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The Carbon-13 Nuclear Magnetic Resonance Spectra of Some 1,3-Dioxans. Part II.† A Demonstration of Non-chair Conformations

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The ¹³C n.m.r. spectra of 36 1,3-dioxans are reported. Substituent effects on the chemical shifts of the ring carbon atoms are derived for a set of compounds known to exist in chair conformations. Using these effects to predict the chemical shifts in compounds that would have 4,6- or 2,4-syn-diaxial interactions in chair conformations results in large discrepancies between observation and prediction. It is concluded that such compounds exist to some extent in non-chair conformations.

In the continued speculation about the chair-boat equilibrium in 1,3-dioxan, the original estimate of the free energy difference between the boat and chair forms of $2\cdot 2 \text{ kcal/mol}^1$ has been continually revised upwards, to over 3 kcal/mol,² and more recently to 7.4 kcal/mol or more.³ One serious difficulty in forming estimates of this parameter is to be certain whether a given 1,3-dioxan exists to any appreciable extent in a non-chair conformation. We have solved this problem by examination of the ¹³C spectra of a large number of 1,3-dioxans having

† Part I. F. G. Riddell, J. Chem. Soc. (B), 1970, 331, is considered to be Part I.

¹ E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, ^c Conformational Analysis, Interscience, New York, 1964, p. 244. ² J. E. Anderson, F. G. Riddell, and M. J. T. Robinson, *Tetrahedron Letters*, 1967, 2017.

³ E. L. Eliel, Symposium on Conformational Analysis, Brussels, September 1969.

⁴ (a) K. Pihlaja and S. Luoma, Acta Chem. Scand., 1968, 22, 2401; (b) K. Pihlaja and J. Heikkila, Acta Chem. Scand., 1967, 21, 2390.

as substituents either methyl groups or a 5-gem-diethyl group. When combined with previous evidence from thermochemical studies,⁴ ¹H n.m.r. spectra,⁵ optical rotation measurements, 6 and a recent study of boiling points 7 in this series, we consider that our data resolves this difficulty.

Since the chemical shifts of ring carbon atoms in cyclic compounds of known conformation can be analysed empirically in terms of substituent effects,^{8,9}

⁵ F. W. Nader and E. L. Eliel, J. Amer. Chem. Soc., 1970, 92, 3050.

J. F. Tocanne, Bull. Soc. Chim. France, 1970, 750.
 G. M. Kellie and F. G. Riddell, unpublished observation.
 D. K. Dalling and D. M. Grant, J. Amer. Chem. Soc., 1967,

89, 6612.

⁹ (a) J. D. Roberts, F. G. Weigert, J. T. Kroschwitz, and M. J. Reich, J. Amer. Chem. Soc., 1970, 92, 1338; (b) F. J. Weigert and J. D. Roberts, J. Amer. Chem. Soc., 1970, 92, 1347; (c) D. E. Dorman, S. J. Angyal, and J. D. Roberts, J. Amer. Chem. Soc., 1970, 92, 1351; (d) D. E. Dorman and J. D. Roberts, J. Amer. Chem. Soc., Chem. Soc., 1970, 92, 1355.

1031

and these effects enable one to make remarkably good predictions for the chemical shifts of carbon atoms in similar compounds, we have used them as a test of conformational homogeneity thus. A set of substituent effects is derived from a series of compounds which exist entirely in chair conformations and predictions are made, by use of these derived effects, for the compound the conformation of which is being examined. Any substantial discrepancy between observed and predicted chemical shifts may then be ascribed to the presence of non-chair or highly deformed chair conformations. We have found such discrepancies in the ¹³C spectra of some 1,3-dioxan derivatives, which we attribute to the presence of non-chair conformations.

