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Absolute configuration of Tröger bases: an X-ray diffraction and circular dichroism study☆

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Abstract—Bis-*ortho*-methyl-bis-*meta*-bromo Tröger base (TB) **2** and bis-*ortho*-methyl TB **3** were prepared in enantiopure form. The absolute configuration for (5*S*,11*S*)-(−)-**2** was determined by X-ray diffraction. The sign of the longest wavelength band in the electronic CD spectrum is negative for both (5*S*,11*S*)-(−)-**2** and (5*S*,11*S*)-(−)-**3**, as well as for the parent *para*-methyl TB (5*S*,11*S*)-(+)-**1**, which is in agreement with TD DFT B3LYP/6-31G(d,p) calculations.

The absolute configuration (AC) of Tröger's base (TB) **1** analogs (*Tröger bases*, TBs) is a topic of both practical and theoretical importance.[1] Among recent advances, TBs were shown to bind stereospecifically to DNA[2] and were used in asymmetric synthesis of C_{60} derivatives with chiral substitution patterns.[3] The historical controversy arose from the assignment of the different AC of TB **1** from its circular dichroism (CD) and optical rotatory dispersion spectra,[4] whereas exciton chirality models were successfully used to interpret the CD spectra of TB chromophores elongated by aromatic fusion.[2b,5] X-ray diffraction analysis[6] (XRD) and, subsequently, vibrational CD and optical rotation calculations[7] finally proved the AC as (5*S*,11*S*)-(+)-**1**. However, reports on electronic CD of simple TBs are, to our knowledge, scarce in the literature. Thus, the sign of the long wavelength band of the CD spectra of TBs was used in empirical assignment of the absolute configuration of ethano-TB[8] and of two *para*-substituted TBs.[3a] This letter adds more factual proof to such assumptions.

Of special significance was the determination of the AC of bis-*ortho*-methyl substituted TBs, as far as *ortho*-alkyl-substituents increase the volume of the hydrophobic pocket of TBs.[9a,b] Bis-*ortho*-methyl-bis-*meta*-bromo TB **2** was prepared by condensation of 3-bromo-2-methylaniline with formaldehyde.[9c] Resolution of **2** (20 mg scale), which crystallizes as a racemic conglomerate (chiral space group $P2_12_12_1$),[9c] was achieved by crystallization of spherical homochiral druses (20–50 mg each) from toluene, followed by manual separation and recrystallization.[10] To our knowledge, this is only the third example of conglomerate crystallization among TBs.[3a,11] Hydrodebromination of racemic (±)-**2** by $LiAlH_4$ gave racemic (±)-**3** in 95% yield, enantiopure (−)-**2** gave (−)-**3** in similar high yield (Scheme 1).[12] The enantiomeric purity of **2** and **3** was monitored by HPLC and did not change significantly during the reaction.[13] The AC of a single crystal of (−)-**2** was determined by XRD and the refinement of the Flack parameter as 5*S*,11*S*.[10] From chemical correlation the AC of (−)-**3** is 5*S*,11*S*.

The CD spectra of compounds **1** (prepared according to Ref. 6), **2** and **3** were measured to link with the AC obtained from XRD (Fig. 1). Thus, the same crystal of **2** after XRD was dissolved in CH_2Cl_2 and its CD spectrum was measured to exclude enantiomeric impurity. For the three (5*S*,11*S*)-configured compounds the longest-wavelength band observed had a negative Cotton effect ($\Delta\varepsilon$) (Table 1). Therefore, an empirical correlation of the AC with this band might be established for these and probably structurally similar compounds.[3a]

Keywords: Absolute configuration; Circular dichroism; Tröger bases; X-ray diffraction analysis; TD DFT Calculations.

☆ Asymmetric Nitrogen. Part 93 (Part 92 see: Ref. 15).

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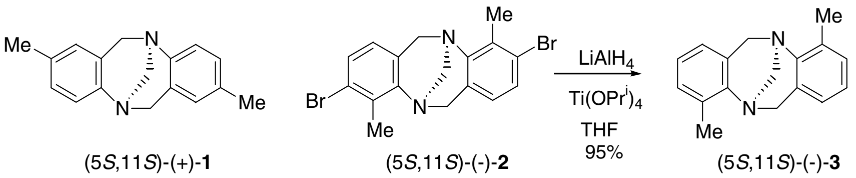

Scheme 1.

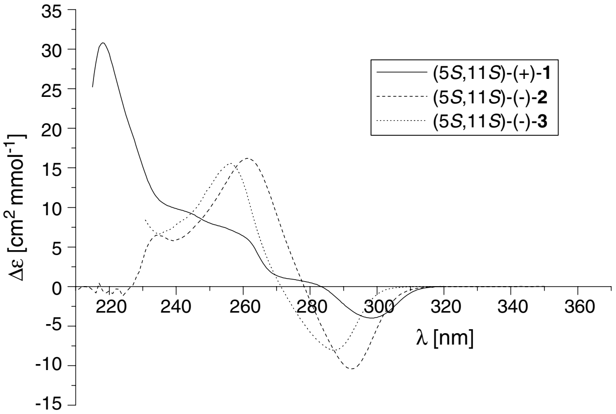

Figure 1. The CD spectra of compounds **1**–**3** at 293 K (Jasco J-720 spectrometer).

