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Redistribution of terpy ligands—approaches to new dynamic combinatorial libraries

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Mixing solutions of homoleptic cobalt(II) complexes $[Co\mathbf{A}_2]^{2+}$ and $[Co\mathbf{B}_2]^{2+}$ results in the establishment of a combinatorial library containing the heteroleptic complex $[Co\mathbf{AB}]^{2+}$. By using enantiomorphic ligands **A** and **B** the reactions may be followed by ^{1}H NMR spectroscopy. Exchange reactions with 6-substituted ligands are slower than those with 5- and 4′-substituted species.

Introduction

Metal-directed self assembly of ligands around metal centres is a powerful and well-established methodology in supramolecular chemistry.[1,2] The methodology allows the preparation of a whole range of topologically and topographically novel compounds in which the final spatial arrangement is determined both by the coordination number and coordination geometry of the metal and the number, type and distribution of coordination sites within the ligands.[3] Both labile and kinetically inert metal centres have been used for the construction of such molecular architectures. Kinetically inert centres, usually d^6 transition metal ions, have the advantage that metal-containing building blocks may be used which retain their structural integrity throughout a prolonged synthetic sequence and have been widely used for the construction of photoactive metallodendrimers and metallopolymers.[4,5] In contrast, the use of labile metal centres allows equilibrium to be reached rapidly and thermodynamic products to be isolated, although a disadvantage is that it is not usually possible to carry labile complexes through subsequent reaction steps. We have recently been investigating the use of d^7 cobalt(II) centres for the assembly of terpy and bipy ligands into linear arrays and metallodendrimers[6–8] and have demonstrated that the facile oxidation of cobalt(II) to kinetically inert d^6 cobalt(III) centres allows the dynamic system to be "frozen". This allows synthetic schemes to be planned in which the advantages of reactions occurring at labile metal centres (rapid reaction, thermodynamic products) may be combined with subsequent reaction steps associated with inert centres (stable complexes, no ligand dissociation processes).

Although combinatorial chemistry has its roots in "organic" synthesis and the bulk of the literature is concerned with reactions involving the formation or breaking of carbon–carbon or carbon–heteroatom bonds,[9] there have been a number of recent developments involving coordination compounds. The construction of combinatorial libraries of related compounds using these "organic" bond formation reactions is predicated upon the development and optimisation of reactions which proceed rapidly and in high yield for as wide a variety of substrates as possible. These constraints have suggested an alternative approach in which traditional assembly of components through covalent carbon–carbon or carbon–heteroatom bond formation is replaced by assembly of suitably functionalised ligands at metal centres. This approach has been elegantly demonstrated by Hamilton and co-workers, who used the assembly of $[Fe(terpy)_2]^{2+}$ or $[Ru(terpy)_2]^{2+}$[10] and $[Cu(phen)_2]^{+}$[11] motifs from functionalised terpy or phen ligands to build libraries of receptors for dicarboxylic acids. Conventional combinatorial libraries contain a statistically defined and fixed number of components. Interest has developed in dynamic combinatorial libraries, in which the components are in dynamic equilibrium. Such libraries offer the possibilty of responding to an environmental challenge, a template molecule for example, by redistribution of the components to produce one predominant species.[12] A prerequisite for such a dynamic library is a reversible bond formation reaction as the key synthetic step and C=N formation/hydrolysis has been successfully utilised for the optimisation of libraries of barbiturate receptors.[13] This concept has been extended to the optimisation of extractants for zinc(II) and cadmium(II) ions, by presenting the metal ion as a challenge to libraries of imines prepared from aminophenols and 2-pyridinecarboxaldehyde.[14] Most recently, cobalt(II)-centred assembly has been used for the preparation of dynamic combinatorial libraries based upon functionalised terpy ligands.[15] In this case, the terpy ligands supported a dynamic library of C=N linked molecular recognition functionality, giving rise to a two-level system. Implicit in a dynamic combinatorial library of this type is the assumption that all of the possible species are present in statistical amounts; a modification of the concept to "virtual combinatorial libraries" in which non-statistical distributions of components are actually present has been made in the case of molecular polygons.[16] In this paper, we discuss the exchange of various substituted terpy ligands at cobalt(II) centres.

Experimental

General

Infrared spectra were recorded on Mattson Genesis Fourier-transform spectrophotometers with samples in compressed KBr discs. ^{1}H NMR spectra were recorded on Bruker AM 250 or 400 MHz spectrometers. UV/VIS measurements were recorded using a Perkin-Elmer Lambda 19 spectrophotometer in acetonitrile at a concentration of $\sim 10^{-4}$ M. FAB and EI mass spectra were recorded on a Kratos MS50 instrument. Time of flight (MALDI) spectra were recorded using a PerSeptive

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Biosystems Voyager-RP Biospectrometry Workstation. CD spectra were recorded on a Jasco J-720 CD spectrometer in 1 mm quartz cuvettes at 25 °C. The ligands **I** and **II** were prepared from 6-bromo-2,2′ : 6′,2″-terpyridine[17] as previously reported,[18] and remaining ligands **III**–**VIII** were prepared by literature methods.[19–23] The complexes $[Co(\mathbf{III})_2][PF_6]_2$,[19] $[Co(\mathbf{IV})_2][PF_6]_2$[20] and $[Co(terpy)_2][PF_6]_2$ were prepared by standard methods.[24]

Preparations

$[Co(\mathbf{I})_2][PF_6]_2$ 1. A solution of $Co(OAc)_2{\cdot}4H_2O$ (12.5 mg, 0.05 mmol) and **I** (38.5 mg, 0.1 mmol) in MeOH (2 cm^3) was stirred for 1 h at room temperature during which period a brown colour developed. The solution was diluted with water (20 cm^3) and any solid was removed by filtration over Celite. An excess of NH_4PF_6 was added to the filtrate and the resultant precipitate was collected by filtration, washed with water, dried (P_2O_5) and further purified by column chromatography (silica gel, 14 : 2 : 1 acetonitrile–saturated aqueous KNO_3–H_2O) to give **1** as an orange–brown crystalline solid (yield 47 mg, 84%). Found: C, 53.2; H, 5.0; N, 7.4. $C_{50}H_{54}F_{12}N_6O_2P_2Co$ requires C, 53.6; H, 4.9; N, 7.5%. $\bar{\nu}_{max}/cm^{-1}$ 2953s, 1601s, 1576s, 1474s, 1268s, 1025m, 843s, 558s. *m/z* (MALDI-TOF) 975 (**1** − PF_6), 830 (**1** − $2PF_6$), 694 {(**I**)Co(Oterpy)}. Circular dichroism λ_{max}/nm (MeCN) 217 ($\Delta\varepsilon_{max}$ −5.9), 268 (−1.2), 291 (+1.0); λ_{max}/nm (MeCN): 274 (ε 15.7×10^4 M^{-1} cm^{-1}), 338 (31.4×10^4).

