

Changing the shape of Tröger's base

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Abstract—The first synthesis of Tröger's base analogues bearing three and four atoms in the apical strap is reported, leading to a dramatic change in the shape of the aromatic scaffold with respect to the Tröger's base framework.
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Tröger's base¹ **1** is a rigid V-shaped compound that is chiral by virtue of the two stereogenic nitrogen atoms in the diazocine bridge (see Fig. 1). It was the first chiral tertiary amine to be successfully resolved as it is unable to undergo pyramidal inversion. Its resolution was achieved with what was perhaps the first example for the use of a chiral stationary phase.²

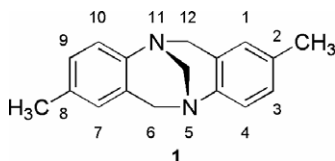


Figure 1. Chemical structure of Tröger's base **1** and the accepted numbering system.

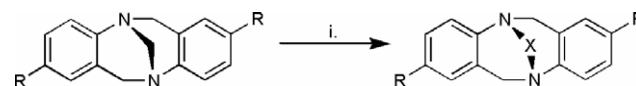
Compounds based on this framework are of interest because of their potential to function as artificial receptors^{3–10} and catalysts in asymmetric transformations.^{11,12} Tröger's base analogues are produced as racemic mixtures from an acid-catalysed condensation of anilines and formaldehyde and much of the chemistry of these systems has focussed on increasing the type of functionality on the aniline units.^{10,13–19}

Although less numerous, modifications to the diazocine bridge region of Tröger's base have also been reported. One of the bridgehead nitrogens can be alkylated,^{20,21} as can one, or both, of the benzylic methylene units.^{12,22} The apical methylene unit can also be removed and the resultant cyclic disecundary amines have been

reacted with several aldehydes and a limited number of ketones to afford systems with a substituted methylene group in the strap.^{23–25} Molecular modelling studies predict that these alterations impart only minor changes on the overall shape of molecules and that the aromatic rings remain at an angle of approximately 90° with respect to one another. In the case of N-methylation an X-ray structure supports the modelling results.²⁰

A more significant change is predicted if the number of atoms strapping the two bridgehead nitrogens is increased.²⁶ The preparation of ethano-strapped 2,8-dimethyl and 2,8-dimethoxy Tröger's base analogues, **2** and **3**, respectively, was reported in 1996,²⁷ (Scheme 1, R = CH₃ or OCH₃ and X = CH₂CH₂) and the same methodology was recently used to obtain an ethano-strapped 2,8-dibromo Tröger's base **4** (Scheme 1, R = Br and X = CH₂CH₂).²⁶ A recent report that treatment of a Tröger's base analogue with activated acetylenes in the presence of ZnBr₂ afforded a three-atom strapped compound²⁸ has since been corrected, with the product found to be a functionalised methano-strapped analogue of Tröger's base.²⁹

We have initiated a study aimed at investigating the scope and limitations of the reaction of methano-strapped Tröger's base analogues with dialkyl halides



Scheme 1. Reagents and conditions: (i) BrCH₂CH₂Br or BrCH₂CH₂CH₂CH₂Br or BrCH₂CH₂CH₂CH₂CH₂Br or α,α' -dibromo-*o*-xylene or 2,3-bis(bromomethyl)quinoxaline, LiCO₃, DMF, 110 °C, 3 days.

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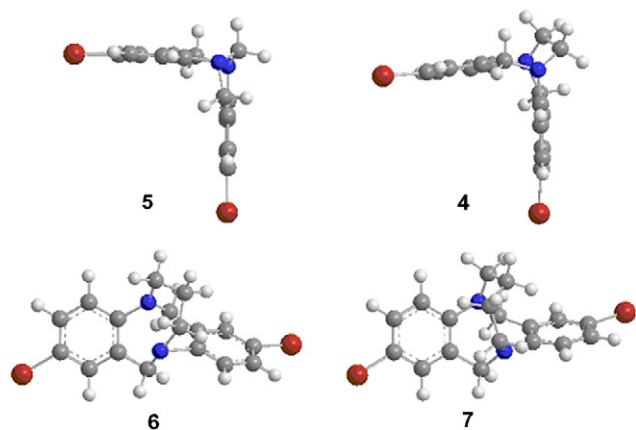


Figure 2. Illustration of the difference in cavity size, as predicted by modelling with CHEM-3D, of methano-, ethano-, propano- and butano-strapped 2,8-dibromo Tröger's base systems **5**, **4**, **6** and **7**, respectively.

(to afford strap-modified analogues) by varying the substituent type, substituent position and the length of the dialkyl halides. Models of 2,8-dibromo Tröger's base **5** and its ethano-, propano- and butano-strapped derivatives, **4**, **6** and **7**, respectively, are shown in **Figure 2**. It is readily apparent that the ethano-strapped derivative **4** is predicted to have a tighter 'bite-angle' than **5**, whilst a strap length of either three or four atoms is predicted to essentially remove any cavity from the compounds.

