Enantiodifferentiation of chiral cationic cages using trapped achiral BF_4^- anions as chirotopic probes

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The addition of enantiopure TRISPHAT anions to chiral cationic cages of type $[Co_4(L)_6(BF_4)]^{7+}$ leads to the enantiodifferentiation of the ligands of the racemic salts and, even more effectively, of the achiral tetrafluoroborate anion trapped inside.

In recent decades, NMR has evolved as one of the methods of choice for the enantiodifferentiation of chiral substances.[1] Today, there are many useful commercially available or readily prepared chiral derivatizing agents, chiral solvating agents (CSA), chiral lanthanide shift reagents (CLSR) or chiral liquid crystalline (CLC) solvents for the rapid and effective discrimination by NMR of the enantiomers of chiral molecules.[2] Whereas the technique has become routine in synthetic and analytical laboratories, the objects that are studied with these reagents can be unique and the results of the analyses significant.

Two studies illustrate the use of such reagents to probe the chirotopicity of the internal cavity of chiral host molecules. In one instance, Hosseini and coworkers showed that the signal of an achiral cesium cation associated with a chiral racemic borocryptate could be split into two signals in the presence of a CLC (^{133}Cs NMR); this study provides a rare example of peristatic chirality.[3] In another instance, Bartik, Collet and Reisse observed, in the presence of a Eu(III) CLSR, two signals using ^{129}Xe NMR for an achiral neutral Xe atom trapped inside a racemic cryptophane.[4] These studies, which showed the existence of two different local environments for the spherical Cs and Xe atoms inside the cavities in the presence of the chiral NMR agents, were beautiful reminders that any point of a molecule that resides in a chiral environment, whether occupied by an atom or not, is chirotopic and hence susceptible to be detected.[5] This type of dissymmetric distinction of achiral guests inside chiral racemic hosts remains however rare and the two studies above mentioned are, to our knowledge, the only reports of this phenomenon so far. Herein, we report a new example in the enantiodifferentiation of an achiral tetrafluoroborate BF_4^- anion trapped inside two racemic tetrametallic cobalt(II) cages using, as external CSA, enantiopure TRISPHAT anions **1**.[6]

Recently, the synthesis of bridging ligands, **L1** and **L2**, containing two *N*,*N*-bidentate pyrazolyl-pyridine chelating units linked to a central aromatic spacer unit (1,2-phenyl or 2,3-naphthyl, respectively, Fig. 1) was reported.[7] Reactions of these ligands with Co(II) salts, followed by treatment with tetrafluoroborate anions, result in assembly of cage complexes having a 4 : 6 metal : ligand ratio; these complexes have a metal ion at each corner of an approximate tetrahedron, and a bis-bidentate bridging ligand spanning each edge. Of most relevance to the current study are the facts that (i) the central cavity is occupied by one tetrahedral counterion which is tightly bound and does not exchange with external anions on the NMR timescale, and (ii) the tetranuclear complexes are chiral, having *T* symmetry in solution with all four metal centres in each complex having the same tris-chelate configuration. The anionic guest BF_4^- is ideally complementary to the surrounding cage in terms of shape, size, and charge and acts as a template for the cage assembly around it. The tetranuclear complexes $[Co_4(\mathbf{L1})_6(BF_4)]^{7+}$ and $[Co_4(\mathbf{L2})_6(BF_4)]^{7+}$ exist as racemic mixtures of ΔΔΔΔ and ΛΛΛΛ enantiomers, and are thus ideal candidates for a study on the enantiodifferentiation of an achiral anionic guest within a chiral cage.

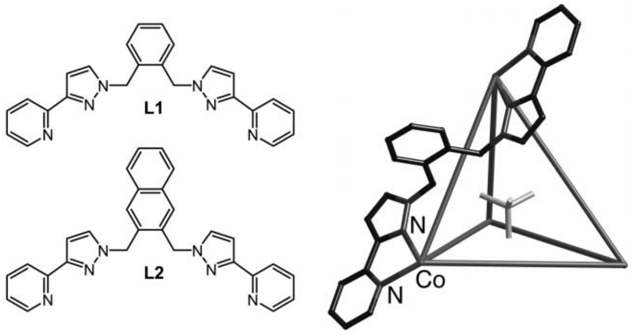
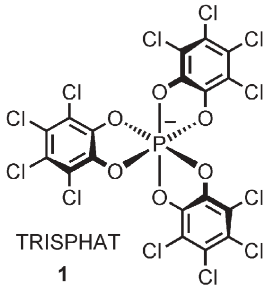


Fig. 1 Ligands **L1** and **L2** and a drawing of cationic cage $[Co_4(\mathbf{L1})_6(BF_4)][BF_4]_7$ showing one bridging ligand and the encapsulated BF_4^- anion.

