Tetrahedron Vol. 33, pp. 1149 to 1154. Pergamon Press 1977. Printed in Great Britain.

CONFORMATIONAL EFFECTS IN COMPOUNDS WITH 6-MEMBERED RINGS—XIII

DETECTION OF TWIST CONFORMERS USING ^{13}C NMR CHEMICAL SHIFTS

D. J. LOOMES and M. J. T. ROBINSON*
The Dyson Perrins Laboratory, University of Oxford, South Parks Road, Oxford OX1 3QY, England

(*Received in the UK 31 August 1976; Accepted for publication 22 October 1976*)

Abstract—^{13}C NMR spectra of derivatives of cyclohexane, piperidine, and thian in chair and twist conformers, and of model compounds, lead to estimates of deshielding ($\Delta\delta$ ~ 3.6 ± 0.2 ppm) for axial CMe_3 on a cyclohexane ring and shielding ($\Delta\delta$ ~ −0.2 to −0.6 ppm) for ψe-CMe_3 in twist conformers, relative to equatorial CMe_3. Ring carbon atoms are considerably shielded in twist conformers relative to chair conformers. The value of ^{13}C chemical shifts in the study of chair-twist equilibria is exemplified by variable temperature measurements on diastereomeric pairs of compounds (**11** and **13**; **38** and **50**).

A reliable interpretation of factors influencing the reactivity of the common chair conformers of 6-membered rings requires that the possible influence of twist conformers shall be known.[1] It is therefore necessary to study the properties of compounds that can be shown to exist, to a considerable extent at least, in twist conformations† and we must be able to detect such conformers in solution. Diffraction methods have been little used to detect twist conformers and only for cyclohexan-1,4-dione has the twist conformation in the solid[2] and vapour[3] been firmly correlated with a twist conformation in solution, using vibration spectra.[4] Unfortunately electron diffraction has failed to determine the conformation of *cis*-1,4-di-t-butylcyclohexane **7**,[5] which probably exists as one or more twist conformers. A twist conformer was first detected using IR spectroscopy,[6] with strong support from ^1H NMR,[7] and these two methods have remained the most commonly used. Proton spectra, however, unless simplified by special structural features or by specific deuteriation, are often difficult to analyse and ^1H-decoupled ^{13}C spectra should be more generally useful. Hitherto there have been few compounds known to be in twist conformations that could be used as a basis for a correlation between conformation and ^{13}C chemical shifts and little has been published.[8,9]

A chair ring has two types of ligand position (axial, equatorial) but a twist ring (note the enantiomeric pair of twist conformers of cyclohexane: in the remainder of this paper we will illustrate only one of each enantiomeric pair of twist conformers) has two unhindered (Ic, ψe)[10] and one hindered type of position (ψa)[10] (Fig. 1). When a very large substituent such as t-butyl is forced to be axial on a chair then one or more twist conformers becomes at least comparable in energy with the chair conformers provided the large substituents can occupy unhindered (Ic or ψe) positions.[10] Derivatives and heterocyclic analogues of cyclohexane have even more twist conformers and these are illustrated for compounds studied in this paper in Figs. 2–5.

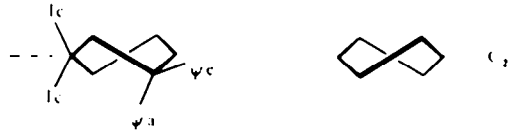


Fig. 1. Enantiomeric twist conformers of cyclohexane.

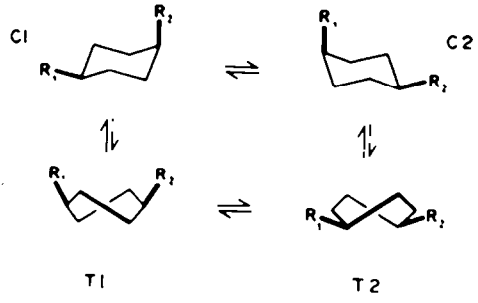


Fig. 2. Conformers of a cis-1,4-disubstituted derivative of cyclohexane (excluding twist conformers with ψa groups).

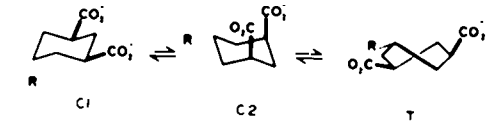


Fig. 3. Conformers of a trans-5-alkylcyclohexane 1,3-di-carboxylate anion (excluding twist conformers with ψa groups).

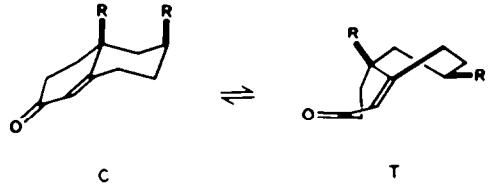


Fig. 4. Chair and twist conformers of the B-ring of a cis-6,10-dialkyl-$\Delta^{1(9)}$-octal-2-one.

†In this paper we are concerned primarily with compounds in which both chair and twist conformers are possible, in contrast to many fused and bridged ring systems.

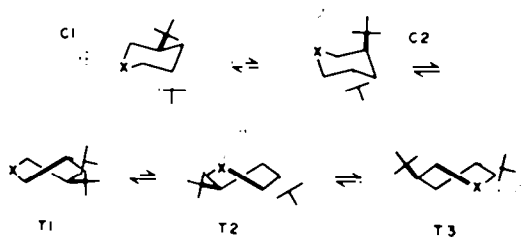


Fig. 5. Chair and twist conformers of 5-substituted derivatives of trans-1,3-di-t-butylcyclohexane and its heterocyclic analogues (excluding twist conformers with ψa groups). When X is pyramidal, e.g. S–Me, the substituent is assumed to be oriented as in formulae **53**, **56** and **57** so that C2 has an "impossible" syn-1,3-diaxial interaction and T2 has a ψa substituent and may be ignored. When X carries two substituents ≠H both C1 and C2 have "impossible" strain and both T2 and T3 have ψa substituents and may be ignored.

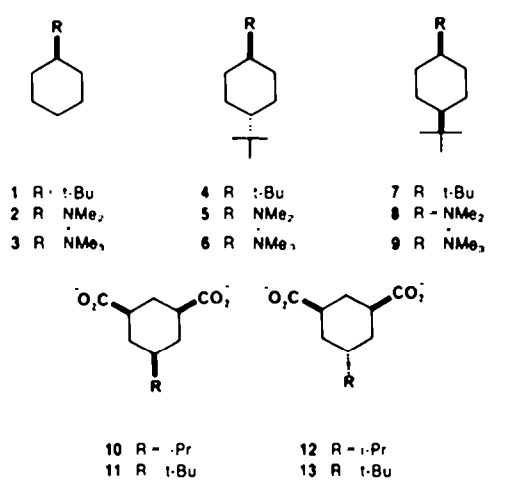
In other research we have prepared a variety of compounds in which twist conformers are expected to be important and we have set out to characterise ^{13}C NMR chemical shifts for t-butyl groups on chair and twist rings and to interpret the effects of ring conformation on the chemical shifts of the ring carbon atoms.

