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Stereochemical Studies of Monoterpene Compounds. VII.[1] Conformational Study of 4-Hydroxymenthones by Temperature-dependent Circular Dichroism[2]

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The conformational analysis of a stereoisomeric pair of 4-hydroxymenthones, (1R:4R)-(−)-4-hydroxymenthone (**1**) and (1R : 4S)-(+)-4-hydroxyisomenthone (**2**), was made by means of temperature-dependent circular dichroism. It was demonstrated that α-hydroxyketone (**1**) exists in the conformational equilibrium: **1a**⇄**1b**; the conformer **1a** exists predominantly in a nonpolar medium, whereas the conformer **1b** is more stable than **1a** in a polar medium. On the other hand, the other isomer, (**2**), exists preferentially in the state of the conformer **2b** in either a polar or a nonpolar solvent. The results were interpreted in terms of the competition of the steric factor and intramolecular hydrogen-bonding.

The measurement of circular dichroism (CD) at different temperatures has been found very useful for investigating the conformational equilibrium in a flexible cyclohexanone structure.[3] α-Hydroxycyclohexanones represent interesting examples because, in addition to a possible ring-

1) Paper VI of this series: T. Suga, T. Shishibori, T. Hirata and T. Matsuura, This Bulletin, **41**, 1180 (1968).

2) Presented at the 21st Annual Meeting of the Chemical Society of Japan, Osaka, April, 1968.

3) "Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry," ed. by G. Snatzke, Heyden & Son Ltd., London (1967), pp. 16 and 335.

Table 1. Variable-temperature C.D. measurements of 4-hydroxymenthones

Compound	Solvent	$[\theta]\times10^{-3}$ (λ_{max}, mμ)			
		+150°C	+25°C	−74°C	−186°C
(1R:4R)-(−)-4-Hydroxymenthone (**1**)	Decalin	−6.40 (288)	−7.73 (288)	−7.84 (286)	
	MI[a]		−7.49 (288)		−7.71 (289)
	EPA[b]		+0.58 (320)	+1.39 (320)	+2.31 (319)
			−5.49 (293)	−3.75 (286)	−3.11 (285)
(1R:4S)-(+)-4-Hydroxyisomenthone (**2**)	Decalin	+5.27 (288)	+5.71 (288)		
	MI		+6.48 (286)		+7.81 (293)
	EPA		+6.33 (286)	+6.71 (286)	+8.00 (291)
(1R:4R)-(+)-4-Acetoxymenthone (**3**)	EPA		+0.90 (293)	+1.12 (293)	+2.00 (293)

a) Ref. 6. b) Ref. 13.

conformational equilibrium, intramolecular hydrogen-bonding between the hydroxyl and the carbonyl groups can be expected. The room-temperature ORD and CD curves of 4-hydroxymenthones in several solvents[4] have been interpreted in terms of these effects. The temperature-dependent CD spectra may be expected to furnish further insight into the interplay of conformational, solvational, and hydrogen-bonding effects in 4-hydroxymenthones. This paper will deal with the conformational analysis of (1R : 4R)-(−)-4-hydroxymenthone (**1**), (1R:4S)-(+)-4-hydroxyisomenthone (**2**), and (1R:4R)-(+)-4-acetoxymenthone (**3**) by means of the temperature-dependent CD

Results and Discussion

The temperature-dependent CD data of compounds **1** and **2** and of the acetate (**3**) of **1** are summarized in Table 1.

(1R : 4R)-(−)-4-Hydroxymenthone (**1**) and (1R:4S)-(+)-4-hydroxyisomenthone (**2**) can exist in two interconvertible chair conformations, **1a** and **1b**, and **2a** and **2b**, respectively. On the basis of steric requirements only, it can be predicted that the conformer **1b** will be energetically favored. However, the conformer **1a** can be stabilized by hydrogen-bonding between the carbonyl and the hydroxyl groups, so a clear-cut evaluation of the difference between the relative energies of **1a** and **1b** is difficult. On the other hand, the conformer **2b** in the conformational equilibrium **2a**⇄**2b** can be predicted to be energetically favored on the basis of steric requirements; also, it can be stabilized by an intramolecular hydrogen bond.

