Vibrational Circular Dichroism Study of Pipitzols and of Their Inverse Epimer Constituents α- and β-Pipitzol

Eleuterio Burgueño-Tapia¹, Mónica Díaz Fernández¹ and Pedro Joseph-Nathan²

Abstract
Inverse epimers are uncommon in nature and a lack of study of their vibrational circular dichroism (VCD) behavior seems evident. This is relevant, among other facts, since in the case of epimers, VCD has been capable of determining the absolute configuration (AC) of 1 stereogenic center in a molecule having 10 stereogenic centers. The case of pipitzol is unique since it took 80 years from its first preparation by thermal intramolecular cycloaddition of perezone (I) to know that the reaction outcome is an equimolar mixture of the 2 inverse epimers α-pipitzol (2: 3R, 3aR, 7R, and 8αS) and β-pipitzol (3: 3R, 3aS, 7S, and 8αR). Evaluation of 2 and 3 reveals that some VCD bands have an opposite phase while other bands show the same phase. The VCD spectrum of the naturally occurring equimolecular mixture was also measured and the 3 experimental spectra were contrasted with density functional theory (DFT) calculated spectra allowing individual band assignments. The comparisons were made in the 1800 to 950 and 1550 to 950 cm⁻¹ ranges and the numerical differences are highlighted thereby showing that carbonyl bands influence such comparisons. The 2 carbonyl absorption bands of 2 and 3 show weak VCD bands and the conjugated double bond band provides an intense AC-dependent VCD band.

Keywords
sesquiterpenoids, inverse-epimeric pairs, vibrational circular dichroism, cedranolides, inverse epimers

Introduction
Inverse epimeric pairs, also referred to as inverse epimers, are a particular type of diastereomer defined as stereoisomers containing more than 2 stereogenic centers that differ in their configuration at all stereogenic centers but one. They are uncommon in nature. Three pairs of compounds isolated from a Streptomyces sp. known as alunycin-A1, -A2, and -A3, because of difficulties in their separation and absolute configuration (AC) assignment, were first described as a single compound, then as a pair of stereoisomers, and finally as 3 pairs of inverse epimers.¹ The cedranolides α- and β-perozol, isolated from Perezia bechdelii;² and α- and β-pipitzol found as constituents of the roots of several species of the genus Perezia,³ also known as Acourtia (Asteraceae), are other interesting examples of natural inverse epimers. As far as we know, these types of compounds have not yet been widely studied by vibrational circular dichroism (VCD).⁵ VCD spectra arise from the differential interaction of infrared light left and right circularly polarized generating absorption bands with positive and negative signs. Specialized software capable of calculating VCD spectra allows the comparison between calculated and experimental spectra for the AC assignment. Therefore, it seems of interest to explore the VCD spectra of inverse epimers since it could be expected that several absorption bands would have the same phase while other bands will show an opposite phase in comparison to a pair of these molecules. A suitable example of inverse epimers to explore the scope of VCD to distinguish this type of diastereoisomers is the pair of pipitzols.

Pipitzol is the thermal intramolecular cycloaddition product of perezone (I) (Figure 1) that was first prepared in 1885.⁶ It took 80 years until it became clear that pipitzol, which was

¹Departamento de Química Orgánica, Escuela Nacional de Ciencias Biológicas, Instituto Politécnico Nacional, Prolongación de Carpio y Plan de Ayala, Mexico City, Mexico
²Departamento de Química, Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional, Mexico City, Mexico

Corresponding Author:
Eleuterio Burgueño-Tapia, Departamento de Química Orgánica, Escuela Nacional de Ciencias Biológicas, Instituto Politécnico Nacional, Prolongación de Carpio y Plan de Ayala, Col. Santo Tomás, Mexico City, 11340 Mexico. Email: eleuteriobt@gmail.com