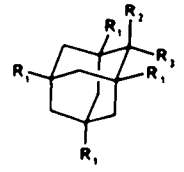
EXPERIMENTAL

^{13}C NMR spectra. These spectra were measured using a Bruker WH90 pulse Fourier transform spectrometer operating at 22.63 MHz in conjunction with a Nicolet B-NC 12 computer. Compounds were studied as 0.5 M solutions in $CDCl_3$ containing 0.5 M Me_4Si as internal reference unless otherwise indicated in Tables 1–6. The majority of spectra were measured with a 2000 Hz sweep width (50° pulse,[11] 1.2s repetition rate) and the FIDs were accumulated in 4 K memory addresses to which were added 4 K empty addresses before FT giving a digital resolution of 0.49 Hz (= 0.022 ppm).

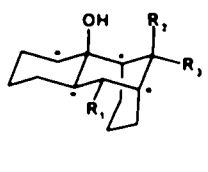
^1H NMR spectra. These spectra were measured using a Perkin Elmer R32 (90 MHz) spectrometer with Me_4Si as internal lock and reference. The complex spectra for **38** and **50** were simplified to first order spectra by the addition of Eu(fod)$_3$ (40 mg) to each ketone (40 mg) in $CDCl_3$ (0.4 ml). Varying the relative amount of the shift reagent did not affect the $^3J_{HH}$ couplings significantly and had only a small effect on $^2J_{HH}$ couplings.

Compounds. Standard methods were used to prepare many of the compounds, i.e. **2**, **3**, **5**, **6**, **8**, **9**;[12] **14–18**, **20**;[13] **26**, **28**, **29**;[14] **30**;[15] **31**;[16] **32**;[17] **33**, **34**;[18] **35**;[9] **39**.[20] Other compounds were available in this laboratory, i.e. **10–13**;[21] **20–22**, **25**;[22] **41–43**, **53–55**;[23] **44–46**, **56**, **57**.[5] The remaining compounds were prepared as follows.

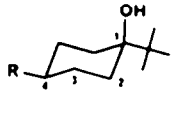




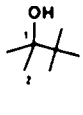
	R_1	R_2	R_3
14	H	H	H
15	H	H	OH
16	H	Me	H
17	H	Me	Me
18	H	Me	OH
19	H	t-Bu	OH
20	Me	H	H
21	Me	H	OH
22	Me	Me	OH
23	Me	t-Bu	OH
24	H	=O	
25	Me	=O	



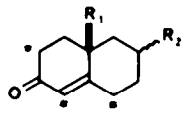
	R_1	R_2	R_3
26	H	OH	H
27	H	OH	t-Bu
28	H	=O	
29	Me	O	



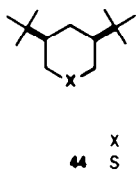
30 R = H
31 R = t-Bu



32



	R_1	R_2
33	H	H
34	Me	H
35	H	α-t-Bu
36	Me	β-t-Bu
37	Me	α-t-Bu



	X		X		X		X
38	CH_2	**44**	S	**50**	CH_2	**56**	S
39	CO	**45**	S=Me	**51**	CO	**57**	S=Me
40	$C(OMe)_2$	**46**	S Me	**52**	$C(OMe)_2$	**58**	S=O
41	NMe	**47**	S=O	**53**	NMe	**59**	SO_2
42	$NHCH_2Ph$	**48**	S O	**54**	$NHCH_2Ph$		
43	NMe_2	**49**	SO_2	**55**	NMe_2		

Derivatives of adamantane and of tricyclo[7.3.1.0^{2,7}]tridecane. The hydroxyketone **28**[14] (2.08 g), m.p. 167–169°, was deuteriated by heating with 1 M NaOD in D_2O–EtOD (1:1), 6 ml) at 100°/3d giving **28**-d_1 (60% after crystallisation from EtOH–H_2O), m.p. 163–167°.

A pure sample of **19**[24] was generously given by Prof. J. L. Fry. When the same preparative procedure was used for **23**, **27** and **27**-d_1 from **25**, **28** and **28**-d_1 the products were only 90% pure (^{13}C NMR). As yet purification from the accompanying secondary alcohols[24] has not been successful but the ^{13}C NMR spectra convincingly confirmed the structures of the main components as well as identifying the secondary alcohols **21** and **26**.

Cis-6-t-butyl-10-methyl-Δ^{1,9}-octal-2-one. The ketone **36** was obtained by dehydrating the appropriate 9-hydroxydecal-2-one[25] (available in this laboratory) with anhydrous oxalic acid in boiling toluene.

Derivatives of 1,3-di-t-butylcyclohexane. 3,5-Di-t-butylphenol was hydrogenated in acetic acid over PtO_2 to give **38**[26] and *cis, cis*-3,5-di-t-butylcyclohexanol which was oxidised to **39**[20] by Jones' chromic acid.[27] Trans-4,6-di-t-butylcyclohexan-1,3-dione[5] (10 g) was reduced with $LiAlH_4$ (4 g) and $AlCl_3$ (40 g) in ether to give trans-3,5-di-t-butylcyclohexene. The latter was (a) reduced with H_2 over PtO_2 to **50**[26] and (b) treated with borane-THF followed by chromic acid[28] to give **51**.[27] The ketones **39** and **51** were converted into the ketals **40** and **52** by the action of methyl orthoformate.

