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Synthesis of Chiral Bridled Porphyrins in their Two Enantiomeric Forms

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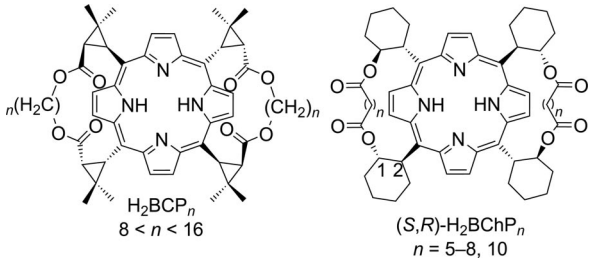
We describe the synthesis of a new family of chiral bridled porphyrins. They were obtained by reaction between pyrrole and a chiral 2-formylcyclohexanol derivative. Thanks to an enzymatic kinetic resolution method, these compounds were obtained in both enantiomeric forms. This resolution method allows easy synthesis of chiral precursors in high yield and on large scale. These new porphyrins exhibited an (αα)(αα) conformation and the less usual (αα)(ββ) one, depending of the bridle length.

Introduction

Chiral metalloporphyrins have been widely used for several years as catalysts for enantioselective epoxidation and aziridination reactions, mainly as single enantiomers.[1,2] It would be of high practical interest to have access to both catalyst enantiomorphs in order to select the favoured enantiomer product, but surprisingly asymmetric syntheses of metalloporpyrins in their two enantiomeric forms are scarce.[3,4] Previous work in our laboratory on chiral porphyrins H_2BCP_n synthesised from biocartol (Scheme 1) suffer from the same difficulties to synthesise both enantiomers of the catalyst.[5] We decided to synthesise a new chiroporphyrin family close to the biocartol one. In this new family, the rigidity of the chiral cyclopropyl substituent is partly held by the use of chiral cyclohexyl substituents. So, we present here a general procedure that enables the synthesis of the two enantiomers of porphyrins bearing chiral *meso* cyclohexyl substituents, obtained by kinetic resolution of a racemic cyclohexanol derivative with Amano PS lipase. This procedure is exemplified by the synthesis of the two enantiomers of the bridled chiroporphyrin (*R*,*S*) or (*S*,*R*)-H_2BChP_n illustrated in Scheme 1. We also describe the unusual conformations exhibited by these new bridled porphyrins, which could lead to practical applications in the field of molecular bistability.[6]



Scheme 1. H_2BCP_n ($8 \leq n \leq 16$) and (*S*,*R*) H_2BChP_n (*S*,*R* refer to 1*S*,2*R*; *n* = 5–8, 10).

Results and Discussion

As reported earlier[2] for the bridled chiroporphyrins derived from biocartol, the synthesis of H_2BChP_n relies on the design of a new chiral bifunctional aldehyde in which a methylene chain is introduced to provide the link between two adjacent *meso* cyclohexyl substituents of the strapped porphyrin. Consequently, the key point of the synthesis was to obtain chiral aldehyde–alcohol **3** in its two enantiomeric forms (Scheme 2).

Protected 1-cyclohexene-1-carboxaldehyde was synthesised according to a published procedure,[7] and the C–C double bond was hydroxylated by a hydroboration–oxidation sequence. The *cis* orientation of the hydroboration reaction led to a racemic mixture of (*R*,*R*)-**3** and (*S*,*S*)-**3**, and the next step was the resolution of this racemate by enzymatic transesterification. Following a classical kinetic enzymatic resolution method,[8] Amano PS lipase in neat vinyl acetate conveniently afforded enantioenriched alcohol (*S*,*S*)-**3** and acetate (*R*,*R*)-**4**. These two compounds were easily separated by column chromatography on basic alumina. The absolute configuration of the enantioenriched alcohol was established by a published NMR procedure[9] and is in agreement with the enantioselectivity of Amano PS lipase established by Kazlauskas.[8] The NMR method enabled quantification of the *ee* value, which was found to be 80% for (*S*,*S*)-**3**. Next, (*R*,*R*)-**3** was obtained with a

