Determination of absolute configuration using circular dichroism: Tröger's Base revisited using vibrational circular dichroism

A. Aamouche, F. J. Devlin and P. J. Stephens*

Department of Chemistry, University of Southern California, Los Angeles, CA 90089-0482, USA.
E-mail: stephens@chem1.usc.edu

Received (in Corvallis, OR, USA) 5th November 1998, Accepted 21st December 1998

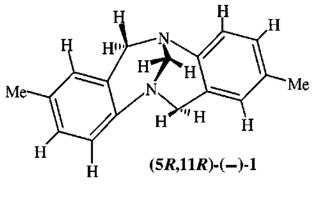
A new methodology for predicting the Vibrational Circular Dichroism (VCD) spectra of chiral molecules using Density Functional Theory (DFT) and Gauge-Invariant Atomic Orbitals (GIAOs) permits the direct determination of the absolute configuration of organic molecules in solution; application to Tröger's Base leads to the opposite absolute configuration from that deduced from electronic CD, confirming the conclusion arrived at from X-ray analysis of a diastereoisomeric salt.

Chiral molecules exhibit circular dichroism (CD).[1] The CD of enantiomers is of identical magnitude and opposite sign at all frequencies. The CD of a molecule can therefore be used to obtain its absolute configuration (AC). Application of CD to the determination of AC requires a methodology predicting the sign (or signs) of the CD for one (or more) transition of the molecule.

In practice there are two main choices to be made in utilizing CD for AC determination. First, the specific spectral region to be used must be selected. Currently, CD can be routinely measured from the mid-infrared[2] to the vacuum ultraviolet[3] encompassing both vibrational and electronic transitions. Second, the methodology to be used in predicting the CD of the transitions to be studied must be chosen. This can range from empirical correlation to *a priori ab initio* quantum mechanical calculation.

Historically, Electronic CD, measured in the near-infrared–visible–ultraviolet spectral region, has been the predominant choice of chemists.[4] Vibrational CD (VCD),[5] measured in the infrared spectral region, has been little utilized since the first measurements in the early 1970s.[6] This can be attributed primarily to the absence of a practical methodology for reliably predicting VCD intensities.

The purpose of this report is to demonstrate that recent developments in *ab initio* Density Functional Theory[7] now make practicable the prediction of VCD intensities in large organic molecules with an accuracy sufficient to permit ACs to be reliably deduced using VCD spectroscopy. The key to this advance has been the development and implementation[8] of analytical derivative techniques for calculating Atomic Axial Tensors (AATs)[9] using Gauge-Invariant Atomic Orbitals (GIAOs).[10] We report a study of the VCD spectrum of Tröger's Base **1**.



(5*R*,11*R*)-(−)-1

Tröger's Base was first resolved in 1944.[11] Its AC was first assigned in 1967[12] by means of the CD of electronic transitions associated with the aromatic rings. The Coupled Oscillator method[13] (also often referred to as the Exciton Coupling method[14]) was used to elucidate the AC from the CD spectrum. In 1991, on the basis of the X-ray structure of a salt of **1** with a chiral anion of known AC, it was reported that the original AC assignment was incorrect.[15]

The unpolarized absorption and CD spectra of **1** over the range 800–1700 cm^{-1} are shown in Fig. 1 and 2, together with the corresponding predicted DFT spectra. DFT calculations were carried out *via* the GAUSSIAN program[16] using the hybrid functional[17] B3PW91[18] and the 6-31G* basis set[19] (321 basis functions) as described previously.[20] All calculations use direct, analytical derivative methods. The calculations are carried out within the harmonic approximation [9] and therefore predict only fundamental transitions. The fundamentals are numbered (1 being lowest) in Fig.1(*b*) and 2(*b*). Comparison of the predicted and experimental absorption spectra (Fig. 1) leads to the assignment detailed in Fig. 1(*a*). In assigning the spectrum we allow for the overall shift of the predicted spectrum to higher frequency, due predominantly to the neglect of anharmonicity in the calculation,[21] and make use not only of frequencies but also of intensities (without the latter, assignment would be much more difficult). We note that almost all observed bands are assignable to fundamentals: only two bands are clearly observed which cannot be so assigned. This confirms the excellence of the harmonic approximation for the mid-IR spectral region. The fundamentals most easily and unambiguously assigned are those corresponding to bands which are resolved from neighboring bands and of significant intensity. The 25 fundamentals 34, 35, 38, 42–44, 50–64, 69, 70, 82 and 83 are in this category. The remaining 29 fundamentals are either unresolved and/or weak; their assignment is less definitive.