Table 1. ^{13}C NMR chemical shifts (ppm from internal Me_4Si) for 1,4-disubstituted derivatives of cyclohexane (0.5 M in $CDCl_3$)

Compound	C-1	C-2(6)	C-3(5)	C-4	δ_{av}^{a}	CMe_3	CMe_3	Other C
[illegible][b]	48.7	26.0	27.6	27.0		32.5	27.5	
[illegible][b]	40.4	28.[illegible]				32.1	27.7	
7[b]	42.8	23.6				32.8	27.6	
2	63.90	29.80	25.85	26.42				41.50 (OMe)
3	64.00	29.16	25.57	47.88	37.12	32.32	27.63	41.73 *
8	60.74	30.03	21.57	48.95	35.49	32.56	27.72	43.84 *
1	74.59	26.66	25.04	24.59				51.81 (OMe)
8	74.59	26.68	25.80	47.35	37.62	32.32	27.52	51.89 *
9	71.26	22.50	21.92	40.50	33.47	32.56	27.50	51.70 *
30	74.[illegible]	30.95	22.06	25.56	-	37.78	25.08	
31	74.55	31.44	22.75	47.75	-	37.47[c] 32.34[d]	25.27[c] 25.57[d]	
32[e]	75.08	25.34			-	37.47	25.45	

[a] Average of chemical shifts for ring carbon atoms (only given for sets of diastereomers).
[b] Derived from data using 1,4-dioxan as internal reference (for neat liquids; see ref. 9).
[c] 1-CMe_3.
[d] 4-CMe_3.
[e] Numbering as in formula 32 to facilitate comparison with 30 and 31.

Table 2. ^{13}C NMR chemical shifts (ppm from internal Me_3COH) for sodium salts of 5-alkylcyclohexane-cis-1,3-dicarboxylic acids (1 M in D_2O)

Compound	T(K)	C-1(3)	C-2	C-4(6)	C-5	δ_{av}^{a}	5-CMe_x	5-CMe_x	$CO_2^{-\,b}$
[illegible]	300	18.60	3.52	2.75	12.68	9.17	3.43	-10.69	156.28
[illegible]	300	22.1[illegible]	3.[illegible]	1.[illegible]	10.[illegible]0	6.55	-4.[illegible]	-9.02	156.50
[illegible]	300	18.7[illegible]	1.[illegible]	0.43	16.48	8.79	3.34	-2.59	156.07
23	300	17.02	0.58	-1.73	10.14	5.28	2.98	-1.2[illegible]	156.05
[δ(23) - δ(22)]		-4.70	-0.9[illegible]	-2.16	-6.34	-3.5[illegible]	-0.37	1.62]	
[illegible]	[illegible]	[illegible].75	1.54	0.45	16.84	8.77	3.42	-3.04	
23	350	[illegible]	0.5[illegible]	-2.09	9.99	4.01	2.[illegible]	-1.68	
[δ(23) - δ(22)]		-4.50	-1.00	-2.54	-[illegible].65	-3.76	-0.76	1.36]	

[a] Average of chemical shifts for ring carbons.
[b] Obtained from spectra with 4000 Hz sweep width (digitisation 0.055 ppm) and *not* measured in the variable temperature experiment.

Derivatives of 3,5-di-t-butylthian. The thian 44[1] was oxidised with N_2O_4[30] to an equilibrium mixture of 47 and 48 (1:2 by ^1H NMR) (Found: C, 67.88; H, 66.44; S, 14.07. $C_{13}H_{26}OS$ requires: C, 67.77; H, 11.37; S, 13.92%), which were not separated, and with ozone to 49, m.p. 140–142° (Found: C, 66.15; H, 6.87; S, 13.41. $C_{13}H_{26}O_2S$ requires: C, 66.07; H, 6.82; S, 13.54%). Similarly 56[1] was oxidised to 58, m.p. 119–121° (Found: C, 66.95; H, 10.94; S, 13.37%) and to 59, m.p. 200–201° (Found: C, 65.91; H, 6.83; S, 13.38%).

RESULTS AND DISCUSSION

The ^{13}C NMR chemical shifts for the compounds 1–59 are collected in Tables 1–6. The assignments are based on standard methods, i.e. relative intensities, off-resonance CW decoupling, deuteriation (effective loss of signal for carbon directly bonded to deuterium, line broadening due to unresolved ^{13}C–^2H coupling and isotope effects of ^{13}C chemical shifts for other nearby carbon atoms) and additivity relationships. Some assignments are uncertain and these are indicated in the Tables. The compounds with axial t-butyl groups, 23, 27 and 27-d_1, proved very difficult to obtain and the best samples, prepared following the most successful method[14] for 19, contained ~10% of the corresponding secondary alcohols, which

Table 3. ^{13}C NMR chemical shifts (ppm from internal Me_4Si) of adamantanes[a] 14–25 (0.5 M in $CDCl_3$)

Compound	C-2 α	C-1(3) β	C-4(9) γsyn	C-8(10) γanti	C-5(7) δ*		C-6 ε	2-Alkyl[b] α'	β'	Apical methyls 1(3)	5,7[c]	
14	37.[illegible]	[illegible]										
15[d]	74.56	35.[illegible]	[illegible]	[illegible]	28.[illegible]	27.59	[illegible]					
16[d]	39.39	34.[illegible]	39.[illegible]	[illegible]	[illegible]	28.[illegible]	39.[illegible]	–[d]				
17[e]	–[e]	37.[illegible]	33.3		2[illegible].7		39.5	27.7				
18	73.[illegible]	39.2[illegible]	35.[illegible]	33.[illegible]	[illegible]	27.07	38.3[illegible]	27.59				
19	77.52	34.[illegible]	35.63	33.[illegible]	27.20	27.07	39.59	39.80	28.9[illegible]			
20	50.49	32.[illegible]									30.29	
21	[illegible]	[illegible]	45.[illegible]	30.[illegible]	[illegible]	[illegible]	50.62			21.29	29.66	29.95
22	[illegible]	38.59	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]		23.21	29.81	29.96
23	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	30.5[illegible]	52.0[illegible]	[illegible]	33.[illegible]	29.3[illegible]	29.[illegible]	29.9[illegible]
24	–[f]	4[illegible].03	39.[illegible]		28.52		3[illegible].37					
25	–[f]	[illegible]	32.6[illegible]		32.0[illegible]		49.5[illegible]			23.5[illegible]	28.67	

[a]The numbering is indicated in the formulae 14–25; Greek letters follow the convention used in ref. 43, which includes evidence for the assignment of the δC atoms in 15.
[b]α', β' refer to the first and second C atoms in the 2-alkyl substituent.
[c]The signals for the 5- and 7-methyl carbons can not be assigned at present.
[d]Ref. 43; the chemical shift of the 2-methyl group was not reported.
[e]Ref. 44; the chemical shift of the 2-carbon atom was not reported.
[f]Not observed.

