Our suggestion is that an analogous experimental study, with the cytochrome P450 enzymes, be carried out.

The possible problems involved are brought out in a recent study using a model iron-porphine system, with iodosylbenzene as the oxygen source.[9] Epoxidation of *cis*-stilbene proceeds with 82% yield to give the cis epoxide, while *trans*-stilbene is almost completely unreactive. The drastic difference in reactivity is easily ascribable to steric constraints at the catalytic site,[9] which would also hinder internal rotation in a biradical intermediate if a radical mechanism is involved.

The strategy we suggest is as follows: Steric factors might be minimized if one could find an olefinic substrate whose cis and trans isomers show similar reactivity toward P450 epoxidation. If one could also reasonably expect that internal rotation in a possible biradical intermediate would not be drastically hindered, such a substrate would provide an acceptable probe of mechanism.

We are currently engaged in further exploration of some of the questions raised in the present study, through modeling the hydroxylation and epoxidation of propene by oxene. Using the methods outlined here, in conjunction with theoretical evaluation of vibrational partition functions and thermodynamic activation parameters,[21] we hope to more rigorously address the reactivity-selectivity problem mentioned above. The allyl and vinyl carbons of propene, for example, represent extremes of reactivity in both ionic and radical reactions. Also, the unsymmetrical environment about the double bond is expected to affect the epoxidation mechanisms, in that two biradical intermediates are possible with, we expect, unequal stabilities.

Acknowledgments. The authors wish to thank Dr. Andrew Komornicki for making his programs, SIGMA, FORCE, and OPTMO, available to them, and James Ferrell and Dr. Stanley Burt for many helpful discussions. They also gratefully acknowledge the financial support provided for this work by National Institute of General Medicine Grant GM27943-01 and National Cancer Institute Contract NCI 1-CP75928.

Vibrational Optical Activity in Para-Substituted 1-Methylcyclohex-1-enes

Prasad L. Polavarapu, Max Diem, and Laurence A. Nafie*[1]

Contribution from the Department of Chemistry, Syracuse University, Syracuse, New York 13210. *Received January 10, 1980*

Abstract: We report Raman optical activity (ROA) between 1300 and 1500 cm^{-1} and vibrational circular dichroism (VCD) between 2800 and 3000 cm^{-1} for (+)-*p*-menth-1-ene and (+)-*p*-menth-1-en-9-ol. The ROA data were obtained from a newly constructed spectrometer, the details of which are described. In addition, we have measured the VCD of (+)-limonene in the CH stretching region which complements the ROA spectrum of (−)-limonene available in the literature. All three molecules have the same ring structure and differ only at the para position. Since the vibrational optical activity (VOA) of these molecules in the regions selected is strongly similar we conclude that, contrary to general expectation, degenerate methyl modes do not make dominant contributions here. Instead, ring methylene modes are implicated as the major source of VOA intensity. It is encouraging that both VCD and ROA reinforce this spectral interpretation and therefore each other. This study of VOA is the first in which new spectral data for both VCD and ROA are presented.

I. Introduction

Current research in vibrational optical activity (VOA) has revealed considerable potential for exploring molecular stereochemistry.[2-5] Recently, correlations between observed Raman optical activity (ROA) and stereochemical details in two series of related molecules have been reported.[6,7] Similar correlations have been noted in the vibrational circular dichroism (VCD) of amino acids,[8,9] peptides,[10] sugars,[11] and several organic molecules.[12-15] In this paper we present VOA spectra for three closely related cyclohexene molecules which differ only by their substituent at the para position. This study is unique in that new experimental data for *both* VCD and ROA are presented. The combined results are then used to interpret the stereochemical origin of the major spectral features. Our approach here is to study VCD and ROA in closely related spectral regions which permits reinforcing interpretations of the data. This circumvents the general problem of lack of overlap between the usual spectral regions of VCD and ROA, although improvements in instrumentation[16-18] in the near future should reduce this problem by

---

(1) Alfred P. Sloan Foundation Fellow.

(2) L. D. Barron, *Adv. Infrared Raman Spectrosc.*, (1978).