$[Co(\mathbf{II})_2][PF_6]_2$ 2. As above for **1**, but with **II** (38.5 mg, 0.1 mmol) (yield 52 mg, 93%). Found: C, 53.2; H, 5.0; N, 7.6. $C_{50}H_{54}F_{12}N_6O_2P_2Co$ requires C, 53.6; H, 4.9; N, 7.5%. Circular dichroism λ_{max}/nm (MeCN) 217 ($\Delta\varepsilon_{max}$ +6.1), 268 (+1.5), 291 (−0.5); λ_{max}/nm (MeCN) 273 (ε 16.2×10^4 M^{-1} cm^{-1}), 338 (30.9×10^4).

$[Co(\mathbf{I}/\mathbf{II})_2][PF_6]_2$ 3. As above for **1**, but with **I** (19 mg, 0.05 mmol) and **II** (19 mg, 0.05 mmol) (yield 43 mg, 85%). Found: C, 53.3; H, 4.9; N, 7.7. $C_{50}H_{54}F_{12}N_6O_2P_2Co$ requires C, 53.6; H, 4.9; N, 7.5%. Circular dichroism λ_{max}/nm (MeCN) no significant absorption bands; λ_{max}/nm (MeCN) 274 (ε 15.7×10^4 M^{-1} cm^{-1}), 338 (31.6×10^4).

$[Co(\mathbf{IV})_2][PF_6]_2$ 4. A solution of **IV** (20 mg, 0.063 mmol) and $[Co(H_2O)_6][BF_4]_2$ (10 mg, 0.032 mmol) in CH_3CN–CH_3OH (1 : 1, 50 cm^3) was stirred for 10 min at room temperature to give a golden yellow solution. Aqueous NH_4PF_6 was added to precipitate **4** as a brown solid (yield 34 mg, 100%). Found: C, 46.76; H, 3.18; N, 9.54. $C_{38}H_{26}F_6CoN_7O_3PS_2{\cdot}4H_2O$ requires C, 47.10; H, 3.54; N, 10.12%). *m/z* (MALDI-TOF) 691 (**4** − $2PF_6$), 317 (H**IV**), 374 (Co(**IV**)). $\bar{\nu}_{max}/cm^{-1}$ 1613m, 1570w, 1550w, 1529w, 1474m, 1429m, 1372w, 1248w, 1029w, 1015w, 839s [PF_6], 791m, 723w, 557m; λ_{max}/nm (MeCN) 283 (ε 4.67×10^4 M^{-1} cm^{-1}), 328 (4.89×10^4), 459 (4.0×10^3), 459 (5.5×10^3); δ_H (CD_3CN) 95.0 (4H, terpy), 56.0 (4H, terpy), 45.1 (4H, terpy), 32.8 (4H, terpy), 14.6 (2H, thienyl), 11.0 (2H, thienyl), 9.1 (6H, terpy + thienyl).

$[Co(\mathbf{IV})_2][PF_6]_3$ 5. Complex **4** (20 mg, 0.02 mmol) was dissolved in CH_3CN (20 cm^3) and an excess of a methanolic solution of Br_2 was added. After 30 min, aqueous NH_4PF_6 was added to precipitate the cobalt(III) complex **5** as a bright yellow solid (yield 23 mg, 100%). Recrystallisation from MeCN by the diffusion of diisopropyl ether vapour into the solution gave analytically pure crystalline **5**. Found: C, 45.37; H, 3.43; N, 8.88. $C_{38}H_{26}F_{12}CoN_7O_3P_2S_2{\cdot}C_6H_{12}O{\cdot}H_2O$ requires C, 45.57; H, 3.48; N, 8.45%). *m/z* (MALDI-TOF) 689 (**5** − $3PF_6$), 979 (**5** − PF_6). $\bar{\nu}_{max}/cm^{-1}$ 1611s, 1555m, 1550w, 1525m, 1480s, 1431s, 1404m, 1376m, 1248m, 1058w, 1044w, 839s [PF_6], 782m, 720m, 558m. λ_{max}/nm (MeCN) 280 (ε 5.75×10^4 M^{-1} cm^{-1}), 376 (5.07×10^4). δ_H (CD_3CN) 7.45 (dd, 4H, H^5), 7.45 (d, 4H, H^6), 8.25 (ddd, 4H, H^4), 8.74 (d, 4H, H^3), 9.14 (s, 4H, H^3), 7.53 (dd, 2H, $H^{4''}$), 8.08 (dd, 2H, $H^{5''}$), 8.43 (dd, 2H, $H^{3''}$).

Synthesis of homoleptic cobalt(II) complexes of VII and VIII. A nitrogen purged solution of $[Co(H_2O)_6][BF_4]_2$ (1 eq.) in CH_3CN was added to a nitrogen sparged solution of ligand (2 eq.) in CH_3OH and the mixture stirred at room temperature for 10 min, after which time an aqueous solution of NH_4PF_6 was added to partially precipitate the complex as a brown solid. The volume was reduced *in vacuo* and water was added. The solid was collected by filtration, and purified by vapour diffusion of diisopropyl ether into a CH_3CN–CH_3OH (1 : 1) solution. Yields were quantitative.

$[Co(VII)_2][PF_6]_4$ 6. δ_H (CD_3CN) 90.0 (4H, terpy), 50.9 (4H, terpy), 33.3 (4H, terpy), 32.9 (4H, terpy), 12.7 (4H), 10.2 (4H), 9.7 (4H), 4.0 (H^{CH_3}). *m/z* (ES-MS) 499.3 (**6** − $2PF_6)^{2+}$, 325.5 (**6** − $3PF_6)^{3+}$, 177.3 (**6** − $4PF_6$).

$[Co(VIII)_2][PF_6]_4$ 7. δ_H (CD_3CN) 90.6 (4H, terpy), 51.3 (4H, terpy), 33.9 (4H, terpy), 33.1 (4H, terpy), 12.7 (4H, pyridyl), 10.1 (4H, pyridyl), 9.9 (4H, terpy), 8.2 (4H, Ph), 7.9 (6H, Ph), 5.8 (4H, CH_2). *m/z* (ES-MS) 575.9 (**7** − $2PF_6)^{2+}$, 401.3 (**7** − PF_6).

