Carbon-13 Magnetic Resonance Studies of Cyclic Compounds

2.[†] Carbon-13 Chemical Shift Parameters for Equatorial and Axial Substituents in Cyclohexane: the Substituents Methyl, Ethyl, Isopropyl, Methoxy and Phthalimido

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Carbon-13 chemical shift parameters for equatorial and axial substituents in cyclohexane are reported for methyl, ethyl, isopropyl, methoxy and phthalimido substituents. The usefulness of the alkyl parameters is demonstrated by the agreement between calculated and observed ¹³C shifts for *trans*-1,4-dialkylcyclohexanes (alkyl = Me, Et, *i*-Pr) and for both conformations of *cis*-1,4-dialkylcyclohexanes (alkyl = Me, Et, *i*-Pr).

The success of ¹³C NMR spectroscopy in structural and stereochemical studies of organic molecules is due in no small measure to the reliability of ¹³C chemical shift parameters.² Early studies by Dalling and Grant^{3,4} led to the ¹³C chemical shift parameters for equatorial and axial methyl groups attached to cyclohexane. We report here the corresponding parameters for ethyl, isopropyl, methoxy and phthalimido groups, in addition to our own parameters for the methyl group. These parameters should find general application to alkylcyclohexanes which may hold, in addition, substituents in the 3- or 4-position. They are not expected to be useful for alkylcyclohexanes substituted in the 2-position; in this case the interaction of substituents will cause ring distortion and lead to an alteration in rotamer populations within the substituents.



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The compounds examined in the present study include trans- and cis-1-alkyl-4-phthalimidocyclohexane [(1) and (2) respectively, R = alkyl]. Previous work,⁵ largely using ¹H NMR spectroscopy, had demonstrated that the bulky phthalimido group had a strong preference for the equatorial orientation, thus ensuring that the cis-isomers exist entirely in the chair conformation (2). As expected, the trans-isomers exist entirely in the chair conformation (1) with both substituents equatorial. Also examined were c-3, r-1dimethyl-c-5-phthalimidocyclohexane (3) and c-3, r-1-dimethyl-t-5-phthalimidocyclohexane (4). Proof that 4 exists largely with phthalimido axial was given in an earlier paper.⁵ The preferred conformation of 3 follows from its preparation from c-3, c-5-dimethylcyclohexylamine (see Experimental) and from its ¹H NMR spectrum, which showed, for H-5 at $\delta 4.07$, a 1,2,1-triplet of 1,2,1-triplets (separations 12.1 and 4.1 Hz) which is typical of the axial hydrogen situated α - to an equatorial phthalimido group.⁵

Carbon-13 chemical shifts are listed in Tables 1,2 and 3. The shifts are quoted to the nearest 0.1 ppm, a figure which is well outside that set by instrumental accuracy and precision, but which is realistic, bearing in mind the effects on shifts of changes in temperature

Table 1. ¹³C Chemical shifts δ (ppm downfield from Me₄Si) for *trans*-1-R-4-phthalimidocyclohexanes (1) (solvent CDCl₃)

		÷=					
Carbon	R =	н	Me	Et	i-Pr	t-Bu	MeO
1		25.2	31.5	38.1	42.8	46.7	78.1
2,6		26.1	34.6	32.1	29.1	26.8	31.2
3,5		29.9	29.5	29.5	29.7	29.8	27.5
4		50.8	50.8	50.9	51.1	50.9	49.9
CH3-			22.3	11.5	19.9	27.5	55.8
_CH	2-			29.5			
>сн-					32.6		_
>°<		—				32.3	
´1', 6' `		132.0	132.1	132.0	132.2	132.1	132.0
2', 5'		122.9	122.9	122.8	122.9	122. 9	123.00
3′, 4′		133.6	133.6	133.8	133.6	133.6	133.7
CO		168.2	168.3	168.1	168.3	168.0	168.0

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Table 2. ¹³C Chemical shifts δ (ppm downfield from Me₄Si) for cis-1-R-4-phthalimidocyclohexanes (2) (solvent CDCl₃)

Carbon	R=	н	Me	Et	i-Pr	t-Bu ^a	MeO
1		25.2	26.2	33.6	39.2	43.9	73.0
2,6		26.1	31.3	29.1	29.2	23.3	29.1
3,5		29.9	24.0	24.3	24.5	27.8	24.0
4		50.8	51.0	50.9	50.9	47.8	50.4
CH3-		_	17.1	12.4	21.2	28.0	55.6
CH2				23.3		_	
>CH−		_			25.3	_	
>c<			_			33.1	_
1', 6'		132.0	132.1	132.2	132.1	132.2	132.0
2', 5'		122.9	122.9	122.9	122.9	122.9	122.9
3', 4'		133.6	133.6	133.7	133.7	133.6	133.7
со		168.2	168.2	168.3	168.3	168.7	168.0