The variable-temperature CD measurements of compounds **1** and **2** afforded a convincing assignment for the preferred conformation. According to the octant rule,[5] the conformers **1a** and **2a**

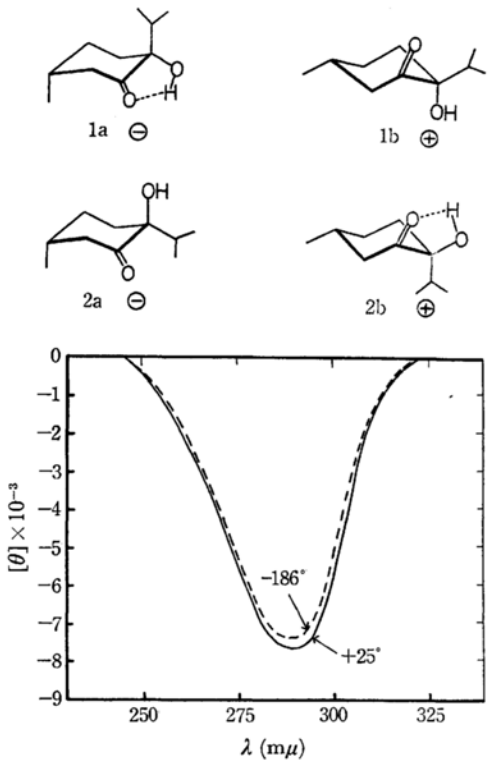


Fig. 1. Circular dichroism curves of (1R:4R)-(−)-4-hydroxymenthone (**1**) in MI at +25 and −186°C.

should exhibit a negative Cotton effect and the conformers **1b** and **2b** a positive one.

(1R : 4R)-(−)-4-Hydroxymenthone (1). As is shown in Fig. 1 and Table 1, the CD curves of **1** in MI solvent[6] and decalin exhibit a negative Cotton effect, and the rotational strength of **1** is almost temperature-independent over the range from 25°C to −186°C in a MI solvent and 25°C to −74°C in decalin. These phenomena observed in CD curves are distinct from those of (−)-

4) T. Suga, T. Shishibori and T. Matsuura, *J. Org. Chem.*, **32**, 965 (1967).

5) W. Moffit, R. B. Woodward A. Moscowitz, W. Klyne and C. Djerassi, *J. Am. Chem. Soc.*, **83**, 4013 (1961).

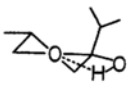
6) MI solvent is composed of methylcyclohexane-isopentane in the ratio 1 : 3 by volume.

menthone[7] and 2-oxo-1-*p*-menthanol,[8] either of which shows a strong temperature-dependence. The negative Cotton effect implies that **1** exists in the **1a** conformation, while the temperature-independence of the rotational strength suggests the conformational homogeneity of **1a** in such a nonpolar solvent as MI and decalin.

The infrared spectrum of **1** in carbon tetrachloride showed only a concentration-independent band at 3495 cm^{-1} resulting from an intramolecular hydrogen-bond between the hydroxyl and the lone-pair electrons on the carbonyl oxygen atom.[9] This indicates that **1** exists in the conformation **1a**, only in which the OH···O=C-type intramolecular hydrogen bond is possible.

A deductive calculation of the conformational energy on the basis of the steric factor shows that the conformer **1a** would be energetically less favored by *ca.* 1.7 kcal/mol[10] than would be **1b** in the conformational equilibrium **1a**⇄**1b**. However, the conformer **1a** can be stabilized by intramolecular hydrogen-bonding between the carbonyl and the hydroxyl group (a saving of *ca.* 2—5 kcal in terms of energy). The results of the variable-temperature CD and the infrared spectral measurements show that the conformer **1a** is stabilized by the intramolecular hydrogen-bonding energy, which is sufficient to overcome the instabilization due to the steric repulsion between groups and atoms.

At a high temperature the strength of the negative CD curve of **1** in decalin was decreased (Table 1). This means that at a high temperature the hydrogen-bonded form of **1a** would be diminished with an increase in the amounts of the nonbonded conformer, **1b**, and/or of the positively-rotating conformer, **1c**, of the twist form.



1c

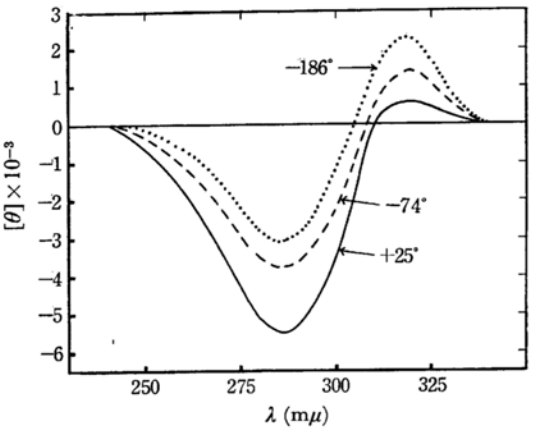


Fig. 2. Circular dichroism curves of (1R:4R)-(−)-4-hydroxymenthone (**1**) in EPA at +25, −74, and −186°C.

