Circular Dichroism Studies of Ring-conformational and rotational Equilibria in 2-Isopropenylcyclohexanones[1]

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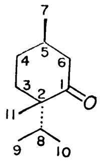
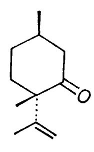
The temperature-dependent circular dichroism of optically active β,γ-unsaturated ketones, (2*S*, 5*R*)-(—)-2-isopropenyl-2,5-dimethylcyclohexanone (**2**) and (2*S*, 5*R*)-(—)-2-isopropenyl-5-methylcyclohexanone (**3**), and of the corresponding saturated ketones, (2*S*, 5*R*)-(—)-2-isopropyl-2,5-dimethylcyclohexanone (**1**), has been measured at the n→π* transition in order to determine the relative disposition between the carbonyl group and the ethylenic bond of the isopropenyl group of the β,γ-unsaturated ketones. The compound (**2**) exhibited the sign of a Cotton effect opposite to that of the corresponding saturated compound (**1**), and the circular dichroism of the compound (**3**) behaved quite differently from menthone (**4**). The result has been discussed mainly in terms of the geometry of the carbonyl group and the ethylenic bond of the isopropenyl group. Thus, it has been concluded that the preferred conformations of the compounds (**1**), (**2**), and (**3**), are **1A**, **2A-III**, and **3A-I** respectively.

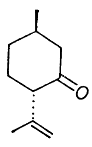
Circular dichroism (CD) measurements at various temperatures have been found to be very useful in studying the conformational analysis of a flexible α,β-unsaturated carbonyl compound, because of the peculiar sensitivity of this method to subtle conformational alteration.[3–5] The long-wavelength β,γ-unsaturated carbonyl transition has been previously pointed out[6,7] to take on some of the aspects usually characteristic of the transitions of dissymmetric chromophores; the amplitude of Cotton effect curves in β,γ-unsaturated ketones is known[6,7] to be critically dependent on the relative disposition between the carbonyl group and the ethylenic bond. This concept has now been applied to the conformational analysis of β,γ-unsaturated carbonyl compounds in a situation where the free rotation may occur. This paper will deal with the relative disposition between the carbonyl chromophore and the ethylenic bond of β,γ-unsaturated ketones, (2*S*, 5*R*)-(—)-2-isopropenyl-2,5-dimethylcyclohexanone (**2**) and (2*S*, 5*R*)-(—)-2-isopropenyl-5-methylcyclohexanone (**3**), as studied by means of the temperature-dependent circular dichroism at the n→π* transition and in comparison with the circular dichroism of the corresponding saturated ketones, (2*S*, 5*R*)-(—)-2-isopropyl-2,5-dimethylcyclohexanone (**1**) and (2*S*, 5*R*)-(—)-2-isopropyl-5-methylcyclohexanone (**4**).[8]



1



2



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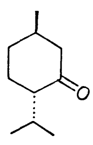

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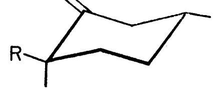
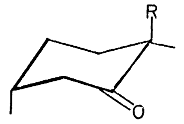
Results and Discussion

The CD curves of (2*S*, 5*R*)-(—)-2-isopropyl-2,5-dimethylcyclohexanone (**1**) in selected solvents showed only a positive Cotton effect. However, a decrease in the rotational strength was observed upon changing the solvent from a nonpolar to a polar one. The methylmenthone (**1**) may exist in two interconvertible chair conformations, **1A**⇄**1B**. According to the octant rule, the conformer **1A** should exhibit a positive Cotton effect, and the conformer **1B**, a negative one. Therefore, the positively-rotating conformer **1A** with an equatorial isopropyl group is preferential in the nonpolar solvents. The temperature-dependent CD curves of the compound (**1**) in the MI (Fig. 1) and the EPA solvents both exhibited only a positive Cotton effect with the increase in the rotational strength upon a lowering of the temperature from 25 to —186 °C. The increase in the positive sign is attributable mainly