* Twist conformation (8).

and concentration. The assignments of Tables 1,2 and 3 relied on the normal considerations of electronegativity, on the observed relative intensities, on the observed multiplicities in off-resonance ¹H decoupled spectra, on spectra obtained with low power selective ¹H decoupling, and on comparisons with published shift data for cyclohexylamines^{6,7} and phthalic anhydride.⁸ Table 4 gives the ¹³C chemical shift parameters for methyl, ethyl, isopropyl, t-butyl, methoxy and phthalimido substituents. These empirical substituent parameters are derived from the ¹³C chemical shifts of the phthalimido compounds in con-junction with the 13 C chemical shift of cyclohexane (27.1 ppm in CDCl₃), and are the effects which occur at α , β , γ and δ carbon atoms in cyclohexane on replacement of equatorial (e) and axial (a) hydrogen atoms by the substituent. The methyl parameters are little different from those of Dalling and Grant^{3,4} and the t-butyl parameters are similar to those which can readily be deduced from the chemical shift data of Roberts et al.⁹ Parameters for the methoxy group were derived by Schneider and Hoppen¹⁰ from low temperature ¹³C NMR studies on methoxycyclohexane, and are close to those given in Table 4.

It was pointed out by Roberts *et al.*⁹ that the change from the chair conformation (5) of *trans* 1,4-di-*t*butylcyclohexane to the twist conformation (6) of the

Table 3. ¹³C Chemical shifts δ (ppm downfield

irom Me ₄ Si) for c-3, r-1-dimethyl-c-5-
phthalimidocyclohexane (3) and c-3,
r-1-dimethyl-t-5-phthalimidocyclohex-
ane (4) (solvent CDCl ₃)

Carbon	3	4
1,3	32.1	28.0
4,6	37.5	37.2
2	42.8	42.3
5	50.2	47.9
CH3-	22.2	22.6
1', 6'	132.1	132.2
2', 5'	122.8	122.8
3', 4'	133.6	133.6
со	167.8	168.9

Table 4.	Empirical ¹³ C		sub	stituent	parameters		due	to	re-
	placement	of	8	cyclohexane-H		by	R	(pj	pm,
	positive = i	ncre	asin	g downf	ield shift)			

	Equator	Axial-R						
R	αe	β.	γe	δe	α_{a}	β.	γa	δa
Me	+6.4	+8.5	-0.4	-0.1	+1.1	+5.2	-5.9	+0.2
Et	+13.0	+6.0	-0.4	+0.1	+8.5	+3.0	-5.6	+0.1
<i>i-</i> Pr	+17.6	+3.0	-0.2	+0.3	+14.1	+3.2	5.4	+0.1
t-Buª	+21.6	+0.7	-0.1	+0.1	_		-	
MeO	+52.9	+5.1	-2.3	-0.9	+47.9	+3.0	-5.9	-0.4
Phthalimido	о ^ь +23.7	+2.8	-1.0	-1.9	+21.4	+2.5	-5.1	-2.4

^a The parameters deduced from Ref. 9 are α_{o} 21.8, β_{o} 1.1, γ_{o} 0.7 and δ_{a} 0.1 ppm.

^b The parameters for axial phthalimido were deduced from the shift data of Table 3 and the parameters for equatorial phthalimides.

cis-isomer was accompanied by an upfield shift of the signals for both C-1 and C-2(6). [The chemical shifts shown in 5 and 6 have been obtained by conversion to a Me₄Si reference from the published figures]. A similar situation holds for the change from the chair conformation (7) of trans-1-t-butyl-4-phthalimido-cyclohexane to the corresponding cis-isomer, lending further support to the earlier suggestions^{5,11} that the cis-molecule exists in the twist conformation (8).



Table 5. ¹³C Chemical shifts (δ ppm downfield from Me₄Si) for dialkylcyclohexanes 9–17 (solvent CFCl₃-CDCl₃, temperature 173 K)

