^{13}C NMR Spectra of Some Methyl Cyclohexanecarboxylates

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^{13}C NMR spectra of a series of stereoisomeric-substituted methyl cyclohexanecarboxylates have been obtained. The resonances for ring carbons of the isomers, in which both the methoxycarbonyl and the other groups have equatorial orientations, usually appear at a field lower than those of the isomers in which one of the two substituents has an axial orientation. No appreciable difference in shift due to the configurational change is observed in the resonances for the substituents. Observed chemical shifts are compared with predicted values.

In ^{13}C NMR spectra it is generally found that various substituents exert shielding effects which are additive for families of compounds. As a result, the positions of ^{13}C signals for closely related materials may often be predicted with good precision in a wide variety of systems.[1] It has been reported that the ^{13}C chemical shifts predicted from those of conformational isomers of cyclohexanol and substituent parameters already reported are in good agreement with those observed in previous studies on series of stereoisomeric substituted 1-methylcyclohexanols[2] and menthols.[3] This paper is a report on a study of the ^{13}C NMR spectra of some substituted stereoisomeric methyl cyclohexanecarboxylates. The ^{13}C chemical shifts observed are compared with those predicted.

Results and Discussion

Natural-abundance 25.15-MHz ^{13}CFT NMR spectra were obtained using the ^{1}H noise decoupling technique. The signals were assigned by comparing signal shifts due to differences of structure between closely related compounds and by the use of the ^{1}H off-resonance decoupling technique.[1] The chemical shifts δ obtained are listed in Table 1.

Ring Carbons. The resonances for ring carbons of isomers, in which the methoxycarbonyl and other groups have an equatorial orientation, usually appear at a field lower than those of isomers, in which one of the two substituents has an axial orientation, except for the C-3 and C-4 resonances in methyl 4-*t*-butylcyclohexanecarboxylate (Table 2).

From the observed ^{13}C chemical shifts of *t*-butylcyclohexane and of stereoisomeric methyl 4-*t*-butylcyclohexanecarboxylates, substituent parameters for a methoxycarbonyl group on ring carbons were estimated. These are tabulated in Table 2.

Parent cyclohexanecarboxylate exists in a conformational mixture, the population of which is estimated as being approximately 89.5% of the equatorial conformer and 10.5% of the axial conformer, since the conformational free energy of a methoxycarbonyl group on a cyclohexane ring is 1.25 kcal/mol.[4] As a cnsequence, the carbon chemical shifts predicted are obtained from those of each set of conformers according to a previously outlined procedure.[2] These values are in good agreement with those observed. Conformational free energies of a methyl and a hydroxyl group on a cyclohexane ring are 1.7 and 0.7 kcal/mol, respectively. The conformational distribution of *cis* 2- and 4- or

TABLE 1. OBSERBED AND PREDICTED ^{13}C CHEMICAL SHIFTS OF METHYL CYCLOHEXANECARBOXYLATES[a,b]

Methyl cyclohexanecarboxylate			C-1	C-2	C-3	C-4	C-5	C-6	OMe	C=O	Me
Parent		Obsd[c]	43.19	29.18	25.60	25.96	25.60	29.18	51.32	176.31	
			43.1	*29.0*	*25.4*	*25.8*	*25.4*	*29.0*	*51.2*	*176.3*	
		Pred[d]	43.6	29.5	26.0	26.5	26.0	29.5	51.3	176.3	
		Diff[e]	−0.4	−0.3	−0.4	−0.5	−0.4	−0.3	0	0	
2-Methyl-	*cis*	Obsd	45.98	31.85	31.60	24.51	22.08	24.51	51.02	175.27	15.65
		Pred	48.8	32.8	32.2	25.1	24.2	26.9	51.3	175.7	21.0
		Diff	−2.8	−0.9	−0.6	−0.6	−2.1	−2.4	−0.3	−0.4	−5.3
	trans	Obsd	51.44	34.52	34.52	26.02	25.60	30.03	51.14	176.37	20.68
		Pred	53.0	35.3	35.2	26.5	26.0	29.7	51.3	176.4	22.8
		Diff	−1.6	−0.8	−0.7	−0.5	−0.4	0.3	−0.2	0	−2.1
3-Methyl-	*cis*	Obsd	43.56	32.27	37.67	34.64	25.72	28.81	51.32	176.18	22.69
		Pred	44.1	38.6	31.9	35.4	26.3	29.4	51.3	176.4	22.8
		Diff	−0.5	−0.9	0.4	−0.8	−0.6	−0.6	0	−0.2	−0.1
	trans	Obsd	31.19	35.73	27.96	33.91	22.08	28.45	51.32	175.88	21.29
		Pred	39.3	36.4	28.3	34.5	22.7	28.5	51.3	176.4	21.0
		Diff	−0.1	−0.7	−0.3	−0.6	−0.6	0	0	−0.5	0.3
4-Methyl-	*cis*	Obsd	40.43	26.33	31.54	30.82	31.54	26.33	51.26	176.43	21.11
		Pred	40.8	26.9	32.2	30.6	32.2	26.9	51.3	176.4	21.0
		Diff	−0.5	−0.6	−0.7	0.2	−0.7	−0.6	0	0	0.1
	trans	Obsd	43.19	29.24	34.46	32.21	34.46	29.24	51.32	176.43	22.56
		Pred	43.8	29.7	35.2	32.1	35.2	29.7	51.3	176.4	22.8
		Diff	−0.6	−0.5	−0.7	0.1	−0.7	−0.5	0	0	−0.2