(3) L. D. Baron in "Optical Activity and Chiral Discrimination", S. F. Mason, Ed., D. Reidel Dordrecht, Holland, 1979, p 219.

(4) P. J. Stephens and R. Clark in ref 3, p 263.

(5) L. A. Nafie and M. Diem, *Acc. Chem. Res.*, **12**, 296 (1979).

(6) L. D. Barron and B. P. Clark, *J. Chem. Soc., Perkin Trans. 2*, 1164 (1979).

(7) L. D. Barron and B. P. Clark, *J. Chem. Soc., Perkin Trans. 2*, 1171 (1979).

(8) M. Diem, P. J. Gotkin, J. M. Kupfer, A. P. Tindall, and L. A. Nafie, *J. Am. Chem. Soc.*, **99**, 8103 (1977).

(9) M. Diem, E. Photos, H. Khouri, and L. A. Nafie, *J. Am. Chem. Soc.*, **101**, 6829 (1979).

(10) M. Diem, P. J. Gotkin, J. M. Kupfer, and L. A. Nafie, *J. Am. Chem. Soc.*, **100**, 5644 (1978).

(11) C. Marcott, H. A. Havel, J. Overend, and A. Moscowitz, *J. Am. Chem. Soc.*, **100**, 7088 (1978).

(12) H. Sugeta, C. Marcott, T. R. Faulkner, J. Overend, and A. Moscowitz, *Chem. Phys. Lett.*, **40**, 397 (1976).

(13) T. A. Keiderling and P. J. Stephens, *J. Am. Chem. Soc.*, **99**, 8061 (1977).

(14) C. Marcott, C. C. Blackburn, T. R. Faulkner, A. Moscowitz, and J. Overend, *J. Am. Chem. Soc.*, **100**, 5262 (1978).

(15) T. A. Keidering and P. J. Stephens, *J. Am. Chem. Soc.*, **101**, 1396 (1979).

(16) L. A. Nafie, M. Diem, and D. W. Vidrine, *J. Am. Chem. Soc.*, **101**, 496 (1979).

(17) H. Boucher, T. R. Brocki, M. Moskovits, and B. Bosnich, *J. Am. Chem. Soc.*, **99**, 6870 (1977).