EXPERIMENTAL

N.m.r. Spectra.-The ¹³C spectra were recorded on a Perkin-Elmer R10 spectrometer operating at 15.1 MHz using stationary 8.5 mm o.d. tubes. A 2.8 mm o.d. capillary tube containing ¹³C-enriched methyl iodide was used both as external reference and trigger for computer sweeps. A Digiac computer was used on line to the n.m.r. spectrometer. Generally between 64 and 256 spectra were accumulated into 1500 channels. Chemical shifts were measured from the lowfield peak of the methyl iodide quartet and corrected for reference to an external CS₂ standard with 213.1 p.p.m. as the shift difference.* Chemical shifts were also corrected for a slight non-linearity of sweep (0-1.0)p.p.m.) and are estimated to be accurate to ca. 1 p.p.m. Differences in chemical shift for carbon atoms in the same region of the spectrum are estimated to be accurate to within 0.5 p.p.m.

Preparation of Compounds.-The compounds used were either gifts of well authenticated materials or were made by standard methods and had physical properties in agreement with the literature.

2,2,4,4,6,6-Hexamethyl-1,3-dioxan. This was made by treatment of 2,4-dimethylpentane-2,4-diol with 2,2-dimethoxypropane in a 1:1 molar ratio, in the presence of a trace of p-toluenesulphonic acid. Methanol was removed by slow fractional distillation. The residue was cooled and treated with anhydrous sodium carbonate. The crude 1,3-dioxan was then purified by filtration and distillation, b.p. 62°/42 mmHg, yield 50%.

2,2,4,4,6-Pentamethyl-1,3-dioxan. This was prepared by the same method, b.p. 147°/760 mmHg, yield 60%.

These compounds had i.r. and ¹H and ¹³C n.m.r. spectra in accordance with their structures. The parent peaks were not visible in the mass spectra which otherwise fitted the assigned structure.

Derivation of Substituent Effects .- The chemical shift of the *x*th ring carbon atom in the *n*th compound ΔC_{xn} can be expressed in the following way. $\Delta C_{xn} = \Delta C_{xp} + aSE_{x1} + aSE_{x1} + aSE_{x1} + aSE_{x2} + aSE_{x2} + aSE_{x2} + aSE_{x2} + aSE_{x2} + aSE_{x2} + aSE_{x3} +$ bSE_{x2} . . . etc. [The numbering system in 1,3-dioxan is shown in formula (I)] where ΔC_{xp} is the chemical shift of the same carbon atom in the parent compound, SE_{x1} etc. are the substituent effects on the chemical shift of the *x*th carbon atom and a, b etc. are the number of times a given effect must be taken into account.

One thus obtains a set of n simultaneous equations with unknowns SE_{x1} etc. These equations were solved on the



Stirling University computer by the use of a least-squares technique, giving best-fit values for each substituent effect.

DISCUSSION

The first task, in analysing the data produced in this work, was to decide on the set of compounds to be used for the least-squares analysis of substituent effects. One factor to be borne in mind during this selection is the occurrence of axial-equatorial conformational equilibria, as in for example 2-methyl-1,3-dioxan. However, for the 2-, 4-, and 6-positions the free energy difference between the two conformations is sufficiently large ¹⁰ for the axial conformation to be neglected in our analysis. The data from these compounds were included in the analysis as if it arose exclusively from the equatorial conformation. This is not possible where an axialequatorial equilibrium of a C-5 methyl group may occur, due to the much lower (ca. 1 kcal/mol) free energy difference in these cases.^{10,11} Such compounds (5methyl, 2,2,5-trimethyl etc.) were omitted from the analysis, but used later to test the substituent effects derived from other compounds. Evidence from proton spectra shows conclusively that 1,3-dioxans with a single axial methyl group, e.g. 2,2-dimethyl-1,3-dioxan, exist in chair conformations.² Compounds in this category were included in the analysis.

Compounds with two or more axial methyl groups which other workers have suggested may be in nonchair conformations 3-6 were not included for the analysis.