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The (R)-AC of perezone (1) was established by chemical correlation with (+)-citronellal and verified by VCD spectroscopy in comparison with calculations performed at several density functional theory (DFT) levels. Given the (R)-AC of perezone (1), the relative stereochemistry and AC of pipitzols 2 and 3 were postulated after the construction of solid state Büchi molecular stereo models and mechanistic considerations as (3R, 3aR, 7R, and 8aS) and (3R, 3aS, 7S, and 8aR). It just remained to know which molecule corresponded to either alternative AC, a dilemma that was settled by optical rotatory dispersion (ORD) of the 2 pipitzols and independently confirmed by single-crystal X-ray diffraction of α-pipitzol benzoate. The mixture provides good quality crystals in the lowest possible symmetry triclinic pseudo group at C-3 in a pseudo-equatorial orientation (Figure 2) and conformer 2b having the methyl group in a pseudo-axial orientation. In the case of β-pipitzol (3), a similar situation occurs, with conformer 3a (pseudo-equatorial methyl) and conformer 3b (pseudo-axial methyl) (Figure 2). The 4 molecular models were independently constructed in the Spartan'04 suite and submitted to molecular mechanics conformational search using the Monte Carlo protocol and MMFF94. In all 4 cases, only a single conformer remained in the initial 10 kcal/mol energy gap. Conformer 2a shows the cyclopentane ring in a twisted envelope conformation with the methyl group at C-3 in a pseudo-equatorial orientation (Figure 2), while conformer 2b shows the methyl group in a pseudo-axial orientation. Conformer 2a turned out to be 2.58 kcal/mol more stable than conformer 2b at this stage. In the case of β-pipitzol, conformer 3a shows the cyclopentane ring in a twisted-envelope conformation with the methyl group at C-3 in a pseudo-equatorial orientation (Figure 2), while conformer 3b shows the methyl group in a pseudo-axial orientation. Conformer 3a was 1.85 kcal/mol more stable than conformer 3b.

These 4 conformers were individually subjected to single-point energy calculation using DFT at the B3LYP/6-31G(d)
were completed at the same level of theory. The conformational level of theory to afford 2a and 2b in a 1.14 kcal/mol energy gap, and 3a and 3b in a 1.98 kcal/mol range. Complete geometry optimization of all conformers, using DFT with the B3LYP functional and the DGDZVP basis set, as implemented in the Gaussian’03 software, completed the calculation procedures. The most stable conformers 2a and 3a contribute 93.2 and 93.7%, respectively, to the total conformational population (Table 1). After optimization, 2a shows C-1–C-2–C-3–C-3a and C-10–C-3–C-3a–C-9 dihedral angles of −38.7 and −98.8°, while for 3a these values were +40.2° and −179.2°, respectively. Finally, IR and VCD frequency calculations considering the conformational ΔG gaps for both conformers of 2 and 3 were completed at the same level of theory.

Visual inspection of the experimental and calculated spectra of 2 (Figure 3) and 3 (Figure 4) shows good agreements. A numerical data comparison for each pipitzol was obtained using the CompareV/0/A software,21 which validates the AC assignment (Table 2) with confidence levels (C) of 100%, confirming the (3R, 3aR, 7R, and 8aS) AC for 2 and the (3R, 3aS, 7S, and 8aR) AC for 3.

Although in most VCD studies the bands associated with carbonyl groups and related signals (1800-1600 cm⁻¹) are not included in comparison procedures, since they are considered as providing non-robust comparison bands due to potential associations of undefined geometries with the solvent,22–24 in the case of α-pipitzol in Figure 3 and of β-pipitzol in Figure 4, these bands are informative. To start with, the 3 bands are quite intense in the IR spectra while this is not the case in the VCD spectra. The cyclopentanone VCD band around 1753 cm⁻¹ is a very weak negative signal in both inverse epimers. The conjugated cyclohexenone carbonyl band around 1673 cm⁻¹ is also a weak band which is positive for 2 and negative for 3, while the double bond band around 1640 cm⁻¹ is intense with positive phase for 2 and negative phase for 3. From a purely speculative point of view, it could be assumed that the slightly dominant cyclopentanone band is associated with the C-3 stereogenic center, the cyclohexenone carbonyl band is slightly dominated by the C-3a stereogenic center, and the double bond band is mainly influenced by the C-7 stereogenic center.

To gain evidence regarding the above tentative interpretation, the VCD bands of 2 and 3 were assigned using GaussView software that allows us to know which vibrations are involved in each band. The results are summarized in Table 3 for 2 and in Table 4 for 3. Its evaluation revealed that the negative band at around 1753 cm⁻¹ is essentially generated by C-9=O stretching accompanied by C-3a–C-9=O and C-7–C-9=O asymmetric stretching, and a weak CH-7 bending. No vibration from the C-1–C-2–C-3–C-3a–C-8a cyclopentane ring was observed. The band at around 1673 cm⁻¹ is due to C-4=O strong stretching, O–C-5–C-6–C-7 asymmetric stretching, and O–H in plane bending. In turn, the band at around 1640 cm⁻¹ is originated by strong C-5=O stretching along with C-3a–C-4–C-5 and O=C-4–C-5=O asymmetric stretching.

