Metal-directed assembly of combinatorial libraries—principles and establishment of equilibrated libraries with oligopyridine ligands

Barbara Brisig, Edwin C. Constable* and Catherine E. Housecroft

Received (in Montpellier, France) 21st May 2007, Accepted 30th May 2007
First published as an Advance Article on the web 19th June 2007
DOI: 10.1039/b707601k

The cobalt(II) complexes $[Co(bpy)_3][PF_6]_2$, $[Co(Me_2bpy)_3][PF_6]_2$ (Me_2bpy = 4,4′-dimethyl-2,2′-bipyridine) and $[Co(phen)_3][PF_6]_2$ give paramagnetically shifted ^1H NMR spectra which may be fully assigned; the complexes are labile and ligand exchange is complete within mixing time in CD_3CN solutions to give libraries of heteroleptic complexes which have been fully characterised by one- and two-dimensional ^1H NMR spectroscopy. A library comprising *mer* and *fac* isomers of $[CoL_3]^{2+}$ (L = 2,2′-bipyridine-5-carbaldehyde) can be amplified by specific reaction of the *fac* stereoisomer with a triamine to give a new hexadentate ligand, although other ligand exchange processes compete.

Introduction

Metal-directed self assembly of ligands around metal centres is a powerful methodology in supramolecular chemistry that allows the preparation of numerous topologically and topographically novel compounds in which the spatial arrangement of organic components 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.[1–10] Both labile and kinetically inert metal centres may be used for the construction of such molecular architectures and the latter, usually d^6 transition metal ions, have the advantage that a building block approach may be used in which metal-containing units retain their structural integrity through a synthetic sequence. This approach has been adopted for the construction of photoactive metallodendrimers and metallopolymers.[11–17] In contrast, labile metal centres allow equilibrium to be reached rapidly and thermodynamic products to be isolated, although a disadvantage is that it is not always possible to carry labile complexes through subsequent reaction steps.

We have recently investigated the use of d^7 cobalt(II) centres for the assembly of tpy and bpy ligands into linear and dendritic systems[18–32] and have demonstrated that oxidation to kinetically inert d^6 cobalt(III) allows the dynamic system to be "frozen". This promises synthetic schemes in which the advantages of labile metal centres (rapid reaction, thermodynamic products) may be combined with subsequent reaction steps associated with inert centres (stable complexes, no ligand dissociation processes).

Combinatorial chemistry has its basis in "organic" synthesis and most is concerned with reactions involving the formation or breaking of carbon–carbon or carbon–heteroatom bonds.[24,25] 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 $[Ru(terpy)_2]^{2+}$,[26] and $[Cu(phen)_2]^+$,[27] motifs from functionalised terpy or phen ligands to build libraries of receptors for dicarboxylic acids. Conventional combinatorial libraries contain a statistically defined number of components. Interest has developed in dynamic combinatorial libraries, in which the components are in dynamic equilibrium.[28–31] Such libraries offer the possibility of responding to a challenge such as a template molecule by redistribution of the components to produce one predominant species. A prerequisite for such a dynamic library is a reversible bond formation reaction as the key synthetic step and imines have been a common motif in these libraries. An obvious extension is to the use of metal–ligand bond formation as the reversible process,[32] and the concept has been established in 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-pyridinecarbaldehyde[33] or optimising receptors for lithium cations.[34,35] A number of examples of metal ion involvement in the establishment of dynamic combinatorial libraries have recently been described[36–47] and the reader is referred to two excellent reviews.[48,49]

Most recently, cobalt(II)-centred assembly has been used for the preparation of dynamic combinatorial libraries based upon chiral bpy ligands[50] or terpy ligands supporting a dynamic library of imines giving rise to a two-level system.[51] 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 present has been made in the case of

Department of Chemistry, Spitalstrasse 51, CH 4056 Basel, Switzerland. E-mail: Edwin.Constable@unibas.ch; Fax: +41 61 267 1005; Tel: +41 61 267 1001

molecular polygons.[30,48,49,52,53] We have discussed the exchange of various substituted terpy ligands at cobalt(II) centers[50,54,55] and demonstrated how electron-transfer between cobalt(II) and cobalt(III) species may be monitored by exchange spectroscopy and used to unambiguously assign the NMR spectra of cobalt(II) species.[56] We now discuss the use of ^{1}H NMR spectroscopy in the establishment and quantification of libraries of bpy and phen ligands with cobalt(II) centres.

Experimental

NMR measurements

^{1}H NMR spectra were measured on Bruker AM250 or AM500 spectrometers using 5 mM stock solutions of the complexes in CD_3CN. 500 MHz gradient COSY and NOESY spectra were recorded at 295 K using the Bruker programs cosygp and noesytp, respectively. All spectra are referenced to the signal of CD_2HCN at δ 1.94 ppm. The chemical shifts are somewhat temperature dependent and all tabulated date refer to spectra measured at 295 K. EXCSY spectra were acquired in the phase-sensitive mode, using the noesytp programme.

Syntheses

The compounds bpy and phen were used as supplied; 2-(1-oxo-2-pyridinioethyl)pyridine iodide[57] was prepared by the literature method.

5-Methyl-2,2′-bipyridine. 2-(1-Oxo-2-pyridinioethyl)pyridine iodide (8.16 g, 25 mmol), 2-methylpropanal (3.00 cm^3, 36 mmol) and ammonium acetate (5.81 g, 75 mmol) were dissolved in methanol (70 cm^3) and the mixture refluxed for 3.5 h. The solution was concentrated and the residue extracted with hexane (6 × 30 cm^3). The combined organic layers were washed with saturated sodium chloride solution (2 × 70 cm^3), dried over sodium sulfate, and the solvent evaporated *in vacuo*. The yellow liquid residue was dried *in vacuo* (3.10 g, 72%). (Found: C 75.61, H 6.43, N 16.14. Calc. for $C_{11}H_{10}N_2 \cdot 1/3H_2O$: C 75.23, H 6.08, N 15.95%); *m*/*z* (ESMS) 250.8 [M + Na + acetone]$^+$, 193.2 [M + Na]$^+$; δ_H/ppm (250 MHz, $CDCl_3$) 8.61 (1H, ddd, *J* 4.9, 1.9, 1.0 Hz, H6′), 8.45 (1H, m, H6), 8.31 (1H, dt, *J* 8.3, 1.0 Hz, H3′), 8.24 (1H, d, *J* 7.5 Hz, H3), 7.72 (1H, td, *J* 8.0, 1.9 Hz, H4), 7.54 (1H, m, H4′), 7.19 (1H, ddd, *J* 7.5, 4.9, 1.3 Hz, H5′), 2.29 (3H, s, CH_3); δ_C/ppm (100 MHz, $CDCl_3$) 156.6, 153.9, 149.9, 149.4, 137.8, 137.2, 133.7, 123.7, 121.1, 120.9, 18.6; IR (ν/cm^{-1}) 3047w, 3001w, 2923w, 2869w, 1558m, 1458s, 1434m, 1380m, 1249w, 1218w, 1126w, 1095w, 1064w, 1033m, 987m, 848m, 786s, 740s, 648w.

5-[2-(*N*,*N*-Dimethylamino)vinyl]-2,2′-bipyridine. A solution of 5-methyl-2,2′-bipyridine (1.32 g, 7.8 mmol) and *tert*-butoxybis(*N*,*N*-dimethylamino)methane (4.50 cm^3, 21.8 mmol) in dry DMF (25 cm^3) was degassed with argon for 15 min and then heated to 140 °C under argon for 17 h. The reaction mixture was cooled to room temperature and water (200 cm^3) was added. The solution was extracted with dichloromethane (5 × 100 cm^3), the combined organic layers dried over sodium sulfate and the solvent evaporated *in vacuo*. Purification of the crude product by column chromatography (aluminium oxide, toluene: diethylamine 40 : 1) gave 5-[2-(*N*,*N*-dimethylamino)-vinyl]-2,2′-bipyridine as a yellow oil (0.534 g, 31%). δ_H/ppm (250 MHz, $CDCl_3$) 8.65 (1H, ddd, *J* 4.8, 1.8, 1.3 Hz, H6′), 8.48 (1H, d, *J* 2 Hz, H6), 8.33 (1H, dt, *J* 7.9, 1.3 Hz, H3), 8.22 (1H, d, *J* 8.2 Hz, H3′), 7.78 (1H, td, *J* 7.9, 2.0 Hz, H4), 7.60 (1H, dd, *J* 8.2, 2.3 Hz, H4′), 7.23 (1H, m, H5′), 6.92 (1H, d, *J* 13.8 Hz, H8), 5.13 (1H, d, *J* 13.8 Hz, H7), 2.88 (6H, s, $N(CH_3)_2$); δ_C/ppm (100 MHz, $CDCl_3$) 157.0, 150.9, 149.4, 145.6, 142.0, 137.2, 130.1, 125.7, 123.1, 121.3, 120.7, 93.8, 41.0.

2,2′-Bipyridine-5-carbaldehyde. 5-[2-(*N*,*N*-Dimethylamino)-vinyl]-2,2′-bipyridine (0.458 g, 2 mmol) was dissolved in 1 : 1 water-THF (130 cm^3) and sodium periodate (1.72 g, 8 mmol) was added. The solution was stirred at room temperature for 4 h after which the insoluble products were filtered off and washed well with THF. The combined THF extracts were evaporated *in vacuo*, the residue dissolved in dichloromethane (100 cm^3) and the solution washed with saturated sodium hydrogen carbonate solution (4 × 50 cm^3). The organic phase was dried over sodium sulfate and evaporated *in vacuo* to give the product as a yellow–brown solid. Purification by column chromatography (Al_2O_3, CH_2Cl_2) yielded a white solid (0.315 g, 86%). (Found: C, 71.45, H 4.63, N 14.95. Calc. for $C_{11}H_8N_2O$: C 71.73, H 4.38, N 15.21%); δ_H/ppm (250 MHz, $CDCl_3$) 10.20 (1H, s, CHO), 9.16 (1H, dd, *J* 2.0, 0.8 Hz, H6), 8.76 (1H, ddd, *J* 4.7, 1.7, 1.1 Hz, H6′), 8.65 (1H, d, *J* 8.0 Hz, H3), 8.54 (1H, dt, *J* 8.0, 1.1 Hz, H3′), 8.32 (1H, dd, *J* 8.0, 2.0 Hz, H4), 7.90 (1H, td, *J* 7.8, 1.7 Hz, H4′), 7.42 (1H, ddd, *J* 7.4, 4.7, 1.4 Hz, H5′); δC/ppm (100 MHz, $CDCl_3$) 190.9, 161.1, 155.2, 152.0, 149.9, 137.5, 137.3, 131.5, 125.2, 122.6, 121.7; *m*/*z* (ESMS) 184.1 [M]$^+$, 155.1 [M − CHO]$^+$; IR (ν/cm^{-1}) 3379w, 3055w, 2916w, 2840w, 2715w, 1697m, 1589m, 1550m, 1450m, 1434m, 1357m, 1303w, 1249w, 1203m, 1141w, 1087w, 1064w, 995w, 840m, 794s, 740s, 663w, 624w. Mp 91.8–93.0 °C.

