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Resolution and Determination of the Absolute Configuration of a Twisted Bis-Lactam Analogue of Tröger's Base: A Comparative Spectroscopic and Computational Study

Ögmundur Vidar Rúnarsson,[†] Christian Benkhäuser,[‡] Niels Johan Christensen,[§] Josep Artacho Ruiz,[†] Erhad Ascic,[†,⊥] Michael Harmata,[∥] Victor Snieckus,[⊥] Kari Rissanen,[#] Peter Fristrup,[§] Arne Lützen,[‡] and Kenneth Wärnmark*[,†]

[†]Centre for Analysis and Synthesis, Department of Chemistry, Lund University, P.O. Box 124, SE-221 00, Lund, Sweden

[‡]Kekulé-Institute of Organic Chemistry and Biochemistry, University of Bonn, Gerhard-Domagk-Str. 1, D-53121, Bonn, Germany

[§]Department of Chemistry, Building 201, Technical University of Denmark, 2800 Kgs, Lyngby, Denmark

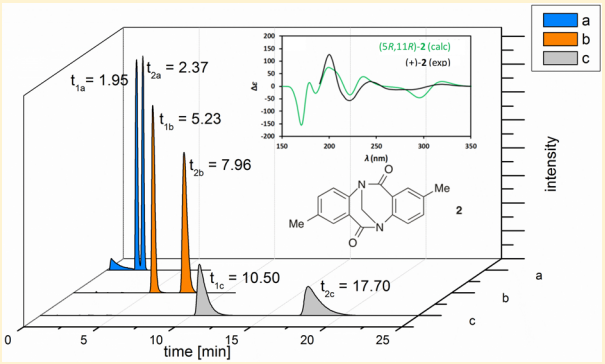
[∥]Department of Chemistry, University of Missouri—Columbia, Columbia, Missouri 65211, United States

[⊥]Department of Chemistry, Queen's University, Kingston, ON K7L 3N6, Canada

[#]Department of Chemistry, Nanoscience Centre, University of Jyvaskyla, P.O. Box 35, FI- 40014, Jyvaskyla, Finland

Supporting Information

ABSTRACT: The first reported twisted bis-lactam, a racemic Tröger's base (TB) analogue (**2**), was resolved into its enantiomers on a chiral stationary phase HPLC column. The absolute configuration of (+)-**2** was determined to be (*R*,*R*)-**2** by comparing experimental and calculated vibrational circular dichroism (VCD) and electronic circular dichroism (ECD) spectra. The absolute configuration of (−)-**2** was determined by comparing experimental and calculated electronic circular dichroism (ECD) spectra. The corresponding theoretical spectra were calculated using the lowest energy conformation of (*R*,*R*)-**2** and (*S*,*S*)-**2** at the B3LYP/6-31G(d,p) level of theory. The absolute configuration of (+)-**2** was also determined to (*R*,*R*)-**2** by anomalous X-ray diffraction (AXRD) in a chiral space group $P2_12_12_1$ using Cu-irradiation resulting in a very low Flack parameter of −0.06(3), despite the heaviest element being an oxygen atom, thus unambiguously confirming the results from the spectroscopic studies. We conclude that, for the Tröger's base (TB) analogue (**2**), we may rank the reliability of the individual methods for AC determination as AXRD ≫ VCD > ECD, while the synergy of all three methods provides very strong confidence in the assigned ACs of (+)-(*R*,*R*)-**2** and (−)-(*S*,*S*)-**2**.



INTRODUCTION

Tröger's base (TB)[1] (**1**, Figure 1) is a rigid V-shaped chiral aromatic diamine with two stereogenic nitrogen atoms. TB has a special role in the field of molecular chirality because it was the first chiral molecule identified that exhibits configurationally stable stereogenic nitrogen atoms at ambient temperature.[2] In addition, TB was one of the first chiral compounds that was resolved on a chiral stationary phase (CSP), (+)-α-lactose hydrate.[2,3] Due to its stereochemical properties and also to the presence of an aromatic cavity, TB is an attractive building block for the construction of molecules for application in the fields of molecular recognition, asymmetric catalysis, medicinal chemistry, and metallosupramolecular aggregates.[4−13]

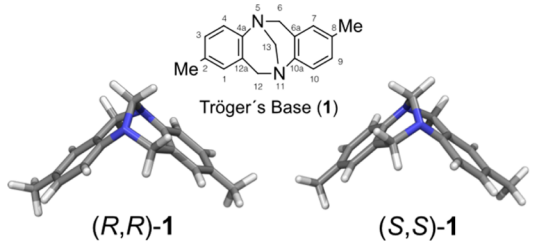


Figure 1. Racemic Tröger's base (TB, **1**) and the molecular mechanics optimized structures of the *R*,*R*- and *S*,*S*-enantiomers of TB.