The experimental VCD spectrum of naturally occurring pipitzols was contrasted with the averaged calculated spectra of α- (2) and β-pipitzol (3), using the CompareV/0/A software, as shown in Figure 5. The pertinent numerical comparisons are summarized in Table 2, from where it can be seen that an excellent concordance is obtained when the comparison was performed in the classical 1550 to 950 cm⁻¹ region, but that it drops to 94% when the carbonyl region is also included, confirming once again that a good region for the comparisons is the 1550 to 950 cm⁻¹ region. In this mixture, some VCD bands roughly cancel mutually between inverse epimers since they correspond to enantiomeric stereogenic centers, while other bands potentiate since the stereogenic center at C-3 has the same AC in both inverse epimers. This situation complicates the overall spectra comparison since a given band has not exactly the same value in both inverse epimers, as can be observed in the band values given in Tables 3 and 4, thus causing imperfect band canceling or potentiating, and as a rough effect causing some signal broadening.

Thus, for example, the positive band at 1456 cm⁻¹ associated with the C-3 stereogenic center is mainly due to CH-10 and CH-3 asymmetric bending along with CH₂-2 scissoring and CH₃-13 bending for 2, while for 3 it is associated with CH₁-10 and CH-3 asymmetric bending along with CH₂-1 scissoring and CH₃-12 bending. The negative band at 1290 cm⁻¹ is an enantiomeric band with a greater rotational strength for 2, which is mainly caused by CH₂-1, CH₂-2, CH-3, and CH-8a symmetric bending, accompanied by C-3–C-3a–C-9–C-7 and C-8–C-8a–C-1 weak asymmetric stretching for 3. An intense band observed in the spectrum of the pipitzols mixture related to only 1 isomer is the negative band at 1032 cm⁻¹ originated by C-2–C-1–C-8a–C-8.
Table 1. Thermochemical Parameters of the Most Stable Density Functional Theory (DFT) B3LYP/DGDZVP Conformers of α-Pipitzol (2) and β-Pipitzol (3).

| Conf. | \( \Delta E_{\text{MMFF94}}^a \) | %b | \( \Delta E_{\text{6-31G}(d)}^c \) | %b | \( \Delta E_{\text{DGDZVP}}^d \) | %b | \( \Delta G_{\text{DGDZVP}}^e \) | %b |
|-------|-----------------|-----|-----------------|-----|-----------------|-----|-----------------|-----|
| 2a    | 0.00            | 98.7| 0.00            | 87.3| 0.00            | 93.2| 0.00            | 90.1|
| 2b    | 2.58            | 1.3 | 1.14            | 12.7| 1.55            | 6.8 | 1.31            | 9.9 |
| 3a    | 0.00            | 95.8| 0.00            | 96.6| 0.00            | 93.7| 0.00            | 95.4|
| 3b    | 1.85            | 4.2 | 1.98            | 3.4 | 1.60            | 6.3 | 1.79            | 4.6 |

*aRelative to 2a \( (E = 70.79 \text{ kcal/mol}) \), 3a \( (E = 70.60 \text{ kcal/mol}) \).  
*bCalculated according to \( \Delta E \approx -RT \ln K \).  
*cRelative to 2a \( (E = -507,840.68 \text{ kcal/mol}) \), 3a \( (E = -507,841.99 \text{ kcal/mol}) \).  
*dRelative to 2a \( (E = -507,904.54 \text{ kcal/mol}) \), 3a \( (E = -507,905.41 \text{ kcal/mol}) \).  
*eRelative to 2a \( (E = -507,726.45 \text{ kcal/mol}) \), 3a \( (E = -507,728.02 \text{ kcal/mol}) \).  

Figure 3. Comparison of the experimental and density functional theory (DFT) B3LYP/DGDZVP calculated IR and vibrational circular dichroism (VCD) spectra of \( \alpha \)-pipitzol (2).

Figure 4. Comparison of the experimental and density functional theory (DFT) B3LYP/DGDZVP calculated IR and vibrational circular dichroism (VCD) spectra of \( \beta \)-pipitzol (3).

and C-3–C-3a –C-9–C-7 asymmetric stretching accompanied by Me-11 and Me-12 bending for 2. Another such band is the positive peak at 1003 cm\(^{-1}\), which is mainly due to C-2–C-3–C-3a–C-8a–C8 and C-11–C-3–C-3a asymmetric stretching, C-3–C-3a–C-4 symmetric stretching, and CH\(_3\)-10 strong bending for 3. A detailed inspection of Tables 3 and 4 also suggests that the molecules under consideration are indeed quite rigid since there are vibration modes in which almost all atoms are involved.

