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Synthetic and stereochemical studies of dinuclear ruthenium(II) complexes with mixed terminal ligands

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The dinuclear ligand-bridged complex systems $[\{Ru(bpy)_2\}(\mu\text{-bpm})\{Ru(Me_2bpy)_2\}]^{4+}$ and $[\{Ru(bpy)(Me_2bpy)\}_2(\mu\text{-bpm})]^{4+}$ (bpm = 2,2′-bipyrimidine; bpy = 2,2′-bipyridine; Me_2bpy = 4,4′-dimethyl-2,2′-bipyridine) exhibit a range of stereoisomers – diastereoisomers, enantiomers and geometric isomers. From synthetic procedures producing mixtures of all possible forms of the respective complexes, the four stereoisomeric forms of the $[\{Ru(bpy)_2\}(\mu\text{-bpm})\{Ru(Me_2bpy)_2\}]^{4+}$ (*viz.* ΔΛ, ΛΔ, ΔΔ and ΛΛ) and the six stereoisomeric forms of $[\{Ru(bpy)(Me_2bpy)\}_2(\mu\text{-bpm})]^{4+}$ (*viz.* ΔΛ-*trans*, ΔΛ-*cis*, ΔΔ-*trans*, ΔΔ-*cis*, ΛΛ-*trans*, and ΛΛ-*cis*) have been isolated using cation-exchange chromatographic techniques. This is the first reported separation of the stereoisomers for a system of the type $[\{Ru(pp)_2\}(\mu\text{-bpm})\{Ru(pp')_2\}]^{4+}$ (pp and pp′ = bidentate polypyridyl ligands; pp ≠ pp′).

Introduction

Ligand-bridged dinuclear species represent the simplest examples of polymetallic assemblies. Where the individual centres are tris(bidentate) in nature, each may inherently possess right- or left-handed chirality (designated Δ or Λ respectively). Accordingly, in the most basic form of a dinuclear species, $[\{M(pp)_2\}_2(\mu\text{-BL})]^{n+}$ {where pp is a symmetrical bidentate ligand (C_{2v} point group symmetry) such as 2,2′-bipyridine (bpy), and BL is a symmetrical (D_{2h}) bridging ligand such as 2,2′-bipyrimidine, bpm}, there are three possible stereoisomers – two diastereoisomers {*meso* (ΔΛ; point group symmetry C_{2h}) and *rac* (point group symmetry D_2)}, with the latter comprising two enantiomeric forms (ΔΔ/ΛΛ). These stereoisomers are shown in Fig. 1 for the representative complex $[\{Ru(bpy)_2\}_2(\mu\text{-bpm})]^{n+}$; the existence and separation of these and analogous systems have been discussed in detail previously.[1–3]

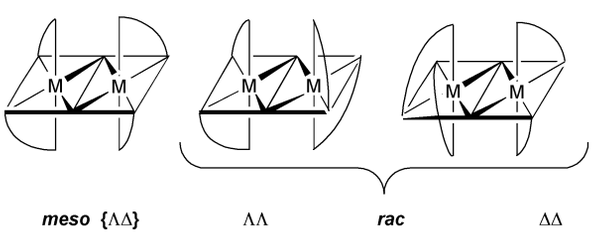

Fig. 1 Stereoisomeric forms of $[\{M(pp)_2\}_2(\mu\text{-BL})]^{n+}$.

When each metal centre of the dinuclear species has two equivalent ligands but the two metal centres are no longer identical, as in the homometallic case $[\{M(pp)_2\}(\mu\text{-bpm})\{M(pp')_2\}]^{n+}$ (pp ≠ pp′) or the heterometallic cases $[\{M(pp)_2\}(\mu\text{-bpm})\{M'(pp)_2\}]^{n+}$ and $[\{M(pp)_2\}(\mu\text{-bpm})\{M'(pp')_2\}]^{n+}$, then the point group symmetry of both the "*meso*" and *rac* forms is lowered to C_2, so that in the former case the ΔΛ and ΛΔ forms constitute an enantiomeric pair (Fig. 2).[1] Although the technique of stereoselective synthesis provides potential access to the individual stereoisomers in such particular cases,[4–6] there are no reports of the isolation of the individual forms other than one associated with the present work.[7]

In the case where the metal centres have mixed terminal ligands{*e.g.* $[\{M(pp)(pp')\}_2(\mu\text{-BL})]^{4+}$ (where pp ≠ pp′ and are both symmetrical)}, the *meso* (ΔΛ) and *rac* (ΔΔ/ΛΛ) diastereoisomers may each also exist in two geometric forms – *cis* and *trans* – where the equivalent ligands are on the same or

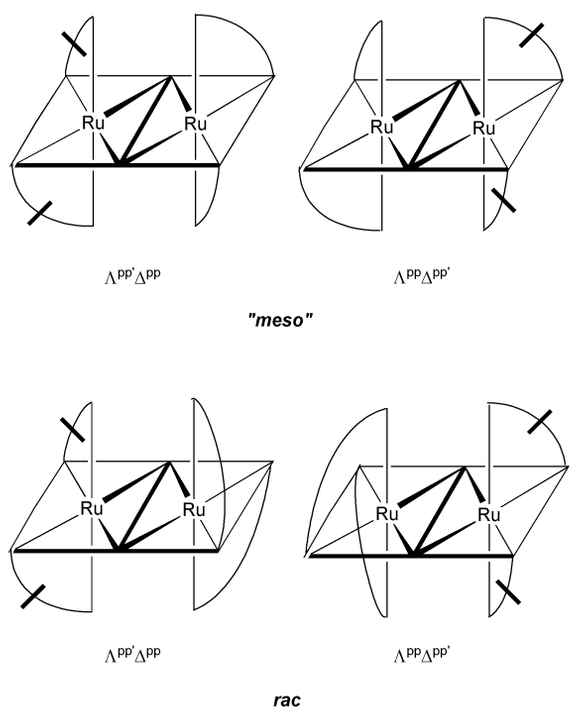

Fig. 2 Schematic representation of the two geometric isomers of "*meso*"- and *rac*-$[\{M(pp)_2\}(\mu\text{-bpm})\{M(pp')_2\}]^{n+}$ (pp ≠ pp′): the terminal ligands pp′ are marked with a bar.

the opposite sides of the plane of the bridging ligand, respectively. For the *meso* diastereoisomer, the *trans* geometic form adopts C_i and the *cis* isomer C_s point group symmetries; the two geometric isomers of the *rac* diastereoisomer have C_2 point group symmetry, but differ with respect to the orientation of the C_2 axis. These stereochemical possibilities are represented schematically in Fig. 3.

