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# Stereochemical Studies of Monoterpene Compounds. XVIII.⁽¹⁾ A Conformational Study of Monoterpene $\alpha,\beta$-Unsaturated Ketones by Means of the Temperature-dependent Circular Dichroism

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The conformations of flexible, cyclic $\alpha,\beta$-unsaturated ketones, (−)-*p*-menth-3-en-5-one (**1**), (+)-carvone (**2**), (−)-piperitone (**3**), (−)-carvenone (**4**), and (+)-pulegone (**5**), were examined by means of the temperature-dependent circular dichroism (CD) in the region of the $n$-$\pi^*$ transition. In polar solvents, the simultaneous occurrence of the conformational equilibrium and the asymmetric solvation was observed markedly for the compound **1** of these compounds, along with a change in the large rotational strength at lower temperatures.

In the region of the ultraviolet absorption, $\alpha,\beta$-unsaturated ketones generally exhibit three optically-active, absorption bands:[2] the first band (320—350 nm) is ascribed to the $n$-$\pi^*$ transition, and the others (240 nm and 210 nm), to the $\pi$-$\pi^*$ transition. The sign of a Cotton effect of the third band has been correlated[3] with the chirality contribution of the $\alpha'$-pseudo-axial bond. On the other hand, the sign of a

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[1] Part XVII of this series: T. Hirata, *J. Sci. Hiroshima Univ. Ser. A*, **35**, 239 (1971).

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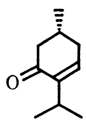
Cotton effect of the second band has been interpreted[4] on the basis of the chirality, or sense of twist, of the enone system, compared with the diene system, while the other one has been related[5] to a normal octant rule for the cisoid enone system and to a reverse octant rule for the transoid one. However, it has recently been shown[6–8] that the sign of a Cotton effect of the last two bands varies irregularly in dependence on the α-axial and the γ-axial substituents, regardless of the alteration in the conformation.

We have now examined the conformations of five *s-trans* and *s-cis* α,β-unsaturated ketones, (−)-*p*-menth-3-en-5-one (**1**), (+)-carvone (**2**), (−)-piperitone (**3**), (−)-carvenone (**4**), and (+)-pulegone (**5**), by means of the temperature-dependent CD in the region of the *n*-π* transition; we chose this region because of the availability and the facility of the band in it.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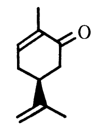
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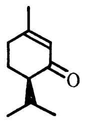
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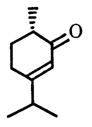
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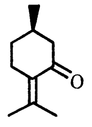
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## Results and Discussion

The predictions of the sign of a Cotton effect for each conformer have been based on the rule[5] of the correlation between the chirality of an enone system and its sign of a Cotton effect for the *n*-π* transition. The alteration of the magnitude of a Cotton effect in the optical rotatory dispersion (ORD) and the CD curves of α,β-unsaturated ketones with a change in the temperature results from the following factors: (i) the conformational alteration, *i.e.*, the increase or the decrease in the population of a conformation with the opposite sign of a Cotton effect, as in the cases of *trans*-2-chloro-5-methylcyclohexane,[9] (−)-menthone, and 1-hydroxymenthone,[10] (ii) the asymmetric solvation,[11] *i.e.*, the association of a solvent molecule, which is more strengthened at lower temperatures, in the asymmetric manner, and (iii) the vibronic effect.[12] The contribution of the last factor is negligible, however, because the compounds used here showed a remarkable increase in the rotational strength at the lower temperature rather than an enhancement of a fine structure.

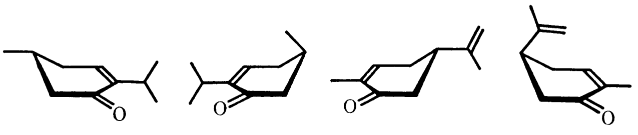

Fig. 1. Preferred conformation of (−)-*p*-menth-3-en-5-one (**1**) and (+)-carvone (**2**).