Cor	npound									
		C-1	C-2, 6	C-3, 5	C-4	CH3-1	CH ₂ (Et)	CH ₃ (Et)	CH(i-Pr)	CH3(i-Pr)
9	Found	33.4	29.6	29.6	34.0	23.3ª	23.3ª	12.7	_	
	Calc.	33.5	29.9	29.6	35.4	_	_	—		
10	Found	27.2	31.7	27.0	40.1	17.4	30.6	11.9		
	Calc.	28.2	31.8	27.1	40.2			_		_
11	Found	33.3	29.7	28.4	39.7	23.7			25.1	21.5
	Calc.	33.5	30.1	29.8	41.0	<u> </u>	_			
12	Found	27.1	31.9	23.7	44.5	17.4			33.3	20.0
	Calc.	28.4	32.0	24.1	44.8	_				
13	Found	40.0	27.5	28.3	40.2	_	30.7	11.9	25.0	21.5
	Calc.	40.1	27.6	29.8	41.2					
14	Found	34.3	29.8	23.9	44.4		23.3	12.7	33.3	19.9
	Calc.	35.8	29.8	24.4	44.7		_	_		_
15	Found ^b	33.2	35.6	33.2	39.5	22.8	30.2	11.4	_	_
	Calc.	33.5	35.1	32.6	39.9			_	_	_
16	Found ^b	33.0	35.7	29.9	44.0	22.8	_	_	33.0	19.9
	Calc.	33.7	35.3	29.6	44.5			_		_
17	Found ^b	39.6	33.1	29.6	44.1		30.3	12.1	33.1	20.0
	Calc.	40.3	32.8	29.6	44.7	_	_			

^a Separate signals below 160 K.

^b Temperature 294 K.

Current investigations of the conformational free energy, enthalpy and entropy differences for ethyl and isopropyl substituents in cyclohexanes required the determination of the position of equilibrium in cis-1methyl-4-ethylcyclohexane $(9 \rightleftharpoons 10)$, cis-1-methyl-4isopropylcyclohexane $(11 \rightleftharpoons 12)$ and cis-1-ethyl-4-isopropylcyclohexane (13 \rightleftharpoons 14). The ¹³C spectra of (9 \rightleftharpoons 10), $(11 \rightleftharpoons 12)$ and $(13 \rightleftharpoons 14)$ were recorded at temperatures sufficiently low to slow the ring inversion process and allow observation of signals due to both chair conformations. The ¹³C spectra of the corresponding trans-compounds (15)-(17) were recorded at room temperature. Table 5 includes the measured chemical shifts for conformations (9)-(17), together with the shifts calculated using the substituent parameters of Table 4 and the shift of cyclohexane (27.0 ppm)in CDCl₃/CFCl₃ at 173 K. Bearing in mind the effect of temperature variation on ¹³C chemical shifts¹² the agreement between experimental and calculated shifts is encouraging. However, it is clear that the signals which are particularly close in chemical shift, and which provide identical multiplicities in the offresonance decoupled spectra, cannot be assigned unambiguously.

EXPERIMENTAL

¹³C NMR pulsed spectra were determined at 25.15 MHz using a JEOL PS100 spectrometer and pulsed programmer, interfaced to a Nicolet 1085 20K 20-bit computer. The pulse width was 4μ s (33° tip) and free induction decays were sampled using 8K data points over a spectral width of 5000 Hz (phthalimido-cyclohexanes) or 2500 Hz (dialkylcyclohexanes). Solvents were CDCl₃ for spectra determined at 294 K, or CFCl₃ (containing 10% CDCl₃) for spectra determined at reduced temperatures. GLC analyses employed a Pye 104 instrument for analytical separations and a Varian Aerograph Autoprep A for preparative separations.

cis- and trans-1,4-Dialkylcyclohexanes were synthesized by a well-established route. A typical synthesis, that of 1-ethyl-4-isopropylcyclohexane, is given below:

(a) 4-Isopropylcyclohexanol (20 g) was treated with sulphuric acid (13.5 cm³ H₂SO₄, 140 cm³ water) containing potassium dichromate (33.0 g), the temperature being maintained at 55–60 °C until the reaction subsided. The mixture was kept at room temperature for 1 h and then diluted with water (140 cm³). Distillation of the solution was effected until 70 cm³ had been collected. The distillate was saturated with sodium chloride and the organic phase was separated and later combined with an ether extract of the separated aqueous phase. The dried (MgSO₄) ethereal solution was evaporated and then distilled, giving 4-isopropylcyclohexanone (9.35 g, 48%), b.p. 62–70 °C at 2 mm Hg. TLC on silica gel, using CHCl₃: MeOH at 95:5 gave one spot, $R_{\rm F}$ 0.74.

(b) The above ketone (7.9 g), in dry ether (50 cm³) was added slowly to a stirred ethereal solution of ethylmagnesium iodide, prepared in the normal manner from ethyl iodide (8.8 g), magnesium turnings (1.37 g) and ether (50 cm³) under dry nitrogen. The mixture was kept at room temperature for 2 h and decomposed with ice and sufficient 2M hydrochloric acid to dissolve the magnesium salts. The ether layer was separated and the aqueous phase was extracted twice with ether. The combined ether extracts were dried (K_2CO_3), evaporated and distilled, giving a mixture of *cis*- and *trans*-1-ethyl-4-isopropylcyclohexan-1-ol (6.72 g, 69%), b.p. 74-82 °C at 1 mm Hg. TLC on silica gel using CHCl₃: MeOH at 95:5 gave two spots, with R_E values of 0.67 and 0.73.