Complex synthesis. The complexes $[Co(bpy)_3][PF_6]_2$, $[Co(Me_2bpy)_3][PF_6]_2$ (Me_2bpy = 4,4′-dimethyl-2,2′-bipyridine) and $[Co(phen)_3][PF_6]_2$ were prepared by reacting one equivalent of $Co(OAc)_2 \cdot 4H_2O$ with three equivalents of the ligand in warm methanol followed by precipitation with ammonium hexafluorophosphate.

Results and discussion

Cobalt(II) centres for the construction of combinatorial libraries

Metal–ligand interactions present a powerful methodology for the preparation of both static and dynamic combinatorial libraries. The basic concept of preparing mixtures is alien to the coordination chemist, whose traditional emphasis has been the isolation of single pure substances. Although one may regard first generations of metal-assembled libraries as nothing more than equilibrium mixtures of complexes, subsequent interactions at the periphery of the ligands may lead to useful molecular recognition events and the potential to select members of the library and perturb the distribution resulting in an amplification of the library.

We have been particularly concerned with the construction of libraries using cobalt(II) centres. The d^7 cobalt(II) ion can exhibit both high- and low-spin electron configurations ($t_{2g}^5e_g^2$ or $t_{2g}^6e_g^1$ descriptions in pure O_h symmetry) and regardless of

the spin state, cobalt(II) complexes possess unpaired electrons and mononuclear complexes will be paramagnetic. The electronic relaxation time is such that in favourable cases, ^{1}H NMR spectra of the complexes can be readily measured and interpreted as a result of the large chemical shift ranges resulting from the perturbation of the local magnetic field by that arising from the unpaired electrons and minimal broadening arising from the coupling of electronic and nuclear spins.[19,22] Ligand exchange reactions at cobalt(II) centres are reasonably fast and even though Co–L bonds are thermodynamically strong, they are also labile. This ensures that systems will rapidly attain equilibrium and establish a library of complexes. To date, few examples of the use of ^{1}H NMR spectroscopy to monitor exchange reactions in such systems have been reported.[56,58]

Speciation in cobalt(II)-bpy (phen) systems

Single ligand. In this section we develop the speciation models for libraries constructed from symmetrical bidentate ligands. The simplest case comprises the cobalt(II) ion and three equivalents of a single ligand A. In this and subsequent discussion, we assume that the thermodynamic stability of $[MA_3]$ (M = cobalt(II), charges omitted for clarity) is such that the involvement of [MA] and $[MA_2]$ species may be disregarded ($\log\beta_3$ $[Co(phen)_3]^{2+}$ 19.9–20.1;[59–61] $[Co(Me_2bpy)_3]^{2+}$ 17.55;[62] $[Co(bpy)_3]^{2+}$ 15.82–17.59[59–66]). Furthermore, within the limits of integration of NMR data, the equilibrium constants may be taken as approximately equal. In this case, the library will consist of two (Δ and Λ) enantiomers of $[MA_3]$. In the absence of a chiral environment (solvent, counterions, substituents *etc.*), NMR studies will detect a single species corresponding to the enantiomeric pair Δ-$[MA_3]$ and Λ-$[MA_3]$.

All NMR spectra were recorded in CD_3CN solution and Evans' method for magnetic moment determinations[67] revealed the parent complexes $[Co(bpy)_3][PF_6]_2$, $[Co(Me_2bpy)_3][PF_6]_2$ (Me_2bpy = 4,4′-dimethyl-2,2′-bipyridine) and $[Co(phen)_3][PF_6]_2$ to be low spin in solution in this solvent.

Fig. 1 presents the 250 MHz ^{1}H NMR spectra of 5 mM solutions of $[Co(bpy)_3][PF_6]_2$, $[Co(Me_2bpy)_3][PF_6]_2$ and $[Co(phen)_3][PF_6]_2$. In each case, paramagnetically shifted and broadened spectra are obtained which show four signals appropriate to a single ligand environment for the pair of enantiomers. Line-widths vary from 10–30 Hz for the majority of the peaks, with the most shifted peak being significantly broader with line-widths 50–120 Hz. From our previous studies, we can assign the spectra to a low spin solution species on the basis of a chemical shift in the region of δ 100 ppm for the bpy H_6 or phen $H_{2,9}$ protons. A comparison of the spectra allows the assignment of the δ 14.6 ppm signal in $[Co(bpy)_3][PF_6]_2$ and the δ 17.3 ppm peak in $[Co(phen)_3][PF_6]_2$ to H_4. Consideration of chemical shifts and equivalent protons in the phen and bpy systems together with COSY studies leads to the complete assignment that is presented in Table 1. The signals are all paramagnetically broadened and no ^{1}H–^{1}H coupling is observed directly.

Two ligands. If two ligands A and B are allowed to equilibrate with a metal centre, then the library of complexes has a greater diversity of species. The most convenient analysis

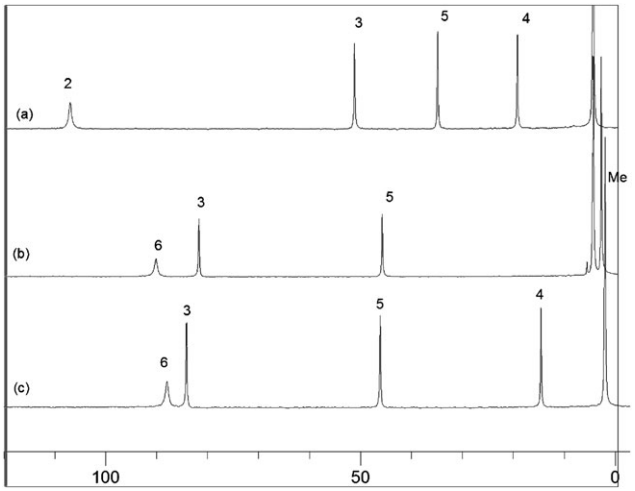


Fig. 1 250 MHz ^{1}H NMR spectra at 298 K of 5 mM CD_3CN solutions of the complexes (a) $[Co(phen)_3][PF_6]_2$, (b) $[Co(Me_2bpy)_3][PF_6]_2$ and (c) $[Co(bpy)_3][PF_6]_2$. Assignments are given using the numbering scheme presented for the free ligands. Chemical shifts in δ/ppm

is presented in Fig. 2, and indicates both the number of species and the contribution to the equilibrium mixture on statistical grounds. At equilibrium, a 1 : 3 : 3 : 1 mixture of $[MA_3]$: $[MA_2B]$: $[MAB_2]$: $[MB_3]$ is expected. In the heteroleptic species $[MA_2B]$ the unique ligand B gives rise to one set of signals as the two rings are in chemically and magnetically identical environments whilst in ligand A the two rings of the bpy are no longer equivalent as one is *trans* to A and the other *trans* to B (Fig. 2). The result is that each pair of chemically unique protons in the free A ligand (which give a single resonance in $[MA_3]$) will give two resonances with equal intensity in $[MA_2B]$ as they are now chemically and magnetically inequivalent. An identical argument applies to the B ligands in $[MAB_2]$.

The intensities of the resonances follow from the statistics and the number of ligands present in each of the species and is illustrated by considering ligand A (exactly similar arguments apply to ligand B). In total, four resonances are expected for any given proton: one from $[MA_3]$, one from $[MAB_2]$ and two from $[MA_2B]$ (see discussion above). The intensities for any proton from an A ligand in a statistical mixture of $[MA_3]$, $[MAB_2]$, $[MA_2B]$ and $[MB_3]$ is given by (number of A ligands × statistical weighting × proton weighting) which yields ratios ($[MA_3]$ $3 \times 1 \times 2 = 6$) : ($[MAB_2]$ $1 \times 3 \times 2 = 6$) : ($[MA_2B]$ $2 \times 3 \times 1 = 6$ and $2 \times 3 \times 1 = 6$) : ($[MB_3]$ = 0); in other words, every proton from A and B should give four signals in a 1 : 1 : 1 : 1 ratio. Proton weightings indicate if the protons of the two

Table 1 Assignment of the 295 K 500 MHz ^{1}H NMR spectra of CD_3CN solutions of $[CoL_3][PF_6]_2$ complexes. The numbering scheme refers to the bpy ligands, with the equivalent or unique protons of the phen ligands denoted in parentheses. Chemical shifts δ/ppm

L	$H_6(H_2)$	$H_5(H_3)$	H_4	$H_3(H_{5,6})$	Methyl
bpy	87.96	46.25	14.58	84.48	
Me_2bpy	89.74	44.50		81.52	0.40
phen	107.5	50.18	17.33	33.43	

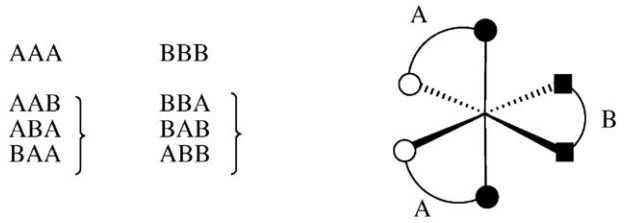


Fig. 2 Statistical equilibration of $[MA_3]$ and $[MB_3]$ will give a 1 : 1 : 3 : 3 mixture of $[MA_3]$, $[MB_3]$, $[MA_2B]$ and $[MAB_2]$. The two rings of each A ligand in $[MA_2B]$ and each B ligand in $[MAB_2]$ are magnetically inequivalent.

rings are equivalent (weighting two) or inequivalent (weighting one).