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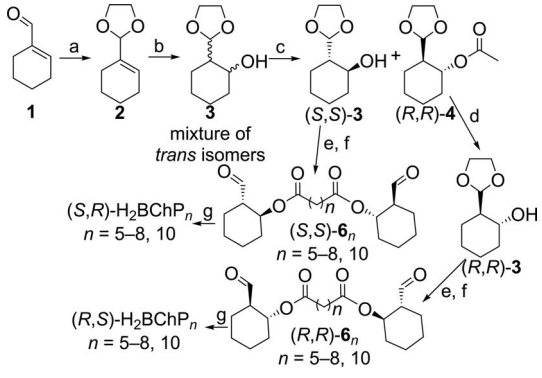

Scheme 2. Synthesis of (*S*,*R*)- and (*R*,*S*)-H_2BChP_n (*n* = 5–8, 10). Reagents and conditions: (a) ethylene glycol/$MgSO_4$/tartaric acid/C_6H_6, reflux, 6 h, 88%; (b) BH_3·DMS/THF room temp., 16 h, $NaBO_3$, 32%; (c) amino lipase PS/neat vinyl acetate, room temp., 10 d, 84% of (*S*,*S*)-**3**; (d) amino lipase PS/THF/water (pH 7.5 buffer) mixture, room temp., 10 d, 87% of (*R*,*R*)-**3**; (e) pyridine/corresponding diacid chloride (*n* = 5–8, 10), room temp., 16 h, 50–80% yield; (f) I_2/acetone, room temp., 16 h then saturated solution of $Na_2S_2O_3$; (g) pyrrole/BF_3·Et_2O/$CHCl_3$ (1%EtOH), room temp., reaction time 48–140 h, then DDQ, 3–15% yield.

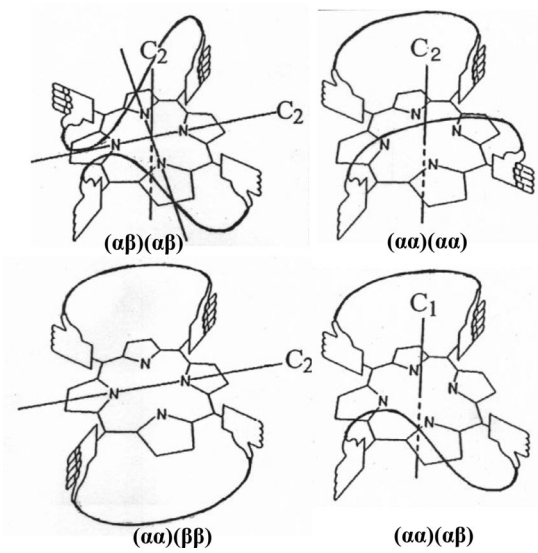

Figure 1. Drawing of chiral bridled porphyrins and symmetry element associated to different conformations.

92%*ee* by hydrolysis of (*R*,*R*)-enantioenriched **4**, which was also catalysed by Amano PS lipase in a THF/pH 7 buffer mixture. To create the bridle, two molecules of enantioenriched **3** were treated with one molecule of an α,ω-diacid chloride (chain length *n* = 5–8 and 10 methylene groups) in pyridine to afford diester $\mathbf{5}_n$. Iodine-catalysed removal of the 1,3-dioxolanne protection afforded dialdehyde $\mathbf{6}_n$. The crude dialdehyde was then allowed to react under Lindsey conditions with pyrrole (2 equiv.) and BF_3·Et_2O (0.3 equiv.) as catalyst. After DDQ oxidation, the new bridled chiroporphyrins (*R*,*S*)- or (*S*,*R*)-H_2BChP_n were obtained in a yield varying from 3% for the shortest bridles (*n* = 5) to 15% for the longer ones (*n* = 8 or 10).

