Carbon-13 NMR Spectra of Stereoisomeric Substituted 2-Methylcyclohexanols and Their Acetates: A Comparison of the Observed and Predicted Chemical Shifts

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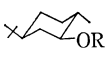
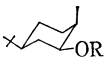
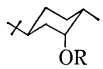
The ^{13}C NMR spectra of stereoisomeric 4-*t*-butyl-2-methylcyclohexanols, 5-*t*-butyl-2-methylcyclohexanols, 2-methylcyclohexanols, and their acetates were measured. The observed chemical shifts were compared with the values estimated by using the substituent parameters of methyl, *t*-butyl, and hydroxyl groups. An appreciable deviation by vicinal substitution was found between the predicted and observed chemical shifts of C-1 and C-2. The substituent parameters of the acetoxyl group on the cyclohexane ring were estimated by means of a comparison of the chemical shifts of *cis*- and *trans*-4-*t*-butylcyclohexyl acetate, and those of *t*-butylcyclohexane.

The simple additivity relationships for carbon chemical shifts within specific families of compounds are very useful for the assignment of a certain signal to a specific carbon atom and for the prediction of the chemical shift of a certain carbon atom.[1] However, when the two substituents on a cyclohexane ring are at a geminal or vicinal position, the predicted values deviate from the observed ones.[2,3] This may be supposed to be caused by the interaction between these two groups. For two methyl groups on the adjacent or the same carbon atoms of cyclohexane, the substituent parameters of vicinal and geminal substitution were reported by Dalling and Grant.[2]

The ^{13}C NMR spectra of four stereoisomers of 5-*t*-butyl-2-methylcyclohexanols (**1**—**4**) and their acetates (**11**—**14**) were measured in order to study the effects of the steric structure of the molecule and of the vicinal substitution of the methyl and hydroxyl or acetoxyl groups on the carbon chemical shifts. The ^{13}C chemical shifts for these compounds are collected in Table 1. The assignments were based on standard methods, *i.e.*, the relative intensities, the off-resonance CW decoupling, and a comparison of the signal shift between closely related compounds. The chemical-shift differences ($\Delta\delta$) between the observed values and those calculated by using the substituent parameters of the methyl,[2] *t*-butyl, hydroxyl[3] and acetoxyl (*vide infra*) groups are also tabulated. Appreciable shift differences were found in the chemical shifts of C-1 and C-2. The chemical-shift differences of most of the other carbons were within ± 1.0 ppm.

The chemical shifts of substituted carbon atoms varied appreciably according to the orientation of the substituent. The signals of carbinol carbon and C-2 with axial substituents appeared at higher fields than those having equatorial ones. For the carbons bearing the *t*-butyl group, the signals appeared at around δ 47 when the hydroxyl or acetoxyl group was in an equa-

Table 1. Carbon-chemical shifts of stereoisomeric 2-methyl-5-*t*-butylcyclohexanols and their acetates

									
		(**1**)	(**11**)	(**2**)	(**12**)	(**3**)	(**13**)	(**4**)	(**14**)
		(R=H)	(R=OAc)	(R=H)	(R=OAc)	(R=H)	(R=OAc)	(R=H)	(R=OAc)
C-1		77.0	78.9	73.3	76.0	71.2	74.0	72.3	75.1
	$\Delta\delta$[a]	−2.9	−4.1	−3.0	−3.4	−3.3	−4.4	1.4	−0.1
C-2		40.2	37.4	33.7	30.8	36.6	35.3	34.1	32.2
	$\Delta\delta$	−0.9	−0.3	−2.8	−2.3	−2.1	−0.9	0.0	0.6
C-3		33.7	33.4	30.9	30.7	28.9	29.5	26.6	26.9
	$\Delta\delta$	−0.5	−0.8	0.3	0.1	−0.9	−1.0	0.7	0.0
C-4		26.8	26.6	20.0	20.0	27.2	26.9	20.9	20.6
	$\Delta\delta$	0.2	−0.1	−0.1	−0.2	−0.3	−0.3	−0.1	−0.1
C-5		47.3	46.7	47.2	47.0	40.3	41.3	41.0	41.9
	$\Delta\delta$	1.2	0.6	1.0	0.8	−0.8	−1.1	−0.5	−0.6
C-6		36.9	33.2	30.0	26.8	34.8	31.9	28.9	26.1
	$\Delta\delta$	0.8	0.5	0.4	0.6	1.1	0.7	1.7	1.4
2-CH_3		18.6	18.3	10.6	11.5	18.4	18.0	16.7	16.3
	$\Delta\delta$	−4.2	−4.5	−6.9	−6.0	−4.4	−4.8	−0.8	−1.2
5-C(CH_3)$_3$		27.6	27.5	27.5	27.5	27.5	27.4	27.4	27.4
5-C(CH_3)$_3$		32.3	32.3	32.3	32.4	32.0	31.2	32.2	32.2
CH_3CO			21.2		21.3		21.1		21.4
CH_3CO			170.3		170.3		170.4		170.2

