). ^1H NMR (400 MHz, $CDCl_3$): δ 8.61 (1H, d), 8.06 (1H, s), 7.94 (1H, d), 7.43 (1H, d), 6.47 (1H, d), 4.80 (2H, s), 3.20 (3H, s), 3.02 (3H, s), 0.98 (9H, s), 0.13 (6H, s). ESMS: *m/z* 321.1 [*M* + H]$^+$. Found: C, 63.3; H, 8.8; N, 8.7%. Required for $C_{17}H_{28}N_2O_2Si$: C, 63.7; H, 8.8; N, 8.7%.

3-[2-{4-[(*tert*-Butyldimethylsilyloxy)methyl]pyridyl}]pyrazole (**4**). A solution of compound **3** (4.2 g, 13.1 mmol) and hydrazine monohydrate (8.4 g, 262 mmol) in EtOH (30 cm^3) was stirred at 60 °C for 30 minutes, after which time the solvent was evaporated *in vacuo* and water (50 cm^3) added to the residue. The crude product mixture was extracted with CH_2Cl_2 (3 x 50 cm^3), and the combined organic extracts were dried ($MgSO_4$) and filtered. Evaporation of the solvent yielded a crude dark brown oil which was purified by column chromatography (silica; CH_2Cl_2/MeOH, 19:1) to afford **4** as a light brown solid (3.40 g, 89 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.58 (1H, d), 7.70 (1H, s), 7.68 (1H, d), 7.23 (1H, d), 6.79 (1H, d), 4.81 (2H, s), 0.10 (9H, s), 0.16 (6H, s). ESMS: *m/z* 290.2 [*M* + H]$^+$. Found: C, 61.8; H, 8.1; N, 14.2%. Required for $C_{15}H_{23}N_3OSi$: C, 62.2; H, 8.0; N, 14.5%.

Compound (5). To a solution of **4** (0.50 g, 1.72 mmol) in dry THF (30 cm^3) under N_2 was added NaH (60% dispersion in mineral oil: 0.138 g, 2 equivalents) and the mixture was stirred for 10 minutes. To this was added a solution of 1,5-dibromonaphthalene (0.27 g, 0.86 mmol) in the minimum amount of dry THF. The reaction mixture was stirred at 70 °C and monitored by TLC (silica; CH_2Cl_2/MeOH, 19:1) until compound **4** has disappeared (36 hours). The reaction was then quenched with MeOH and solvents removed. Purification by column chromatography (silica; CH_2Cl_2/MeOH, 19:1) afforded a yellow oil (0.58 g, 46 %). ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.62 (1H, d), 8.07 (1H, d), 7.91 (1H, d), 7.50 (1H, t), 7.36 (1H, d), 7.27 (1H, d), 7.27 (1H, s), 6.90 (1H, d), 5.88 (2H, s), 4.82 (2H, s), 0.98 (9H, s), 0.14 (6H, s). ESMS: *m/z* 731.4 [*M* + H]$^+$, 753.4 [*M* + Na]$^+$. Found: C, 68.6; H, 7.6; N, 11.3%. Required for $C_{42}H_{54}N_6O_2Si_2$: C, 69.0; H, 7.4; N, 11.5%.

Ligand L^w. A solution of the protected ligand (compound **5**; 0.58 g, 0.79 mmol) and tetrabutylammonium fluoride (0.50 g, 1.58 mmol) in dry THF (30 cm^3) was stirred at room temperature overnight. After 16 hours the THF was evaporated off; water (15 cm^3) and CH_2Cl_2 (15 cm^3) were added to the residue and the mixture was thoroughly agitated. The resulting white suspension was allowed to stand for 1 hour during which time a white solid precipitated; collection via filtration gave afforded pure **L^w** as a white solid (0.37 g, 93 %). ^{1}H NMR (400 MHz, DMSO): δ 8.47 (1H, d), 8.22 (1H, d), 7.88 (1H, d), 7.88 (1H, s) 7.58 (1H, t), 7.27 (1H, d), 7.20 (1H, d), 6.84 (1H, d), 5.94 (2H, s), 5.45 (1H, t), 4.56 (2H, s). ESMS: *m/z* 503.2 [*M* + H]$^+$. Found: C, 64.8; H, 5.4; N, 14.6%. Required for $C_{30}H_{26}N_6O_2 \bullet 3H_2O$: C, 64.7; H, 5.8; N, 15.1%.