The resolution of TB into its enantiomers by crystallization of diastereomeric salts is not feasible since TB undergoes racemization in dilute acidic media (0.1 N HCl in EtOH, 2.83 mg in 0.91 μL).[2] On the other hand, in concentrated acid (35% aq DCl) in which both nitrogen atoms are protonated, TB is not able to undergo ring cleavage to the iminium species,[14] which is proposed to be the key intermediate in the

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racemization process. However, Wilen and co-workers isolated the salt of (+)-**1** and (−)-1,1′-binaphthalene-2,2′-diyl hydrogen phosphate from a racemic mixture of TB.[15] This was made possible by an asymmetric transformation, driven by solubility differences between the two possible diastereomeric salts and led to the isolation of (+)-**1** in high yield. This salt was also used to assign the (+)-(*S*,*S*)-**1** absolute configuration by XRD analysis (*vide infra*). Several attempts have been made to use a crystallization-induced asymmetric transformation (CIAT) to resolve TB, with limited or controversial success.[16−19] Recently, however, Jameson and co-workers successfully employed CIAT for this purpose using (+)- and (−)-dibenzoyl-L or D-tartaric acid to obtain the respective enantiomers in good yields (63−91%).[20] Finally, Lenev, Sergeyev, and Kostyanovsky were able to crystallize TB derivatives and analogues as conglomerates and separate the enantiomers by optical inspection and manual separation.[21−23] In spite of these results, the lack of a general method to produce diastereomeric salts of TB analogues by selective crystallization makes HPLC on a chiral stationary phase (CSP) an attractive option for the separation of racemic TB analogues into their antipodes. In recent years, this has proven to be an effective method for the separation of enantiomers of various TB analogues and derivatives using either commercial or tailor-made CSPs.[24−27]

The determination of the absolute configuration of enantiopure molecules is important so that properties can be related to structure. Ideally, if X-ray diffraction (XRD) data can be obtained by either anomalous diffraction of heavy atoms (Mo- and Cu-irradiation for heavier and lighter atoms, respectively) or by comparing the relative configuration of the enantiomer of unknown absolute configuration to a reference compound with known absolute configuration in the same crystal. Using these methods, the absolute configuration of the enantiomer can be determined. However, if this cannot be achieved, one has to rely on the chiroptical properties of the enantiomer to predict the absolute configuration. For this purpose, empirical methods have been developed to relate chiroptical properties to the absolute configuration, *i.e.*, the determination of the Cotton effect using the *octant rule* by electronic circular dichroism (ECD) based on optical rotary dispersion (ORD).[28] Empirical NMR methods have also been developed, such as the popular Mosher's ester method.[29,30] Less reliable are methods based on optical rotation, by which the optical rotation of a compound with an unknown configuration is compared to a structurally related molecule with a known absolute configuration. Today, advances in density functional theory (DFT) calculations of chiroptical properties such as OR, ECD, and vibrational circular dichroism (VCD) have made it possible to determine the absolute configuration of a broad spectrum of chiral molecules by comparing experimental values and/or spectra of one of the enantiomers with calculated results.[31−35]

For the determination of the absolute configuration of a molecule in solution, VCD is considered to be the most reliable and informative technique. This is due to the large number of well-separated signals, in combination with the high accuracy of the calculations of vibrational transitions that are ground state configurations. On the other hand, for ECD excited state configurations have to be included, making the calculations more difficult.[31,35−37] The advances in VCD methodology and the increased availability of commercial VCD instruments, as well as the reliability of calculated VCD spectra using DFT and the availability of quantum mechanics programs, have made the VCD method increasingly more convenient to use for the assignment of the absolute configuration of chiral molecules.[38−40]

Reports emphasizing the use of DFT methods to calculate ECD spectra have stimulated the use of ECD for the establishment of the absolute configuration, although the assignments rely on only a few signals due to the relatively featureless electronic absorption transitions measured in the UV region of organic compounds.[32,41−46] ECD and OR are the most common methods used to date for the assignment of the absolute configuration, due to their high sensitivity and accessibility. However, the ECD spectra usually do not show as many distinct signals as compared to the VCD spectra. For OR there is a risk of the wrong assignment of the absolute configuration despite the comparison with the OR of a similar compound because a very small difference in the structure of two compounds can result in the change of sign of the OR signal.[47] At present, anomalous diffraction of X-ray spectra is used to assign the absolute configuration of molecules that contain an appropriate amount of heavy atoms; typically, one Cl-, P-, or S-atom for 15 carbons atoms in a molecule is sufficient. However, to grow a single crystal with large enough anomalous diffraction power and of an overall good quality is frequently the bottleneck in the determination of absolute configuration. Recently, the use of quotients in the refinement of the Flack parameter has opened a possibility to reliably determine the absolute configuration of a molecule/structure containing only weak anomalous scatterers like C-, N- and O-atoms.[48]

When the absolute configuration of TB was first proposed, its chiroptical properties were determined and compared with a similar molecule, the alkaloid argemonine.[49] The (+)-(*S*,*S*)-**1** absolute configuration was assigned in this way. However, the configuration was reassigned to *R*,*R* based on near-ultraviolet ECD measurements,[50] using the coupled oscillator or exciton coupling methodology.[51,52] In 1991, Wilen and co-workers reported an XRD analysis of a diastereomerically pure salt of monoprotonated (+)-**1** salt containing an enantiomerically pure counterion, in which the originally assigned *S*,*S* absolute configuration was confirmed,[15] showing the difficulties particularly in the use of the ECD methodology, even on a conformationally restricted system such as TB. The (+)-(*S*,*S*)-**1** absolute configuration was further confirmed by VCD studies.[53] The absolute configuration of analogues of TB have also been determined by ECD using TB itself as a reference compound, without the knowledge of the correct absolute configuration of (+)- and (−)-**1**.[54] The above results demonstrate that there are many problems associated with the assignment of the absolute configuration, even for a relatively rigid molecule such as TB. This motivated the present study in which different methods are used and compared in the assignment of the absolute configuration of the first example of a new class of TB derivatives, the TB twisted bis-lactam (**2**) (Figure 2). We recently reported the synthesis of **2** as a racemate.[55]