Results and discussion

Broadly speaking, coordination chemistry may be subdivided into the study of complexes with labile or with kinetically inert (or non-labile) metal centres. Ligand exchange rates range from the very slow (~10^{-6} s^{-1}) to the very fast (~10^{10} s^{-1}) and although this distinction between labile and non-labile is somewhat empirical, exchange processes with pseudo-first order rate constants of a few seconds or less are described as labile whilst those with rate constants of a few minutes or greater are described as non-labile.[25] For the synthetic chemist, the important difference is that labile complexes respond to the challenge of an additional ligand by establishing an equilibrium between coordinated and non-coordinated species, whereas non-labile complexes undergo little if any ligand exchange.

It follows that ligand exchange processes at labile metal centres may be used to increase structural diversity and build libraries of complexes. Specifically, a system comprising two ligands **A** and **B** and a metal ion M which can bind two ligands will generate a library containing [M$\mathbf{A}_2$], [M$\mathbf{B}_2$] and [M**AB**] and in general a library of $\Sigma_{n=0}^{n=i} n_i$ complexes will result from *n* ligands. If the formation constants of all of the complexes are similar, the equilibrium mixture will contain all species in a close to statistical ratio. If additional intramolecular interactions stabilise or destabilise particular components, then the distribution will be non-statistical. In the limiting case, in which one component is sufficiently stabilised to be the dominant solution species, or a number of components are sufficiently destabilised so as to be effectively absent, a *virtual library* is formed.[16] In this paper, we address some of the interactions which might lead to non-statistical distributions within libraries of labile complexes.

Elements of chirality in 6-substituted terpy complexes

It is well known that chelating didentate ligands **A** form chiral complexes *cis*-[M$\mathbf{A}_2\mathbf{X}_2$] (C_2 symmetry) and [M$\mathbf{A}_3$] (D_3 symmetry) (**X** is a monodentate ligand) with six-coordinate metal ions.[26] The chirality of these complexes is usually described using the notation Δ and Λ (Fig. 1) to relate the absolute configuration to defined skew lines.[27] In the case of a terpy ligand **L**, or a terpy derivative in which substituents are attached symmetrically about the mirror plane running through the nitrogen and C4 of the central pyridine ring (*e.g.* 4′-Xterpy, 4,4″-X_2terpy, 6,6″-X_2terpy, 3′,5′-X_2terpy *etc.*), the complexes

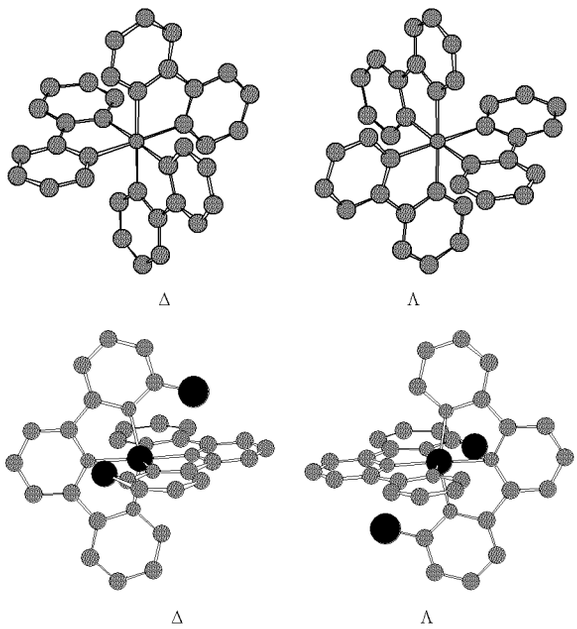


Fig. 1 Stereochemical relationships in six-coordinated complexes of bipy and terpy. The stereochemical descriptors Δ and Λ may be used to describe the absolute configuration of the chiral complexes obtained with 6-substituted terpy ligands. The skew line convention adopted places the substituted ring of the terpy with highest priority.

[ML_2] (D_{2d} symmetry) are achiral. However, if the ligand is not symmetrically substituted, as is the case for 6-Xterpy, the [ML_2] complexes possess C_2 symmetry and are chiral. The convention adopted for describing the chirality using Δ and Λ descriptors in these complexes is indicated in Fig. 1

The coordination of an achiral 6-Xterpy ligand **L** to a metal ion will give a racemic mixture comprising the enantiomeric pair of compounds Δ-[ML_2] and Λ-[ML_2]. In an achiral environment, the pair of enantiomers possess identical spectroscopic properties and give rise to, for example, identical ^{1}H NMR spectra.

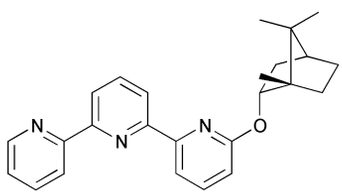
In the event that the X-substituent itself is chiral, the system is rather more complex. If the ligand contains a single, configurationally stable stereogenic centre, the absolute configuration of the ligand may be conveniently indicated using the Cahn–Ingold–Prelog *R* and *S* descriptors.[28] The stereochemical relationships in the complexes are best seen in Fig. 2. It is convenient (if strictly incorrect) to think in terms of two types of chirality within these complexes—the *R* or *S* chirality of the substituent and the Δ or Λ chirality of the complex. The combination of either (*R*)-**L** or (*S*)-**L** with the metal centre can give rise to a total of four different stereoisomers. Reaction with (*S*)-**L** alone will give two complexes—(*S,S*)-Δ-[ML_2] and (*S,S*)-Λ-[ML_2]. Similarly, (*R*)-**L** will give (*R,R*)-Δ-[ML_2] and (*R,R*)-Λ-[ML_2]. When all of the chiral descriptors in a pair of compounds are inverted, they are enantiomers; (*S,S*)-Δ-[ML_2] and (*R,R*)-Λ-[ML_2] are enantiomers, as are (*S,S*)-Λ-[ML_2] and (*R,R*)-Δ-[ML_2]. All other combinations, for example (*S,S*)-Δ-[ML_2] and (*R,R*)-Δ-[ML_2], are diastereomers or diastereoisomers.

Diastereomers should give different ^{1}H NMR spectra. The ^{1}H NMR spectrum of [ML_2] prepared from (*S*)-**L** should consist of two sub-spectra, one corresponding to (*S,S*)-Δ-[ML_2] and the other to diastereomeric (*S,S*)-Λ-[ML_2]. The ^{1}H NMR spectrum of [ML_2] from (*R*)-**L** should be identical, since the two species in solution, (*R,R*)-Λ-[ML_2] and (*R,R*)-Δ-[ML_2], are enantiomers of (and hence have identical spectra to) (*S,S*)-Δ-[ML_2] and (*S,S*)-Λ-[ML_2], respectively.

