Pergamon

Tetrahedron: *Asymmetry* 9 (1998) 1107–1110

TETRAHEDRON: *ASYMMETRY*

Vibrational circular dichroism spectroscopy of chiral pheromones: frontalin (1,5-dimethyl-6,8-dioxabicyclo[3.2.1]octane)

C. S. Ashvar,[a] P. J. Stephens,[a,*] T. Eggimann[b] and H. Wieser[b]

[a]*Department of Chemistry, University of Southern California, Los Angeles, CA 90089-0482, USA*
[b]*Department of Chemistry, University of Calgary, Calgary, Alberta, Canada T2N 1N4*

Received 4 February 1998; accepted 25 February 1998

Abstract

Ab initio density functional theory (DFT) is used to predict the vibrational absorption and circular dichroism spectra of the insect pheromone 1,5-dimethyl-6,8-dioxabicyclo[3.2.1]octane: frontalin. Excellent agreement with experimental spectra is obtained for the structure in which the six-membered ring is in a chair conformation and the seven-membered ring is in a boat conformation. Vibrational circular dichroism (VCD) intensities, predicted on the basis of the previously determined absolute configuration, are in excellent agreement with experiment. We conclude that VCD spectroscopy, in combination with *ab initio* DFT, is now an efficient tool for determining the absolute configuration and/or conformation of chiral organic molecules, including pheromones. © 1998 Elsevier Science Ltd. All rights reserved.

Frontalin, 1,5-dimethyl-6,8-dioxabicyclo[3.2.1]octane (**1**), has been identified as a pheromone in several members of the *Scolytidae* insect family, including *Dendroctonus frontalis* (the Southern pine beetle), whence it derives its name.[1] Synthesis of the enantiomers of **1**[2] established their absolute configuration [(1R,5S)-(+) and (1S,5R)-(−)] and permitted the relationship between molecular chirality and biological activity to be elucidated. In the case of *D. frontalis* and *D. brevicomis*, (1S,5R)-(−)-**1** is the active enantiomer.[3]

We report a study of the vibrational circular dichroism (VCD) of **1**. VCD is the circular dichroism of vibrational transitions of chiral molecules.[4] VCD spectroscopy can be used to elucidate the stereochemistries of chiral molecules, including their absolute configurations. Recent developments in *ab initio* density functional theory (DFT) have greatly improved the accuracy and efficiency of the prediction of VCD spectra,[5] substantially enhancing the utility of VCD spectroscopy. Here, we exploit these developments in the analysis of the VCD spectrum of **1**.

The experimental unpolarized vibrational absorption (IR) and VCD spectra of **1** over the frequency range 800–1500 cm^{-1} are shown in Fig. 1; the VCD spectrum is of the (1R,5S)-(+) enantiomer. Spectra