Investigation of this source of isomerism has only recently become possible due to the advancement of methodologies for synthesis of ruthenium metal centres with three different bidentate ligands {*i.e.* tris(heteroleptic) complexes} by this laboratory[8] and subsequently by other groups.[9–12] There has only been one known example where this occurrence of isomerism has been adequately addressed, and separation was achieved using a combination of stereoselective synthesis and chromatographic separation techniques.[13]

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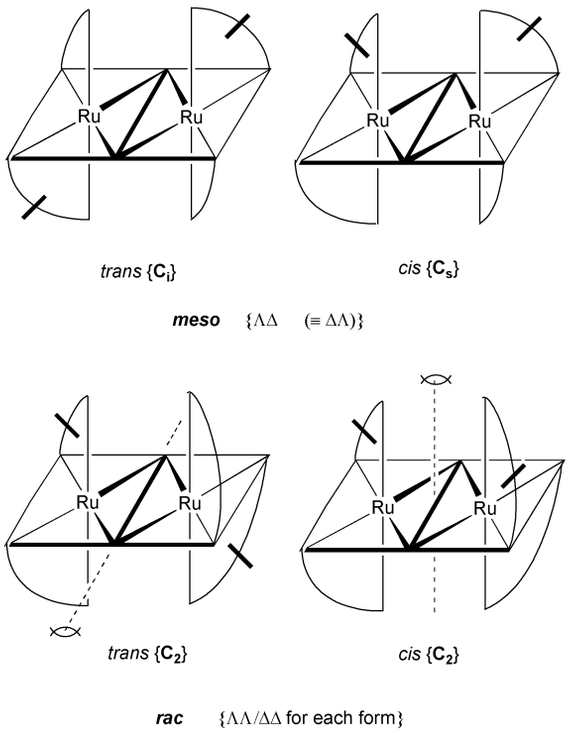

Fig. 3 Schematic representation of the two geometric isomers of *meso*- and *rac*-$[\{M(pp)(pp')\}_2(\mu\text{-}BL)]^{4+}$ (C_2 axes are shown).[13]

The existence of geometrical isomerism places the $[\{M(pp)(pp')\}_2(\mu\text{-}BL)]^{4+}$ system in a different category to those previously discussed: while the diastereoisomeric identity of these complexes (and the enantiomers of the *rac* form) can be controlled by stereoselective synthetic procedures, the geometric forms cannot be controlled and will necessarily require a chromatographic procedure for their isolation.

Recent studies on the interactions of $[\{Ru(bpy)_2\}_2(\mu\text{-}bpm)]^{4+}$ and $[\{Ru(Me_2bpy)_2\}_2(\mu\text{-}bpm)]^{4+}$ (bpy = 2,2′-bipyridine; Me_2bpy = 4,4′-dimethyl-2,2′-bipyridine; bpm = 2,2′-bipyrimidine) with oligonucleotides have shown that the ligand identity (in terms of methyl substitution) and stereoisomeric identity of dinuclear complexes gave rise to differential affinity for various regions of DNA.[14] To gain insight into the nature of the interaction of these and other metal complex systems, a range of dinuclear species was needed to further elucidate the mode and the site of interaction with important bio-molecules, such as DNA. The complex systems $[\{Ru(bpy)_2\}(\mu\text{-}bpm)\{Ru(Me_2bpy)_2\}]^{4+}$ and $[\{Ru(bpy)(Me_2bpy)\}_2(\mu\text{-}bpm)]^{4+}$ were chosen for this role as they offer a range of topologies – diastereoisomers, enantiomers and geometric isomers – in addition to providing a wide and systematic variation of distributions of the methyl substituents on the periphery of the dinuclear species. The present paper reports the isolation of the four stereoisomeric forms of the $[\{Ru(bpy)_2\}(\mu\text{-}bpm)\{Ru(Me_2bpy)_2\}]^{4+}$ (*viz.* ΔΛ, ΛΔ, ΔΔ and ΛΛ) and the six stereoisomeric forms of $[\{Ru(bpy)(Me_2bpy)\}_2(\mu\text{-}bpm)]^{4+}$ (*viz.* ΔΛ-*trans*, ΔΛ-*cis*, ΔΔ-*trans*, ΔΔ-*cis*, ΛΛ-*trans*, and ΛΛ-*cis*). A brief description of the interaction of ΔΔ-$[\{Ru(bpy)_2\}(\mu\text{-}bpm)\{Ru(Me_2bpy)_2\}]^{4+}$ with a bulge-containing tridecanucleotide has already been reported[7] – a detailed report of the interaction of the other species with oligonucleotides will be published separately.

Experimental

Materials

Potassium hexafluorophosphate (KPF_6; Aldrich), trimethylamine *N*-oxide hydrate (TMNO; Fluka), sodium octanoate (Aldrich) and sodium toluene-4-sulfonate (Aldrich) were used as supplied. Solutions of (−)-*O*,*O*′-dibenzoyl-L-tartrate and (−)-di-*O*,*O*′-4-toluoyl-L-tartrate were produced by neutralisation of the corresponding acids (Fluka) using NaOH. Dowex® anion-exchange resin (1 × 8 50–100 mesh; strongly basic, Cl^-; Aldrich) was washed several times with water before use. SP Sephadex C-25 (Amersham-Pharmacia-Biotech) was used for chromatographic purification of ruthenium complexes. Reagent solvents were used without further purification unless otherwise specified. Acetonitrile (CH_3CN; Aldrich; HPLC grade) was used for circular dichroism measurements.

The complexes $[Ru(dmso)_4Cl_2]$,[15] $[Ru(bpy)_2(bpm)](PF_6)_2$,[16] $[Ru(Me_2bpy)_2(CO)_2](PF_6)_2$, $[Ru(bpy)(Me_2bpy)(CO)_2](PF_6)_2$,[8] and $[Ru(bpy)(Me_2bpy)(bpm)_2](PF_6)_2$ [16] were synthesised according to literature procedures.

Physical measurements

Circular dichroism (CD) spectra were recorded in acetonitrile solution at concentrations of *ca.* $2–3 \times 10^{-5}$ M in a 0.1 dm cell, using a JASCO J-715 spectropolarimeter. CD spectra have been corrected for concentration and presented as $\Delta\varepsilon$ ($dm^3\ mol^{-1}\ cm^{-1}$) *vs.* wavelength, λ (nm).

Electronic spectra were recorded using a Cary 5E UV/Vis/NIR spectrophotometer, and 1D and 2D ^1H NMR spectra were performed on a Varian Mercury 300 MHz spectrometer. ^1H NMR of all complexes are reported relative to 99.9% d_3-acetonitrile (CD_3CN, δ = 1.93 ppm) unless otherwise specified.