The most convenient way of following the equilibration involves mixing the preformed homoleptic complexes $[MA_3]$ and $[MB_3]$ and this has been done with the three binary combinations from the three complexes $[Co(bpy)_3][PF_6]_2$, $[Co(Me_2bpy)_3][PF_6]_2$ and $[Co(phen)_3][PF_6]_2$. In each case, equal amounts of 5 mM solutions in CD_3CN were mixed to give solutions 5 mM in cobalt and 7.5 mM in each of the ligands. In all cases, equilibration was complete by the time that the NMR spectra were recorded (within 5 min of mixing) and four signals were observed for every chemically unique proton in the ligands (Fig. 3).

The detailed analysis of the $[Co(Me_2bpy)_3][PF_6]_2$ and $[Co(phen)_3][PF_6]_2$ mixture will be given, but this differs in no way from the other two combinations. The first thing of note is that every peak from the parent homoleptic species is now split to a 1 : 1 : 1 : 1 set of four peaks. Within any cluster of four peaks, one may be immediately assigned to the known homoleptic $[Co(Me_2bpy)_3][PF_6]_2$ or $[Co(phen)_3][PF_6]_2$ species. The remaining three peaks belong to the $[Co(phen)_2(Me_2bpy)]^{2+}$ and $[Co(phen)(Me_2bpy)_2]^{2+}$ species, but cannot be further assigned from these spectra. We were extremely surprised that dispersion in the cobalt(II) shifted spectra was sufficient to clearly allow the resonances of the inequivalent rings of the major species in the heteroleptic complexes to be distinguished. This is even possible with the methyl signals of the Me_2bpy ligand and the $H^{5,6}$ resonances of the phen ligands, which are rather remote from the paramagnetic centre. Remarkably, all 32 resonances may be observed as equal intensity signals in each spectrum. This experiment establishes both the utility of the cobalt(II) complexes in quantifying the components of the library and that statistical equilibrium distributions of compounds are obtained.

A full assignment of the spectrum follows from spectra recorded with variable ratios of the reactants. Consider a 2 : 1 mixture of $[MA_3]$ and $[MB_3]$; a statistical mixture will contain the species $[MA_3]$, $[MA_2B]$, $[MAB_2]$ and $[MB_3]$ in the ratio 8 : 12 : 6 : 1. For any given proton in ligand A, we expect four signals, corresponding to $[MA_3]$, the two environments in $[MA_2B]$ and $[MAB_2]$. The intensities for a proton from ligand A in the mixture of $[MA_3]$, $[MAB_2]$, $[MA_2B]$ and $[MB_3]$ is given by (number of A ligands × statistical weighting × proton weighting) which yields ratios ($[MA_3]$ $3 \times 8 \times 2 = 48$) : ($[MAB_2]$ $1 \times 6 \times 2 = 12$) : ($[MA_2B]$ $2 \times 12 \times 1 = 24$ and $2 \times 12 \times 1 = 24$) : ($[MB_3]$ $= 0$); in other words, every proton

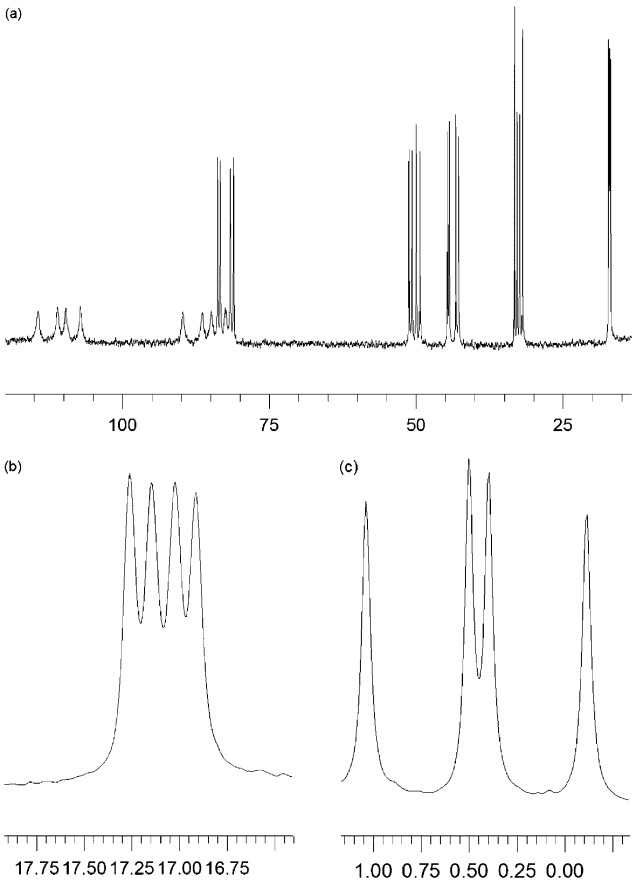


Fig. 3 (a) Sections of the 250 MHz ^1H NMR spectrum at 298 K of a 1 : 1 mixture of 5 mM CD_3CN solutions of the complexes $[Co(phen)_3][PF_6]_2$ and $[Co(Me_2bpy)_3][PF_6]_2$ showing how four peaks are obtained for a given ligand proton. Sections (b) and (c) show the splitting of phen H_4 and Me_2bpy methyl signals, respectively. Chemical shifts in δ/ppm

from A and B should give four signals in a 4 : 2 : 2 : 1 ratio. Once again, we discuss the case of the $[Co(Me_2bpy)_3][PF_6]_2$ and $[Co(phen)_3][PF_6]_2$ mixture in detail, but a similar analysis is made for the other binary combinations. Spectra were recorded with 1 : 2 and 2 : 1 mixtures of $[Co(Me_2bpy)_3][PF_6]_2$ and $[Co(phen)_3][PF_6]_2$. We now consider the phen H_4 signals in detail to clarify the analysis (Fig. 4). In the 1 : 1 mixture, four peaks of equal intensity are observed at δ 17.29, 17.18, 17.06 and 16.96 ppm. The peak at δ 17.29 ppm corresponds to the single peak observed in pure $[Co(phen)_3][PF_6]_2$ and may be assigned to this species. In the 1 : 2 $[Co(Me_2bpy)_3][PF_6]_2$–$[Co(phen)_3][PF_6]_2$ mixture, the four peaks are observed in a 4 : 2 : 2 : 1 ratio of intensities. It follows immediately that the δ 17.29 ppm is from $[Co(phen)_3][PF_6]_2$, the 17.18 and 17.06 peaks to the non-equivalent rings of the phen in $[Co(phen)_2(Me_2bpy)][PF_6]_2$ and the δ 16.96 ppm peak to $[Co(phen)(Me_2bpy)_2][PF_6]_2$. Final confirmation comes from the 2 : 1 $[Co(Me_2bpy)_3][PF_6]_2$–$[Co(phen)_3][PF_6]_2$ mixture, in which the four peaks are observed in a 1 : 2 : 2 : 4 ratio of intensities. Additional information regarding assignments and the establishment of statistical distributions of complexes in the libraries comes from the ^1H NMR spectra of solutions containing the parent complexes in a 3 : 1 ratio. In this case,

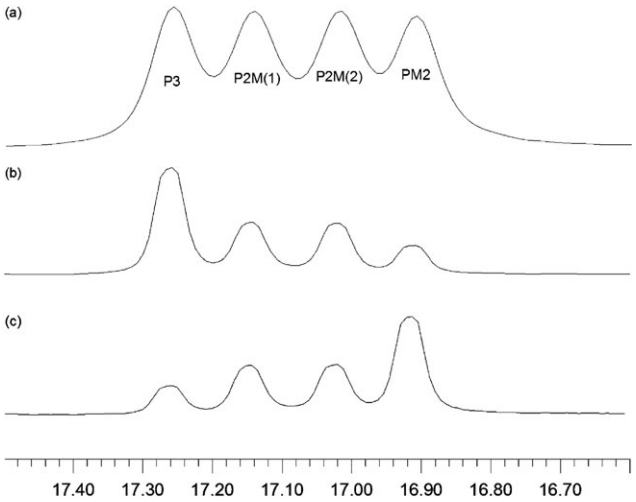


Fig. 4 The phen H_4 signals observed in (a) 1 : 1 (b) 1 : 2 and (c) 2 : 1 mixtures of $[Co(Me_2bpy)_3][PF_6]_2$ and $[Co(phen)_3][PF_6]_2$ (CD_3CN, 298 K, 5 mM in cobalt(II) 250 MHz). The abbreviations P3, P2M and PM2 refer to the signals from the species $[Co(phen)_3]^{2+}$, $[Co(phen)_2(Me_2bpy)]^{2+}$ and $[Co(phen)(Me_2bpy)_2]^{2+}$. There are two environments for the phen in the P2M species. Chemical shifts in δ/ppm.

the expectation values for a 3 : 1 mixture of $[MA_3]$ and $[MB_3]$ are 27 : 27 : 9 : 1 ratio of $[MA_3]$, $[MA_2B]$, $[MAB_2]$ and $[MB_3]$. Applying the weighting scheme for the number of protons in each compound, we predict that each proton of each ligand will give rise to four signals in a 9 : 3 : 3 : 1 ratio. This is illustrated for the methyl protons of a 3 : 1 mixture of $[Co(Me_2bpy)_3][PF_6]_2$–$[Co(phen)_3][PF_6]_2$ in Fig. 5; within experimental error, the expected 9 : 3 : 3 : 1 ratio of peaks is obtained.