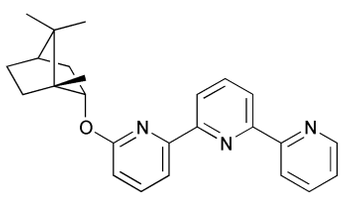
Because the total energy of diastereomers differs, the reaction with, for example, (*S*)-**L** is expected to lead to unequal amounts of (*S,S*)-Δ-[ML_2] and (*S,S*)-Λ-[ML_2]. The difference in energy arises from different steric interactions in the two diastereomers.

Cobalt(II) complexes of chiral terpy ligands—synthesis and characterisation

The pair of chiral ligands **I** and **II** were prepared as previously described in the stereoretentive reaction of 6-bromo-2,2′ : 6′,2″-terpyridine with the alkoxides derived from (1*S*)-*endo*-(−)borneol or (1*R*)-*endo*-(+)borneol respectively.[18] The homoleptic complexes [Co(**I**)$_2$][PF_6]$_2$ **1** and [Co(**II**)$_2$][PF_6]$_2$ **2** were prepared by the reaction of **I** or **II**, respectively, with cobalt(II) acetate in methanol followed by precipitation of the orange hexafluorophosphate salts. In most respects, the two complexes have identical spectroscopic and spectrometric properties. In each case, the MALDI-TOF mass spectrum reveals peaks assigned to (CoL_2·PF_6)$^+$ and (CoL_2)$^+$ and the electronic spectra reveal intense absorptions at 274 and 338 nm. The complexes are redox active and both show a very poorly defined cobalt(II)/cobalt(III) process at ≈0.1 V (*vs.* Fc/Fc$^+$).



S-**I**



R-**II**

As discussed above, each ligand can give complexes with Δ or Λ configurations and the isolated species are expected to be mixtures (Δ-**1** and Λ-**1**) or (Δ-**2** and Λ-**2**). Even if the reaction gives exactly equal amounts of Δ and Λ complexes, the overall mixture will still be chiral as these compounds are diastereomers. The CD spectra of the complexes **1** and **2** exhibit equal and opposite responses within experimental error, showing features with maxima at 217, 268 and 291 nm. As expected, there was a null CD response from the mixture of complexes obtained from the reaction of cobalt(II) acetate with a racemic mixture of **I** and **II**.

Cobalt(II) complexes of chiral terpy ligands—^{1}H NMR spectra

Cobalt(II) possesses a d^7 electron configuration and all complexes will possess at least one unpaired electron. Within the O_h point group this corresponds to high spin $t_{2g}^5e_g^2$ and low spin $t_{2g}^6e_g^1$ arrangements; although this description should be modified for the lower C_2 symmetry in **1** and **2**, it is approximately accurate. In the solid state, [Co(terpy)$_2$]$^{2+}$ complexes are close to the spin crossover, with the spin state being dependent upon the counter-ions and lattice solvent.[29] The ^{1}H NMR spectra of cobalt(II) complexes are subject to two effects associated with the paramagnetism of the metal centre; firstly, the local magnetic field at the proton will be significantly different from the applied field, as a result of the magnetic field associated with the unpaired electrons, and secondly, the signals will be broadened as a result of the coupling between electronic and magnetic spin, providing a very efficient relaxation mechanism.[24,30,31] The combined effect in the case of cobalt(II) complexes is ^{1}H NMR spectra which are paramagnetically shifted over a chemical shift range of several hundred ppm,

