# The First [2.2]Cyclophane with Free N–H in the Bridge

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The synthesis, absolute configuration, chiroptical properties and hydrogen bonding of the helical-chiral title compound **1** are reported, which is the first strained [2.2]phane that has an unsubstituted nitrogen in the bridge; an X-ray structure analysis shows **1** to crystallise spontaneously enantiomerically pure, and the presence of the sulfur atom allowed the determination of the absolute configuration of the (−)-enantiomer to be established as a left-handed (*M*) helix.

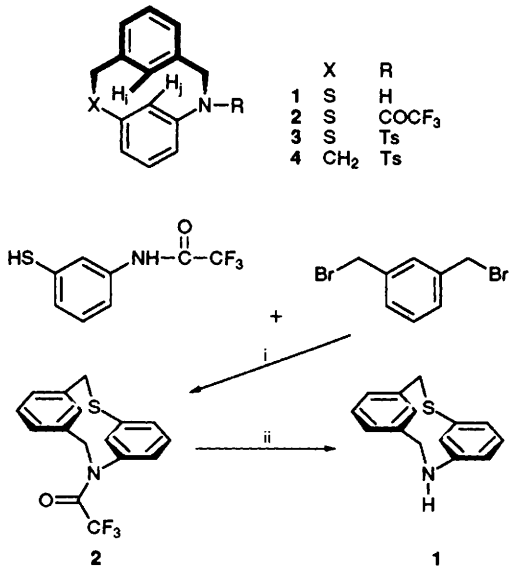
[2.2]Metacyclophanes of type **3** and **4** have proved to be inherently helical-chiral due to the different length of their two bridges.[1] Their helicity and transannular strain can be tailored gradually by using different bridge atoms X. The resulting propeller-shaped molecules are interesting objects for studying deformation,[2] spectroscopic consequences[3] and relations between structure and circular dichroism (CD).[4]

Apart from the known *N*-tosyl-substituted compounds **3** and **4**, no free 1-aza[2.2]phane could be prepared as yet. They are interesting with regard to nitrogen inversion in strained rings[5] and they could also serve in asymmetric synthesis, using the helicity of the [2.2]metacyclophane skeleton as chiral information. Fixing chromophores (*e.g.* NO, $NO_2$, halogen) at the nitrogen atom would lead to chiral compounds relevant for structure–chiroptics correlations and comparison with substituted aziridines[6] and pyrrolidines.[7]

The reason why all hitherto known aza[2.2]cyclophanes are *N*-tosylated[8] is that the tosyl group ($p$-$MeC_6H_4SO_2$) was considered to be necessary for activating the nitrogen and to promote the formation of the ten-membered cycle. All attempts to remove it after synthesis were unsuccessful for strained *N*-heterocycles.

The tosyl group has a strong electronic and steric influence on nitrogen and this makes the comparison of experimental results (CD, X-ray) with theoretical calculations difficult. Moreover, the large tosyl group hinders the separation of the enantiomers by HPLC.

In order to yield the free amine **1** for the first time, we prepared the hitherto unknown trifluoroacetyl (TFA) substituted cyclophane **2** (Scheme 1). By using the dilution principle and the solvent combination acetone–DMF, we reduced the *O*-alkylation side-reaction and obtained **2** in 40% yield,† which is surprisingly high for C–X-coupling reactions to such strained compounds.




**Scheme 1** i, Acetone–DMF–$Cs_2CO_3$ (high dilution); ii, KOH–MeOH

The crystal structure‡ of **2** (Fig. 1) shows a nearly planar geometry at nitrogen (bond angles at nitrogen 119, 127, 115°), similar to the corresponding *N*-tosyl compound **3**.[9]

Abstraction of the TFA-protecting group yielded the desired free amine **1** in quantitative yield by simple hydrolysis under smooth conditions.† Both racemates **1** and **2** could be split into the enantiomers by HPLC, using chiral column material.§ The CD spectra (Fig. 2) were measured down to