In general, twisted amides are compounds with steric repulsion or structural constraints that impair the overlap of the nitrogen lone-pair electrons with the carbonyl-π bond of the amide functionality. Compound **2** is the first reported twisted bis-amide as well as bis-lactam, and it shows unusual structural, physical, and chemical properties compared to normal amides as expected from other reports of twisted amides.[56−58] For instance, the N−C(O) bond of bis-lactam **1** undergoes hydrolysis faster compared to normal N−C(O)

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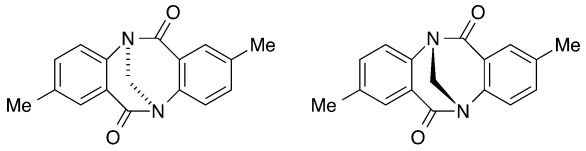

Figure 2. Two enantiomers of the twisted bislactam analogue of Trögerś base, compound **2**.[55,63]

bonds. In addition, having a [3.3.1]bicyclic framework, compound **2** is a good model for rather rigid molecular structures that are common in Nature such as garsubellin A[59,60] and huperzine A,[61] which are promising therapeutic agents against, *inter alia*, Alzheimer's disease.[62]

Herein, we report on the resolution and the assignment of the absolute configuration of twisted bis-lactam **2**, representing a rigid system with strong chromophores, by comparison of experimental and calculated ECD and VCD spectra of twisted bis-lactam **2** and by anomalous X-ray diffraction (AXRD) using Cu-irradiation.

The different methods are compared to suggest general guidelines for the determination of the absolute configuration of rigid systems with strong chromophores such as **2**.

RESULTS AND DISCUSSION

Separation of the Enantiomers. The racemate of twisted bis-lactam **2** was successfully resolved on an analytical scale (a few μg of **2**) using a chiral HPLC column ((*S*,*S*)-Whelk-01) with mixtures of CH_2Cl_2 and *n*-heptane as eluents and at different flow rates (Figure 3). By increasing the flow rate from

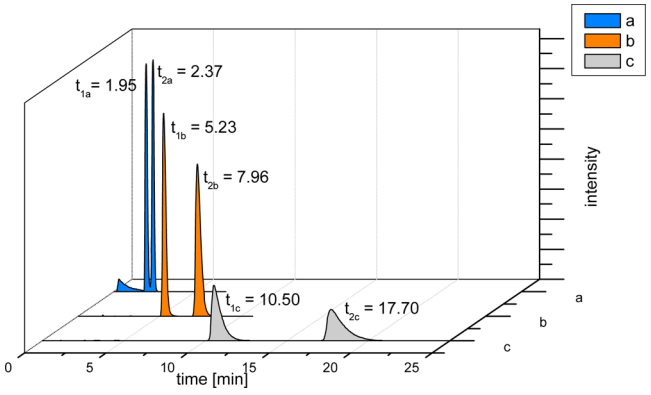

Figure 3. Chromatogram showing the separation of racemic twisted bis-lactam analogue of Tröger's base (**2**) in its two enantiomers on an analytical scale (a few μg of **2**) using different ratios of CH_2Cl_2/*n*-heptane as eluent: (a) ratio 40:60 (flow rate = 2 mL min^{-1}), (b) ratio: 25:75 (flow rate = 2 mL min^{-1}), and (c) ratio 10:90 (flow rate = 3 mL min^{-1}).

2 to 3 mL min^{-1} and changing the eluent from 40:60 CH_2Cl_2/*n*-heptane to 10:90, the differences in retention times of enantiomer **E1** and enantiomer **E2** of **2** increased from 0.42 to 7.20 min, respectively, resulting in a baseline separation of the two enantiomers (Figure 3). For the resolution on a semipreparative column (ca. 3 mg of **2**), a small amount of triethylamine (Et_3N) was used to improve the resolution, giving a baseline separation at 2.33 min using the eluent CH_2Cl_2/*n*-heptane/Et_3N (25:70:5) at a flow rate of 3 mL min^{-1} (see Supporting Information).

Having the two enantiomers resolved, the next task was to investigate their chiroptical properties. Specific rotation measurements revealed that the first eluting enantiomer **E1** has a negative specific optical rotation of $[\alpha]_D^{20} = -85.1$ deg mL dm^{-1} g^{-1} (c = 0.56 mol L^{-1}) and the second eluting enantiomer **E2** has a positive optical rotation of $[\alpha]_D^{20} = +85.3$ deg mL dm^{-1} g^{-1} (c = 0.45 mol L^{-1}) in acetonitrile solution. It is has been shown that it is impossible to assign the absolute configuration of two enantiomers of TB derivatives and analogues merely on the basis of these data by comparison with data of other TB derivatives of known configuration.[26,27] We therefore decided, as the next step, to record VCD and ECD spectra in order to compare them with simulated spectra obtained from quantum chemical calculations and thereby assign the absolute configuration of the resolved enantiomers.