0002-7863/80/1502-5449$01.00/0

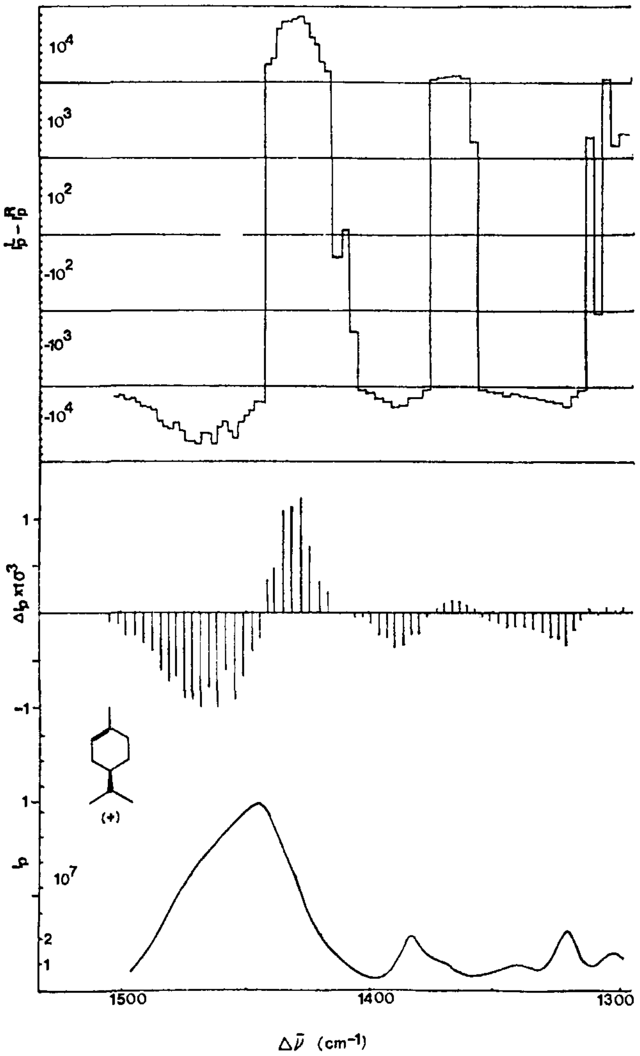

Figure 1. Depolarized ROA and Raman spectra of (+)-*p*-menth-1-ene. $(I_p^L - I_p^R)$ spectrum (top), as recorded, is presented on a scale that is linear in each decade range, but logarithmic between decades. Middle and bottom displays, on a purely linear scale, correspond to $I_p^L - I_p^R$ and $I_p^L + I_p^R$ spectra, normalized by the maximum intensity of 7.4×10^7 photoelectron counts at 1445 cm^{-1}.

permitting routine mid-infrared VCD observation[4] as well as higher frequency ROA data.[19]

In this article we report the ROA spectra of (+)-*p*-menth-1-ene and (+)-*p*-menth-1-en-9-ol in the CH bending region between 1300 and 1500 cm^{-1} and the VCD spectra of these same molecules, as well as (+)-limonene, in the CH stretching region between 2800 and 3000 cm^{-1}. Together with previously published ROA data for (−)-limonene,[6] we compare the VOA spectra for all three of these molecules. Because of strong similarities in the observed VOA spectra, we conclude that the major source of intensity comes from the cyclohexene methylene ring modes and not from degenerate methyl antisymmetric modes. This result is at first sight surprising owing to the presence of signals resembling couplets for both ROA and VCD in regions close to the methyl frequencies and since couplets are expected on a theoretical basis at these locations for molecules containing methyl groups. Our results do not preclude the presence of methyl couplets in the reported spectra, but rather place upper limits on their magnitude and, in fact, two of the three VCD spectra show small signals which may indeed be methyl couplets.

Since there is nothing remarkable about the ring structure common to these molecules, the significance of our findings is that coupled methylene groups in ring molecules in general may well be major sources of reproducible VOA intensity and thereby serve as reliable markers of ring structure, conformation, and configuration.

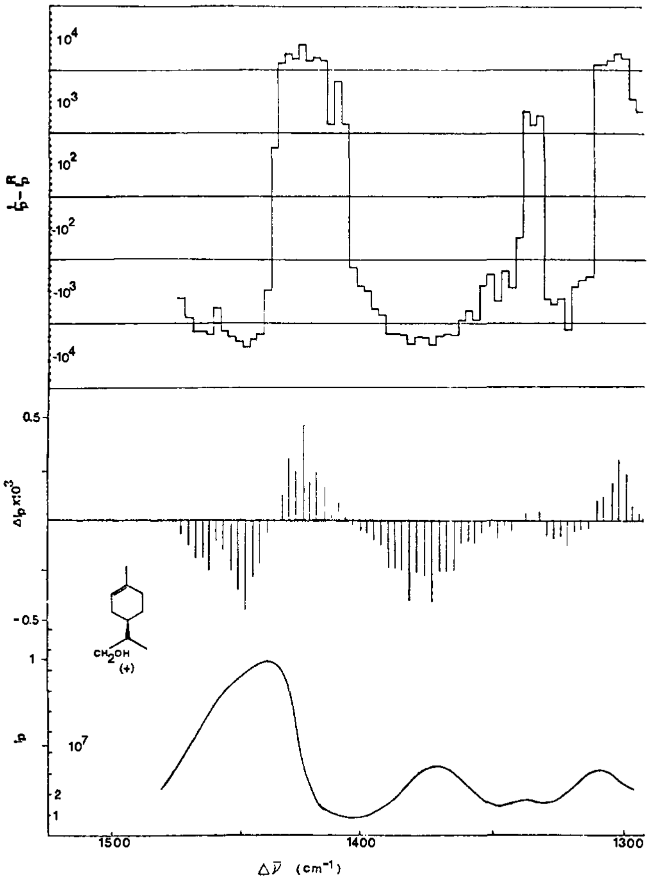

Figure 2. Depolarized ROA and Raman spectra of (+)-*p*-menth-1-en-9-ol. $(I_p^L - I_p^R)$ spectrum (top), as recorded, is presented on a scale that is linear in each decade range, but logarithmic between decades. Middle and bottom displays, on a purely linear scale, correspond to $I_p^L - I_p^R$ and $I_p^L + I_p^R$ spectra, normalized by the maximum intensity of 8.4×10^7 photoelectron counts at 1440 cm^{-1}.