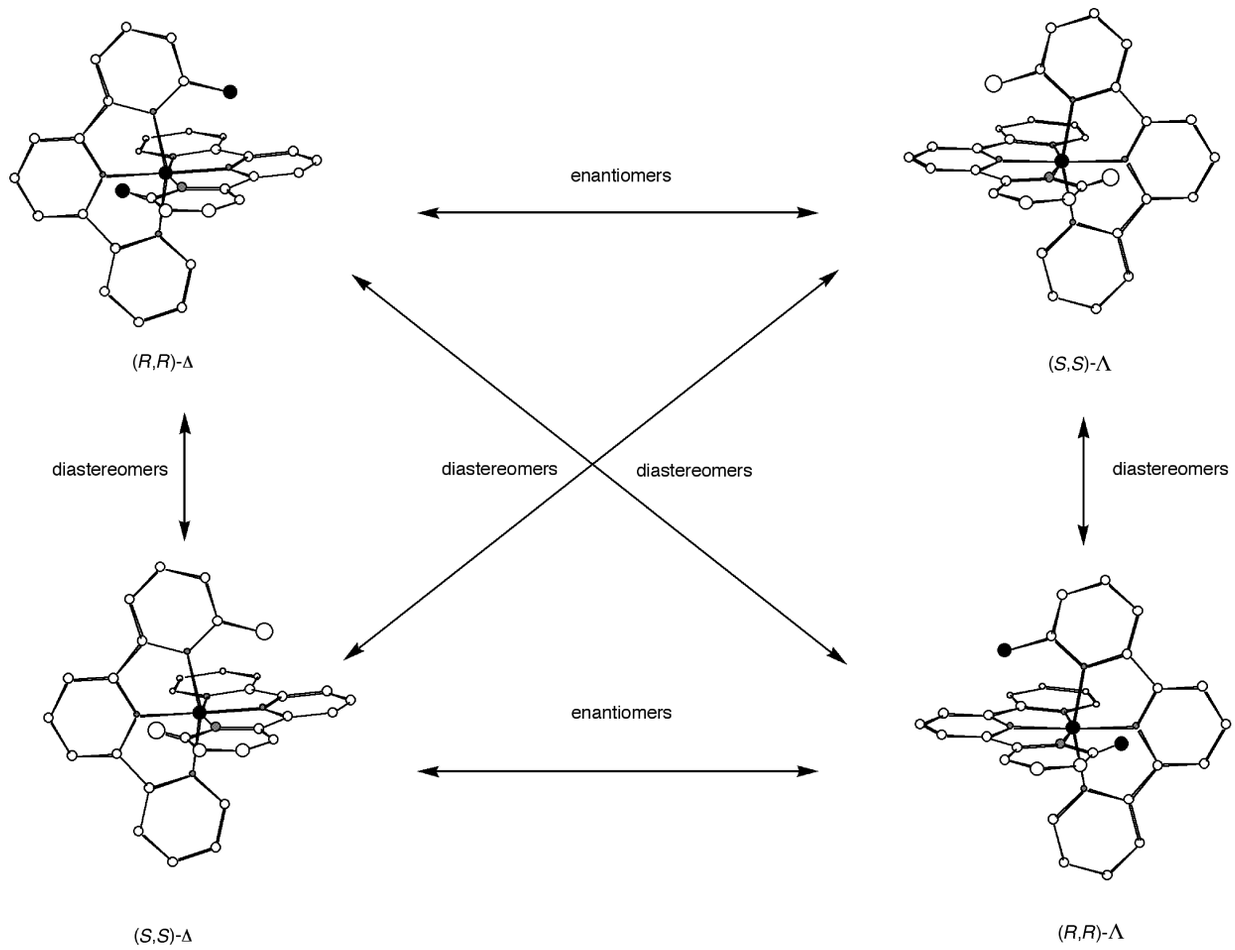


Fig. 2 Stereochemical relationships in complexes containing two chiral 6-substituted terpy ligands. The chirality within the substituents is represented by full or open circles. The various enantiomeric and diastereomeric relationships are indicated.

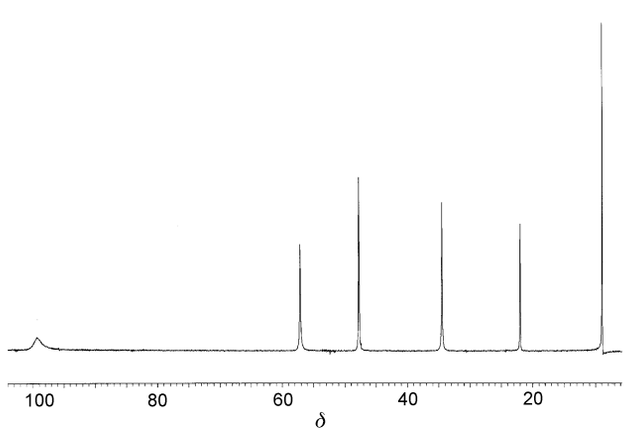


Fig. 3 The 250 MHz ^{1}H NMR spectrum of a CD_3CN solution of $[Co(terpy)_2][PF_6]_2$ **8** showing the six paramagnetically shifted resonances. The complex is low spin, with the lowest field resonance at $\delta \approx 100$.

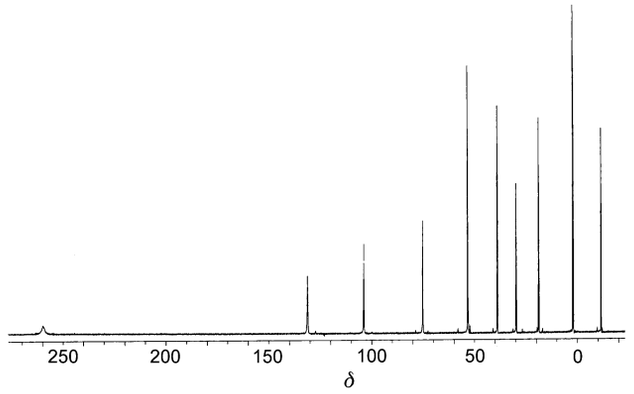


Fig. 4 The 250 MHz ^{1}H NMR spectrum of a CD_3CN solution of $[Co(6\text{-}Brterpy)_2][PF_6]_2$ showing the ten paramagnetically shifted resonances arising as a result of the lower symmetry of the complex compared to $[Co(terpy)_2][PF_6]_2$ **8**. The complex is high spin in solution with a characteristic shifting of the lowest field peak to $\delta \approx 250$. The solution comprises a racemic mixture of magnetically equivalent Δ and Λ enantiomorphs.

but which are still reasonably sharp (line widths at half height >40 Hz), although broadened sufficiently to lose any J coupling information. This is illustrated in Fig. 3, which presents the ^{1}H NMR spectrum of $[Co(terpy)_2][PF_6]_2$ in CD_3CN; this complex is low spin in solution, as confirmed by Evans' method magnetic measurement determination,[32] and the D_{2d} symmetry is indicated by the observation of a total of six resonances. The observation of the lowest field resonance, assigned to H^6, at $\approx\delta$ 100 is characteristic of a low spin $\{Co(terpy)_2\}^{2+}$ motif. The introduction of a substituent at the 6-position of the terpy ligands lowers the symmetry to C_2, with a concomitant increase in the number of proton environments. This is illustrated in Fig. 4, which presents the ^{1}H NMR spectrum of a CD_3CN solution of $[Co(6\text{-}Brterpy)_2][PF_6]_2$ (6-Brterpy = 6-bromo-2,2′ : 6′,2″-terpyridine).[17] A number of features are apparent; firstly, the presence of the 6-substituent results in steric interactions between the ligands and a weakening of the ligand field such that the complex is high spin with a characteristic lowest field resonance at $\approx\delta$ 260 and, secondly, the total number of resonances has increased, in this case to a total of ten aromatic environments. This complex consists of a racemic

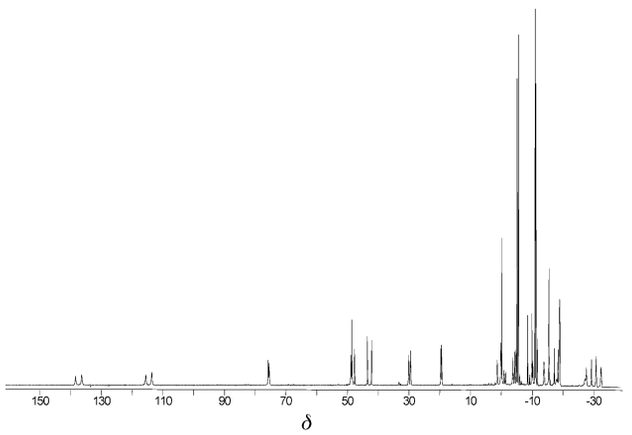


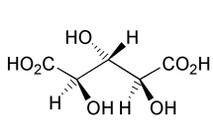
Fig. 5 250 MHz ^{1}H NMR spectrum of a CD_3CN solution (5 mM) of complex **1**. The lowest field pair of resonances is omitted. The solution clearly shows the doubling up of all signals corresponding to the Δ and Λ diastereomers. The spectrum of a solution of **2** is identical.

mixture of Δ and Λ species, which possess identical ^{1}H NMR spectra.