Column chromatography

Routine preliminary purifications of complexes following syntheses were performed using cation-exchange column chromatography with SP Sephadex® C-25 cation exchanger as the support. Complexes were loaded onto columns in aqueous solutions (Cl^- form, obtained directly from the reaction mixture or by stirring an aqueous suspension with DOWEX® anion-exchange resin). Eluents used were typically 0.2 M NaCl and the column dimensions ranged in diameter but lengths of 30–40 cm were common. Details that differ significantly from these specifications have been mentioned where appropriate.

For the subsequent separation of stereoisomers (diastereoisomers, geometric isomers and enantiomers), a variety of eluents was used.[1] The required column length sometimes exceeded that physically available: in such cases, columns were sealed after loading of the complex and equilibration of the support material with the eluent was completed, enabling the substrate to be re-cycled several times down its length with the aid of a peristaltic pump.[17] Owing to diffusion of the substrate over successive column lengths, collection of the front and rear of the broadening band was required to keep the extremities from "lapping" each other. The columns used were *ca.* 1 m in length so that the "Effective Column Length" (ECL) of a separation (or resolution) may be estimated using the number of revolutions completed prior to collection. Owing to the substantial clipping of the bands, ECL in this work is quoted to the centre of the recycling band at completion.

Synthesis of complexes

$[\{Ru(bpy)(Me_2bpy)\}_2(\mu\text{-}bpm)](PF_6)_4$. *Rac*-$[Ru(bpy)(Me_2bpy)(bpm)](PF_6)_2$ (58.5 mg, 0.066 mmol) and *rac*-$[Ru(bpy)(Me_2bpy)(CO)_2](PF_6)_2$ (103.5 mg, 0.132 mmol) were combined in 2-methoxyethanol (28 cm^3) and sparged with N_2 for 15 min. Trimethylamine *N*-oxide (TMNO; 0.4 mmol) was added and the temperature increased to *ca.* 120 °C for 4 h. Water (150 cm^3) was added to the reaction mixture and the products purified using cation-exchange chromatography (SP Sephadex C-25; 0.2–0.5 M NaCl gradient elution as eluent). The major green band was collected, the product precipitated with saturated KPF_6 solution and collected by filtration. The product was washed with cold water (3 × 2 cm^3), copious amounts of diethyl ether and dried *in vacuo*. Yield *ca.* 101 mg (95%). Anal. calc. for $C_{52}H_{46}N_{12}F_{24}P_4Ru_2$: C, 38.5; H, 2.86; N, 10.4. Found: C, 38.3; H, 2.79; N, 10.0%.

[{Ru(bpy)$_2$}(μ-bpm){Ru(Me$_2$bpy)$_2$}](PF$_6$)$_4$. *Rac*-[Ru(bpy)$_2$(bpm)](PF$_6$)$_2$ (100 mg, 0.12 mmol) and *rac*-[Ru(Me$_2$bpy)$_2$(CO)$_2$](PF$_6$)$_2$ (180 mg, 0.22 mmol) were combined in 2-methoxyethanol (50 cm^3) and sparged with N_2 for 15 min. Trimethylamine *N*-oxide (TMNO; 0.88 mmol) was added and the temperature increased to 120 °C for 3.5 h. After cooling, the mixture was diluted to 200 cm^3 with water and purified using cation-exchange chromatography (SP-Sephadex C-25; 0.4 M NaCl eluent). The major green band was collected, precipitated with saturated KPF_6 solution and collected by filtration. Yield 188 mg (98%). Anal. calc. for $C_{52}H_{46}N_{12}F_{24}P_4Ru_2$: C, 38.5; H, 2.86; N, 10.4. Found: C. 38.2; H, 2.67; N, 10.2%.

Separation of the stereoisomers

Separation of the diastereoisomers of [{Ru(bpy)(Me$_2$bpy)}$_2$(μ-bpm)]$^{4+}$, and chiral resolution of the *rac* form. The complex was converted to the chloride salt and loaded onto a cation-exchange column (SP-Sephadex® C-25). Upon elution with 0.15 M sodium (−)-*O*,*O*′-dibenzoyl-L-tartrate solution the *meso* form was separated within 40 cm and was collected after 1 m of travel. The trailing *rac* band was left to recycle on the column to resolve the two enantiomers. Resolution occurred with an ECL of 2 m and the two bands (ΔΔ and ΛΛ) collected after 3 m. Recovery of the products was achieved by the addition of aqueous KPF_6 solution to the eluted bands, followed by extraction with dichloromethane. In each case the organic layer was dried (Na_2SO_4) and the dichloromethane removed by rotary evaporation.

Separation of geometric isomers of [{Ru(bpy)(Me$_2$bpy)}$_2$(μ-bpm)]$^{4+}$. Only the *meso* form could be separated completely into *cis* and *trans* isomers, whereas the two *rac* forms (ΔΔ and ΛΛ) were enriched to *ca.* 90%. Each stereoisomer of the complex (*meso*-, ΔΔ- and ΛΛ-) was treated in a similar fashion. In a typical example, 80 mg of the dinuclear complex was absorbed onto a cation-exchange column (SP Sephadex® C-25 cation exchanger) from an aqueous solution of the Cl^- form. Recycling chromatographic methods, using 0.25 M sodium toluene-4-sulfonate (*meso*) or sodium octanoate (*rac*) solutions as eluents and multiple clipping of the head and tail, afforded the separation of the *cis* and *trans* isomers from the *meso* diastereoisomer and allowed enrichment of the two forms in the *rac* complexes. The ECLs for the *cis*- and *trans*-*meso* separation was 6 m. For the 90% enrichment of *cis*- and *trans*-*rac* complexes, column lengths up to 25 m were employed. ^{1}H NMR (**CD$_3$**CN) (proton numbering scheme is as illustrated in Fig. 4).

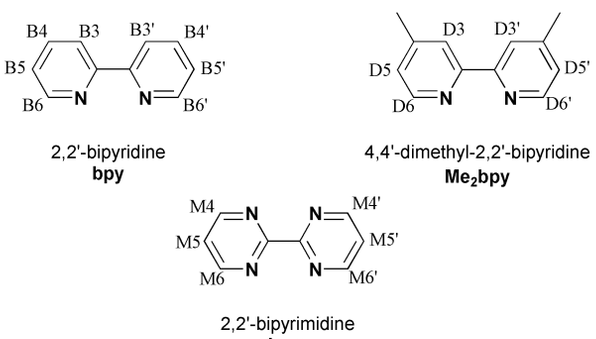

Fig. 4 Proton numbering employed for ^{1}H NMR discussion.