II. Experimental Section

The experimental arrangement for our ROA measurements is similar to one reported earlier.[2] Incident radiation from an argon ion laser (Spectra-Physics Model 166-03) in excess of 1 W at 488 nm is modulated between left and right circular polarization, using an electro-optic modulator (Lasermetrics 3116). The modulator is driven by a variable frequency square-wave generator followed by a high-voltage amplifier and diode clipping circuit to maintain constant positive and negative voltage levels. The scattered light is focused at the slit of a double monochromator (Spex 1401) and detected by a photomultiplier (RCA 31034) having less than 20 cps (counts per second) dark current. The photomultiplied pulses are amplified (PARC Model 1120) and sent to a dual-channel photon counter (PARC Model 1112) where they are gated into either the "left" channel or the "right" channel by a reference signal from the modulator.[2] Sum and difference counts are then recorded separately on chart paper.

The VCD spectra were obtained with an instrument which has been described previously[10] with the exception that a CaF_2 modulator (Hinds-International Model JCK-CF) has replaced our ZnSe modulator.

Samples were obtained from Aldrich Chemical Co. and used without further purification. ROA spectra were obtained from neat liquids in strain-free optical cells, using 10-cm^{-1} spectral resolution and 1.2-W laser power. VCD spectra were obtained from dilute solutions in CCl_4, using a variable path length cell. VCD spectra of these molecules as neat liquids were also obtained, but the results were the same, to within experimental error, as the dilute solution spectra.

III. Results

In Figures 1 and 2 we present the ordinary Raman and ROA spectra for (+)-*p*-menth-1-ene and (+)-*p*-menth-1-en-9-ol in the 1300–1500-cm^{-1} region. All spectra are depolarized; i.e., the

---

(18) W. Hug and H. Surbeck, *Chem. Phys. Lett.*, **60**, 186 (1979).

(19) W. Hug, H. Surbeck, and B. Cuony, Abstracts of the 34th Symposium on Molecular Spectroscopy, Columbus, Ohio, 1979, Paper TH10.

Table I. Vibrational Frequencies, ROA and Raman Intensities, and Assignments

molecule	Raman shift, cm^{-1} ^{a}	$(I_P{}^L - I_P{}^R) \times 10^{-4}$	$(I_P{}^L + I_P{}^R) \times 10^{-7}$	$q_P \times 10^3$	principal modes
(+)-*p*-menth-1-ene	1467	−7.5	5.7	−2.6	antisymmetric ring CH$_2$ deformation
	1430	9.0	4.7	3.8	
	1390	−2.7	1.2	−4.5	
	1367	1.0	1.1	1.8	HCC deformation
	1320	−2.5	2.4	−2.1	
(+)-*p*-menth-1-en-9-ol	1455	−3.0	7.5	−0.8	antisymmetric ring CH$_2$ deformation
	1430	5.0	3.5	2.9	
	1380	−3.5	3.0	−2.3	
	1305	2.5	3.0	1.7	HCC deformation
(−)-limonene	1475	4.0	5.0	1.6	antisymmetric ring CH$_2$ deformation
	1435	−3.5	35	−0.20	
	1400	3.5	10	0.70	

^{a} Frequencies listed correspond to ROA peak positions. ^{b} The ROA chirality number, q_P, equals $2(I_P{}^L - I_P{}^R)/(I_P{}^L + I_P{}^R)$ for an enantiomerically pure sample.[19]

