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CARBON-13 PULSE FOURIER TRANSFORM NMR SPECTRA OF SUBSTITUTED 1-METHYLCYCLOHEXANOLS

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Abstract—^{13}C NMR spectra of a series of stereoisomeric substituted 1-methylcyclohexanols have been determined. The ring carbon resonances of the isomers having an equatorial OH group appeared at lower fields than those of the axial counterparts except the C-4 resonance of 1,2-dimethylcyclohexanol indicating an opposite trend. The signal of an axial Me group on C-1 appeared at a higher field than that of the equatorial counterpart; this is interpreted in terms of the γ-effect. Chemical shifts of ring carbons observed are compared with those predicted.

^{13}C NMR spectroscopy has proved to be a powerful tool for stereochemical investigations of cyclic compounds. ^{13}C NMR spectra of several 6-membered ring systems have been examined in detail; and in general, it has been found that axial substituents tend to shield the neighboring carbons relative to those in the equatorial analogs.[1] We wish to report the results of a ^{13}C NMR study of a series of substituted 1-methylcyclohexanols comparing the ^{13}C chemical shifts for *cis* and *trans* stereoisomers. In addition, the chemical shifts observed are compared with those predicted by the substituent effects already reported.[2]

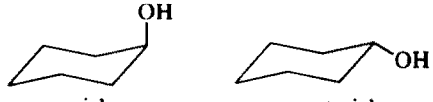
RESULTS AND DISCUSSION

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

Ring carbons. The assignments of C-1 signals were straightforward; they appeared at δ 68·80–75·47, being close to those of secondary cyclohexanols.[3] The C-1 resonances for *cis* isomers of 2- or 4-substituted 1-methylcyclohexanols and those for *trans* isomers of 3-substituted 1-methylcyclohexanols appeared at lower fields than those for the stereoisomeric counterparts. This implies that the C-1 resonances for the isomers having an equatorial OH group appeared at lower fields than those having an axial one. In the cases of 3- and 4-substituted 1-methylcyclohexanols, the C-1 bearing an equatorial OH group showed the resonances at δ 70·56–71·59 and those of isomeric counterparts at δ 68·80–70·07. The C-1 bearing an equatorial OH group was shielded to δ 75·47 and 72·98 in 2-t-Bu and 2-Me compounds, respectively, and those bearing an axial one to δ 73·83 and 70·98, respectively.

The C-1 shieldings of 2-substituted 1-methylcyclohexanols were less than those of 3- or 4-substituted 1-methylcyclohexanols. C-2 signals appeared at lower field (δ 54·84 and 56·36) when it carries a t-Bu group than the others including the C-6 signal which appeared at δ 38·40–49·50. Similarly, signals due to C-4 bearing a t-Bu group appeared at lower field (δ 47·74 and 47·94) than the others (δ 25·48–34·76). Similarly to the case of C-1 resonances, the resonances of other ring carbons of the isomers carrying an equatorial OH group were observed at lower fields than those carrying an axial one except the C-4 resonance of 1,2-dimethylcyclohexanol (2), indicating an opposite trend.

The OH groups of *cis* and *trans* 4-t-butylcyclohexanols are considered to take exclusively an axial and an equatorial orientation, respectively. Comparisons of the ^{13}C chemical shifts of t-butylcyclohexane with those of parent cyclohexane revealed the substituent effects for the t-Bu group upon C-1, C-2, C-3 and C-4 to be +21·2, +0·5, +0·1, and −0·5 ppm, respectively.[1b]* By use of these substituent effects for a t-Bu group, chemical shifts of the individual carbons of the axial and the equatorial cyclohexanols have been estimated as follows:



	axial	equatorial
C-1	δ 65·5	δ 70·9
C-2	33·2	35·6
C-3	20·5	25·2
C-4	27·0	26·1

Since conformational free energy of an OH group on a cyclohexane ring is 0·7 kcal/mol, the distribution of conformational isomers is estimated as approximately 77% of the equatorial and 23% of the axial conformer. As a consequence, the C-1 chemical shift is expected to be δ 69·7 using the method of Eliel[4] from the following relation:

$$K_e = (\delta - \delta_a)/(\delta_e - \delta) \qquad (1)$$

where K_e is the equilibrium constant, and δ, δ_a and δ_e are the C-1 chemical shift of a mobile system, that of the axial and the equatorial conformers, respectively. The estimate agrees with the observed chemical shift of δ 69·95; this confirms that the C-1 chemical shifts of the axial and equatorial conformers are reasonable. The substituent effects for a Me group on a cyclohexane ring reported by Grant *et al*[2] were applied to this system. The substituent effects for a t-Bu group on a cyclohexane ring was obtained by comparison of t-butylcyclohexane with the parent cyclohexane.