Table 4. ^{13}C NMR chemical shifts (ppm from internal Me_4Si) of derivatives of 2-hydroxytricyclo[7.3.1.0^{2,7}]tridecane[a]

Compound	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	C-11	C-12	C-13
26	[illegible]	75.[illegible]	37.[illegible]	30.[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
27[b]	45.[illegible][c]	[illegible]	[illegible][c]	[illegible]	[illegible]	[illegible]	40.[illegible][c]	[illegible]	35.[illegible][c]	[illegible].93	[illegible]	[illegible]	[illegible]
28[b]	59.2[illegible][c]	[illegible]	[illegible].59[c]	30.[illegible]	25.2[illegible]	[illegible]	[illegible][c]	[illegible]	[illegible][c]	34.99	30.[illegible]	[illegible]	–[d]
29	59.[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	37.5[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	–[d]

[a]In view of the small number of compounds studied the assignments of some similar chemical shifts must be regarded as tentative.
[b]d_0 and d_1 derivatives were studied (• marks site of deuterium substitution in formulae).
[c]Not observed in d_1 species.
[d]Not observed.

Table 5. ^{13}C NMR chemical shifts (ppm from internal Me_4Si) for derivatives of $\Delta^{1(9)}$-octal-2-one (0.5 M in $CDCl_3$)

Compound[a]	C-1	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10
33[b]	124.37	36.55[c]	2[illegible]	34.52	2[illegible].59	26.[illegible]7	35.60[c]	167.44	37.93[c]
34	124.[illegible]	33.96	38.10	41.64	21.79	27.23	37.80	170.42	35.95
35[b]	123.99	36.65[c]	29.49	35.62	47.19	27.24	35.62[c]	167.25	37.94[c]
36[d]	124.61	34.45	39.59	34.71	44.[illegible]	25.66	29.14	172.09	35.61
37[a,e]	(123.5)	(34.1)	(38.9)	(42.7)	(43.4)	(27.6)	(32.8)	(170.2)	(36.0)

[a]The C-2 (CO) resonance was not observed.
[b]d_0 and d_1 species studied (• marks the site of deuteriation in formulae).
[c]Not observed in d_1 species.
[d]Average chemical shift for B-ring carbons 5–10 is 56.52 ppm for 36 and 58.8 ppm for 37.
[e]Estimated from chemical shifts of 33–35 assuming additivity (see text).

were positively identified in the ^{13}C spectra of 23 and 27 (d_0 and d_1). We accordingly studied related compounds (Tables 3 and 4) in order to make nearly complete assignments of the ^{13}C chemical shifts in 23 and 27. Ironically in the $\Delta^{1(9)}$-octal-2-ones (Table 5) the very strained compound 36 is comparatively readily prepared whereas 37, with a chair B ring, has as yet only been obtained as a relatively minor component in mixtures.[21] We accordingly estimated ^{13}C chemical shifts for 37 from those for 33–35 assuming additivity for the ring carbon atoms in order to derive an average value for the carbon atoms in ring B; the difference between the two averages (Table 5) is much greater than any uncertainty resulting from assumed additivity of substituent effects for well separated groups.

The chemical shifts for t-butyl groups cover a rather

Table 6. ^{13}C NMR chemical shifts (ppm from internal Me_4Si) of derivatives[a] and heterocyclic analogues of 1,3-di-t-butylcyclohexane (0.5 M in $CDCl_3$)[b]

Compound	C-1	C-2,6	C-3,5	C-4	δ_{av}^{c}	CMe_3	$\underline{C}Me_3$	Other C atoms
38 (298K)	27.38	27.57	48.92	28.72	34.87	32.90	27.74	
50 (298K)	22.92	23.71	42.37	26.41	30.25	33.42	27.90	
Δδ	-4.47	-3.86	-6.55	-2.31	-4.62	+0.52	+0.16	
38 (183K)	27.23	27.23	48.15	28.10	34.55	32.99	27.64	
50 (183K)	22.18	22.52	41.59	25.78	29.51	33.29	27.84	
Δδ	-5.05	-4.72	-6.56	-2.54	-4.99	+0.30	0	
39	-[d]	43.22	48.01	27.63	42.62	32.90	27.32	
51	-[d]	40.17	41.36	24.95	37.60	33.05	27.07	
40	67.82	33.80	43.73	27.59	41.74	32.46	27.59	47.52[e] 47.34[e]
52	65.95	32.33	39.95	25.26	39.50	32.70	27.16	51.27[e]
41	-	57.76	47.10	26.05	47.14	33.93	27.80	46.35[f]
53	-	56.75	42.33	24.58	44.55	32.86	26.55	47.10[f]
42[g]	-	54.22	43.78	25.47	44.29	32.34	27.24	61.69[h]
54[g]	-	50.30 48.53	39.72 37.93	22.92	39.66	32.90 32.35	27.03 26.90	60.18[h]
43[g]	-	64.74	41.27	25.04	47.41	32.62	27.61	58.0[j,k] 49.3[k,l]
55[g]	-	62.96	38.62	23.30	45.33	32.59	26.97	54.8[l,k]
44	-	29.42	50.23	28.64	37.59	33.61	27.39	
56	-	25.85	44.40	25.38	32.38	33.72	27.33	
45	-	46.25	40.69	27.07	40.20	34.56	27.50	26.25[m]
46	-	40.42	35.64	26.37	35.69	34.33	27.26	19.23[m]
57	-	36.03 35.52	40.84 38.53	24.63	35.07	34.43 33.98	27.59 27.00	25.25[m]
47[n]	-	51.29	43.96	27.3	43.53	33.56	27.1	
48[n]	-	45.06	37.77	27.3	38.60	32.96	27.1	
58	-	48.27 46.56	38.45 36.03	24.87	38.83	33.16 32.90	27.39 26.90	
49	-	53.02	44.90	27.44	44.66	33.03	27.24	
59	-	51.70	40.84	24.37	42.89	33.16	26.87	

[a] Numbering of C atoms assumes t-butyl groups at positions 3 and 5.

[b] 1 M solutions used for VT measurements on 38 and 50 (data quoted only for extreme temperatures); chemical shifts for 0.5 M solutions at 300 K differ by 0.05 ppm on average from data for 1 M solutions at 298 K.

[c] Average chemical shifts for ring carbon atoms.

[d] Not observed.

[e] OMe.

[f] NMe.

[g] 0.25 M in $CDCl_3$–CD_3OD (1:1).

[h] $\underline{C}H_2Ph$; aromatic carbon resonances were folded and not measured.

[i] Eq-NMe.

[j] Broadened by ^{14}N coupling.

[k] Ax-NMe.

[l] SMe.

[m] Studied as mixture; the overlapping signals for C-4 and for $C\underline{Me}_3$ can not be measured precisely.

small range and these small differences are validly interpretable only if each set of diastereomers is measured under closely controlled conditions. It is known that concentration effects on chemical shifts of t-butyl groups in conformationally homogeneous molecules are remarkably small, e.g. in Ref. 31 compounds were studied either as neat liquids or as saturated solutions in CS_2 yet δ values for t-butyl groups in comparable positions varied by $\geq$0.5 ppm, which includes remote substituent as well as concentration/solvent effects. Nevertheless measurements were made for covalent compounds in solutions in $CDCl_3$ at a concentration (0.5 M) below which significant changes in chemical shifts would not occur, as was confirmed in a few instances. Some of the salts had low solubility and the thianium and piperidinium salts were studied at 0.25 M.