* Corresponding author. E-mail: stephens@chem1.usc.edu

PII: S0957-4166(98)00099-8

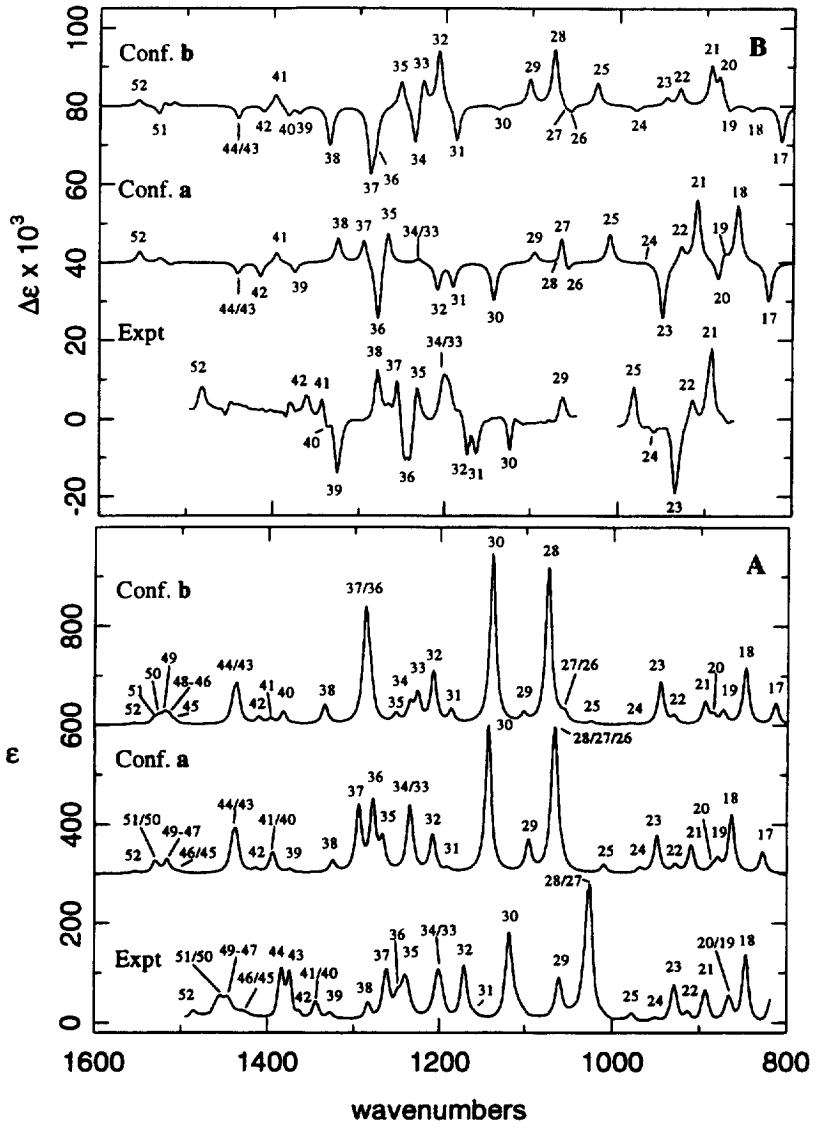

Fig. 1. Unpolarized absorption spectra, A, and VCD spectra, B, of **1**. The experimental spectra are for CCl_4 solutions; solvent baselines were subtracted. Calculated spectra assume Lorentzian bandshapes of constant width (half-width at half-height 4 cm^{-1}). The experimental VCD spectrum was obtained using (1R,5S)-(+)-**1**, synthesized as described previously;[13] the optical purity was 95%. See Eggimann[14] for further details of the experimental spectroscopy. Fundamentals are numbered

were obtained using a Nicolet 8000 FTIR spectrometer, modified to permit measurement of VCD.[6] The resolution is 4 cm^{-1}.

Absorption and VCD spectra of **1** have been predicted using *ab initio* DFT.[7] Calculations were carried out at the harmonic level of approximation using the B3LYP functional[8] and the 6-31G* basis set.[9] Efficient direct, analytical derivative methods were used and, in the calculation of VCD intensities, GIAO basis sets.[5a,10] Calculations were carried out on a Silicon Graphics Power Challenge using the GAUSSIAN program,[11] as previously described.[5]

Absorption and VCD spectra of **1** have been predicted for the two conformations, **a** and **b**:

(1R,5S)-a (1R,5S)-b

In conformation **a** the six-membered ring is in a chair conformation and the seven-membered ring is in a boat conformation; in **b** the six- and seven-membered rings are in boat and chair conformations respectively. The B3LYP/6-31G* calculations predict that conformation **a** is lower in energy than **b** by 4.4 kcal/mol and, therefore, that **a** is the very predominant conformer. VCD spectra are predicted for the (1R,5S) absolute configuration. The predicted spectra are shown in Fig. 1.

