Direct Determination of Absolute Configuration of Methyl-Substituted Phenyloxiranes: Combined Experimental and Theoretical Approach

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Three possible methyl-substituted phenyloxiranes have been synthesized in enantioenriched form (89−99% enantiomeric excess (ee)), and their vibrational absorption (VA) and vibrational circular dichroism (VCD) spectra have been recorded. The experimental spectra are compared to theoretical spectra obtained from quantum mechanical calculations (density functional theory with the B3LYP hybrid exchange correlation functional with 6-31++G**, aug-cc-pVDZ, or aug-cc-pVTZ basis set) and related to the physical structure of the compounds. The absolute configuration could be established directly in each case by comparing experimental and theoretical spectra. In addition, we have been able to document the changes that occur both in structures and in the VA and VCD spectra due to substituent effects on the oxirane ring.

Introduction

Asymmetric synthesis in general, and enantioselective catalysis in particular, is one of the major areas of interest in contemporary organic chemistry.[1] In any research program devoted to the chemical synthesis of chiral compounds in nonracemic form, it is essential to have reliable methods for the determination of absolute configuration. While indirect methods for this (e.g., derivatization and/or degradation followed by chemical correlation) are available, it is highly desirable to develop and refine methods for the direct determination of absolute configuration.[2]

Advanced chiroptical methods such as vibrational circular dichroism (VCD)[3] and Raman optical activity (ROA),[4] along with improved theoretical understanding,[5] have allowed the direct determination of the absolute configuration of an impressive range of small to medium-sized molecules by simple comparison of the calculated and experimental spectra.[6] In addition, for biomolecules, where multiple conformers are the rule rather than the exception, vibrational absorption (VA) and VCD have been used to monitor the conformational changes that occur for these flexible molecules as a function of solvent, pH, and ionic strength (for those molecules that can exist as a mixture of conformers, a Boltzmann-weighted average of the calculated spectra is compared to the experimental data).[3,7] Natural products have recently proved to be useful test cases for theoretical developments,[8] but small synthetic molecules such as phenyloxirane have also been important in the refinement and benchmarking of theory.[9] Oxiranes (three-membered rings containing two carbons and an oxygen) are important intermediates in synthetic organic chemistry, and a number of methods have been developed for the synthesis of chiral oxiranes of high enantiomeric and diastereomeric purity.[10] However, the direct determination of the absolute configuration of even simple chiral oxiranes is often not a trivial task. In this paper we present a comparison between experiment (VCD) and theory (DFT/B3LYP) for the three methyl-substituted phenyloxiranes shown in Figure 1. Our work complements an earlier study by Ashvar et al.,[9] in which the molecular structure of phenyloxirane itself was studied by a combination of vibrational unpolarized absorption and circular dichroism spectroscopies and ab initio theory. Here we also wish to underline the importance of earlier studies using even simpler oxiranes in the development and benchmarking of theoretical methods.[11]

Materials and Methods

Synthesis. The oxiranes were prepared in enantioenriched form (**1**, 95% enantiomeric excess (ee);[12] **2**, 89% ee;[10c] **3**, 99% ee[13]) according to literature procedures. The (1*R*,2*S*)-2-methylphenyloxirane (**2**) sample contained 10% (1*R*,2*R*)-2-methylphenyloxirane (**3**) (73% ee with surplus of (1*S*,2*S*)-2-methylphenyloxirane, the enantiomer of **3**) as a consequence of lack of stereospecificity in the enantioselective Mn(salen)-catalyzed epoxidation. The racemic epoxides were synthesized as reported previously using either *m*-chloroperoxybenzoic acid (MCPBA) in dichloromethane (**2** and **3**) or quinuclidine as achiral ligand in the osmium-catalyzed dihydroxylation (**1**).[12] The enantiomeric excess for each sample was determined by chiral gas chromatography (GC) using either Chrompack CP Chirasil-Dex CB 0.25 mm × 25 m column (90 °C isothermal used for **2** and **3**) or Supelco *β*-Dex 120 0.25 mm × 30 m column (100 °C isothermal used for **1**).

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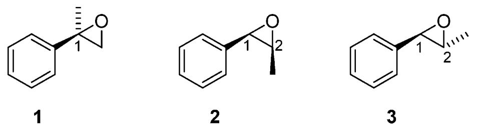

Figure 1. The three methyl-substituted phenyloxiranes under investigation: (1*R*)-1-methylphenyloxirane (**1**), (1*R*,2*S*)-2-methylphenyloxirane (**2**), and (1*R*,2*R*)-2-methylphenyloxirane (**3**). Hydrogen atoms were omitted for clarity.

