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In flagrante metallo-cyclophane self-assembly?†

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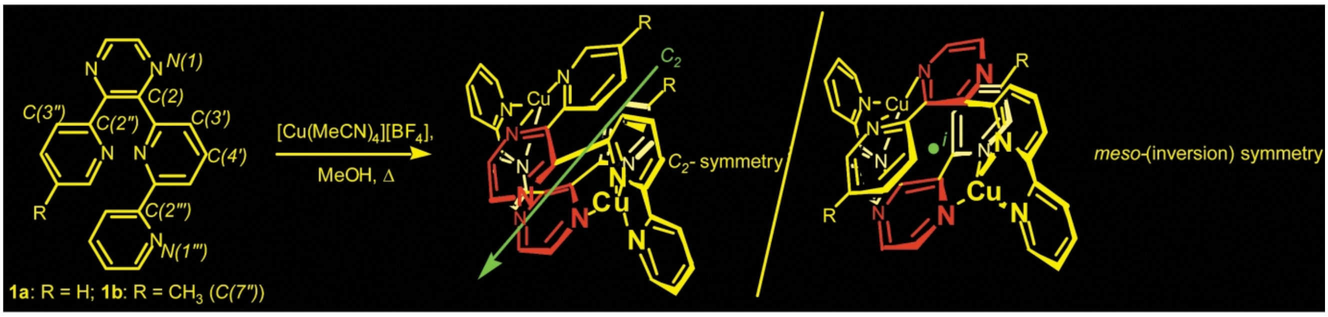
The dimeric self-assembly of an alkyl-substituted pyrazine–pyridine hybrid ligand with copper(I) initially affords its sterically congested, C_2-symmetric stereoisomer, which then undergoes partial isomerisation to a dynamic mixture containing the less crowded *meso*-configured diastereomer.

Prediction and switching between self-assembled supramolecular diastereomers are current challenges[1] relevant to diverse applications.[2] Its expression may be through *meso*/helical-type symmetry as a consequence of one stereogenic center predisposing the stereochemistry of subsequent binding sites.

Self-assembled metallo-cyclophanes have internal arenes in cofacial alignment, separated by graphitic distances and interconnected through metallo-organic binding. These stacking interactions may stabilize diastereomeric arene alignment during the self-assembly process,[3] and are accentuated by steric bias and a sharply angular arrangement of ligand-binding domains.[4,5]

The electron-deficient character of pyrazine derivatives is amplified by metal coordination,[6] which makes their derivatives efficient participants in π-stacked self-assembly. Such 2,3-disubstituted derivatives furthermore undergo a sterically induced, right-angle partitioning of their binding domains. This contributes to a dimeric self-assembly pattern,[4,7,8] as opposed to relatively unhindered 2,5-disubstituted pyrazine derivatives, which may form larger architectures.[9] Ligand **1a** self-assembles with copper(I) to a dimeric metallo-cyclophane cation $[\mathbf{1a}_2Cu_2]^{2+}$.[7] Stacking of pyrazine rings promotes solution- and solid-state (*rac*) C_2-symmetry in this dication, over a *meso*-configured metallo-cyclophane having double pyrazinyl-pyridyl hetero-overlaps. The C_2-symmetry of the *rac*-stereoisomer differs from that of conventional helicate-type complexes[2] by virtue of a lesser number of C_2-rotational axes. The postulated existence of both forms is supported by molecular model studies and semi-empirical calculations (Scheme 1). Pyrazine solid-state stacking occur in the same and related ligands.[10] We expected that selective substitution of alkyl groups into the molecular scaffolding of ligand **1a** (*e.g.*, **1b**)[10] would destabilize these stacking interactions *via* intermolecular steric effects, thus inducing a preference for the *meso*-stereoisomer.