1A: R=Isopropyl
2A: R= Isopropenyl



1B: R=Isopropyl
2B: R=Isopropenyl

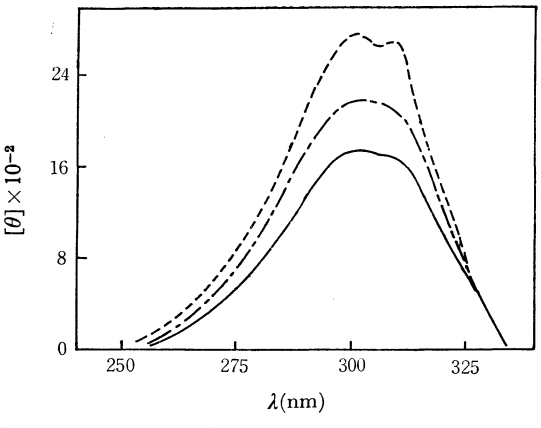


Fig. 1. CD curves of (2*S*, 5*R*)-(—)-2-isopropyl-2,5-dimethylcyclohexanone (**1**) in the MI solvent: —— at +25 °C, ——— at —74 °C, and - - - at —186 °C.

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[1] This paper had been read at the 24th Annual Meeting of the Chemical Society of Japan, Osaka, April, 1971 and forms Part XXI[2] in the Hiroshima University series of "Stereochemical Studies of Monoterpene Compounds,"

[2] Paper XX, T. Hirata, This Bulletin, **45**, 3458 (1972).

[3] G. Snatzke and E. Schwinum, *Tetrahedron*, **22**, 761 (1966).

[4] T. Suga, K. Imamura, and T. Shishibori, This Bulletin, **45**, 545 (1972).

[5] T. Suga and K. Imamura, *ibid.*, **45**, 2060 (1972).

[6] A. Moscowitz, K. Mislow, M. A. W. Glass, and C. Djerassi, *J. Amer. Chem. Soc.*, **84**, 1945 (1962).

[7] K. Mislow and J. G. Berger, *ibid.*, **84**, 1956 (1962).

[8] K. M. Wellman, P. H. A. Laur, W. S. Briggs, A. Moscowitz, and C. Djerassi, *ibid.*, **87**, 66 (1965).

to the contribution of the ring conformation, and also partly to the rotational preferred conformation of the isopropyl group.[9] In that case, the isopropyl group contributes to the rotational strength only when the compound (**1**) takes the conformer **1A**. Therefore, this positive increase implies that the positively-rotating conformer, **1A**, is more stable than the conformer **1B** in respect to the energetic and steric requirements. Thus, the compound (**1**) exclusively exists in the conformer **1A**, frozen out, at −186 °C.

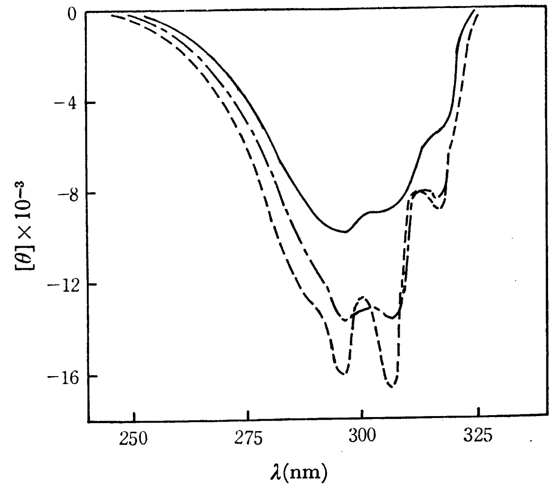

Fig. 2. CD curves of (2*S*, 5*R*)-(−)-2-isopropenyl-2,5-dimethylcyclohexanone (**2**) in the MI solvent: —— at +25 °C, – – – – at −74 °C, and - - - at −186 °C.