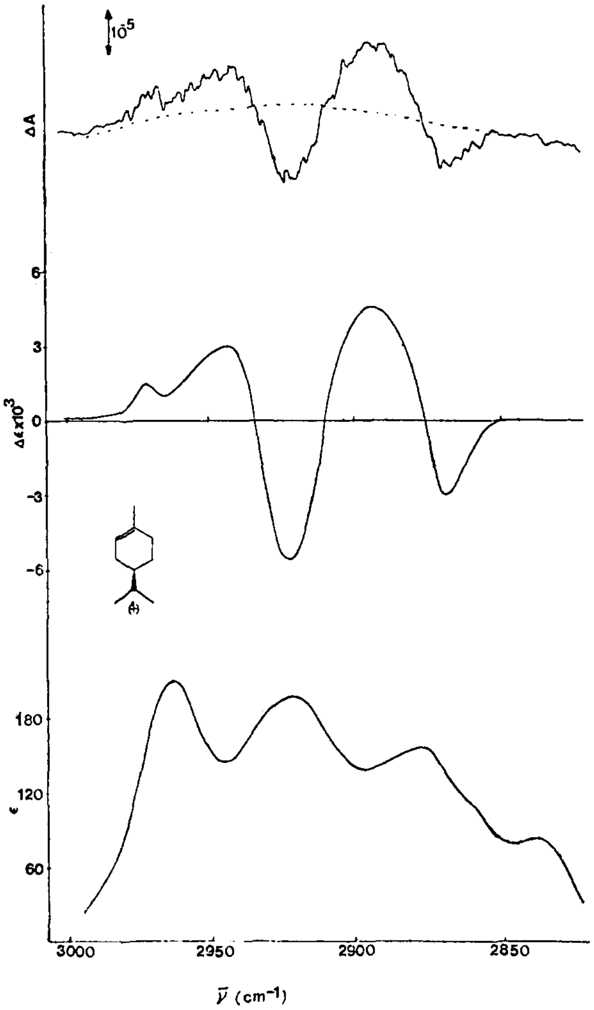

Figure 3. VCD and IR absorption spectra of (+)-*p*-menth-1-ene. The Δ*A* spectrum (top) is recorded as 0.3 M solution in CCl$_4$, with 115-μm path length. This spectrum is replotted in the middle display in terms of Δε. The VCD base line is deduced from that of 0.3 M *dl*-3-methylcyclohexanone. In the bottom display, transmission spectra have been used to obtain the absorption spectrum in terms of ε.

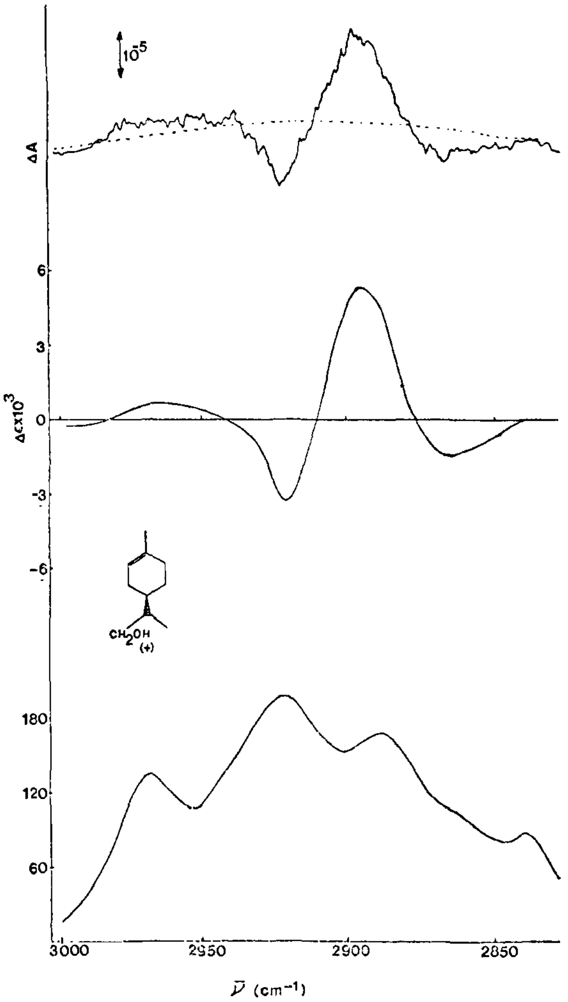

Figure 4. VCD and IR absorption spectra of (+)-*p*-menth-1-en-9-ol. The Δ*A* spectrum (top) is recorded as 0.33 M solution in CCl$_4$ with 110-μm path length. This spectrum is replotted in the middle display in terms of Δε. The VCD base line is deduced from that of 0.3 M *dl*-3-methylcyclohexanone. The bottom display gives the absorption spectrum in terms of ε.