NMR spectroscopy suggested that the conformation of these free base porphyrins is dependent on the bridle length (Supporting Information, Figure 1). Indeed, the porphyrin with the shortest straps, H_2BChP_5, exhibits a ^{1}H NMR spectrum with four doublets for the β-pyrrolic proton resonances corresponding to a C_2 symmetry with the C_2 axis perpendicular to the porphyrin core, that is, a (αα)(αα) conformation (Figure 1).[10]

When one more methylene group is added to the strap, a different behaviour is observed. In the immediate H_2BCChP_6 product, two different conformers can be isolated by chromatography in roughly the same amounts. Their ^{1}H NMR spectra (Supporting Information, Figure 2) are very different: the less polar one exhibits two singlets and two doublets for its β-pyrrolic proton signals, indicating a C_2 symmetry with the C_2 axis parallel to the porphyrin core and a (αα)(ββ) conformation. In contrast, the more polar fraction exhibits a (αα)(αα) conformation as deduced from the four doublets observed in the β-pyrrolic region. Surprisingly, if the (αα)(ββ) atropisomer is left in solution for several hours, it slowly converts quantitatively into the (αα)(αα) form. Thus, the (αα)(αα) form is considered to be the more thermodynamically stable atropisomer of the H_2BCChP_6 porphyrin. This also suggests that the porphyrinogen intermediate is probably stabilised in the (αα)(ββ) conformation. After DDQ oxidation the corresponding porphyrin slowly rearranges to the more stable (αα)(αα) conformation.

For porphyrins with longer bridles (*n* = 8, 10), the NMR spectra become more intricate as these compounds exist as mixtures of atropisomers, which cannot be isolated by chromatographic methods. Nevertheless, the prevalent and therefore more stable atropisomer becomes (αα)(ββ) as the chain length increases beyond *n* = 6. Thus for H_2BCChP_{10} the (αα)(ββ) atropisomer is the predominant species in the mixture (Supporting Information, Figure 1). This is corroborated by the crystal structure of (*S*,*R*)-H_2BCChP_{10} (Figure 2), which exhibits the (αα)(ββ) conformation.

The structure shows a rather distorted porphyrin core in the ruffle mode, probably resulting from steric hindrance of the *meso* substituents. As an attempt from the synthesis conditions, the ester strap and the porphyrin are linked in an *anti* fashion on the cyclohexyl ring. One bridle is above and the other one is below the porphyrin mean plane, corresponding to a (αα)(ββ) conformation. Short distances between some bridle hydrogen atoms and the porphyrin mean plane (around 2.5 Å) suggest some kind of C–H–π interaction. A similar disposition is expected to be adopted in solution, as the chemical shifts of some methylene protons of the strap are largely upfield shifted (ca. –4 ppm) in the ^{1}H NMR spectrum. This shift is due to the anisotropic cone of the porphyrin.[12] This bridle layout may explain the conformational changes observed on going from the shortest bridle (*n* = 5), where the bridles do not interact sterically in a (αα)(αα) conformation, to the longest (*n* = 10), where a strong steric constraint is created if the bridles are on the same side of the porphyrin, which forces a (αα)(ββ) conformation to be adopted.

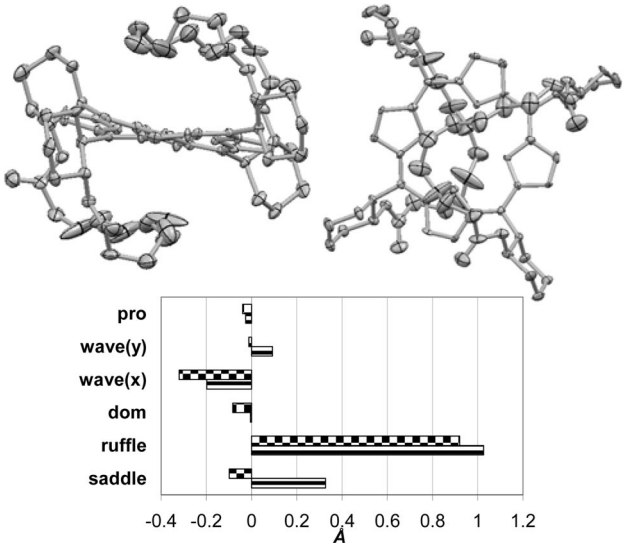

Figure 2. Top: X-ray structure (ORTEP view 30% probability) of (*S*,*R*)-H_2BChP_{10} (top and side view of one of the two independent molecules of the asymmetric unit). Bottom: NSD analysis[11] of the porphyrin core distortion (for the two independent molecules of the asymmetric unit).

