

Paper: a cheap yet effective chiral stationary phase for chromatographic resolution of metallo-supramolecular helicates

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Simple paper chromatography using brine as an eluent affords the two enantiomers of metallo-supramolecular triple-helicates. The technique may be scaled up for preparative resolution by using cellulose columns in conventional column chromatography.

We have recently described a facile route for assembly of metallo-supramolecular architectures from inexpensive commercial reagents.^{1–3} One of the architectural motifs that we have prepared through this technology is a class of metallo-supramolecular helicates¹ that have a cylindrical architecture of similar dimensions to protein binding units that target the major groove of DNA.² Excitingly these synthetic tetracationic units also recognise the major groove of DNA and induce remarkable structural effects, wrapping up double-stranded DNA in an intramolecular fashion.² Such structural effects are unprecedented with synthetic DNA binders. Being helical, these supramolecular cylinders exist in two enantiomeric forms and we have been keen to resolve these as we anticipated that the DNA-binding of the two enantiomers might be quite different. There has been considerable recent interest in the resolution of metal complexes, much of which centres around resolution of DNA-binding metal polypyridyl complexes. The main techniques traditionally employed involve the use of chiral anions either to achieve diastereoselective crystallisation or as a component of a chiral chromatographic mobile phase.^{4,5} Similar methods have also been applied to some polypyridyl and benzimidazole based metallo-helicates.^{4,6}

We have attempted diastereoselective crystallisations of our supramolecular cylinders with a range of chiral anions without success. Chromatographic techniques have proved a little more successful, with some resolution being achieved on SP Sephadex C25 with aqueous disodium (–)-*O,O'*-dibenzoyl-(L)-tartrate solution as the mobile phase.⁷ The deep purple colour of the bis iron(II) cylinder (arising from an MLCT transition) makes it very easy to follow by eye under chromatographic conditions. Although some resolution is apparent, passing these supramolecular cylinders down Sephadex columns did not lead to the formation of two discrete bands even after multiple cycles. Instead a broad, streaked band was obtained, the front and back of which contained enantio-excesses of the two respective helical isomers. Changing to other chiral anions (e.g. sodium *d*-antimonytartrate, (S)-(+)-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate) or to the other enantiomer of the chiral dibenzoyl tartrate anion did not seem to offer further improvement. Frustrated with these conventional chromatographic techniques, we considered whether DNA itself might be used to separate the two enantiomers. To use DNA as a stationary separation phase, we impregnated chromatographic paper with DNA following a previously outlined procedure,⁸ and then added a racemic mixture of the di-iron cylinders. Washing the paper with ethanol afforded a solution containing an enantio-excess of one of the isomers (as evidenced by a strong CD spectrum). Solutions containing an excess of the other enantiomer could be obtained by extended washing of the residue with

ethanol. Alternatively the DNA-impregnated paper could be used for chromatography using 0.16 M aqueous sodium acetate solution (pH 6.90) as eluent. This led to a spot remaining fixed to the baseline and a spot moving up the plate (associated with some streaking). Washing these two spots off the paper with ethanol gave solutions with opposite CD spectra. However, the solutions obtained from the DNA-impregnated paper technique showed an instability towards hydrolysis (as evidenced by the loss of the MLCT absorption signal over a period of hours), not observed with pure solutions of the compound, indicating that the procedure had introduced some reactive impurities.

Since paper itself is chiral (being essentially a cellulose derived product) we decided to examine whether the chiral fibres in paper might themselves be capable of affording separation. The compound was spotted onto Whatman 3MM CHR chromatography paper, and paper chromatography conducted with brine (aqueous 20 mM NaCl solution) as the eluent. To our surprise and delight the purple product split beautifully into two distinct spots as shown in Fig. 1. Washing the spots from the paper (with saturated aqueous sodium chloride followed by addition of ethanol) afforded solutions with opposite CD spectra (Fig. 2). The UV-Vis absorption and mass spectra of the solutions are identical, confirming that the chromatography is affording two enantiomers and not two otherwise alternate species. The solutions obtained by this method show no evidence of hydrolytic instability. This separation technique has been scaled up to allow preparative separation simply by using commercially available cellulose particles (~20 micron; Aldrich) as the stationary phase in a column and this allows ready resolution of the di-iron and di-nickel triple helical complexes.⁹