Lately, the chemistry of chiral hexacoordinated phosphate anions has been revitalized as anions like TRISPHAT **1** (Λ or Δ enantiomers, Fig. 2) have been shown to be valuable CSAs for chiral cationic species.[8] Anion **1** has particularly effective NMR



TRISPHAT
1

Fig. 2 TRISPHAT anion **1** (Δ enantiomer).

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enantiodifferentiation properties when associated with complementary three-bladed propeller metal complexes of type $[M(diimine)_3]^{2+}$.[9] The efficiency of the chiral discrimination is not influenced by the diamagnetic or paramagnetic nature of the complexes.[10,11] As such, anion **1** is well suited for a study on the enantiodifferentiation of chiral cationic cages $[Co_4(\mathbf{L})_6(BF_4)][BF_4]_7$ and of, possibly, the chirotopic anion inside.

To begin, it was necessary to find a solvent medium that would ensure both solubilisation of $[Co_4(\mathbf{L1})_6(BF_4)][BF_4]_7$ and $[Co_4(\mathbf{L2})_6(BF_4)][BF_4]_7$, and a maximum NMR discrimination of the enantiomeric complexes in presence of anions **1** – these two conditions being conflicting parameters to satisfy. Both complexes $[Co_4(\mathbf{L})_6(BF_4)][BF_4]_7$ are soluble in high polarity solvents, which disfavor efficient chiral recognition among ions as a result of weaker electrostatic interactions and solvent competition.[9] A good balance between high polarity solvent conditions for solubility and a low polarity medium for effective enantiodifferentiation was provided using 5% CD_3NO_2 in $CDCl_3$ – the complex with **L2** remaining however less soluble than that of **L1**.

In the ^1H NMR spectra, the paramagnetism of the high-spin Co(II) centers meant that the signals from the ligand protons were dispersed over a 10–90 ppm range. The expected resonances, with the exception of two signals, could be readily observed. The ^1H NMR spectra of $[Co_4(\mathbf{L1})_6(BF_4)][BF_4]_7$ and $[Co_4(\mathbf{L2})_6(BF_4)][BF_4]_7$ are indicated in Fig. 3 and 4 respectively (spectra a). The ^{19}F NMR spectra of both salts $[Co_4(\mathbf{L})_6(BF_4)][BF_4]_7$ revealed two peaks: a major one whose position corresponds exactly to free $[BF_4]^-$ (δ *ca.* −145 ppm), and a minor one at much lower frequency (δ *ca.* −245 ppm) for the trapped anion; the presence of these two signals is an indication of slow exchange kinetics between the free and trapped anions on the NMR time scale.

As foreseen, addition of 2.0–8.0 equiv. of TRISPHAT Δ-**1**, as salt [Bu$_4$N][Δ-**1**],[12] to solutions of [*rac*-$Co_4(\mathbf{L1})_6(BF_4)][BF_4]_7$ and [*rac*-$Co_4(\mathbf{L2})_6(BF_4)][BF_4]_7$ in 5% CD_3NO_2 in $CDCl_3$ led to the enantiodifferentiation of the protons of the ligands. Decent resolution of the ^1H NMR spectra of the cations was achieved in both cases. The resulting spectra at 500 MHz are shown in Fig. 3 and 4 (spectra b, c and d) and are compared to that of the same solutions in the absence of TRISPHAT. Few of the signals remained unsplit (essentially protons H (and I) belonging to the aromatic spacer). Not too surprisingly, the magnitude of the separation increases with the amount of CSA reagent. In both cases, the signal of proton D around 53 ppm was the most sensitive to the presence of the chiral anion. Decent values of 0.40 and 0.36 ppm were measured for the difference in chemical shifts ($\Delta\delta_{max}$) of the split signal of that proton upon addition of [Bu$_4$N][Δ-**1**] (8.0 equiv.).

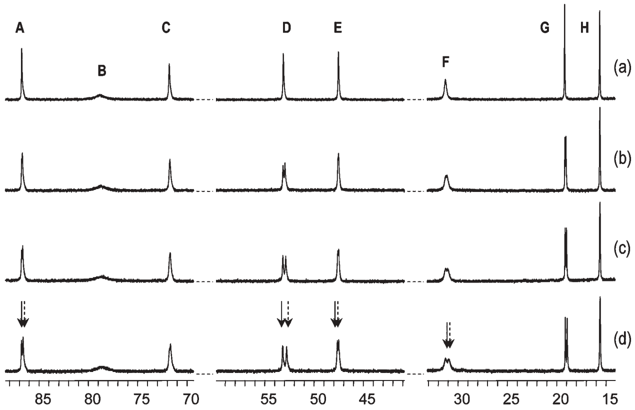

Fig. 3 ^1H NMR spectra (500 MHz, parts, 5% CD_3NO_2 in $CDCl_3$) of $[Co_4(\mathbf{L1})_6(BF_4)][BF_4]_7$ in the presence of (a) 0, (b) 2.0, (c) 4.0 and (d) 8.0 equivalents of [Bu$_4$N][Δ-**1**].