Vibrational Circular Dichroism Spectroscopy. VCD spectra of the (+)-**2** (**E2**) enantiomer of the TB twisted bis-lactam were recorded in deuterated dichloromethane (CD_2Cl_2). CD_2Cl_2 was chosen as the solvent for recording the VCD spectra for two reasons: first, because it is a good solvent for compound **2** and, second, because the carbon–deuterium bond vibration occurs well below 1000 cm^{-1}, and hence, allows a clear view on the mid-IR fingerprint region of the spectrum of **2** without interference from solvent, as would have been the case if we had used CH_2Cl_2. However, the intensities of the individual VCD signals were still an issue as they are typically 4–5 times weaker than normal IR bands. Therefore, we had to accumulate data for about 20 h to obtain the well-resolved spectrum of the twisted bis-lactam analogue of TB, (+)-**2** (Figure 4).

In order to assign the absolute configuration, we compared the experimental VCD spectra with the VCD spectra obtained from DFT calculations of the 5*R*,11*R* and 5*S*,11*S* enantiomers of **2**, respectively (Figure 4). Common functionals used for calculating VCD spectra include the hybrid B3LYP or B3PW91 with the 6-31G(d) basis set.[64] For small molecules, even better results may be obtained by using a larger basis set, such as cc-p-VTZ and TZ2P.[65] However, for the TB analogues studied here, we found that the B3LYP/6-31G(d,p) level of theory provided a good balance between computational demands and agreement with experiment, and we thus employed this level of theory for the calculation of the VCD and ECD spectra. We applied implicit solvation for the experimental solvent (CH_2Cl_2) in all calculations of spectra, as this slightly improved agreement with experiment. In order to validate the computational scheme, VCD (and ECD) calculations for **2** at additional levels of theory, e.g. using the larger 6-311++G(d,p) basis set, were carried out and confirmed the assignments made at the B3LYP/6-31G(d,p) level; see Supporting Information sections S4.4 and S4.5.

The measured VCD spectra for the single enantiomer (+)-**2** is superimposed on the calculated VCD spectra for both enantiomers 5*R*,11*R* and 5*S*,11*S* of **2** in Figure 4a and Figure 4b, respectively. Disregarding the well-known blue shift of calculated frequencies due to anharmonicity neglect and basis set incompleteness,[66] the striking agreement between the calculated and experimental spectra in Figure 4a strongly suggests that the absolute configuration of enantiomer (+)-**2** is 5*R*,11*R*. The calculated VCD and experimental spectra show good agreement in the lactam region and, in general, correlate very well, showing sharp and well-resolved signals. Several bands across the spectrum can be correlated band-for-band and in some instances sign-for-sign. Also, an unmistakable agree-

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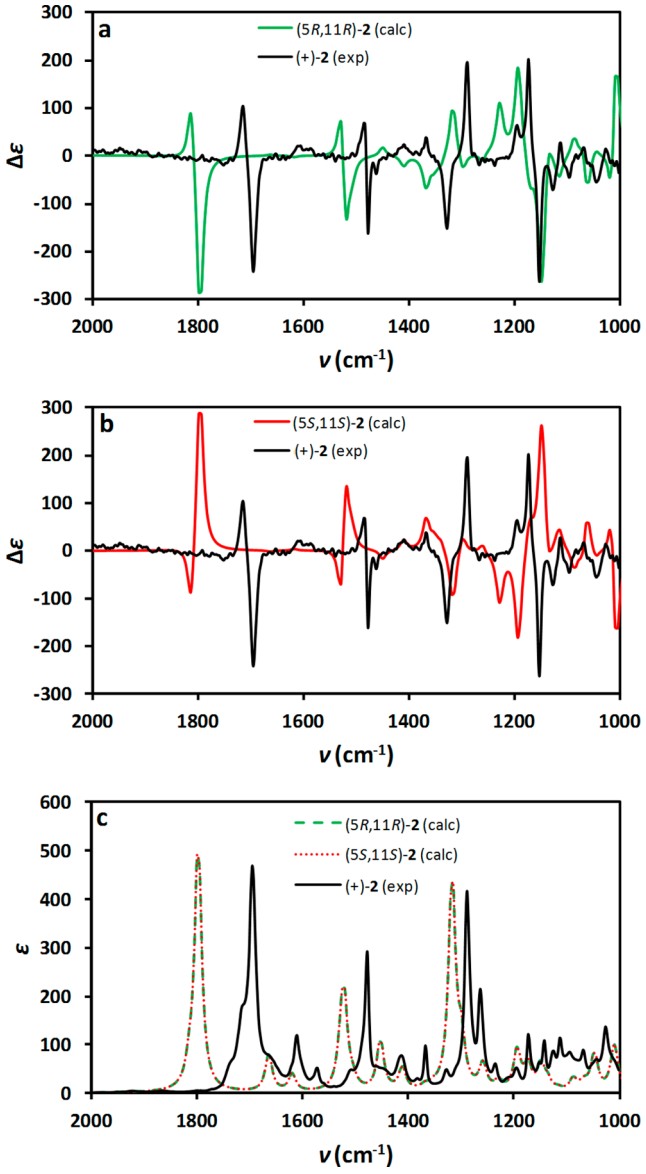

