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Ligand self-recognition in the stereoselective assembly of [2 + 2] metallomacrocycles from racemic chiral bisbipyridyl molecular clefts and zinc(II)

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The synthesis of racemic and optically pure ligand **L**, in which two 6,6′-disubstituted bipyridines are connected by methyleneoxy linkers to the molecular cleft dibenzobicyclo[*b*,*f*][3.3.1]nona-5a,6a-diene-6,12-dione, is reported. In the presence of 2 equivalents of zinc(II) trifluoromethansulfonate (±)-**L** undergoes slow reversible coordination over 24 h to form a pair of enantiomeric [2 + 2] metallomacrocycles, $[Zn_2(+)\mathbf{L}_2](OTf)_4$ and $[Zn_2(-)\mathbf{L}_2](OTf)_4$ respectively, that contain either two (+)-**L** ligands or two (−)-**L** ligands. This assignment was confirmed by independent studies with either (+)-**L** or (−)-**L** which formed the same complexes but at a significantly faster rate (3 h), and circular dichroism spectra of $[Zn_2(+)\mathbf{L}_2](OTf)_4$ and $[Zn_2(-)\mathbf{L}_2](OTf)_4$ which gave signals of the same intensity with the opposite sign. Treatment of (±)-**L** or optically pure **L** with copper(I) showed rapid formation of a mixture of oligomers as well as the [2 + 2] metallomacrocycle. The complex $Zn_2\mathbf{L}_2(OTf)_4$ exhibits slow exchange between two species on the NMR time scale at room temperature. The results are consistent with the formation of a library of metal complexes in which the zinc(II) binds initially to the most accessible bipyridyl binding sites in (±)-**L**. Equilibration over several hours results in self-recognition of enantiomeric ligands to form a pair of enantiomeric metallomacrocycles, which have been tentatively assigned as having the helical configuration. Slow exchange is attributed to the preference for both metal centres to adopt 6-coordinate geometries involving the linker oxygens, but are limited to exchanging 5-coordinate complexes due to the shape of the cleft and the short linker.

Introduction

Numerous studies of the assembly of helicates, metallomacrocycles, catenanes and related supramolecular architectures that incorporate pyridyl and bipyridyl groups have identified important features in ligand design that allow the controlled assembly of both chiral and achiral metal complexes.[1–8] Most studies have used achiral ligands that result in the formation of mixtures of complexes. However, the use of optically pure ligands has allowed the stereoselective assembly of metallomacrocycles and helicates in a predictable manner.[8–15] In contrast, the controlled assembly of a single enantiomeric pair of metal complexes from racemic ligands and two chiral metal centres is challenging due to the number of possible stereoisomers that may be formed. An elegant example demonstrating ligand self-recognition has been reported in which reaction of a racemic bispyridyl ligand generated only homochiral complexes containing a single enantiomeric ligand.[16]

Our contributions in this area have been in the assembly of chiral and achiral [2 + 2] metallomacrocycles encoded with recognition features to allow binding of aromatic substrates.[17–20] The design features required to allow exclusive assembly of the chiral [2 + 2] metallomacrocycle were identified by a systematic study of bisbipyridyl ligands containing an aromatic spacer separated by a short linker. The low stereochemical preference of zinc(II) allowed a range of coordination geometries, and hence metallomacrocycles of different shapes and dimensions, to be assembled. In addition, zinc(II) coordination provided a mechanism whereby the dimensions of the cavity were altered for optimal binding of aromatic substrates.[19] The rigidity and length of the linker allowed exclusive assembly of the helical metallomacrocycle with a naphthalenediimide spacer.[17,19] In contrast, exclusive assembly of the non-helical, achiral metallomacrocycle occurred with a longer, more flexible linker and a pyrene aromatic spacer.[18]

In this paper we report the stereoselective assembly of metallomacrocycles from the optically active bisbipyridyl ligand **L** that incorporates the chiral molecular cleft, dibenzobicyclo[*b*,*f*][3.3.1]nona-5a,6a-diene-6,12-dione.[21] This cleft is reminiscent of Tröger's base but contains different dimensions and additional carbonyl (or alcohol) groups that may be utilised in molecular recognition studies.[22] This cleft was incorporated into the ligand design as it allows entry into optically active ligands, and as the dimensions and recognition properties of the resultant metallomacrocycles offer new opportunities to target the molecular recognition of different classes of substrates. In the presence of zinc(II), racemic ligands undergo an unusual slow equilibration to form the thermodynamic [2 + 2] metallomacrocycles which contain a single ligand enantiomer.

Results

Synthesis

Ligand **L** was prepared under standard Williamson ether formation conditions from the bisphenol cleft **4** and 6-methyl-6′-bromomethyl-2,2′-bipyridine (Scheme 1). As in our previous studies,[17–20] the methylene group was included in the linker as a ^{1}H NMR reporter group that could be used to monitor metal complexation, and an aryl ether linker was selected due to synthetic ease.

Two routes to prepare the bisphenol **4** were investigated. In the first route, the cleft was prepared using a similar procedure to that reported for the parent cleft and derivatives from the methyl ether **3**.[21] Thus, *p*-methoxybenzylnitrile was converted to the mixture of stereoisomeric bisnitriles **1** which were not purified but hydrolyzed directly to the mixture of bisacids **2**. In agreement with the literature reports on a related compound,[23] attempted intramolecular Friedel-Crafts acylation of **2** in concentrated sulfuric acid, the standard conditions that gave good yields of related clefts including the bromocleft **5**,[21,24] was unsuccessful. The methoxy group activates the aromatic rings to sulfonation, and a mixture of water soluble products was obtained. Hence polyphosphoric acid was used to effect cyclization of the bisacids **2** to the molecular cleft **3**. While the bismethyl ether **3** was formed, the reaction was not reproducible and highly variable yields of product were obtained (0–35%). The best isolated yield (35%) was obtained only on small scale (<0.5 g) reactions. Demethylation of **3** by slow addition of the BBr_3 at a low

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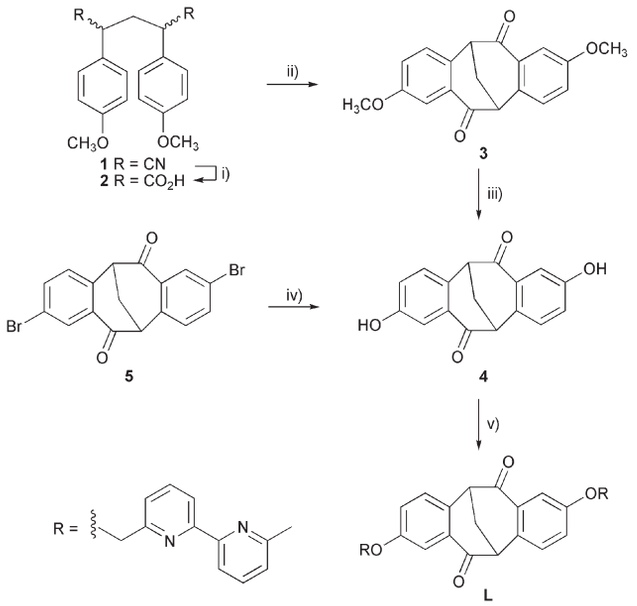