Vibrational Absorption and VCD Experiments. All VA and VCD experiments were carried out on a Thermo-Nicolet Nexus 870 Fourier transform infrared (FTIR) instrument equipped with a VCD compartment. The following properties were used to convert experimentally determined absorbances to molar extinction coefficients: M_w 134.2 g/mol; densities at 20 °C for (*R*)-1-methylphenyloxirane (**1**), (1*R*,2*S*)-2-methylphenyloxirane (**2**), and (1*R*,2*R*)-2-methylphenyloxirane (**3**), respectively, 1.02, 1.01, and 1.01 g/cm^3.[14] The diastereomeric purity of **2** was taken into account when converting absorbance to molar extinction coefficients.

Experiments on neat samples were carried out using a cell with BaF_2 windows and a 15 μm spacer. Experiments on 1.3 M samples of **1**−**3** in CCl_4 were carried out in a sealed KBr cell with a path length of 100 μm. VA measurements were carried out on samples diluted by a factor of 10 to ensure that no significant solute−solute interactions exist in the concentrated samples. In all cases the VCD spectrum was determined using an optically active sample and the corresponding racemic sample as background, running 8000−30 000 scans with a resolution of 4 cm^{-1}. Collection times ranged from about 2 to 8 h. The photoelastic modulator was set at either 1400 or 1500 cm^{-1}. The standard deviation has been plotted to allow an estimation of the uncertainty in the measurements.

Theoretical Methods. The initial investigations of the potential energy surface for the methyl-substituted phenyloxiranes were carried out using DFT/B3LYP[15] in Jaguar v. 4.2 build 77[16] employing the 6-311++G** basis set.[17] Calculations of vibrational and electronic properties were carried out using the Gaussian03 program package[18] on Linux-based PCs at the Technical University of Denmark. The method employed was DFT/B3LYP with the 6-31++G**, aug-cc-pVDZ, or aug-cc-pVTZ basis set[19] on all atoms for both geometry optimizations, and for calculation of VA and VCD spectra.[20] Lorentzian line shapes were assumed with a half-width of 4 cm^{-1} in the theoretical VA and VCD spectra, and a frequency scaling factor of 0.98 was used throughout to account for the combined error resulting from anharmonicity and basis set. This scaling factor was selected based on our experimental results and lies within the uncertainty of values listed for similar methods in the Computational Chemistry Comparison and Benchmark DataBase.[21] The calculations were all carried out with the (*R*)-configuration at the benzylic position, which is the expected enantiomer for all three compounds with the asymmetric reactions used in this work.[10c,12,13] For the reported VCD spectra, molar extinction coefficients were scaled according to the enantiomeric purity as determined by chiral GC (see Materials and Methods, Synthesis). For sample **2**, which contains a minor amount of **3** having the (*S*)-configuration at the benzylic position, the theoretical VCD spectrum was corrected by subtracting 10% of the calculated VCD spectrum of **3**.

Results and Discussion

Conformational Search. Calculations were performed to explore the potential energy surface of the methyl-substituted phenyloxiranes using DFT/B3LYP with the 6-31++G** basis set in Jaguar. In particular, the rotation of the phenyl ring with respect to the remainder of the molecule was investigated by performing a series of geometry optimizations with different values for the appropriate dihedral angle α in intervals of 10° (Figure 2).

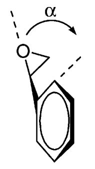

Figure 2. Sign convention used for the dihedral angle α.

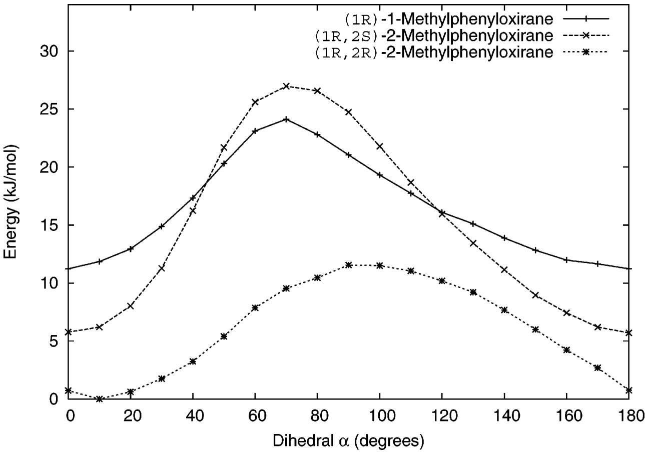

Figure 3. Energy profiles for the rotation of the phenyl group in the three phenyloxiranes. All energies are relative to the minimum for (1*R*,2*R*)-2-methylphenyloxirane (**3**).

For all three compounds there exists only one minimum energy conformation (Figures 3 and 4), which is stabilized by an electrostatic interaction between an ortho-H on the phenyl ring and the oxygen atom (typical Mulliken charges[22] with aug-cc-pVTZ basis: O −0.30 and H +0.16, distance 2.5 Å). In compounds **1** and **2** the steric influence from the proximal methyl causes the phenyl ring to occupy a position coplanar with the closest C−O bond, resulting in an α close to zero. In compound **3** the methyl group is situated at the opposite side of the oxirane ring and cannot obstruct rotation of the phenyl group, thus leading to a minimum energy conformation with α equal to 20°. The use of a polarized continuum (PCM) solvation model does not affect the overall structural features of the minimum energy conformation.