In many of the compounds studied one may safely assume strongly preferred ring conformations as follows:

(a) Chair conformations when all large substituents, i.e. t-butyl, NMe_3, are equatorial, as in **1–6**, **8**, **10–12**, **30–35**, **38–49**.

(b) Twist conformations with unhindered (ψe or Ie) substituents when chair conformations would lead to "impossible" syn-1,3-diaxial interactions between t-butyl groups and atoms or groups larger than hydrogen, i.e. **36** in T (Fig. 4); **52**, **55** and **59** in T1 (Fig. 5). The values of vicinal couplings ^3J (2H, 3H) (see Experimental) for **55** ($J_{cis} > 4$ Hz; $J_{trans} = 12.7$ Hz) and **59** ($J_{cis} > 4$ Hz; $J_{trans} = 12.4$ Hz) are similar to those for the diastereomers **43** ($J_{cis} > 4$ Hz; $J_{trans} = 12.4$ Hz) and **49** ($J_{cis} > 4$ Hz; $J_{trans} = 12.7$ Hz) and are therefore consistent with conformation T1 but *not* with C1⇌C2 (Fig. 5).

(c) Chairs with axial t-butyl groups in the derivatives of adamantane **19**, **23** and tricyclo[7.3.1.0^{2,7}]tridecane **27**.

In most of the remaining compounds with strained chair conformations such as C1 and C2 (Fig. 5) there is a variety of evidence for the presence of relatively large amounts of twist conformers:

(*a*) **7**: see Ref. 5 for a variety of circumstantial evidence.

(*b*) **50**: thermodynamic data ($\Delta S°$ (**37**→**49**))[26] and IR spectra.[27]

(*c*) **51**: (as T1, minimising torsion strain[11]): thermodynamic data ($\Delta S°$ (**39**→**51**)).[14] We have obtained supporting evidence from ^{1}H NMR coupling constants (see Experimental). The geminal coupling ^2J(2H, 2H) for **51** is 16.3 Hz and this implies that the C=O does *not* approximately eclipse either of the C2(6)–H bonds as in C1 or C2,[28] whereas in **39** ^2J(2aH, 2eH) = 13.5 Hz as expected for a chair conformer. The vicinal couplings ^3J(2H, 3H) for **51**, 4.4 Hz (J_{cis}) and 12.3 (J_{trans}), are consistent with T1 but *not* with C1⇌C2 and are very similar to those in **39** ($J_{cis} > 3$ Hz, $J_{trans} = 13.5$ Hz).

(*d*) **53**: equilibrium constants for the formation of the borane adduct.[21]

(*e*) **56**, **57**: ^3J(2H, 3H) coupling constants.[7]

(*f*) **54**: the ^3J(2H, 3H) coupling constants for the N-methyl analogue measured in pyridine-D_2O (1:1), in which the N–Me and N–H exchange positions rapidly through a small amount of the free amine thereby giving rise to a dynamic symmetry equivalent of T1 (Fig. 5), are 6.3 Hz(J_{cis}) and 11.7 Hz (J_{trans}). These values are not consistent with a predominance of C1⇌C2 but indicate that chair conformers probably contribute significantly to the conformational equilibrium. It was shown in separate experiments that ^3H(2H, 3H) couplings are the same in $CDCl_3$ and in pyridine-D_2O for **43** ($J_{trans} = 12.4$ Hz in $CDCl_3$ and 12.5 Hz in py-D_2O) and for the N-methyl analogue of **42** ($J_{trans} = 11.7$ Hz in $CDCl_3$ and 11.9 Hz in py-D_2O; the $^3J_{cis}$ couplings were all >4 Hz and were not resolved).

Finally compounds **9**, **57** and **58** are assumed by analogy with related compounds discussed above to exist to a large extent in twist conformers, while **13** is considered later.

It is customary to refer to α-, β-, γ-effects, etc., to denote the change of chemical shift of a carbon atom caused by a substituent one, two, three bonds, etc away.[29] Unfortunately this simple terminology omits any indication of the spatial relationship between the substituent and the ^{13}C nucleus. The large and reliable shielding effects of γ-substituents in a gauche relation to carbon has been expressed as a "γ-gauche effect" which is immediately understandable but which is not readily generalised to δ or more distant relationships. One way of dealing with the five distinct δ-effects possible with staggered bond arrangements of a single chain of four bonds joining the carbon atom and the δ-substituent is simply to use numerical subscripts but it is then necessary to refer to a diagram for each effect δ_1, δ_2, etc.[30] and there is no way of dealing with, e.g. a rotating group like t-butyl (Fig. 6c) or a multiple path (Fig. 6d). We suggest that where there is a fixed spatial relationship between a carbon atom and a substituent it should be indicated by descriptors for the torsion angles defined by successive trios of bonds from the carbon to the substituent preceding the usual Greek letter. Thus the very common shielding γ-effect may be specified as g-γ and the relatively large deshielding δ-effect in crowded systems is g,g′-δ (or g g′-δ): Fig. 6 shows examples of classification relevant to this paper, including rotation of a t-butyl group and multiple bonding paths.

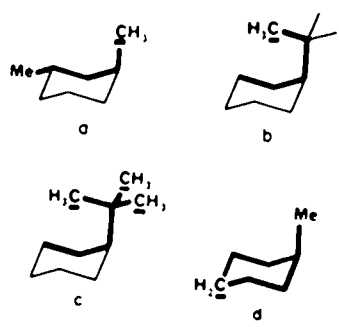


Fig. 6. Designation of shielding (or deshielding) δ-effects in molecules of fixed conformation with staggered bonds (working *from* the perturbed carbon nucleus *to* the relevant substituent): (a) gt-δ-effect, equatorial methyl group acting on the axial methyl carbon; (b) g,g′-δ-effect, ring methylene acting on the "inside" CH_3 of the t-butyl group, without allowing for the rotation of the latter; (c) (g, t)g-δ-effect, as in (b) except that the rotation of the t-butyl group is included; (d) g,g′-δ-effect of axial methyl group on CH_2 directly across the ring, with two four bond paths separating the methyl group and the CH_3.