Table 1 Continued

Methyl cyclohexanecarboxylate			C-1	C-2	C-3	C-4	C-5	C-6	OMe	C=O	Me
2-Hydroxy-	*cis*	Obsd	47.01	66.85	32.15	20.20	24.87	23.66	51.63	175.81	
		Pred	49.3	68.9	32.0	21.0	24.9	23.7	51.3	176.1	
		Diff	−2.3	−2.0	0.2	−0.8	0	0	0.3	−0.3	
	trans	Obsd	51.69	70.86	34.15	24.51	25.05	28.45	51.69	175.82	
		Pred	52.3	73.2	34.5	24.4	25.0	27.5	51.3	176.4	
		Diff	−0.6	−2.3	−0.3	0.2	0.1	1.0	0.4	0.6	
3-Hydroxy-	*cis*	Obsd	41.98	37.91	69.40	34.82	23.47	28.21	51.63	176.61	
		Pred	41.9	37.9	69.8	34.7	24.1	28.4	51.3	176.1	
		Diff	0.1	0	−0.4	0.1	−0.6	−0.2	0.3	0.5	
	trans	Obsd	37.67	35.49	65.64	32.70	19.89	28.15	51.63	175.76	
		Pred	37.3	35.7	65.1	33.1	20.0	28.6	51.3	176.4	
		Diff	0.4	−0.2	0.5	−0.4	−0.1	−0.4	0.3	−0.6	
4-Hydroxy-	*cis*	Obsd	41.31	23.84	32.03	66.43	32.03	23.84	51.57	176.00	
		Pred	42.2	23.7	32.0	66.2	32.0	23.7	51.3	176.1	
		Diff	−0.9	0.1	0	0.2	0	0.1	0.3	−0.1	
	trans	Obsd	42.28	27.36	34.40	69.40	34.40	27.36	51.57	176.24	
		Pred	42.8	27.5	34.5	70.0	34.5	27.5	51.3	176.4	
		Diff	−0.5	−0.1	−0.1	−0.6	−0.1	−0.1	0.3	−0.2	
2-Methoxycarbonyl-	*cis*	Obsd	42.71	42.71	26.39	23.90	23.90	26.39	51.57	174.12	
		Pred	43.3	43.3	26.5	24.3	24.3	26.5	51.3	175.9	
		Diff	−0.6	−0.6	−0.1	−0.4	−0.4	0.1	0.3	−1.8	
	trans	Obsd	44.89	44.89	29.06	25.36	25.36	29.06	51.63	175.27	
		Pred	46.3	46.3	28.6	25.4	25.4	28.6	51.3	176.4	
		Diff	−1.4	−1.4	0.5	0	0	0.5	0.3	−1.1	
3-Methoxycarbonyl-	*cis*	Obsd	42.53	31.18	42.53	28.45	24.93	28.45	51.50	175.33	
		Pred	43.0	31.9	43.0	28.7	25.2	28.7	51.3	176.4	
		Diff	−0.5	−0.7	−0.5	−0.2	−0.3	−0.2	0.2	−1.1	
	trans	Obsd	39.07	29.56	39.07	27.96	22.10	27.96	51.50	175.33	
		Pred	39.4	30.4	39.4	28.2	22.5	28.2	51.3	175.9	
		Diff	−0.3	−0.8	−0.3	−0.2	−0.4	−0.2	0.2	−0.6	
4-Methoxycarbonyl-	*cis*	Obsd	40.71	26.14	26.14	40.71	26.14	26.14	51.44	175.15	
		Pred	41.1	26.5	26.5	41.1	26.5	26.5	51.3	175.9	
		Diff	−0.4	−0.4	−0.4	−0.4	−0.4	−0.4	0.1	−0.6	
	trans	Obsd	42.46	28.15	28.15	42.46	28.15	28.15	51.50	175.76	
		Pred	43.1	28.6	28.6	43.1	28.6	28.6	51.3	175.4	
		Diff	−0.6	−0.4	−0.4	−0.6	−0.4	−0.4	0.2	0.4	
1,3-Cyclohexanecarbolactone		Obsd	39.07	(37.67)	77.90	(28.75)	18.50	(26.57)		178.91	