Scheme 1 Reagents and conditions: (i) KOH, Δ; (ii) polyphosphoric acid (PPA), Δ; (iii) BBr_3 −5 °C–rt; (iv) bis(pinacolato)diboron, $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$, KOAc followed by H_2O_2; (v) KO^{t}Bu, 6-bromomethyl-6′-methyl-2,2′-bipyridine.

temperature (−5° to 0° C) gave the desired bisphenol **4**. Treatment of the bisphenol **4** with base followed by 6-bromomethyl-6′-methyl-2,2-bipyridine[25,26] afforded ligand **L** in 60% yield. Use of the bulky, non-nucleophilic base, potassium *tert*-butoxide, allowed the reaction to be performed without protection of the carbonyl groups on the cleft.

We have previously reported the successful resolution of the bisbromocleft **5** and the corresponding bismethyl cleft using chiral HPLC.[24,27] However, attempts to resolve the enantiomers of either the bimethoxycleft **3**, the bisphenol **4**, or ligand **L** by HPLC using different chiral supports and a range of solvent systems were unsuccessful. The alternate route to optically pure **L** involved the use of the readily available optically pure clefts, (+)-**5** and (−)-**5**.[27] These clefts were converted to the corresponding bisphenols, (+)-**4** and (−)-**4** *via* the corresponding pinacol boronate esters under standard Miyaura conditions,[28] followed by conversion to (+)-**L** [(*R*)(*R*)–**L**] and (−)-**L** [(*S*)(*S*)–**L**].

Metal complexation studies with zinc(II)

Racemic ligand. Addition of 2 equivalents of zinc trifluoromethanesulfonate (triflate, OTf) to a CD_3CN solution of (±)-**L** gave a pale yellow solution. Electrospray mass spectrometry was consistent with the formation of a [2 + 2] complex $Zn_2\mathbf{L}_2(OTf)_4$ **6** with peaks at *m*/*z* 1868 $[Zn_2\mathbf{L}_2(OTf)_3]^+$, 1502.9 $[Zn\mathbf{L}_2OTf]^+$ and 859.1 $[Zn_2\mathbf{L}_2(OTf)_2]^{2+}$. The NMR spectrum of this solution (Fig. 1b) econtained multiple, broad signals consistent with the formation of several complexes and/or oligomers. However, over several hours, the appearance of the spectrum changed significantly and after 24 h a spectrum containing a single set of sharp signals was obtained (Fig. 1e). A notable feature of the spectrum was the change in appearance of the methylene protons in the ligand from a singlet (δ 5.23 ppm, Fig. 1a) to an AB quartet (δ 5.35 ppm, Ha,b Fig. 1e). 2D COSY and NOESY spectroscopy showed that this AB quartet was in exchange with a second AX system (Hc,d) in which one of the two methylene protons was dramatically shifted upfield (δ 2.34 ppm, Hc, Fig. 2).

Variable temperature measurements and NOESY spectra of $Zn_2\mathbf{L}_2(OTf)_4$ **6** were used to identify the dynamic process(es) occurring on the NMR time scale. While NOESY spectra at 300 K (Fig. 2, Fig. 3a) confirmed the presence of two species in exchange, these spectra were complicated by transferred NOE peaks arising from exchange. Hence tr-ROESY experiments, recorded at 250 K where there was no exchange on the NMR time scale (Fig. 3b), were used to identify the NOEs, and allowed full assignment of all signals

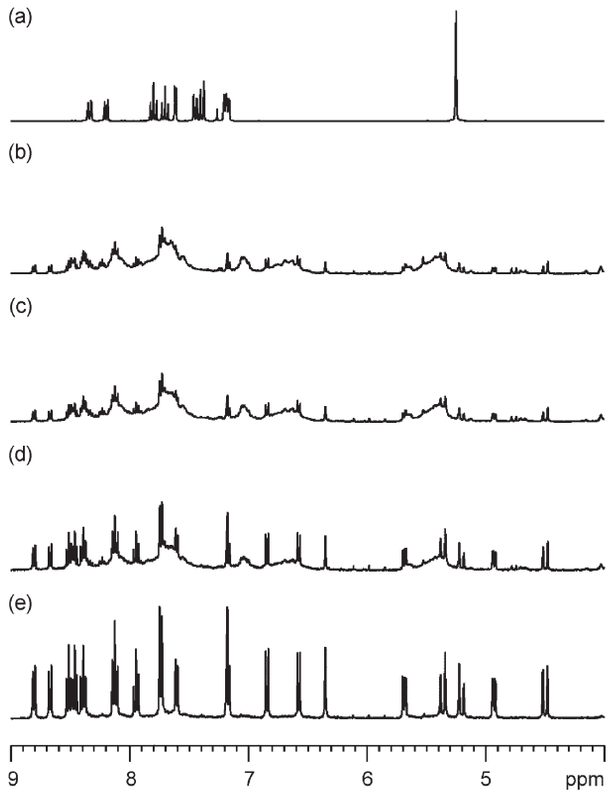

Fig. 1 400 MHz ^{1}H NMR spectra at 300 K of (a) (±)-**L** in $CDCl_3$ and (±)-**L** and $Zn(OTf)_2$ (2 equivalents) in CD_3CN after (b) 15 min, (c) 1 h, (d) 6 h, (e) 24 h.

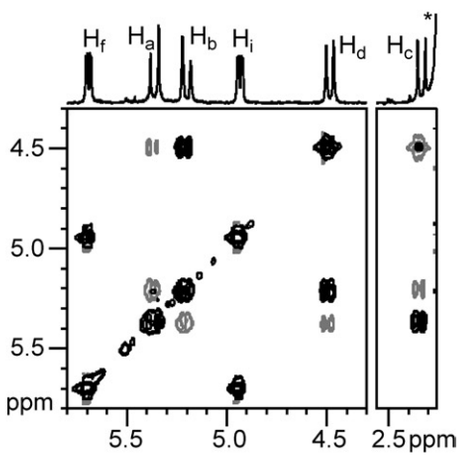

Fig. 2 400 MHz NOESY spectrum of $Zn_2\mathbf{L}_2(OTf)_4$ in CD_3CN at 300 K showing methylene protons. Exchange peaks in black, NOEs in grey; * = water.

in the spectrum. As shown in Fig. 3, two sets of bipyridyl resonances were observed (labelled H3,4,5/3′4′5′ and H6,7,8/6′,7′,8′), in exchange with one another. Similarly, unique signals for the six cleft aromatic protons (He–j) were detected with He,f,g in exchange with Hh,i,j.