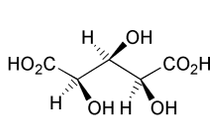
As discussed in the previous section, the coordination of **I** or **II** leads to pairs of diastereomeric compounds. The aromatic signals of these complexes are expected to comprise 20 resonances in the aromatic region; one subset of ten from the Δ and one set of ten from the Λ diastereomers. The ^{1}H NMR spectrum of a CD_3CN solution of **1** is shown in Fig. 5—the spectrum of **2** is identical in all respects. Comparison of Fig. 4 and 5 reveals the expected doubling of signals corresponding to the spectroscopically distinguishable Δ and Λ diastereomers. It is also apparent from Fig. 5 that the two diastereomers are not present in the equilibrium mixture in exactly equal amounts. The major diastereomer is present in a modest 4.6% diastereomeric excess. This corresponds to a free energy difference of 228 kJ mol^{-1} at 298 K and an equilibrium constant $K = 1.096$. Naturally, it is not possible to determine what the configuration of the major diastereomer is from these data.

Ligand exchange reactions in 1 and 2

A mixture of **1** and **2** may be used to quantify ligand exchange processes. If a ligand is exchanged between these two complexes a new heteroleptic species, [Co(**I**)(**II**)][PF_6]$_2$ **3**, will be formed. This compound is of interest from a theoretical point of view. The two ligands are enantiomorphic and the overall chirality resides only in the Δ or Λ configuration at the metal. This arrangement is closely related to that at a *pseudoasymmetric* carbon centre,[28,33] but differs in one very significant feature. A pseudoasymmetric carbon is a stereogenic centre lying in a plane of symmetry of the molecule, for example, the 3-carbon in ribaric or xylaric acid is a pseudoasymmetric centre and, as it lies in the plane of symmetry, the two molecules are achiral but diastereomers. In the case of **3**, with a six-coordinate stereogenic centre, the complex retains an overall chiral structure. Furthermore, the **I** and **II** ligands in **3** are no longer magnetically equivalent, leading to additional complexity in the observed spectrum. The result is that the mixture of enantiomorphic Δ-**3** and Λ-**3** will give rise to two subspectra. The first is due to the **I** ligand in Δ-**3** and the **II** ligand in Λ-**3** and the second due to the **I** ligand in Λ-**3** and the **II** ligand in Δ-**3**. It should, thus, be possible to monitor ligand exchange processes through the ^{1}H NMR spectra of the cobalt(II) complexes.



ribaric acid



xylaric acid

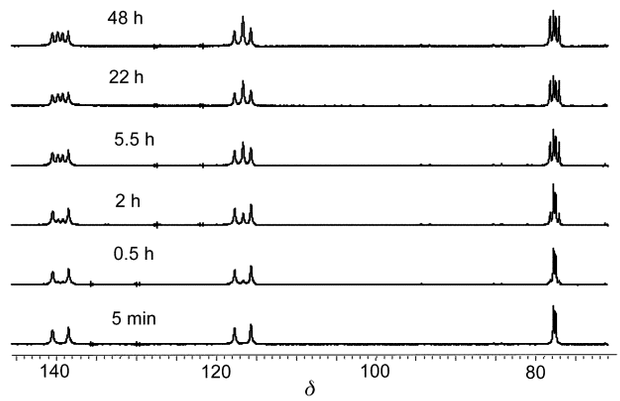


Fig. 6 Time-dependent 250 MHz ^{1}H NMR spectra of the midfield region of a solution containing equimolar amounts (5 mM) of **1** and **2**. The initial spectrum shows pairs of signals assigned to the Δ and Λ diastereomers of **1** and **2**. Over time, another pair of signals appears, assigned to the magnetically non-equivalent **I** and **II** ligands in the spectroscopically identical Δ and Λ enantiomorphs of the heteroleptic complex **3**.

To summarise, the ^{1}H NMR spectra of **1** and **2** are identical and consist of two subspectra, corresponding to the Δ and Λ diastereomers. If exchange occurs to form **3** another two subspectra will develop, arising from the magnetically inequivalent **I** and **II** ligands in the enantiomorphic Δ and Λ complexes.

Fig. 6 shows the ^{1}H NMR spectra that result from mixing equal volumes of 5 mM solutions of **1** and **2**. A number of features are immediately evident. Firstly, an equilibrium is eventually attained in which the number of resonances is doubled, in accord with the formation of **3** as discussed above. This is most clearly seen by considering the pair of resonances at δ 141 and 138.5 in the spectrum of **1** or **2**. Over a period of time, two new resonances at δ 139.5 and 140.5 develop, corresponding to the two ligand environments in the heteroleptic complex. The second feature, is the long period of time required before equilibrium is reached. At the 5 mM concentrations studied, the solution only fully equilibrates after 22 h and a second order rate constant of 6×10^{-5} M^{-1} s^{-1} is estimated from the NMR data. In contrast to the 5,5″-ligands studied by Lehn,[15] ligand exchange of **I** and **II** at the "labile" cobalt(II) centre only proceeds at a modest rate (contrast 1300 M^{-1} s^{-1} for the 5,5″-disubstituted compounds). Both steric and electronic effects will be of importance, as **1** and **2** are high spin, whilst those studied by Lehn are low spin. We have made no detailed mechanistic studies of this process, in part because of the unique nature of the system, but we have no reason to believe that they differ in significant detail from established processes for terpy and related complexes.[34] There are no changes in the electronic absorption spectrum associated with the ligand exchange and the only means of monitoring the reaction is by ^{1}H NMR spectroscopy.

The studies above establish the formation of the library of complexes through ligand exchange processes. Allowing for the very small diastereomeric excess of the δ 138.5 resonance over that at δ 141, the final equilibrium mixture is close to the statistical 1 : 2 : 1 distribution (giving an approximately 1 : 1 : 1 : 1 set of peaks).

Chiroptical properties of cobalt(II) complexes of I and II

As mentioned in passing above, the electronic spectra of **1**, **2** and **3** are identical, exhibiting a broad absorption at 330–340 nm (ε 30000 M^{-1} cm^{-1}) tailing into the visible. No d–d transitions were observed. The strong yellow colour of the complexes precluded direct measurement of the optical rotation. However, the CD spectra proved to be of interest and Fig. 7 presents the CD spectra of the three complexes (in each case as a mixture of the Δ and Λ forms).