a) The values in parentheses have not been assigned to specific carbons. b) The values in italics are taken from M. Gordon, S. H. Grover, and J. B. Stothers, *Can. J. Chem.*, **51**, 2092 (1973). c) Observed (δ) d) Predicted (δ) e) Difference (ppm); the observed chemical shift minus the predicted value.

TABLE 2.

^{13}C chemical shift (δ) of		C-1	C-2	C-3	C-4	OMe	C=O	Me	$\underline{C}Me_3$
t-Butylcyclohexane[a]		26.87	27.42	27.78	48.53			27.60	32.58
		27.2	*27.8*	*28.2*	*48.9*			*27.7*	*32.7*[b]
Methyl 4-*t*-butylcyclohexanecarboxylate	*cis*	39.01	28.15	23.96	48.11	51.26	175.40	27.54	32.51
		38.9	*28.0*	*23.8*	*47.9*	*51.2*	*175.4*	*27.4*	*32.4*[c]
	trans	43.50	29.66	23.96	47.56	51.26	176.37	27.54	32.39
		43.4	*29.5*	*26.6*	*47.3*	*51.2*	*176.4*	*27.4*	*32.3*[c]
Substituent parameter (ppm) of									
COOMe	Axial	12.1	0.7	−3.8	−0.4				
	Equatorial	16.6	2.2	−1.1	−1.0				

a) The numbering system follows the methyl *t*-butylcyclohexanecarboxylate. b) These values are taken from J. D. Roberts, F. J. Weigert, J. I. Kroschwitz, and H. J. Reich, *J. Am. Chem. Soc.*, **92**, 1338 (1970). c) These values are taken from M. Gordon, S. H. Grover, and J. B. Stothers, *Can. J. Chem.*, **51**, 2092 (1973).

trans 3-methylcyclohexanecarboxylates, therefore, are estimated to be approximately 67% of the equatorial methyl conformers and 33% of their axial methyl counterparts, and those of *cis* 2- and 4- or *trans* 3-hydroxycyclohexanecarboxylates are estimated to be approximately 28% of the equatorial hydroxyl conformers and 72% of their axial hydroxyl counterparts. Taking into account the substituent parameters of the methyl group reported by Grant and Dalling[5] and those of the hydroxyl group which are estimated from the chemical shifts for *t*-butylcyclohexane and stereoisomeric 4-*t*-butylcyclohexanols,[2] the chemical shifts predicted are obtained in a way similar to those of the parent cyclohexanecarboxylate. *cis* 1,2- and 1,4- or *trans* 1,3-Cyclohexanedicarboxylates undergo rapid interconversion between equivalent conformers, while alternatives exist exclusively in more stable conformations. These chemical shifts are also tabulated in Table 1. Most of them are in good agreement with those observed, deviations being within $\pm$0.9 ppm.*

Appreciable deviations between predicted and observed values appear in 2-substituted cyclohexanecarboxylates, especially for C-1 and C-2 resonances. The δ values observed are smaller than those predicted. Grant and Dalling[5] also found that the upfield shift caused by some of the gross effects appeared for the C-1 and C-2 resonances in 1,2-dimethylcyclohexanes. These shifts may be due to the bond deformation of these carbons by the gauche interaction between two vicinal substituents.

Substituents. The resonances for the carbonyl carbons of the ester groups in *cis* and *trans* 4-*t*-butylcyclohexanecarboxylates appear at δ 175.40 and 176.37, respectively. No shift difference is observed for the carbon of the ester methyl group in a set of stereoisomers. These results show that the orientational difference of the methoxycarbonyl group has a slight effect on the chemical shifts of their own carbons. Practically, very small shift differences occur in each pair of isomers. The ^{13}C NMR spectra of stereoisomeric 1-*t*-butyl-4-methylcyclohexanes show that the chemical shift for an axial methyl group in a cyclohexane ring is δ 17.53 and that that for an equatorial group is δ 22.53.[3] Using these δ values, the chemical shifts predicted for the methyl groups of methylcyclohexanecarboxylates are estimated (Table 1). In the case of 2-methylcyclohexanecarboxylate, there are appreciable shift differences between the observed and predicted values, while the chemical shifts for 3- and 4-methylcyclohexanecarboxylate are in good agreement with the predicted values, deviations being within $\pm$0.3 ppm. Such deviations for 2-methyl isomers suggest that the gauche interaction between these two vicinal substituents plays a major role in shifts to higher field.