Figure 4. VCD and IR absorption spectra of compound **2** from experiments in CD_2Cl_2 (black) and DFT calculations with implicit CH_2Cl_2 solvent (red, green). The experimental spectra are for the single enantiomer (+)-**2** (**E2**), whereas calculated spectra are for each enantiomer of **2**. (a) Calculated VCD spectrum of (5*R*,11*R*)-**2** (green) versus the experimental VCD spectrum for (+)-**2** (black). (b) Calculated VCD spectrum of (5*S*,11*S*)-**2** (red) versus the experimental spectrum of (+)-**2** (black). (c) Calculated IR spectra of both enantiomers (5*R*,11*R*)-**2** (green) and (5*S*,11*S*)-**2** (red) versus the experimental IR spectrum of (+)-**2** (black). A frequency-scaling factor was not applied to the calculated spectra to correct for anharmonicity, which explains the calculated spectra appearing at a higher wavenumber. Frequency-scaled versions of the calculated spectra are included in the Supporting Information, Section S4.4. Experimental VCD and IR spectra amplitudes were multiplied by factors of 5×10^6 and 2000, respectively.

ment is seen between the calculated and measured IR absorption spectra (Figure 4c), further strengthening the reliability of the computational−experimental comparison. In Figure 4b, the "anti" signals are well visible, verifying that the measured enantiomer (+)-**2** and the calculated 5*S*,11*S* enantiomer are indeed different. In summary, the VCD analysis suggests that (+)-**2** has the (5*R*,11*R*)-**2** absolute configuration. This assignment was also strongly indicated when VCD/IR spectra were calculated at the B3LYP/6-311++G(d,p) level of theory; see Supporting Information, section S4.4.

Electronic Circular Dichroism (ECD) Spectroscopy. As discussed in the Introduction, the ECD method has proven to be a very valuable tool for stereochemical assignments and the absolute configuration of TB analogues has been assigned using ECD analysis.[45,46,54,55,67] The correlation between the lowest-energy Cotton effect in the CD spectra and the structure of TB has been illustrated and confirmed by anomalous X-ray diffraction.[21] However, Lützen and co-workers showed that the Cotton effect could drastically change depending on the electronic character of substituents and/or their positions on the aromatic ring, thus suggesting caution in the use of this technique.[26,27] In case of doubt, the recorded spectra should be compared to those obtained from quantum mechanical calculations. This comparison in theory allows unambiguous assignment of chirality, although limitations in the computational methods may yield spectra deviating from experiment, complicating the assignment in practice. Time-dependent DFT (TDDFT) is widely employed for the calculation of ECD spectra, since it offers the best balance of accuracy and computational cost of all QM methods.[68] A number of drawbacks of the TDDFT method are known,[69] including the inherent tendency to underestimate the excitation energies for high-lying excited states. Despite such limitations, TDDFT has proven to be highly successful in chirality assignment via ECD for a wide range of compounds.[70] We therefore undertook DFT calculations of the ECD spectra for the optimized structures of (5*R*,11*R*)-**2** and (5*S*,11*S*)-**2** as described in the Experimental Section.

As seen in Figure 5, there is indeed an excellent agreement between calculated spectra and the experimental UV−vis and ECD spectra of enantiomerically pure compounds recorded in CH_2Cl_2. These results nicely corroborate the assignment derived from the VCD analysis and confirm that the (−)-enantiomer, **E1**, has the 5*S*,11*S* absolute configuration and the (+)-enantiomer, **E2**, has the 5*R*,11*R* absolute configuration.

However, while the overlays of calculated and measured ECD spectra in Figure 5 support the chirality assignment from VCD analysis, it appears that the determination of the absolute configuration of **2** cannot be completely reliably based on ECD analysis alone. This is due mainly to the ambiguous reproduction of "fingerprint" features in the calculated ECD spectra, such as the comparatively weak asymmetry of the Cotton effect at 200 nm. Furthermore, the experimental Cotton effect at 242 nm is absent and the Cotton effect at 310 nm is disproportionately amplified. TDDFT calculations at three other commonly used levels of theory (see Supporting Information, section S4.5) gave ECD spectra in overall agreement with the B3LYP/6-31G(d,p) level calculations, with no method reproducing all features of the experimental spectra. Thus, a calculated spectrum may erroneously become aligned with the experimental spectrum for the opposite enantiomer, in particular if frequency scaling is employed without caution. Therefore, the assignment of the absolute configuration of the TB analogues investigated by ECD spectroscopy is strengthened considerably by having access to VCD spectroscopy.