Most of the compounds used may exist essentially in a single conformer but *cis*-1,2- (2), *trans*-1,3- (4) and *cis*-

*Positive values represent shifts of lower field.

Table 1. Observed and predicted ^{13}C chemical shifts of substituted 1-methylcyclohexanols[a]

1-Methylcyclohexanol		C-1	C-2	C-3	C-4	C-5	C-6	1-Me	Other Me (including t-butyl Me)	$^{-C}Me_3$
Parent alcohol (1)	Obs.[b]	69.77	39.67	22.87	25.96	22.87	39.67	29.54		
	Pred.[c]	69.8	39.6	22.6	26.5	22.6	39.6	30.4		
	Diff.[d]	0.0	0.1	0.3	-0.5	0.3	0.1	-0.9		
cis-2-Methyl- (cis-2)	Obs.	72.98	42.28	32.21	25.48	24.26	41.49	20.80	15.47	
	Pred.	76.1	41.8	32.1	25.4	23.8	39.3	21.4		
	Diff.	-3.1	0.5	0.1	0.1	0.5	2.2	-0.6		
trans-2-Methyl- (trans-2)	Obs.	70.98	40.46	30.69	26.08	22.14	40.10	28.75	15.28	
	Pred.	72.7	40.2	31.1	26.4	21.9	39.3	28.9		
	Diff.	-1.7	0.3	-0.4	-0.3	0.2	0.8	-0.1		
cis-2-t-Butyl- (cis-3)	Obs.	75.47	56.36	27.24	27.24	24.75	46.89	22.56	30.39	34.40
	Pred.	72.2	62.1	25.1	26.8	24.1	41.0			
	Diff.	3.3	-5.7	2.1	0.4	0.7	5.9			
trans-2-t-Butyl- (trans-3)	Obs.	73.83	54.84	24.45	27.11	22.14	44.59	32.88	31.18	34.76
	Pred.	69.9	60.5	22.7	26.6	21.7	39.4			
	Diff.	3.9	-5.7	1.8	0.5	0.4	5.2			
cis-3-Methyl- (cis-4)	Obs.	69.77	47.68	27.78	34.58	21.72	38.40	31.85	22.56	
	Pred.	69.4	48.2	27.8	35.4	22.2	39.0	31.4		
	Diff.	0.4	-0.5	0.0	-0.8	-0.5	-0.6	0.5		
trans-3-Methyl- (trans-4)	Obs.	71.16	49.50	30.63	34.76	23.84	40.16	26.02	22.69	
	Pred.	71.3	49.5	29.9	35.4	24.2	40.5	25.6		
	Diff.	-0.1	0.0	0.7	-0.6	-0.4	-0.3	0.4		
cis-3-t-Butyl- (cis-5)	Obs.	70.07	39.98	42.77	26.57	22.14	38.64	32.15	27.48	32.15
	Pred.	69.5	39.8	43.4	27.0	22.3	38.8	31.4		
	Diff.	0.6	0.2	-0.6	-0.4	-0.2	-0.2	0.8		
trans-3-t-Butyl- (trans-5)	Obs.	71.59	41.98	45.80	26.87	24.02	40.04	26.08	26.27	32.09
	Pred.	71.8	41.4	45.8	27.2	24.7	40.4	25.4		
	Diff.	-0.2	0.6	0.0	-0.3	-0.7	-0.4	0.7		
cis-4-Methyl- (cis-6)	Obs.	70.56	39.80	32.39	31.91	32.39	39.80	25.90	21.65	
	Pred.	70.9	39.3	32.1	31.2	32.1	39.3	26.8		
	Diff.	-0.3	0.5	0.3	0.7	0.3	0.5	-0.9		
trans-4-Methyl- (trans-6)	Obs.	68.80	38.64	30.45	31.36	30.45	38.64	31.97	22.26	
	Pred.	69.1	39.3	31.1	32.0	31.1	39.3	31.4		
	Diff.	-0.3	-0.7	-0.6	-0.6	-0.6	-0.7	0.6		
cis-4-t-Butyl-* (cis-7)	Obs.	71.23	40.96	25.13	47.94	25.13	40.96	25.42	27.86	32.47
trans-4-t-Butyl-* (trans-7)	Obs.	68.86	39.37	22.69	47.74	22.69	39.37	31.42	27.76	32.39

