Conformational diastereoisomerism in a chiral pretzelane†

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The introduction of a stereogenic center by a stereospecific synthesis into an optically active, donor–acceptor pretzelane, that exhibits helicity as well as fixed chirality, leads to a marked preference for one conformational diastereoisomer over the other in both acetone and dimethylsulfoxide that can be understood from computational models.

Mechanically interlocked molecular compounds,[1] such as catenanes,[2] rotaxanes,[2] knots,[2,3] and Borromean links[4] are amongst some of the more exotic products of template-directed synthesis[5] that have evolved on the back of molecular recognition and self-assembly processes.[6] In the meantime, stereochemistry and chirality have become an important consideration and phenomenon in mechanically interlocked molecules[7] following on from their influence and role in host–guest[8] and supramolecular[9] chemistry. Different elements of chirality, including stereogenic centres,[10,11] and chiral axes[10] and planes[10,12] have been identified in hosts, while helicity has been located[13] in supermolecules. Apart from stereogenic centres, chiral axes and planes, as well as helicity, have all been identified in [2]catenanes.[7] Recently, a class of pretzelanes[14] has been assembled[15] using template-directed protocols[5] on the basis of the donor–acceptor interactions that exist between π-electron rich ring systems (*e.g.*, hydroquinone, 1,5-dioxynaphthalene, *etc.*) and π-electron poor units (*e.g.*, bipyridinium, diazapyrenium, *etc.*). An inherent structural feature of such pretzelanes is the stereochemistry[16] associated with the relative spatial arrangements of the two interlocked ring components. For instance, in the pretzelane **1**·4PF_6 (Scheme 1), helical chirality is present.‡ It arises from the location of the crown ether on either one of the two bipyridinium units on the tetracationic cyclophane. As a result, a pair of (*P*) and (*M*) enantiomers is observed with a free energy of activation ($\Delta G^{\ddagger}$) of 17.5 kcal mol^{-1} for their inversion in CD_3COCD_3 solution. In this communication, we describe an investigation of the effect of chiral induction on introducing a stereogenic centre into the linker that connects the two ring components together. Would one of the two conformations—(*P*) or (*M*)—be favoured over the other one in response to the presence of an additional chiral element in the linker? To answer this question, a chiral pretzelane (*S*)-(*PM*)-**2**·4PF_6 was synthesised† and studied by dynamic ^{1}H NMR spectroscopy and circular dichroism (CD). In addition, molecular modelling was employed to obtain insight into the origin of any conformational diastereoisomeric preference.

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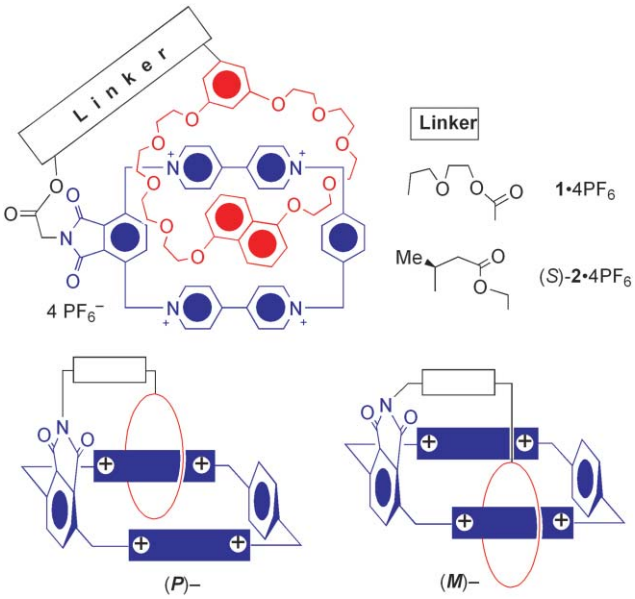
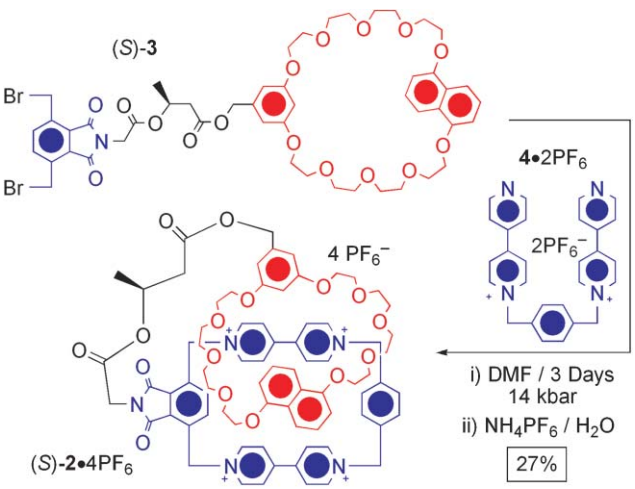


Scheme 1 Pretzelanes $\mathbf{1}^{4+}$ and (*S*)-(*PM*)-$\mathbf{2}^{4+}$ and the associated (*P*)- and (*M*)-conformations.