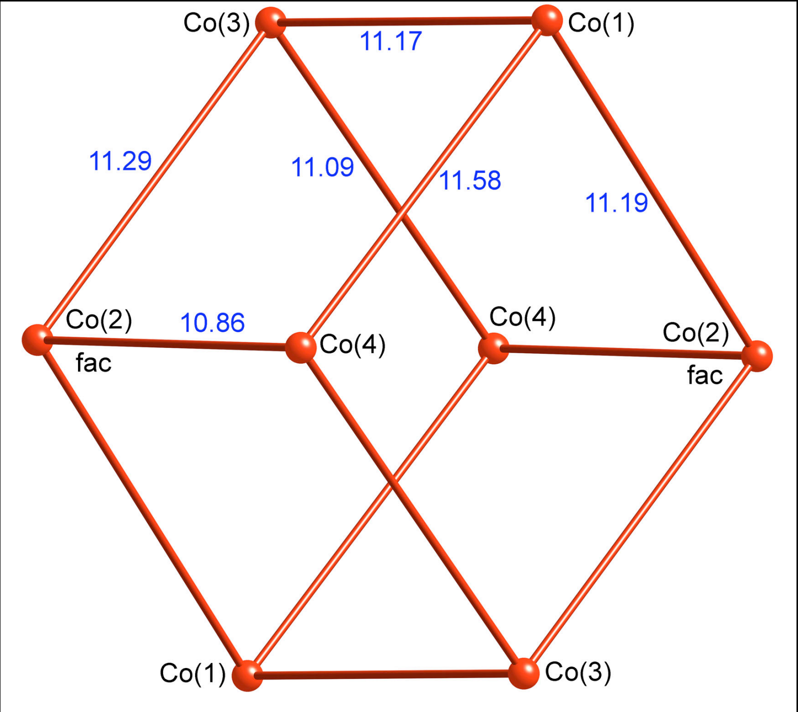
Synthesis of the complex $[Co_8(L^w)_{12}](BF_4)_{16}$. A teflon-lined autoclave was charged with $Co(BF_4)_2$ (0.014 g, 0.041 mmol), $\mathbf{L^w}$ (0.030 g, 0.060 mmol), and methanol (9 cm^3). The mixture was heated to 100 °C for 12 hours and then cooled slowly at 0.1 °C min^{-1} to room temperature to yield X-ray quality crystals. ESMS: *m/z* 1885.9 $\{[Co_8(L^w)_{12}][BF_4]_{12}\}^{4+}$; 1491.8 $\{[Co_8(L^w)_{12}][BF_4]_{11}\}^{5+}$; 1228.7 $\{[Co_8(L^w)_{12}][BF_4]_{10}\}^{6+}$; 1040.8 $\{[Co_8(L^w)_{12}][BF_4]_9\}^{7+}$; 899.9 $\{[Co_8(L^w)_{12}][BF_4]_8\}^{8+}$; 790.3 $\{[Co_8(L^w)_{12}][BF_4]_7\}^{9+}$ (see figure in main text). For high-resolution expansions of selected peaks in the ES mass spectrum see below. ^{1}H NMR: see main text. The vacuum-dried material was hygroscopic and elemental analytical data were consistent with presence of ≈30 water molecules *per* complex cage, which is reasonable given the presence of 24 H-bonding hydroxyl groups on the external surface plus additional solvent binding sites in the central cavity (*cf.* the extensive solvation seen in the crystal structure). Found: C, 50.9; H, 4.1; N, 11.8%. Required for $[Co_8(C_{30}H_{26}N_6O_2)_{12}](BF_4)_{16} \bullet 30H_2O$: C, 51.2; H, 4.5; N, 12.0%.

1. A. El Hadri and G. Leclerc, *J. Heterocycl. Chem.,* 1993**, 30**, 631.
2. I. S. Tidmarsh, T. B. Faust, H. Adams, L. P. Harding, W. Clegg and M. D. Ward, *J. Am. Chem. Soc.,* 2008, **130**, 15167.

Detailed comparison of structure of hosts H and H^{w}

(i) A summary of unique Co•••Co separations (Å) in the two cubic host cages is shown here: the average Co•••Co separation between the two cages differs by ≈ 1.3%.