For the derivation of substituent effects we first used a simple set consisting only of effects due to equatorial and axial groups. This gave a fair fit between observed and predicted chemical shifts, but in compounds containing substituents grouped closely together (e.g. 4,5,5-trimethyl) the fit was poor. In order to improve the fit we introduced a wide variety of different terms for various substitution patterns in addition to the original basic set. It was found that certain of the new terms (e.g. 4eq6eq) were appreciable (say >1 p.p.m.) and others small (say <1 p.p.m.). For our final analysis we rejected all terms, which had earlier appeared as less than 1 p.p.m. except those in our basic set. The final values of the substituent effects are given in Table 1 and the final plot of observed versus predicted chemical shifts is shown in the Figure. Table 2 lists the observed and predicted chemical shifts in our reference set of compounds.

¹⁰ E. L. Eliel and M. C. Knoeber, J. Amer. Chem. Soc., 1966, 88, 5347; 1968, 90, 3444. ¹¹ F. G. Riddell and M. J. T. Robinson, Tetrahedron, 1967, 23,

3417.

^{*} Value from Professor J. B. Stothers (personal communication). This value differs slightly from that used previously; we have therefore remeasured our previously reported shifts and our revised values are included in the Tables.

The introduction of alkyl groups to a cyclic compound will have several important effects. Firstly the molecular orbitals of the molecules will be changed and a new electron distribution obtained. Secondly small changes of ring geometry will occur, which will lead to secondary changes in the electron distribution.* Since it is the electron distribution in a molecule that largely determines ¹³C chemical shifts, temperature and solvent effects being generally small,¹² the substituent effects derived in this and other work will reflect both types of electronic change. For instance, imagine the introduction of a gem-dimethyl group, the total changes in electron distribution in the ring will not be simply the sum of the changes on introducing each methyl group separately. It is therefore reasonable that there should be an additional chemical-shift parameter associated with the introduction of geminal groupings. The same



FIGURE (a) Plot of observed versus predicted chemical shifts of C-2; O, compound in reference series; \Box , compound with 2,4- or 4,6-syn-diaxial interaction in a chair conformation. Standard deviation 0.32 p.p.m. Regression coefficient 0.996



FIGURE (b) Plot of observed versus predicted chemical shifts of C-4,6; O, compound in reference series; D, compound with 2,4- or 4,6-sym-diaxial interaction in a chair conformation. Standard deviation 0.37 p.p.m. Regression coefficient 0.997



Plot of observed versus predicted chemical shifts of FIGURE (c) C-5; \bigcirc , compound in reference series; \square , compound with 2,4- or 4,6-syn-diaxial interaction in a chair conformation. Standard deviation 0.25 p.p.m. Regression coefficient 0.998

TABLE 1

Substituent effects on ¹³C chemical shifts in p.p.m.*

		No. of			
	On C-2	On C-4	On C-6	On C-5	rences *
C(2)eqMe	-5.3		0.1	+0.8	16
C(2)axMe	+1.7	+'	7.3	-0.1	5
C(4)eqMe	-0.8	-5.7	+0.1	-7.3	19
C(4)axMe	+9.0	-0.6	+5.3	-3.7	6
C(5)eqMe	+0.2		5.8	3-1	7
C(5)axMe	-0.4		4·5	-3.1	6
C(6)eqMe	0.8	+0.1	-5.7	-7.3	19
C(6)axMe	+9.0	+5.3	0.6	3.7	6
C(4)gemdiMe	-2.3	+2.0	1.5	+0.8	3
C(6)gemdiMe		-1.5	+2.0	+0.8	3
C(5)gemdiMe		-	- '	+2.3	5
C(5)gemdiEt	-0.3	-	7.7	8.5	3
C(4,6)eqdiMe	+1.6		_		5
$C(4)eq(\hat{6})axdiMe$	-1.1				5
C(4)eq(5)eqdiMe		+1.9	-1.8	+4.5	3
C(5)eq(6)eqdiMe		-1.8	+1.9	+4.5	3
C(4)ax(5)eqdiMe			-1.4	-3.2	1
C(5)eq(6)axdiMe		-1.4		-3.2	1

* Certain terms appear twice in this Table as they are related by the symmetry of positions 4 and 6.

argument can be applied to the other joint parameters found in this and other work.⁸

Pihlaja has produced evidence of a flattening of the 1,3-dioxan ring when a 4,4,5- or 4,5,5-trimethyl group is present.¹³ This flattening could well be represented by some of the substituent effects that we observe, the largest being 4eq5eq or 5eq6eq at C-5 = +4.5 p.p.m.