a) The observed chemical shift minus that predicted.

Table 2. Carbon-chemical shifts of *cis*- and *trans*-2-methylcyclohexanols and their acetates

		 (5) (R=H)	(15) (R=OAc)	 (6) (R=H)	(16) (R=OAc)
C-1		71.1 (71.4) [a]	73.6	76.3 (76.9)	78.2
	$\Delta\delta$[b]	−3.7	−5.2	−3.4	−4.6
C-2		36.2 (36.1)	35.0	40.4 (40.0)	37.7
	$\Delta\delta$	−2.6	−2.6	−1.1	−0.4
C-3		29.2 (29.6)	29.9	34.0 (34.3)	33.9
	$\Delta\delta$	−0.5	−0.6	0.0	−0.2
C-4		25.4 (24.5)	25.1	26.0 (26.1)	25.7
	$\Delta\delta$	−0.5	−0.6	−0.1	−0.5
C-5		21.2 (21.8)	21.4	25.7 (25.7)	24.9
	$\Delta\delta$	0.1	−0.5	0.8	0.0
C-6		32.7 (32.1)	30.0	35.7 (35.4)	32.1
	$\Delta\delta$	0.1	−1.4	0.2	−0.1
2-CH_3		16.7	17.2	18.7	18.5
	$\Delta\delta$	−5.3	−4.8	−4.0	−4.2
$\underline{C}H_3CO$			20.9		20.9
$CH_3\underline{C}O$			169.8		169.9

a) The values in parentheses were reported by Roberts *et al.* (J. D. Roberts, F. J. Weigert, J. I. Kroschwitz, and H. J. Reich, *J. Am. Chem. Soc.*, **92**, 1338 (1970)). b) The observed chemical shift minus that predicted.

Table 3. Carbon-chemical shifts of stereoisomeric 2-methyl-4-*t*-butylcyclohexanols and their acetates

		 (7) (R=H)	(17) (R=OAc)	 (8) (R=H)	(18) (R=OAc)
C-1		70.0	72.6	76.5	78.4
	$\Delta\delta$[a]	−4.0	−5.5	−2.9	−4.1
C-2		36.9	36.0	40.2	37.7
	$\Delta\delta$	−2.3	−0.7	−1.4	−0.5
C-3		29.1	30.3	34.9	35.0
	$\Delta\delta$	−0.8	−0.6	0.3	0.4
C-4		48.1	47.9	47.5	47.6
	$\Delta\delta$	−0.1	0.0	0.2	0.2
C-5		20.3	20.9	26.1	25.8
	$\Delta\delta$	−0.4	−0.8	0.7	0.4
C-6		33.9	31.2	35.7	32.2
	$\Delta\delta$	−1.6	0.4	0.8	−0.1
2-CH_3		18.9	18.6	19.0	18.7
	$\Delta\delta$	−3.9	−4.2	−3.8	−4.1
4-$C(\underline{C}H_3)_3$		27.6	27.6	27.7	27.7
4-$\underline{C}(CH_3)_3$		32.5	32.5	32.2	32.2
$\underline{C}H_3CO$			21.2		20.9
$CH_3\underline{C}O$			169.9		169.8

a) The observed chemical shift minus that predicted.