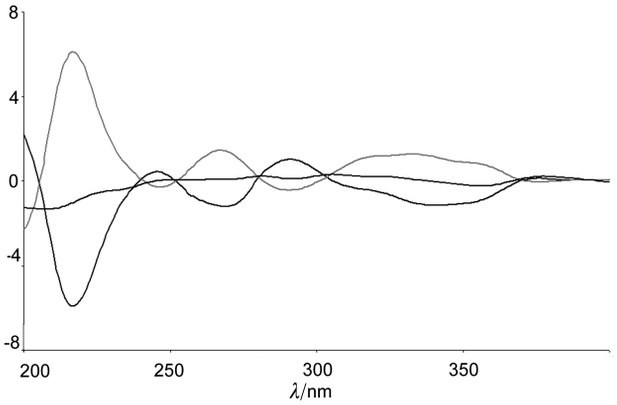


Fig. 7 Circular dichroism spectra of mixtures of the Δ and Λ forms of **1** (black trace, negative Δε at 220 nm), **2** (grey trace, positive Δε at 220 nm) and a 1 : 1 mixture of **1** and **2** (black central trace).

The CD spectra of **1** and **2** are close to mirror images, as expected for solutions containing near equal amounts of the Δ and Λ diastereomers; the slight differences arise from the slight diastereomeric excess of one of the two forms. This interpretation is supported by the intensities of the CD spectra. Diastereomerically pure metal complexes usually have strong CD responses associated with the metal-centred chirality; the small observed values of $\Delta\varepsilon < 10$ M^{-1} cm^{-1} are typical of the free ligands. The CD spectra of **I** and **II** show two strong responses at 264 and 299 nm ($\Delta\varepsilon$ − 1.6 and −1.5 M^{-1} cm^{-1} for **I** and +1.5 and +1.7 M^{-1} cm^{-1} for **II**), but are silent to lower energy. The sign of the Cotton effect ($\Delta\varepsilon$) at various wavelengths has been used to assign absolute configurations for simple compounds based upon the sector rule,[35] but is not reliable for transition metal complexes.[37] Accordingly, we note at this juncture that the small excesses of diastereomers present in **1** and **2** give rise to negative and positive Cotton effects between 300 and 350 nm respectively. We also note, that the successful application of exciton coupling models in combination with solid state structural data has led to the assignment of related structures based on the correlation of a positive Cotton effect with a Δ configuration.[26,30,36,37] If this analogy holds, then the diastereomer in excess in **1** possesses the Λ configuration, whilst in **2**, the dominant species possesses a Δ configuration.

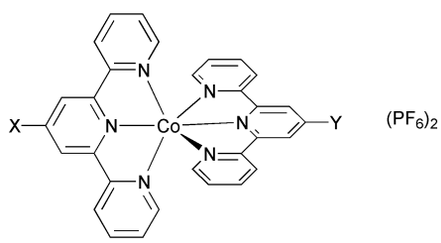
The equilibrium mixture resulting from the reaction of **1** and **2** should be essentially CD silent (ignoring the very small diastereomeric excesses in the parent compounds). The reaction mixture consists of three racemic pairs of complexes ({Δ-**1** and Λ-**2**}, {Δ-**2** and Λ-**1**} and {Δ-**3** and Λ-**3**}) in accord with the near null response shown in Fig. 7.

Constructing libraries using 4′-substituted 2,2′ : 6′,2″-terpyridines

The studies reported above confirm that near statistical libraries are established, albeit slowly, with 6-substituted 2,2′ : 6′,2″-terpyridines. Exchange processes are significantly faster with 5,5″-disubstituted derivatives,[15] and we decided to extend the studies to 4′-substituted ligands. The principal driving force for this study was to utilise the wide range of 4′-substituted terpy ligands to try to significantly perturb the distribution of complexes within the final equilibrium mixture. In particular, it seemed likely that upon mixing complexes $[Co\mathbf{D}_2]^{2+}$ (**D** = terpy with electron-releasing substituent) and $[Co\mathbf{A}_2]^{2+}$ (**A** = terpy with electron-withdrawing substituent) the heteroleptic complex $[Co\mathbf{AD}]^{2+}$ might be especially favoured. Other than the recent work of Lehn,[15] there is only a single report of a heteroleptic cobalt(II) complex with terpy ligands.[38] In the light of the studies we report in this paper, it seems likely that the previously described compound is an equilibrium mixture of homoleptic and heteroleptic complexes.

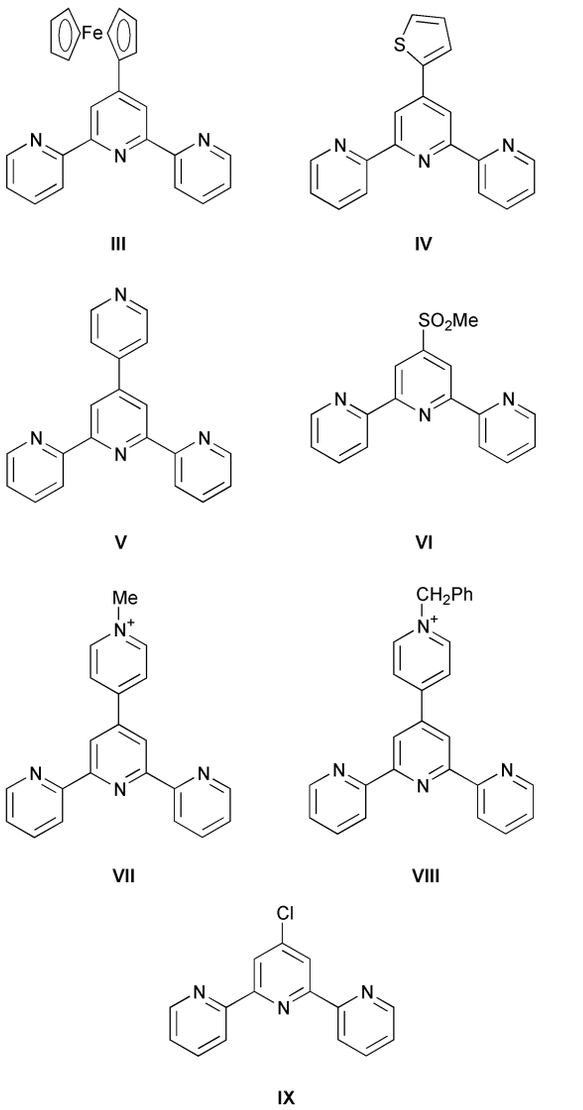
We chose a suite of ligands, including terpy itself; **III**[19] and **IV**[20] with electron-releasing substituents, **V**[21] with a pendant basic site and **VI**,[22] **VII**·PF_6[23,28] and **VIII**·PF_6[23] with electron-withdrawing substituents.

