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Determining Absolute Configuration by Vibrational Circular Dichroism: (+)-(1*S*,5*S*,6*S*)- and (−)-(1*R*,5*R*,6*R*)-Spiro[4.4]nonane-1,6-diol

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There are only two physical−chemical methods capable of determining absolute configuration *directly*, namely Bijvoet analysis[1] of either X-ray diffraction or neutron scattering and circular dichroism (CD) spectroscopy. Each has drawbacks which limit their usefulness. Of the two CD spectroscopic methods, electronic CD suffers from the restriction that an electronic chromophore must be present in the compound of interest, and hence, only relatively few transitions are observable. With vibrational CD (VCD) spectroscopy, on the other hand, a wide range of vibrational transitions offers the likely possibility that at least one of the 3N-6 fundamentals gives rise to a distinctive and readily observable signature that uniquely identifies one of the enantiomers. Moreover, these features are usually characteristic for chiral sites. Although VCD is not as widely established as other methods, rapid and extensive progress has been made during the past two decades, and while it cannot yet claim to be a routine method, its potential has been amply demonstrated. The many reviews that have appeared over the years attest to the vigorous interest VCD has captured, albeit by relatively few investigators.[2]

Two approaches for establishing absolute configurations by VCD have been explored, namely empirical correlations among observed VCD spectra of a variety of analog compounds, a method of only limited utility, and the comparison of experimental with theoretically simulated spectra. The latter approach, although much more powerful in principle, has seen but few applications and then only for small molecules.[3]

In this paper we show how enantiomers of *cis,cis*-spiro[4.4]nonane-1,6-diol (**1** in Scheme 1) can be uniquelyidentified as (+)-1*S*,5*S*,6*S* and (−)-1*R*,5*R*,6*R* by comparing observed and calculated VCD spectra. We draw attention to the potential applicability of the method for a direct, reliable, and relatively simple method to determine the correct absolute stereochemistry. While recording VCD spectra is still cumbersome, the ability to measure them relatively routinely appears at least within grasp,[4] and while complete *ab initio* computations are still demanding, emerging computer technologies and possibly new theoretical approaches will soon place the necessary capabilities within reach of most laboratories.[5]

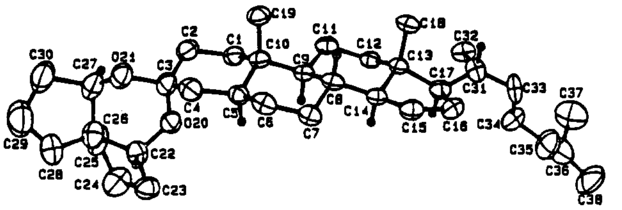
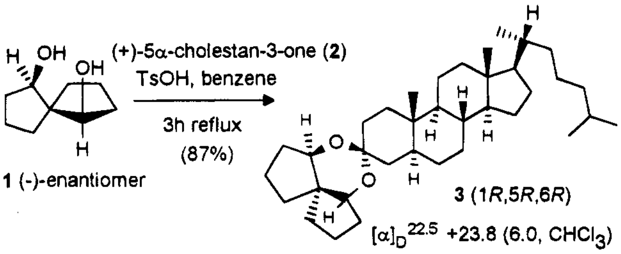


Figure 1. Thermal-ellipsoid representation of ketal **3** as defined by using optically pure (+)-5α-cholestan-3-one. Melting point 122−122.5 °C, orthorombic $P2_12_12$, $a = 41.261(2)$ Å, $b = 12.2083(8)$ Å, $c = 6.4622(4)$ Å, $Z = 4$. The ellipsoids are drawn at the 25% probability level; hydrogen atoms are represented as spheres with an arbitrary radius. Only relevant hydrogen atoms are drawn. The disordered parts are represented by those of larger occupancy factors. Bijvoet analysis was not performed since optically pure ketone **2** was used.