We use the simple carbocyclic compounds **1**, **4–6**, **11**, **30**, **31**, **35** and **38–40** to derive the chemical shifts of carbon atoms in unhindered equatorial t-butyl groups. A comparison of **32** with **30** and **31** shows that the t-γ effects of the ring carbon atoms in **30** and **31** have little effect on the t-butyl chemical shifts.† It is therefore reasonable to take the chemical shifts of t-butyl groups in **19** and **27** as appropriate to axial t-butyl groups on cyclohexane rings.

Significant changes in deshielding with changes in conformation were found for both types of carbon atom in t-butyl groups but we will consider mainly the carbon atoms in the methyl groups because the chemical shifts of the quaternary carbon atoms vary rather irregularly, perhaps partly because they are nearer the heteroatoms in many of the compounds than the methyl carbon atoms are. The α-carbon atoms in isopropyl groups (as in **10** and **12**) show the expected difference for axial (strongly shielded) and equatorial positions, by analogy with methyl.[31] In contrast the quaternary α-carbon atom of the t-butyl group in **19** or **27** is *de*shielded relative to equatorial t-butyl groups, e.g. in **30** or **31**, and the effect is much greater in **23**. In **13**, the only other compound believed to have a substantial amount of axial t-butyl on a

†This conclusion is supported by comparisons of data for other pairs of analogous acyclic and cyclohexane derivatives, e.g. 2,2,3-trimethylbutane[32] and t-butylcyclohexane,[33] but unfortunately such comparisons are usually less reliable than one would wish because the data have not been obtained under similar conditions.

chair ring, however, the α-carbon atom is slightly shielded relative to that in **11**, while in the remaining compounds conformational effects on such α-carbon atoms are small and irregular. The chemical shifts of the β-methyl carbon atoms in t-butyl groups, however, are more regular.

The methyl carbon atoms in an axial isopropyl group are *de*shielded relative to those in an equatorial isopropyl group (compare **10** and **12** in Table 1) and a similar deshielding is observed for ax-NMe_2 in **8** (predominantly in conformer C1 in Fig. 2) compared with eq-NMe_2 in **2** and **5**. Such differences are attributable, in part at least, to the different rotameric equilibria for axial and equatorial $CHMe_2$ and NMe_2 substituents. A much larger effect (CMe_3 at 28.94 ppm in **19** and 28.52 ppm in **27**, 3.6 ± 0.2 ppm higher than the average, 25.12 ppm, for analogous eq-CMe_3 in **30** and **31**) is observed for t-butyl, with a single distinguishable rotamer for each ring conformer, and this is attributable to the strong steric repulsion between the "inside" methyl and the δ-methylene groups, i.e. the g.g -δ-effect (Fig. 6) is *strongly* deshielding when allowance is made for the rotation of the t-butyl group. A similar conclusion has been drawn for CMe_3 in 9-t-butyl-9-aza[3.3.1]bicyclononan-2-one.[38] Deshielding δ-effects have also been observed for hydroxyl[11] and for oxygen (in 5(ax)-t-butyl-1,3-dioxans[39]) but appear to be considerably larger for methylene acting on methyl (in t-butyl groups) and may therefore be a genuinely steric effect. In agreement with this the deshielding in **23** with four methyl or methylene groups in g.g -δ-relationships with a methyl group in CMe_3 is *more* than twice the deshielding effect in **19**, with two methylene groups in g.g -δ-relationships with methyl, the non-additive excess effect in **23** being common with steric effects in crowded systems.

For those pairs of compounds (**35** and **36**; **40** and **52**; **43** and **55**; **49** and **59**) for which we are certain that one member is in a chair and the other in a twist conformation (**36**T; **51**, **54** and **58**T1) there is a shielding effect (−0.36 to −0.64 ppm) on the -CMe_3 carbons in the twist conformers relative to the chairs and this may be taken as characteristic of ψe t-butyl groups. Unfortunately we have no example of isoclinal t-butyl groups on "locked" twist conformers but circumstantial evidence (see below) suggests that isoclinal t-butyl groups are not shielded relative to chair equatorial t-butyl groups.

In those compounds believed to exist mainly but not overwhelmingly in twist conformers, i.e. **7**, **9**, **50**, **51**, **53**, **54**, **56–58** the small shielding and deshielding effects, relative to diastereomers in chair conformers, on the CMe_3 chemical shifts (as also the small shielding of the NMe_3 in **9** relative to **6**, although there is no model for an axial-NMe_3 group) probably result from a balance between small shielding effects in relatively abundant twist conformers and larger deshielding in chair conformers with one strongly deshielded ax-CMe_3 and one eq-CMe_3. This is supported for **50** (deshielded CMe_3) by the temperature variation of the chemical shifts relative to comparable carbon atoms in **38**. Allinger *et al.*[32] showed from a variable temperature study of the IR spectrum of **50** that two conformers were present and took these to be the chair (C1⇌C2, Fig. 5) and twist (T1 and/or T2⇌T3), with the latter lower in enthalpy. Pihlaja[40] reinterpreted data[26,32] for **38** and **50** as indicating that the chair conformer of **50** has a lower enthalpy than the twist conformers. The ^{13}C chemical shifts of 50 show *increased* shielding at low temperatures for CMe_3, C-4(6) and C-5 and are therefore consistent with Allinger's conclusion while excluding Pihlaja's. A third possibility, that Allinger *et al.*[32] observed an equilibrium between twist conformers T1 and T2⇌T3, is also excluded because the small enthalpy difference (1.7 kJ mol^{-1}) combined with probably very small differences in chemical shifts (particularly for CMe_3) would not be expected to lead to significant temperature effects.

The largest difference between ^{13}C chemical shifts for t-butyl groups in a pair of diastereoisomers is found for **11** and **13**. If one assumes that an axial CMe_3 is deshielded by 3.6 ± 0.2 ppm (see above) then the observed difference between **11** (−2.86 ppm, relative to Me_3COH in D_2O) and **13** (−1.30 ppm) is consistent with ~45% of conformer C1 (Fig. 3).[21] The temperature variation of the chemical shifts of 13 relative to 11 is substantial even over a relatively small temperature range (Table 2) and is consistent with $\Delta S°(C1 \rightarrow T) \sim +20$ J mol^{-1} K^{-1}, in satisfactory agreement with other chair⇌twist equilibria.[26,34] The changes in all the other chemical shifts are consistent with the twist conformer **13**T having strongly shielded carbon atoms, particularly C4(6), C5 and CMe_3, relative to **13**C1.