Optically pure ligands. Identical metal complexation studies were performed by addition of 2 equivalents of zinc(II) triflate to a CD_3CN solution containing either (+)-**L** or (−)-**L** to give $[Zn_2(+)\mathbf{L}_2](OTf)_4$ and $[Zn_2(-)\mathbf{L}_2](OTf)_4$ respectively. In each experiment, the same ^{1}H spectrum as that shown in Fig. 1e was obtained. However, the rate of sharpening of the signals was significantly faster than that observed with (±)-**L**. Thus, while equilibration of (±)-**L** required approximately 24 h until only signals arising from a single complex **6** were observed, under the same conditions, (+)-**L** or (−)-**L** required only 3 h to give **6**. The CD spectra of $[Zn_2(+)\mathbf{L}_2](OTf)_4$ and $[Zn_2(-)\mathbf{L}_2](OTf)_4$ (Fig. 4) confirm that the complexes are enantiomers, with each complex giving rise to signals of the same intensity at the same concentration, but opposite in sign.

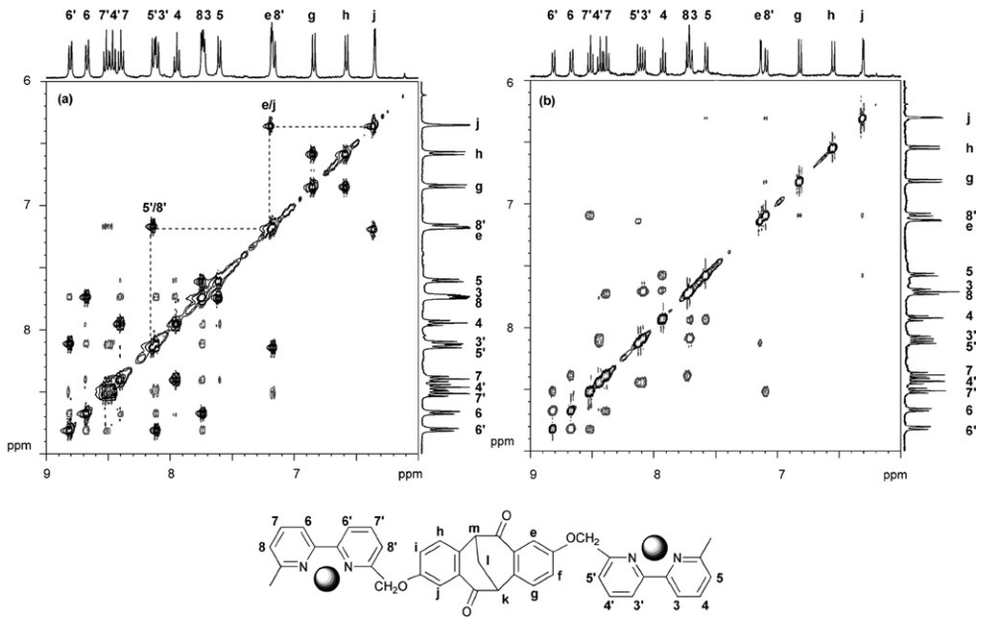

Fig. 3 400 MHz spectra of $Zn_2\mathbf{L}_2(OTf)_4$ in CD_3CN showing peak assignments in (a) NOESY at 300 K, (b) tr-ROESY at 250 K. Exchange peaks in black are highlighted for bipyridyl protons H5′/H8′ and cleft protons He/j. NOEs are shown in grey.

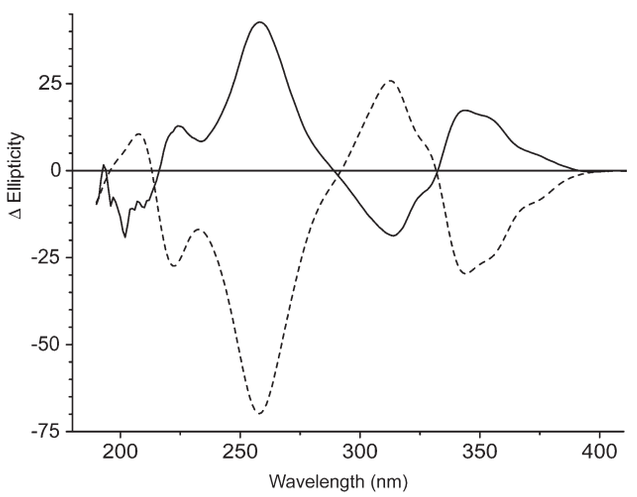

Fig. 4 Circular dichroism spectra (CD_3CN) of $[Zn_2(-)\mathbf{L}_2](OTf)_4$ (3.2 μM, solid line) and $[Zn_2(+)\mathbf{L}_2](OTf)_4$ (3.7 μM, dotted line).

Stability of complex 6. The stability of **6** in different solvents hampered efforts to obtain crystals suitable for X-ray diffraction. Diffusion of either ether or methanol into a dichloromethane or acetonitrile solution of **6** gave an amorphous solid with an NMR spectrum similar to Fig 1a *i.e.*, reformation of a mixture of metal complexes followed by equilibration over several hours to form metallomacrocycle **6**. Once formed the complex **6** is quite stable. Provided the solvent is unchanged, heating an CD_3CN solution to 65 °C showed the expected signal broadening but signal coalescence would require the use of a higher boiling solvent. The appearance of the NMR spectrum of **6** (Fig. 1e) was independent of sample concentration, and removal of CD_3CN followed by redissolving the sample gave an identical spectrum to Fig. 1e.

Metal complexation studies with copper(I)

Fig. 5 shows the ^{1}H NMR spectrum obtained on addition of copper(I) triflate to a solution of (±)-**L** in CD_3CN. In contrast to the corresponding spectra obtained with zinc(II), the NMR spectrum did not change in appearance with time, and the methylene protons showed only minor upfield shifts compared to the ligand. Analysis of the sample by electrospray mass spectrometry showed peaks consistent with the formation of the [2 + 2] metallomacrocycle $Cu_2\mathbf{L}_2(OTf)_4$, along with other unidentified complexes.