Host **H** (from ref. 8)



Long diagonals:

Co(1)•••Co(1'), 19.95 Å

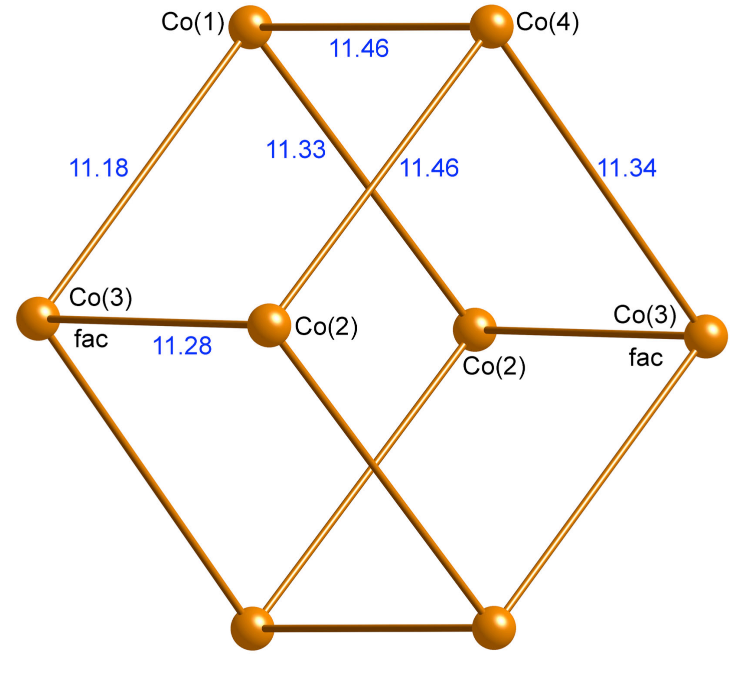
Co(2)•••Co(2'), 18.13 Å

Co(3)•••Co(3'), 19.74 Å

Co(4)•••Co(4'), 19.72 Å

Average: 19.39 Å

Host **H**^{w} (this work)



Long diagonals:

Co(1)•••Co(1'), 20.27 Å

Co(2)•••Co(2'), 20.24 Å

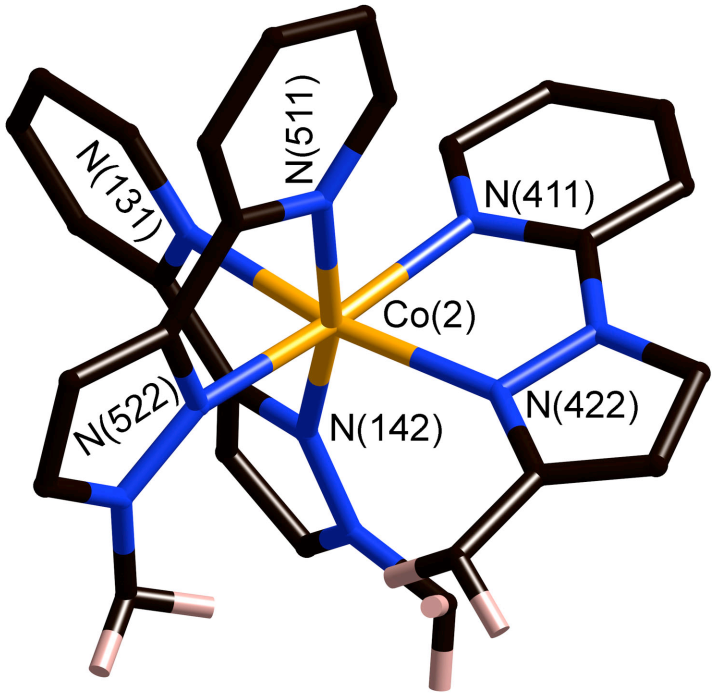
Co(3)•••Co(3'), 18.22 Å

Co(4)•••Co(4'), 19.77 Å

Average: 19.63 Å

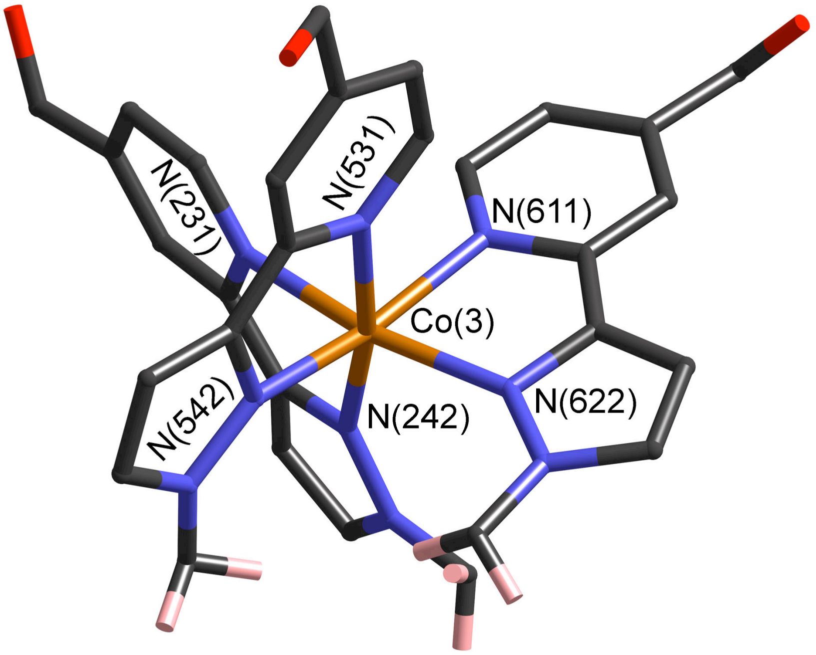
(ii) Comparison of detailed coordination geometries around the *fac* tris-chelate binding sites: bond distances are in Å and angles are in degrees.

