Tetrahedron Vol. 31, pp. 2905 to 2908. Pergamon Press 1975. Printed in Great Britain

^{13}C PULSE FOURIER TRANSFORM NMR OF MENTHOL STEREOISOMERS AND RELATED COMPOUNDS

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(*Received in Japan* 26 *June* 1975; *Received in UK for publication* 31 *July* 1975)

Abstract—^{13}C NMR spectra of menthol stereoisomers have been determined. The correlations of chemical shifts of these ring carbons with those of stereoisomeric 2-isopropylcyclohexanols are examined. Observed chemical shifts of 1-Me carbons are compared with those predicted from the chemical shifts of stereoisomeric 1-methyl-4-t-butylcyclohexanes. ^{13}C NMR spectra of menthyl acetates, and *cis* and *trans* *p*-menthanes have also been examined.

^{13}C NMR spectroscopy has proved to be a powerful method for stereochemical investigations.[1] It has been reported that the ^{13}C chemical shifts predicted from those of the conformational isomers of cyclohexanols and the substituent parameters already reported[2] are in good agreement with those observed in a previous study of a series of stereoisomeric substituted 1-methylcyclohexanols.[3] Now, we wish to report a ^{13}C NMR study of menthol stereoisomers, their acetates, and related compounds. Some of chemical shifts observed are compared with those predicted.

RESULTS AND DISCUSSION

The natural-abundance 25·15 MHz ^{13}C FT-NMR spectra were obtained using the ^{1}H noise decoupling technique. The signal was assigned by comparing signal shifts due to differences in structures between closely related compounds and by use of the ^{1}H off-resonance decoupling technique.[1] The chemical shifts δ obtained are listed in Table 1. Conformations of menthol stereoisomers are illustrated in Fig. 1.

The ^{13}C NMR spectrum of menthol (**1**) gave agreeable chemical shifts with those appeared in the literature.[4] The δ values for ring carbons of **1** are larger than those of other menthol stereoisomers are except C-5 and C-6 of neomenthol (**2**); the C-1 resonance in **1** appears at δ 31·79, while those in other isomers at δ 25·84–27·42. The higher-field shift of the C-1 resonance in **2** which is considered to exist in a single conformation (Fig. 1) is due to the γ-effect[1,2,5] by the axial OH group. Since conformational free energies of a Me, an OH, and an i-Pr group on a cyclohexane ring are 1·7, 0·7 and 2·15 kcal/mol,[6] respectively, the distribution of conformational isomers of isomenthol (**3**) is estimated as approx. 87% of the equatorial alcohol and 13% of the axial. The higher-filed shift of the C-1 resonance in **3** is due to the 1-Me group mainly existing in an axial orientation. Neoisomenthol (**4**) is considered to exist approximately in a distribution of 91% of the equatorial alcohol and 9% of the axial counterpart from conformational free energies of the substituents. This distribution suggests that the higher-field shift of the C-1 resonance in **4** than in **1** results from the Me and the OH groups taking axial orientations in the minor conformer (**4a**). Assignments of the C-3 signals were straightforward. The C-3 resonances of **1** and **4** appear at δ 71·22 and 70·80, while those of **2** and **3** at δ 67·52 and 67·58, respectively. The higher-field shift of the C-3 resonance in **2** compared to that in **1** is due to the difference in an orientation of the OH group which is the only difference between these two isomers. The higher-field shift of the C-3 resonance in **3** whose OH group takes mainly an equatorial oreintation, are caused by the

Table 1. ^{13}C chemical shifts of menthol stereoisomers and related compounds, δ[a,b]

	C-1	C-2	C-3	C-4	C-5	C-6	CH_3	$\underline{C}H(CH_3)_2$	$CH(\underline{C}H_3)_2$		$CO\underline{C}H_3$	$\underline{C}OCH_3$
Menthol												
—	31.79	45.13	71.22	50.05	23.17	34.70	22.26	25.80	16.01	21.11		
	32.2	*45.9*	*71.2*	*50.7*	*23.3*	*35.3*	*22.6*	*26.1*	*16.3*	*21.3*		
Neo-	25.84	42.83	67.52	48.23	24.26	35.31	22.44	29.12	20.80	21.17		
Iso-	26.02	40.04	67.58	48.60	19.65	30.69	18.20	27.86	20.06	21.17		
Neoiso-	27.42	39.13	70.80	47.44	22.38	31.06	22.02	28.75	21.53			
Menthyl acetate												
—	31.42	41.01	74.07	47.08	23.60	34.33	22.02	26.39	16.44	(20.74)	(21.23)	170.48
Neo-	26.57	39.31	71.04	46.89	25.11	35.00	22.26	29.30	(20.80)	(20.93)	(21.17)	170.30
Iso-	26.45	36.03	71.53	45.96	20.93	30.21	19.05	27.88	(20.50)	(20.98)	(21.29)	170.18
Neoiso-	27.90	35.55	72.74	45.98	22.08	30.88	21.35	28.09		(20.80)	(21.35)	170.18
p-Menthane												
Cis-	29.54	31.72	25.70	43.45	25.70	31.72	19.99	30.79	20.42			
Trans-	35.95	33.23	30.13	44.22	30.13	33.23	22.67	35.95	19.41			
	36.0	*33.4*	*30.2*	*44.4*	*30.2*	*33.4*	*22.8*	*36.0*	*19.3*			