anlyzing polarizer for the scattered light was set parallel to the scattering plane, and this arrangement is designated by the subscript p for all Raman intensity symbols,[20] e.g., I_p and q_p. The figures contain the raw ROA data on a logarithmic–linear plot as well as the Raman total intensity. The latter are also normalized to unity at the maximum peak intensity and the ROA data are replotted on a purely linear scale relative to this normalized intensity.

These spectral results along with those for (−)-limonene[6] are summarized in Table I. Here we provide the values of the sum and difference intensities for the major ROA features in this region, along with the calculated chirality numbers. Also given are vibrational assignments of the major contributing modes as determined by group frequency expectations and our overall spectral observations in this study.

---

(20) P. L. Prasad and L. A. Nafie, *J. Chem. Phys.*, **70**, 5582 (1979).

Table II. Vibrational Frequencies, VCD and IR Intensities, and Assignments

molecules	VCD frequencies, cm^{-1}	$\Delta\epsilon \times 10^3$	IR frequencies, cm^{-1}	$\epsilon \times 10^{-2}$	principal modes
(+)-*p*-menth-1-ene	2972	1.5	2967	2.09	methyl antisymmetric stretch
	2942	3.0			ring methylene antisymmetric stretch
	2925	−5.5	2925	1.97	C*-H stretch + ring methylene antisymmetric stretch
	2895	4.5	2890	1.56	ring methylene antisymmetric stretch
	2870	−3.0	2880	1.07	ring methylene symmetric stretch
			2840	0.82	
(+)-*p*-menth-1-en-9-ol	2970	0.9	2965	1.35	same as above
	2945	0.5			
	2923	−3.9	2923	1.98	
	2893	5.3	2887	1.66	
	2865	−1.9	2865	1.01	
			2840	0.87	
(+)-limonene	2970	1.7	2968	0.94	same as above
	2942	3.0			
	2928	−4.8	2928	1.72	
	2893	4.9	2897	1.12	
	2868	−2.2	2860	0.79	
			2840	0.77	

In Figures 3–5, we present VCD and absorption spectra for these same three molecules in the 2800–3000-cm^{-1} region. In addition to the raw VCD data we provide redrawn VCD curves as $\Delta\epsilon$, where the effects of noise and a slightly curved base line have been removed. We have also determined the total absorption spectra in units of ϵ from single-beam transmission data.

The spectral intensities for the major observed bands for these molecules are summarized in Table II. Owing perhaps to a larger number of overlapping vibrational transitions in the VCD region compared to that of ROA, the locations of VCD maxima do not generally correspond to absorption maxima and hence we tabulate the VCD and IR frequency maxima separately. General assignments are offered for broad spectral locations as a guide to our discussion and interpretation.

IV. Discussion

Theoretically, it has been shown that the degenerate vibrational modes for a methyl group in a chiral environment can split in frequency and give rise to an ROA couplet having equal and opposite intensity.[2,21] A number of molecules have shown such splitting in degenerate methyl deformation modes centered at approximately 1450 cm^{-1} and excellent correlation between the sign of the couplet and the absolute configuration of the chiral center to which the methyl group is attached is found.[21-24] More recently, this simple interpretation has come under some question, owing to the failure of the couplet to appear in certain cases.[21] Nevertheless, good stereochemical correlation exists when the couplet does appear and the methyl group plays a central role in the effect.

For the ROA under consideration here, there is a couplet for all three molecules centered at 1450 cm^{-1} which correlates with the absolute configuration of the para substitution of the cyclohexene ring. These molecules also contain at least two methyl groups and the question arises as to whether one or more of these methyl groups play a major role in this stereochemical correlation.