A half-chair form of four possible conformations of a cyclohexenone ring has been suggested[13] as being stable on the basis of the conformational analysis of the cyclohexene ring. Therefore, (−)-*p*-menth-3-en-5-one (**1**) and (+)-carvone (**2**), 2,5-disubstituted cyclohexenone, may exist in two interconvertible half-chair conformations, **1a** and **1b**, and **2a** and **2b**, respectively (Fig. 1). A positive Cotton effect may be predicted for the **1a** and **2b** conformers, whereas the opposite one may be predicted for the **1b** and **2a** conformers. The CD curves of the compounds **1** and **2** showed the double-humped

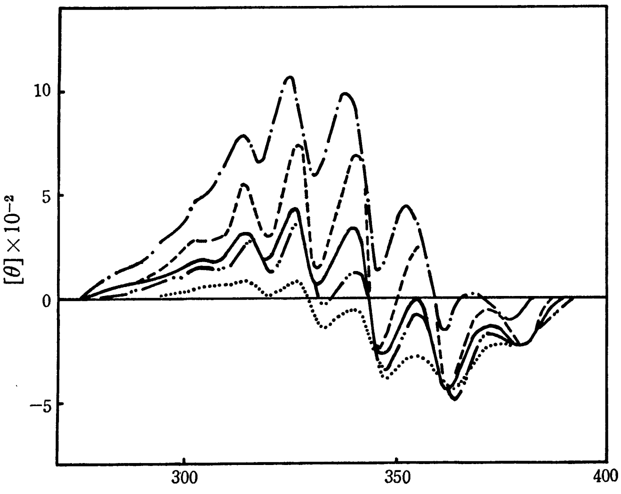

Fig. 2. CD curves of (−)-*p*-menth-3-en-5-one (**1**):—, at 25°C, ----, at −92°C, and —·—, at −186°C in the MI solvent, and —··—, at 25°C and ······, at 147°C in decalin.

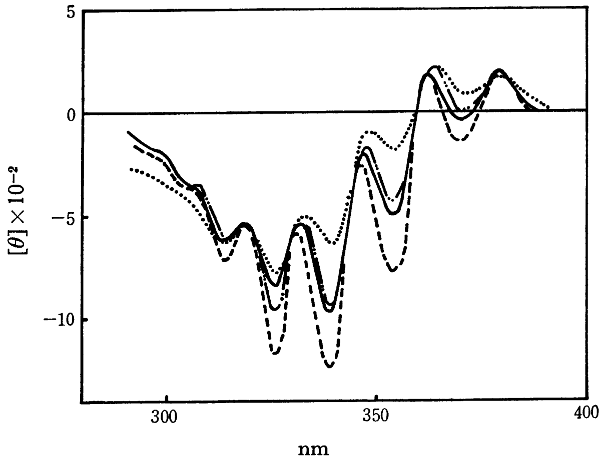

Fig. 3. CD curves of (+)-carvone (**2**): —, at 25°C and ----, at −92°C in the MI solvent, and —··—, at 25°C and ······, at 146°C in decalin.

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Cotton effect with an increase in the positive rotational strength for the compound **1** and the negative one for the compound **2** in the shorter-wavelength region with a lowering of the temperature in both the MI solvent and decalin (Figs. 2 and 3). These observations indicate a conformational alteration, but not an asymmetric solvation and, accordingly, the predominance of the **1a** conformer with an *eq*-methyl group and the **2a** conformer with an *eq*-isopropenyl group in the conformational equilibrium, as is shown in Fig. 1.

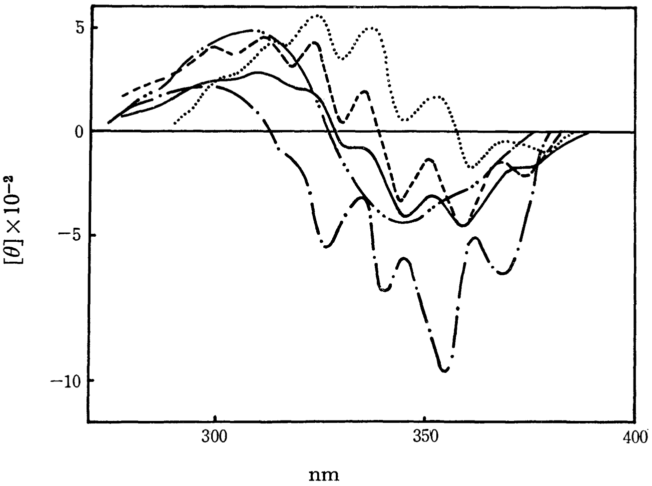
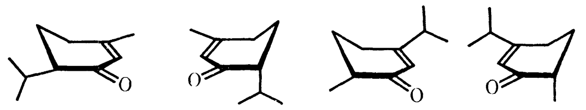


Fig. 4. CD curves of (−)-*p*-menth-3-en-5-one (**1**): ······, at 25°C in isooctane, —··—, at 25°C in ethanol, and —, at 25°C, ----, at −92°C, and —·—, at −186°C in the EPA solvent.