Three compounds expected to exist mainly in twist conformations have diastereotopic t-butyl groups. In **54** the t-butyl-CMe_3 atoms are both slightly shielded relative to the isomer **42** (chair conformation). In **57** and **58** one CMe_3 is slightly shielded and one is slightly deshielded relative to those in the cis isomers (**45** and **46**; **47** and **48**). From what has gone before it is clear that ψe-CMe_3 groups are significantly shielded and that the chemical shifts of eq-CMe_3 (and presumably also CMe_3 on twist rings) are not very sensitive to the orientations of 1-substituents in chair conformers (compare **45** and **46**; **47** and **48**). The results for **57** and **58** therefore suggest *either* that conformers T3 contribute substantially and that Ic-CMe_3 atoms (cis to the 1-substituent) are not shielded relative to CMe_3 on chair rings *or* that chair conformers C1 (Fig. 5) are minor but significant contributors to the conformational equilibria in **56** and **57** and that the deshielding of the ax-CMe_3 in C1 (trans to the 1-substituent) offsets the shielding of CMe_3 in twist conformers. An examination of Dreiding models strongly suggests that a sulphur atom in a twist ring favours conformer T3 relative to T1 (Fig. 5) whereas nitrogen appears to be equally suited to T1 and T3, with the former having the N–H in **54** more open to hydrogen bonding to the solvent as well as ψe-t-butyl groups, which appear to be slightly more favourable than Ic-t-butyl.[40] We accordingly suggest that Ic-CMe_3, i.e. those cis to the 1-substituents in **57** and **58** in the T3 conformer, are not shielded relative to analogous groups on chair rings, unlike ψe groups, as in **54**T1 which may predominate in **54**. A more certain interpretation of these chemical shifts, however, will only be possible when definite assignments of chemical shifts can be made and the conformational equilibria can be determined with reasonable accuracy.

The chemical shifts of the ring carbon atoms are too dependent on substituent as well as on ring conformation effects for detailed interpretation at present but it is noteworthy that the average values are generally considerably smaller for the compounds in twist conformers in any given set of diastereomers (Tables 1, 2, 5 and 6), a difference already noted for **4** and **7**.[9] Unfortunately a single axial substituent such as methyl on a chair ring can bring about a comparable change in the average shielding of the ring carbon atoms (compare **44**, **45** and **56** in Table 6). In such instances the only clear distinction lies with the

carbon atom directly across the ring from the substituent because g.g.-δ effects (Fig. 6) across chair rings are generally small. The C-4 atoms in **50–59**, in various twist conformers predominantly, are all significantly shielded, by 1.54–4.25 ppm, relative to diastereomers in chair conformers, **38–49**, whereas a change in configuration of a substituent on a chair ring (compare **45** and **46**; **47** and **48**) usually has a small effect on C-4, as has been found for cyclohexane[9,16] and piperidine derivatives.[4] When there is an approximate balance between chair and twist conformers, as in **13**, the large temperature dependence of ^{13}C chemical shifts will often be the best evidence for twist conformers. The latter became increasingly favoured at higher temperatures because $\Delta S°$(ch→tw) is commonly large and positive. Furthermore the large axial groups such as t-butyl that are often the cause of instability in chair conformers are unlikely to cause as large shielding effects as axial methyl (compare the ^{13}C chemical shifts of C7(9) in **15**, **18** and **19**, or in **21–23** and examples of the effects of axial t-butyl groups in 1,3-dioxans[11] and in a 9-azabicyclo[3.3.1]nonane derivative[17]) and the shielding resulting from change in ring conformation shows up clearly. We have reasonable estimates of chemical shifts for chair and twist conformers only for the CMe_3 carbons of **13** and the large shielding effects apparent for other ring carbon atoms may well represent changing substituent effects as well the change in ring conformation.

CONCLUSION

^{13}C NMR chemical shifts provide several criteria for detecting twist conformers in 6-membered ring compounds. When t-butyl or other large multiply branched substituents, e.g. NMe_3, would be axial in a chair conformer the *absence* of significant deshielding caused by the (t, g)g-δ-effect (up to −4 ppm for CMe_3) in the axial group may be taken as good evidence for a predominance of twist conformers (see Tables 1 and 6 for several examples). When such a group is significantly deshielded but no model compound with it axial is available a chair-twist equilibrium will be detected by the temperature dependence of the ^{13}C chemical shifts, relative to a chair model compound with equatorial groups (see **11** and **13** in Table 2), with increased shielding at high temperatures (particularly when the term $-T\Delta S°$ balances a substantial $\Delta H°$ making $\Delta G°$ small, so that the percentage changes in the conformer populations is as large as possible).

The presently available compounds include few carbon containing substituents other than t-butyl but an unhindered methyl group on a twist ring has a chemical shift closer to those of equatorial than of axial methyl groups on chair rings (compare SMe in **45**, **46** and **57**; NMe in **43** and **55**). Clearly this will only be useful when the methyl group must be axial in the accessible chair conformer: this will often be so in polycyclic systems although it is not in **57**. Less symmetrical groups such as OMe may be more useful than simple ones like methyl. The OMe carbons in **52** are considerably deshielded relative to both axial *and* equatorial OMe in **40**. This is presumably caused by differences in g-γ effects of differently oriented 2- and 6-CH_2 groups in **40** and **52** and suggests that ^{13}C chemical shifts will be useful in studying rotameric equilibria.

At present it is not possible to interpret the chemical shifts of carbon atoms in twist rings in detail because there are so many uncertainties about the equilibria between different twist conformers. It is clear, however, that carbon atoms on twist rings are on *average* considerably more shielded relative to those in diastereomers in chair conformers with *equatorial* substituents. When it is possible to estimate additively the shielding effects of axial substituents on ring carbons in chair conformers the average chemical shifts will often be useful for demonstrating the probable occurrence of twist conformers in compounds with strained chair conformers. As with carbon containing substituents, the temperature dependence of ^{13}C chemical shifts of ring carbons, relative to diastereomeric compounds in chair conformers, will be particularly informative when $|\Delta G°$(ch→tw)| is fairly small.

Acknowledgements—We thank Prof. J. L. Fry for a generous gift of **19**, Drs. B. J. Armitage, D. R. Elliott, N. W. J. Pumphrey and H. J. F. Tarratt, Mrs. P. J. Hall (née Johnson) and Mr. M. G. Ward for many of the compounds used in this work, and the Science Research Council for a grant towards the cost of the Brüker WH90 spectrometer.