Table 4. Carbon-chemical shifts of *cis*- and *trans*-4-*t*-butylcyclohexyl acetates[a] and of *t*-butylcyclohexane[b,c]

	(9) *cis*	(10) *trans*	*t*-Butyl-cyclohexane
C-1	69.2 (69.3)	73.5 (73.1)	26.9 (27.2)
C-2	30.8	32.2	27.4 (27.8)
C-3	21.8	25.6	27.8 (28.2)
C-4	47.9	47.3	48.5 (48.9)
4-$C(\underline{C}H_3)_3$	27.5	27.7	27.6 (27.7)
4-$\underline{C}(CH_3)_3$	32.3	32.2	32.6 (32.7)
$\underline{C}H_3CO$	21.2	21.2	
$CH_3\underline{C}O$	169.9	169.9	

a) The values in parentheses were reported by Buchanan and Stothers (G. W. Buchanan and J. B. Stothers, *Can. J. Chem.*, **47**, 3605 (1969)). b) The carbon numbering relates, for the purposes of comparison, to the equivalent carbon in the cyclohexanol series. c) The values in parentheses were reported by Roberts *et al.* (J. D. Roberts, F. J. Weigert, J. I. Kroschwitz, and H. J. Reich, *J. Am. Chem. Soc.*, **92**, 1338 (1970)).

torial position, but at around δ 40—41 when it was in an axial position.

The NMR spectra of stereoisomeric 2-methylcyclohexanols (**5**, **6**), 4-*t*-butyl-2-methylcyclohexanols (**7**, **8**), and their acetates (**15**—**18**) were also measured (Tables 2 and 3). Most of the carbon resonances of the isomers whose hydroxyl or acetoxyl group is equatorial appeared at lower fields than those of the axial isomers.

The carbon-chemical shifts of stereoisomeric 4-*t*-butylcyclohexyl acetates (**9**, **10**) are listed in Table 4. The acetoxyl groups of *cis*- and *trans*-4-*t*-butylcyclohexyl acetates have been supposed to take exclusively an axial and an equatorial orientation respectively, judging from the confromational free energies of the acetoxyl and *t*-butyl groups.[4] Comparisons of the carbon-chemical shifts of t-butylcyclohexane, the chemical shifts of which are also tabulated in Table 4, with those of **9** and **10** give the substituent parameters for the axial and equatorial acetoxyl groups of the individual carbons of cyclohexane.

Substituent parameters of the acetoxyl group (ppm)

	Axial	Equatorial
C-1	42.3	46.6
C-2	3.4	4.8
C-3	−6.0	−2.2
C-4	−0.7	−1.2

The distribution of the conformational isomers of **5** and **15** is simply estimated from the conformational free energies[4] of the methyl, hydroxyl, and acetoxyl groups as being approximately 84% axial and 16% equatorial hydroxyl or acetoxyl conformers, while the corresponding values of **6** and **16** are 2% axial and 98% equatorial. The predicted chemical shifts of the ring carbons for each conformer are calculated using

the substituent parameters. The predicted values for these isomers can be obtained from the above conformational distribution by using the Eliel equation.[5] Similarly to the case of *t*-butylmethylcyclohexanols, appreciable shift differences between the observed and predicted values are found for the chemical shifts of C-1 and C-2.

In order to examine the correlation of the $\Delta\delta$ values with the stereochemical relationship of the methyl and hydroxyl or acetoxyl groups on the vicinal position, these values of *t*-butylmethylcyclohexanols and their acetates, the substituents of which are conformationally rigid, were compared with each other. The chemical-shift deviation of C-1 and C-2, the substituents on which are in a gauche-*cis* relation, is larger than that in gauche-*trans*, while that in anti is the smallest. These findings indicate that the dihedral angle between the methyl and hydroxyl or acetoxyl groups contributes to the magnitude of the γ-effect.

The chemical shifts for the equatorial 2-methyl groups are around δ 18—19 for **1**, **3**, **7**, **8**, and their acetates. The resonance signals for the axial methyl groups shift to higher fields, appearing at δ 10.6 for **2**, 11.5 for **12**, 16.7 for **4**, and 16.3 for **14**. The NMR spectra of stereoisomeric 1-*t*-butyl-4-methylcyclohexanes show that the chemical shift for an axial methyl group on the cyclohexane ring is δ 17.5 and that for an equatorial methyl group is δ 22.8.[6] By comparing the chemical shifts on the 2-methyl groups of **1**—**4**, **7**, **8**, and their acetates with those of the corresponding 1-*t*-butyl-4-methylcyclohexanes, the deviation can be regarded as the γ-effect parameters of the hydroxyl group on the methyl group. The values, -3.9——-6.9 ppm for gauche- and -0.8——-1.2 ppm for anti-relation, are smaller than those of the corresponding γ-effect parameters of the hydroxyl group on the cyclohexane-ring carbons, which are found to be -7.2 ppm for gauche- and -2.5 ppm for anti-relation. This is similar to the case of the methyl group, the γ-gauche effect of which has been reported to be -6.37 ppm on the cyclohexane-ring carbons and -2.82 ppm on the vicinal methyl carbon.[2] Such a difference is attributable to the situation of γ-carbons; the 2-methyl group, which can rotate freely around the carbon–carbon bond, is less restricted than the ring carbons. The predicted chemical shifts of the methyl carbons of **5**, **6**, **15**, and **16** were obtained by taking account of the conformational distributions and the carbon chemical shifts of the methyl group in stereoisomeric 1-*t*-butyl-4-methylcyclohexanes.