Comparison of calculated and experimental absorption and VCD spectra confirms that **1** possesses the **a** conformation and the (1R,5S) absolute configuration. Allowing for the overall shift of the calculated spectrum to higher frequency due to the absence of anharmonicity,[12] the predicted absorption spectrum of **1a** is in excellent qualitative agreement with experiment, while the spectrum of **1b** is not. The predicted VCD spectrum of (1R,5S)-**1a** is in good qualitative agreement with experiment, allowing for the substantially lower signal-to-noise ratio; predicted VCD spectra of (1R,5S)-**1b**, (1S,5R)-**1a** and (1S,5R)-**1b** are not.

Comparison of the predicted absorption spectrum of **1a** with the experimental spectrum leads to the assignment detailed in Fig. 1. Fundamentals 18, 21–25, 29–32, 35–39, 42–44 and 52 are clearly resolved. Modes 19/20, 26/27/28, 33/34, 40/41 and 45–51 are unresolved. Fundamentals 21–23, 25, 29–32, 35–39, 41, 42 and 52 are clearly resolved in the experimental VCD spectrum. For each of these modes, except mode 42, predicted and experimental VCD agree in sign. The VCD of modes 19, 20, 24, 40 and 43–51 is comparable to or less than the noise level, consistent with the relative weakness of their predicted intensities. Modes 33 and 34 are unresolved; the experimental VCD agrees with the prediction in sign.

Quantitative comparison of experimental rotational strengths to the theoretical values for (1R,5S)-**1a** and (1S,5R)-**1a** is shown in Fig. 2. Experimental parameters were obtained by Lorentzian fitting.[5d,5e] Comparison is limited to resolved fundamentals since analysis of bands containing two or more unresolved modes is not unambiguous. Agreement for (1R,5S)-**1a** is qualitatively excellent (Fig. 2A) and quantitatively comparable to that observed in prior studies of 6,8-dioxabicyclo[3.2.1]octane,[5b] camphor,[5c,d] fenchone[5c,d] and α-pinene.[5e] Conversely, observed rotational strengths are inconsistent with calculated values for (1S,5R)-**1a** (Fig. 2B).

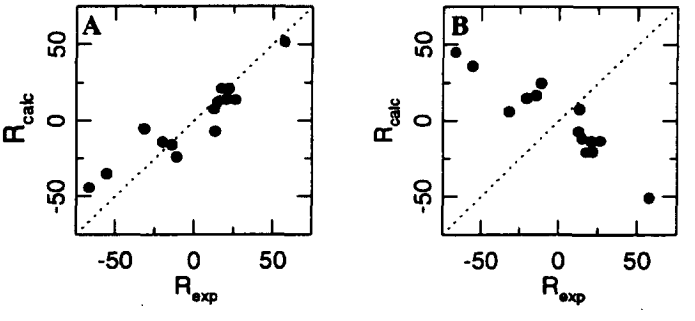

Fig. 2. Comparison of calculated and experimental rotational strengths (in 10^{-44} esu^2 cm^2) for modes 21–23, 25, 29–32, 35–39 and 42. Calculated rotational strengths are for A) (1R,5S)-**1a**; B) (1S,5R)-**1a**. Perfect agreement would place all points on the dashed line of slope +1

We have demonstrated the current capabilities of VCD spectroscopy, in combination with *ab initio* DFT, in determining the absolute configuration and molecular conformation of chiral organic molecules. Improvements in *ab initio* methods, including more accurate functionals for DFT calculations and more

efficient techniques for calculations on very large molecules ('linear scaling'), will further expand the range and efficiency of *ab initio* DFT calculations of VCD spectra in the near future.

Pheromones form a large class of chiral organic molecules whose biological activities are a function of their absolute configurations and molecular conformations.[15] VCD spectroscopy should become increasingly useful in the characterisation of pheromone stereochemistries.

Acknowledgements

We are grateful to Dr. M. J. Frisch and Dr. J. R. Cheeseman for the GAUSSIAN code, to Dr. F. J. Devlin for technical assistance and to NIH for financial support.

