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Resolution of a porphyrin analogue of Tröger's base by making use of ligand binding affinity differences of the enantiomers

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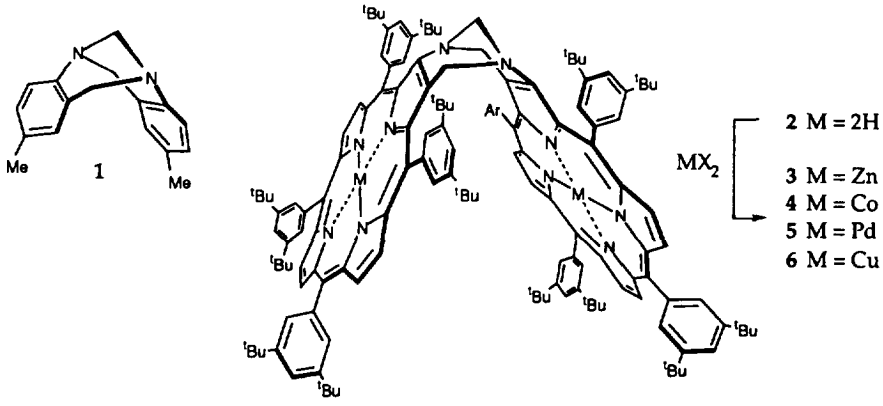
Abstract: The dizinc(II) bis-porphyrin Tröger's base analogue **3** can be resolved on a moderate scale by chromatography over a mixed silica–L-histidine benzyl ester medium.

Compounds based on Tröger's base[1] **1** are very useful building blocks in supramolecular chemistry.[2] The rigidity, chirality and concave shape of the Tröger's base architecture forms the basis for several receptor type molecules. Tröger's base analogues have been used in racemic form to study host–guest interactions[2,3] and DNA intercalation,[4] although enantiomerically pure Tröger's base derivatives have been prepared by template synthesis[5] and by chromatographic resolution of the racemate.[6–8] Indeed Tröger's base **1** itself was resolved on an α-D-lactose column,[6] in one of the earliest examples of chiral column chromatography.



We have recently reported the synthesis of the bis-porphyrin **2** and some metallated derivatives,[9] the first Tröger's base analogues not based on a substituted aniline. We also found that the dizinc(II) compound **3** exhibits highly enantioselective binding of bidentate amino acid esters within its chiral cavity.[10] Small scale resolution of racemic **3** was achieved on a commercial analytical chiral HPLC column (Pirkle Type 1A).[10] The enantiomers (+)-**3** and (−)-**3** displayed extremely high specific rotation, consistent with their helicity.[10] Each enantiomer possesses a C_2 axis of symmetry, shows strong exciton coupling between the identical porphyrin chromophores and shows a split Cotton effect in its circular dichroism spectrum. This allowed assignment of the (−)-**3** enantiomer as having the two porphyrins in an *M*-configuration[11] (left-handed screw arrangement) as in Figure 1.[10]

In order to study further their potential as chiral receptor molecules, we required a method for the resolution of bis-porphyrin Tröger's base analogues on a preparative scale. In earlier work we found that the enantiomer (+)-**3** binds L-histidine benzyl ester in toluene much stronger (K=1.1×10^8 dm^3 mol^{-1}) than the enantiomer (−)-**3** (K=1.2×10^7 dm^3 mol^{-1}); this corresponds to $\Delta\Delta G$=−5.4

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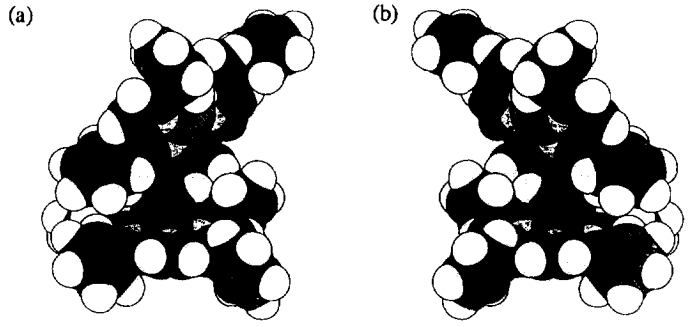

Figure 1. Space-filling models[12] of the two enantiomers of dizinc(II) bis-porphyrin Tröger's base analogue **3** showing (a) right-handed screwness of (+)-enantiomer, *P*-(+)-**3**, and (b) left-handed screwness of (−)-enantiomer, *M*-(−)-**3**. (The *tert*-butyl groups at the 3- and 5-positions of the phenyl rings are omitted for clarity.)