The CD curves of (2*S*, 5*R*)-(−)-2-isopropenyl-2,5-dimethylcyclohexanone (**2**) in various solvents exhibited only a negative Cotton effect with an increase in the rotational strength upon changing the solvent from a polar to a nonpolar one, in contrast with the case of the corresponding saturated compound (**1**). The CD curves in the MI solvent are illustrated in Fig. 2. The methylisopulegone (**2**) may exist in two interconvertible chair conformations, **2A**$\rightleftharpoons$**2B**, as well as the corresponding saturated compound (**1**). The conformer **2B** should exhibit a negative Cotton effect. If the free rotation of the isopropenyl group of the conformer **2A** is assumed not to contribute to the sign of a Cotton effect, the conformer **2A** may exhibit a positive Cotton effect. Therefore, the negative sign of a Cotton effect observed may be caused by the conformer **2B**. As has been mentioned above, however, the most preferred conformation of the methylmenthone (**1**) is the conformer **1A** with the equatorial isopropyl group at lower temperatures. The replacement of the isopropyl group with the slightly less bulky isopropenyl one is considered not to induce the inversion of the alkylated cyclohexane skeleton. Accordingly, the most preferred conformation for the compound (**2**) should be the conformer **2A** with the equatorial isopropenyl group at lower temperatures. The negative Cotton effect observed for the compound (**2**) should, consequently, be attributable to the relative disposition between the carbonyl group and the ethylenic bond of the isopropenyl group in the conformer **2A**, as has been pointed out previously.[6,7] The sign and the rotational strength of the Cotton effect of β,γ-unsaturated ketones are critically dependent on the array of double bonds.

The possible preferred conformations of the isopropenyl group in the conformer **2A** by the Newman projection with the corresponding octant projection, as viewed from C-8 to C-2, may be represented as is shown in Chart 1, judging from the conformation of 1-butene[10] and the energy barrier of *n*-butane.[11] The maximum interaction between the 9-methyl group and the 3-methylene or the 11-methyl group may be approximated by a butane function with a maximum value of 6.0 kcal/mol. The signs of a Cotton effect shown were predicted by an examination of the model[12] for each conformation in Chart 1. The conformers **2A-I** and **2A-II** should exhibit a positive Cotton effect and the conformer, **2A-III**, a negative one. The strong negative sign of the compound (**2**) at −186 °C was thus attributed to the conformer **2A-III**. Therefore, the conformer **2A-III** in the chair form is preferential at lower temperatures and in nonpolar solvents.

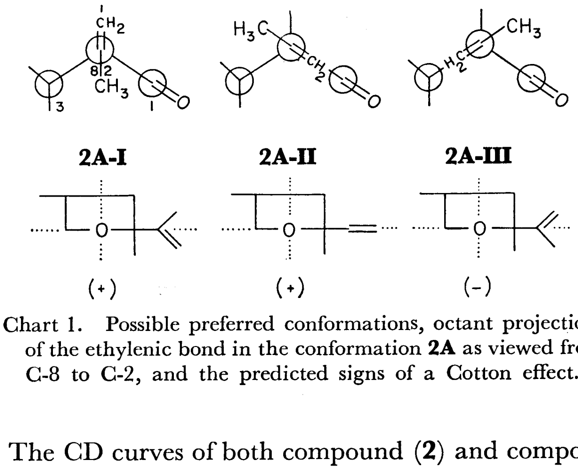

Chart 1. Possible preferred conformations, octant projections of the ethylenic bond in the conformation **2A** as viewed from C-8 to C-2, and the predicted signs of a Cotton effect.

The CD curves of both compound (**2**) and compound (**1**) in decalin showed a decrease in the rotational strength with the change of the temperature from −74 to +150 °C, although the signs are opposite. This implies that the positively-rotating conformer, **1A**, decreased with an increasing population of the unstable conformer, **1B**, when the temperature was raised. The negatively-rotating conformer, **2B**, like the compound (**1**), will increase at higher temperatures, exhibiting an augmentation of the negative CD curves. However, the opposite situations observed in the CD cruves of the compound (**2**) and the compound (**1**) seem to indicate that the contribution of a Cotton effect caused by the free rotation of the isopropenyl group in the conformer **2A** overcomes the contribution of a Cotton effect of the increasing conformer, **2B**.

The CD curves of isopulegone, (2*S*, 5*R*)-(−)-2-isopropenyl-5-methylcyclohexanone (**3**), showed only a

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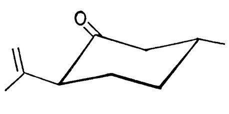
[9] K. M. Wellman, W. S. Briggs, and C. Djerassi, *J. Amer. Chem. Soc.*, **87**, 73 (1965).