Cis-meso-: δ 2.53 (s, 6H, CH_3); 2.56 (s, 6H, CH_3); 7.27 (dd, *J* = 5.9, 1.5 Hz, 2H, D5); 7.38 (t, *J* = 5.7, 1H, M5); 7.43 (t, *J* = 5.7, 1H, M5); 7.44 (ddd, *J* = 7.5, 5.6, 1.2 Hz, 2H, B5); 7.45 (dd, *J* = 5.9, 1.5 Hz, 2H, D5); 7.48 (d, *J* = 5.9 Hz, 2H, D6); 7.57 (ddd, *J* = 7.5, 5.6, 1.2 Hz, 2H, B5); 7.68 (ddd, *J* = 5.6, 1.4, 0.7 Hz, 2H, B6); 7.79 (d, *J* = 5.9 Hz, 2H, D6); 7.97 (d, *J* = 5.7 Hz, 2H, M4); 7.99 (d, *J* = 5.7 Hz, 2H, M4); 8.02 (ddd, *J* = 5.6, 1.4, 0.7 Hz, 2H, B6); 8.06 (m, 2H, B4); 8.09 (m, 2H, B4); 8.31 (dd, *J* = 1.5, 0.7 Hz, 2H, D3); 8.33 (dd, *J* = 1.5, 0.7 Hz, 2H, D3); 8.44 (m, 2H, B3); 8.46 (m, 2H, B3). *Trans-meso*-: δ 2.53 (s, 6H, CH_3); 2.55 (s, 6H, CH_3); 7.27 (dd, *J* = 5.9, 1.5 Hz, 2H, D5); 7.40 (t, *J* = 5.7, 2H, M5); 7.44 (ddd, *J* = 7.5, 5.6, 1.2 Hz, 2H, B5); 7.42 (dd, *J* = 5.9, 1.5 Hz, 2H, D5); 7.48 (d, *J* = 5.9 Hz, 2H, D6); 7.59 (ddd, *J* = 7.5, 5.6, 1.2 Hz, 2H, B5); 7.67 (ddd, *J* = 5.6, 1.4, 0.7 Hz, 2H, B6); 7.80 (d, *J* = 5.9 Hz, 2H, D6); 7.98 (ABX coupling between M4 & M6, 4H, M4); 7.99 (ddd, *J* = 5.6, 1.4, 0.7 Hz, 2H, B6); 8.07 (m, 2H, B4); 8.10 (m, 2H, B4); 8.31 (dd, *J* = 1.5, 0.7 Hz, 2H, D3); 8.32 (dd, *J* = 1.5, 0.7 Hz, 2H, D3); 8.44 (m, 2H, B3); 8.46 (m, 2H, B3). *Cis-rac*-: δ 2.54 (s, 6H, CH_3); 2.57 (s, 6H, CH_3); 7.22 (dd, *J* = 5.9, 1.5 Hz, 2H, D5); 7.24 (dd, *J* = 5.9, 1.5 Hz, 2H, D5); 7.37 (t, *J* = 5.7, 2H, M5); 7.39 (ddd, *J* = 7.5, 5.6, 1.2 Hz, 2H, B5); 7.40 (d, *J* = 5.9 Hz, 2H, D6); 7.42 (ddd, *J* = 7.5, 5.6, 1.2 Hz, 2H, B5); 7.51 (d, *J* = 5.9 Hz, 2H, D6); 7.61 (ddd, *J* = 5.6, 1.4, 0.7 Hz, 2H, B6); 7.75 (ddd, *J* = 5.6, 1.4, 0.7 Hz, 2H, B6); 8.02 (d, *J* = 5.7 Hz, M4); 8.03 (d, *J* = 5.7 Hz, M4); 8.08 (m, 2H, B4); 8.16 (m, 2H, B4); 8.36 (dd, *J* = 1.5, 0.7 Hz, 2H, D3); 8.39 (dd, *J* = 1.5, 0.7 Hz, 2H, D3); 8.50 (m, 2H, B3); 8.53 (m, 2H, B3). *Trans-rac*-: δ 2.52 (s, 6H, CH_3); 2.62 (s, 6H, CH_3); 7.22 (dd, *J* = 5.9, 1.5 Hz, 2H, D5); 7.24 (dd, *J* = 5.9, 1.5 Hz, 2H, D5); 7.37 (t, *J* = 5.7, 2H, M5); 7.39 (ddd, *J* = 7.5, 5.6, 1.2 Hz, 2H, B5); 7.40 (d, *J* = 5.9 Hz, 2H, D6); 7.42 (t, *J* = 5.7, 2H, M5); 7.42 (ddd, *J* = 7.5, 5.6, 1.2 Hz, 2H, B5); 7.54 (d, *J* = 5.9 Hz, 2H, D6); 7.61 (ddd, *J* = 5.6, 1.4, 0.7 Hz, 2H, B6); 7.73 (ddd, *J* = 5.6, 1.4, 0.7 Hz, 2H, B6); 8.02 (d, *J* = 5.7 Hz, M4); 8.03 (d, *J* = 5.7 Hz, M4); 8.07 (m, 2H, B4); 8.17 (m, 2H, B4); 8.37 (dd, *J* = 1.5, 0.7 Hz, 2H, D3); 8.39 (dd, *J* = 1.5, 0.7 Hz, 2H, D3); 8.50 (m, 2H, B3); 8.53 (m, 2H, B3).