It is of relevance to evaluate the capability of VCD for the distinction of inverse epimers, since in the case of the epimeric cedranolidescedrol and isocedrol, in which 4 out of 5 stereogenic centers are common and only C-6 differs, excellent VCD results were obtained. Furthermore, in the study of the epoxidation of the sole double bond of lupanone, which has a total of 9 stereogenic centers, it was possible to ascertain the AC of the 10 newly formed stereogenic centers. Consequently, cross-comparisons of calculated and experimental VCD spectra of 2 and 3 were made and compared with the cross-comparisons made for cedrol and isocedrol.

Inspection of Table 2 reveals that comparing the experimental spectrum of 2 with the calculated spectrum of 3 in diethyl ether the 1550 to 950 and the 1800 to 950 cm\(^{-1}\) ranges provide enantiomer similarity indexes \( (E_{\text{SI}}) \) of –62.0 and –70.9, respectively, and confidence levels of 100% in both cases. This is a very poor VCD result since it suggests that 2 and 3 are enantiomers when in reality they are inverse epimers. In turn, comparison of the experimental spectrum of
Table 2. Comparison of Experimental and Density Functional Theory (DFT) B3LYP/DGDZVP Calculated IR and Vibrational Circular Dichroism (VCD) spectra of 2, 3, and Pipitzols at 2 Ranges.

| Compound  | Range (cm⁻¹) | aHتف | SIR | S1c | S2d | ESI | Cf |
|-----------|--------------|-------|------|------|------|-----|-----|
| α-pipitzol (2) | 1550 to 950 | 0.98  | 83.8 | 81.2 | 6.2  | 75.0 | 100 |
| α-pipitzol (2) | 1800 to 950 | 0.97  | 80.3 | 82.5 | 3.9  | 78.6 | 100 |
| β-pipitzol (3) | 1550 to 950 | 0.98  | 88.0 | 84.6 | 6.9  | 77.7 | 100 |
| β-pipitzol (3) | 1800 to 950 | 0.97  | 74.1 | 85.0 | 3.9  | 81.1 | 100 |
| Pipitzols      | 1550 to 950 | 0.98  | 82.2 | 73.5 | 16.7 | 56.0 | 100 |
| Pipitzols      | 1800 to 950 | 0.98  | 61.9 | 65.8 | 14.9 | 50.9 | 94  |
| exp 2 versus 3 | 1550 to 950 | 0.98  | 90.1 | 9.7  | 71.7 | 62.0 | 100 |
| calc 3         | 1550 to 950 | 0.97  | 80.5 | 5.4  | 76.3 | 70.9 | 100 |
| exp 2 versus 3 | 1550 to 950 | 0.97  | 89.2 | 17.5 | 65.0 | 47.5 | 91  |
| calc 2         | 1550 to 950 | 0.97  | 81.4 | 10.6 | 74.4 | 63.9 | 100 |

3 with the calculated spectrum of 2 provides ESI values of −47.5 and −63.9, with C values of 91% and 100%, in the 1550 to 950 and 1800 to 950 cm⁻¹ ranges, respectively. The result in the narrower range is a very modest one suggesting that 3 and 2 are not epimers, while the values in the 1800 to 950 cm⁻¹ range suggest that 3 and 2 are enantiomers. The latter is again a very poor VCD result and both comparison ranges again evidence that the 1550 to 950 cm⁻¹ range is a better comparison range than the wider 1800 to 950 cm⁻¹ range. These appreciations derive from the results obtained from a VCD study of a pair of closely related epimeric cedranolides. 25 Comparison of the experimental spectrum of cedrol, which has the (2R, 3aR, 6aS, 7R, and 8aS) AC with the calculated spectrum of isocedrol having the (3R, 3aR, 6S, 7R, and 8aS) AC provided a confidence level of 43%, while the reverse comparison, that is the experimental spectrum of isocedrol with the calculated spectrum of cedrol, provided a confidence level of 44%. Both cases clearly show that these molecules differ in their AC.

During the final structure elucidation studies of perezone (1), made as a direct consequence of the structure elucidation of the pipitzols, both a stepwise 12 and a concerted intramolecular cycloaddition 27 path were proposed. To clarify this point a regioselective deuterium labeling of the (E)-methyl group of the terminal isopropylidene residue of perezone (1) was developed, 27 showing that this unique transformation is the coexistence of a sigmatropic change of order

Table 3. Vibrational Circular Dichroism (VCD) Frequencies of Relevant Vibrational Modes for α-Pipitzol (2).