In the MA_2B complexes, each proton of the A ligand gives rise to two signals and two sub-spectra are obtained which can

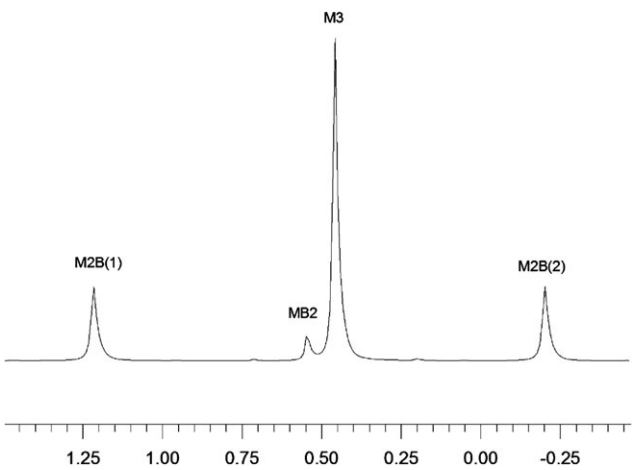


Fig. 5 The resonances of the methyl protons in a 3 : 1 mixture of $[Co(Me_2bpy)_3][PF_6]_2$ and $[Co(phen)_3][PF_6]_2$. The solution is in CD_3CN at 298 K and is 5 mM in cobalt(II) and was recorded on a 250 MHz instrument; within experimental error, the expected 9 : 3 : 3 : 1 ratio of peaks is obtained. The abbreviations M3, M2B and MB2 refer to the species $[Co(Me_2bpy)_3]^{2+}$, $[Co(Me_2bpy)_2(bpy)]^{2+}$ and $[Co(Me_2bpy)(bpy)_2]^{2+}$, respectively. There are two environments for Me_2bpy in the M2B species. Chemical shifts δ/ppm.

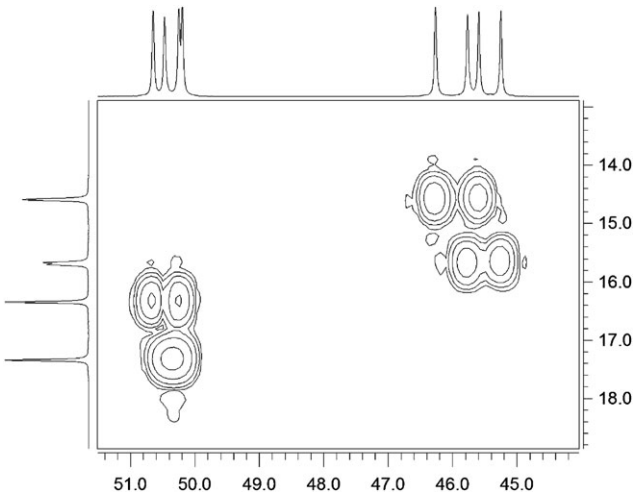


Fig. 6 Part of the 500 MHz ^1H–^1H COSY spectrum of a 1 : 1 mixture of $[Co(bpy)_3][PF_6]_2$ and $[Co(phen)_3][PF_6]_2$ showing the correlation of the phen H_3 and bpy H_5 protons with bpy and phen H_4 signals The solution is in CD_3CN at 298 K and is 5 mM in cobalt(II). Chemical shifts in δ/ppm

be further assigned using COSY spectroscopy of the 1 : 1 mixtures.[31] It is not possible to completely assign these to rings trans to A or B through NOSY spectroscopy, as exchange cross-peaks will also be obtained.[31] The signals for the H_6 protons of bpy and Me_2bpy and the $H_{2,9}$ protons of phen are too broad and show no detectable cross-peaks in the COSY spectrum. The COSY technique is illustrated in Fig. 6, which shows the correlation of the phen H_3 and bpy H_5 protons with bpy and phen H_4 signals. The final assignments for the binary combinations are presented in Table 2.

It follows from the statistical distribution of complexes, that the dimensionless equilibrium constant for the equilibration reaction

$$CoA_3 + CoB_3 = CoA_2B + CoB_2A$$

given by

$$K = \frac{[CoA_2B][CoB_2A]}{[CoA_3][CoB_3]}$$

will be $(3)^2/(1)^2 = 9$.

Three ligands. The analysis for an equilibrium mixture of three ligands A, B and C is presented in Fig. 7, and indicates both the number of species and the contribution to the equilibrium mixture on statistical grounds. A total of ten chemical species are present; of these ten species, only the heteroleptic complex [MABC] will give rise to signals in the ^1H NMR spectrum which have not already been observed in the binary mixtures. At statistical equilibrium, a 1 : 1 : 1 : 3 : 3 : 3 : 3 : 3 : 3 : 6 mixture of species is expected, of which the minor components with relative concentration 1 are the homoleptic compounds, the species of intensity 3 are the various binary complexes and the dominant component is the heteroleptic compound [MABC]. In the heteroleptic compound, each ring of each ligand is magnetically independent. Once again, the analysis will be given in detail considering a pair of protons

Table 2 500 MHz ^{1}H NMR spectra (295 K) of CD_3CN solutions of complexes (B = bpy, M = Me_2bpy or P = phen). Chemical shifts δ/ppm

	B				M				P			
	H_5	H_4	H_3	H_6	H_5	H_3	Methyl	H_2	H_3	H_4	H_5	
BBB	88.0	46.25	14.58	84.48								
MMM					89.74	44.50	81.52	0.40				
PPP									107.20	50.18	17.33	33.43
BBP	84.5[a]	45.57	14.58	86.58					113.7	50.64	16.33	31.73
	83.9[a]	45.76	15.69	86.16						—		
PPB	80.9	45.24	15.66	88.13					110.7[a]	50.46	17.33	32.64[a]
									110.0[a]	50.23	16.33	32.58[a]
MBB	88.6/88.0	47.32	15.32	85.51	87.10	44.31	80.71	0.50				
	88.6/88.0	45.31	14.53	84.26								
MMB	90.7	46.41	15.26	85.28	89.5/88.8	43.39[a]	81.73	1.16[a]				
					89.5/88.8	45.38[a]	80.51	−0.25[a]				
PMM					86.4	44.79[a]	83.78	1.06	114.8	50.89	17.00	32.06
					84.9	42.89[a]	82.06	−0.12[a]				
MPP					82.5	43.35[a]	84.22	0.49	111.5[a]	51.40	17.10	33.01[a]
									110.0[a]	49.51	17.22	32.52[a]

[a] Assignment to individual subsystem is ambiguous.

that are chemically and magnetically equivalent in free ligand A. Ligand A is present in six of the ten species; in $[MA_3]$, $[MAB_2]$ and $[MAC_2]$ the two rings of A remain in identical environments and each species will give a single A resonance, whereas in $[MA_2B]$, $[MA_2C]$ and [MABC] the rings are inequivalent and each A ligand will give rise to two resonances. Thus each chemically unique proton in the free ligand A will give a total of nine resonances.

The intensities of the resonances again follow from the statistics and the number of ligands present in each of the species and is illustrated considering ligand A. As shown above, nine resonances are expected for any proton from A: one each from $[MA_3]$, $[MAC_2]$ and $[MAB_2]$, and two each from $[MA_2B]$, $[MA_2C]$ and [MABC]. The intensities in a statistical mixture of $[MA_3]$, $[MAB_2]$, $[MAC_2]$, $[MA_2B]$, $[MA_2C]$ and [MABC] will be $(3 \times 1 \times 2 = 6) : (1 \times 3 \times 2 = 6) : (1 \times 3 \times 2 = 6) : (2 \times 3 \times 1 = 6) + (2 \times 3 \times 1 = 6) : (2 \times 3 \times 1 = 6) + (2 \times 3 \times 1 = 6) : (1 \times 6 \times 1 = 3)$. Every proton from A (and by a similar analysis every proton from B and C) should give nine signals of equal intensity.

The only new signals which have not been observed in the binary mixtures are the two assigned to the non-equivalent rings of each ligand in $[Co(bpy)(phen)(Me_2bpy)]^{2+}$. Fig. 8(a)–(c) present parts of the ^{1}H NMR spectra of the ternary mixture and clearly show the occurrence of eight peaks for every chemically unique proton in the ligand. The assignment presented in Table 3 follows from a COSY spectrum of the ternary mixture.

The 1 : 1 : 1 : 3 : 3 : 3 : 3 : 3 : 3 : 6 statistical distribution of complexes, according to the equation

$$7CoA_3 + 7CoB_3 + 7CoC_3 = 3CoA_2B + 3CoB_2A + 3CoA_2C + 3Co\,AC_2 + 3CoB_2C + 3CoBC_2 + 3CoABC$$

leads to an equilibrium constant given by

$$K = \frac{[CoA_2B]^3[CoAB_2]^3[CoA_2C]^3[CoAC_2]^3[CoB_2C]^3[CoBC_2]^3[CoABC]^3}{[CoA_3]^7[CoB_3]^7[CoC_3]^7}$$

and numerically equal to $(27)^6 \times (6)^3/1 = 8.37 \times 10^{10}$.

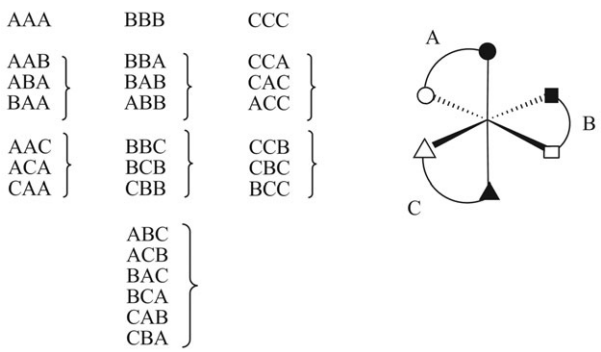


Fig. 7 Statistical equilibration of $[MA_3]$, $[MB_3]$ and $[MC_3]$ will give a 1 : 1 : 1 : 3 : 3 : 3 : 3 : 3 : 3 : 6 mixture of $[MA_3]$, $[MB_3]$, $[MC_3]$, $[MA_2B]$, $[MAB_2]$, $[MAC_2]$, $[MA_2C]$, $[MB_2C]$, $[MBC_2]$ and [MABC]. In [MABC] each ring of each ligand is magnetically inequivalent.