X-ray Diffraction (XDR) Analysis. Finally, to confirm the VCD and ECD assignment based on the absolute configuration, we were also able to grow suitable single crystals of the

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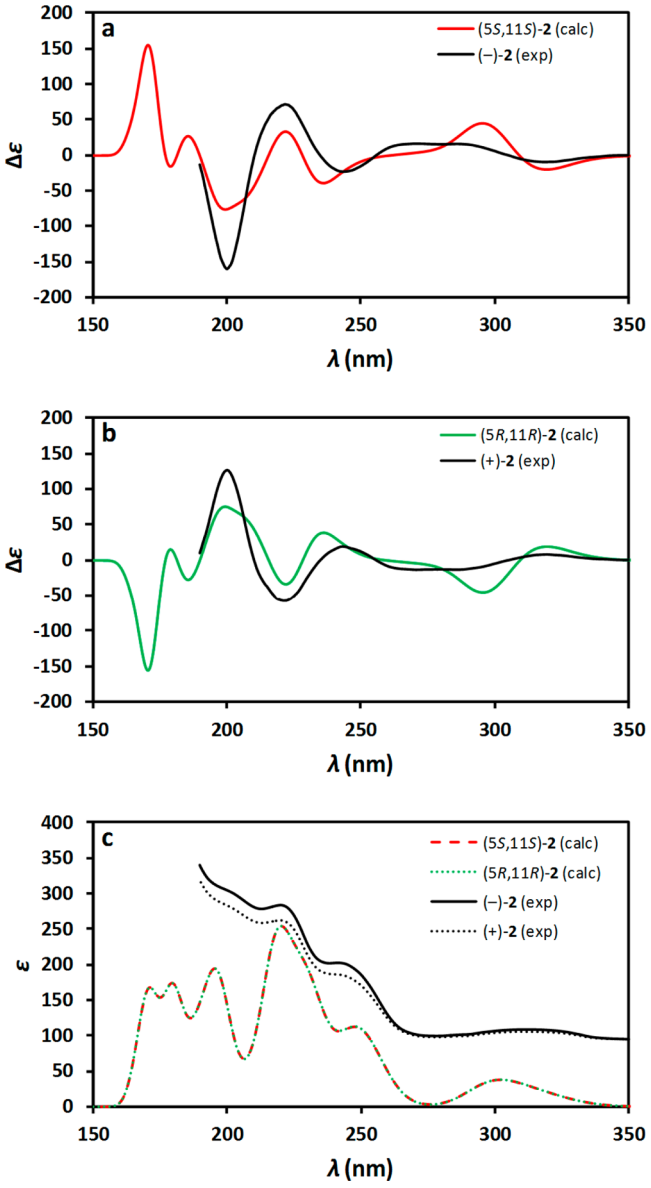

Figure 5. ECD and UV absorption spectra of the enantiomers of **2** from experiments in CH_2Cl_2 (black) and DFT calculations (green, red). (a and b) Calculated spectra in implicit solvent (CH_2Cl_2) for enantiomers (5*S*,11*S*)-**2** and (5*R*,11*R*)-**2**, respectively, superimposed on the best fitting experimental spectrum. (c) UV absorption spectra from experiments in CH_2Cl_2 (black) and calculations with implicit CH_2Cl_2 solvent (green, red). Experimental and calculated UV absorption intensities have been scaled with the factors 100 and 0.005, respectively.

(+)-enantiomer (**E2**) for XRD measurements via slow evaporation of a mixture of CH_2Cl_2 covered by *n*-heptane in a 3:1 ratio. The crystallization yielded excellent diffraction-quality crystals in an orthorhombic crystal system. A very careful full sphere data collection using Cu-radiation enabled the unambiguous determination of the absolute configuration of enantiomer (+)-**2** to be 5*R*,11*R*. Despite the lack of heavy atoms in the molecule, the excellent diffraction quality coupled with refinement of the Flack parameter (x) with Parsons' quotients[48] results in a very low value of x (−0.06) with an esd of ±0.03. The twist angle τ in the twisted TB analogue (+)-(5*R*,11*R*)-**2**, describing the deviation from coplanarity between the carbonyl p orbital and the nitrogen lone pair, was previously determined to be 43.78° for the racemic TB analogue **1** (*rac*-**1**) and may be compared to the τ = 0° or 180° commonly found in unconstrained *cisoid* and *transoid* amides, respectively.[71] In (+)-(5*R*,11*R*)-**2**, the τ values are −42.3° (N1/O2) and −47.0° (N2/O1) (Figure 6). The difference in τ

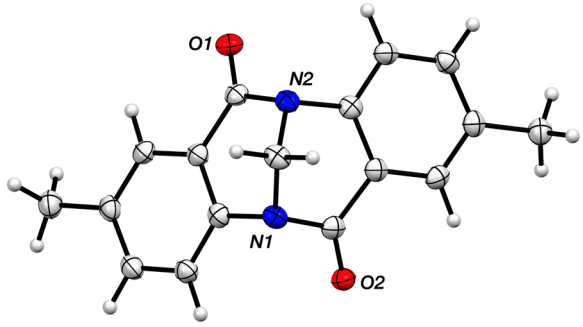

Figure 6. Molecular structure of TB (+)-(5*R*,11*R*)-**2** with the thermal displacement parameters at 50% probability level.

values between the two lactam functionalities in the molecule is probably due to packing forces. Furthermore, the overall distortion parameter Θ,[58] an additive term that provides a quantitative description of the combined deformation or pyramidality of the nitrogen and carbonyl carbon together with the twist angle, was determined to be 102.9° (N1/O2) and 109.2° (N2/O1) (see Supporting Information), whereas that of a simple planar amide is Θ = 0°; for the *rac*-**1**, it is 106.1°.[55] The difference in Θ parameter between the two lactam functionalities in the molecule is probably due to packing forces.