In the present work, methano-strapped 2,8-dibromo Tröger's base **5** was reacted separately with 1,2-dibromoethane, 1,3-dibromopropane, 1,4-dibromobutane, α,α' -dibromo-*o*-xylene and 2,3-bis(bromomethyl)quinoxaline according to the conditions outlined in **Scheme 1** ($R = \text{Br}$).

The reaction with 1,2-dibromoethane afforded **4** in 67% yield (**Table 1**), comparable with the reported yields of **2** (76%) and **3** (72%). An analogous reaction with 1,3-dibromopropane afforded **6** in a yield of only 10%.

The poor yield of **6** was not unexpected as it involves the formation of an eight-membered ring (cf. the 6- and 7-membered rings, incorporating the apical unit, that are present in methano- and ethano-strapped analogues, respectively).

Attempts to incorporate an additional methylene unit in the strap with the use of 1,4-dibromobutane to afford **7**

Table 1. Yields of the alternate-strapped 2,8-dibromo Tröger's base compounds **4** and **6–8**

	R	X	Yield (%)
4	Br	CH ₂ CH ₂	67
6	Br	CH ₂ CH ₂ CH ₂	10
7	Br	CH ₂ CH ₂ CH ₂ CH ₂	—
8	Br	<i>o</i> -(CH ₂) ₂ C ₆ H ₄	40
9	Br	2,3-(CH ₂) ₂ C ₈ H ₄ N ₂	38

were unsuccessful. In this instance no evidence of a Tröger's base material was observed in the ¹H NMR spectra of crude reaction mixtures after work-up. In fact, only a minor percentage of the expected organic mass was recovered from the organic extracts. We believe this may be the result of a combination of two factors: firstly, mono-N-alkylation, which would give rise to the formation of salts and secondly, the possibility that 1,4-dibromobutane may serve as a dimerising/oligomerising unit via a reaction with nitrogen atoms of two different Tröger's base molecules.

A more rigid four-atom strap was incorporated successfully through the use of either α,α' -dibromo-*o*-xylene or 2,3-bis(bromomethyl)quinoxaline to afford **8** and **9** in yields of 40% and 38%, respectively. The double bond present as part of the aromatic rings removes one degree of freedom in comparison with a saturated C4 chain, making the final C–N bond formation and ring-closure reaction more entropically favourable.

Compounds **4**, **6**, **8** and **9** were obtained as racemic mixtures and all retain the two stereogenic nitrogen centres present in the methano-strapped precursor. In fact, the resolution of **2** through diastereomeric salt formation has been previously reported.²⁷

Having prepared a number of Tröger's base derivatives with modified straps, we next compared their solid state structures with those predicted by molecular modelling studies. The X-ray crystal structure of methano-strapped 2,8-dibromo Tröger's base **5** has been previously reported and the two aromatic rings were found to be held at an angle of 94.5° with respect to one another.³⁰ This dihedral angle lies within the range of 82°¹⁸ to 108°³¹ which are the lower and upper limits that have been found across a range of simple methano-strapped dibenzo Tröger's base analogues. An X-ray crystal structure of **4** revealed the equivalent dihedral angle to be 86.1° (**Fig. 3**). This is a reduction greater than 8° and is in agreement with the smaller cavity predicted by modelling studies (**Fig. 2**).³²

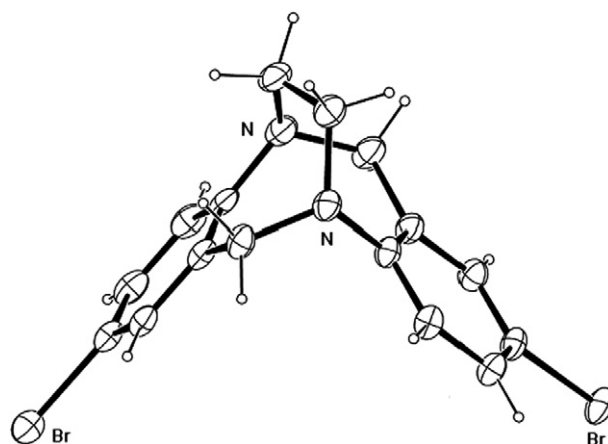


Figure 3. ORTEP plot of the molecular structure of 2,8-dibromo ethano-strapped Tröger's base **4**. Thermal ellipsoids are shown at the 50% probability level.

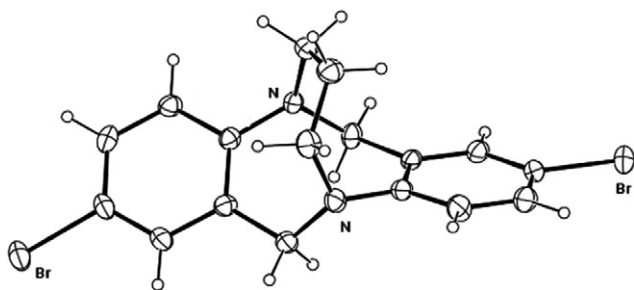


Figure 4. ORTEP plot of the molecular structure of 2,8-dibromo propano-strapped Tröger's base **6**. Thermal ellipsoids are shown at the 50% probability level.