[a] The values in parentheses have not been assigned to specific carbons.
[b] The values in italics are taken from Weigert *et al.* (Ref. 4).

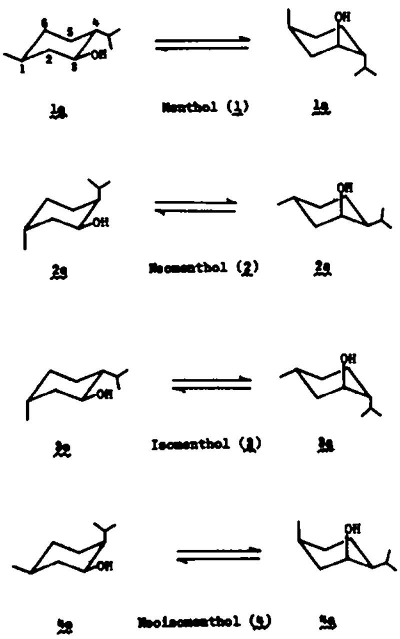

Fig. 1.

γ-effect of the 1-Me group. The configurational difference between 1 and 4 is that the i-Pr group of the latter takes mainly an axial orientation. The fact that the C-3 resonances in both compounds appear at similar positions indicates that an orientation of the i-Pr group on C-4 little affects the chemical shift of β-carbon. The i-Pr group on C-4 exclusively or mainly takes an equatorial orientation except for the case of 4. The signal of C-5 at the γ-position of both OH and 1-Me is expected to appear at a higher field compared to that of 1, when one of these substituents takes an axial orientation. In the case of 3 whose 1-Me takes an axial orientation, the signal appears at the highest field (δ 19·65) of the four. No appreciable shift due to the axial OH was observed in 2, though C-1 was shielded more than that of 1 was. The C-6 in 2 was more deshielded compared to that in 1. The configurational difference between 1 and 2 is only an orientation of the OH group. This shift, therefore, is attributed to the OH orientation similarly to the case of two conformers of cyclohexanol.[3,7]

^{13}C NMR spectra of *cis* and *trans* 2-isopropylcyclohexanol (*cis*- and *trans*-5) were examined. Since 1 exists in a single conformation, the chemical shifts for *trans*-5 were compared with those of 1. By use of the substituent parameters of an equatorial Me group,[2] the predicted chemical shifts of *trans*-5 are derived from those of 1 as shown in Table 2. Deviations between the predicted and observed values were within ±0·6 ppm. The good agreement between the predicted and observed values indicates that such mathematical treatment is reasonable. *Cis*-5 is assumed to undergo rapid interconversion between the axial OH (92%) and the equatorial OH (8%) conformers by taking into account the conformational free energies of an OH and an i-Pr group (Fig. 2). Similarly to the case of 2, no γ-effect of the OH group which takes mainly an axial orientation, upon the C-5 (Fig. 2) resonance was observed. These observations infer that in the most stable rotational conformation, the i-Pr group is rotated producing a certain interaction between one of the Me of i-Pr and the CH_2 at the 5 position, when the OH group takes exclusively or mainly an axial oreintation.

In order to obtain the predicted chemical shifts for *cis*-5 the following tentative estimation was performed (Table 3). Neomenthol is considered to exist exclusively in a single conformation having an axial OH. Similarly to the case of 1, the observed chemical shifts for 2 and the substituent parameters of an equatorial Me gave the predicted chemical shifts for one of the conformers of *cis*-5, the OH group of which takes an axial orientation (Table 3). If it is assumed that there is no extra steric effect on the chemical shifts of ring carbons caused by the syn-diaxial interaction between the Me and OH groups, these values and substituent parameters of an axial Me[2] gave the predicted chemical shifts for minor conformer of 4 (Table 3). Chemical shifts for minor conformer of 4 and

Table 2. Observed and predicted ^{13}C chemical shifts of stereoisomeric 2-isopropylcyclohexanols and their acetates[a,b]