Since the three phenyloxiranes are constitutional isomers, we have plotted the energies obtained by the calculations in the gas phase relative to the most stable conformation of compound **3**, which is the overall energy minimum for all three compounds. In **2** there is additional internal energy due to unfavorable steric interactions between the methyl group and the phenyl ring, which are situated in a cis fashion on the oxirane backbone. In **3** the two groups point in opposite directions and the energy barrier for rotation of the phenyl group is only ca. 12 kJ/mol. In both **1** and **2** the position of equilibrium has the plane of the phenyl ring coplanar with the proximal C−O bond, corresponding to α = 0° or 180°. For these two compounds the minimum energy is higher than for **3**, by 6 kJ/mol for **2** and 11 kJ/mol for **1**.

The validity of the minimum energy structure was verified further by also performing restricted minimizations for the rotation of the methyl group in each of the three compounds. For all three compounds the rotational barriers were symmetrical with heights of 8−10 kJ/mol.

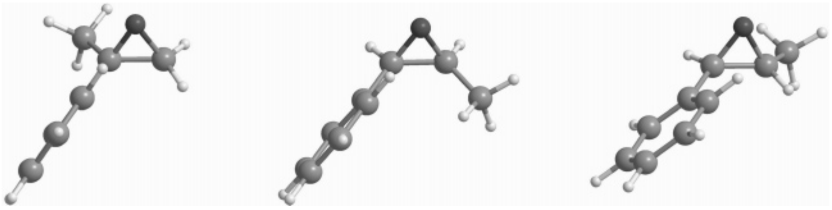

Figure 4. Structures of the three methyl-substituted phenyloxiranes optimized with the aug-cc-pVTZ basis set in Gaussian03.

TABLE 1: Dihedral Angle, α, in the Fully Optimized Structures Used To Calculate Spectroscopic Properties

	α (deg)		
	6-31++G**	aug-cc-pVDZ	aug-cc-pVTZ
(1*R*)-1-methylphenyloxirane (**1**)	0.8	3.3	0.0
(1*R*,2*S*)-2-methylphenyloxirane (**2**)	2.8	1.7	2.0
(1*R*,2*R*)-2-methylphenyloxirane (**3**)	16.6	19.1	18.6

Having established an approximate structure for the minimum energy conformation of each methyl-substituted phenyloxirane, a full energy minimization in Gaussian03 was undertaken followed by calculations of spectroscopic properties. The dihedral angles α in the fully minimized structures are listed in Table 1.

Comparison of Calculated Spectra. To estimate the importance of the basis set on the calculated spectra (in particular VCD), the VA and VCD spectra for all three compounds were calculated using three different basis sets. The smallest basis set was 6-31++G**, which is a split valence double-ζ basis set with an additional diffuse function and a polarization function on all atoms. We have also included Dunning's augmented correlation-consistent double-ζ[23] and triple-ζ basis sets, denoted aug-cc-pVDZ and aug-cc-pVTZ.[24] Inclusion of solvation using a polarized continuum model did not lead to significant changes in the calculated spectra; thus the discussion in the following text has been based on the gas-phase calculations only.

The numbering is based on the calculated fundamentals, starting with the lowest wavenumber mode, and the modes in the mid-IR (800−1800 cm^{-1}) correspond to modes 18−44 out of a total of $3N - 6 = 54$ (with 20 atoms in the molecules). The calculated VA and VCD spectra for (*R*)-1-methylphenyloxirane (**1**) are shown in Figure 5, and a visualization of the most prominent absorptions can be found in the Supporting Information. When examining the calculated VA spectra, it is