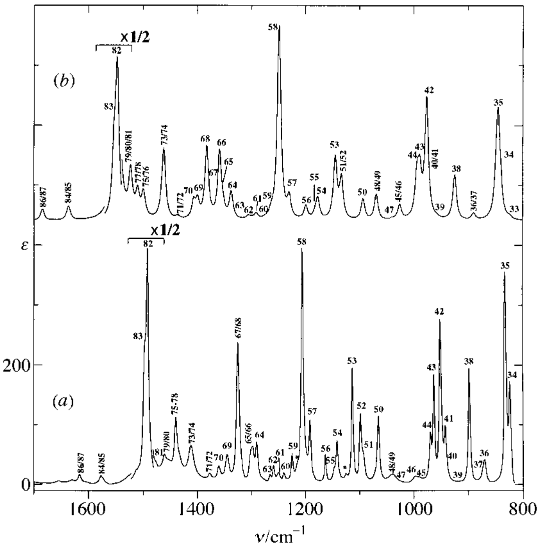


Fig. 1 Mid-IR absorption spectra of **1**: (*a*) Experimental spectrum in CCl_4 solution; 0.20 M (−)-**1**, 156 μ pathlength (800–1480 and 1525–1700 cm^{-1}); 0.10 M (−)-**1**,104 μ pathlength (1480–1525 cm^{-1}); resolution 1 cm^{-1}; (*b*) DFT/B3PW91/6-31G* spectrum; band shapes are Lorentzian (γ = 4.0 cm^{-1}). Fundamentals are numbered. Asterisks indicate bands assigned as non-fundamentals.

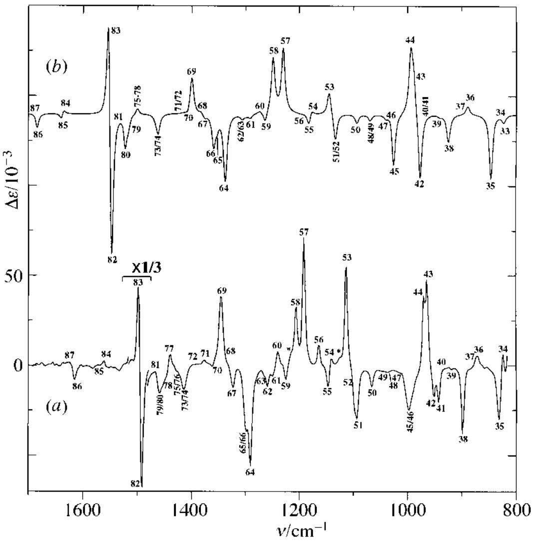


Fig. 2 Mid-IR VCD spectra of **1**: (*a*) Experimental spectrum of (−)-**1** in CCl$_4$ solution; concentrations and pathlengths are as in Fig. 1. Resolution 4 cm^{-1}. The spectrum is one-half of the difference in spectra of (−)-**1** and (+)-**1**. Scan time of each spectrum was 1 h. VCD was measured using a Bomem/BioTools Chiral*IR* spectrometer; (*b*) DFT/B3PW91/6-31G* spectrum of (5*R*,11*R*)-**1**; band shapes are Lorentzian (γ = 4.0 cm^{-1}). Fundamentals are numbered. Asterisks indicate bands assigned as non-fundamentals.