Host **H** (from ref. 8)



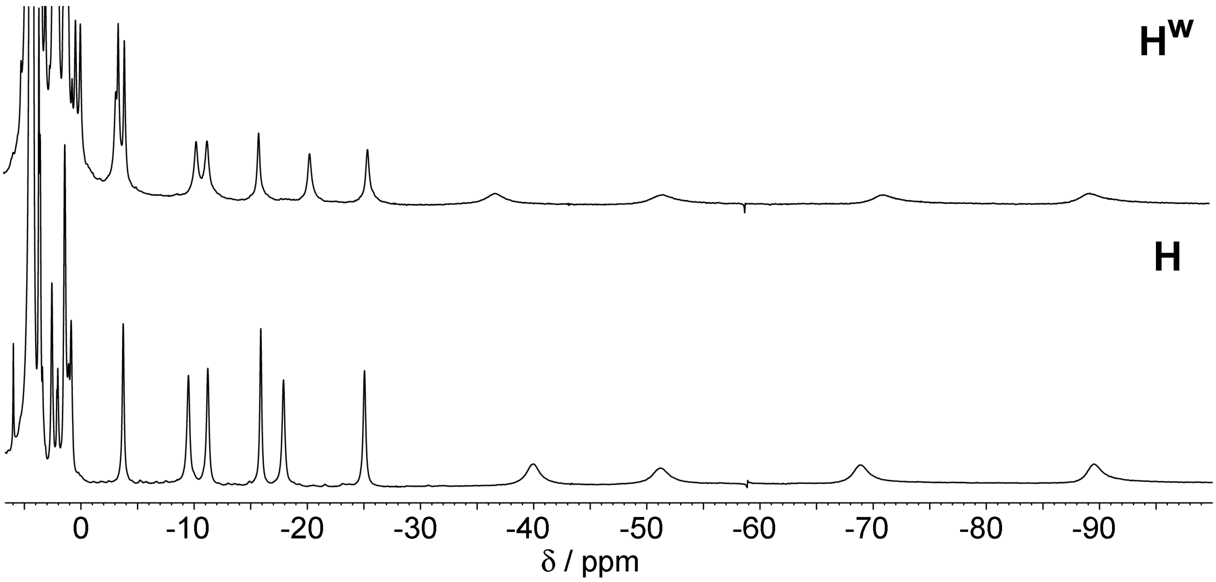
Co–N(pyridyl) distances	
Co(2)-N(511)	2.146(5)
Co(2)-N(411)	2.183(5)
Co(2)-N(131)	2.147(5)
Co–N(pyrazolyl) distances	
Co(2)-N(142)	2.140(5)
Co(2)-N(422)	2.141(5)
Co(2)-N(522)	2.179(4)
Trans N–Co–N angles	
N(142)-Co(2)-N(511)	168.16(18)
N(422)-Co(2)-N(131)	168.35(17)
N(522)-Co(2)-N(411)	171.43(17)
Ligand bite angles	
N(142)-Co(2)-N(131)	76.33(19)
N(511)-Co(2)-N(522)	76.28(16)
N(422)-Co(2)-N(411)	75.72(17)
Other cis N–Co–N angles	
N(422)-Co(2)-N(522)	102.94(16)
N(142)-Co(2)-N(422)	101.68(17)
N(142)-Co(2)-N(522)	99.36(17)
N(422)-Co(2)-N(511)	90.06(17)
N(511)-Co(2)-N(131)	92.45(19)
N(131)-Co(2)-N(522)	88.71(17)
N(142)-Co(2)-N(411)	89.19(17)
N(511)-Co(2)-N(411)	95.21(17)
N(131)-Co(2)-N(411)	92.71(18)

