Helical chirality control in zinc bilinone dimers

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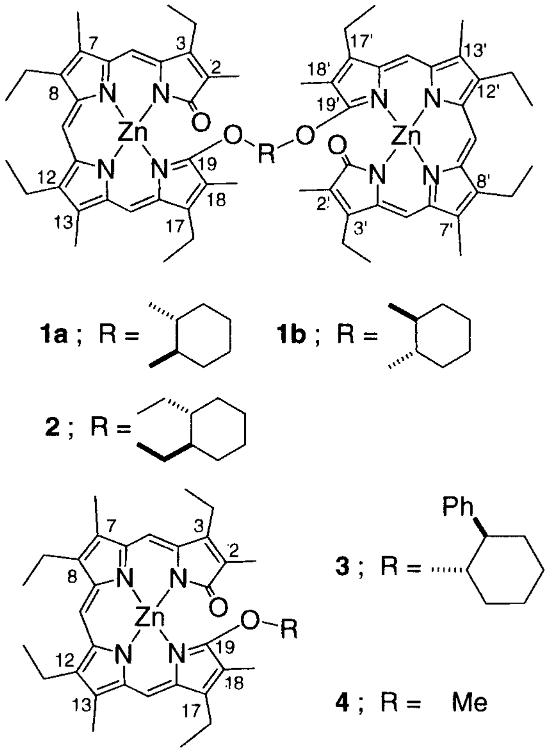
Helical chirality of zinc bilinone is completely regulated by dimerizing bilinone units through a chiral cyclohexane spacer.

Zinc bilinone (ZnBL) is a helical molecule[1,2] with the low energetic barrier between the *P*- and *M*-helix conformers leading to rapid racemisation at room temperature.[3] Upon complexation with chiral amino acid esters and amines, the racemisation equilibrium is driven to a preferred enantiomer, implying the possible use of zinc bilinones as a framework for a chiral receptor.[4] For this purpose, however, the conformational flexibility of zinc bilinones should be limited. As an approach to rigidly fix the helical chiral conformation, we report here the synthesis of ZnBL dimers and complete control of the chirality by use of a rigid chiral spacer. Two ZnBL frameworks that are assembled *via* a chiral *trans*-cyclohexane-1,2-dioxy spacer gave a homochiral structure exclusively.

The bilinone dimer **1** was synthesized by a nucleophilic ring-opening reaction of oxoniaporphyrin by an alkoxide generated *in situ* from optically active *trans*-(*R*,*R*)- or (*S*,*S*)-1,2-cyclohexanediol, followed by zinc insertion using zinc(II) acetate.[5–7] The total yield of **1** from the oxoniaporphyrin was 35–46%. The structure of dimer **1** was confirmed by ^{1}H and ^{13}C NMR, UV–VIS, high resolution mass spectrometry and elemental analysis. Full assignments of all the protons and carbons were achieved by ^{1}H–^{1}H COSY, ROESY, and ^{1}H–^{13}C HSQC spectra. In the ^{1}H NMR spectrum of **1**, each bilinone moiety is magnetically equivalent, indicating that **1** adopts a C_2 symmetric conformation.



Circular dichroism spectra of **1**, **2** and **3** are shown in Fig. 1. The signs of the Cotton effects show that the *P*-helix conformation is more abundant than that of the *M*-helix in **1a**, and *vice versa* in **1b**.[8–11] The Cotton effects observed for **2** were much smaller than those for **1** or for the ZnBL monomer **3** bearing a chiral auxiliary. Previously we found that the magnitude of Cotton effects of ZnBL derivatives is directly in proportion to the efficiency of helical chirality induction.[4,12,13] Therefore, these CD spectral studies revealed that the helical chirality induction in **1** is much more effective than in **2** and **3**.

Variable-temperature ^{1}H NMR and CD studies offered more conclusive evidence for chiral induction in **1**: one set of the signals [Fig. 2(a)] was observed in the ^{1}H NMR spectrum over the temperature range 288–198 K. UV–VIS and CD spectra showed small changes upon cooling from 288 to 198 K: a 2 nm blue shift and a 9 nm red shift in the higher energy band and the lower energy band respectively, in the UV–VIS while CD spectra suggested a minor conformational equilibrium, but indicative of no changes in distribution among (*P*,*P*)-, (*P*,*M*)- and (*M*,*M*)-conformers. In contrast to this observation, monomeric ZnBL **3**, exhibited a drastic change in the CD intensity upon cooling from 288 to 223 K ($\Delta\varepsilon_{405}$ = -65.2 dm^3 mol^{-1} cm^{-1} at 288 K, $\Delta\varepsilon_{402}$ = -88.2 dm^3 mol^{-1} cm^{-1} at 223 K), where the diastereomeric excesses of the helical structure were 51 and 72%, respectively. All these results indicate that both ZnBL moieties of **1a** exclusively adopt the (*P*)-conformation.