In Fig. 2 the experimental VCD spectrum is for the (−)-isomer of **1** and the calculated VCD spectrum is for the (5*R*,11*R*)-enantiomer. The assignment of the experimental VCD spectrum follows from the assignment of the absorption spectrum and is shown in Fig. 2(*a*). Comparison of the calculated and experimental spectra shows that predicted VCD signs and intensities are in excellent overall agreement with experimental signs and intensities. The comparison of calculated and experimental VCD signs and intensities is most straightforward for the 25 fundamentals resolved in the absorption spectrum. Of these, VCD is clearly observed for 19: fundamentals 35, 38, 42–44, 50, 53–60, 62, 64, 69, 82 and 83. In every case except for one (56) the predicted sign agrees with the experimental sign. We conclude directly that (−)-**1** has the (5*R*,11*R*) AC. This result is opposite to that arrived at from the electronic CD of **1** and consistent with the conclusion deduced by X-ray crystallography.[15]

Complete quantitative analysis of the spectra, based on the assignments shown in Fig. 1 and 2, is accomplished using Lorentzian fitting.[20] The absorption spectrum yields the frequencies and dipole strengths; the VCD spectrum yields the rotational strengths. In Fig. 3 we plot the experimental rotational strengths obtained for the 19 fundamentals resolved in the VCD spectrum against the corresponding calculated rotational strengths. In Fig. 3(*a*) and 3(*b*) the calculated rotational strengths are for the (5*R*,11*R*) and (5*S*,11*S*) enantiomers respectively. Perfect agreement of calculated and experimental rotational strengths for the correct enantiomer leads to a straight line of slope +1; comparison to the opposite enantiomer leads to a slope of −1. The plots in Fig. 3 simultaneously confirm the correctness of the identification of the (−)-isomer with the (5*R*,11*R*) AC and define the quantitative reliability of the DFT methodology.

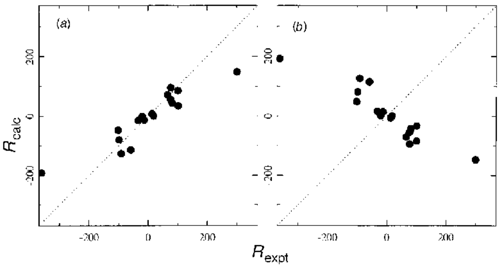


Fig. 3 Comparison of calculated and experimental rotational strengths for (*a*) (5*R*,11*R*)-**1** and (−)-**1**; (*b*) (5*S*,11*S*)-**1** and (−)-**1**. Experimental rotational strengths were obtained by Lorentzian fitting (ref. 20). The dashed line is of slope +1.

The advantages of Vibrational CD over Electronic CD are clearly exposed by this study. VCD can be measured for many transitions, in contrast to the small number of transitions generally accessible to Electronic CD measurement. The widths of vibrational transitions are much narrower than of electronic transitions, leading to more highly resolved spectra. VCD intensities depend only on ground electronic state properties and are more easily and reliably predicted than Electronic CD intensities which depend on excited electronic states in addition. The DFT/GIAO methodology for predicting VCD intensities is general and of high accuracy; it is not necessary to resort to simplified models to interpret VCD spectra. Recent developments incorporated in GAUSSIAN 98[16] have greatly enhanced the efficiency of DFT/GIAO calculations; 6-31G* calculations are now practicable for molecules possessing more than 100 atoms.

We are grateful to NIH for support (GM051972); and to Elf Aquitaine, Inc. for a post-doctoral fellowship (to A. A.).

Notes and references

1 E. Charney, *The Molecular Basis of Optical Activity: Optical Rotatory Dispersion and Circular Dichroism*, Wiley, New York, 1979.