In approaching this question, we first ruled out the methyl group adjacent to the cyclohexene double bond. In addition to being in an sp^2-planar environment, this group is three bonds away from the nearest chiral center. In contrast, the methyl group in the para substituent is only one bond away from a chiral center, and in menthenol it is also directly attached to a second chiral center. However, the environment of this substituent methyl group varies drastically among these three molecules. In fact, in menthene there are two such methyl groups which eliminate the second chiral center present in menthenol and therefore tend to counteract each other's local chiral influence. In spite of these wide variations in methyl-group environment, the strong couplet at 1450 cm^{-1} persists in all three molecules modified only by its intensity relative to the total Raman intensity.

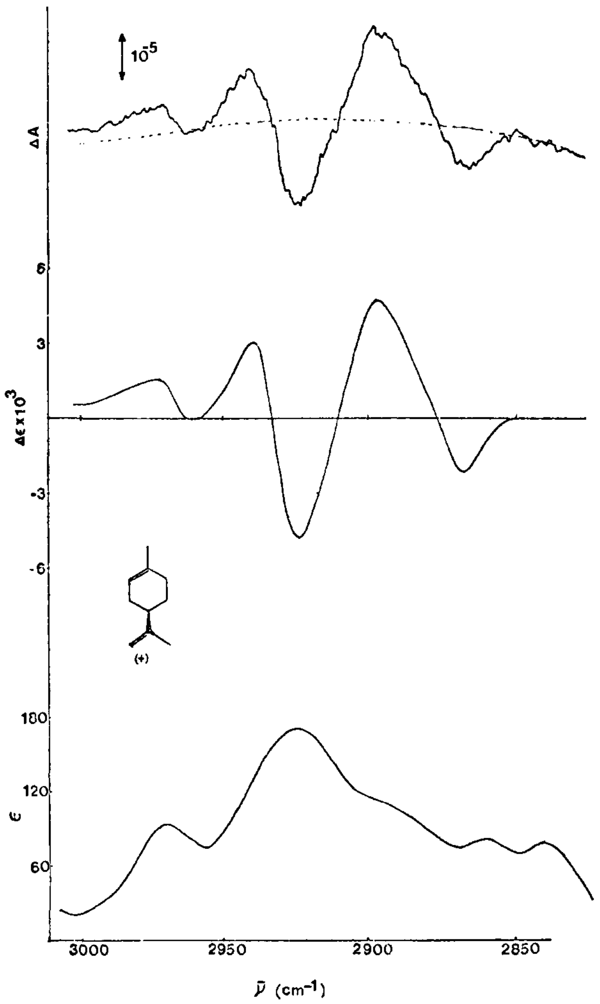

Figure 5. VCD and IR absorption spectra of (+)-limonene. The ΔA spectrum (top) is recorded as 0.36 M solution in CCl_4 with 110-μm path length. This spectrum is replotted in the middle display, in terms of $\Delta\epsilon$. The VCD base line is deduced from that of 0.3 M *dl*-3-methylcyclohexanone. The bottom display gives the absorption spectrum in terms of ϵ.

An alternate interpretation of the couplet involves the ring methylene deformation modes which also generally appear in the

---

[21] L. D. Barron, *J. Chem. Soc., Perkin Trans. 2*, 1970 (1978).

[22] W. Hug, S. Kint, G. F. Bailey, and J. R. Scherer, *J. Am. Chem. Soc.*, **97**, 5589 (1975).

[23] L. D. Barron, *Nature (London)*, **255**, 458 (1975).

[24] L. D. Barron and R. Clark, *J. Chem. Res. (S)*, 36 (1979).

1400-cm^{-1} region. This explanation is appealing since these molecules possess essentially the same cyclohexene ring structure. The ROA evidence then suggests the involvement of these ring modes with little dependence on the nature of the para substituent. In particular, there are three ring methylene groups which will yield three associated deformation modes which are related as phase variants of the same basic methylene group motion. Further inspection of the ROA spectra reveals that these molecules share a triad of bands (negative–positive–negative for the (+) enantiomers) rather than just a couplet of two bands. Thus, one possible explanation is that three ring deformation modes give rise to the observed triad. Contribution from ring HCC deformations to these ROA features via coupling, especially in the negative ROA feature at 1390 cm^{-1}, is also highly probable.