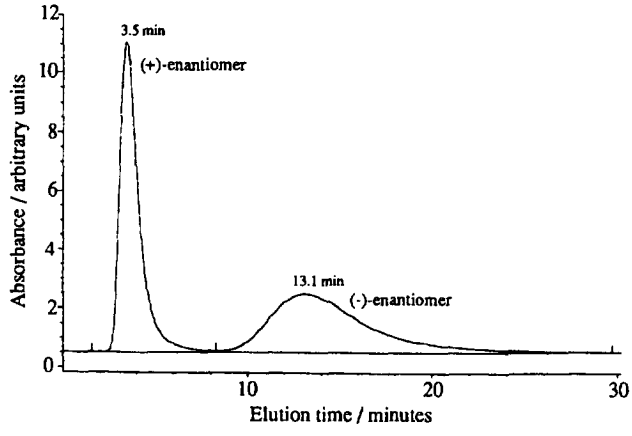

Figure 2. Trace of the HPLC separation of (±) bis-porphyrin **3** on a silica pre-saturated with L-histidine benzyl ester column (25 cm × 3.2 mm ID); eluant, 9:1 pentane:chloroform mixture; flow rate 1.0 mL/min (UV/VIS detector at 430 nm).

kJ mol^{-1}.[10] We now report that a moderate scale resolution of **3**, utilising its highly specific chiral recognition properties, can be achieved with flash column chromatography.

Initial attempts to resolve **3** by chromatography of pre-formed complexes with L-histidine benzyl ester failed because of dissociation of the diastereomers on the column and subsequent tight binding of the amino acid to the silica support. Attempts to overcome this difficulty by adding considerable excess of the amino acid to the eluting solvent also failed.

Resolution of **3** was achieved by chromatography over silica that had been pre-saturated with L-histidine benzyl ester. The separation was very sensitive to the solvent used. A 9:1 pentane:chloroform mixture gave complete separation, while 10:1 and 8:1 mixtures resulted in a poorly resolved separation. Pure enantiomer was obtained in each case by concentration of the fraction and further chromatography through a short plug of silica to remove co-eluted amino acid. An analytical HPLC column packed with the same medium also achieved base-line resolution (Figure 2).

Interestingly, the (+)-enantiomer (+)-**3**, which has a stronger binding interaction with L-histidine benzyl ester, was eluted from the column first indicating that it had a lessened interaction with the solid phase! Differences in colour of the eluting fractions suggested that the (+)-enantiomer was being chromatographed as the (+)-**3**·histidine complex whereas the (−)-enantiomer was mainly free compound, a fact confirmed by visible spectroscopy of the fractions collected straight from the column and of pure **3** (Figure 3). The Q-bands in the electronic spectrum of **3** shift upon complexation with

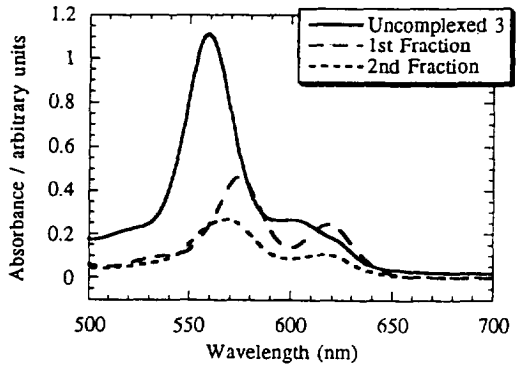

Figure 3. UV Absorption spectra of **3** and of the two fractions obtained in the resolution of **3** collected straight from the column, recorded on a Cary 5E spectrophotometer.

diamines.[9] The absorption bands at 559 and 600 nm in **3** shift to 575 and 619 nm, respectively, upon full complexation with histidine benzyl ester. In the electronic spectrum of the first fraction the Q-bands are observed to be shifted to 575 and 618 nm indicating that (+)-**3** is indeed fully complexed during the column separation. The second fraction showed Q-bands that were shifted only to 568 and 615 nm, an indication that the (−)-**3** enantiomer only partly formed a complex with L-histidine benzyl ester on the column.