Separation of the diastereoisomers of [{Ru(bpy)$_2$}(μ-bpm){Ru(Me$_2$bpy)$_2$}]$^{4+}$, and chiral resolution of the *rac* form. The separation of "*meso*" and *rac* diastereoisomers, and the resolution of the *rac* form were completed using one chromatographic step as described above for [{Ru(bpy)(Me$_2$bpy)}$_2$(μ-bpm)]$^{4+}$. ^{1}H NMR (**CD$_3$**CN) (proton numbering scheme is illustrated in Fig. 4). "*Meso*"-: δ 2.53 (s, 6H, CH_3); 2.54 (s, 6H, CH_3); 7.27 (dd, *J* = 5.7, 1.5 Hz, 2H, D5); 7.40 (t, *J* = 5.7, 2H, M5); 7.41 (dd, *J* = 5.9, 1.5 Hz, 2H, D5); 7.44 (ddd, *J* = 7.5, 5.6, 1.2 Hz, 2H, B5); 7.47 (d, *J* = 5.9 Hz, 2H, D6); 7.60 (ddd, *J* = 7.5, 5.6, 1.2 Hz, 2H, B5); 7.68 (ddd, *J* = 5.6, 1.4, 0.7 Hz, 2H, B6); 7.81 (d, *J* = 5.9 Hz, 2H, D6); 7.98 (ABX coupling between M4 & M6, 4H, M4); 8.02 (ddd, *J* = 5.6, 1.4, 0.7 Hz, 2H, B6); 8.08 (m, 2H, B4); 8.10 (m, 2H, B4); 8.30 (dd, *J* = 1.5, 0.7 Hz, 2H, D3); 8.32 (dd, *J* = 1.5, 0.7 Hz, 2H, D3); 8.45 (m, 2H, B3); 8.48 (m, 2H, B3). *Rac*-: δ 2.54 (s, 6H, CH_3); 2.61 (s, 6H, CH_3); 7.21 (dd, *J* = 5.9, 1.5 Hz, 2H, D5); 7.24 (dd, *J* = 5.9, 1.5 Hz, 2H, D5); 7.40 (t, *J* = 5.7, 2H, M5); 7.41 (ddd, *J* = 7.5, 5.6, 1.2 Hz, 2H, B5); 7.42 (d, *J* = 5.9 Hz, 2H, D6); 7.42 (ddd, *J* = 7.5, 5.6, 1.2 Hz, 2H, B5); 7.54 (d, *J* = 5.9 Hz, 2H, D6); 7.62 (ddd, *J* = 5.6, 1.4, 0.7 Hz, 2H, B6); 7.75 (ddd, *J* = 5.6, 1.4, 0.7 Hz, 2H, B6); 8.03 (ABX coupling between M4 & M6, 4H, M4); 8.08 (m, 2H, B4); 8.19 (m, 2H, B4); 8.36 (dd, *J* = 1.1, 0.7 Hz, 2H, D3); 8.38 (dd, *J* = 1.1, 0.7 Hz, 2H, D3); 8.52 (m, 2H, B3); 8.54 (m, 2H, B3). **CD** {λ/nm, Δε (ΔΔ, ΛΛ), CH_3CN}: 210 (−66.1, 66.1); 255 (58.5, −60.3); 279 (−146.8, 147.5); 319 (−43.9, 44.4); 389 (29.3, −28.7).

Resolution of "*meso*"-[{Ru^B(bpy)$_2$}(μ-bpm){Ru^D(Me$_2$bpy)$_2$}]$^{4+}$ (Δ^{B}Λ^D/Λ^{B}Δ^D). The "*meso*" complex was re-applied to a cation-exchange chromatography column (SP Sephadex® C-25) and the two enantiomers (Δ^{B}Λ^D and Λ^{B}Δ^D) resolved using the recycling technique with 0.15 M sodium (−)-*O*,*O*′-toluoyl-L-tartrate solution as eluent: resolution was observed after an ECL of *ca.* 8 m. By clipping the front of Band 1 and the tail of Band 2 until an ECL of *ca.* 15 m, two bands were collected and the products isolated as above. Bands 1 and 2 were determined to be Δ^{B}Λ^D and Λ^{B}Δ^D, respectively. **CD** {λ/nm, Δε (Δ^{B}Λ^D, Λ^{B}Δ^D), CH_3CN}: 219 (31.8, −31.3); 249 (−18.1, 17.0); 276 (16.1, −16.3); 296 (−21.7, 23.7).

Results and discussion

Synthesis of the stereoisomers of the ligand-bridged dinuclear ruthenium complex $[\{Ru(bpy)(Me_2bpy)\}_2(\mu\text{-bpm})]^{4+}$

In previous work from our laboratory, all stereoisomers {*trans*- and *cis-meso* (ΔΛ); *trans*- and *cis-rac* (ΔΔ and ΛΛ)} of the complex $[\{Ru(Me_4bpy)(phen)\}_2(\mu\text{-bpm})]^{4+}$ {where Me_4bpy = 4,4′,5,5′-tetramethyl-2,2′-bipyridine and phen = 1,10-phenanthroline} were obtained using a combination of stereoselective synthesis and column chromatography.[13] During the course of this earlier study it was shown that the synthesised mixture of stereoisomers could be separated and resolved into the individual diastereoisomers and enantiomers (of the *rac* form) using column chromatography alone, as the separations and resolution were of considerably different efficiencies and therefore did not interfere. Separation into geometric isomers was performed subsequently on each individual diastereoisomer/enantiomer, as it is significantly more difficult than the other separations. Consequently, in the study now reported, the synthesis of $[\{Ru(bpy)(Me_2bpy)\}_2(\mu\text{-bpm})]^{4+}$ was undertaken in a manner that was not stereoselective, obviating the requirement for chiral precursors: this involved the decarbonylation reaction of *rac*-$[Ru(bpy)(Me_2bpy)(CO)_2](PF_6)_2$ with trimethylamine *N*-oxide (TMNO) in 2-methoxyethanol in the presence of the bridging ligand bpm, resulting in a mixture of the six possible stereoisomers. The overall separation sequence is given in Fig. 5, and is described in detail below.

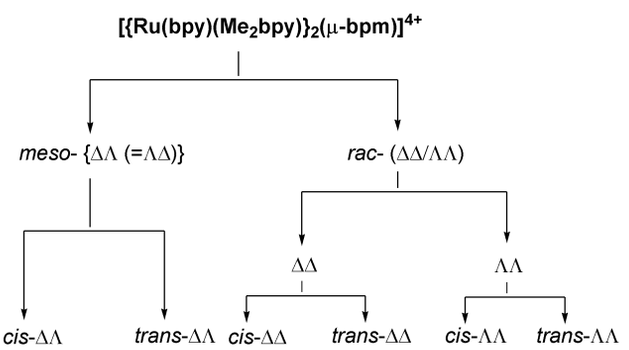

Fig. 5 Separation scheme adopted for the isolation of the six stereoisomers of $[\{Ru(bpy)(Me_2bpy)\}_2(\mu\text{-bpm})]^{4+}$.

Separation of diastereoisomers and chiral resolution of racemic form

The separation of diastereoisomers {*meso* (ΔΛ) and *rac* (ΔΔ/ΛΛ)} and the resolution of the *rac* form (ΔΔ and ΛΛ) of the dinuclear complex $[\{Ru(bpy)(Me_2bpy)\}_2(\mu\text{-bpm})]^{4+}$ was undertaken in one chromatographic step using established techniques.[1–3,6] This goal was realised by eluting a sample of the dinuclear complex with the chiral eluent sodium (−)-*O*,*O*′-dibenzoyl-L-tartrate, affording the collection of the separated *meso* band at the end of the first passage down the length of the column (1 m). The column was then sealed and the trailing *rac* band left to recycle on the column, where during the second metre of travel resolution could be confirmed visually. The individual enantiomers were collected at the end of the third passage down the column (ECL = 3 m).