References

1. (a) Kinzer, G. W.; Fentiman, A. F.; Page, T. F.; Foltz, R. L.; Vite, J. P.; Pitman, G. B. *Nature*, **1969**, *221*, 477; (b) Borden, J. H. In *Comprehensive Insect Physiology*, Biochemistry and Pharmacology, Vol. 9, Eds., Kerkut, G. A. and Gilbert, L. I. Pergamon, 1985, Chapter 6, pp. 257–285.
2. Mori, K. *Tetrahedron*, **1975**, *31*, 1381.
3. (a) Wood, D. L.; Browne, L. E.; Ewing, B.; Lindahl, K.; Bedard, W. D.; Tilden, P. E.; Mori, K.; Pitman, G. B.; Hughes, P. R. *Science*, **1976**, *192*, 896; (b) Stewart, T. E.; Plummer, E. I.; McCandless, L. L.; West, J. R.; Silverstein, R. M. *J. Chem. Ecol.*, **1977**, *3*, 27.
4. (a) Stephens, P. J.; Lowe, M. A. *Ann. Rev. Phys. Chem.*, **1985**, *36*, 213; (b) Nafie, L. A. *Appl. Spectr.*, **1996**, *50*, 14A.
5. (a) Cheeseman, J. R.; Frisch, M. J.; Devlin, F. J.; Stephens, P. J. *Chem. Phys. Lett.*, **1996**, *252*, 211; (b) Stephens, P. J.; Ashvar, C. S.; Devlin, F. J.; Cheeseman, J. R.; Frisch, M. J. *Mol. Phys.*, **1996**, *89*, 579; (c) Devlin, F. J.; Stephens, P. J.; Cheeseman, J. R.; Frisch, M. J. *J. Am. Chem. Soc.*, **1996**, *118*, 6327; (d) Devlin, F. J.; Stephens, P. J.; Cheeseman, J. R.; Frisch, M. J. *J. Phys. Chem.*, **1997**, *101*, 6322; (e) Devlin, F. J.; Stephens, P. J.; Cheeseman, J. R.; Frisch, M. J. *J. Phys. Chem.*, **1997**, *101*, 9912.
6. Shaw, R. A.; Ibrahim, N.; Wieser, H. *J. Phys. Chem.*, **1990**, *94, 125*.
7. *Chemical Applications of Density Functional Theory*, ACS Symposium Series 629, Eds., Laird, B. B.; Ross, R. B. and Ziegler, T. ACS, Washington, D.C., 1996.
8. Stephens, P. J.; Devlin, F. J.; Chabalowski, C. F.; Frisch, M. J. *J. Phys. Chem.*, **1994**, *98*, 11623.
9. Hehre, W. J.; Schleyer, P. R.; Radom, L.; Pople, J. A. *Ab Initio Molecular Orbital Theory*, Wiley, 1986.
10. Bak, K. L.; Devlin, F. J.; Ashvar, C. S.; Taylor, P. R.; Frisch, M. J.; Stephens, P. J. *J. Phys. Chem.*, **1995**, *99*, 14918.
11. GAUSSIAN 95, Development Version, Frisch, M. J. et al., Gaussian Inc., Pittsburgh, PA (1995).
12. Finley, J. W.; Stephens, P. J. *Theochem., J. Mol. Str.*, **1995**, *357*, 225.
13. Ibrahim, N.; Eggiman, T.; Dixon, E. A.; Wieser, H. *Tetrahedron*, **1990**, *46*, 1503.
14. Eggiman, T. Ph.D. Thesis, U. Calgary, 1991.
15. (a) Mori, K. In *Techniques of Pheromone Research*, Eds., Hummel, H. E. and Miller, T. Springer 1984, Ch. 12, pp. 323–370; (b) Mori, K. In *Total Synth. Nat. Prod.*, Vol. 9, Eds. ApSimon, J. Wiley 1992, pp. 1–521.