However, the compound **1** showed unexpected temperature-dependent CD curves in the EPA solvent (Fig. 4); the positive rotational strength in the shorter-wavelength region increased with a change in the temperature from 25 to −92°C, while the negative one in the longer-wavelength region increased at the expense of the positive one with the hypsochromic shift of the band when the temperature was further lowered from −92 to −186°C. Considering the conformational equilibrium between the **1a** and **1b** conformers, this phenomenon may be explained as follows: a lowering of the temperature to −92°C increases the population of the unsolvated conformer **1a** with a positive Cotton effect, rather than resulting in an increase in the solvated species, but a further lowering of the temperature to −186°C favors the solvated form **1b** with a negative Cotton effect, as has been shown for pulegone oxide.[14] With changing a solvent from a nonpolar solvent to a polar one, the magnitude of a negative Cotton effect of the compound **1** in the longer-wavelength region remarkably increased with the hypsochromic shift of the band; this suggests an asymmetric solvation, but not a conformational change (Fig. 4). These observations of the temperature-dependent CD curves seem to indicate that the asymmetric solvation principally contributes to the preference of the conformation of *p*-menth-3-en-5-one in the polar solvents. For the compound **2**, such a phenomenon was also observed, but it was very small in magnitude in a comparison with that of the compound **1**.



**3a** **3b** **4a** **4b**

Fig. 5. Preferred conformation of (−)-piperitone (**3**) and (−)-carvenone (**4**).

(−)-Piperitone (**3**) and (−)-carvenone (**4**), 3,6-disubstituted cyclohexenone, may also exist in two interconvertible half-chair conformations, **3a** and **3b**, and **4a** and **4b**, respectively (Fig. 5). The predicted Cotton effect is positive for the **3a** and **4a** conformers and negative for the **3b** and **4b** conformers.

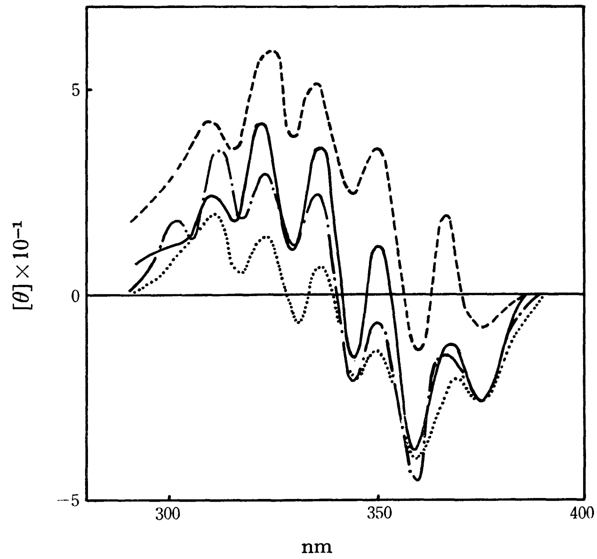


Fig. 6. CD curves of (−)-piperitone (**3**): —, at 25°C and ----, at −92°C in the MI solvent, and —·—, at 25°C and ······, at 146°C in decalin.

The CD curves of the compound **3** showed a double-humped Cotton effect at 25°C in both the MI solvent and decalin. The positive rotational strength of the Cotton effect in the shorter-wavelength region increased at the expense of the negative one in the longer-wavelength region with a lowering of the temperature in both the solvents (Fig. 6). This indicates the preference of the **3a** conformer with an *eq*-isopropyl group in the conformational equilibrium between **3a** and **3b**.

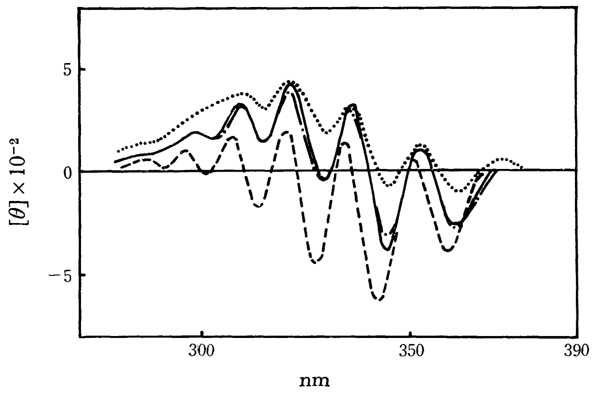
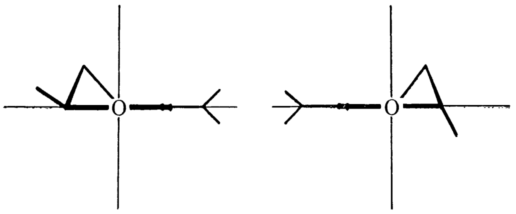


Fig. 7. CD curves of (−)-carvenone (**4**): —, at 25°C and ----, at −127°C in the MI solvent, and —·—, at 25°C and ······, at 149°C in decalin.