In the EPA solvent,[13] **1** exhibits a multiple-Cotton-effect CD curve (Fig. 2). The double-humped Cotton effects arising from $n \rightarrow \pi^*$ transitions in a saturated ketone can be explained in terms of solvational equilibria[14] and/or conformational equilibria. If a solvational equilibrium were solely responsible for the double-humped Cotton effect observed in **1**, the short-wavelength CD band could be attributed to the solvational species, and the long-wavelength band, to the unsolvated form. If this were the case, the apparent rotational strength of the blue-shifted band would increase at lower temperatures. Actually, the opposite result was obtained in EPA (Fig. 2).

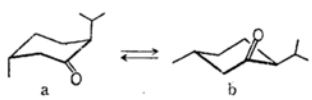
The CD data were favorably explained on the basis of a conformer equilibrium as follows. According to the octant rule,[5] the negative CD band at a short wavelength may be attributed to the conformer **1a**, and the red-shifted positive band, to the conformer **1b**. These assignments are also in agreement with the following findings: an equatorial hydroxyl group adjacent to the carbonyl group causes a blue-shift of the ORD curve peak, whereas an axial hydroxyl group results in a red-shift. If the CD band assignment is accepted, the enlargement of the long-wavelength band at lower temperatures indicates that the conformer **1b** is energetically favored in a polar solvent, EPA.

7) K. M. Wellman, P. H. A. Laur, W. S. Briggs, A. Moscowitz and C. Djerassi, *J. Am. Chem. Soc.*, **87**, 66 (1965).

8) K. M. Wellman, W. S. Briggs and C. Djerassi, *J. Am. Chem. Soc.*, **87**, 73 (1965).

9) T. Suga, T. Shishibori and T. Matsuura, This Bulletin, **41**, 944 (1968); M. Ōki, H. Iwamura, J. Aihara and H. Iida, This Bulletin, **41**, 176 (1968); L. Joris and P. von R. Schleyer, *J. Am. Chem. Soc.*, **90**, 4599 (1968).

10) A free energy difference ($-\Delta G$) for the equilibrium



a⇄b of menthone was estimated by Richborn[11] to be 2.4 kcal/mol based on the menthone-isomenthone isomerisation. Assuming ΔG of the hydroxyl group adjacent to the carbonyl to be −0.7 kcal/mol,[12] the free energy difference for the equilibrium 1a⇄1b is estimated *a priori* to be *ca.* 1.7 kcal/mol.

11) a) B. Richborn, *J. Am. Chem. Soc.*, **84**, 2414 (1962), b) W. D. Cotterill and M. J. T. Robinson, *Tetrahedron*, **20**, 777 (1964).

12) E. L. Eliel, N. L. Allinger, S. T. Angyal and G. A. Morrison, "Conformational Analysis," John Wiley & Sons, Inc., New York (1965), p. 58.

13) EPA solvent is composed of ether-isopentane-ethanol in the ratio 5 : 5 : 2 by volume.

14) Ref. 3, p. 329.

Such a result may be interpreted in terms of the competition of the steric factor and intramolecular hydrogen-bonding. In hydrocarbon solvents, the stabilization due to the intramolecular hydrogen-bonding overcomes the steric repulsion, as has been described above. However, the stabilizing intramolecular hydrogen bond will be broken in the polar solvent, so that the steric requirements mainly dominate the conformation of **1**. Therefore, the sterically-favored conformer, **1b**, is preferred in EPA.

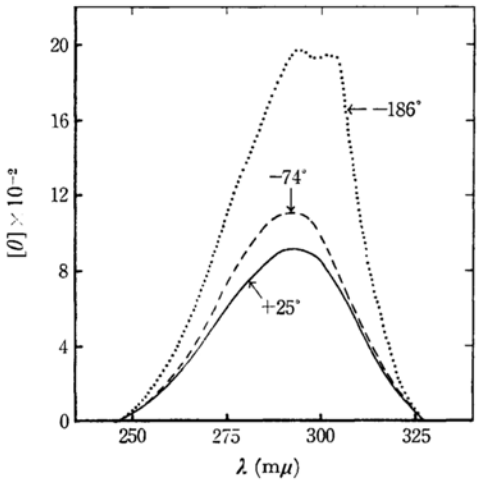
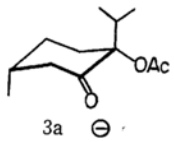
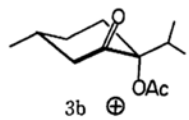


Fig. 3. Circular dichroism curves of (1R:4R)-(+)-4-acetoxymenthone (**3**) in EPA at +25, −74, and −186°C.