CONCLUSION

The first reported twisted bis-lactam analogue **2** (Figure 2) of racemic Tröger's base **1** (Figure 1) was successfully resolved via HPLC separation on a chiral stationary (*S*,*S*)-Whelk-01 phase. The absolute configuration of the enantiomers was unambiguously assigned using the combination of three independent approaches: Comparison of experimental/calculated VCD and ECD spectra, and AXRD. Together, these methods prove that the (−)-**2** is the (5*S*,11*S*)-**2** enantiomer and that (+)-**2** is the (5*R*,11*R*)-**2** enantiomer without the necessity to rely on any empirical rules that may lead to false assignments. When considering the reliability of the individual methods for the determination of the absolute configuration of **2**, we found that the assignment afforded by AXRD was strongly supported by the highly unambiguous comparison of calculated (DFT) and experimental VCD spectra, whereas the comparison of experimental and calculated (TDDFT) ECD spectra was more ambiguous. Thus, in the many practical cases where X-ray crystal structure analysis is not possible, we expect that the combined DFT/VCD approach may be a reliable single alternative for AC assignment of rigid compounds similar to **2**, while relying solely on a typical TDDFT/ECD approach (as presented here) may be less reliable.

In general, for both VCD and ECD, the calculated spectrum may erroneously become aligned with the experimental spectrum for the opposite enantiomer due to wrong frequency scaling especially in cases such as ours, in which the signals for the (+) and (−) enantiomers are in close proximity. Thus, the assignment of the absolute configuration of the resolved twisted bis-lactam TB analogue **2** was strengthened considerably by

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having access to both experimental and calculated ECD and VCD spectra as well as anomalous X-ray diffraction.

EXPERIMENTAL SECTION

General. All chemicals were used as received from commercial sources. Racemic **2** (*rac*-**2**) was synthesized according to our procedure.[56] Chiral HPLC was performed by using a Prominence console (binary system consisting of two pumps, degasser, diode array detector, and a fraction collector). Chiral analytical and semi-preparative stationary phases ((*S*,*S*)-Whelk-01 phase) were applied, and solvent mixtures of *n*-heptane and CH_2Cl_2 (HPLC quality) were used as eluant. VCD spectra were acquired in CD_2Cl_2 (7.8 mg/0.75 mL) by Biotools Inc., Jupiter, Florida, USA, using a BioTools ChiralIR-2X VCD spectrometer equipped with DualPEM technology. A 100 mm path-length cell with BaF2 windows were used. A 20 h collection time for the sample and the background solvent, respectively, was used. The instrument was optimized at 1400 cm^{-1} The solvent-subtracted VCD spectra are displayed. Crystal structures were edited with the Diamond 3.0 software. The solvents were dried, distilled, and stored under argon according to standard procedures.

Separation of the Enantiomers of 2. Analytical column (a few μg of **2**) HPLC: chiral phase (*S*,*S*)-Whelk-01, L = 300 mm, D = 4.0 mm, and d_p = 10 μm; eluent: *n*-heptane/CH_2Cl_2; (a) 40:60, f = 2 mL min^{-1}, (b) 25:75, f = 2 mL min^{-1}, (c) 10:90, f = 3 mL min^{-1}, and (d) semipreparative column (3 mg of **2**) HPLC: chiral phase (*S*,*S*)-Whelk-01, L = 250 mm, D = 10 mm, and d_p = 10 μm; eluent: *n*-heptane/CH_2Cl_2/TEA: 25:70:5, f = 3 mL min^{-1}.

*First Eluting Enantiomer (−)-(5S,11S)-**2** (**E1**).* Retention time: (a) 1.95 min, (b) 5.23 min, (c) 10.50, (d) 6.57; α_D^{25} = −85.1 deg mL dm^{-1} g^{-1} (c = 0.56 in ACN). Calcd for $C_{17}H_{14}N_2O_2 \cdot {}^5/_3H_2O$: C, 66.22; H, 5.67; N, 9.09. Found: C, 66.27; H, 5.41; N, 8.99.

*Second Eluting Enantiomer (+)-(5R,11R)-**2** (**E2**).* Retention time: (a) 2.37 min, (b) 7.96 min, (c) 17.70 min, (d) 9.30; α_D^{25}: +85.3 deg mL dm^{-1} g^{-1} (c = 0.46 in ACN). Calcd for $C_{17}H_{14}N_2O_2 \cdot {}^2/_7H_2O$: C, 72.03; H, 5.18; N, 9.88. Found: C, 72.33; H, 5.44; N, 9.43. Single crystals suitable for XRD analysis were grown via slow evaporation of a mixture of CH_2Cl_2 covered by *n*-heptane in a 3:1 ratio.