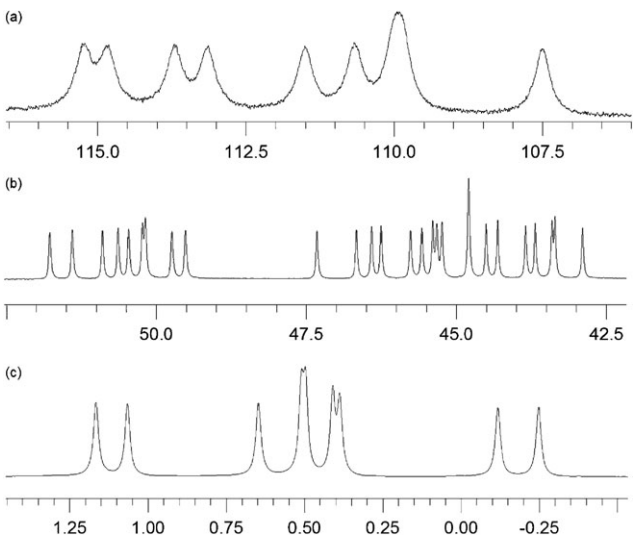
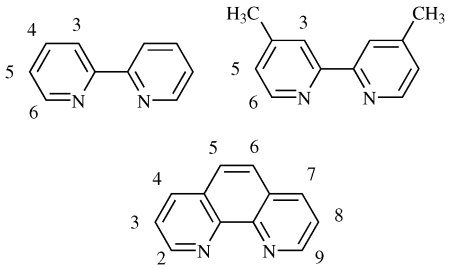


Fig. 8 Sections of the 500 MHz ^{1}H NMR spectrum at 295 K of a 1 : 1 : 1 mixture of 5 mM CD_3CN solutions of the complexes $[Co(phen)_3][PF_6]_2$, $[Co(bpy)_3][PF_6]_2$and $[Co(Me_2bpy)_3][PF_6]_2$ showing how nine peaks are obtained for a given ligand proton; (a) the phen H_2 signals (b) the phen H_3, bpy H_5 and Me_2bpy H_5 signals and (c) the methyl signals of Me_2bpy, respectively. Chemical shifts in δ/ppm.

Table 3 Assignment of the ternary complex $[Co(bpy)(Me_2bpy)(phen)]^{2+}$ in a 1 : 1 : 1 mixture of 5 mM CD_3CN solutions of the complexes $[Co(phen)_3][PF_6]_2$, $[Co(bpy)_3][PF_6]_2$ and $[Co(Me_2bpy)_3][PF_6]_2$ as determined from the 500 MHz ^1H and ^1H–^1H COSY NMR spectra. The numbering scheme refers to the bpy ligands, with the equivalent or unique protons of the phen denoted in parentheses. Each chemically unique proton within the ligands gives rise to two signals in the ternary complex. These are grouped in subspectra, but cannot be correlated between ligands. Chemical shifts δ/ppm



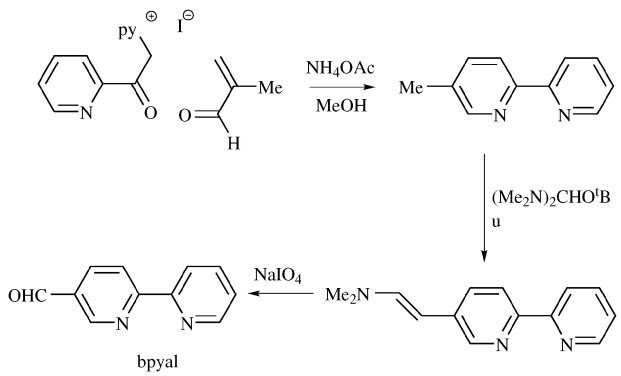
L	$H_6(H_2)$	$H_5(H_3)$	H_4	$H_3(H_{5,6})$	Methyl
Bpy	87.96	46.66	15.32	87.58	
		44.79	15.59	85.91	
Me_2bpy	89.74	43.84[a]		82.79[a]	0.38[a]
		43.68[a]		82.30[a]	0.64[a]
Phe	115.2[a]	51.77	17.07	32.00[a]	
	113.1[a]	49.74	16.25	31.69[a]	

[a] Assignment to individual sub-spectrum ambiguous.

Asymmetric ligands—*mer* and *fac* isomers

Although the establishment of the libraries with the cobalt(II) complexes is elegant, it serves no significant purpose if the information cannot be read-out or the distribution of species within the library cannot be altered by external constraints. Accordingly, we have extended the studies to systems containing functional groups which can react in subsequent steps. Initially, we considered the use of the monofunctionalised bpy ligand, 2,2′-bipyridine-5-carbaldehyde, bpyal.

The ligand bpyal[68–75] was prepared in a two-step procedure in which the known compound 5-methyl-2,2′-bipyridine[76] was converted to the *N*,*N*′-dimethylaminovinyl derivative by reaction with Bredereck's reagent and then oxidised to bpyal with sodium periodate (Scheme 1) in a reaction sequence directly analogous to the one we have reported for the synthesis of 2,2′-bipyridine-4-carbaldehyde.[77]



Scheme 1 Synthesis of 2,2′-bipyridine-5-carbaldehyde.

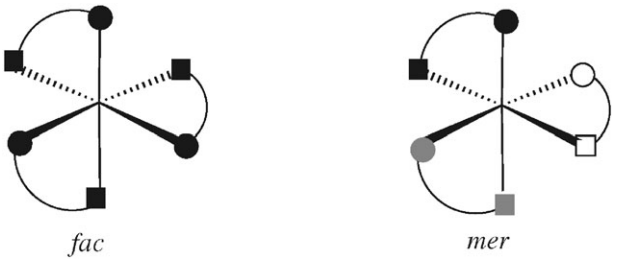


Fig. 9 The *mer* and *fac* stereoisomers of a complex containing three 2,2′-bipyridine-5-carbaldehyde ligands. The colouring (black, grey or white) indicates the three chemically and magnetically inequivalent ligands in the *mer* diastereomer.

In the case of the asymmetrical ligand bpyal, the speciation involves the formation of *mer* and *fac* stereoisomers of the tris complex (Fig. 9). For a complex of the type $[ML_3]$ with chelating bidentate ligands, a statistical distribution of 1 : 3 *fac* : *mer* is expected.[78]

In the *fac* stereoisomer, each chemically unique proton will give a single signal as all three ligands are chemically and magnetically equivalent, whereas in the *mer* stereoisomer each chemically unique proton of each ligand is in a magnetically unique environment. Using our usual analysis, with the expectation ratio of 1 : 3 *fac* : *mer*, the intensities in a statistical mixture of *fac* and *mer* $[MA_3]$ will be $(1 \times 3 = 3) : (3 \times 1 = 3) + (3 \times 1 = 3) + (3 \times 1 = 3)$. Every proton will give four signals of equal intensity. Fig. 10 presents regions of the 500 MHz ^1H NMR spectrum of the mixture of *mer* and *fac* complexes. It is immediately evident that all signals are present in sets of four of equal intensity.

The ^1H NMR spectrum of the *mer*/*fac* mixture consists of a number of sets of four signals (Fig. 10(a)–(c)). Eight broad signals (δ 105.5, 99.3, 96.4, 91.4, 90.9, 86.0, 84.5 and 79.6 ppm) are assigned to H_6 and $H_{6'}$ (Fig. 10(a)); no COSY or NOESY peaks are observed and further assignment was not possible. A set of eight peaks in the range δ 74–92 ppm (Fig. 10(a)) are assigned to H_3 and $H_{3'}$, whilst four peaks between δ 51.80, 51.67, 46.39 and 46.29 ppm (Fig. 10(b)) are assigned to $H_{5'}$. A remaining set of 12 signals in the range δ 19–7 ppm (Fig. 10(c)) are due to H_4, $H_{4'}$ and the aldehyde CHO protons. A more detailed assignment follows from the ^1H–^1H COSY spectrum. Although the resonances of the H_6 and $H_{6'}$ protons are too broad to show any detectable COSY cross peaks, the remaining *J*-coupled signals do, even though the line-width is so great that no coupling is observed in the 1D spectra. Commencing with the twelve peaks in the range 19–7 ppm, the four peaks at δ 13.71, 10.97, 9.66 and 7.24 ppm show no cross peaks and are assigned to the aldehyde protons. Of the remaining eight signals, four show cross peaks to the $H_{5'}$ signals and are unambiguously assigned to $H_{4'}$ (Fig. 11(a)). Similarly, the H_3 and $H_{3'}$ signals may be unambiguously correlated with the H_4 and $H_{4'}$ signals (Fig. 11(b)). The full assignment of the spectrum is given in Table 4.

Although the statistical distribution of complexes is strong evidence for a dynamic equilibrium between *mer* and *fac* stereoisomers, we have established the dynamic equilibrium through the use of EXCSY spectroscopy in a similar manner to that demonstrated for electron exchange between cobalt(II)

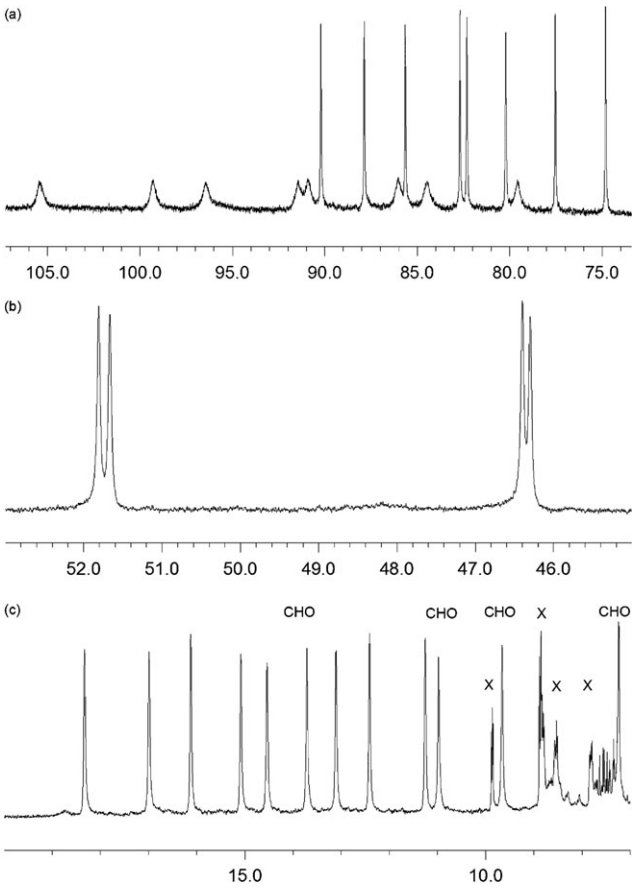


Fig. 10 Regions of the 500 MHz ^{1}H NMR spectrum of a CD_3CN solution of the statistical mixture of diastereoisomeric *mer* and *fac* complexes $[Co(\mathbf{I})_3]^{2+}$; (a) shows the eight broad signals arising from the H_6 and $H_{6'}$ and the eight sharper signals from H_3 and $H_{3'}$, (b) presents the four signals from H_5 and (c) shows the twelve signals arising from H_4, $H_{4'}$ and the aldehyde, with the latter signals denoted. Chemical shifts in δ/ppm.