Combining **1b** and one equivalent of copper(I)tetrakis(acetonitrilo) tetrafluoroborate, refluxing in methanol, precipitation with ammonium tetrafluoroborate and re-precipitatation from diethyl ether–acetonitrile gave a dark red-coloured solid. The results of FAB-MS and combustion analysis confirmed the dimeric composition, $[\mathbf{1b}Cu]_2[BF_4]_2$.† The ^{1}H NMR spectrum of $[\mathbf{1b}Cu]_2[BF_4]_2$ in CD_3CN at 298 K displayed the expected aromatic shifts and a singlet at δ 2.16 ppm. Upon cooling to 233 K, de-coalescence to two singlets of similar intensity occurred (Fig. 1); the aromatic signals only underwent minor shifts. The low temperature dependence of this ratio implies comparable thermodynamic stabilities and low relative entropic factors for the involved dynamic species. Assignment of the ^{1}H- and ^{13}C spectra of $[\mathbf{1b}Cu]_2[BF_4]_2$ at 233 K agreed with a single ligand equivalent and 12 aromatic protons. The spectrum recorded in CD_3NO_2 at 303 K displayed similar aromatic, however different aliphatic shifts relative to CD_3CN. Two singlets appeared at δ 2.20 and 2.10, and these underwent no coalescence phenomena over 243–303 K ($\Delta\delta$ ~ 0.02 ppm). At no temperature and field strength (270–600 MHz) was a doubling of the aromatic signals observed. A NOESY experiment in CD_3NO_2 at 303 K revealed through-space correlation of the singlet of C(7″) at δ 2.20 to H(6″) in the partner ligand; this interaction is only possible for contacts < 6 Å, which allows assignment to the C_2-symmetric diastereomer (Fig. 2). The relative magnitudes of the T_1 values (0.77 ± 0.09 *vs.* 0.38 ± 0.05 s for C_2- and *meso*-isomers, respectively), and thus dipolar relaxation rates, are a result of increased asymmetric tumbling in the C_2-symmetric isomer.[11] Dissimilarity in T_2 relaxation times (*r.e.*, spin state lifetimes and



Scheme 1 Stereochemistry of metallo-cyclophane self-assembly. Symmetry operators indicated in green.

† Electronic Supplementary Information (ESI) available: preparation and characterization of $[\mathbf{1b}Cu]_2[BF_4]_2$, detailed NMR spectroscopic assignments, variable temperature ^{1}H NMR shift plots, X-ray crystallographic data (CIF file) and .pdb files of energy-minimized structures. See http://www.rsc.org/suppdata/cc/b3/b310558j/

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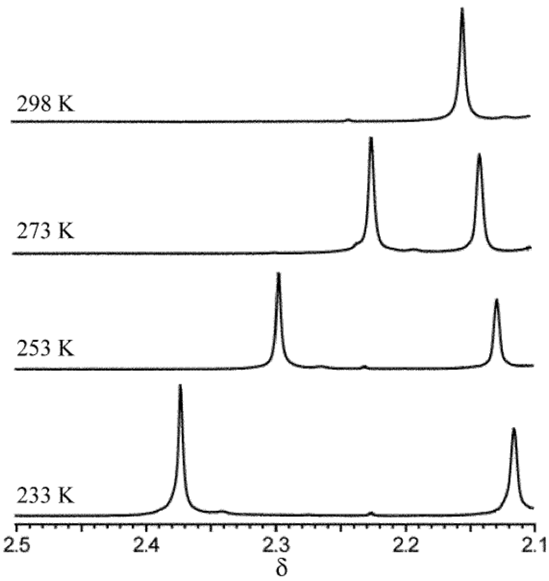

Fig. 1 ^{1}H NMR spectroscopic coalescence behavior of C(7″) methyl group of [**1b**Cu]$_2$[BF$_4$]$_2$ in CD_3CN (400 MHz).

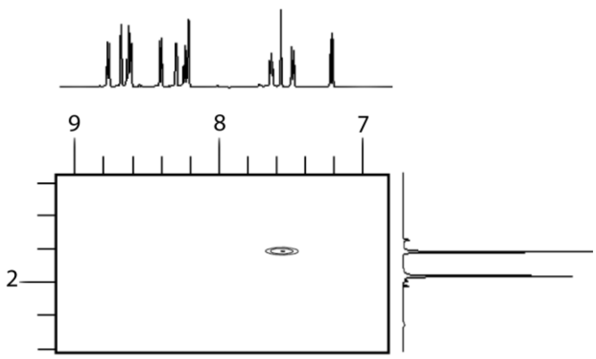

Fig. 2 NOESY correlation of C(7″) methyl group in C_2-symmetric [**1b**Cu]$_2$[BF$_4$]$_2$ diastereomer to H(6″) in CD_3NO_2 (600 MHz, 303 K).

relative spin populations) accounts for the asymmetric coalescence behavior.