In order to rule out signal broadening due to exchange between the labile copper(I) centres and acetonitrile, variable temperature spectra

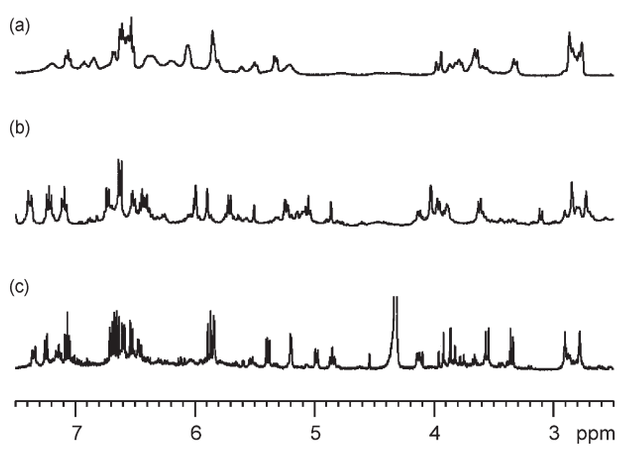

Fig. 5 400 MHz ^{1}H NMR spectra of (±)-**L** and $Cu(OTf)_2$ (a) in CD_3CN after 15 min at 300 K, (b) in CD_3CN at 235 K, (c) in CD_2Cl_2 at 300 K.

in CD_3CN were recorded (Fig. 5b), and the solvent was changed to CD_2Cl_2 (Fig. 5c). While some slight sharpening of the signals was observed at lower temperatures, there were no significant changes compared with the NMR spectrum obtained at room temperature. An identical result was obtained with either (+)-**L** or (−)-**L**.

Discussion

Unequivocal assignment of the structure of the [2 + 2] metallomacrocycle **6** formed from racemic and optically pure ligands **L** is challenging due to the need to consider both the chirality of the ligands and the metal centres, and a number of unusual features exhibited by the complex. First, slow equilibration of a library of oligomeric complexes to form a single stable complex was observed with either (+)-**L**, (−)-**L** or (±)-**L** (Fig. 1). The fact that identical NMR spectra were obtained with either (+)-**L** or (−)-**L** or (±)-**L**, provides clear evidence for the self-recognition of the enantiomeric ligands in the assembly of the [2 + 2] metallomacrocycle from racemic (±)-**L**. No evidence for the formation of a diastereomeric complex containing one (+)-**L** and one (−)-**L** ligand was detected. However, since the rate of formation of **6** was significantly slower with (±)-**L** than with the pure enantiomers, initial coordination of zinc(II) to both (+)-**L** and (−)-**L** must occur at the kinetically most accessible binding sites followed by equilibration to the thermodynamic product **6**.

Second, the changes in chemical shift of the methylene protons are significantly different to those observed in related copper(I) and zinc(II) [2 + 2] metallomacrocycles in which the metals adopt tet-

rahedral or distorted tetrahedral geometries.[17,19,20] The large upfield shift of the methylene proton Hc $\Delta\delta = 3$ ppm (Fig. 2) is reminiscent of changes in a related achiral [2 + 2] zinc(II) metallomacrocycle in which octahedral coordination of two ether oxygens to zinc(II) resulted in significant shielding of these protons.[18] The chemical shifts of Hc,d (Fig. 2) strongly suggests coordination of the oxygen attached to the methylene protons (Hc,d) to one of the zinc(II) binding sites in the complex **6**. The presence of 5- or 6-coordinate zinc(II) in **6** in which the vacant sites are occupied by oxygen from the linker and/or solvent is consistent with the fact that the complex re-equilibrates to mixtures in different solvents and is supported by studies with copper(I) (Fig. 5) where multiple complexes/oligomers were formed; the more rigorous requirement for tetrahedral complexation with 6,6-disubstituted bipyridyls does not allow formation of **6**.

Third, while the NMR spectra showed formation of a single complex **6**, slow exchange between two species occurred on the NMR time scale (Figs. 2, 3). Prior to assigning the origin of this exchange, the stereochemistry at the metal centres is addressed. There are 16 possible stereoisomers (8 pairs of enantiomers) that may be formed in a [2 + 2] metallomacrocycle as a result of the new chirality from the two metal centres and the two chiral ligands in (±)-**L**. The fact that a single set of resonances was observed in Fig. 1e shows that ligand–ligand recognition has occurred in the assembly process. The independent experiments with (+)-**L** (and (−)-**L**) have allowed us to determine that the ligand enantiomers in (±)-**L** undergo self-recognition to give rise to a pair of enantiomeric complexes, $[Zn_2(+)\mathbf{L}_2](OTf)_4$ and $[Zn_2(-)\mathbf{L}_2](OTf)_4$ respectively, that give rise to identical NMR spectra.

Fig. 6 shows a schematic of the four diastereomeric helical (**6a, 6b**) and non-helical complexes (**6c, 6d**) that may be formed from two (+)-**L** ligands. The presence of a single set of resonances when (+)-**L** was treated with zinc(II) indicates that a single diastereomer was formed. We have assigned the complexes $Zn_2\mathbf{L}_2(OTf)_4$ tentatively as having the helical configuration (illustrated in Fig. 6 for **6a**). This structure is consistent with the asymmetry of the ligands in the complex, and the exchange on the NMR time scale, which we propose is due to slow exchange in geometry at each metal centre (Fig. 7). The distinct chemical shifts of Ha,b and Hc,d suggest that each metal centre is 5-coordinate (or 6-coordinate including solvent), which results in shielding of Hc by the aromatic ring of the cleft. This proposed exchange is also consistent with initial formation of oligomers and polymers in solution; initial zinc(II) coordination to the most accessible bipyridyl sites is followed by slower reorganisation to form the metallomacrocycle. Steric effects prevent zinc(II) from simultaneous formation of 6-coordinate geometries by binding to both linker oxygens adjacent to the bipyridyls at both metal centres. Slow exchange between one metal centre in an octahedral geometry from coordination of both bipyridyls and the two linker oxygens, and the second metal in a tetrahedral geometry was also considered. However, model building suggested that the aromatic rings of the cleft would prevent simultaneous binding of two oxygens to zinc(II), and NOE data was not consistent with this structure.