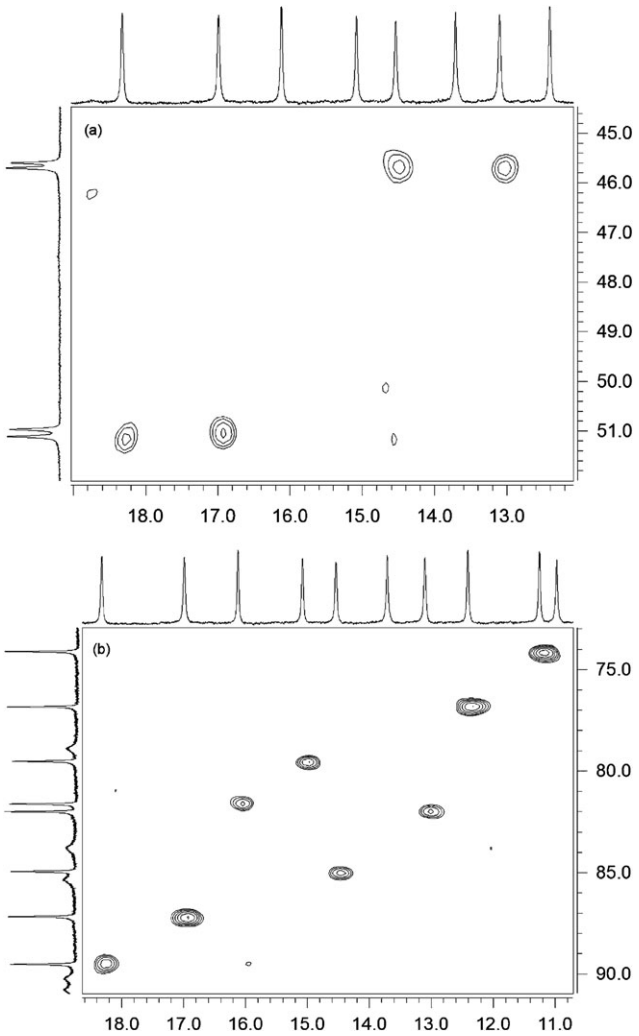


Fig. 11 500 MHz ^{1}H–^{1}H COSY spectra (295 K, CD_3CN) correlating the H_4 and $H_{4'}$ signals with $H_{5'}$, H_3 and $H_{3'}$ in the mixture of *mer* and *fac* stereoisomers of $[Co(\mathbf{I})_3]^{2+}$. Chemical shifts in δ/ppm.

and cobalt(II) terpy complexes.[56] The standard NOESY (noesytgp) spectrum of the mixture of *mer* and *fac* isomers exhibited EXCSY cross peaks corresponding to chemical exchange but no detectable NOESY peaks. This is illustrated in Fig. 12 which shows the region of the H_3 protons and demonstrates that every H_3 proton shows an exchange peak with every other H_3 environment; in other words, the ligand exchange is occurring both between the *mer* and *fac* isomers and between the three sites of the *mer* isomer.

Amplification—selective reaction and interconversion of *mer* and *fac* isomers

We now have a system which fulfills the prerequisites for a dynamic combinatorial library—two reactive aldehyde complexes in dynamic equilibrium with one another. Both 2,2′-bipyridine-5-carbaldehydes and 2,2′-bipyridine-5,5′-carbaldehydes[50] are known to react with tris(2-aminoethyl)amine (tren) to give open-chain (cap) or encapsulating ligands, respectively[73,79,80] and we planned to use this reaction to amplify the library of complexes.

Modelling and the known crystallographic data for the tris(imines) confirmed the expectation that only the minor

Table 4 Assignment of the 295 K 500 MHz ^{1}H NMR spectrum of a CD_3CN solution of the mixture of *mer* and *fac* $[Co(bpyal)_3]^{2+}$ complexes. The spin systems A to C for the (H_3/H_4) and the ($H_{3'}$/$H_{4'}$/$H_{5'}$) are not correlated with one another and the aldehyde, H_6 and $H_{6'}$ proton groups are not correlated with the other groups as they are either too broad or show no NOE cross peaks. The groups of peaks are assigned from COSY spectra but cannot be unambiguously attributed to particular rings in particular complexes. Chemical shifts δ/ppm

	A	B	C	D
H_3	82.31	80.20	77.53	74.80
H_4	16.12	15.08	12.41	11.25
$H_{3'}$	90.20	87.86	85.64	82.68
$H_{4'}$	18.32	16.99	14.54	13.10
$H_{5'}$	51.80	51.66	46.29	46.39
$H_{6,6'}$	105.5, 99.3, 96.43, 91.4, 90.9, 86.0, 84.5, 79.6			
CHO	13.71, 10.97, 9.66, 7.24			

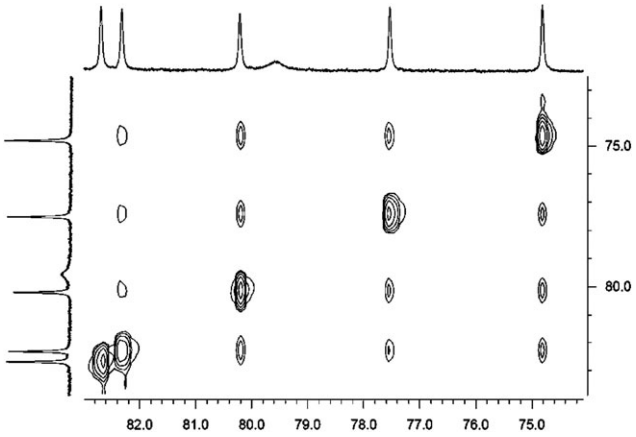
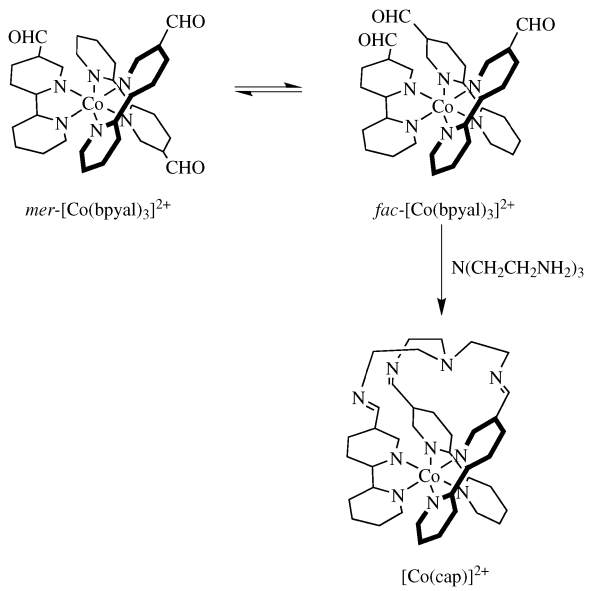


Fig. 12 Part of the ^1H–^1H NOESY spectrum of a CD_3CN solution of a mixture of *mer* and *fac* $[Co(bpyal)_3]^{2+}$ complexes showing the exchange of all four H_3 environments. Chemical shifts in δ/ppm.

component *fac* stereoisomer can react with tren and the consequence will be conversion of *mer* isomer to *fac* to return to equilibrium (Scheme 2).

The addition of one equivalent of tris(2-aminoethyl)amine to the equilibrium mixture of *mer* and *fac* $[Co(bpyal)_3]^{2+}$ complexes resulted in the immediate loss of all ^1H NMR signals of these compounds and the development of the spectrum of a new paramagnetically shifted species.

Before discussing the formation of $[Co(cap)]^{2+}$ we make an observation and describe a separate series of experiments. First, we note that the solutions of $[Co(bpyal)_3]^{2+}$ contained no free bpyal, which has a characteristic resonance in CD_3CN solution at δ 10.2 ppm assigned to the aldehyde proton. At first sight, complexes related to $[Co(bpy)_3]^{2+}$ (with $\log\beta_3$ 15.82–17.59[59–66]) are expected to be stable with respect to displacement by tren ($\log K_1$ 12.4–14.7[81–90]). However inspection reveals that this may not strictly true. Firstly, complexes



Scheme 2 Amplification of the library of *mer* and *fac* stereoisomers of $[Co(bpyal)_3]^{2+}$ by reaction with tren to give $[Co(cap)]^{2+}$.