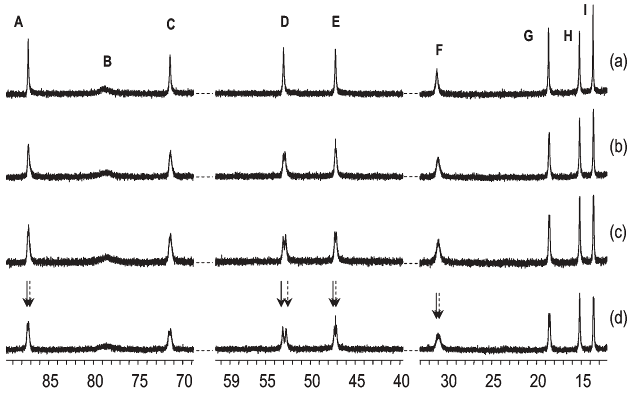

Fig. 4 ^1H NMR spectra (500 MHz, parts, 5% CD_3NO_2 in $CDCl_3$) of $[Co_4(\mathbf{L2})_6(BF_4)][BF_4]_7$ in the presence of (a) 0, (b) 2.0, (c) 4.0 and (d) 8.0 equivalents of [Bu$_4$N][Δ-**1**].

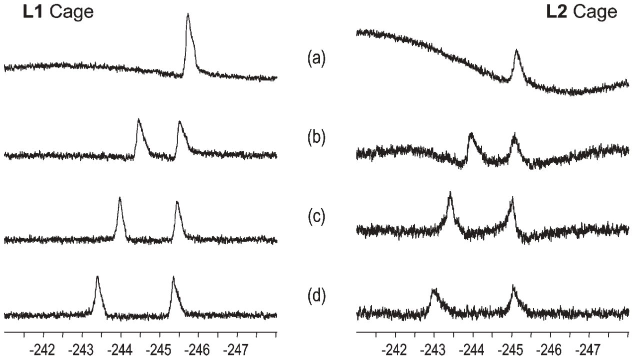

Fig. 5 ^{19}F NMR spectra (470 MHz, δ −241 to −248 ppm, 5% CD_3NO_2 in $CDCl_3$) of $[Co_4(\mathbf{L1})_6(BF_4)][BF_4]_7$ (left) and $[Co_4(\mathbf{L2})_6(BF_4)][BF_4]_7$ (right): with (a) 0, (b) 2.0, (c) 4.0 and (d) 8.0 equivalents of [Bu$_4$N][Δ-**1**].

More interestingly for this study, the addition of 2.0–8.0 equiv. of TRISPHAT Δ-**1** to solutions of [*rac*-$Co_4(\mathbf{L1})_6(BF_4)][BF_4]_7$ and [*rac*-$Co_4(\mathbf{L2})_6(BF_4)][BF_4]_7$ led also to the enantiodifferentiation of the ^{19}F NMR signal (~ -245 ppm) of the encapsulated BF_4^- anion (Fig. 5); that of the free counterions remaining unchanged. A drift towards higher frequencies can be noticed for the ^{19}F NMR signal of the encapsulated anion, with one signal being significantly more perturbed than the other, presumably in the more tightly-bound diastereoisomeric ion pair between the cage cation and the TRISPHAT anion.

Again, the magnitude of the separation increased with higher amount of added CSA reagent. A rather large value ($\Delta\delta_{max} \sim 2.0$ ppm) was measured for the difference in chemical shifts of the split signals upon addition of [Bu$_4$N][Δ-**1**] (8.0 equiv.). This difference, corresponding to the discrimination of the entrapped diastereomeric BF_4^- anion, is all the more impressive when compared to that obtained, under the same conditions, for the protons of the chiral shell ($\Delta\delta_{max}$ 0.40 ppm) which are spatially closer to the TRISPHAT anion.

In conclusion, we have shown that chiral environments can be indeed detected through the enantiodifferentiation of achiral guest molecules trapped inside the cage. Herein, we have demonstrated that the concept can be extended from NMR sensitive atoms (^{133}Cs, ^{129}Xe) to whole molecules, in this case BF_4^-. The discrimination of the trapped achiral molecule is even easier than that of the surrounding chiral cages ($\Delta\delta \sim 2.0$ and 0.4 ppm in ^{19}F and ^{1}H NMR respectively) – something not so intuitive at first sight.

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