In the region between 1375 and 1300 cm^{-1} little similarity exists for these molecules, indicating substantial dependence on the para substituent. One plausible assignment for this region is to ring HCC modes strongly coupled to HCC modes in the para substituent.

As a consequence of these results favoring ring methylene vibrations as major contributors to the ROA intensity in the CH deformation region we decided to investigate the VCD of these molecules in the CH stretching region and to look for analogous effects. Overall, we found that the VCD are quite similar between 2850 and 2950 cm^{-1} and then show variation between 2950 and 3000 cm^{-1}. No VCD was observed from the olefinic CH stretching modes above 3000 cm^{-1}.

As seen from Table II, the regions of large, similar VCD can be associated primarily with ring methylene stretching modes and the methyne stretching mode, whereas the region above 2950 cm^{-1}, showing smaller, widely varying effects, is associated with the methyl antisymmetric region. We contend that the reproducible negative–positive–negative sequence of three VCD bands has its origin in the ring methylene and methyne vibrations and that these three bands undergo only small variations in intensity due to the para substituent. The width and variation of shape of the two higher frequency VCD bands strongly suggest that they are composites of two or more vibrational contributions. Further unraveling of the composition of these bands cannot be made at this time and must await detailed normal coordinate analyses for these molecules. It is interesting, however, that in spite of their underlying complexity a reproducible pattern is nevertheless present.

The VCD above 2950 cm^{-1} shows small intensity variations which remain essentially positive in sign. This variation is different for all three of these molecules, although those for menthene and limonene bear a certain resemblance. The position of positive–negative VCD variation near 2970 cm^{-1} of these last two molecules with respect to the position of the antisymmetric methyl stretching absorption band suggests that the effects of the splitting of degenerate vibrations in this region might be present. If this is the case, this result differs from the apparent absence of such effects in the methyl deformation region near 1450 cm^{-1}. Nevertheless, the methyl VCD effects are only small signals which appear to be superimposed on the trailing edge of larger signals originating in the ring methylene modes.

The results of both our ROA and VCD spectra point strongly to the importance of ring methylene vibrations in generating large, reproducible VOA for molecules containing the same basic ring structure. The rationale for this result is that the ring methylene groups tend to be held in the same fixed conformation and are also well coupled vibrationally. The fixed ring conformation has an advantage over noncyclic substituents, which may vary more widely in conformation and have less distinctive VOA contributions. The strong vibrational coupling of the ring leads to vibrational modes which are more delocalized in space and have correspondingly larger VOA contributions (at least from a theoretical argument based on magnetic moment arms). Thus, ring methylene modes may serve as a point reference in the interpretation of VOA in regions of their occurrence and variations in the VOA of these modes may serve as a probe of the influence of differing substituents for a series of related molecules.

On the other hand, our results point away from the general utility of the methyl group as a chiral probe in ring molecules containing methylene groups since VOA from the methyl groups did not give dominating or distinctive signals. In addition, the utility of the methyl group may become obscured when more than one type of methyl group is present, as in the molecules studied here. More likely, the methyl group may better serve as a chiral probe in simpler molecules where only one methyl group is attached directly to the only chiral center in the molecule.

V. Summary

We have found that the ROA and VCD of menthene, menthenol, and limonene contain major common features in the CH deformation and stretching regions, respectively. Both the ROA and VCD results point to hexene ring methylene vibrations as the major source of these reproducible patterns and we expect that other para-substituted 1-methylcyclohex-1-ene molecules will show similar VOA effects. Contrary to expectation, degenerate antisymmetric methyl modes do not play a significant role in these recurring patterns even though stereochemical patterns in other methyl-containing molecules have been reported.

In this work the techniques of VCD and ROA have been focused on a common problem by studying related spectral regions. It is both interesting and encouraging that both methods lead to the same general conclusion regarding the origin of the observed effects. It is not difficult to imagine that even more spectral detail could be extracted from these molecules if both VCD and ROA could be obtained for the same, rather than related, spectral regions. The results of this study indicate that combined VCD–ROA investigations are a useful addition to present methods of investigation in vibrational optical activity.

Acknowledgments. The authors wish to acknowledge support in part from the National Science Foundation (CHE 76-07514) and the National Institutes of Health (GM 23567).