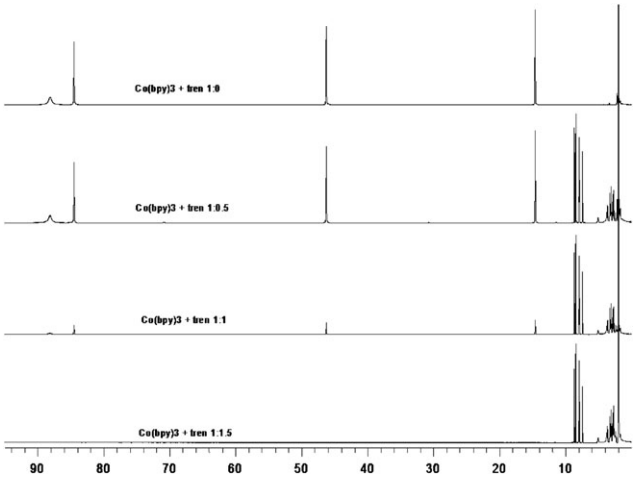


Fig. 13 250 MHz ^1H NMR spectra (in CD_3CN) of $[Co(bpy)_3][PF_6]_2$ before and after the addition of different equivalents of tren. Chemical shifts in δ/ppm.

of bpyal are likely to be less stable than those of bpy as they have an electron-withdrawing substituent and secondly, when the stability constants are expressed in conventional concentration units, β_3 and K ($= \beta_1$) have units of mol^{-3} L^3 and mol^{-1} L (or mol^3 L^{-3} and mol^2 L^{-2} if acetonitrile solvent is explicitly included), respectively and they are dimensionally incommensurate. Accordingly, we investigated the worst case by titrating tren into a CD_3CN solution of $[Co(bpy)_3]^{2+}$ (Fig. 13). After the addition of half an equivalent of tren to the solution, the ^1H NMR spectrum shows resonances assigned to $[Co(bpy)_3]^{2+}$, free bpy and a tren complex. After the addition of 1.5 equivalents of tren, the solution contains no $[Co(bpy)_3]^{2+}$. These results indicate that the desired capping reaction with tren is likely to compete with the displacement of the bpyal by tren.

The ^1H NMR spectra of the mixtures with the complex to template ratios 1 : 0.5, 1 : 1 and 1 : 1.6 are shown in Fig. 14. After the addition of half an equivalent of tren, new paramagnetically shifted signals in addition to the starting mixture

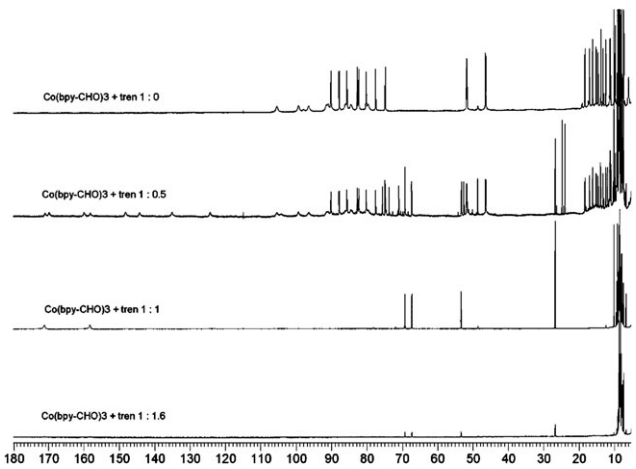
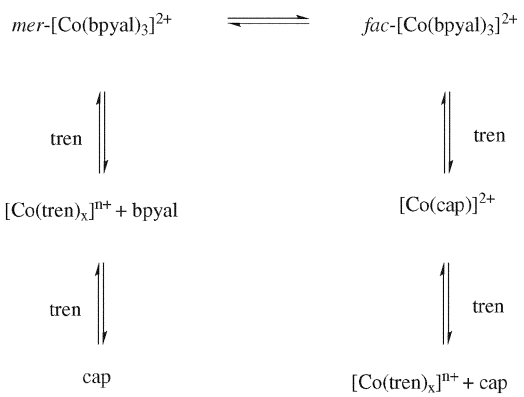


Fig. 14 250 MHz ^1H NMR spectra of the paramagnetically shifted region of equilibrated solutions of $[Co(bpy\text{-}CHO)_3][PF_6]_2$ in CD_3CN before and after addition of tren. Chemical shifts in δ/ppm.

of *mer* and *fac* isomers of the bpyal complex ar observed. The chemical shift of the most downfield peaks ($\delta > 170$ ppm) is typical of high-spin cobalt(II) solution species.[63] It was therefore assumed that whatever new species had formed, the spin state of the central cobalt(II) had changed from low-spin to high-spin. After the addition of one equivalent of tren, the ^{1}H NMR spectrum showed that all signals of the starting bpyal complex had disappeared and a single new paramagnetic species was present. This showed a pattern of NMR signals typical of a high spin cobalt(II) complex with signals at δ 171, 158, 69.2, 67.2, 53.3, 26.7, 9.35, 8.83 ppm together with peaks assigned to the aliphatic protons. The interpretation is that the tren reacted with the *fac* isomer of $[Co(bpy\text{-}CHO)_3]^{2+}$ and formed the cap complex, driving the dynamic library to form a single complex through the conversion of *mer* bpyal complex to the *fac* isomer, which then subsequently reacts with additional tren. COSY spectra allowed the assignment of the paramagnetically shifted peaks as follows: $H_{6/6'}$ δ 171/158 ppm, $H_{6/6'}$ δ 171/158 ppm, $H_{3'}$ δ 69.2 ppm, H_3 δ 67.2 ppm, $H_{5'}$ δ 53.3 ppm, $H_{4'}$ δ 9.35 ppm, H_4 δ 8.83 ppm, N=C*H* δ 26.7 ppm.

As anticipated, competition between imine formation and ligand displacement does complicate the reaction. The ^{1}H NMR spectrum in the region δ 1–11 ppm is complicated, but contains peaks in the "normal" aromatic region in addition to poorly resolved signals assigned to tren and tren complexes. Comparison with known standards revealed that these peaks corresponded to free bpyal and possibly free cap. This is compatible with the observations made with bpy. Even after the addition of 0.5 equivalents of tren, there is a significant concentration of free bpyal (δ 10.2 ppm).

We have not investigated the speciation in the reaction of $[Co(bpyal)_3]^{2+}$ with tren at all concentrations in detail, but we may make a number of comments. In the presence of excess tren, the only cobalt-containing species are tren complexes. The solutions containing $[Co(bpyal)_3]^{2+}$ and tren at a 1 : 1 ratio contain $[Co(cap)]^{2+}$ and free bpyal. The solutions containing $[Co(bpyal)_3]^{2+}$ and tren at a 1 : 1.6 or greater ratio contain no $[Co(cap)]^{2+}$, $[Co(bpyal)_3]^{2+}$ or free bpyal. Integration of the ^{1}H NMR spectrum of a 1 : 1 $[Co(bpyal)_3]^{2+}$ to tren solution revealed that the ratio of the δ 26.7 ppm peak to that of the δ 10.2 ppm peak (*i.e.* the $[Co(cap)]^{2+}$ complex to the free bpyal) was 1 : 3. Over hours to days, the spectrum of bpyal is replaced by a new species identified as free cap. From this we may construct the scheme presented in Scheme 3 and we see that the apparent amplification of the *mer* and *fac* library in the reaction of $[Co(bpyal)_3]^{2+}$ with tren is actually a destructive process in which the *mer* compound is lost in a competing reaction. Specifically, we see that the capping reaction occurs selectively with the *fac* isomer to give $[Co(cap)]^{2+}$. However, the displacement of bpyal from *mer*-$[Co(bpyal)_3]^{2+}$ by tren is faster than the interconversion of *mer*-$[Co(bpyal)_3]^{2+}$ to *fac*-$[Co(bpyal)_3]^{2+}$.



Scheme 3 Amplification of the library of *mer* and *fac* stereoisomers of $[Co(bpyal)_3]^{2+}$ by reaction with tren to give $[Co(cap)]^{2+}$, bpyal and cap through reaction of the stereoisomers in different pathways.

Conclusions

We have shown that ^{1}H NMR spectroscopy is a powerful technique for the analysis of libraries of paramagnetic cobalt(II) complexes. The establishment of a dynamic library with the ligand bpyal has been demonstrated by the use of EXCSY spectroscopy. The amplification of the library occurs by reaction of the *fac*-$[Co(bpyal)_3]^{2+}$ to give $[Co(cap)]^{2+}$ whilst the *mer*-$[Co(bpyal)_3]^{2+}$ reacts to give bpyal and cobalt(II)–tren complexes.

Acknowledgements

We thank the University of Basel and the Swiss National Science Foundation for financial support. We particularly wish to thank Professor Andreas Zuberbühler for numerous helpful discussions in the course of this work and Drs K. Kulicke, V. Jullien and A. Mahmood for measurement of ^{1}H NMR spectra.

References

1 *Comprehensive Supramolecular Chemistry*, ed. J. L. Atwood, J. E. D. Davies, D. D. MacNicol and F. Vögtle, Pergamon Press, Oxford, 1996, vol. 9.
2 G. F. Swiegers and T. J. Malefetse, *Chem. Rev.*, 2000, **100**, 3483.
3 G. F. Swiegers and T. J. Malefetse, *Chem.–Eur. J.*, 2001, **7**, 3637.
4 G. F. Swiegers and T. J. Malefetse, *Coord. Chem. Rev.*, 2002, **225**, 91.
5 E. C. Constable, *Metals and Ligand Reactivity*, VCH, Weinheim, 1995.
6 E. C. Constable, *Chem. Ind. (London)*, 1994, 56.
7 O. Costisor and W. Linert, *Rev. Inorg. Chem.*, 2003, **23**, 289.
8 M. Fujita, *Chem. Soc. Rev.*, 1998, **27**, 417.
9 C. J. Jones, *Chem. Soc. Rev.*, 1998, **27**, 289.
10 V. G. Machado, A. S. Mangrich and J.-M. Lehn, *J. Braz. Chem. Soc.*, 2003, **14**, 777.
11 G. R. Newkome, E. F. He and C. N. Moorefield, *Chem. Rev.*, 1999, **99**, 1689.
12 V. Balzani and A. Juris, *Coord. Chem. Rev.*, 2001, **211**, 97.
13 A. M. Juris, A. M. Venturi, P. Ceroni, V. Balzani, S. Campagna and S. Serroni, *Collect. Czech. Chem. Commun.*, 2001, **66**, 1.
14 S. Kelch and M. Rehahn, *Chem. Commun.*, 1999, 1123.
15 S. Kelch and M. Rehahn, *Macromolecules*, 1999, **32**, 5818.
16 E. C. Constable, in *Comprehensive Coordination Chemistry II Chemistry*, ed. J. A. McCleverty and T. J. Meyer, Elsevier, Oxford, 2003.
17 E. C. Constable, *Chem. Commun.*, 1997, 1073.
18 E. C. Constable and A. M. W. Cargill Thompson, *J. Chem. Soc., Dalton Trans.*, 1995, 1615.
19 E. C. Constable, P. Harverson and C. E. Housecroft, *J. Chem. Soc., Dalton Trans.*, 1999, 3693.
20 E. C. Constable, P. Harverson and M. Oberholzer, *Chem. Commun.*, 1996, 1821.