Scheme 1



1 (-)-enantiomer

3 (1*R*,5*R*,6*R*)

$[\alpha]_D^{22.5}$ +23.8 (6.0, CHCl$_3$)

Although the synthesis and resolution of (**1**) were described previously,[6] the absolute stereochemistry was not determined unambiguously. Ketal (**3**) was therefore synthesized in 87% yield (Scheme 1) by mixing the (−)-enantiomer of diol (**1**) with (+)-5α-cholestan-3-one (**2**) in the presence of a catalytic quantity of *p*-toluenesulfonic acid in benzene, followed by the azeotropic removal of water. The X-ray crystal structure of ketal **3** (Figure 1)[9] unambiguously shows that the (−)-enantiomer of spiro-[4.4]nonane-1,6-diol (**1**) has the (1*R*,5*R*,6*R*) absolute configuration.

Using a Bomem MB100 interferometer described in detail elsewhere,[4] the VCD spectra were obtained with the following conditions: 1.3 M in CCl$_4$, 0.15 mm NaCl, 4 cm^{-1} resolution, 5000 ac/500 dc scans, enantiomer corrected; less than 2% background noise relative to the maximum VCD peak as estimated from half of the sum of independently recorded VCD spectra of both enantiomers. The absorption spectrum shows extensive hydrogen bonding resulting from the high concentration of the solution necessary for obtaining the VCD spectrum with acceptable signal-to-noise. Attempts to distinguish between absorptions arising from inter- and intramolecularly hydrogen bonded or free molecules were not successful due to solvent absorptions occurring with dilutions and commensurate path lengths needed in these circumstances.

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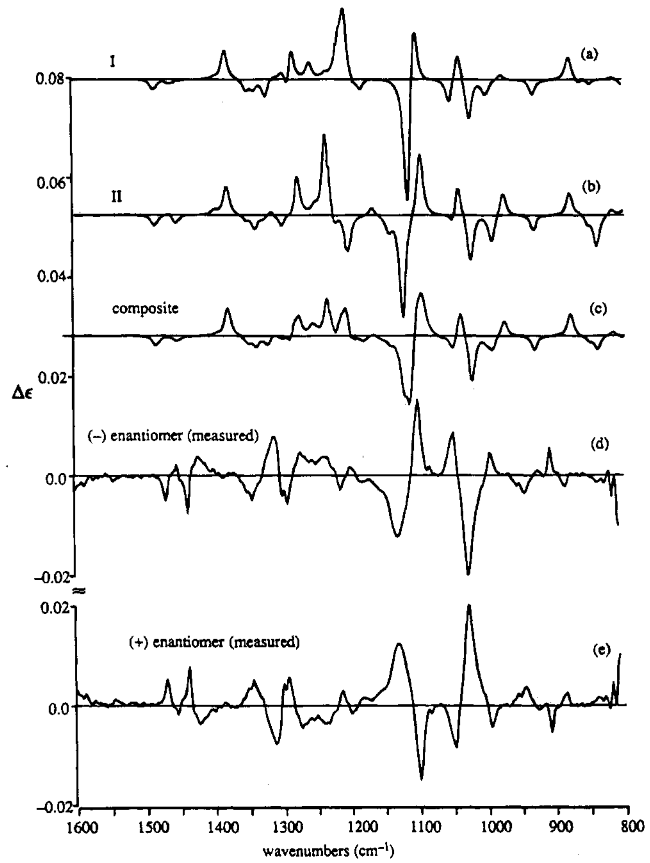

Figure 2. Calculated VCD spectra of (−)-(1*R*,5*R*,6*R*)-spiro[4.4]nonane-1,6-diol: 6-31G$^{*(0.3)}$ geometry, force field, and atomic polar tensors; 6-31G atomic axial tensors; calculated frequencies scaled by 0.9; Lorentzian line shapes of 5 cm^{-1} half width at half height: (a) conformer I; (b) conformer II; (c) composite of six conformers. Measured VCD spectra of both enantiomers (see text for measurement conditions): (d) (−)-isomer, $[\alpha]23_D = -101.4$ (11.0, absolute ethanol), 100% ee; (e) (+)-isomer, $[\alpha]23_D = +97.1$ (9.0, absolute ethanol), 100% ee (ee as determined by ^{1}H NMR on the camphor ketal).[6]