While the assignment of the helical configuration is supported by model building and a weak NOE between Hi and He (data not shown), formation of the non-helical complex, either **6c** or **6d** was also considered. This complex lacks a symmetry axis and CPK models suggested that this complex is more strained than the cor-

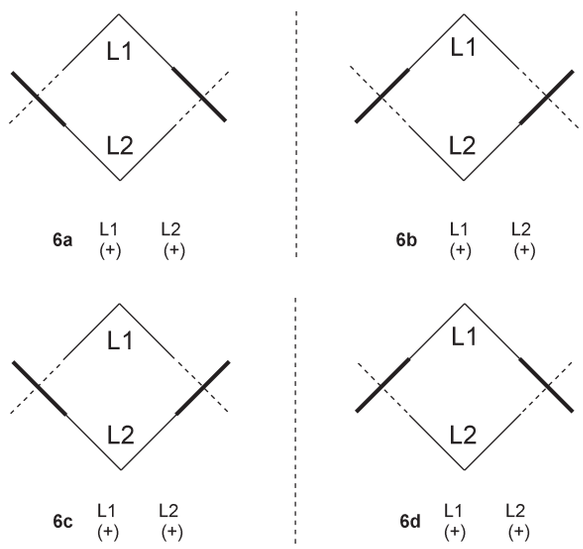

Fig. 6 Schematic of four possible stereoisomers that can be formed from two (+)-**L** ligands and two metal ions in a tetrahedral or pseudo-tetrahedral geometry.

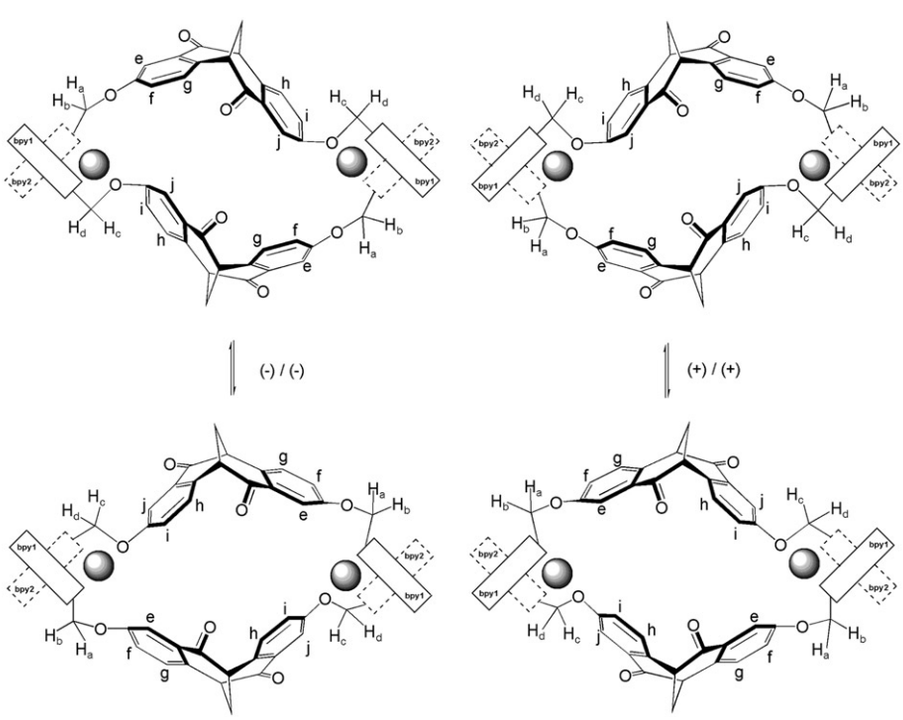

Fig. 7 Proposed structures of enantiomeric helical complexes formed from either two (−)-**L** or two (+)-**L** ligands, showing slow exchange of ether oxygen coordination to zinc(II) on the NMR time scale and peak assignments as shown in Fig. 3. Coordination geometry at each metal centre unknown but assumed to be 5-coordinate involving one linker oxygen or 6-coordinate including solvent.

responding helical complexes **6a** or **6b**. In addition, this structure is not consistent with the NOE detected between Hi and He. The CD spectra of the complexes formed from either (+)-**L** or (−)-**L** are equal in intensity and opposite in sign (Fig. 4), and thus provide direct experimental evidence for the formation of enantiomeric complexes consistent with the fact that identical NMR spectra were obtained with (+)-**L** and (−)-**L** and zinc(II). However, due to the chiral ligands in each complex, both the helical and non-helical complexes are chiral and therefore would give rise to signals in the CD spectrum and detailed analysis of the transitions that give rise to the CD signals are required. Compared to the CD spectra of (+)-**L** and (−)-**L** (data not shown), the CD spectra of the complexes gave an increase in absorption at 258 nm which supports the assignment of the complex as the chiral helicate rather than the achiral complex.

In principle, CD can be used to assign the absolute configuration of *M*- and *P*-helicates.[13] However, direct correlation of the sign of the CD spectra and Cotton effects with absolute configuration is not straightforward in complexes that are chiral as a result of optically active ligands plus the chirality introduced by the metal centres.[13] In studies where CD spectra of helicates have been used to deduce chirality, these assignments have been supported independently by X-ray crystallography, or the absolute configuration has been assumed on comparison of the spectra to related published structures. In the absence of further data, assignment of the *M* or *P* configuration to the complex has not been attempted.

X-ray diffraction is required to confirm the full structure of the complexes. However, obtaining crystals of pure **6** is almost impossible due to the labile coordination geometry at zinc(II) in different solvents. Similar difficulties have been noted in a recent study by Prabaharan and Fletcher in which labile, 5-coordinate zinc(II) complexes involving solvent prevent crystallisation for unambiguous determination of stereochemistry.[10] Equilibration over several hours to the thermodynamically stable chiral metallomacrocycle (Fig. 1b) is consistent with the proposed structure of complex **6** in which both metal centres prefer to adopt 6 coordination geometries but are limited to exchanging 5-coordinate complexes due to the shape of the cleft and the short linker.

While it has not been possible to assign the absolute configuration of the complex **6**, this study illustrates that chiral ligand design in combination with the choice of transition metal can direct the self-assembly of metallomacrocycles to result in self-recognition of ligand enantiomers in a racemic mixture. The use of zinc(II) is essential to this assembly process by providing reversible labile coordination to the kinetically accessible binding sites that are present in both ligand enantiomers, followed by formation of the thermodynamic complex. Oxygen coordination to zinc(II) is also a requirement for the stereoselectivity observed.

Conclusions

The addition of zinc(II) to the racemic molecular cleft (±)-**L** results in the formation of [2 + 2] metallomacrocycles in which the (+) and (−) ligands undergo self-recognition to form a pair of enantiomeric metallomacrocycles. To our knowledge, the slow equilibration of zinc(II) complexes on the NMR time scale observed with **L** is unprecedented with bisbipyridyl ligands. The equilibration may be attributed to incorporation of the cleft in the ligand design which orients the metal binding groups (including the oxygen in the linker) in restricted locations. The assembly involving the racemic ligand is one of the few examples where enantiomeric ligand ligand self-recognition has been achieved in the assembly of metallomacrocycles. The formation of oligomers with copper(I) suggests that the methyleneoxy linker is slightly too long and flexible to promote exclusive assembly of [2 + 2] metallomacrocycles. This result, along with the coordination of oxygen to zinc(II) in **6** suggest that ligands containing a methylene linker directly connecting the bipyridyls to the cleft may allow controlled assembly of a single, stable diastereomer with both copper(I) and zinc(II). Further studies on the assembly and molecular recognition properties of these, and related cleft-containing metallomacrocycles, are underway in our laboratories.