[a] All chemical shifts are expressed in δ (ppm downfield from internal tetramethylsilane). Each observed chemical shift is estimated to be accurate to ±0·05 ppm; [b] Observed; [c] Predicted; [d] Observed chemical shift minus that predicted; [e] Comparing the observed chemical shifts for ring carbons and 1-methyl groups of 1-methyl-4-t-butylcyclohexanols with primarily obtained predicted ones, the substituent effects for C-1 unit on the ring carbons and those for the hydroxyl group on the 1-methyl group were obtained. The observed and the finally obtained predicted values, therefore, become naturally equal.

1,4-dimethylcyclohexanol (**6**) exist in conformational equilibrium mixtures, the populations of which are estimated by the conformational free energies of a Me and an OH group as approximately 77:23, 96:4, and 77:23, respectively. Consequently, predicted chemical shifts for these compounds can be obtained from the distribution of a set of conformers using the method of Eliel (eqn 1).

The operation of substituent effects due to an OH and a Me group on the same C atom can also be expected. Grant *et al.*[2] obtained the substituent effects of geminal dimethyl groups on C-1 and C-2 shieldings to be −3·4 and −1·2 ppm, respectively. In order to obtain such effects quantitatively, the primarily obtained predicted values* and the observed ones for 1-methyl-4-t-butylcyclohexanol (**7**), in which a weak substituent effect for the t-Bu group is expected on the C-1 unit including the Me and the OH groups on the same C atom, were compared (Table 2). The deviation is supposed as the substituent effects for the C-1 unit.

Regarding the vicinal substitution, Grant *et al.*[2] obtained

*The predicted values which are derived from the chemical shifts of cyclohexanol and the substituent effects for the Me and the t-Bu groups on the ring C atoms.

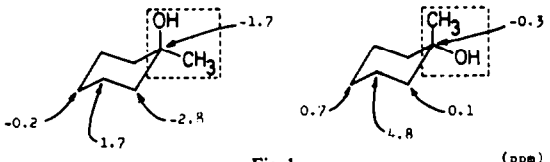


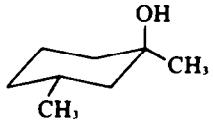
Fig. 1.

−2·3 ppm for *trans*-1,2-dimethylcyclohexane (**8**) (diequatorial) and −3·1 ppm for the *cis* isomer (axial-equatorial). More precise estimation for the chemical shifts of ring carbons has been performed on introduction of the substituent effects obtained above for the C-1 unit including the OH and the Me groups and those of the gauche interaction for the two Me groups on the vicinal C atoms (γ-effect)[1,2] to the primarily obtained predicted chemical shifts. These are also tabulated in Table 1.

An example of the chemical shift estimation is indicated as follows;

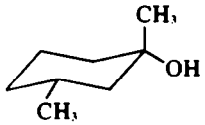
Carbon-2

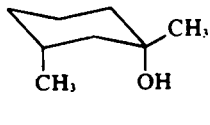
cis-1,3-Dimethylcyclohexanol (*cis*-**5**)



Chemical shift of parent cyclohexanol	δ 33·2
Substituent effect for	
1-equatorial Me	+8·9[2] (ppm)
3-equatorial Me	+8·9[2]
C-1 unit	−2·8
C-2 chemical shift estimated	δ 48·2

trans-1,3-Dimethylcyclohexanol (*trans*-**5**)





Chemical shift of parent cyclohexanol	δ 35·6	δ 33·2
Substituent effect for		
1-axial Me	+5·2[2] (ppm)	—
1-equatorial Me	—	+8·9[2] (ppm)
3-axial Me	—	+5·2[2]
3-equatorial Me	+8·9[2]	—
C-1 unit	+0·1	−2·8
C-2 chemical shift of conformers	δ 49·8	44·5
Population of equilibrium mixture	96%	4%
C-2 chemical shift estimated from eqn 1	δ 49·5	