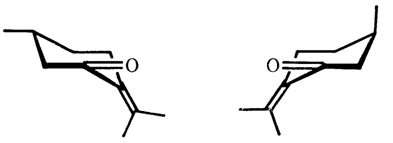
On the other hand, the compound **4** also showed a double-humped Cotton effect, but a less amplified one, on its CD curves (Fig. 7) in the MI solvent at room temperature. The curves exhibited an increase in the negative rotational strength in the longer-wavelength region with a lowering of the temperature in both the MI solvent and decalin. These facts seem to imply the preference of the **4b** conformer with an *ax*-methyl group in the conformational equilibrium between **4a** and **4b**. However, a small shift ($\delta^{CDCl_3}-\delta^{C_6H_6}=0.00$ ppm and $\delta^{CCl_4}-\delta^{C_5H_5N}=-0.09$ ppm) of the α-methyl signal of the compound **4** was observed in the examination of the NMR solvent effects.15,16) This fact favors the conformer with an *eq*-methyl group, which has been recognized to be more stable energetically.17) These observations may be successfully explained in terms of a conformational equilibrium between the two envelope forms,18) **4c** and **4d**, where the planes of the C=C and C=O double bonds are coplanar. From the energetic point of view, the conformational energy between the envelope form and the half-chair one of a cyclohexenone system is small. The reverse octant rule can be applied5) to the envelope forms; it predicts a negative Cotton effect for the **4c** conformer and a positive one for the **4d** conformer (Fig. 8). Thus, the CD and NMR spectral data indicate the predominance of the **4c** conformer with the *eq*-methyl group in the conformational equilibrium between **4c** and **4d**. This is also supported by the rotational strength, which is smaller than that of the other compounds at lower temperatures.



**4c** **4d**

Fig. 8. The octant projection diagrams of the envelope forms, (**4c**) and (**4d**), of (—)-carvenone (**4**).

(+)-Pulegone (**5**), a *s-cis*, α,β-unsaturated ketone, may exist in two interconvertible half-chair conformations, (**5a**) and (**5b**), as is shown in Fig. 9. A positive Cotton effect is predicted for the **5a** conformer, and a negative one, for the **5b** conformer. The CD curves of the compound **5** exhibited a positive Cotton effect without the double hump and a fine structure in both the MI solvent and decalin at various temperatures (Fig. 10). The increase in the positive rotational strength with a lowering of the temperature indicates the predominance of the **5a** conformer with an *eq*-methyl group in the conformational equilibrium between **5a** and **5b**. We have recently estimated19) the conformational energy in this equilibrium to be 1.1 kcal/mol; we also estimated the rotational strengths of the **5a** and **5b** conformers.



**5a** **5b**

Fig. 9. Preferred conformation of (+)-pulegone (**5**).

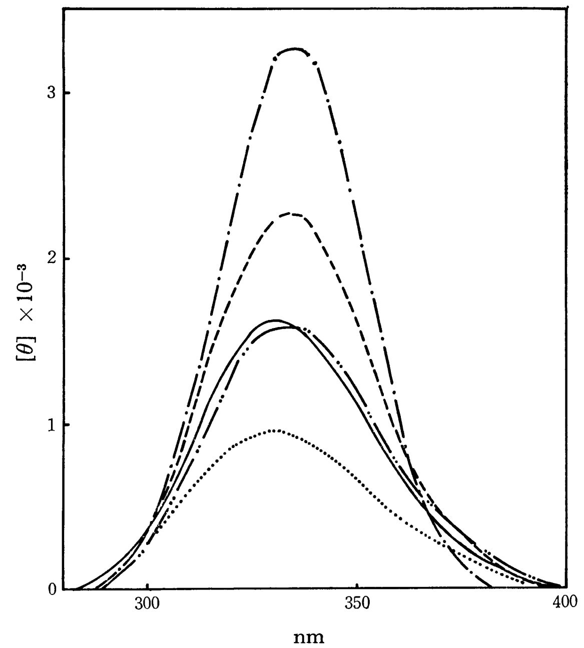


Fig. 10. CD curves of (+)-pulegone (**5**): —, at 25°C and ----, at −67°C, and —·—, at −186°C in the MI solvent, and —··—, at 25°C and ······, at 152°C in decalin.