		C-1	C-2	C-3	C-4	C-5	C-6	$\underline{C}H(CH_3)_2$	$CH(\underline{C}H_3)_2$		$CO\underline{C}H_3$	$\underline{C}OCH_3$
Cyclohexanol												
Cis-	Obs.[c] (δ)	19.89	34.15	67.10	48.65	24.32	26.51	29.42	20.74	21.05		
	Pred.[d] (δ)	20.4	33.6	67.8	48.3	24.2	26.1					
	Diff.[e] (ppm)	-0.5	0.6	-0.7	0.4	0.1	0.4					
Trans-	Obs.	25.98	36.28	71.71	50.53	23.78	25.84	25.23	16.19	21.05		
	Pred.	26.2	36.2	71.2	50.3	23.2	25.8					
	Diff.	-0.2	-0.1	0.5	0.2	0.6	0.0					
Acetate												
Cis-	Obs.	20.50	30.82	70.62	47.26	25.11	26.14	29.60	(20.68)		(21.11)	170.12
	Pred.	21.2	30.1	71.2	47.1	24.9	25.8					
	Diff.	-0.7	0.7	-0.6	0.2	0.2	0.3					
Trans-	Obs.	25.66	32.45	74.13	47.68	24.32	24.81	26.69	16.68		20.68	169.93
	Pred.	25.8	32.1	74.1	47.4	23.6	25.4					
	Diff.	-0.1	0.4	0.0	0.3	0.7	-0.6					

[a] The numbering system follows that of menthol (see Fig. 2).

[b] The values in parentheses have not been assigned to specific carbons.

[c] Observed.

[d] Predicted; estimated from the predicted chemical shifts of two conformers of corresponding stereoisomeric compounds.

[e] Difference; observed chemical shift minus that predicted.

cis 2-Isopropylcyclohexanol (cis-5)

Fig. 2.

cis p-Menthane (cis-6)

Fig. 3.

the observed ones for 4 (conformational mixture) lead to those of the alternative conformer from the following relation;[8]

$$K_e = (\delta - \delta_a)/(\delta_e - \delta)$$

where K_e is the equilibrium constant and δ, δ_a and δ_e are the chemical shifts of specific carbons of the conformational mixture, that of the axial and the equatorial alcohols, respectively. The chemical shifts for one of the conformers of *cis*-5, the OH group of which takes an equatorial orientation, is estimated from the predicted chemical shifts for 4 and the substituent parameters of an equatorial Me. Predicted chemical shifts for conformational mixture of *cis*-5 can be obtained from those for two conformers and their conformational distribution using the Eliel method.[8] The estimated δ values are in fairly good agreement with those observed (Table 2). The deviations were within ±0·7 ppm.

The ^{13}C NMR spectra of *cis* and *trans* *p*-menthane (6) were measured as related compounds of the menthol stereoisomers. The chemical shifts are tabulated in Table 1. The ^{13}C NMR spectra of stereoisomeric 1-methyl-4-t-butylcyclohexanes (7) were also measured as model compounds having a fixed conformation. The 1-Me signal of the *cis* isomer appears at δ 17·53 and that of the *trans* at δ 22·75. These indicate the chemical shifts of an axial and an equatorial Me on a cyclohexane ring. The 1-Me group of *trans*-6 exclusively takes an equatorial orientation and its chemical shift, δ 22·87 is in good agreement with that obtained from *trans*-7. *Cis*-6 exists in a conformational mixture, the distribution of which is estimated to be approx. 68% of the axial Me and 32% of the equatorial Me conformer. As a consequence, the Me chemical shift is expected to be δ 19·20 using the Eliel method.[8] The chemical shift observed is agreeable to that predicted. Although the Me signals of 1 have been completely assigned,[4] those of the other menthol stereoisomers were difficult to be assigned. The signals were tentatively assigned by the following way. The Me resonance of 3 is assumed to appear at δ 18·21 by the Eliel method.[8] The observed signal at δ 18·20 corresponds to this carbon. If it is possible to consider that the shielding of the 1-Me carbon is not affected by the axial i-Pr group in 4, the conformational distribution of 4 indicates that the 1-Me chemical shift should be δ 22·28, which corresponds to be observed signal at δ 22·02. Since 2 exist in a single conformer, the OH orientation is only the configurational difference between these two isomers. The signal appearing at δ 22·44 was thus assigned to the 1-Me (Table 4).

The two Me resonances of i-Pr of 5 and the menthol stereoisomers appeared separately except for the case of 4. The Me chemical shift of i-Pr of *trans*-6 was δ 19·41 and that of *cis*-6 was δ 20·42. This indicates that the Me signal of the axial i-Pr group which exists in a minor conformer of *cis*-6 appeared at a field lower than that of the equatorial, and this shift should be attributed to the δ-effect[5,9] for Me *vs* CH$_2$ carbons at C-2 and C-6. The Me and CH resonances of the i-Pr group of *cis*-5 appeared at a field lower than those of *trans* isomer did. In the case of menthol stereoisomers, chemical shifts of the Me and CH of the i-Pr group which is in *cis* relation to the OH group were larger than those of alternative relation.