(+)-4-Acetoxymenthone. The variable-temperature CD curves of (+)-4-acetoxymenthone (**3**), the acetylated compound of **1**, gave further support to the above deduction. The CD curve (Fig. 3) of **3** in EPA showed a weak positive Cotton effect and an increase in strength upon the lowering of the temperature. This implies that the positively-rotating conformer **3b** is preferred. Since the stabilization due to the intramolecular hydrogen-bonding is absent in the acetylated compound **3**, the conformer **3b** is energetically favored by the



3a ⊖



3b ⊕

steric requirements. If one bears in mind that the conformational energy of the hydroxyl group[12] in **1** is comparable with that of the acetoxyl group in **3**, the stabilizing intramolecular hydrogen bond can be found to contribute to the conformational preference of **1a** in a nonpolar solvent.

(1R : 4S)-(+)-4-Hydroxyisomenthone (2). The CD curves of **2** in decalin and MI (Table 1) and in EPA (Fig. 4) show a positive Cotton effect, with

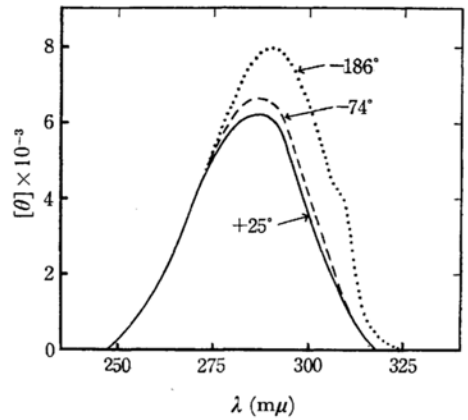
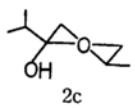


Fig. 4. Circular dichroism curves of (1R:4S)-(+)-4-hydroxyisomenthone (**2**) in EPA at +25, −74, and −186°C.

only a single maximum at room temperature. The increase in the rotational strength upon a change to lower temperatures in EPA and MI indicates that the positive rotating conformer, **2a**, is the more stable in either a polar or nonpolar medium. This behavior in CD curves is similar to that of (+)-isomenthone.[7] The infrared spectra of **2** in carbon tetrachloride showed only a concentration-independent band at 3495 cm^{-1} resulting from an intramolecular hydrogen bond between the hydroxyl and the carbonyl groups. The stabilization due to the intramolecular hydrogen bond contributes to the preference of the conformer **2b**. On the basis of steric requirements, the conformer **2b** can also be predicted to be energetically favored by *ca.* 1.9 kcal/mol.[15] more than **2a**. The results of the low-temperature CD curves are in agreement with the above proposal.

The CD curves of **2** in decalin showed a decrease in rotational strength upon a change to higher temperatures (Table 1). This suggests that the less stable conformer in the conformational equilibrium of **2** would not be the twist form **2c**, which would be highly positive, but the negatively-rotating chair form **2a**.



2c

15) The conformational energy ($-\Delta G$) of the methyl group situated at β-position to the carbonyl is estimated to be *ca.* 1.8 kcal/mol,[11b] and of the isopropyl group adjacent to carbonyl to be *ca.* 0.6 kcal/mol.[11b] Assuming ΔG of the hydroxyl group adjacent to the carbonyl group to be −0.7 kcal/mol, the free energy difference for the equilibrium 2a⇄2b is estimated deductively to be *ca.* 1.9 kcal/mol.

Experimental

Materials. (1R : 4R)-(−)-4-Hydroxymenthone (**1**), (1R : 4S)-(+)-4-hydroxyisomenthone (**2**), and (1R : 4R)-(+)-4-acetoxymenthone (**3**) are the same as were prepared in a previous paper[4] of this series.

Spectral Measurements. The IR spectra in the hydroxyl-stretching region were measured with a Perkin-Elmer Model 621 Grating Infrared Spectrometer at 25°C. A sodium chloride absorption cell, 20 mm long, was used; the concentration of the solution was 0.005 mol/*l*, at which the association of the solute is negligible. The CD curves were obtained by a Japan Spectroscopic Co., Ltd., automatically-recording spectropolarimeter, Model ORD/UV-5, equipped with a circular dichroism attachment. The low- and high-temperature CD curves were obtained by the same spectrometer, using low- and high-temperature CD cells[16] designed and constructed by the authors. All the measurements were performed using spectrograde or purified solvents, a 10 mm cell, and *c* 0.1. The volume contraction of the solvents was corrected.

16) T. Suga, T. Shishibori and T. Matsuura, JASCO Report (published by Japan Spectroscopic Co., Ltd., Tokyo), to be presented.