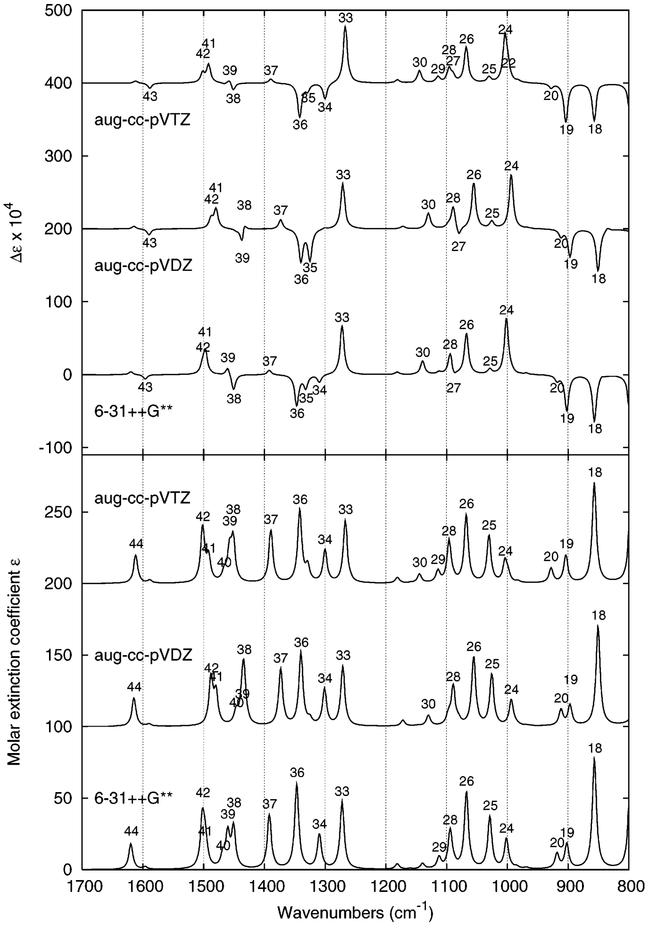

Figure 5. Calculated VA (bottom) and VCD (top) spectra for (*R*)-1-methylphenyloxirane (**1**) with DFT/B3LYP and three different basis sets as indicated. Spectra are offset for clarity, and most fundamentals have been numbered.

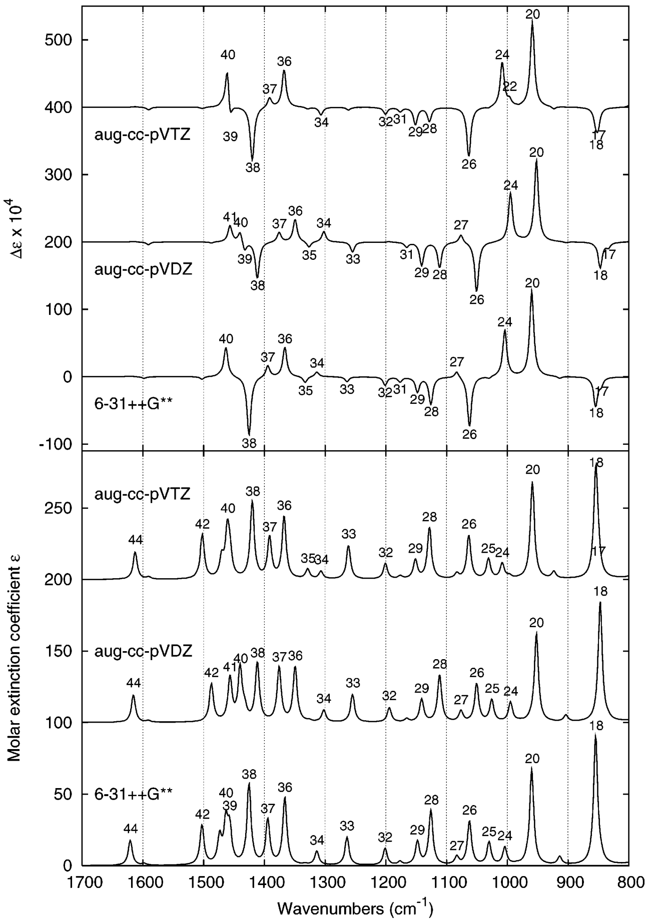

Figure 6. Calculated VA (bottom) and VCD (top) spectra for (1*R*,2*S*)-2-methylphenyloxirane (**2**) using DFT/B3LYP and three different basis sets.

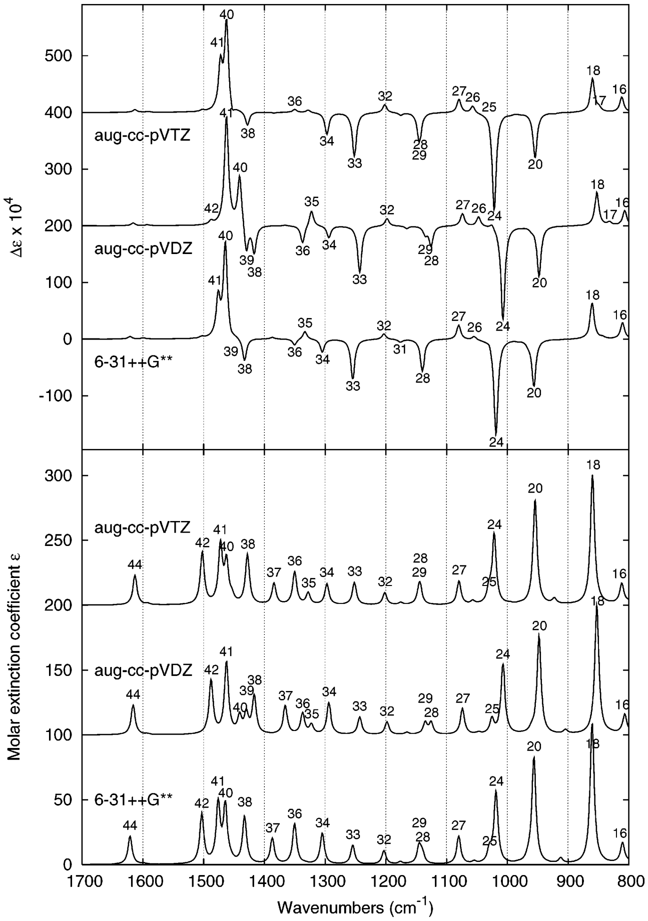

Figure 7. Calculated VA (bottom) and VCD (top) spectra for (1*R*,2*R*)-2-methylphenyloxirane (**3**) using DFT/B3LYP and three different basis sets.