21 E. C. Constable, C. E. Housecroft, V. Jullien, M. Neuburger and S. Schaffner, *Inorg. Chem. Commun.*, 2006, **9**, 504.
22 E. C. Constable, C. E. Housecroft, M. Neuburger, S. Schaffner and L. J. Scherer, *Dalton Trans.*, 2004, 2635.
23 E. C. Constable, *Coord. Chem. Rev.*, submitted.
24 *Combinatorial Chemistry. A Practical Approach*, ed. H. Fenniri, OUP, Oxford, 2000.
25 *Combinatorial Chemistry. A Practical Approach*, ed. W. Bannwarth and E. Felder, Wiley-VCH, Weinheim, 2000.
26 M. S. Goodman, V. Jubian and A. D. Hamilton, *Tetrahedron Lett.*, 1995, **36**, 2551.
27 Goodman, A. D. Hamilton and J. Weiss, *J. Am. Chem. Soc.*, 1995, **117**, 8447.
28 J.-M. Lehn, *Chem.–Eur. J.*, 1999, **5**, 2455.
29 P. A. Brady and J. K. M. Sanders, *J. Chem. Soc., Perkin Trans. 1*, 1997, 3237.
30 I. Huc and J.-M. Lehn, *Proc. Natl. Acad. Sci. USA*, 1997, **94**, 2106.
31 L. J. Prins, P. Timmerman and D. N. Reinhoudt, *Pure Appl. Chem.*, 1998, **70**, 1459.
32 M. Albrecht, *J. Incl. Phenom. Macrocycl. Chem.*, 2000, **36**, 127.
33 D. M. Epstein, S. Choudhary, M. R. Churchill, K. M. Keil, A. V. Eliseev and J. R. Morrow, *Inorg. Chem.*, 2001, **40**, 1591.
34 I. Saur, R. Scopelliti and K. Severin, *Chem.–Eur. J.*, 2006, **12**, 1058.
35 R. L. E. Furlan, Y. F. Ng, S. Otto and J. K. M. Sanders, *J. Am. Chem. Soc.*, 2001, **123**, 8876.
36 T. Haino, H. Mitsuhashi, Y. Ishizu and Y. Fukazawa, *Tetrahedron Lett.*, 2006, **47**, 7915.
37 N. Giuseppone, J. L. Schmitt and J.-M. Lehn, *J. Am. Chem. Soc.*, 2006, **128**, 16748.
38 C. Gennari, C. Monti and U. Piarulli, *Pure Appl. Chem.*, 2006, **78**, 303.
39 J. G. de Vries and L. Lefort, *Chem.–Eur. J.*, 2006, **12**, 4722.
40 A. Buryak and K. Severin, *J. Comb. Chem.*, 2006, **8**, 540.
41 C. Monti, C. Gennari, U. Piarulli, J. G. de Vries, A. H. M. de Vries and L. Lefort, *Chem.–Eur. J.*, 2005, **11**, 6701.
42 F. Dumitru, E. Petit, A. van der Lee and M. Barboiu, *Eur. J. Inorg. Chem.*, 2005, 4255.
43 P. Dastidar, S. Okabe, K. Nakano, K. Iida, M. Miyata, N. Tohnai and M. Shibayama, *Chem. Mater.*, 2005, **17**, 741.
44 C. Monti, C. Gennari and U. Piarulli, *Tetrahedron Lett.*, 2004, **45**, 6859.
45 M. Horn, J. Ihringer, P. T. Glink and J. F. Stoddart, *Chem.–Eur. J.*, 2003, **9**, 4046.
46 E. L. Doyle, L. Riera and D. S. Wright, *Eur. J. Inorg. Chem.*, 2003, 3279.
47 K. Severin, *Chem. Commun.*, 2006, 3859.
48 P. J. Corbett, J. Leclaire, L. Vial, K. R. West, J.-L. Wietor, J. K. M. Sanders and S. Otto, *Chem. Rev.*, 2006, **106**, 3652.
49 J. R. Nitschke, *Acc. Chem. Res.*, 2007, **40**, 103.
50 E. C. Constable, C. E. Housecroft, T. Kulke, C. Lazzarini, E. R. Schofield and Y. Zimmermann, *J. Chem. Soc., Dalton Trans.*, 2001, 2864.
51 V. Goral, M. I. Nelen, A. V. Eliseev and J. M. Lehn, *Proc. Natl. Acad. Sci. USA*, 2001, **98**, 1347.
52 M. Hochgurtel, H. Kroth, D. Piecha, M. W. Hofmann, C. Nicolau, S. Krause, O. Schaaf, G. Sonnenmoser and A. V. Eliseev, *Proc. Natl. Acad. Sci. USA*, 2002, **99**, 3382.
53 T. Nishinaga, A. Tanatani, K. C. Oh and J. S. Moore, *J. Am. Chem. Soc.*, 2002, **124**, 5934.
54 E. C. Constable, T. Kulke, M. Neuburger and M. Zehnder, *New J. Chem.*, 1997, **21**, 1091.
55 E. C. Constable, in *Education in Advanced Chemistry, Perspectives in Coordination Chemistry*, ed. A. M. Trzeciak, P. Sobota and J. J. Ziolkowski, University Publishing House, Wydawnictwa Uniwersytetu Wroclawskiego, 2000, vol. 7, p. 159.
56 H. S. Chow, E. C. Constable, C. E. Housecroft, K. J. Kulicke and Y. Q. Tao, *Dalton Trans.*, 2005, 236.
57 F. Krohnke, *Synthesis*, 1976, 1.
58 S. G. Telfer, X. J. Yang and A. F. Williams, *Dalton Trans.*, 2004, 699.
59 G. Anderegg, *Helv. Chim. Acta*, 1963, **46**, 2397.
60 H. Irving and D. Mellor, *J. Chem. Soc.*, 1962, 5222.
61 H. Irving and D. Mellor, *J. Chem. Soc.*, 1962, 5237.
62 H. Schwarz, C. Creutz and N. Sutin, *Inorg. Chem.*, 1985, **24**, 433.
63 P. Langer, S. Fallab and H. Erlenmeyer, *Helv. Chim. Acta*, 1955, **38**, 92.
64 R. Davies and K. Dunning, *J. Chem. Soc.*, 1965, 4168.
65 P. Daniele, G. Ostacoli and V. Zelano, *Ann. Chim. (Rome)*, 1975, **65**, 617.
66 I. Ozherelev, T. Spolitak and D. Palade, *Zh. Neorg. Khim.*, 1992, **37**, 341.
67 D. F. Evans, *J. Chem. Soc.*, 1959, 2003.
68 V. Amendola, L. Fabbrizzi, C. Mangano, A. M. Lanfredi, P. Pallavicini, A. Perotti and F. Ugozzoli, *J. Chem. Soc., Dalton Trans.*, 2000, 1155.
69 J. Polin, E. Schmohel and V. Balzani, *Synthesis*, 1998, 321.
70 S. Leroy, T. Soujanya and F. Fages, *Tetrahedron Lett.*, 2001, **42**, 1665.
71 S. Tanji, T. Shibata, I. Sato and K. Soai, *J. Chem. Soc., Perkin Trans. 1*, 2001, 217.
72 S. Belvedere and R. Breslow, *Bioorg. Chem.*, 2001, **29**, 321.
73 V. Amendola, L. Fabbrizzi, C. Mangano, H. Miller, P. Pallavicini, A. Perotti and A. Taglietti, *Angew. Chem., Int. Ed.*, 2002, **41**, 2553.
74 A. Gonzalez-Cabello, P. Vazquez, T. Torres and D. M. Guldi, *J. Org. Chem.*, 2003, **68**, 8635.
75 R. Prabaharan, R. E. Oakes, N. C. Fletcher and M. Nieuwenhuyzen, *Tetrahedron: Asymmetry*, 2004, **15**, 2527.
76 T. L. J. Huang and D. G. Brewer, *Can. J. Chem.*, 1981, **59**, 1689.
77 E. Figgemeier, L. Merz, B. Hermann, Y. C. Zimmermann, C. E. Housecroft, H.-J. Güntherodt and E. C. Constable, *J. Phys. Chem. B*, 2003, **107**, 1157.
78 A. von Zelewsky, *Stereochemistry of Coordination Compounds*, Wiley, Chichester, 1996.
79 J. de Mendoza, E. Mesa, J.-C. Rodriguez-Ubis, P. Vazquez, F. Vögtle, P. M. Windscheif, K. Risannen, J.-M. Lehn, D. Lilienbaum and R. Ziessel, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 1331.
80 N. Weibel, L. J. Charbonniere and R. F. Ziessel, *J. Org. Chem.*, 2002, **67**, 7876.
81 G. Anderegg and V. Gramlich, *Helv. Chim. Acta*, 1994, **77**, 685.
82 D. A. Buckingham and C. R. Clark, *Inorg. Chem.*, 1994, **33**, 6171.
83 H. A. Gazzaz, N. M. E-Guindi and A. A. El-Awady, *J. Chem. Soc., Dalton Trans.*, 1993, 2313.
84 D. J. Aymes, A. Suifil, E. Collange and M. R. Paris, *Bull. Soc. Chim. Fr.*, 1990, 145.
85 S. A. Bedell and A. E. Martell, *J. Am. Chem. Soc.*, 1985, **107**, 7909.
86 R. J. Motekaitis, A. E. Martell and D. A. Nelson, *Inorg. Chem.*, 1984, **23**, 275.
87 R. J. Motekaitis, A. E. Martell, J.-M. Lehn and E. I. Watanabe, *Inorg. Chem.*, 1982, **21**, 4253.
88 R. M. Jellish and L. C. Thompson, *J. Coord. Chem.*, 1975, **4**, 199.
89 G. McLendon and A. E. Martell, *J. Coord. Chem.*, 1975, **4**, 235.
90 J. E. Prue and G. Schwarzenbach, *Helv. Chim. Acta*, 1950, **33**, 963.