The chiral pretzelane (*S*)-(*PM*)-**2**·4PF_6 was obtained (Scheme 2) from the clipping reaction between the crown ether-appended dibromide§ (*S*)-**3** and the dicationic precursor[17] **4**·2PF_6 after counterion exchange. The ^{1}H NMR spectrum of (*S*)-(*PM*)-**2**·4PF_6 recorded in CD_3CN at room temperature indicates the presence of two diastereoisomers in unequal proportions. All the protons are heterotopic and so give rise to well-resolved signals, indicating that any dynamic exchange processes, such as crown ether pirouetting



Scheme 2 Synthesis of the chiral pretzelane (*S*)-(*PM*)-**2**·4PF_6.

or rotation of the aromatic units within the tetracationic cyclophane, are slow on the ^{1}H NMR timescale. Resonances corresponding to the methyl protons on the linker are observed, respectively, at δ = 1.44 and 1.53 ppm in a ratio of 9 : 1, which corresponds to a free energy difference (ΔG°) of 1.3 kcal mol^{-1} between the two diastereoisomers. Their proportions are solvent dependent and change to 6 : 1 when CD_3SOCD_3 is the solvent. Dynamic ^{1}H NMR spectroscopy was performed using the methyl proton resonances as probes. Upon heating (Fig. 1a) a CD_3SOCD_3 solution of (*S*)-(*PM*)-**2**·4PF$_6$ up to 100 °C, the methyl resonances begin to coalesce as a result of several site-exchange processes,[15] suggesting that the two diastereoisomers are undergoing fast interconversion at higher temperatures. The $\Delta G^\ddagger$ value for the interconversion of the minor conformation into the major one was found to be 17.8 kcal mol^{-1} at 310 K as a result of spin saturation transfer experiments,[18] an activation barrier which is comparable[15] to the one ($\Delta G^\ddagger$ = 17.5 kcal mol^{-1}) for the inversion between the pair of enantiomers of **1**·4PF$_6$.

CD spectra of (*S*)-(*PM*)-**2**·4PF$_6$ were recorded (Fig. 1b) at different temperatures in MeCN. A significant CD response in the charge-transfer region at λ_{max} = 506 nm is observed, along with a much stronger one at λ_{max} = 340 nm for the bipyridinium units' absorption maximum. Clearly, the stereogenic centre in the linker provides a chiral influence that has a strong impact upon the electronic transitions arising from the donor–acceptor interactions and also on the π–π* transitions associated with the two bipyridinium units. The moderate decrease in the intensities of the CD bands on heating is most likely a result of some loss of diastereoselectivity at higher temperatures.

Force-field modelling[19] has been employed to provide insight into the diastereoisomeric conformational preference, namely that the (*M*)-isomer is preferred over the (*P*)-isomer in (*S*)-**2**$^{4+}$. The diastereoisomers (*S*)-(*M*)-**2**$^{4+}$ and (*S*)-(*P*)-**2**$^{4+}$ were investigated using several force fields and the GB/SA solvent model[20] for $CHCl_3$. The initial geometries of the two conformational isomers were constructed with the aid of the X-ray crystal structure[14] of **1**·4PF$_6$ by preserving the relative dispositions of the two macrocycles and reconstructing the linker. Although they differ a little quantitatively, the calculated energy differences (ΔE) using four different force fields (Table 1) indicate qualitatively that the (*S*)-(*M*)-**2**$^{4+}$ isomer is more stable than the (*S*)-(*P*)-**2**$^{4+}$ one. Amongst the different methods, the calculation based on the MM2 force field matches closely that of the experimental ΔG° value of 1.3 kcal mol^{-1}. The energy minimized structures associated with both conformations retain (Fig. 2) the expected noncovalent bonding interactions, including the [π···π],[21] [C–H···π][22] and [C–H···O][23] interactions that are operative when the 1,5-dioxynaphthalene unit is located inside the cavity of the tetracationic cyclophane. The conformations adopted by the linkers, however, are quite different (Fig. 2) in the two diastereoisomers. The methyl group on the linker in the (*S*)-(*P*)-**2**$^{4+}$ isomer points in towards (Fig. 2a and c) the cavity formed by one of the tetraethylene glycol loops of the crown ether component and one of the bipyridinium units in the tetracationic cyclophane while, in the case of the (*S*)-(*M*)-**2**$^{4+}$ isomer, the methyl group points away (Fig. 2b and d) from this cavity. The crowding that this methyl group experiences in the (*S*)-(*P*)-**2**$^{4+}$ isomer is presumably the origin of the preference for the (*S*)-(*M*)-**2**$^{4+}$ isomer. Furthermore, the computational studies indicate that the methyl protons in the (*S*)-(*P*)-**2**$^{4+}$ isomer are oriented edge-on to the aromatic plane of the 1,5-dioxynaphthalene ring system and hence experience a diamagnetic ring current. This finding matches well with the experiment observation that this methyl group in the

Table 1 Energies of the two diastereoisomers of **2**$^{4+}$ calculated using different force fields. Solvent: $CHCl_3$