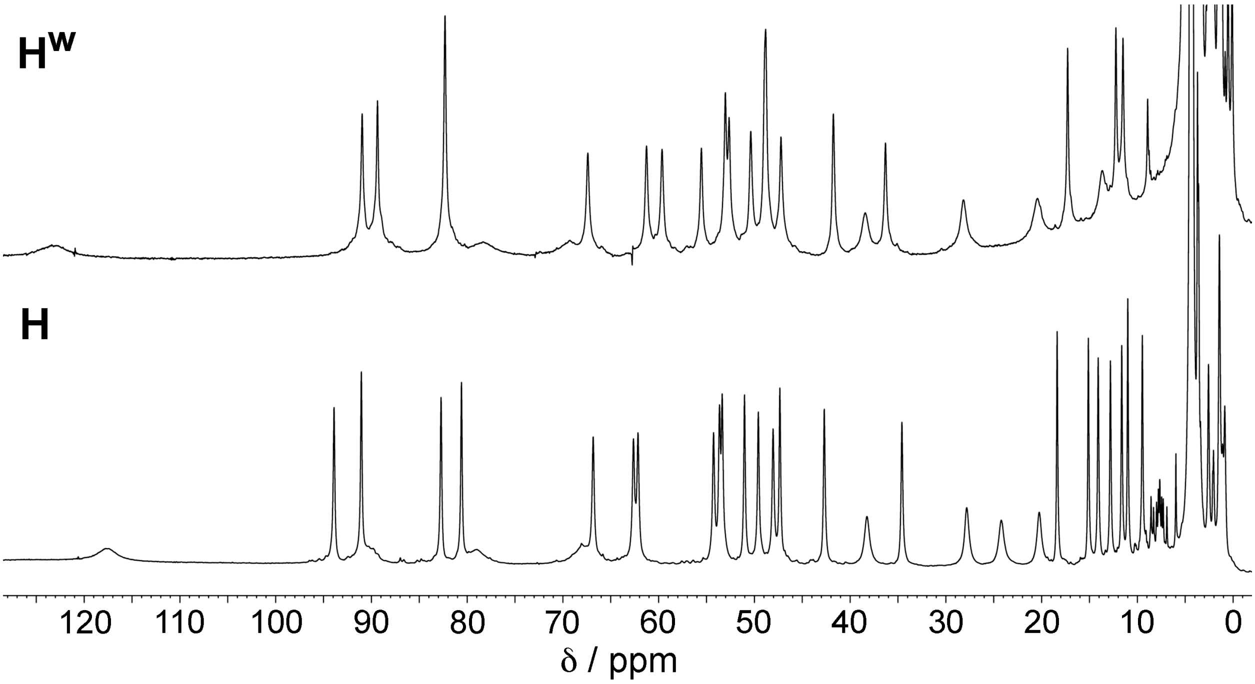
Host **H**^{w} (this work)



Co–N(pyridyl) distances	
Co(3)-N(531)	2.181(4)
Co(3)-N(611)	2.204(5)
Co(3)-N(231)	2.158(5)
Co–N(pyrazolyl) distances	
Co(3)-N(622)	2.116(5)
Co(3)-N(542)	2.143(4)
Co(3)-N(242)	2.145(4)
Trans N–Co–N angles	
N(622)-Co(3)-N(231)	166.4(3)
N(242)-Co(3)-N(531)	169.9(2)
N(542)-Co(3)-N(611)	168.4(2)
Ligand bite angles	
N(242)-Co(3)-N(231)	75.9(2)
N(542)-Co(3)-N(531)	75.7(2)
N(622)-Co(3)-N(611)	76.8(3)
Other cis N–Co–N angles	
N(622)-Co(3)-N(542)	102.8(2)
N(622)-Co(3)-N(242)	100.9(2)
N(542)-Co(3)-N(242)	101.2(2)
N(542)-Co(3)-N(231)	90.8(2)
N(622)-Co(3)-N(531)	89.2(2)
N(231)-Co(3)-N(531)	94.4(3)
N(242)-Co(3)-N(611)	90.3(2)
N(231)-Co(3)-N(611)	89.9(3)
N(531)-Co(3)-N(611)	92.6(2)

(iii) Comparison of paramagnetically-shifted ^1H NMR spectra of **H** and **H^w** in the same solvent (CD_3NO_2, 298K)





(iv) Selected expansions from high resolution ES mass spectra of $\mathbf{H^w}$ showing the peaks for $\{[Co_8(L^w)_{12}][BF_4]_{11}\}^{5+}$ (top) and $\{[Co_8(L^w)_{12}][BF_4]_9\}^{7+}$ (bottom).