Separation of geometric isomers (*cis* and *trans*) in a ligand-bridged dinuclear ruthenium complex

In the analogous system $[\{Ru(phen)(Me_4bpy)\}_2(\mu\text{-bpm})]^{4+}$ investigated previously,[13] the nature of the Me_4bpy and the phen ligands were sufficiently diverse to provide a significant difference between *cis* and *trans* isomers. In the current work, the terminal ligands (bpy and Me_2bpy) are by nature more similar, so that it was anticipated that the separation of the geometric isomers might prove somewhat more difficult using the same techniques.

This proved to be the case. Using a 1 m chromatographic column and recycling peristaltic pumps, the separation of the geometric isomers of the *meso* form occurred in *ca*. 6 m. For the *rac* forms, separation into the *cis* and *trans* isomers was not complete even after column lengths of up to 25 m were employed – however, under such conditions 90% enrichment of *cis* and *trans* in the each enantiomer of the *rac* diastereoisomer was achieved. This allowed the characterisation of the species using NMR spectroscopy as discussed below.

NMR spectra

In the discussion of the NMR spectra, the conventional numbering schemes are used with the ligands bpy (B), Me_2bpy (D) and bpm (M) – Fig. 4. In all four species, each ligand is related by symmetry elements to an equivalent ligand on the other metal. However, regardless of symmetry, the two halves of each peripheral ligand remain magnetically non-equivalent giving rise to eight (two aliphatic and six aromatic) non-equivalent protons for the Me_2bpy and eight (all aromatic) for bpy. The bpy ligands exhibit familiar AMX and A′M′X′ proton coupling systems, with the expected coupling constants:[5] $J_{3,4} \approx 8$ Hz, $J_{3,5} = 1.2$ Hz, $J_{4,5} = 7.5$ Hz, $J_{3,6} \approx 0.7$ Hz, $J_{4,6} = 1.4$ Hz and $J_{5,6} \approx 5.6$ Hz. The designation has been adopted that rings furthest from the bridging ligand (bpm) are marked with a prime. For bpm, the non-primed protons are positioned under the bpy ligands in the *meso-cis* and *rac-trans* forms. In the *meso-trans* and *rac-cis* isomers, the distinction between the rings is not important (as a consequence of symmetry), but the additional convention is adopted that the 4-positions of the bpm are nearer to the bpy ligand. It should be noted that no notational distinction has been made between individual pyridyl rings in the data presented. Using anisotropic effects, it is conceivable that the correct ring orientation may be determined but was unnecessary in this case.[4,17–21]

The symmetry elements of the stereoisomers of this system were discussed above. As far as the bpm bridge is concerned, for *meso*-$[\{Ru(bpy)(Me_2bpy)\}_2(\mu\text{-bpm})]^{4+}$, one M5 triplet resonance ($J = 5.7$ Hz) will be observed for the *trans* isomer (C_i) as symmetry renders M5 and M5′ equivalent. Additionally, the M4/M6′ and the M4′/M6 protons of the bpm bridge are also equivalent because of the inversion centre. The resonances observed from these two sets of equivalent protons comprise a complex ABX coupling pattern due to the similar environments of the two non-equivalent protons. In the *meso-cis* form, the point group symmetry is lower (*viz.* C_s) and the M5 and M5′ protons are no longer equivalent so that two triplets ($J = 5.7$ Hz) are observed. This non-equivalence of the two ends of the bpm ligand, coupled with the plane of symmetry running through the centre of the bridging ligand, means that the M4/M6 and the M4′/M6′ protons are equivalent and they each show a doublet ($J = 5.7$ Hz), arising from coupling to the M5 and M5′ protons, respectively.

For the *rac* diastereoisomer, both geometric isomers possess C_2 point group symmetry, however, in the *cis* isomers the C_2 axis is perpendicular to the plane of the bridging bpm ligand, whereas in the *trans* isomer it is in the plane of the bpm ligand running perpendicular to the Ru–Ru axis (through M5 and M5′). In the former case, the axis renders the M5 and M5′ protons equivalent, as well as the two pairs of protons M4/M6′ and M4′/M6 giving rise to a triplet ($J = 5.7$ Hz) and two doublets of doublets ($J = 5.7$, 1.4 Hz), respectively. In the second case (the *trans* isomer) the C_2 axis renders the M4/M6 and the M4′/M6′ protons equivalent, giving rise to two doublets ($J = 5.7$ Hz); however, the M5 and M5′ protons will become non-equivalent.

The resonances of the bridging bpm ligand are summarised in Table 1 to emphasise the effects of symmetry in the systems $[\{Ru(bpy)(Me_2bpy)\}_2(\mu\text{-bpm})]^{4+}$ (above) and $[\{Ru(bpy)_2\}(\mu\text{-bpm})\{Ru(Me_2bpy)_2\}]^{4+}$ (below).

Table 1 ^{1}H NMR resonances (ppm; CD_3CN solvent) associated with the protons of the bpm bridge for the complexes reported in this study. The numbering scheme is given in Fig. 4, and details of the multiplicity and coupling are provided in the Experimental section with the isolation of each individual stereoisomer

Dinuclear complex	H5	H4/H6
"*meso*"-$[\{Ru(bpy)_2\}_2(\mu\text{-bpm})\{Ru(Me_2bpy)_2\}]^{4+}$	7.40	7.98
rac-$[\{Ru(bpy)_2\}_2(\mu\text{-bpm})\{Ru(Me_2bpy)_2\}]^{4+}$	7.40	8.03
cis-meso-$[\{Ru(bpy)_2\}\{Ru(Me_2bpy)_2\}_2(\mu\text{-bpm})]^{4+}$	7.38, 7.43	7.97, 7.99
trans-meso-$[\{Ru(bpy)_2\}\{Ru(Me_2bpy)_2\}_2(\mu\text{-bpm})]^{4+}$	7.40	7.98
cis-rac-$[\{Ru(bpy)_2\}\{Ru(Me_2bpy)_2\}_2(\mu\text{-bpm})]^{4+}$	7.37	8.02, 8.03
trans-rac-$[\{Ru(bpy)_2\}\{Ru(Me_2bpy)_2\}_2(\mu\text{-bpm})]^{4+}$	7.37, 7.42	8.02, 8.03

Synthesis of the diastereoisomers and enantiomers of the ligand-bridged dinuclear ruthenium complex $[\{Ru^B(bpy)_2\}(\mu\text{-bpm})\{Ru^D(Me_2bpy)_2\}]^{4+}$

The synthesis of $[\{Ru(bpy)_2\}(\mu\text{-bpm})\{Ru(Me_2bpy)_2\}]^{4+}$ was undertaken in a non-stereoselective manner, for reasons discussed above for the system $[\{Ru(bpy)(Me_2bpy)\}_2(\mu\text{-bpm})]^{4+}$. $[Ru(bpy)_2bpm]^{2+}$ and $[Ru(Me_2bpy)_2(CO)_2]^{2+}$ were heated in 2-methoxyethanol after the addition of TMNO to yield a mixture of all four possible stereoisomers. Owing to the non-equivalence of the two ends of the dinuclear complex $[\{Ru(pp)_2\}(\mu\text{-bpm})\{Ru(pp')_2\}]^{4+}$, *i.e.* pp ≠ pp′, both "*meso*" and *rac* diastereoisomers exist as a pair of enantiomers as discussed previously. The separation sequence is summarised in Fig. 6 and is discussed below.

