

BioTools

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Determination of Absolute Configuration

BioTools, Inc.

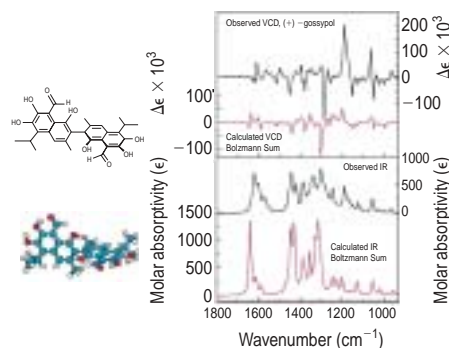
Determination of Absolute Configuration (AC) of chiral molecules is an important step in any field related to chirality but nowhere is it as critical as in the pharmaceutical industry. The phenomenon of “chiral recognition” — in which the enantiomers of a chiral drug may exhibit differences in biological activity or other processes such as distribution, uptake, and metabolism — makes it a necessity (or requirement) to know the AC not only of the final molecule but as early in the process of development as possible.

Within the past few years it has been conclusively demonstrated that Vibrational Circular Dichroism (VCD) is a reliable method for AC determinations (1). VCD offers a novel alternative to X-ray crystallography, permitting AC determinations on neat liquid, oil, and solution samples. VCD requires no derivitization of the sample or growth of a pure single crystal. VCD is defined as the differential absorption of a molecule for left circularly polarized infrared (IR) light versus the right during a vibrational transition. VCD combines the structural specificity of vibrational IR absorption spectroscopy with the stereochemical sensitivity of chiroptical spectroscopy such as CD (2). The absolute stereochemistry is established by comparing the solution-phase VCD spectrum to the results of an *ab initio* quantum chemistry calculation. The calculations are easily carried out in commercial packages such as Gaussian03 (Gaussian, Inc., Pittsburgh, PA). Here, we show an example of determination of AC for the polyphenolic binaphthyl dialdehyde, gossypol. Gossypol is known for its ability to inhibit maturation in human sperm and has recently attracted considerable interest for its potential as an antineoplastic agent (3).

Experimental

Experimental VCD spectra are typically collected in the mid-IR region from 800 to 2000 cm^{-1} . In the example shown here, spectra were collected on the commercially available ChiralIR™ FT-VCD spectrometer. The optimum sampling conditions achieve an average IR absorbance intensity of ~ 0.5 for the bands of interest; here the concentration used was 0.096 M in CDCl_3 , 95- μm pathlength BaF_2 cell. Collection times vary from five minutes to several hours depending on the size of VCD signal and quality desired. Spectra presented were measured for four hours at a resolution of 4 cm^{-1} and are solvent subtracted. Calculations were carried out with Gaussian98 at the DFT level (B3LYP functional / 6-31G* basis set).

Figure 1. Comparison of IR (lower frame) and VCD (upper frame) spectra of (+)-gossypol (upper traces, right axes) with calculated spectra for Boltzmann-weighted sum of three lowest *P*-conformers (lower traces, left axes). The structure of *P*-gossypol and its optimized geometry, in ball-and-stick, are shown on the left.



Results and Conclusion

Figure 1 shows a comparison between spectra of Boltzmann-population weighted composite of the calculated spectra of three lowest conformers for the *P*-configuration and the observed spectra of (+)-gossypol (3). Gossypol is a symmetric dimer molecule that is chiral by the sense of the twist, in this case a *P*-twist, about its axial bond. Excellent correlation is found between the observed and calculated features, establishing the configuration of (+)-gossypol as (*P*). The availability of VCD commercial instrumentation and computational technology has opened the door for the routine use of VCD in studies of many stereochemical problems in a variety of industries, particularly the pharmaceutical industry.

References

1. T.B. Freedman, X. Cao, R. K. Dukor, and L.A. Nafie, *Chirality*, in press.
2. R. K. Dukor and L. A. Nafie, "Vibrational Optical Activity of Pharmaceuticals and Biomolecules" in *Encyclopedia of Analytical Chemistry*, R.A. Meyers (Ed.), pp. 662–676 (John Wiley & Sons, Hoboken, NJ, 2000).
3. T. B. Freedman, X. Cao, R. V. Oliveira, Q. B. Cass, and L. A. Nafie, *Chirality* 15, 196–200 (2003).

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