The ^{13}C NMR spectra of menthyl acetates and stereoisomeric 2-isopropylcyclohexyl acetates were also measured (Table 2). Similarly to the case of menthol stereoisomers, the correlations of chemical shifts of menthyl acetates and 2-isopropylcyclohexyl acetates were examined. These are tabulated in Tables 2 and 3. The 1-Me chemical shifts are predicted by the same method as the case of menthol stereoisomers. These values are also tabulated in Table 4. Other Me signals were impossible to assign to the specific carbons.

Table 3. Predicted ^{13}C chemical shifts of two conformers of *cis* 2-isopropylcyclohexanol and its acetate

			 (9%)	Neoisomenthyl compound equilibrium mixture	 (91%)	
C-1	(R=H)	20.2	21.3	27.4	28.0	22.4
	(R=Ac)	21.0	22.1	27.9	28.5	22.9
C-2	(R=H)	33.9	39.1	39.1	39.1	30.2
	(R=Ac)	30.4	35.6	35.6	35.8	26.7
C-3	(R=H)	67.5	62.1	70.8	71.7	71.7
	(R=Ac)	71.0	65.6	72.7	73.4	73.4
C-4	(R=H)	48.5	48.4	47.4	47.3	47.6
	(R=Ac)	47.2	47.1	46.0	45.9	46.2
C-5	(R=H)	24.3	18.9	22.4	22.7	22.7
	(R=Ac)	25.1	19.7	22.1	22.3	22.3
C-6	(R=H)	26.4	31.6	31.1	31.1	22.2
	(R=Ac)	26.1	31.3	30.9	30.9	22.0

Table 4. Observed and predicted ^{13}C chemical shifts of 1-methyl carbons of menthol stereoisomers and related compounds

	Observed (δ)	Predicted (δ)	Difference[a] (ppm)
cis 1-Methyl-4-t-butylcyclohexane	17.53	-	-
trans 1-Methyl-4-t-butylcyclohexane	22.75	-	-
cis *p*-Menthane	19.99	19.20	0.8
trans *p*-Menthane	22.87	22.75	0.1
Menthol	22.26	22.75	-0.5
Neomenthol	22.44	22.75	-0.3
Isomenthol	18.20	18.21	0.0
Neoisomenthol	22.02	22.28	-0.3
Menthyl acetate	22.02	22.75	-0.7
Neomenthyl acetate	22.26	22.75	-0.5
Isomenthyl acetate	19.05	18.20	-0.9
Neoisomenthyl acetate	21.35	22.28	-0.9

[a] Observed chemical shift minus that predicted.

EXPERIMENTAL

NMR spectra. ^{13}C FT-NMR spectra were obtained at 25·15 MHz with a JEOL JNM-MH-100 instrument equipped with a JNM-MFT-100 Fourier transform accessory; the instrument was controlled with a JEC-6 spectrum computer. Samples were dissolved into $CDCl_3$, the deuterium signal of which provided a field frequency lock; the concentrations were 30% (w/v). Measurement conditions were as follows; pulse width, 27·5 μsec (*ca.* 45°): repetition time, 1 sec: spectral width, 6·25 kHz: data point, 8192: acquisition time, 0·655 sec. Noise modulated proton decoupling was carried out at a nominal power of 20 W. All chemical shifts are expressed in δ (ppm downfield from internal Me_4Si). Each observed chemical shift is estimated to be accurate to δ ±0·05.

Materials. A mixture of menthol stereoisomers was obtained from thymol by the Raney Ni hydrogenation under high pressure and high temp. Isomenthol was separated from the mixture by preparative GLC. Neomenthol and neoisomenthol were prepared from corresponding ketones by the Rh-carbon hydrogenation.[10] These isomers were purified by preparative GLC. Menthol was prepared from menthone upon reduction with LAH-$AlCl_3$ under equilibrating condition.[11] Hydrogenation of 2-isopropylcyclohexanone over Rh-carbon gave *cis* 2-isopropylcyclohexanol,[10] which was purified by recrystallisation from n-hexane. Alternative isomer was prepared from ketone upon reduction with LAH-$AlCl_3$ under equilibrating condition,[11] followed by purification with preparative GLC. Acetates were prepared with Ac_2O in pyridine. *Cis* and *trans* *p*-menthanes were obtained from D-limonene by the hydrogenation over PtO_2 in AcOH, followed by the separation with preparative GLC.

All compounds were checked by analytical GLC and IR and ^1H NMR spectra.

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