REFERENCES

[1] P. J. Halfpenny, P. J. Johnson, M. J. T. Robinson and M. G. Ward, *Tetrahedron* **32**, 1873 (1976).
[2] P. Grothard and O. Hassel, *Proc. Chem. Soc.* 218 (1963); A. Mossel, C. Romers and E. Havinga, *Tetrahedron Letters* 1247 (1963).
[3] O. Bastiansen, H. M. Seip and J. E. Boggs, *Perspectives in Structural Chemistry* (Edited by J. D. Dunitz and J. A. Ibers), Vol. 2, p. 60. Wiley, New York (1971).
[4] N. L. Allinger and L. A. Freiberg, *J. Am. Chem. Soc.* **83**, 5028 (1961).
[5] A. Haaland and L. Schäfer, *Acta Chem. Scand.* **21**, 2474 (1967); H. van Bekkum, M. A. Hoefnagel, L. de Lavieter, A. van Veen, P. E. Verkade, A. Wemmers, B. M. Wepster, J. H. Palm, L. Schäfer, H. Dekker, C. Mosselman and G. Somsen, *Rec. Trav. Chim.* **86**, 1363 (1967).
[6] D. H. R. Barton, D. A. Lewis and J. F. McGhie, *J. Chem. Soc.* 2907 (1957).
[7] R. J. Abraham and J. S. E. Holker, *Ibid.* 806 (1963).
[8] G. M. Kellie and F. G. Riddell, *J. Chem. Soc. (B)* 331 (1970); 1030 (1971).
[9] J. D. Roberts, F. J. Weigert, J. I. Kroschwitz and H. J. Reich, *J. Am. Chem. Soc.* **92**, 1338 (1970).
[10] G. M. Kellie and F. G. Riddell, *Topics in Stereochemistry* (Edited by E. L. Eliel and N. L. Allinger), Vol. 8, p. 225. Wiley-Interscience, New York (1974).
[11] R. R. Ernst and W. A. Anderson, *Rev. Sci. Instr.* **37**, 93 (1966).
[12] P. J. Brignell, K. Brown and A. R. Katritzky, *J. Chem. Soc.* (B) 1462 (1968); K. Rawalingam, M. Balasubramanian and V. Bella, *Ibid.* 2287 (1971).
[13] F. C. Fort and P. von R. Schleyer, *Chem. Rev.* **82**, 4645 (1964).
[14] *See e.g.* J. Plesek and P. Munk, *Chem. Listy* **51**, 633 (1957); S. Julia and D. Varech, *Bull. Soc. Chim. Fr.* 1127 (1959); S. Julia, D. Varech, T. Bürer and H. H. Gunthard, *Helv. Chim. Acta* **43**, 1623 (1960).
[15] L. Schmerling, *J. Am. Chem. Soc.* **69**, 1121 (1947).
[16] G. D. Meakins, R. K. Percy, E. E. Richards and R. N. Young, *J. Chem. Soc. (C)* 1106 (1968).
[17] A. E. Favorskii, N. Sakara, N. Shibaev, E. Opel and S. Karolev, *J. Russ. Phys.-Chem. Soc.* **50**, 43 (1920).
[18] E. C. DuFeu, F. J. McQuillin and R. Robinson, *J. Chem. Soc.* 708 (1949).
[19] M. Maes, R. Ottinger, J. Reisse and G. Chiurdoglu, *Tetrahedron* **25**, 5163 (1969).
[20] M. Hanack and K. Heinz, *Annalen* **682**, 75 (1965).
[21] B. J. Armitage, G. W. Kenner and M. J. T. Robinson, *Tetrahedron* **20**, 723, 747 (1964).
[22] H. J. F. Tarratt, D. Phil. Thesis, Oxford (1969).
[23] P. J. Halfpenny, A. N. Hunt, P. J. Johnson, D. J. Loomes, M. J. T. Robinson and M. G. Ward, unpublished work.

[54]J. L. Fry, E. M. Engler and P. von R. Schleyer, *J. Am. Chem. Soc.* **94**, 4628 (1972).
[55]D. R. Elliott, Ph.D. Thesis, Liverpool (1965).
[56]N. L. Allinger and L. A. Freiberg, *J. Am. Chem. Soc.* **82**, 2393 (1960).
[57]B. A. Bowers, T. G. Halsall, E. R. H. Jones and A. J. Lemin, *J. Chem. Soc.* 2548 (1953).
[58]H. C. Brown and C. P. Garg, *J. Am. Chem. Soc.* **83**, 2951 (1961).
[59]B. Rickborn and M. T. Wuesthoff, *Ibid.* **92**, 6894 (1970).
[60]C. R. Johnson and D. McCants, *Ibid.* **87**, 1109 (1965).
[61]A. J. Jones, E. L. Eliel, D. M. Grant, M. C. Knoeber and W. F. Bailey, *Ibid.* **93**, 4772 (1971).
[62]N. L. Allinger, J. A. Hirsch, M. A. Miller, I. J. Tyminski and F. A. Van-Catledge, *Ibid.* **90**, 1199 (1968).
[63]R. Bucourt, *Topics in Stereochemistry* (Edited by E. L. Eliel and N. L. Allinger), Vol. p. 159. Wiley-Interscience, New York (1974).
[64]N. L. Allinger, H. M. Blatter, L. A. Freiberg and F. M. Karkowski, *J. Am. Chem. Soc.* **88**, 2999 (1966).
[65]M. Barfield and D. M. Grant, *Ibid.* **85**, 1899 (1963); R. C. Cookson, T. A. Crabb, J. J. Frankel and J. Hudec, *Tetrahedron, Supplement No.* 7, 355 (1966).
[66]*See, e.g.* J. B. Stothers, *Carbon-13 NMR Spectroscopy*. Academic Press, New York (1972).
[67]S. H. Grover, J. P. Guthrie and J. B. Stothers, *J. Mag. Res.* **10**, 227 (1973); S. H. Grover and J. B. Stothers, *Can. J. Chem.* **52**, 870 (1974).
[68]J. R. Wiseman and H. O. Krabbenhoft, *J. Am. Chem. Soc.* **97**, 3222 (1975).
[69]K. Pihlaja, *J. Chem Soc. Perkin II* 890 (1974).
[70]B. van der Graaf and B. M. Wepster, *Tetrahedron Letters* 2943 (1975).
[71]P. J. Crowley, M. J. T. Robinson and M. G. Ward, *Tetrahedron* **33**, 915 (1977).
[72]H. Duddeck and W. Dietrich, *Tetrahedron Letters* 2925 (1975).
[73]G. E. Macil, H. C. Dorn, R. L. Greene, W. A. Kleschick, M. R. Peterson and G. H. Wahl, *Org. Mag. Res.* **6**, 178 (1974).
[74]W. D. Graham, P. von R. Schleyer, E. W. Hagaman and E. Wenkert, *J. Am. Chem. Soc.* **95**, 5785 (1973)