There is good agreement between the predicted and observed values with exception for C-1 and C-6 of **2**, and C-1, C-2, C-3, and C-6 of 1-methyl-2-t-butylcyclohexanol (**3**). The remaining deviation is due mainly to the substituent effects caused by the vicinal interactions between the Me and the OH groups in **2**, and those between the t-Bu group and the Me or the OH group in **3**. A fairly large deviation appeared on the C-3 shielding of **3**. Altona[5] indicated that, in the most stable rotational conformation, the t-Bu group of t-butylcyclohexane is rotated by approx. 17°, accompanied by a twisting of the cyclohexane ring, producing a strong repulsive interaction between one of the t-Bu methyls and the 2-equatorial hydrogen (Fig. 2). The situation of **3** is not necessarily the same but C-3 may realise an appreciable steric interaction by one of the t-Bu methyls.

Table 2. Comparison of observed and primarily obtained predicted ^{13}C chemical shifts of 1-methyl-4-t-butylcyclohexanols[a]

Isomer		C-1	C-2	C-3	C-4	C-5	C-6
cis	Obs.[b]	71.23	40.96	25.13	47.94	25.13	40.96
	Pred.[c]	71.5	40.9	20.3	47.2	20.3	40.9
	Diff.[d]	-0.3	0.1	4.8	0.7	4.8	0.1
trans	Obs.	68.86	39.37	22.69	47.74	22.69	39.37
	Pred.	70.6	42.2	21.0	47.9	21.0	42.2
	Diff.	-1.7	-2.8	1.7	-0.2	1.7	-2.8

[a] All chemical shifts are expressed in δ (ppm downfield from internal tetramethylsilane); [b] Observed; [c] Predicted; [d] Observed chemical shift minus that predicted.

Substituents

1-*Methyl group*. The signal of the axial Me group on C-1 appeared at a higher field than the equatorial one. This shift must be caused by the gauche interaction with C-3 (γ-effect). Chemical shifts of the 1-Me carbons on 3- or 4-substituted 1-methylcyclohexanols show almost constant values with respect to their steric configurations. Chemical shifts of the Me carbons of *trans* 3- and *cis* 4-substituted 1-methylcyclohexanols are δ 25·42–26·08 and those of the corresponding counterparts are δ 31·42–32·15. This observation suggests that, even if there is a single isomer of 3- or 4-substituted 1-methylcyclohexanols, it is possible to assign its steric configuration, presumably except for the case of 3-axial substituted compounds. The chemical shift of the 1-Me carbon of *cis*-1,3,3,5-tetramethylcyclohexanol (equatorial

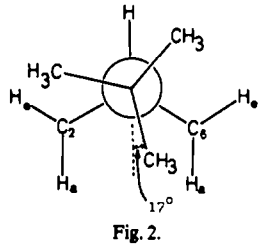


Fig. 2.

1-Me) appeared at δ 33·12 in which there may be some steric shifts caused by the 3-axial Me group with the C-1 unit. Large steric shifts by *syn*-axial interaction (δ-effect)[6] can be expected on the 1-Me carbon of the *trans* counterpart (axial 1-Me).

On the other hand, both axial and equatorial 1-Me signals in **2** appeared at higher fields than the corresponding ones of **4** and **6**. This must be due to the gauche interaction of the vicinal dimethyl groups. The Me resonance in *trans*-1,4-dimethylcyclohexane (**9**) appears at δ 23·3 and that of *cis*-**9** at δ 20·7.[2] The Me group of *trans*-**9** is considered to take exclusively an equatorial orientation, while *cis*-**9** undergoes rapid interconversion between equivalent conformers as shown in Fig. 3 and its Me shielding is assumed to represent an averaged

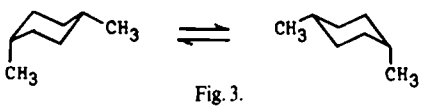


Fig. 3.