The achievement of a chiral synthesis of two porphyrin enantiomers was confirmed by circular dichroism (CD) measurements. Indeed, the two enantiomeric porphyrins present opposite CD spectra as expected (Figure 3). For a given enantiomer of a bridled porphyrin [(*S*,*R*) for example], a link between the porphyrin conformation and the sign of the Cotton effect on the Soret region of the CD spectra can be outlined. For instance, porphyrins of (αα)(αα) conformation [(*S*,*R*)-H_2BCChP_5 or the more polar (*S*,*R*)-H_2BCChP_6 fraction] exhibit a negative Cotton effect, whereas a positive effect is observed for the (αα)(ββ) conformer [less polar (*S*,*R*)-H_2BCChP_6 fraction]. In this last case, when the atropisomer composition changes from (αα)(ββ) to (αα)(αα), we also notice a signal inversion on the CD spectrum (see the Supporting Information).

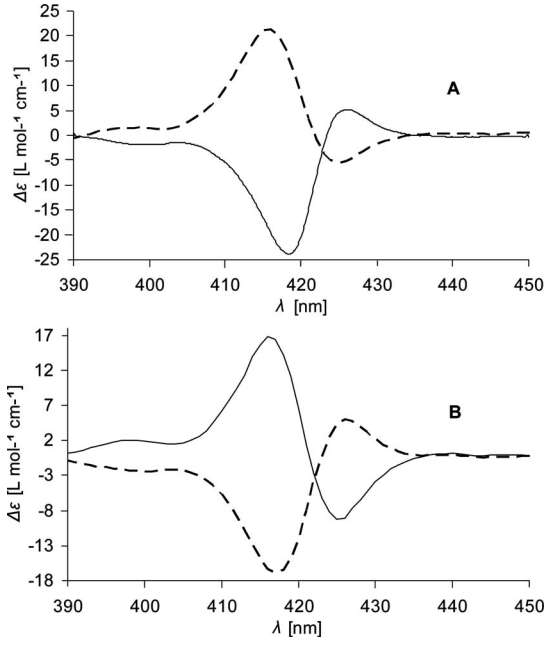

Figure 3. Circular dichroism spectrum in the Soret band of (A) (*R*,*S*)-H_2BChP_5 (dashed line) and (*S*,*R*)-H_2BChP_5 (solid line) and (B) (*S*,*R*)-H_2BChP_{10} (solid line) and (*R*,*S*)-H_2BChP_{10} (dashed line).

The CD spectra of porphyrins that are isolated as a mixture of atropoisomers present a more complex feature. However, even in that case (i.e., for the H_2BCChP_n where n = 8, 10), an opposite signal is still observed for the two enantiomers, confirming the achievement and the repeatability of the chiral synthesis.

Conclusions

In summary, we have achieved the synthesis of a new family of chiral porphyrins. Thanks to an enzymatic kinetic resolution method, these compounds were obtained in both their enantiomeric forms. This resolution method allows the easy synthesis of chiral precursors in high yield and on a large scale. These new porphyrins exhibit an unusual (αα)(ββ) conformation, in sharp contrast to biocartol-derived bridled porphyrins, which are isolated in the (αβ)(αβ) or (αα)(αα) conformation. An influence of the bridle length on the atropisomer distribution was observed. The influence of metal complexation on the conformations of these free-base porphyrins is under investigation and will be reported in due course.

CCDC-703905 [for (*S*,*R*)-H_2BChP_{10}] for contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see footnote on the first page of this article): Experimental procedures and characterisation data (^{1}H and ^{13}C NMR spectra, UV/Vis spectra) for **2**–**6**$_n$ and the corresponding porphyrins; evolution of the ^{1}H NMR and CD spectra of (αα)(ββ) H_2BChP_6 with time.

Acknowledgments

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