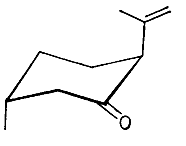
[10] A. A. Bother-By, C. Naar-Colin, and H. Gunther, *ibid.*, **84**, 2748 (1962).

[11] K. Ito, *ibid.*, **75**, 3430 (1953).

[12] Examined by "Dreiding Stereomodels," W. Buchi Manufacture of Glass Apparatus Flawil, Switzerland.

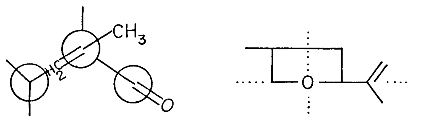


3A



3B

negative Cotton effect with an increase in the rotational strength in a nonpolar solvent, such as carbon tetrachloride, over that in a polar one. The ketone (**3**) may exist in two interconvertible chair conformations, **3A** and **3B**. The negative Cotton effect should be attributed to the conformer **3B** and/or to the conformer **3A-I** shown in Chart 2, in the same way as has been discussed in connection with the compound (**2**). The observation of a strong negative Cotton effect for the compound (**3**) in nonpolar solvents obviously indicates that the compound is composed of the conformer **3A-I** and the conformer **3B** in a conformational equilibrium, **3A**$\rightleftharpoons$**3B**, since, even if the isopropyl group of (−)-menthone (**4**) is replaced by the slightly less bulky isopropenyl group, the populations of the unstable diaxial conformer with a strong negative Cotton effect will probably comprise at least 3%, in a manner similar to that in the case of the parent compound, (−)-menthone (**4**).[8]



3A-1 (−)

Chart 2. The preferred conformation, the octant projection of the ethylenic bond in the conformation **3A** as viewed from C-8 to C-2, and the predicted sign of a Cotton effect.

This interpretation is further supported by the variable temperature circular dichroism. Upon the lowering of the temperature from +25 to −186 °C, the CD curves of the compound (**3**) exhibited a negative Cotton effect with the increase in the rotational strength in the EPA solvent (Fig. 3), but with the decrease in the MI solvent (Fig. 4). The decrease in the rotational strength of a neagtive Cotton effect in the nonpolar solvent was interpreted as an indication of the increase in the energetically more stable, diequatorial conformer, **3A**, at the sacrifice of the diaxial conformer, **3B**, with the stronger rotational strength, upon the lowering of the temperature. This result is further supported by high-temperature CD curves in decalin. At higher temperatures, the CD curves exhibited an increase in the negative sign, implying the augmentaion of the unstable diaxial conformer, **3B**, with the strong rotational strength, analogously to the case of (−)-menthone (**4**).[8] On the other hand, the increase in the rotational strength of the negative sign in the EPA solvent at lower temperatures implies the preference of the conformer **3A** at room temperature and the increase in the population of the conformer **3A-I** upon the lowering of the temperature. Thus, it seems likely that the most preferred conformation of the compound (**3**) is **3A-I**.

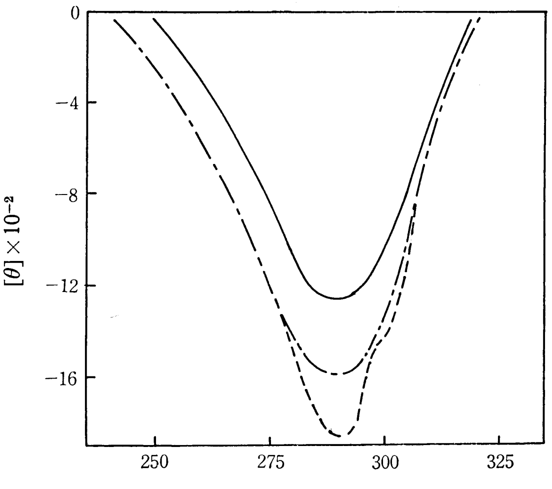


Fig. 3. CD cruves of (2*S*, 5*R*)-(−)-2-isopropenyl-5-methylcyclohexanone (**3**) in the EPA solvent: —— at +25 °C, – – – at −74 °C, and ---- at −186 °C.