The temperature-dependent CD curves of the compounds **3**, **4**, and **5** in the EPA solvent acted the same as in both the MI solvent and decalin at various temperatures. Thus, it may be said that temperature-dependent CD measurements offer useful information about the conformational alteration of the optically-active, flexible α,β-unsaturated ketones. However, it should be noted that there is a possibility of the occurrence of such unexpected behavior as in cases of (—)-*p*-menth-3-en-5-one (**1**) and (+)-carvone (**2**), on the CD curves of the α,β-unsaturated ketones in the polar solvent because of the asymmetric solvation.

## Experimental

*Measurements.* The temperature-dependent CD curves were measured by means of a Japan Spectroscopic Co. Ltd., ORD/UV-5, automatically-recording spectrometer equipped with a CD attachment in the MI solvent (methylcyclohexane-isopentane, 1: 3 by volume), the EPA solvent (ether–isopentane–ethyl alcohol, 5:5:2 by volume), and decalin, using a variable-temperature CD cell. The NMR spectra were recorded on a Hitachi Perkin-Elmer, R-20, high-resolution spectrometer at 60 MHz, using tetramethylsilane as the

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internal standard. Gas chromatography was carried out on a Hitachi Perkin-Elmer, F-6D, apparatus attached with a column packed with 20% DEGS on Diasolid L (60—80 mesh) and with 20% PEG 6000 on Celite (60—80 mesh) at 120°C.

*Materials.* *(−)-p-Menth-3-en-5-one (1)*: Into a pyridine (45 m*l*) solution of 4-hydroxy-menthone (1.0 g) prepared from 3-*p*-menthene following the method reported in the literature,[20] we dropped phosphorus oxychloride (23 m*l*) at 0°C. The reaction mixture was left at room temperature for 36 hr and then treated in the usual manner. The refinement of the product by column chromatography on silica gel gave the compound **1** (0.23 g) in a 100% purity (as determined on the basis of analytical glc) and with the following properties: bp 55.0°C/2 mmHg, $[\alpha]_D^{25}-72.4°$ (*c* 2.78, ethanol) (lit,[21] $[\alpha]_D^{20}-78.0°$, neat).

*(+)-Carvone (2)*: A commercial sample was purified by converting it to the sodium bisulfite adduct and by also rectifying the regenerated oil. The compound **2** thus obtained was 100% pure (as determined on the basis of analytical glc) and showed the following properties: bp 74.0—77.0°C/4 mmHg, $n_D^{25}$ 1.4967, $d_4^{25}$ 0.9567, $[\alpha]_D^{25}+61.7°$ (neat) (lit,[22] $[\alpha]_D^{20}+62.3°$, neat).

*(−)-Piperitone (3)*: A commercial sample was purified by rectification under a reduced pressure to give the compound **3** (95.0% pure by analytical glc), with the following properties: bp 94.0°C/8 mmHg, $n_D^{25}$ 1.4808, $d_4^{25}$ 0.9280, $[\alpha]_D^{25}-5.20°$ (neat) (lit,[23] $[\alpha]_D^{20}-51.5°$, neat).

*(−)-Carvenone (4)*: (−)-Dihydrocarvone (2.0 g; bp 105.0—106.5°C/18 mmHg, $n_D^{25}$ 1.4685, $d_4^{25}$ 0.9227, $[\alpha]_D^{25}-18.6°$ (neat), prepared[24] by the reduction of (+)-carvone, was treated with a mixture of acetic acid (25.6 m*l*) and hydrobromic acid (25.6 m*l*) for 30 min at room temperature. The reaction mixture was then poured into water and extracted with ether. The oil (1.97 g) obtained after the removal of the solvent was refined by column chromatography on silica gel. The compound **4** (100% pure by analytical glc) showed the following properties: bp 70.0—72.0°C/4.5 mmHg, $n_D^{25}$ 1.4799, $d_4^{25}$ 0.9231, $[\alpha]_D^{25}-41.0°$ (neat) (lit,[25] $[\alpha]_D^{25}+45.4°$ (neat) for the enantiomer of **4**).

The NMR spectra of the methyl proton signal at the 1-position appeared at $\delta$ 1.13 in both deuterochloroform and benzene, at 1.06 in carbon tetrachloride, and at 1.15 ppm in pyridine.

*(+)-Pulegone (5)*: The purification of pennyroyal oil by means of the formation of the sodium bisulfite adduct, followed by regeneration and then distillation, gave the compound **5**, with the following properties: bp 65.5°C/2.5 mmHg, $n_D^{25}$ 1.4845, $d_4^{25}$ 0.9352, $[\alpha]_D^{25}+22.7°$ (neat) (lit,[26] $[\alpha]_D^{20}+23.4°$, neat).

The authors are indebted to the Takasago Perfumery Co., Ltd., Tokyo, for the gift of samples of carvone, piperitone, and pulegone.

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