The general sense of the substituent effects found here is in line with that found by Grant.^{† 8} However some

* Both these effects will of course occur together and we have separated them here for the sake of the argument.

† Some of the discrepancies noted in Part I arose from a misinterpretation of the presentation of results in ref. 8.

¹² J. W. Emsley, J. Feeney, and L. H. Sutcliffe, 'High Resolution Nuclear Magnetic Resonance Spectroscopy,' Pergamon, Oxford, 1966, vol. II. ¹³ K. Pihlaja, Suomen Kemi., 1969, **42**, 74.

of these effects deserve further comment. Firstly the effect at C-2 of a 2-axial methyl group is positive. This is probably an artefact of our set of compounds for no compound with a 2-axial methyl group as the sole C-2 substituent was considered. What this term does mean is that the addition of an axial methyl to a C-2 already carrying an equatorial methyl group leads to a small shielding. If the term associated with geminal substitution at C-2 is similar to that at C-4,6 or C-5 (+2 p.p.m.) the effect of an isolated axial methyl group at C-2 would be ca. -1 p.p.m.

These discrepancies are largest for the 2,4-syn-interaction and somewhat smaller for the 4,6-interaction. Previous work $^{4-7}$ has shown that certain of these compounds probably do not have chair conformations. The discrepancies we observe confirm and correlate the previous conclusions. Although the results do not allow one to say with absolute certainty that these compounds have boat * rather than badly deformed chair conformations the circumstantial evidence points overwhelmingly in this direction.

The interaction between 4,6-syn-diaxial methyl groups

Table	2
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Observed and predicted chemical shifts in p.p.m. from CS₂ for set of compounds used in least-squares analysis

	1		C-2	C-4,6 *		C-5	
Compound	Substituents	Obs.	Pred.	Obs.	Pred.	Obs.	Pred.
(1)		99.7	99.7	126.6	126.6	165.9	165.9
(2)	2-Me	94.7	94.4	127.2	126.5	167.6	166.7
$(\overline{3})$	2 2-DiMe	96.2	96.1	134.0	133.8	167.0	166.4
(4)	4-Me	98.9	98.9	120.4	120.9	158.8	158.6
(*)	1-110	000	000	126.7	126.7		
(5)	4 4-DiMe	105.7	105.8	123.2	122.3	156.1	155.7
(0)	1,1 Dinio		1000	130.7	130.5		
(6)	5.5-DiMe	100.2	99.5	116.6	116.3	$162 \cdot 1$	162.0
$(\overline{7})$	2 4-cis-DiMe	94.0	93.6	120.6	120.8	159.2	159.4
(•)	2,4 003 Dinie		000	126.7	126.6		
(8)	2 5 5-TriMe	93.4	94.2	116.0	116.2	162.7	162.8
	2 4 6-cis-TriMe	94.6	94.5	120.9	120.9	152.0	$152 \cdot 1$
(10)	4 6-cis-DiMe	100.4	99.8	121.7	121.0	151.9	151.3
in	4 6-trans-DiMe	106.9	106-9	126.6	126.1	$155 \cdot 2$	154.9
$\langle 12 \rangle$	2 2 4-TriMe	95.3	95.3	128.2	128.1	159.0	159.3
(12)		000		132.9	133.9		
(13)	2.2.4.6-cis-TetraMe	95.5	96.2	128.2	128.2	151.9	152.0
(14)	4 4 6-TriMe	105.3	105.5	$122 \cdot 2$	$122 \cdot 4$	148.6	148.5
()	2,2,0 222.20			124.7	$124 \cdot 8$		
(15)	2.2.5.5-TetraMe	96.2	95.9	123.4	123.5	162.7	162.7
(16)	2.4-cis-5-trans-6-cis-TetraMe	101.7	101.8	120.7	120.7	153.9	153.9
(-0)	_,			120.7	120.7		
(17)	5.5-DiEt	99.3	99·4	119.1	118.9	157.5	157.4
(18)	2.2-DiMe-5.5-DiEt	96.2	95.8	126.0	$126 \cdot 2$	157.9	158.1
(19)	2.4-cis-6-trans-TriMe	101.7	101.6	$125 \cdot 8$	126.0	$155 \cdot 5$	155.7
(-0)	_,			$125 \cdot 8$	126.0		
(20)	2.4.4.6-cis-TetraMe	100.4	100.2	121.6	$122 \cdot 3$	148.8	1 4 9·3
()	_,_,.,_			124.5	124.6		
(21)	2.4.5.5-cis-TetraMe	$93 \cdot 2$	93 ·5	112.9	112.3	160.2	160.0
()	_,_,_,_			114.8	114.4		
(22)	4.5.5-TriMe	98.8	98·8	111.8	112.3	159.9	$159 \cdot 2$
()	_,_,_			114.2	114.5		
(23)	2.5-cis-DiMe	94·2	94 ·0	$121 \cdot 9$	122.0	163 ·6	163·6
(24)	2.5-trans-DiMe	94.9	94.6	120.6	120.7	163-6	163-6
(25)	2-Me-5.5-diEt	93.8	94.1	118.8	118.8	$158 \cdot 2$	158.2