To verify this empirical assignment, we used time-dependent DFT with the Becke3LYP hybrid functional and 6-31G(d,p) basis set as implemented in the Gaussian 03 package[14] to calculate the electronic spectra of compounds **1**–**3** using their C_2 geometries, which were optimized at the B3LYP/6-31G(d,p) level. The first three excited states were taken into consideration. For (5*S*,11*S*)-**1** to (5*S*,11*S*)-**3** the calculations predict one common feature: the transition to the lowest-energy excited state (singlet B) (essentially the HOMO→LUMO n–π* transition) at 271–287 nm with the rotational strengths (*R*) of −20 to −25 cgs units. The calculated rotational strengths and wavelengths correspond favorably with the observed CD spectra of (5*S*,11*S*)-(+)-**1** to (5*S*,11*S*)-(−)-**3**, respectively (Table 1).

In conclusion, functionalized bis-*ortho*-methyl-bis-*meta*-bromo TB **2** and the bis-*ortho*-methyl TB **3** have been obtained in enantiopure form and their absolute configurations have been determined by X-ray diffraction and chemical correlation, respectively. The sign of the longest wavelength band in the electronic CD spectrum is negative for both (5*S*,11*S*)-(−)-**2** and (5*S*,11*S*)-(−)-**3**, as well as for the parent TB (5*S*,11*S*)-(+)-**1**, which is in agreement with TD DFT B3LYP/6-31G(d,p) calculations. An empirical correlation of the AC with this band might be established for structurally similar Tröger bases.

Acknowledgement

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Table 1. The longest-wavelength bands in the CD spectra of compounds **1**–**3**, observed bands and calculated (TD DFT B3LYP/6-31G(d,p)) transitions

Compound	Longest wavelength band, $\lambda_{\min}$ (nm) observed	$\lambda_{\min}$ (nm) calculated	$\Delta\varepsilon$ ($\lambda_{\min}$) (cm^2 mmol^{-1})	*R* (cgs units) calculated	Solvent
(5*S*,11*S*)-(+)-**1**	298.5	287	−4.0	−20	*n*-Hexane
(5*S*,11*S*)-(−)-**2**	292.0	277	−10.4	−25	CH_2Cl_2
(5*S*,11*S*)-(−)-**3**	287.0	271	−8.0	−20	*n*-Hexane

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10. Compound (±)-**2**: mp of racemic mixture 214–218 °C. Compound (−)-(5*S*,11*S*)-**2**: mp 263–264 °C, $[\alpha]_{406}$ -530 ± 5, $[\alpha]_{578}$ -212 ± 5 (*c* 0.29, CH_2Cl_2). ESI-MS: $[M+H]^+$ *m*/*z* 406.97524 (for $C_{17}H_{17}Br_2N_2^+$ calculated 406.97530), ee >95%. Compound (+)-(5*R*,11*R*)-**2**: mp 259–262 °C; $[\alpha]_{406}$ $+519 \pm 5$, $[\alpha]_{578}$ $+216 \pm 5$ (*c* 0.27, CH_2Cl_2). ESI-MS: $[M+H]^+$ *m*/*z* 406.97518 (for $C_{17}H_{17}Br_2N_2^+$ calculated 406.97530), ee >95%. A single crystal was grown from EtOAc/*n*-hexane mixture under slow evaporation conditions. The details of the XRD analysis and absolute configuration determination of (5*S*,11*S*)-(−)-**2** (excluding structure factors) were deposited at the Cambridge Crystallographic Data Centre as supplementary No. 253570. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].
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12. Compound (±)-**3** was obtained from (±)-**2** by $LiAlH_4$ reduction in THF using 10 mol % $Ti(OPr^i)_4$ as catalyst (0.5 h at 80 °C). Yield 95%. Mp 96–98 °C, ^1H NMR (400 MHz, $CDCl_3$): 2.41 (s, 2Me, 6H) 4.00 (d, 2H, ^2J −17 Hz), 4.33 (s, NCH_2N, 2H), 4.59 (d, 2H, ^2J −17 Hz), 6.77 (d, 2H, ^3J 7.4 Hz), 6.92 (t, 2H, ^3J 7.4 Hz), 7.04 (d, 2H, ^3J 7.4 Hz). For $C_{17}H_{18}N_2$ calculated (%): C 81.56, H 7.25, N 11.19. Found (%): C 81.72, H 7.40, N 11.06. Compound (−)-(5*S*,11*S*)-**3** was obtained from (−)-(5*S*,11*S*)-**2** by the same method with similar yield. Colorless oil. $[\alpha]_{406}$ -140 ± 5, $[\alpha]_{578}$ -81 ± 5 (*c* 2.0, C_6D_6). ESI-MS: $[M+H]^+$ *m*/*z* 251.15420 (for $C_{17}H_{19}N_2^+$ calculated 251.15428), ee >95%.
13. Compound **2**: Macherey-Nagel column Nucleodex-β-PM. Mixture of MeCN and water (1:1) was used as the mobile phase (1 ml/min flow rate). The retention times of the enantiomers are 10.3 and 11.5 min, the first eluted enantiomer was (5*S*,11*S*)-(−)-**2**. Compound **3**: Daicel column Chiralcel OD. 0.5% isopropanol/hexane was used as the mobile phase (0.8 ml/min flow rate). The first eluted enantiomer was (5*S*,11*S*)-(−)-**3**, with a retention time of 9.7 min, (+)-**3** elutes after 12.2 min. The resolutions were monitored by UV absorbance at 254 nm.
14. Computations were performed in the computing center of Cologne University (RRZK) using Gaussian 03, Revision B.04, Gaussian, Inc., Pittsburgh, PA, 2003.
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