clear that there are only small differences among the three basis sets. Also, for the VCD spectra there are many similarities among the three basis sets, although some differences can also be noted, for example, the relative intensity of the two negative VCD signals arising from fundamentals 18 and 19. With the largest basis set (aug-cc-pVTZ) the two are of equal intensity, whereas for both of the smaller basis sets the intensity of fundamental 18 is predicted to be larger than that of 19. For the two medium-intensity negative signals, 35 and 36, the latter is predicted to be of larger intensity using 6-31++G** and aug-cc-pVTZ basis sets, whereas the prediction from aug-cc-pVDZ is equal intensity for these two fundamentals. For the two very weak signals arising from fundamentals 38 and 39, there is a difference in sign when the aug-cc-pVDZ basis set is used.

The calculated VA and VCD spectra for (1*R*,2*S*)-2-methylphenyloxirane (**2**) are shown in Figure 6, and a visualization of the most prominent absorptions can be found in the Supporting Information. Upon examination of the calculated VA spectra it is clear that there are only small differences among the three basis sets except for the splitting of fundamentals 40 and 41, which is also seen for the spectra calculated with the aug-cc-pVDZ basis set. Also for the VCD spectra, there are many similarities among the three basis sets, although minor differences must be noted. For example, the relative intensity of the absorption arising from the fundamentals 28 and 29 shifts with increasing size of the basis set, with the latter having the strongest absorption with the largest basis set. Also, the sign of fundamental 34 is different with the largest basis set compared to the two smaller basis sets. The pattern around 1350−1450 cm^{-1} is quite different with the aug-cc-pVDZ basis set, compared to the two other basis sets used in this work.

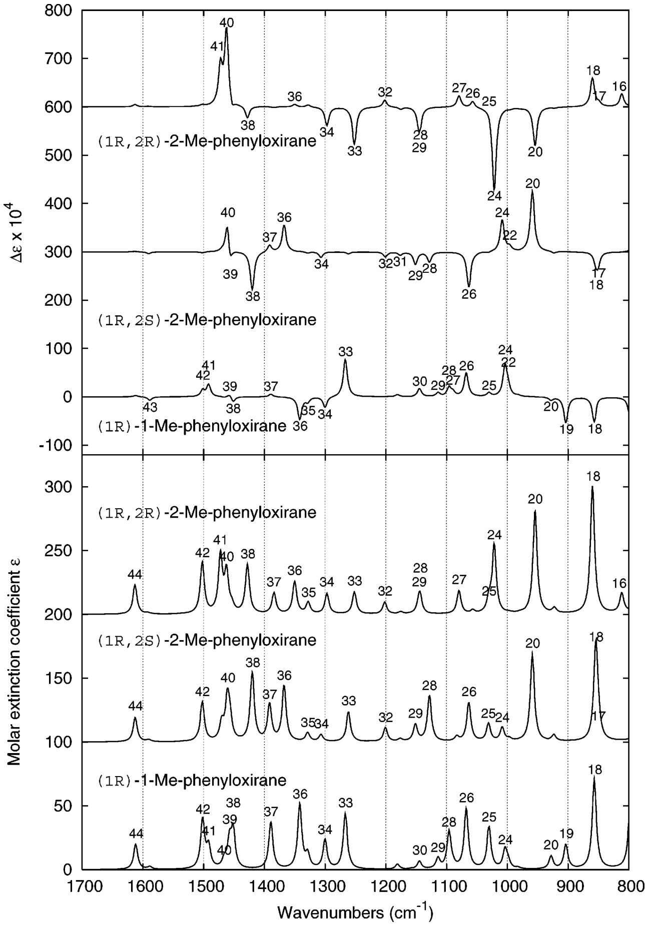

Figure 8. Comparison of calculated VCD spectra (top) and VA spectra (bottom) for **1**, **2**, and **3** using DFT/B3LYP with the augmented cc-pVTZ basis set.