shielding for the axial and equatorial environments. On the assumption that there is no mutual operation of substituent effects on the shieldings for both Me groups, the chemical shift of the axial Me carbon can be estimated to be δ 18·1 using the method of Eliel (eqn 1). If the equatorial 4-t-Bu group has a slight affect on the 1-Me shielding, the observed chemical shift of the Me carbon of **7**, where no substituent is present in the vicinity of C-1, gives the substituent effect for the OH group on the Me located on the same C atom to be approximately +8·1 ppm (on the equatorial Me by the axial OH) and approximately +7·3 ppm (on the axial Me by the equatorial OH). Since the chemical shifts of the Me carbons of 1,3-dimethylcyclohexanes (**10**) are very similar to those of **9**, the 3-Me group is also supposed to have a slight affect on the shielding of the 1-Me carbon in **4**. As a consequence, the axial and the equatorial Me shieldings for **4** may be the same as those of the corresponding isomers of **6**. The chemical shift of the Me carbon of *cis*-**8** is δ 16·3 and that of the *trans* isomer is δ 20·8. These values are appreciably different from those for **9** and **10**. This may also be due to the steric interaction between the vicinal dimethyl groups. Similarly in the case of **9**, the Me groups of *trans*-**8** are considered to take exclusively an equatorial orientation, while *cis*-**8** undergoes rapid interconversion between two equivalent conformers, and its Me shielding is assumed to represent an averaged shielding for the axial and equatorial environments. The chemical shift of the axial Me carbon of **8** can be estimated to be δ 11·8. By an application of the substituent effect for the OH group on these values, chemical shifts of the axial and the equatorial Me carbons on C-1 of **2** was predicted to be δ 19·1 and 28·9, respectively. The predicted 1-Me shieldings are in good agreement with observed ones.

Table 3. ^{1}H chemical shifts for 1-methyl group of substituted 1-methylcyclohexanols[a]

1-Methylcyclohexanol	OH-axial	OH-equatorial
Parent (1)	1.19	
2-Methyl- (2)	1.16	1.07
2-t-Butyl- (3)	1.38	1.26
3-Methyl- (4)	1.18	1.20
3-t-Butyl- (5)	1.20	1.22
4-Methyl- (6)	1.20	1.20
4-t-Butyl- (7)	1.18	1.20
3,3,5-Trimethyl-	1.17	—

[a] All chemical shifts are expressed in δ (ppm downfield from internal tetramethylsilane).

The resonance of the axial Me carbon of **3** appeared at higher field than those of the corresponding 3- or 4-substituted compounds, while lower-field shifts were observed in the 1-equatorial Me counterparts. This must be due to the competitive operation of γ- and δ-effects by the t-Bu quarternary carbon and the t-Bu methyls, respectively.

Other substituents. The chemical shifts of the Me carbons of **4** and **6** were observed to be δ 21·65–22·69. No significant steric shift was observed between each set of two stereoisomers. The Me signal in **2** was shifted higher field, appearing at δ 15·28 for the *trans* and δ 15·47 for the *cis* isomer. This may also be due to the gauche interaction with the 1-Me and the 1-OH groups (γ-effect). Chemical shifts of the t-Bu methyls of **7** were δ 27·86 for the *cis* and δ 27·76 for the *trans* isomer, but those of **3** were deshielded to δ 30·39 for the *cis* and 31·18 for the *trans* isomer. This downfield shift may be due to the δ-effect (*syn*-axial interaction) with the Me group on the adjacent C atom as suggested earlier.

The ^{1}H NMR spectra were also measured. The signals of 1-Me protons appeared around δ 1·07–1·38. These are tabulated in Table 3. Only a very small shift difference was observed in a set of stereoisomeric 3- or 4-substituted 1-methylcyclohexanols, but large steric shifts were observed in 2-substituted 1-methylcyclohexanols. The differences appeared as 0·09 ppm in **2** and 0·12 ppm in **3**. Contrary to 3- or 4-substituted 1-methylcyclohexanols, the equatorial Me signals appeared at lower fields than did the axial counterparts.

EXPERIMENTAL

NMR spectra. The ^{13}C FT-NMR spectra were obtained at 25·15 MHz on 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 on 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.

Materials. Substituted 1-methylcyclohexanols other than *cis*-**3** were prepared from the corresponding substituted cyclohexanones with MeMgI. Isomeric mixtures of **2**[7], **3**, **4**[8] and **6** were separated by preparative gas chromatography. Isomeric mixtures of **5** and **7**[9] were separated by Al_2O_3 column chromatography with hexane or benzene, respectively, followed by the recrystallisation from pentane. The Grignard reaction of 3,3,5-trimethylcyclohexanone with MeMgI gave exclusively *cis*-1,3,3,5-tetramethylcyclohexanol by oxymercuration-demercuration procedure.[11] The purity of *cis*-**3** obtained was 98% by analytical gas chromatography. All compounds were checked by analytical gas chromatography.

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