| Band | νcalc | νexp | SIR | ESI | Cst |
|------|-------|------|-----|-----|-----|
| 1    | 1828  | 1755 | 47.5 | 91  | 100 |
| 2    | 1726  | 1672 | 43  | 70  | 100 |
| 3    | 1687  | 1641 | 62.0 | 100 |
| 4    | 1532  | 1470 | 62.0 | 100 |
| 5    | 1513  | 1456 | 91  | 100 |
| 6    | 1401  | 1354 | 91  | 100 |
| 7    | 1399  | 1319 | 91  | 100 |
| 8    | 1322  | 1290 | 62.0 | 100 |
| 9    | 1303  | 1272 | 62.0 | 100 |
| 10   | 1236  | 1215 | 91  | 100 |
| 11   | 1232  | 1203 | 91  | 100 |
| 12   | 1215  | 1190 | 91  | 100 |
| 13   | 1175  | 1151 | 91  | 100 |
| 14   | 1150  | 1128 | 91  | 100 |
| 15   | 1112  | 1089 | 91  | 100 |
| 16   | 1101  | 1080 | 91  | 100 |
| 17   | 1042  | 1032 | 91  | 100 |
| 18   | 1012  | 995  | 91  | 100 |
| 19   | 994   | 983  | 91  | 100 |
| 20   | 975   | 962  | 91  | 100 |

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$\alpha$-uncorrected for anharmonicity factor.
1,9] and a class B cycloaddition, since the pipitzols derived from this experiment showed deuterium labeling at only 1 methyl of the gem-dimethyl arrangement. Considering that deuteration is the minimum modification that can be implemented into a molecule, in this case even generating the new C-8 stereogenic center, the isotope labeling procedure was repeated to generate separate samples of both pipitzols regioselectively deuterated at 1 methyl group of the gem-dimethyl arrangement of 2 and 3. However, there was no VCD spectral change observed in the 1800-950 cm$^{-1}$ region induced by the newly generated C-8 stereogenic center. This is in severe contrast with the results obtained for deuterated flavonones in which spectacular spectral changes were generated.

### Conclusions

Considering the limited information available, since inverse epimers are quite uncommon in nature, it seems that VCD is hardly capable of distinguishing the inverse epimers $\alpha$- (2) and $\beta$-pipitzol (3), which have 3 enantiomeric stereogenic centers and 1 stereogenic center with a common AC. This is in severe contrast with the capability that VCD has shown for the distinction of epimers belonging to the same cedranolides series of sesquiterpenoids, like cedrol having the (3$R$, 3a$R$, 6$R$, 7$R$, and 8a$S$) AC and isocedrol having the (3$R$, 3a$R$, 6$R$, 7$R$, and 8a$S$) AC, which could be distinguished nicely by VCD. It may be useful to evaluate other pairs of inverse epimers to learn where would be the distinction limit. In the case of epimers, the limit for the moment seems to be the study of the epoxidation of lupanone, where 1 stereogenic center out of a total of 10 such centers could be assessed.

### Experimental

#### General Experimental Procedures

**Compounds.** Samples of $\alpha$- (2) and $\beta$-pipitzol (3), and of pipitzols were available from previous studies. Their identity and purity were verified by $^1$H NMR measurements.

**VCD Measurements.** They were made on BioTools ChiralIR2X and ChiralIR dual photoelastic modulator (PEM) Fourier
transform (FT) spectrophotometers operated at a resolution of 4 cm⁻¹. Samples of 7.5, 7.1, and 9.5 mg of 2, 3, and pipitzols, respectively, dissolved in 150 μL of 100% atom-D CDCl₃ were placed in cells equipped with BaF₂ windows and a path length of 0.1 mm. Five 1 h data blocks for 2 and 3, and 6 h blocks for pipitzols were added. The baseline was corrected by subtracting the spectrum of the solvent, which was acquired under identical instrumental conditions. The samples stability was monitored by 1H NMR measurements performed immediately before and after the VCD determinations.

Computational Methods. Monte Carlo searches of 2a, 2b, 3a, and 3b were individually performed using MMFF94 as implemented in the Spartan’04 software (Wavefunction Inc.). The single-point energy of each conformer was calculated using DFT with the B3LYP functional and the 6-31G(d) basis set. The conformers were submitted to further conformational optimization using DFT at the B3LYP/DGDZVP levels of theory using the Gaussian’03 software (Gaussian Inc.). The IR and VCD frequencies calculations were carried out at the same levels of theory. All minimum energy geometries were tested for the absence of imaginary frequencies and their relative free energies were used to calculate the Boltzmann distributions of 2 and 3. The Boltzmann-weighted IR and VCD spectra were calculated with Lorentzian functions and a bandwidth of 6 cm⁻¹. Calculated and experimental spectra were compared using the CompareV/0.4 software (BioTools).²¹

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Declaration of Conflicting Interests

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ORCID iD

Pedro Joseph-Nathan https://orcid.org/0000-0003-3347-3990

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