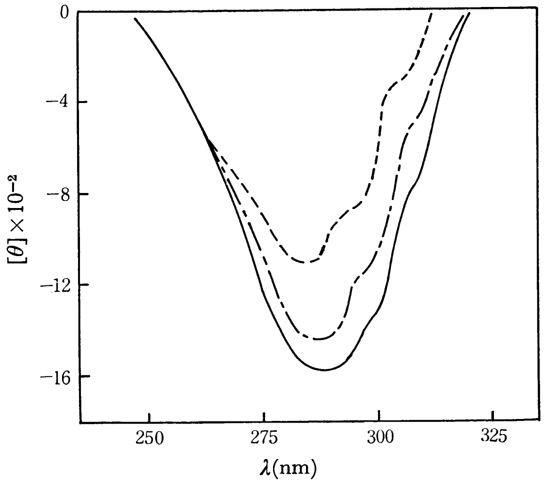


Fig. 4. CD curves of (2*S*, 5*R*)-(−)-2-isopropenyl-5-methylcyclohexanone (**3**) in the MI solvent: —— at +25 °C, – – – at −74 °C, and ---- at −186 °C.

The absolute value of the rotational strength of the β,γ-unsaturated ketones was four to five times that of the corresponding saturated compounds. It is likely that the array between the carbonyl group and the ethylenic bond in the conformer **2A-III** and **3A-I** contributes to the increase in their molecular ellipticity by several times, as compared with the corresponding saturated compounds.

Experimental

Measurements. The CD curves were obtained by means of a Japan Spectroscopic Co., Ltd., automatically-recording spectropolarimeter, Model ORD/UV-5, equipped with a circular dichroism attachment, using a variable-temperature CD cell. The EPA solvent was composed of ether–isopentane–ethanol in the ratio of 5 : 5 : 2 by volume. The MI solvent was composed of methylcyclohexane–isopentane of the ratio of 1 : 3 by volume. The NMR, IR, and UV spectra, although not shown below completly, exactly supported the structure of the compounds on which the CD curves were measured. Gas-chromatographic analyses were made at 100—150 °C, using a Hitachi Perkin-Elmer F6-D gas chromatograph with a flame ionization-type detector and a 3 mm × 1 m column packed with 10%-polyethylene glycol-6000 on Celite.

(2S, 5R)-(−)-2-Isopropyl-2,5-dimethylcyclohexanone (1). The catalytic hydrogenation of methylisopulegone (**2**) (200 mg) (described later) in methanol on 10% palladium-charcoal gave the compound (**1**) (150 mg) with the following properties: bp 176 °C, n_D^{25} 1.4543, $[\alpha]_D^{25}$ −7.3° (MeOH, *c* 0.1636); 99.7% pure by analytical glc; NMR (CCl_4) 0.72—1.00 ppm (m, 12H, $-CH_3$); ν_{max}^{liq} 1700 (C=O), 1378, and 1392 cm^{-1} (isopropyl group); λ_{max}^{MeOH} 291 nm (ε 38.0); CD (max) in MeOH (*c* 0.164): $[\theta]_{308}^{+25°}$ +932, in dioxane (*c* 0.189): $[\theta]_{308}^{+25°}$ +1467, in isooctane (*c* 0.192): $[\theta]_{311}^{+25°}$ +1530, in CCl_4 (*c* 0.163): $[\theta]_{311}^{+25°}$ +1973, in decalin (*c* 0.184): $[\theta]_{300}^{-74°}$ +1452, and $[\theta]_{310}^{-74°}$ +1531, $[\theta]_{300}^{+25°}$ +1333, $[\theta]_{305}^{+74°}$ +935, $[\theta]_{305}^{+150°}$ +606, in EPA (*c* 0.131): $[\theta]_{300}^{+25°}$ +1379 and $[\theta]_{310}^{+25°}$ +1352, $[\theta]_{300}^{-74°}$ +2023 and $[\theta]_{310}^{-74°}$ +2071, $[\theta]_{299}^{-190°}$ +3698 and $[\theta]_{308}^{-190°}$ +3742.