The calculated VA and VCD spectra for (1*R*,2*R*)-2-methylphenyloxirane (**3**) are shown in Figure 7, and a visualization of the most prominent absorptions can be found in the Supporting Information. For the calculated VA spectra it is clear that there are only small differences among the three different basis sets, although it seems that the aug-cc-pVDZ basis set once again gives results different from those obtained using the two other basis sets. When the VCD spectra are compared, there is an overall good agreement in the low wavenumber range (800−1200 cm^{-1}), but for fundamentals 34, 35, and 36 there are relatively large differences. The intensity of the VCD signal arising from fundamental 34 is somewhat larger with the largest basis set when compared to the two smaller ones. Fundamental 35 is predicted to be very small with the largest basis set, whereas the two smaller basis sets predict an absorption of medium intensity. This is also the case for fundamental 36.

The relative intensity and the splitting are very different for fundamentals 40 and 41 when using the aug-cc-pVDZ basis set compared to the two other basis sets.

Comparison between Isomers. The calculated VA and VCD spectra with the largest basis set for all three methyl-substituted phenyloxiranes have been collected in Figure 8. By simple examination of the VA spectra all three compounds can be easily distinguished. For example, the presence of the strong absorption around 960 cm^{-1} (fundamental 20) arising from having an H and a methyl attached to the same carbon in the oxirane ring is present in **2** and **3** but not in **1**. Interestingly, due to the opposite

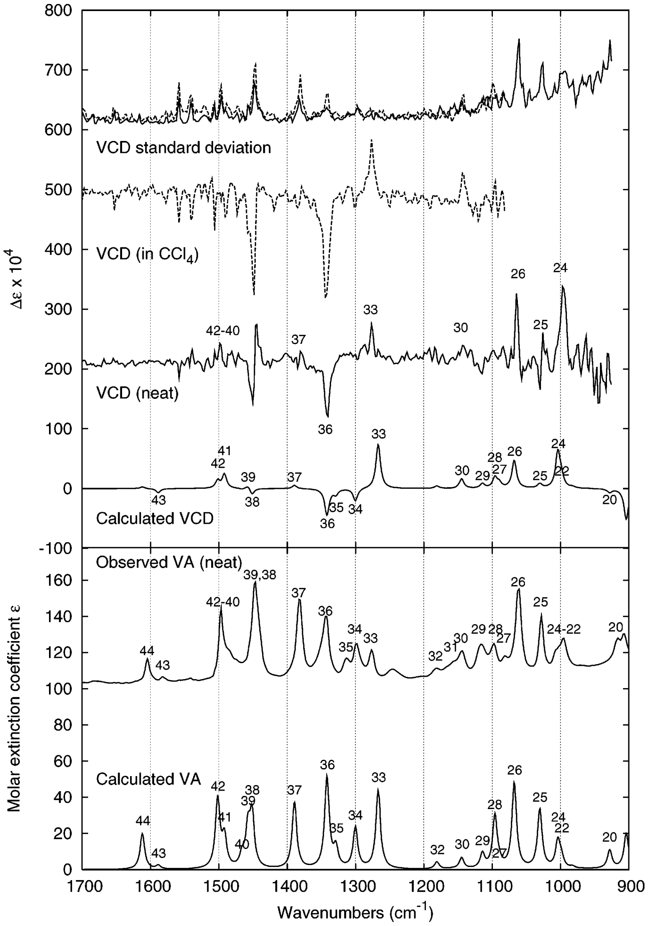

Figure 9. Comparison of experimental and calculated (B3LYP/aug-cc-pVTZ) VCD spectra (top) and VA spectra (bottom) for (*R*)-1-methylphenyloxirane (**1**).

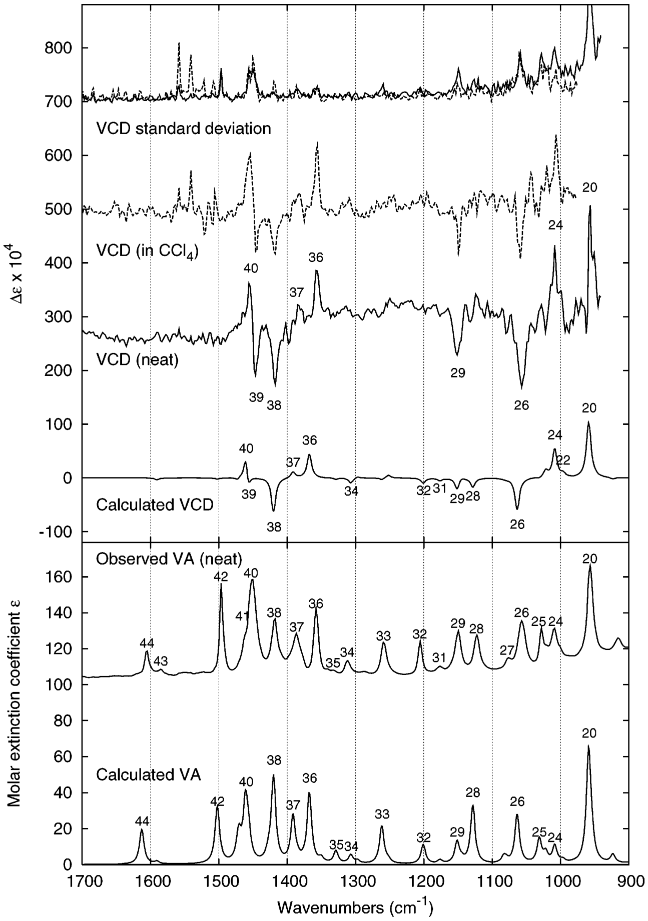

Figure 10. Comparison of experimental and calculated (B3LYP/aug-cc-pVTZ) VCD spectra (top) and VA spectra (bottom) for (1*R*,2*S*)-2-methylphenyloxirane (**2**).