In the ^{1}H NMR spectra of a more flexible dimer **2**, three sets of signals were observed in the region of the methine protons and the methylene protons adjacent to the oxygens, which were

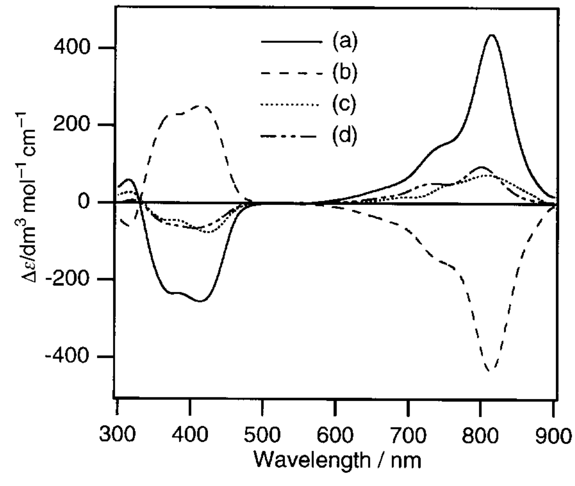


Fig. 1 Circular dichroism (CD) spectra of (a) **1a** (1.97×10^{-5} M), (b) **1b** (1.53×10^{-5} M), (c) **2** (1.99×10^{-5} M) and (d) **3** (3.68×10^{-5} M) in CH_2Cl_2 at 288 K.

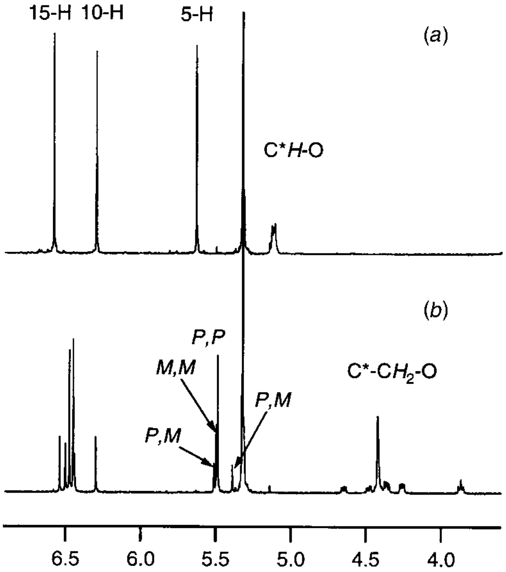


Fig. 2 Expanded region of ^{1}H NMR spectra of (a) **1a** and (b) **2** in CD_2Cl_2 at 288 K. [**1a**] = 2.57 mM and [**2**] = 2.50 mM.

ascribed to (*P,P*)-, (*P,M*)- and (*M,M*)-conformers, respectively [Fig. 2(b)]. The ratio of these three isomers determined by the signal integrations of the 5-H proton was (*PP*) : (*MM*) : (*PM*) = 51 : 27 : 22, indicating that homochiral conformers are preferred over *M*-helix, with a 24% excess of the *P*-helix of ZnBL. Therefore, extra methylene groups in **2** led to larger rotational freedom and less efficient helical chirality induction. It is noteworthy that, even in the flexible dimer **2**, homochiral conformers were preferred over the heterochiral one.

A further remarkable feature of **1** is that an anomalous upfield shift of one of the peripheral methyl groups was found in the ^{1}H NMR spectrum: the chemical shift of the 18-Me protons of **4** was observed at δ 1.72, whereas that of **1** was at δ 1.01. Other methyl protons appeared in a narrow region (δ 1.75, 2.01 and 2.07 for 2-, 7- and 13-methyl protons in **4**). This upfield shift is most likely caused by the proximity of the 18-methyl group of **1** to the ring current anisotropy of the other ZnBL. These NMR results and conformational search by force field/molecular orbital calculations afforded one of the possible conformers as shown in Fig. 3. In this conformation, the distance between the 18-Me carbon of ZnBL and the C-2′ carbon of the other ZnBL was 3.51 Å, indicating the van der Waals contact between the methyl group at the 18-Me and the A-ring pyrrole moiety of the other ZnBL. These van der Waals forces effectively fix the homochiral conformation.

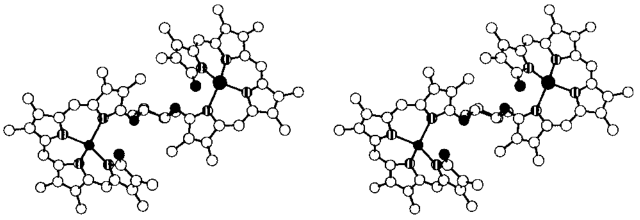


Fig. 3 Stereoview of one of the possible conformers of a model compound of **1a**, in which all the peripheral ethyl groups were replaced by methyl groups. All hydrogen atoms are omitted for clarify. The C_2 symmetric conformer was found by use of the grid conformational search program of Sybyl and the geometry was further optimized by MO calculations at the PM3 level (Spartan version 3).

Preliminary experiments showed that the (*P,P*)-conformer of **1a** was stable even in the presence of excess amounts of (*M*)-conformer-inducing L-amino acid esters.[4] Therefore, dimerization of the highly flexible framework of zinc bilinone led to the robust structure of **1**, which should be suitable as a framework of receptors.

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