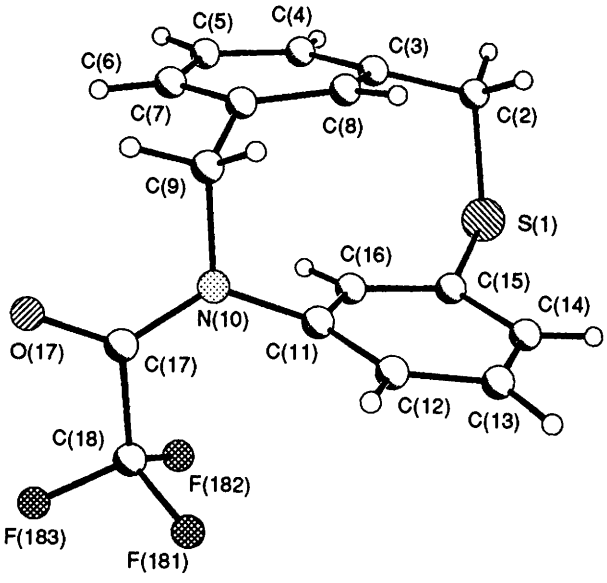



**Fig. 1** X-Ray crystal structure of **2** (perspective view)

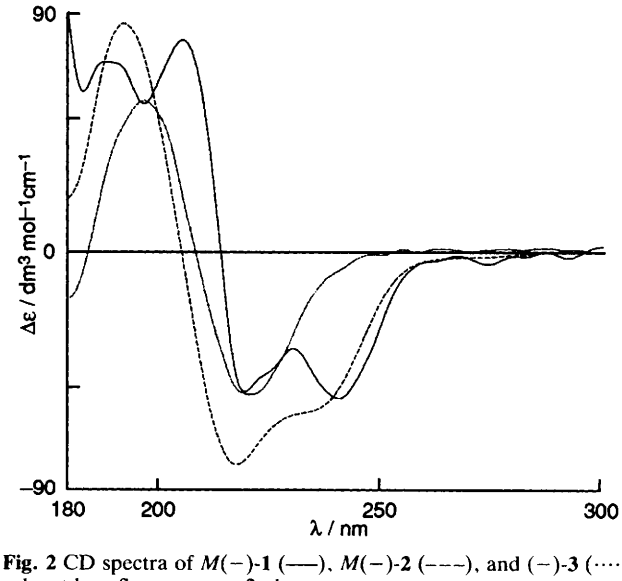



**Fig. 2** CD spectra of *M*(−)-**1** (——), *M*(−)-**2** (– – –), and (−)-**3** (····); solvent hexafluoropropan-2-ol

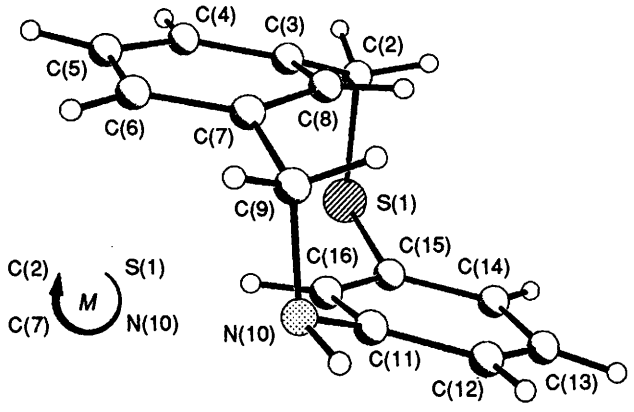



**Fig. 3** X-Ray structure of *M*(−)-**1**

short wavelength (180 nm), which allowed the investigation of aromatic transitions. With the tosylamides **3** and **4**, interpretations of such transitions were not possible. The curves show, compared with the tosyl compound **3**, a finer resolution of single Cotton effects (CE), allowing a better assignment of the corresponding transitions, whereas the CD of **3** contains too many transitions caused by the additional tosyl chromophore, which overlap with the CD of the metacylophane skeleton.

1-Thia-10-aza[2.2]metacyclophane **1** remarkably crystallises spontaneously as pure enantiomers. The presence of the sulfur atom in the molecule enables the determination of the absolute configuration using anomalous dispersion of X-rays (Fig. 3).‡ The helicity was determined as *M* (left-handed) for (−)-**1**.[10] The assignment of the configuration to the CD spectra of *M*(−)-**1** could be ascertained by measuring the CD spectra of the crystal used for the X-ray analysis. Corresponding to this assignment, the helicity of **2** can be assumed to be the same as for *M*(−)-**1**, because the transitions responsible for the CD are known, and are of equal sign for both compounds.