A survey of the chiral separation literature (Chirbase) seeking examples of metal complexes being separated on paper or cellulose, revealed that Dwyer and Sargeson¹⁰ had used a

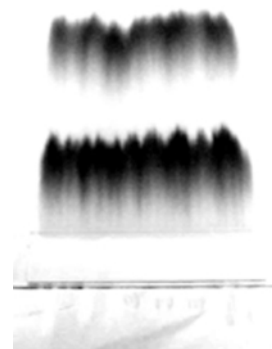


Fig. 1 Photograph of a paper chromatograph of the di-iron triple helical complex on Whatman 3MM CHR paper using 20 mM aqueous NaCl solution as the eluent.

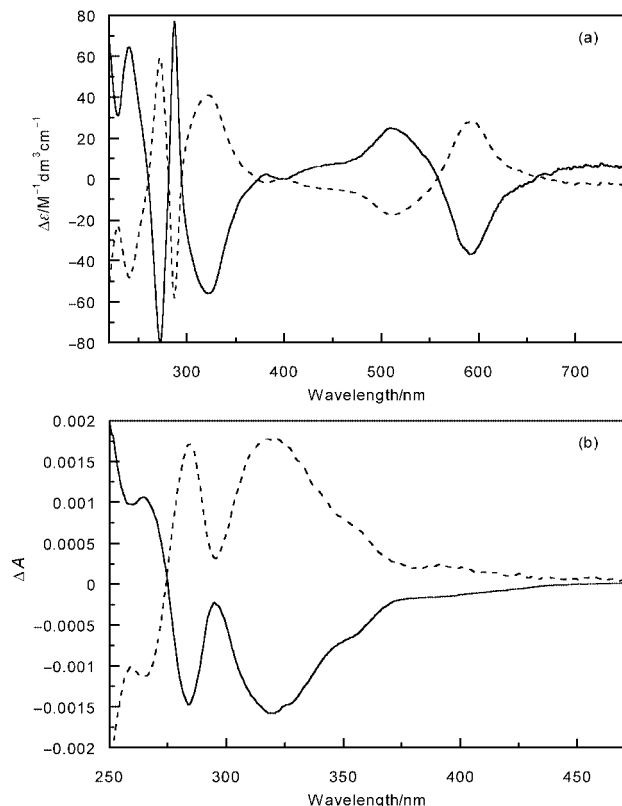


Fig. 2 CD spectra of the two bands eluted from the column for (a) the iron(II) complex ($\Delta\epsilon$ determined using $\epsilon_{545} = 14000$; The retention of one compound is significantly greater than the other and so the concentration of the eluted sample is lower for the retained enantiomer) and (b) the nickel(II) complex.

similar technique in 1963 to separate *diastereo*-isomers of cobalt(III) complexes with propane-1,2-diamine ligands but the technique does not subsequently appear to have been widely applied to the separation of enantiomeric metal complexes, although resolution of ruthenium polypyridyls on HPLC columns containing silica modified with cellulose derivatives has recently been described.¹¹

We have shown that simple paper chromatography is a powerful method of separating the two enantiomers of our metallo-supramolecular helical cylinders, and that this can be

extended to preparative scale resolution using cellulose columns. We are currently investigating the application of this technique to other metal complexes and other metallo-supramolecular architectures, and also investigating the DNA-binding of our resolved cylinders.

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- 11 D. Heseck, Y. Inoue, S. R. L. Everitt, H. Ishida, M. Kunieda and M. G. B. Drew, *Chem. Commun.*, 1999, 403. Cellulose-derivatised columns are widely used in chiral HPLC and many are commercially available.