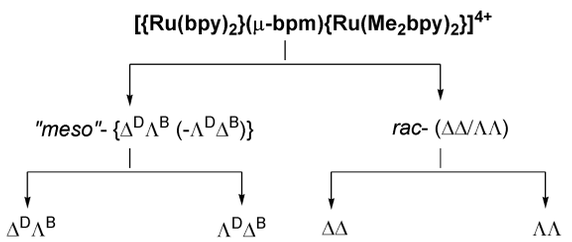

Fig. 6 Separation scheme adopted for the isolation of stereoisomers of $[\{Ru(bpy)_2\}(\mu\text{-bpm})\{Ru(Me_2bpy)_2\}]^{4+}$.

Separation of diastereoisomers and resolution of the racemic form

Separation of the "*meso*" and *rac* diastereoisomers and resolution of the *rac* form was achieved using a single chromatographic step as described above for the $[\{Ru(bpy)(Me_2bpy)\}_2(\mu\text{-bpm})]^{4+}$ system; however, the "*meso*" form was handled separately, as described below. The CD spectra of ΔΔ- and ΛΛ-$[\{Ru(bpy)_2\}(\mu\text{-bpm})\{Ru(Me_2bpy)_2\}]^{4+}$ are shown in Fig. 7. The configurational assignments can by made by comparison of the CD spectra with those of stereoselectively synthesised ΔΔ- and ΛΛ-$[\{Ru(bpy)_2\}_2(\mu\text{-bpm})]^{4+}$ [5] and the analogous forms of $[\{Ru(Me_2bpy)_2\}_2(\mu\text{-bpm})]^{4+}$.[2]

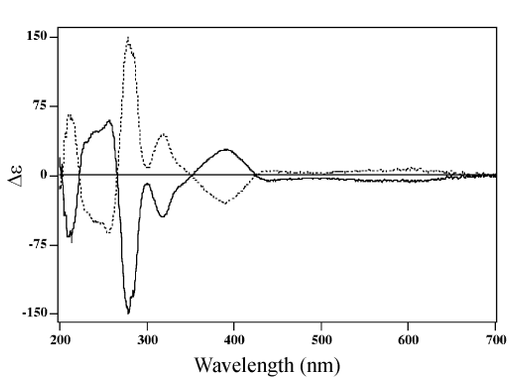

Fig. 7 CD spectra of ΔΔ- and ΛΛ-$[\{Ru(bpy)_2\}(\mu\text{-bpm})\{Ru(Me_2bpy)_2\}]^{4+}$: band 1 [ΔΔ, (——)] and band 2 [ΛΛ, (- - -)].

Resolution of "*meso*"-$[\{Ru^B(bpy)_2\}(\mu\text{-bpm})\{Ru^D(Me_2bpy)_2\}]^{4+}$ ($\Delta^B\Lambda^D/\Lambda^B\Delta^D$)

As discussed above, dinuclear ligand-bridged complexes that possess non-equivalent metal centres will give rise to a "*meso*" form that will consist of two enantiomers – designated $\Delta^B\Lambda^D$ and $\Lambda^B\Delta^D$ where the superscripts B and D represent the centre with bpy and Me_2bpy ligands, respectively. Enantiomers of this form have not been resolved previously and inspection reveals it to be a challenging prospect. Unlike the homochiral enantiomers of the *rac* form, the "*meso*" form has two centres of opposite chirality: the only difference here is whether the methyl substituents are associated with the Δ or the Λ centre.

To predict the most efficient eluent for the chromatographic resolution of "*meso*"-$[\{Ru^B(bpy)_2\}(\mu\text{-bpm})\{Ru^D(Me_2bpy)_2\}]^{4+}$, the dinuclear complex was considered to behave as two independent tris(bidentate) complexes $\{[Ru(bpy)_3]^{2+}$ and $[Ru(Me_2bpy)_3]^{2+}\}$ always travelling together. It follows that the resolution of the Δ-$[Ru(bpy)_3]^{2+}$–Λ-$[Ru(Me_2bpy)_3]^{2+}$ pair from Λ-$[Ru(bpy)_3]^{2+}$–Δ-$[Ru(Me_2bpy)_3]^{2+}$ would rely on two competing processes – the resolution of Δ/Λ-$[Ru(bpy)_3]^{2+}$ and Δ/Λ-$[Ru(Me_2bpy)_3]^{2+}$.

The chiral resolution of the enantiomers of $[Ru(bpy)_3]^{2+}$ and $[Ru(Me_2bpy)_3]^{2+}$ by the chromatographic techniques used in the present work have been reported previously, using the sodium salts of the chiral anions (−)-*O*,*O*′-dibenzoyl-L-tartrate {(−)-DBT} and (−)-di-*O*,*O*′-4-toluoyl-L-tartrate {(−)-DTT} as eluents.[17] These studies revealed that (−)-DBT was more efficient for resolution of $[Ru(Me_2bpy)_3]^{2+}$, whereas (−)-DTT was more effective for $[Ru(bpy)_3]^{2+}$, with the discrimination being greater in the latter case. Accordingly, it might be predicted that (−)-DTT would be more effective for the resolution of "*meso*"-$[\{Ru^B(bpy)_2\}(\mu\text{-bpm})\{Ru^D(Me_2bpy)_2\}]^{4+}$. Further, as the observed order of elution for mononuclear complexes was Δ followed by the Λ, the resolution of "*meso*"-$[\{Ru^B(bpy)_2\}(\mu\text{-bpm})\{Ru^D(Me_2bpy)_2\}]^{4+}$ with (−)-DTT should elute the $\Delta^B\Lambda^D$ species first. Using the elution data from the earlier paper, it would also be predicted that if (−)-DBT were used as the eluent, the resolution of the Me_2bpy-containing centre would occur more readily, reversing the order of elution so that the $\Lambda^B\Delta^D$ enantiomer would elute first.