Semi-empirical, *in vacuo* strain energy calculations (PM3(d))[12] showed the *meso*-stereoisomer to be *ca*. 33 kJ mol^{-1} lower in energy. Lesser charge separation between copper cations and coordinating nitrogens is also apparent in the C_2-isomer (−1.087/0.677 and −1.110/0.692 for Cu/N of C_2/*meso*, respectively), indicating a weaker electrostatic interaction. This is supported by longer Cu–N bond lengths in the C_2 model.† Since these calculations do not consider π-stacking interactions, this difference from the approximate experimental isomer ratios plausibly reflects the importance of π-stacking stabilization.

Attempts to obtain X-ray quality crystals of [**1b**Cu]$_2$[BF$_4$]$_2$ by recrystallization of the previously isolated complex invariably resulted in non-crystalline material. However, heating under reflux and stirring a degassed, methanolic solution of the ligand and one equivalent of the copper salt reproducibly gave single crystals within 30 min. Further heating induced transformation into non-crystalline material and crystalline material did not form from hot methanolic treatment of [**1b**Cu]$_2$[BF$_4$]$_2$ isolated from acetonitrile solution. Thus we exclude the greater calculated dipole of the C_2-stereoisomer inducing preferred crystallization *via* dipolar packing forces. The single crystals' ^{1}H NMR spectrum, recorded within five minutes of preparing a CD_3NO_2 solution, indicated a *ca.* 1 : 1 mixture of the diastereomers. Rapid isomerization of the chiral form in a non-coordinating solvent and exchange in a coordinating solvent therefore delineate the diastereomeric interconversion rate.

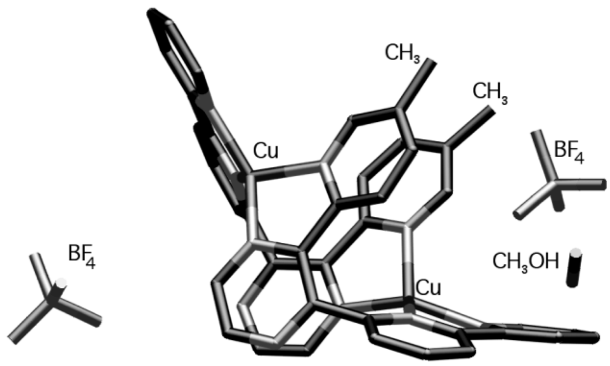

Fig. 3 X-Ray structure of one $\Delta,\Delta/\Lambda\Lambda$-enantiomer of the C_2-symmetric form of [**1b**Cu]$_2$[BF$_4$]$_2$·CH_3OH.

The crystalline complex§ has a virtual C_2-symmetry in the solid state and occurs as racemic $\Delta\Delta/\Lambda\Lambda$-enantiomers (Fig. 3). One equivalent of methanol coordinates to tetrafluoroborate. Copper-nitrogen bond lengths are shorter for Cu to pyrazinyl (1.988–2.007 Å) than to complexed pyridyl (av.: 2.022 Å); N–Cu–N bond angles are 80.92–141.46°. Steric interactions and inter-deck stacking are evident from the 3.81 Å separation between the methyl groups (calculated separation: 3.96 Å), interatomic distances between stacked rings (3.04–3.47 Å) and deviations from parallel cofacial alignment between the stacked pairs (pyrazinyl–pyrazinyl: 4.99°; pyridyl–pyridyl: 9.02°). Initial formation of exclusively the C_2-symmetric stereoisomer implicates pyrazine homostacking prior to metallo-cyclophane closure.

Notes and references

§ **Crystal data.** $C_{41}H_{34}B_2Cu_2F_8N_{10}O$, M = 983.48, orthorhombic, a = 20.5945(8), b = 8.6556(3), c = 22.8050(8) Å, U = 4065.2(3) Å^3, T = 100 K, space group $Pna2_1$ (no. 33), Z = 4, μ(Mo–K$_\alpha$) = 1.13 mm^{-1}, absolute structure param. 0.010(7), 39488 reflections measured, 12600 unique (R_{int} = 0.044), R1(F, $\mathbf{I} > 2\sigma(\mathbf{I})$) = 0.037. The final $wR(F^2)$ was 0.079 (all data) and min/max residual density was +0.57/−0.37 eÅ^{-3}. CCDC 218202. See http://www.rsc.org/suppdata/cc/b3/b310558j/ for crystallographic data in .cif or other electronic format.

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