Computational Studies. Both enantiomers of the twisted bis-lactam analogue of Tröger's base (**2**) were built in Maestro[72] and subjected to a conformational search with 1000 Monte Carlo steps using the mixed torsional/low-mode sampling method with the OPLS_2005 force field and implicit water solvation.[73] A single conformer for each enantiomer was found within a window of 5 kcal mol^{-1}. These structures were optimized in the gas phase in Jaguar[72] at the B3LYP/6-31G(d,p) level of theory (optimized Cartesian coordinates are available in Supporting Information, section S4.1). Frequency calculations were undertaken at the same level of theory, and the absence of imaginary frequencies confirmed that the optimized structures were minima of the potential energy surface (PES).

IR absorption and VCD spectra were calculated in Jaguar using the standard Poisson−Boltzmann continuum solvation model with CH_2Cl_2 parameters[74,75] at the B3LYP/6-31G(d,p) level of theory as well as the B3LYP/6-311++G(d,p) level for validation (Supporting Information, section S4.4) using both enantiomers of **2** optimized to PES minima at the same levels of theory. The VCD calculation yielded discrete vibrational frequencies and rotational strengths for each vibrational mode (Table S2). In order to simulate spectra, the discrete rotational strengths were convoluted with Lorentzian functions with a half-bandwidth (full width at half-maximum) of 8 cm^{-1} using the "Spectrum Plot" function in Maestro. This choice of bandwidth agrees with typical values used in simulation of VCD spectra at the B3LYP/6-31G(d) level of theory.[35]

Rotatory strengths and UV spectra for the electronic transitions from the ground state to the singly excited states were calculated by time-dependent DFT (TDDFT) calculations in Gaussian 09[76] at the B3LYP/6-31G(d,p) level of theory[77−79] using the implicit solvation CPCM model[80,81] for CH_2Cl_2. To cover the experimental spectral range for each enantiomer of **2**, 50 excited states were calculated. For validation, additional calculations were carried out at the CAM-B3LYP/6-31G(d,p), BP86/6-31G(d,p), and B3LYP/6-311++G-(3df,3pd) levels of theory (Supporting Information, section S4.5). The TDDFT calculations gave rotatory strengths in both dipole velocity (DV) and dipole length (DL) representation at discrete transition frequencies (Tables S3 to S6). At the B3LYP/6-31G(d,p) level of theory, only minor differences between DV and DL representations were found (Table S3), and we thus used only rotatory strengths in the DV representation for the simulation of ECD spectra. With this choice of representation, the rotatory strengths become invariant to molecular translation. In order to simulate ECD spectra from the discrete transition frequencies and rotatory strengths, we associated Gaussian shape functions with each rotatory strength with intensities proportional to the absolute rotatory strength, in agreement with the approach described by Stephens and Harada.[82] Ample spectral resolution was achieved with half the bandwidth at 1/e of the peak height set to 0.2 eV.

X-ray Crystallographic Analysis of Enantiomer (+)-2 (E2). Data were collected on an Agilent SuperNova Dual source diffractometer with an Atlas detector equipped with an Oxford Cryostream low temperature device using mirror-monochromated Cu Kα radiation (l = 1.54184 Å). The CrysAlisPro software[83] was used for data collection, integration, and reduction as well as applying the analytical absorption correction. The structure was solved by charge flipping (Superflip[84]) and refined by full-matrix least-squares on F^2 (SHELXL-2014[85]) through the OLEX2[86] interface. All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were located from the difference Fourier map and were refined isotropically with no restraints.

(+)-**2**: Crystal dimensions 0.163 × 0.196 × 0.295 mm^3, colorless block, $C_{17}H_{14}N_2O_2$, M = 278.30, orthorhombic, space group $P2_12_12_1$, a = 10.15555(5) Å, b = 10.97604(5) Å, c = 12.05239(9) Å, V = 1343.45(1) $Å^3$, Z = 4, ρ = 1.376 g cm^{-3}, μ = 0.742 mm^{-1}, $F(000)$ = 584, 24 935 reflections ($2\Theta_{max}$ = 135.37°) measured (2815 unique, R_{int} = 0.0257, completeness = 99.9%), Final R indices ($I > 2\sigma(I)$): R_1 = 0.0261, wR_2 = 0.0715, R indices (all data): R_1 = 0.0262, wR_2 = 0.0715. GOF = 1.053 for 247 parameters, largest diff. peak and hole 0.200/−0.165 $eÅ^{-3}$, Flack parameter x = −0.06(3), ext. param. 0.0025(6). CCDC-1037524 contains the supplementary data for this structure. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: + 44 1223 336033.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01236.

X-ray data (CIF)

Other ECD, VCD, special optical rotation, additional chromatograms and spectra, calculation of parameters related to the distortion from planarity of the amide group of (*R*,*R*)-**2**, computational details, and supporting DFT/TDDFT calculations, including tables of Cartesian coordinates of energy-minimized structures (PDF)

AUTHOR INFORMATION

Corresponding Author

*E-mail: kenneth.warnmark@chem.lu.se.

Notes

The authors declare no competing financial interest.

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