E/kcal mol^{-1}	MMFF	AMBER*	OPLS	MM2
(*S*)-(*M*)-**2**$^{4+}$	279.6	−4.5	−52.3	−154.0
(*S*)-(*P*)-**2**$^{4+}$	285.9	0.5	−49.1	−151.7
[(*S*)-(*M*)-**2**$^{4+}$] – [(*S*)-(*P*)-**2**$^{4+}$]	−6.3	−5.0	−3.2	−2.3

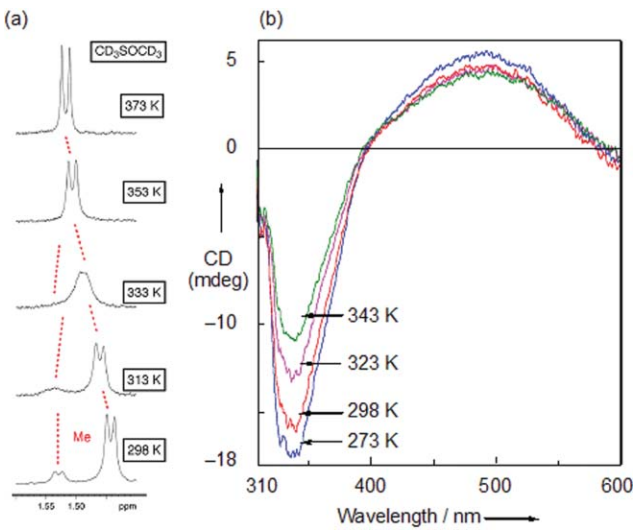


Fig. 1 Partial (a) ^{1}H NMR and (b) CD spectra of the chiral pretzelane (*S*)-(*PM*)-**2**·4PF$_6$ recorded at different temperatures in CD_3SOCD_3 and MeCN, respectively.

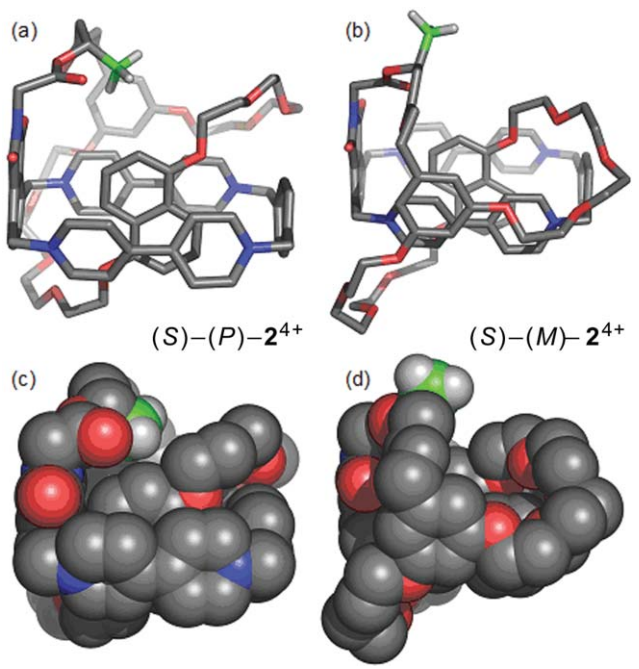


Fig. 2 MM2-optimised structures of the (*S*)-(*P*)-**2**$^{4+}$ and (*S*)-(*M*)-**2**$^{4+}$ isomers as portrayed by (a and b) framework and (c and d) space-filling representations, respectively.

minor conformation displays a downfield shift (δ = 1.53 ppm) in the ^{1}H NMR spectrum (Fig. 1a) relative to the δ value of 1.44 ppm for the methyl group of the major conformation.

What are the wider implications of the results reported herein? They are to be found in the fact that both the ΔG° and $\Delta G^\ddagger$ values for the two equilibrating diastereoisomeric pretzelanes are almost a perfect match for those thermodynamic parameters that have been shown[24] very recently in solution to characterise bistable, donor–acceptor [2]catenanes and [2]rotaxanes which exhibit metastabilities in a range of different environments,[25] including molecular switch tunnel junctions in molecular electronic devices[26,27] capable of functioning as random access memory. In the immediate future, we can foresee that, by replacing the methyl group in the chiral pretzelane with bulkier substituents (*e.g.*, *t*-butyl, phenyl, *etc.*), improved diastereoselectivities might be obtained without sacrificing the high energy barrier to interconversion of the diastereoisomers. Such investigations on optically active pretzelanes might lead to new opportunities for the construction of chiroptical switches that can be electrochemically activated.

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Notes and references

‡ In principle there is another element of chirality present in $\mathbf{1}^{4+}$, namely the planar chirality associated with the 1,5-dioxynaphthalene ring system, giving rise to both (*pR*)- and (*pS*)-conformations. In practice, only the (*pR*)-(*P*)/(*pS*)-(*M*) enantiomeric pair of diastereoisomers are observed (see ref. 15) in the solid state and in solution for $\mathbf{1}\cdot 4PF_6$, *i.e.*, the planar chirality is determined by the helical chirality. We have assumed this same situation holds for $\mathbf{2}\cdot 4PF_6$.

§ Synthesis of the precursor **3** is described in the Supporting Information.

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