The homoleptic complex $[Co(\mathbf{IV})_2][PF_6]_2$ **4** was prepared in quantitative yield as an orange–brown solid by the reaction of **IV** with cobalt(II) tetrafluoroborate in MeOH–MeCN. Like all $[Co\mathbf{L}_2]^{2+}$ complexes with 4′-substituted terpy ligands, **4** is low spin in solution, as might be expected from the stronger ligand field in the absence of steric interactions associated with the 6-position. The ^{1}H NMR spectrum exhibits a lowest field peak at δ 91 and a total of eight resonances are observed. The complex is redox active and shows a reversible cobalt(II)/cobalt(III) process at −0.138 V and a series of near or quasi-reversible ligand based reductions at −1.09, −1.38, −1.89 and −2.38 V (all potentials *vs.* Fc/Fc^+). Chemical oxidation with bromine gave the homoleptic cobalt(III) complex $[Co(\mathbf{IV})_2][PF_6]_3$ **5** in quantitative yield. This diamagnetic complex was fully characterised by spectroscopic methods and elemental analysis. The complexes **6** and **7** containing the cationic ligands **VII** and **VIII**, respectively, were also prepared by direct coordination of the free ligand to cobalt(II). The complexes are both high spin and were fully characterised by normal spectroscopic methods.



Complex	X Ligand	Y Ligand
4	**IV**	**IV**
6	**VII**	**VII**
7	**VIII**	**VIII**
8	terpy	terpy
9	**IX**	**IX**
10	**VI**	**VI**
11	**III**	**III**
12	terpy	**III**

The general experimental protocol involved mixing equal volumes of equimolar (≈mM) CD_3CN solutions of homoleptic cobalt(II) in an NMR tube and running the spectrum as soon as possible after mixing (2–4 minutes). Permutations of the complexes with ligands **III**–**IX** were investigated, and in the cases of {**4** + **8**}, {**4** + **9**}, {**10** + **6**}, {**10** + **7**} and {**6** + **7**} equilibration was complete within ten minutes of mixing. This behaviour is comparable with that observed for the 5,5″-disubstituted ligands where exchange is also rapid.[15] In all the cases we investigated, the distribution of complexes in the final equilibrium mixture was statistical within experimental error, suggesting that purely electronic effects associated with the substituents will not be large enough to enrich libraries in individual components. Only in the case of exchange between **8** and **11** was it possible to follow the reaction by ^{1}H NMR spectroscopy, although we have no explanation for the slowness of this reaction. The ^{1}H NMR spectrum of the final equilibrium mixture is presented in Fig. 8. The situation is analogous to, but somewhat simpler than, that with the chiral ligands. In this case, the complex is achiral and possesses D_{2d} symmetry. The terpy protons in the homoleptic parent complexes **8** and **11** give rise to six and five resonances, respectively. In the heteroleptic complex **12**, the terpy and **III** ligands are chemically and magnetically inequivalent and are expected to give rise to a total of 11 terpy resonances. If the magnetic environments of the terpy and **III** ligands in **12** differ from those in **8** and **11**, respectively, then the ^{1}H NMR spectrum of the equilibrated mixture of **8** and **11** will consist of 22 terpy



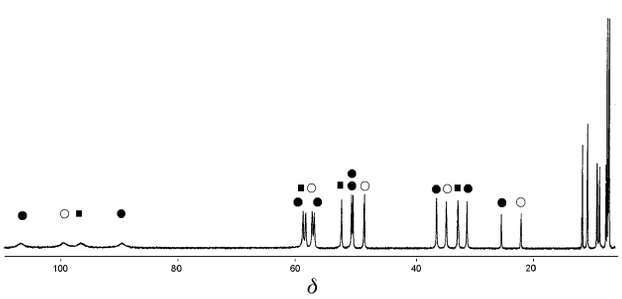


Fig. 8 250 MHz ^{1}H NMR spectrum of an equilibrated CD_3CN solution originally containing equimolar amounts of **8** and **11**. The spectrum exhibits resonances due to **8** (open circle), **11** (filled square) and the heteroleptic complex **12** (filled circle).

resonances. This is clearly seen in Fig. 8, which also confirms the statistical 1 : 2 : 1 distribution of the complexes giving rise to clusters of four resonances of equal intensity (H^X from terpy in **8**, H^X from **III** in **11**, H^X from terpy in **12**, H^X from **III** in **12**). Fig. 9 shows the time evolution of the ^{1}H NMR spectrum of a 1 : 1 mixture of **8** and **11**. From these data, we estimate a rate constant of $k_2 \approx 2 \times 10^{-4}$ M^{-1} s^{-1} for this reaction.

Conclusions

We have shown that the exchange of ligands between homoleptic cobalt(II) complexes of substituted terpy ligands may be used as an experimental protocol for the preparation of combinatorial libraries of complexes, even if some of the individual

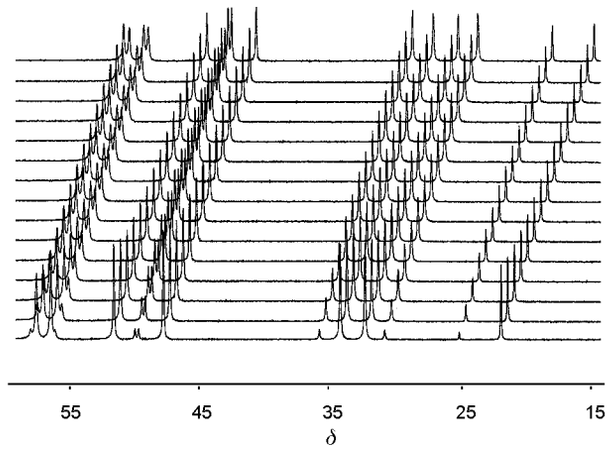


Fig. 9 Time-dependent 250 MHz ^{1}H NMR spectra of the midfield region of a solution containing equimolar amounts (3 mM) of **8** and **11**. The initial spectrum shows pairs of signals assigned to **8** and **11**. Over time, another pair of signals appears, assigned to the magnetically non-equivalent **III** and terpy ligands in the enantiomorphic Δ and Λ forms of the heteroleptic complex **12**. The first spectrum was recorded 4 min after mixing and subsequent spectra are at 10.5 min intervals.

component may not be isolable. The rates of exchange are dependent upon the pattern of substitution in the ligands, with the exchange of 6-substituted ligands being slower than that of 4′-substituted terpy compounds.

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