Rather than being a separation based on shape selective interaction of an enantiomer with a chiral stationary phase, the basis of the separation appears to involve just the right solubility of L-histidine benzyl ester in the liquid phase to exploit the difference in binding constants of the enantiomers, coupled with very different polarities of four and five coordinate zinc porphyrin species. Out-of-plane (the porphyrin four nitrogens) displacement of the zinc(II) towards the ligand is observed in X-ray structures of zinc porphyrins with coordinating ligands (typical displacement of 0.35 Å).[13] In the present case, the zinc(II) ion of **3** should be drawn into the cavity from the plane of the porphyrin on complexation with the bidentate ligand thereby lessening the relatively pronounced zinc(II)–silica interactions seen in the chromatography of simple zinc(II) porphyrins. Calculations using the semi-empirical PM3 program supported this view.[14] The minimised structure of a zinc(II) porphyrin–imidazole complex shows that the zinc(II) is about 0.5 Å out-of-plane towards the nitrogen of the bound ligand and that the charge on the zinc(II) ion increases from −0.2 in uncomplexed zinc(II) porphyrin to −0.8 when the imidazole is coordinating, decreasing the interaction with the silica even further.

As would be expected on the basis of the above discussion, this resolution technique is highly specific for the dizinc(II) bis-porphyrin–histidine ester/silica system. In separate experiments the dicobalt(II), dipalladium(II) or dicopper(II) derivatives **4**–**6** (all prepared by standard metallation reactions and fully characterised and all of which have the same shape as **3**) were not resolved with silica/L-histidine benzyl ester, probably due to their low affinity towards L-histidine benzyl ester. Furthermore, when L-serine benzyl ester, which binds with a selectivity of $\Delta\Delta G = -3.8$ kJ mol^{-1} to the (+)-**3** enantiomer, or (1*R*,2*R*)-(+)-1,2-diphenylethylenediamine (also bound by (+)-**3** enantioselectively) were used instead of L-histidine benzyl ester as the chiral medium, no resolution of **3** was observed; in these cases the absolute affinity for the ligand is some orders of magnitude less that for the histidine ester. A number of other approaches did not result in resolution of the racemic parent free-base compound **2** and its racemic metallated derivatives **3**–**6**; these experiments included chromatography over α-D-lactose, sucrose, and the commercially available chiral HPLC columns NUCLEOSIL®, CHIRAL-2, ChiraSpher® and ChiraDex® as chiral stationary phases. In ongoing work, we are investigating systems that involve the use of immobilised amino acid derivatives for resolution of Tröger's base analogues and the use of immobilised derivatives of (+)-**3** and (−)-**3** for the separation of amino acids.

As zinc(II) porphyrins can be readily demetallated under mild acid conditions, and as many different metal ions can be chelated with porphyrins, optically pure free-base and a range of metallo- and dimetallo-bis-porphyrin Tröger's base analogues are easily accessible from the enantiomerically pure (+)-**3** and (−)-**3** isomers. Work in our laboratory is now directed towards making use of such stereochemically pure derivatives as chiral receptor molecules and as catalysts.

Procedure for the resolution of (±)-3

L-Histidine benzyl ester (3.3 g, 13.6 mmol) was dissolved in dichloromethane (500 mL) and pre-absorbed onto silica gel (Merck Type 60H) (70 g). This was used to pack a column (14 cm × 4.5 cm ID) and 50 mg of (±)-**3** was eluted with pentane:chloroform (9:1). Two bands were collected independently, concentrated and then filtered through a short plug of silica (10 g). The first band yielded (+)-**3** {$[\alpha]_D^{20}$ +2000 (*c* 1.2×10^{-2}, $CHCl_3$)} having the *P*-configuration and the second band yielded (−)-**3** {$[\alpha]_D^{20}$ −2000 (*c* 1.2×10^{-2}, $CHCl_3$)} having the *M*-configuration. The combined yield was 90–95% and the solution spectroscopic properties of each enantiomer were identical with those of the fully characterised racemate.[9]

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