(2S, 5R)-(−)-2-Isopropenyl-2,5-dimethylcyclohexanone (2). This compound was synthesized by the methylation of (+)-pulegone (bp 81—82 °C/5 mmHg, n_D^{25} 1.4843, d_4^{25} 0.9303, $[\alpha]_D^{25}$ +23.0° (neat)) following the method in the literature.[13] It was found to be 99.5% pure by analytical glc and showed the following physical properties: bp 69—70 °C/8 mmHg, n_D^{25} 1.4682, d_4^{25} 0.9231, $[\alpha]_D^{25}$ −139.2° (neat); the semicarbazone derivative, mp 201—202 °C; NMR (CCl_4) 0.96 ppm (d, *J*=6.0 Hz, 3H, $CH-CH_3$), 1.10 (s, 3H, $-CH_3$), 1.68 (s, 3H, $=C-CH_3$), 4.76 and 4.88 (m, 2H, $=CH_2$); ν_{max}^{liq} 3075, 1640, 890 ($C=CH_2$), 1706 cm^{-1} (C=O); λ_{max}^{MeOH} 294 nm (ε 51.6); CD (max) in MeOH (*c* 0.135): $[\theta]_{296}^{+25°}$ −6411, in dioxane (*c* 0.175): $[\theta]_{295}^{+25°}$ −6642, in isooctane (*c* 0.042): $[\theta]_{298}^{+25°}$ −9782, in CCl_4 (*c* 0.095): $[\theta]_{300}^{+25°}$ −10841, in decalin (*c* 0.062): $[\theta]_{307}^{-74°}$ −14300, $[\theta]_{297}^{+25°}$ −12016, $[\theta]_{298}^{+74°}$ −10598, $[\theta]_{300}^{+150°}$ −8487, in EPA (*c* 0.063): $[\theta]_{298}^{+25°}$ −8765, $[\theta]_{301}^{-74°}$ −9794 and $[\theta]_{306}^{-74°}$ −10406, $[\theta]_{297}^{-190°}$ −13416 and $[\theta]_{305}^{-190°}$ −14522.

(2S, 5R)-(−)-2-Isopropenyl-5-methylcyclohexanone (3). The oxidation of (−)-isopulegol (bp 93.0 °C/10 mmHg, n_D^{25} 1.4676, d_4^{25} 0.9052, $[\alpha]_D^{25}$ −22.3° (neat)) with a chromium trioxide-pyridine complex afforded the compound (**3**): bp 86 °C/10 mmHg, n_D^{25} 1.4670, d_4^{25} 0.9252, $[\alpha]_D^{25}$ +7.9° (neat); 94% pure by analytical glc; NMR (CCl_4) 1.40 ppm (d, *J*=4.0 Hz, 3H, $CH-C\underline{H}_3$), 1.70 (s, 3H, $=C-CH_3$), 4.63 and 4.79 (m, 2H, $=CH_2$); ν_{max}^{liq} 3050, 1649, 890 ($C=CH_2$), 1712 cm^{-1} (C=O); λ_{max}^{MeOH} 297 nm (ε 29.7); CD (max) in MeOH (*c* 0.166): $[\theta]_{288}^{+25°}$ −1104, in dioxane (*c* 0.185): $[\theta]_{294}^{+25°}$ −1598, in isooctane (*c* 0.166): $[\theta]_{294}^{+25°}$ −1510, in CCl_4 (*c* 0.125): $[\theta]_{295}^{+25°}$ −1685, in decalin (*c* 0.185): $[\theta]_{293}^{-74°}$ −1510, $[\theta]_{294}^{+25°}$ −1518, $[\theta]_{294}^{+74°}$ −1598, $[\theta]_{296}^{+150°}$ −1635.

The author wishes to thank Dr. Takayuki Suga of Hiroshima University for his guidance and encouragement, and the Takasago Perfumery Co. for its gifts of pulegone and isopulegol.

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[13] T. Suga and S. Watanabe, This Bulletin, **45**, 340 (1972).