Experimental

General

Melting points were determined using a Reichert heating stage and are uncorrected. 1D ^{1}H NMR spectra were recorded using a Bruker AC 200B, Avance DPX 300 or AMX 400 spectrometer and are reported as parts per million (ppm) downfield shift from residual solvent peak. Peak assignments in the experimental are labeled according to the numbering scheme shown in Figs. 2 and 3. IR spectra were recorded on Perkin-Elmer 1600 fourier transform spectrophotometer. UV VIS spectra were recorded on a Carey 5E UV-Vis-NIR spectrophotometer at 20 °C. Optical rotations were obtained using a POLAAR 2001 Polarimeter at 589.3 nm in the indicated solvent and concentration (g/100 cm^3) at 22 °C. LR electron impact (EI) mass spectra were recorded on a Finnigan PolarisQ ion trap mass spectrometer using electron impact ionisation mode at 40 or 70 eV. LR electrospray ionisation (ES) spectra were recorded on a Finnigan LCQ Ion Trap spectrometer, using a capillary voltage of 10 V. High resolution electron impact spectra were recorded on a Kratos MS902 mass spectrometer. High resolution electrospray mass spectrometry were recorded on a Bruker ApexII Fourier Transform Ion Cyclotron Resonance mass spectrometer, 7.0 T magnet at the University of New South Wales. Microanalyses were performed by the Microanalytical Unit at the University of Otago, New Zealand. CD measurements were recorded on a Jasco J-710 spectropolarimeter using a 0.1 cm cell and the following parameters; range 200–500 nm, accumulation 10 scans, temperature 20 °C, step 0.5 nm, speed 50 nm min^{-1}, response 2 s and bandwidth 1.0 nm.

NMR spectroscopy

2D Spectra were recorded on a Bruker AMX 400 spectrometer using a 5 mm probe fitted with *z*-gradients and standard Bruker pulse programmes. Spectra were acquired in the phase sensitive mode using time-proportional phase incrementation. Data sets resulting from 256 increments of t_1 were acquired and zero filled to 1024 points, with each free induction decay composed of 4096 data points. Typically 24 transients were recorded for each increment of t_1 with a recycle delay of 1.3–1.5 s. NOESY[29,30] spectra were recorded with gradient pulses in the mixing time of 600 ms. ROESY[31,32] spectra were recorded with a spinlock pulse of 600 ms.

(±)-2,8-Dimethoxydibenzobicyclo[*b*,*f*][3.3.1]nona-5a,6a-diene-6,12-dione 3

p-Methoxybenzylnitrile (3.7 cm^3, 27 mmol) and powdered potassium hydroxide (1.52 g, 27 mmol) were dissolved in diiodomethane (1.3 cm^3, 16 mmol) and refluxed at 155 °C for 45 min. The reaction mixture was cooled to room temperature, diluted with water, and extracted with dichloromethane (5 × 50 cm^3). The combined organic extracts were washed with water (100 cm^3), dried (Na_2SO_4) and concentrated *in vacuo* to give crude (±, *meso*)-2,4-bis(*p*-methoxyphenyl)pentanedinitrile **1** as a red/brown oil (5.8 g). The crude bisnitrile **1** was dissolved in ethanol (40 cm^3), aqueous potassium hydroxide (40%, 30 cm^3) was added and the mixture heated at 80 °C for 18 h. The ethanol was removed *in vacuo* and the resultant thick oily residue was diluted with water (50 cm^3) and washed with dichloromethane (4 × 75 cm^3) until the organic phase was clear. The aqueous phase was acidified to pH < 1 with aqueous HCl (3 M, 100 cm^3) to give a cloudy cream coloured suspension, which was extracted with ethyl acetate (4 × 75 cm^3). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give crude (±, *meso*)-2,4-bis(*p*-methoxyphenyl)pentanedioic acid **2** as a light yellow residue (4.615 g) which was used without further purification.

Polyphosphoric acid (85%, 10 cm^3) was heated to 100 °C, until it began to reflux and was immediately cooled to 85 °C and the crude acid **2** (0.5074 g) was added. The resulting reaction mixture was stirred for 10 min at 85 °C resulting in formation of an intense scarlet solution. The reaction was quenched, without cooling, by pouring onto ice (100 g) with repeated heating to the reaction flask to promote the transfer of the viscous fluid. The resultant green/brown

suspension was extracted with dichloromethane (8 × 75 cm^3). The combined organic extracts were washed with aqueous potassium hydroxide (5% w/v, 500 cm^3), dried (Na_2SO_4) and concentrated *in vacuo* to give the crude product as a red/brown residue (0.170 g). Purification by flash chromatography on silica (100% dicholoromethane) afforded a white solid, which was recrystallised from dichloromethane to give bismethoxycleft **3** as white fluffy crystals (160 mg, 35%, mp 194.0–195.0 °C). Anal. calc. for $C_{19}H_{16}O_4$ [308] C, 74.0; H, 5.23; O, 20.76. Found: C, 70.41; H, 5.14; O, 24.45%); ν_{max}/cm^{-1} (CH_2Cl_2) 1704; λ_{max}/nm (CH_2Cl_2) 253 (ε/dm^{-3} $mol^{-1}cm^{-1}$ 33500), 323 (sh), 345 (sh), 355 (sh), 375 (sh); δ_H (300 MHz; $CDCl_3$) 2.96 (2H, t, *J* 3.0 Hz, H-l), 3.78 (6H, s, OCH_3), 3.94 (2H, t, *J* 3.0 Hz, H-k, H-m), 7.06 (2H, dd, *J* 8.5, 2.9 Hz, H-f, H-i), 7.36 (2H, d, *J* 8.5 Hz, H-g, H-h), 7.43 (2H, d, *J* 2.8 Hz, H-e, H-j). EI *m*/*z* 308 ($M^{+\cdot}$, 100), 291 (25), 280 (40), 237 (26), 165 (20%).