Using $Na_2\{(-)\text{-DTT}\}$ solution as the eluent, chiral resolution of "*meso*"-$[\{Ru(bpy)_2\}(\mu\text{-bpm})\{Ru(Me_2bpy)_2\}]^{4+}$ was observed with an ECL ≈ 5 m. The resolution was confirmed by circular dichroism and the CD spectra are shown in Fig. 8. Owing to the heterochiral nature of the dinuclear species, the intensity of the response is significantly diminished from that observed for homochiral dinuclear species (see Fig. 7). The configurational identity of the two bands was assigned by comparison of the CD data with those of the enantiomers of $[\{Ru(bpy)_2\}_2(\mu\text{-bpm})]^{4+}$ and $[\{Ru(Me_2bpy)_2\}_2(\mu\text{-bpm})]^{4+}$.[17]

The resolution was also attempted using $Na_2\{(-)\text{-DBT}\}$ solution as the eluent: it led to only partial resolution and the order of elution was reversed compared with the case using $Na_2\{(-)\text{-DTT}\}$, as predicted. This illustrates that consideration of the two centres of a dinuclear complex as individual mononuclear components competing for resolution is a reasonable guide for chromatographic separation.

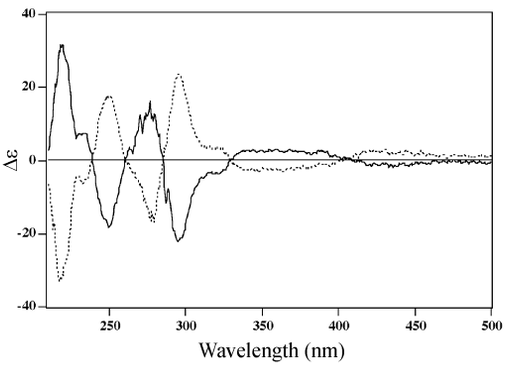

Fig. 8 CD spectra of $\Delta^B\Lambda^D$- and $\Lambda^B\Delta^D$-[{$Ru^B(bpy)_2$}(μ-bpm){$Ru^D(Me_2bpy)_2$}]$^{4+}$: band 1 [$\Delta^B\Lambda^D$, (——)], band 2 [$\Lambda^B\Delta^D$, (- - -)].

NMR spectra

Both diastereoisomers of [{$Ru(bpy)_2$}(μ-bpm){$Ru(Me_2bpy)_2$}]$^{4+}$ possess C_2 point group symmetry, with the C_2 axis running through both metal atoms and bisecting the bridging ligand. As a consequence of the C_2 axis, each pair of bpy and Me_2bpy ligands will give rise to only one set of resonances. Additionally, the two halves of the bridging ligand are also equivalent (Table 1). Characterisation was achieved by performing COSY experiments and the individual pyridyl rings of the bpy, Me_2bpy and bpm ligands could be identified.

Interestingly, the ^{1}H NMR spectrum of "*meso*"-[{$Ru(bpy)_2$}-(μ-bpm){$Ru(Me_2bpy)_2$}]$^{4+}$ was found to be almost identical to that of *trans-meso*-[{$Ru(bpy)(Me_2bpy)$}$_2$(μ-bpm)]$^{4+}$. Close inspection of the two complexes revealed that they have similar local environments.

The ^{1}H COSY spectrum for the system *trans-meso*-[{$Ru(bpy)(Me_2bpy)$}$_2$(μ-bpm)]$^{4+}$ is given in Fig. 9 as an exemplar of such data to allow chemical shift assignment in the present study.

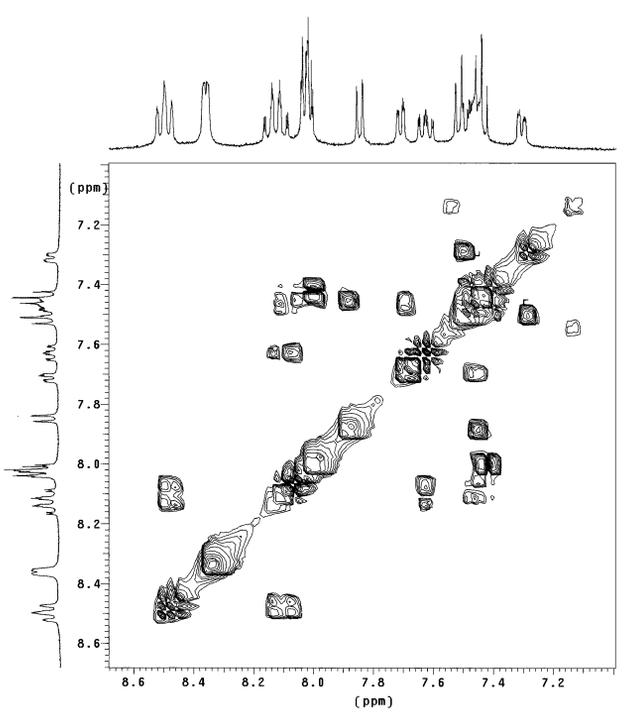

Fig. 9 ^{1}H COSY spectrum (300 MHz) of *trans-meso*-[{$Ru(bpy)(Me_2bpy)$}$_2$(μ-bpm)]$^{4+}$ (PF_6^- salt; CD_3CN solvent).

Conclusions

The present work has led to the isolation of the four stereoisomers of the dinuclear complex [{$Ru(bpy)_2$}(μ-bpm)-{$Ru(Me_2bpy)_2$}]$^{4+}$ – the first such separation for a system of the type [{$Ru(pp)_2$}(μ-bpm){$Ru(pp')_2$}]$^{4+}$ – and the six diastereoisomers of [{$Ru(bpy)(Me_2bpy)$}$_2$(μ-bpm)]$^{4+}$, which is a significant achievement given the similarity of the terminal ligands bpy and Me_2bpy.

Studies on the interaction of ligand-bridged dinuclear complexes with oligonucleotides are in progress. Initial results suggest that there is a substantial specificity in the association of single *rac* enantiomers of [{$Ru(Me_2bpy)_2$}$_2$(μ-bpm)]$^{4+}$ towards GC-rich regions of oligonucleotides [14] and also bulges in DNA.[7] The isolation of the individual stereoisomers of the analogous partially-methylated systems in the present study was undertaken to allow an intimate probe of the influences of both the stereochemical factors and ligand substitution patterns in such interactions. These studies will be reported in detail in due course.

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