The ^{1}H NMR spectra of cyclohexanols **1**—**4** were also examined in search of any possible spectral correlation with their configurational structures. These compounds showed no appreciable difference in the stereochemical heterogeneity. The signals of the C-1 protons of **1** and **2**, which have an equatorial hydroxyl group, appeared at δ 3.64 and 3.67 respectively as a multiplet, while those of **3** and **4**, which have an axial hydroxyl, appeared at δ 3.77 as a broad singlet. The signals of the 2-methyl protons partially overlapped with those of the 5-*t*-butyl methyl protons, so that it is impossible to read their positions accurately from the spectra. On the other hand, the carbon-chemical shifts for the 2-methyl groups reported here have made it possible to determine the confirgurations of all the stereoisomers of the molecule.

The $\Delta\delta$ values of *t*-butylmethylcyclohexanols and their acetates are regarded as the parameters of the vicinal substitution of methyl and hydroxyl or acetoxyl groups. These values are useful for the prediction of the chemical shifts of those compounds which have 2-methylcyclohexanol or its acetate moiety.

Experimental

NMR Spectra. The ^{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 by means of a JEC-6 spectrum computer. The samples were dissolved in $CDCl_3$, the deuterium signal of which provided a field-frequency lock; the concentrations were 30% (w/v). The measurement conditions were as follows: pulse width, 27.5 μs (*ca.* 45°); repetition time, 4 s; spectral width, 6250 Hz; data point, 8192; acquisition time, 0.65 s. Noise-modulated proton decoupling was carried out at a nominal power of 20 W. All the chemical shifts are expressed in δ (ppm downfield from internal Me_4Si). Each observed chemical shift is estimated to be accurate to $\pm$0.1 ppm.

5-t-Butyl-2-methylcyclohexanols[7,8] ***(1)—(4) and Their Acetates***[7] ***(11)—(14).*** The hydrogenation of *cis*-5-*t*-butyl-2-methyl-2-cyclohexenol[9] over Raney Ni in ethanol gave a mixture of **1** and **2** (**1**, 73%; **2**, 27%); yield, 85%. The hydrogenation of *trans*-5-*t*-butyl-2-methyl-2-cyclohexenol[9] over PtO_2 in ethanol gave a mixture of **3** and **4** (**3**, 66%; **4**, 34%); yield, 91%. The mixtures were separated by preparative GLC. Alcohols **1** and **4** were identified by a comparison of the relative retention times of GLC with those of the hydroboration products[10] of 4-*t*-butyl-1-methylcyclohexene. Alcohols **2** and **3** were identified by a comparison of the relative retention times of GLC with those of the LAH-reduction products[11] of *cis*- and *trans*-5-*t*-butyl-2-methylcyclohexanone (**1**, 70%; **3**, 30% from *cis*-ketone: **2**, 95%; **4**, 5% from *trans*-ketone). The acetates were prepared with Ac_2O in pyridine.

4-t-Butyl-2-methylcyclohexanols,[12] ***(7) and (8), and Their Acetates,***[13] ***(17) and (18).*** The hydrogenation of 4-*t*-butyl-2-methylphenol over the Rh–Al_2O_3 catalyst in ethanol, followed by Al_2O_3 column chromatography using benzene as the eluent, gave pure **7**; yield, 42%. *cis*-4-*t*-Butyl-2-methylcyclohexanone, which had been prepared by the $Na_2Cr_2O_7$ oxidation of **7**, was reduced with LAH to give a mixture of **8**[10] (86%) and **7** (14%); yield, 89%. The mixture was separated by Al_2O_3 column chromatography, using benzene as the eluent. The acetates were prepared with Ac_2O in pyridine.

The structure of each isomer was confirmed by the ^{1}H NMR spectra and by the analytical GLC.

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