2 L. A. Nafie, in *Advances in Applied Fourier Transform Infrared Spectroscopy*, ed. M. W. Mackenzie, Wiley, New York, 1988, ch. 3, p. 67; T. A. Keiderling, in *Practical Fourier Transform Infrared Spectroscopy*, Academic Press, New York, 1990, ch. 5, p. 203.

3 W. C. Johnson, Jr., *Rev. Sci. Instrum.*, 1971, **42**, 1283; A. Gedanken and M. Levi, *Rev. Sci. Instrum.*, 1977, **48**, 1661; P. Snyder, *Photochem. Photobiol.*, 1986, **44**, 237.

4 P. Crabbe, *Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry*, Holden-Day, 1965.

5 P. J. Stephens and M. A. Lowe, *Annu. Rev. Phys. Chem.*, 1985, **36**, 213; L. A. Nafie, *Annu. Rev. Phys. Chem.*, 1997, **48**, 357.

6 G. Holzwarth, E. C. Hsu, H. S. Mosher, T. R. Faulkner and A. Moscowitz, *J. Am. Chem. Soc.*, 1974**, 96**, 251; L. A. Nafie, J. C. Cheng and P. J. Stephens, *J. Am. Chem. Soc.* **1975**, *97*, 3842; c) L. A. Nafie, T. A. Keiderling and P. J. Stephens, *J. Am. Chem. Soc.,*1976, **98**, 2715.

7 *Chemical Applications of Density Functional Theory,* ACS Sympp. Ser. 629, ed. B. B. Laird, R. B. Ross and T. Ziegler, ACS, Washington, D.C., 1996.

8 J. R. Cheeseman, M. J. Frisch, F. J. Devlin and P. J. Stephens, *Chem. Phys. Lett.,* 1996, **252**, 211.

9 P. J. Stephens, *J. Phys. Chem.*, 1985, **89**, 748; P. J. Stephens, *J. Phys. Chem.* ,1987, **91**, 1712.

10 Also referred to as London orbitals.

11 V. Prelog and P. Wieland, *Helv. Chim. Acta*, 1944, **27**, 1127.

12 S. F. Mason, G. W. Vane, K. Schofield, R. J. Wells and J. S. Whitehurst, *J. Chem. Soc. B*, 1967, 553.

13 Ref. 1, ch. 4.

14 N. Harada and K. Nakanishi, *Circular Dichroic Spectroscopy: Exciton Coupling in Organic Stereochemistry,* University Science Books, 1983.

15 S. H. Wilen, J. Z. Qi and P. G. Williard, *J. Org. Chem.,* 1991, **56**, 485.

16 GAUSSIAN 95 (Development Code) and GAUSSIAN 98, Gaussian, Inc., Pittsburgh, PA, 1998.

17 A. D. Becke, *J. Chem. Phys.*, 1993, **98**, 1372; A. D. Becke, *J. Chem. Phys.*, 1993, **98**, 5648.

18 P. J. Stephens, F. J. Devlin, C. F. Chabalowski and M. J. Frisch, *J. Phys. Chem.*, 1994, **98**, 11623.

19 W. J. Hehre, P. R. Schleyer, L. Radom and J. A. Pople, *Ab Initio Molecular Orbital Theory*, Wiley, New York, 1986.

20 P. J. Stephens, J. R. Cheeseman, M. J. Frisch, C. S. Ashvar and F. J. Devlin, *Mol. Phys.*, 1996, **89**, 579; F. J. Devlin, P. J. Stephens, J. R. Cheeseman and M. J. Frisch, *J. Phys. Chem.,*1997, **101**, 6322; F. J. Devlin, P. J. Stephens, J. R. Cheeseman and M. J. Frisch, *J. Phys. Chem.*, 1997, **101**, 9912.

21 J. W. Finley and P. J. Stephens, *J. Mol. Struct. (THEOCHEM),* 1995, **357**, 225.

Communication 8/08677J