(c) The foregoing mixture of tertiary alcohols (6.3 g) was heated under reflux with *p*-toluenesulphonic acid (1.2 g) at 100 °C for 1 h. Water was removed by distillation at 760 mm Hg. The residue was then distilled at 0.4 mm Hg, the boiling point being 38-40 °C.

The product, a mixture of 1-ethyl-4-isopropylcyclohex-1-ene (90%) and 1-ethylidene-4-isopropylcyclohexane (10%) was separated from water by extraction into ether and evaporation of the dried (CaCl₂) extracts (4.60 g, 82%). The ¹H NMR spectrum in CDCl₃ included signals for olefinic protons at δ 5.63 (major) and δ 5.64 (minor).

(d) The foregoing mixture (4.0 g) was hydrogenated for 5 h over Adam's platinum oxide catalyst (0.42 g) at room temperature and atmospheric pressure (uptake 1.2 mol H₂). The product (3.97 g, 98%) was separated by pipette from the spent catalyst and shown by analytical GLC $[5' \times \frac{1}{4}]$ column of 5-ring polymetaphenyl ether (25%) on Chromosorb P (70-80 mesh) at 67 °C, flow rate 30 cm³ min⁻¹] to consist of trans-1ethyl-4-isopropylcyclohexane (53%), cis-1-ethyl-4isopropylcyclohexane (44%) and an unidentified impurity (3%). In this instance, a complete separation by preparative GLC was not possible. In the other cases of mixtures of cis-and trans-1,4-dialkylcyclohexanes, complete separations were achieved by preparative GLC using a $5' \times \frac{1}{4}''$ column of Apiezone L (30%) on Chromosorb W (80-100 mesh) at 110 °C, flow rate $30 \text{ cm}^3 \text{ min}^{-1}$.

c-3, r-1-Dimethyl-c-5-phthalimidocyclohexane (3).c-3, c-5-Dimethylcyclohexanone oxime⁵ (8.0 g) was reduced by sodium (21 g) in boiling ethanol (225 cm³) according to the procedure of Lycan et al.¹⁴ The usual method of working-up gave crude c-3, c-5-dimethylcyclohexylamine (3.5 g 49%) as a colourless liquid, b.p. 68.5 °C at 13 mm Hg. Treatment with phthalic anhydride (see Ref. 13) gave c-3, r-1dimethyl-c-5-phthalimidocyclohexane as colourless plates, m.p. 93-94 °C (Found: C, 74.6; H, 7.2; N, 5.3. C₁₆H₁₉NÔ₂ requires C, 74.7; H, 7.4; N, 5.5%).

The remaining phthalimides were synthesized as described earlier.^{5,13}

REFERENCES

- 1. H. Booth and D. V. Griffiths, J. Chem. Soc. Perkin Trans 2 842 (1973).
- 2. F. W. Wehrli and T. Wirthlin, Interpretation of Carbon-13 NMR Spectra, Heyden, London (1976).
- 3. D. K. Dalling and D. M. Grant, J. Am. Chem. Soc. 89, 6612 (1967).
- 4. D. K. Dalling and D. M. Grant, J. Am. Chem. Soc. 94, 5318 (1972).
- 5. H. Booth and P. R. Thornburrow, J. Chem. Soc. B 1051 (1971).
- 6. H. Booth and M. L. Jozefowicz, J. Chem. Soc. Perkin Trans 2 895 (1976).
- 7. D. Doddrell, I. Burfitt and N. V. Riggs, Austr. J. Chem. 28, 369 (1975).
- 8. L. F. Johnson and W. C. Jankowski, Carbon-13 NMR

- Spectra, Wiley, New York (1972). 9. J. D. Roberts, F. J. Weigert, J. I. Kroschwitz and H. J. Reich, J. Am. Chem. Soc. 92, 1338 (1970). 10. H-J. Schneider and V. Hoppen, Tetrahedron Lett. 579,
- (1974).
- 11. H. Booth and G. C. Gidley, Tetrahedron Lett. 1449 (1964).
- 12. H-J. Schneider and W. Freitag, J. Am. Chem. Soc. 98, 478 (1976).
- 13. H. Booth, G. C. Gidley and P. R. Thornburrow, J. Chem. Soc. B 1047 (1971).
- 14. W. H. Lycan, S. V. Puntambeker and C. S. Mavel, Org. Synth. Coll. Vol. II, 318 (1943).

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