absolute configuration of the carbon atom in the oxirane, the VCD signal from this particular absorption is positive for **2** and negative for **3**, allowing for easy discrimination of these two compounds. This is also the case for fundamental 24 in **2** and **3**, which is the asymmetric pendant to fundamental 20. Fundamental 26 in compounds **1** and **2** can also be used to discriminate efficiently between these two compounds since it gives a positive VCD signal for **1**, a negative VCD signal for **2**, and practically no signal for **3**. Fundamental 33 gives a positive VCD for **1** from a vibration involving the ortho-hydrogens and the oxirane ring. In compounds **2** and **3** fundamental 33 corresponds to a C−C stretching motion within the phenyl ring coupled to the oxirane ring. This vibration results in negative VCD for **3** but does not give any signal for **2**. Fundamental 36 gives negative VCD for **1** from a C−C stretch within the three-membered ring, a motion not responsible for significant VCD in **2** and **3**. The fundamental also numbered 36 in these compounds reflects a symmetric bending motion of the β-hydrogen attached directly to the oxirane ring. This vibration gives a positive VCD for **2**, but almost no signal for **3** despite the structural similarity between the two compounds.

Fundamental 38 is a symmetric stretch/bend motion of the meta- and para-hydrogens on the phenyl ring. This vibration gives a dominant negative VCD for **2**, a much less intense signal for **3**, and no signal for **1**.

The symmetric and asymmetric stretch/bend motion of the methyl group was located as fundamentals 41 and 42 in **1** and 40 and 41 in compounds **2** and **3**. In all three cases these vibrations give rise to VCD absorptions but with different appearances. The absorption is medium intensity for **1** and is located at a higher wavenumber than for **2** and **3**. In **2** only a single absorption is seen, whereas for **3** these vibrations give two dominant positive VCD signals, which are among the strongest ones in the entire spectrum.

Experimental Results

The experimental VA and VCD spectra for **1** obtained neat and in CCl_4 solution are shown in Figure 9, along with calculated spectra using the large aug-cc-pVTZ basis set. The experimental and calculated spectra display a high degree of similarity, allowing for assignment of the individual peaks in the experimental spectra. The similarity of the calculated and experimental VA spectra implies that the theoretically optimized structure lies very close to the real molecular structure. There are, however, minor differences between the calculated and experimental spectra. For **1** the dipole strength of fundamentals 27/28 and 33 seems to be overestimated in the theoretical calculation, whereas modes 37 and 38 seem to be slightly underestimated. In the VCD spectrum obtained using the neat liquid, the fundamentals 24 and 28 give rise to positive signals. The positive VCD signal from fundamental 30 is more clearly seen in CCl_4 solution than in the neat liquid. The signals from fundamentals 33 (positive) and 36 (negative) are easily recognized in both experimental spectra. The strong VA absorption from fundamentals 38 and 39 combined with very small predicted VCD intensity gives rise to artifacts in this region (~1450 cm^{-1}), which is documented by the higher noise level.