(±)-2,8-Dihydroxydibenzobicyclo[*b*,*f*][3.3.1]nona-5a,6a-diene-6,12-dione 4

Method 1. Dione **3** (195 mg, 0.63 mmol) was dissolved in dry, distilled dichloromethane and cooled to −5 °C. Boron tribromide was added in aliquots (2 × 640 mm^3, 1.27 mmol) over 1 h, and the reaction was stirred at room temperature for 17 h. The reaction was quenched by addition of water (10 cm^3) and was extracted with ether (5 × 18 cm^3). The combined ether extracts were washed with a saturated aqueous solution of sodium hydrogen carbonate (2 × 10 cm^3) and brine (2 × 10 cm^3), dried (Na_2SO_4) and the solvent removed to give a brown/white solid (183 mg). Recrystallisation from dicholoromethane afforded the product **4** as white crystals (102 mg, 58%, mp 206–207 °C). λ_{max}/nm (MeOH) 224 (ε/dm^{-3} $mol^{-1}cm^{-1}$ 25900), 252 (sh), 326 (sh), 350 (sh); δ_H (200 MHz, MeOD) 2.90 (2H, t, *J* 3.6 Hz, H-l), 3.84 (2H, t, *J* 3.6 Hz, H-k, H-m), 6.98 (2H, dd, *J* 2.8, 8.5 Hz, H-f, H-i), 7.26 (2H, d, *J* 8.4 Hz, H-g, H-h), 7.27 (2H, d, *J* 2.8 Hz, H-e, H-j); EI *m*/*z* 280 ($M^{+\cdot}$, 100), 252 (20), 223 (20%); HRMS: $C_{17}H_{12}O_4$ requires 280.0730; found 280.0736.

Method 2. A solution of dibromide **5** (50 mg, 0.12 mmol) in DMSO (2 cm^3) was added to a stirred mixture of bis(pinacolato)diboron (78.8 mg, 0.31 mmol), Pd(dppf)Cl_2·CH_2Cl_2 (6.1 mg, 0.01 mmol) and anhydrous potassium acetate (97.4 mg, 0.99 mmol) under nitrogen. The mixture was stirred at 80 °C under nitrogen for 22 h. Ethyl acetate (10 cm^3) was added, and the mixture filtered through sintered glass. The filtrate was added to aqueous sodium chloride (20%, 10 cm^3) and the aqueous phase extracted with ethyl acetate (2 × 10 cm^3). The combined organic layers were washed with brine (3 × 10 cm^3), dried (Na_2SO_4) and concentrated *in vacuo* to give the crude product as a brown oil. Purification by flash chromatography on silica (50% ethyl acetate/dichloromethane) afforded the boronate as white crystals (37 mg, 60%). δ_H (200 MHz; $CDCl_3$) 1.29 (12H, s, 4 × CH_3), 2.98 (2H, t, *J* 2.9 Hz, H-l), 4.03 (2H t, *J* 2.9 Hz, H-k, H-m), 7.44 (2H, d, *J* 7.6 Hz, H-g, H-h), 7.89 (2H, dd, *J* 1.4, 7.6 Hz, H-f, H-i), 8.38 (2H, d, *J* 1.2 Hz, H-e, H-j); EI (*m*/*z*) 500 (100, $M^{+\cdot}$), 414 (20), 229 (35), 227 (20%). The boronate was immediately dissolved in methanol (4 cm^3) and a solution of hydrogen peroxide in water (30%, 1 cm^3) added. The mixture was stirred for 1.5 h, extracted with dichloromethane (5 × 10 cm^3), dried (Na_2SO_4) and concentrated *in vacuo* to give **4** as a yellow solid in quantitative yield. The product has spectroscopic data identical to that produced by method A.

(±)-2,8-Bis[1′-(6‴-methyl-2″,2‴-bipyridin-6″-yl)methoxy]diben zobicyclo[*b*,*f*][3.3.1]-nona-5a,6a-diene-6,12-dione L

Potassium *tert*-butoxide (28 mg, 0.25 mmol) was added to a solution of bisphenol (±)-**4** (29 mg, 0.103 mmol) in THF (3 cm^3), under nitrogen. After 1 h, a solution of 6-bromomethyl-6′-methyl-2,2′-bipyridine (65 mg, 0.25 mmol) in THF (2 cm^3) was added dropwise to the yellow, opaque solution. The reaction mixture was refluxed for 40 h, filtered to remove a fine brown precipitate, and the solvent removed to give crude ligand (64 mg) as a pale yellow oil. Purification by flash chromatography on silica (1% methanol/dichloromethane) afforded a clear yellow oil, which was triturated with hot methanol to produce a white solid that was collected and washed with methanol (51.8 mg). Recrystallisation from dichloromethane with infusion of methanol afforded ligand (±)-**L** as a fine white solid (35 mg, 52%, mp 187.5–189.0 °C). Anal. calc. Found: C 76.1, H 5.0, N 8.8 $C_{41}H_{32}N_4O_4$ [644] requires C 76.4, H 5.0, N 8.7%.; ν_{max}/cm^{-1} ($CHCl_3$) 1574, 1604, 1682; λ_{max}/nm ($CHCl_3$) 291 (ε/dm^{-3} $mol^{-1}cm^{-1}$ 32 000), 302 (sh), 324 (sh); δ_H (400 MHz, $CDCl_3$) 2.63 (6H, s, CH_3), 2.95 (2H, app.t, *J* 2.8 Hz, H-l), 3.94 (2H, app.t, *J* 2.8 Hz, H-k, H-m), 5.23 (4H, s, H-a,b /H-c,d), 7.16–7.20 (4H, m, H-f, H-i, H-5/8), 7.38 (2H, d, *J* 8.6 Hz, H-g, H-h), 7.44 (2H, d, *J* 7.6 Hz, H-5′/8′), 7.61 (2H, d, *J* 2.7 Hz, H-e, H-j), 7.70 (2H, t, *J* 7.8 Hz, H-4/7), 7.80 (2H, t, *J* 7.8 Hz, H-4′/7′), 8.19 (2H, d, *J* 7.8 Hz, H-3/6), 8.32 (2H, d, *J* 7.8 Hz, H-3′/6′); ES *m*/*z* 645 ([M + H]$^+$, 100%); HRMS: $C_{41}H_{33}N_4O_4$ requires 645.2502; found 645.2496.