The addition of an extra methylene unit in the strap of **6** imparts a dramatic change on the shape of the molecule, effectively removing any cavity between the two aromatic rings as the molecule is 'flattened out' (Fig. 4), again as predicted by modelling studies. The dihedral angle was determined to be 134.7° and the two aromatic rings are in a propeller-like orientation with respect to one another.³²

This basic propeller-like shape is maintained in the *o*-xyleno- and 2',3'-dimethanoquinoxalino-strapped derivatives **8** and **9** (Figs. 5 and 6).³²

In the case of compound **8**, the dihedral angle between the two bromo-bearing aromatic rings was measured as 132.4° and a new cavity was created, with the xyleno-strap forming one of the walls. The dihedral angle between the two walls of this new cavity was found to be 48.9° , whilst the corresponding angles in **9** were 127.0° and 52.1° .

In the solid-state structures of **8** and **9**, and to a lesser extent **6**, it is apparent that the two bromo-bearing aromatic rings are no longer equivalent to one another as the strap is located over one of the aromatic rings. This phenomenon is not reflected in the solution-state NMR spectra of the compounds, where C_2 symmetry typified by the methano- and ethano-strapped compounds **5** and **4** is readily apparent. ^1H NMR spectra of **9** obtained at low temperature (218 K, CDCl_3) did not exhibit any significant changes in comparison with spectra obtained at room temperature. This suggests that in

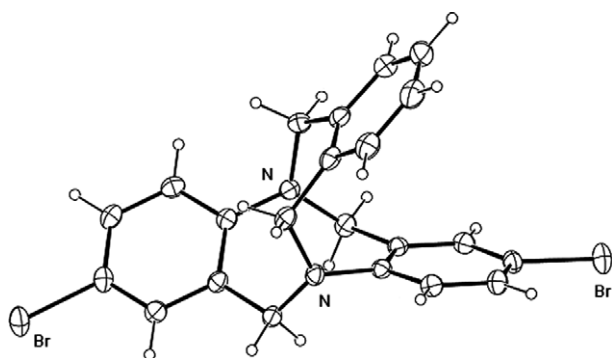


Figure 5. ORTEP plot of the molecular structure of 2,8-dibromo *o*-xyleno-strapped Tröger's base **8**. Thermal ellipsoids are shown at the 50% probability level.

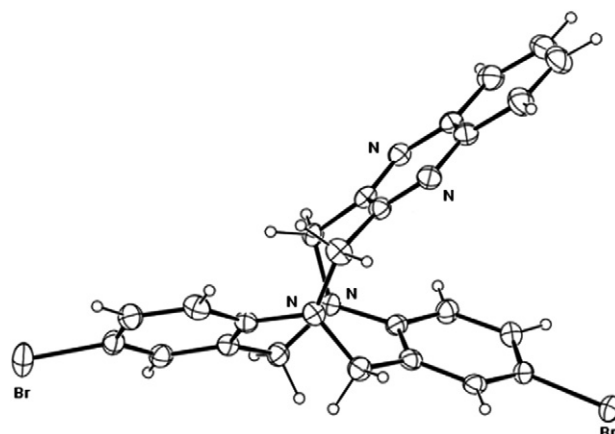


Figure 6. ORTEP plot of the molecular structure of 2,8-dibromo-2',3'-dimethanoquinoxalino-strapped Tröger's base **9**. Thermal ellipsoids are shown at the 50% probability level.

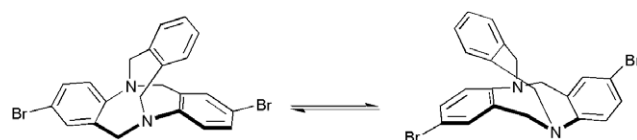


Figure 7. Possible conformational twisting in Tröger's base **8** that would account for the observed C_2 symmetry in solution ^1H NMR studies.

the solution state the compounds either adopt a C_2 conformation or exist in a rapid equilibrium between two conformations in which the strap is able to flip from lying over one halogen-bearing ring to the other as illustrated in Figure 7 for compound **8**.

In summary, we have reported the first examples of Tröger's base analogues bearing three and four atom straps, and the first solid-state structures of Tröger's base analogues bearing two, three and four atoms in the straps. The ability to alter the nature of the cavity in these systems will have implications for their application in the design of new catalysts and host-guest complexes. Investigations in both of these areas are underway in our laboratory and our findings will be reported in due course.

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32. The crystallographic data (excluding structure factors) for the structures in this Letter have been deposited with the Cambridge Crystallographic Data Centre as Supplementary Publication Nos CCDC 631380 (4); CCDC 631381 (6); CCDC 631383 (8); and CCDC 631382 (9). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk or <http://www.ccdc.cam.ac.uk>).