The crystal structure of *M*(−)-**1** (Fig. 3) shows a remarkably short intermolecular N–H···N distance of 233 pm, leading to the formation of dimeric species in the solid state. These pairs are stacked, resulting in a channel structure. The formation of the chiral crystal is probably favoured by this hydrogen bond pattern. The nitrogen atom of the amine has a pyramidal geometry, with C(9)–N(10)–C(11) 112°, so that there are two possible positions for the hydrogen. Calculations indicate that these are energetically nearly degenerate and there is only a very small barrier for this type of inversion process.[11] The classical pyramidal inversion at nitrogen (complete interconversion of the two enantiomers) is not possible because of the rigidity of the [2.2]metacyclophane skeleton.[12]

The possibility of fixing suitable substituents (chromophores) at the nitrogen atom of **1**, combined with further theoretical studies, is expected to result in new knowledge about the inversion behaviour of nitrogen, and will be the object of future work.

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## Footnotes

† Selected data (**1** and **2** gave analytical data fully consistent with their structures): **1**, mp 137 °C, $^1$H NMR ($CDCl_3$) δ 2.80 (s, 1H, $D_2O$ exchangeable), 4.35 (t, 1H, $H_i$), 4.63 (t, 1H, $H_i$); **2**, mp 122 °C, $^1$H NMR ($CDCl_3$) δ 4.60 (t, 1H, $H_i$), 4.72 (t, 1H, $H_i$).

‡ *Crystallographic data for M*(−)-**1**: $C_{14}H_{13}NS$, $M$ = 227.3, orthorhombic, space group $P2_12_12_1$, colourless crystals, dimensions 0.55 × 0.15 × 0.05 mm, $a$ = 5.178(1), $b$ = 13.239(1), $c$ = 16.467(1) Å, $V$ = 1128.8(2) Å$^3$, $D_c$ = 1.34 g cm$^{-3}$, $Z$ = 4, μ(Cu-Kα) = 2.27 mm$^{-1}$, $T$ = 193 K, 1672 symmetry independent reflections were used for the structure solution (direct methods) and refinement (full-matrix least squares on $F^2$, 148 parameters), non-hydrogen atoms were refined anisotropically, H-atoms localised by difference electron density and refined using a 'riding' model, the H(N) was refined free. $wR2$ = 0.126{$R_1$ = 0.051[$I > 2\sigma(I)$]}. A semiempirical absorption correction on the basis of ψ-scans was applied. Absolute structure parameter $x$ = −0.02(4) (Flack parameter).

*Crystallographic data* for **2**: $C_{16}H_{12}F_3NOS$, $M$ = 323.3, monoclinic, space group $P2_1/c$, $a$ = 5.428(1), $b$ = 16.478(1), $c$ = 16.607(1) Å, β = 98.66(1)°, $V$ = 1468.4(3) Å$^3$, $D_c$ = 1.46 g cm$^{-3}$, $Z$ = 4, μ(Cu-Kα) = 2.29 mm$^{-1}$, $T$ = 293 K, 2501 symmetry independent reflections were used for the structure solution (direct methods) and refinement (full-matrix least squares on $F^2$, 200 parameters), non-hydrogen atoms were refined anisotropically, H-atoms localised by difference electron density and refined using a 'riding' model. $wR2$ = 0.218{$R_1$ = 0.065[$I > 2\sigma(I)$]}. Extinction and semiempirical absorption corrections (ψ-scans) were applied. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1.

§ Chromatographic separation: **1**, Chiralpak OP stationary phase, solvent *n*-hexane–propan-2-ol (95:5); **2**, Chiracel OD, *n*-hexane–propan-2-ol (99:1)

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10 For definitions of *P*, *M*, (+), (−); see G. Snatzke in *Chirality—From Weak Bosons to the α-Helix*, ed. R. Janoschek, Springer, Heidelberg, 1991.
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