The *ab initio* calculations were performed at the RHF/6-31G$^{*(0.3)}$ level[7a] using the Gaussian system of programs[8] for geometries, force fields, and atomic polar tensors. A conformational search revealed six lowest energy conformers differing in the conformations of the rings and the orientations of the hydroxyl groups seemingly forming intramolecular hydrogen bonds. With this level of theory the two principal conformers that constitute 86% of the composite population differ in the ring conformation and hydrogen bonding and are separated by about 0.3 kJ/mol ($\Delta E \approx \Delta H$). Both are lower by about 5 kJ/mol than the two next highest in energy which contribute a further 7%, and by an additional 3 kJ/mol lower than the two most energetic conformers making up the remaining 7%. The VCD spectra were generated with the vibronic coupling theory at the distributed origin gauge with atomic axial tensors calculated at the 6-31G level.[7b] The computed VCD and absorption spectra of the two lowest energy conformations of (−)-(1*R*,5*R*,6*R*)-spiro[4.4]nonane-1,6-diol are displayed in Figures 2 and 3, respectively, as well as the corresponding spectra of the composite of all six conformers and the experimental spectra. The frequencies were scaled by 0.9.

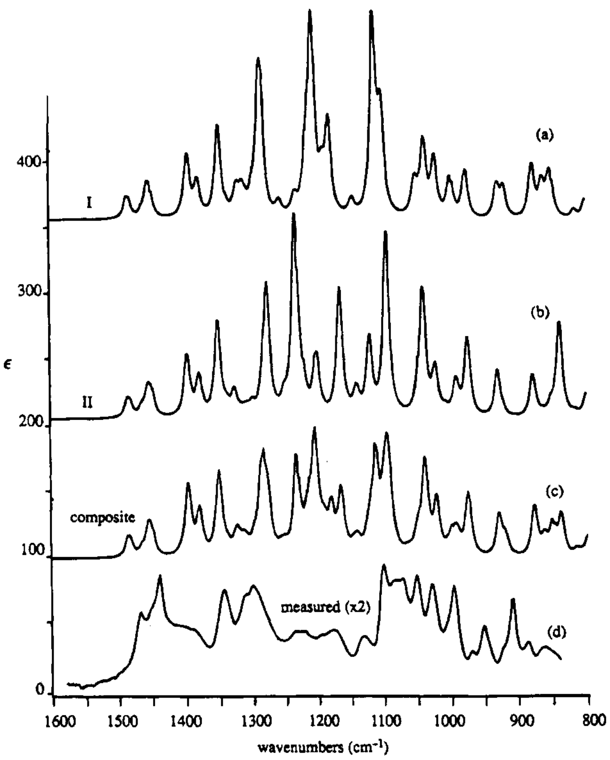

Figure 3. Calculated absorption spectra of spiro[4.4]nonane-1,6-diol; 6-31G$^{*(0.3)}$ geometry, force field, and atomic polar tensors; calculated frequencies scaled by 0.9; Lorentzian line shapes of 5 cm^{-1} half width at half height: (a) conformer I; (b) conformer II; (c) composite of six conformers. Measured absorption spectrum (d); see Figure 2 and text for measurement conditions.

The most distinctive and dominant features in the theoretical VCD spectrum occur between 1150 and 1000 cm^{-1}, appearing as negative−positive and positive−negative bands in the (−)-enantiomer (Figure 2). These features resemble unmistakably those measured for the enantiomer that was unambiguously identified by X-ray crystallography as the (−)-(1*R*,5*R*,6*R*) configuration. Noteworthy also is that hydrogen bonding does not interfere with this identification, whereas it complicates the absorption spectrum to such an extent that the measured spectrum appears to be not well reproduced by calculation.

This clearly demonstrates that a definitive identification of the absolute configuration is possible by comparing the observed with calculated VCD spectra of even a relatively large molecule. In this particular instance, the conformational flexibility somewhat complicates the process since a conformational search and computations for more than one conformer are required. The agreement is nonetheless very gratifying and suggests that the method has reached the necessary maturity to serve the purpose of determining absolute configurations in general.

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(9) The author has deposited atomic coordinates for **3** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.