The ^{13}C NMR spectrum of the lactone of 3-hydroxycyclohexanecarboxylic acid (1,3-cyclohexanecarbolactone) was obtained. The cyclohexane ring of this compound is considered to be more puckered than that of ordinary cyclohexanes produced by lactone formation. Since C-5 is the γ-position of both axial alkoxycarbonyl and acyloxy groups, a significant upfield shift is expected. The resonance at δ 18.50 corresponds to this carbon. The resonances at δ 37.67 and 28.75 cannot be assigned to specific carbons.

^{1}H NMR spectra of cyclohexanecarboxylates were also examined. ^{1}H signals for the methyl groups on the cyclohexane ring appear at about δ 0.83—0.90 and those for the methoxycarbonyl groups at about δ 3.60—3.67. Only a very small shift difference was observed in a set of stereoisomeric cyclohexanecarboxylates.

Since ^{13}C chemical shifts are affected by stereochemical differences, the predicted chemical shifts derived from the A values and the substituent parameters are helpful to a certain extent in assigning the resonance signals to specific carbons.

TABLE 3. ^{1}H CHEMICAL SHIFTS FOR METHYL GROUPS OF METHYL CYCLOHEXANECARBOXYLATES[a,b]

Methyl cyclohexanecarboxylate	COOMe		Me	
	cis	*trans*	*cis*	*trans*
Parent	3.65		—	—
4-*t*-Butyl-	3.64	3.60	0.83	0.85
2-Methyl-	3.60	3.63	0.89	0.86
			(7.6)	(6.0)
3-Methyl-	3.64	3.61	0.89	0.90
			(6.8)	(6.4)
4-Methyl-	3.64	3.61	0.89	0.88
			(5.6)	(5.6)
2-Hydroxy-	3.65	3.67	—	—
3-Hydroxy-	3.64	3.62	—	—
4-Hydroxy-	3.64	3.64	—	—
2-Methoxycarbonyl-	3.63	3.62	—	—
3-Methoxycarbonyl-	3.64	3.64	—	—
4-Methoxycarbonyl-	3.63	3.63	—	—

a) All chemical shifts are expressed in δ (ppm downfield from internal Me_4Si). b) The values in parentheses are coupling constants, J(Hz).

* Positive values represents shifts toward lower field.

Experimental

NMR Spectra. The ^{13}CFT-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 in $CDCl_3$, 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 μs (*ca.* 45°); repetition time, 4 s; spectral width, 6.25 kHz; data points, 8192; acquisition time, 0.655 s. 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 within δ $\pm$0.05.

Materials. All the materials employed in this work are known compounds. *o*-Toluic acid was hydrogenated over PtO_2 in AcOH to give 2-methylcyclohexanecarboxylic acid. The composition of the resulting mixture was 92% of the *cis* and 8% of the *trans* acids. A part of this was refluxed with KOH in ethylene glycol giving mixture of 78% of the *trans* and 22% of the *cis* isomers. The PtO_2 hydrogenation of *p*-toluic acid gave a mixture of 95% *cis* and 5% *trans* 4-methylcyclohexanecarboxylic acids, the isomerization of which gave a mixture of 84% of the *trans* and 16% of the *cis* isomers. The

PtO_2 hydrogenation of *m*-toluic acid gave 83% of *cis* and 17% of *trans* 3-methylcyclohexanecarboxylic acids. Methyl hydroxycyclohexanecarboxylates were prepared by the method of Kilpatrick and Morse.[6] *cis* and *trans* Cyclohexane-1,2-dicarboxylic acids and *cis* cyclohexane-1,4-dicarboxylic acid were obtained commercially. Isomerization of *cis* cyclohexane-1,4-dicarboxylic acid with KOH, followed by recrystallization from H_2O gave pure *trans* isomer. Cyclohexane-1,3-dicarboxylates were prepared from isophthalic acid by the method of Smith and Byrne.[7] The Raney Ni hydrogenation of methyl *p*-*t*-butylbenzoate at high hydrogen pressure and high temperature gave a mixture of 60% *cis* and 40% *trans* methyl 4-*t*-butylcyclohexanecarboxylates. All carboxylic acids were converted to methyl esters by treatment with diazomethane in the usual manner. Each mixture of methyl 2-, 3- or 4-methylcyclohexanecarboxylates, or methyl 4-*t*-butylcyclohexanecarboxylates was subjected to preparative gas chromatography to give a pure *cis* or *trans* isomer.

References

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