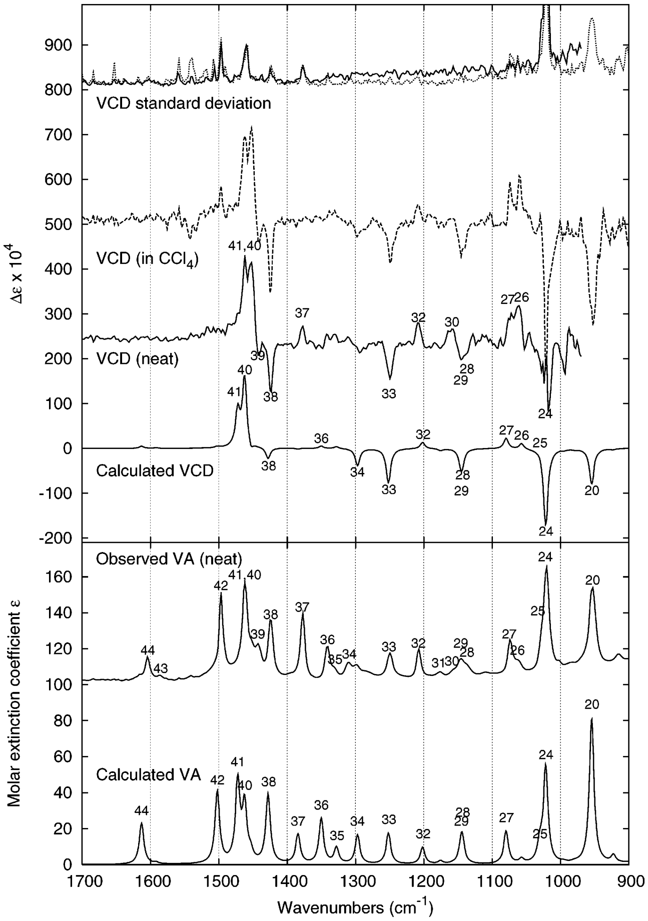

Figure 11. Comparison of experimental and calculated (B3LYP/aug-cc-pVTZ) VCD spectra (top) and VA spectra (bottom) for (1*R*,2*R*)-2-methylphenyloxirane (**3**).

From comparison of theory and experiment, we conclude that the synthesized enantiomer of **1** is the (*R*)-enantiomer at the benzylic position based primarily on the strong VCD absorptions from fundamentals 33 and 36, and further substantiated by the weaker absorptions from fundamentals 24, 26, 30, and 33.

The experimental VA and VCD spectra for **2** obtained neat and in CCl_4 solution are shown in Figure 10 along with calculated spectra using the large aug-cc-pVTZ basis set. Also, for **2** there are small discrepancies between experimental and calculated absorption spectra. In particular, for fundamentals 26 and 28 the calculated dipole strength is too small, whereas for fundamental 38 the calculated dipole strength is too large. When the low wavenumber region of the VCD spectra of the neat liquid is examined, fundamental 20 gives rise to a large positive VCD signal which is in accordance with the calculated spectrum, although the large absorbance gives rise to a relatively high noise level. Fundamentals 24, 26, and 29 are all clearly seen in the experimental spectra; however, it seems that the rotational strength of fundamental 29 is underestimated in the calculation. At higher wavenumbers fundamentals 36, 37, and 38 also give rise to well-defined absorptions in the experimental spectra, thus clearly identifying **2** as having the (*R*)-configuration at the benzylic position. Also, for this compound the intense absorbance at ~1460 cm^{-1} makes the VCD signal there unreliable.

The experimental VA and VCD spectra for **3** obtained neat and in CCl_4 solution are shown in Figure 11 along with calculated spectra using the large aug-cc-pVTZ basis set. Here, the calculated dipole strengths of fundamentals 20 and 38 appear to be overestimated, whereas fundamental 37 seems to be slightly underestimated. The assignment of fundamentals 34–36 was difficult due to overlapping signals and/or insufficient resolution in the experimental spectra.

When the VCD spectra are examined, the agreement between experiment and theory is markedly better for **3** than for **1** and **2**, which is probably a consequence of the fact that the sample consists of essentially a single enantiomer (ee = 99%). In the VCD spectra of the neat liquid the absorption from fundamental 20 was too large to allow for VCD measurements; however, in CCl_4 the VCD signal seems to be reliable. Fundamentals 24, 28/29, 32, 33, 38, 40, and 41 were all easily interpretable in the experimental spectra, and we can confidently assign the synthesized enantiomer as having the (*R*)-configuration at the benzylic position. The weak absorptions arising from fundamentals 26 and 34 could be clearly distinguished from the background noise only in the spectrum of the neat liquid. In this respect the measurements on the neat liquid and in CCl_4 solution complement each other.

Conclusions

Theoretical calculations of dipole strengths and rotational strengths were carried out for the three methyl-substituted phenyloxiranes **1**–**3** having the (*R*)-configuration at the benzylic position using DFT/B3LYP with 6-31++G**, aug-cc-pVDZ, and aug-cc-pVTZ basis sets. Differences among these three basis sets were commented upon, and an overall good agreement between the 6-31++G** basis set and the aug-cc-pVTZ basis set was noted, whereas the aug-cc-pVDZ basis set often yielded markedly different results.

Oxiranes **1**–**3** have been synthesized in enantioenriched form, their VA and VCD spectra were recorded, and the experimental spectra were compared to theoretical spectra obtained using the largest basis set (aug-cc-pVTZ). There was very good agreement between the experimental and calculated VA spectra, allowing for direct assignment of most absorptions to the fundamental vibrations determined by calculation, indicating that the molecules in solution or as neat liquid indeed possess the physical structure obtained by energy minimization in the gas phase, or that the changes which occur at ambient temperature do not affect the overall spectral properties of the molecules. The absolute configuration of all three compounds could be established directly by comparing experimental and theoretical VCD spectra.

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Supporting Information Available: *XYZ* coordinates and SCF energies are available for all structures discussed along with tables containing the calculated dipole strengths and rotational strengths. Visual representations of the fundamental vibrational modes are also included. Dipole and rotational strengths have been extracted from the experimental spectra and compared to the calculated values. This material is available free of charge via the Internet at http://pubs.acs.org.

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