Using the same method as above and diol (+)-**4** (68 mg, 243 µmol), ligand (+)-**L** was obtained as as a white solid (26 mg, 17%, mp 185.2–187.0 °C). $[a]_D^{22}$ +0.333 (*c*, 0.145, CH_2Cl_2); δ_H (400 MHz, $CDCl_3$) 2.63 (6H, s, CH_3), 2.95 (2H, app.t, *J* 2.9 Hz, H-l), 3.94 (2H, app.t, *J* 2.9 Hz, H-k, H-m), 5.25 (4H, s, H-a,b /H-c,d), 7.15–7.20 (4H, m, H-f, H-i, H-5/8), 7.39 (2H, d, *J* 8.5 Hz, H-g, H-h), 7.44 (2H, d, *J* 7.6 Hz, H-5′/8′), 7.61 (2H, d, *J* 2.8 Hz, H-e, H-j), 7.69 (2H, t, *J* 7.8 Hz, H-4/7), 7.80 (2H, t, *J* 7.8 Hz, H-4′/7′), 8.19 (2H, d, *J* 7.8 Hz, H-3/6), 8.32 (2H, d, *J* 7.8 Hz, H-3′/6′); ES *m*/*z* 645 ([M + H]$^+$, 100%), 667 ([M + Na]$^+$, 25%); HRMS: $C_{41}H_{32}N_4O_4Na$ requires 667.2315; found 667.2301.

Using the same method as above and (−)-**4** (26 mg, 93 µmol), ligand (−)-**L** was obtained as a white solid (16 mg, 27%, mp 190.5–192.5 °C). $[a]_D^{22}$ −0.333 (*c*, 0.165, CH_2Cl_2); δ_H (400 MHz, $CDCl_3$) 2.63 (6H, s, CH_3), 2.95 (2H, app.t, *J* 2.9 Hz, H-l), 3.94 (2H, app.t, *J* 2.9 Hz, H-k/H-m), 5.25 (4H, s, H-a,b /H-c,d), 7.16–7.20 (4H, m, H-f, H-i, H-5/8), 7.39 (2H, d, *J* 8.5 Hz, H-g, H-h), 7.44 (2H, d, *J* 7.7 Hz, H-5′/8′), 7.61 (2H, d, *J* 2.8 Hz, H-e, H-j), 7.70 (2H, t, *J* 7.8 Hz, H-4/7), 7.80 (2H, t, *J* 7.8 Hz, H-4′/7′), 8.18 (2H, d, *J* 7.8 Hz, H-3/6), 8.32 (2H, d, *J* 7.8 Hz, H-3′/6′); ES *m*/*z* 645 ([M + H]$^+$, 100%), 667 ([M + Na]$^+$, 25%); HRMS $C_{41}H_{32}N_4O_4$ requires 645.2502; found 645.2495.

Zinc(II) complexes

Ligand (±)-**L** (2.1 mg, 3.3 mmol) and zinc(II) triflate (2.3 mg, 6.3 mmol) were suspended in CD_3CN (500 mm^3). Vigorous stirring resulted in dissolution to give a clear, colourless solution. After 30 h the sample was analyzed. δ_H (400 MHz, CD_3CN) 2.09 (3H, s, CH_3), 2.12 (3H, s, CH_3), 2.34 (1H, d, *J* 15.0 Hz, H-c), 2.97 (2H, qt, *J* 2.8 Hz, *J* 13.4 Hz, H-l), 3.87 (2H, br. d, *J* 10.5 Hz, H-k, H-m), 4.48 (1H, d, *J* 15.0 Hz, H-d), 4.93 (1H, dd, *J* 2.8 Hz, *J* 8.4 Hz, H-i), 5.20 and 5.35 (2H, ABq, *J* 16.4 Hz, H-b, H-a), 5.68 (1H, dd, *J* 2.9 Hz, *J* 8.5 Hz, H-f), 6.35 (1H, d, *J* 2.7 Hz, H-j), 6.57 (1H, d, *J* 8.4 Hz, H-h), 6.84 (1H, d, *J* 8.6 Hz, H-g), 7.16 (1H, d, *J* 8.0 Hz, H-8′), 7.18 (1H, d, *J* 2.9 Hz, H-e), 7.60 (1H, d, *J* 7.8 Hz, H-3/5), 7.72 (1H, d, *J* 7.9 Hz, H-3/5), 7.74 (1H, d, *J* 7.8 Hz, H-8), 7.94 (1H, t, *J* 7.9 Hz, H-4), 8.10 (1H, d, *J* 8.1 Hz, H-3′/5′), 8.13 (1H, d, *J* 7.9 Hz, H-3′/5′), 8.40 (1H, t, *J* 8.0 Hz, H-7), 8.46 (1H, t, *J* 8.0 Hz, H-4′), 8.51 (1H, t, *J* 8.0 Hz, H-7′), 8.66 (1H, d, *J* 8.1 Hz, H-6), 8.80 (1H, d, *J* 8.1 Hz, H-6′); ES *m*/*z* 1502 ([ZnL_2OTf]$^+$, 3%), 1352 ([ZnL_2 − H]$^+$, 1), 1008 ([$ZnLOTf_2$ + H]$^+$, 2), 645 ([**L** + H]$^+$, 74), 323 ([**L** + H]$^{2+}$, 100).

Ligand (+)-**L** (2.4 mg, 3.73 µmol) and zinc(II) triflate (2.7 mg, 7.45 µmol) were suspended in CD_3CN (500 mm^3). Vigorous stirring resulted in dissolution to give a clear, colourless solution. After 3 h the sample was analysed. δ_H (400 MHz) gave identical spectra to (±)-**6** with Zn.

Ligand (−)-**L** (2.1 mg, 3.26 mg) and zinc(II) triflate (2.5 mg, 6.52 µmol) were suspended in CD_3CN (500 mm^3). Vigorous stirring resulted in dissolution to give a clear, colourless solution. After 3 h the sample was analysed. δ_H (400 MHz, CD_3CN) gave identical spectra to (±)-**L** with Zn.

Copper(I) complexes

Ligand **L** (2.5 mg, 3.9 mmol) and copper(II) triflate (1.4 mg, 3.9 mmol) were suspended in CD_3CN (500 mm^3), resulting in

dissolution to give a yellow/orange solution. Hydrazine hydrate (0.2 mm^3, 4 mmol) was added and the reaction mixture darkened to give a red/orange solution. ^1H NMR (400 MHz, CD_2Cl_2) δ_H 2.27 (s, CH_3), 2.80 (s, CH_3), 2.88 (m, H-l), 3.77 and 3.91 (m, H-k, H-m), 4.35 and 4.56 (ABq, *J* 9.4 Hz), 4.85 and 4.94 (ABq, *J* 15.6 Hz); ES *m*/*z* 1738 ($[Cu_2L_2OTf_2 + Na]^+$, 1%), 1582 ($[Cu_2L_2OTf + H_2O]^+$, 2), 1565 ($[Cu_2L_2OTf]^+$, 4), 707 ($[Cu_2L_2]^{2+}$/$[CuL]^+$, 100%)

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