* In cases where two shifts are reported the upper value refers to C-4 and the lower to C-6.

Secondly there is a similarity between the effect of substituents at C-2 and C-4; for instance 2eq at C-2 = $-5\cdot3$ p.p.m. and 4eq at C-4 = $-5\cdot7$ p.p.m., or 2eq at C-4 = $-0\cdot1$ p.p.m., and 4eq at C-2 = $-0\cdot8$ p.p.m.

The terms found for C-5 are somewhat different from those for C-2 and C-4,6, for example 5eq at C-5 = $3\cdot 1$ p.p.m. This may be a reflection of the much less hindered environment of C-5 compared to C-2 and C-4,6.

Compounds with Non-chair Conformations.—The main object of this work was to detect compounds with nonchair conformations. Substantial discrepancies between observed and predicted chemical shifts which are far greater than the standard deviations of our fits were found for C-2, -4, and -6 in compounds that would have syn-diaxial interactions in chair conformations (Table 3). 00 would be expected to be lower than the 2,4-syn-diaxial interaction. Since the compounds that would have the 4,6-interaction in a chair form (30, 31) deviate less from our predictions than those with 2,4-interactions (26, 27, 28, 29, 32), and deviations are noted only for C-4 and -6, we suggest that these compounds exist with appreciable amounts of boat and chair conformations. This conclusion has recently been borne out by the observation of an ultrasonic relaxation in these compounds attributed to a boat-chair equilibrium.¹⁴

There has been speculation recently about the conformation of *trans*-2,4,4,6-tetramethyl-1,3-dioxan.^{3,5} It

* This includes ' twist ' forms.

¹⁴ G. M. Kellie, F. G. Riddell, E. Wyn Jones, and G. Eccleston, unpublished observations.

J. Chem. Soc. (B), 1971

has been suggested that at room temperature a substantial fraction of the molecules of this compound may exist in a chair conformation with an axial C-2 methyl.⁵ The deviations between the observed and predicted ¹³C chemical shifts make it more likely that there is a considerable proportion of boat form present in this compound, a conclusion borne out by the 220 MHz proton spectrum.⁷ were able to identify and assign the signals of the alkyl substituents on the 1,3-dioxan ring. The compounds then examined carried small numbers of well separated alkyl groups. In the more complicated systems examined here we have not been able to assign these signals. The difficulty is twofold. Firstly it is difficult to identify all the lines of each quartet in a crowded region of the spectrum. Secondly even for the quartets

TABLE 3

Observed and predicted chemical shifts in p.p.m. from CS₂ for compounds possibly existing in boat conformations

Compound	Substituents	C-2		C-4,	6 a	C-5	
		Obs.	Pred.	Obs.	Pred.	Obs.	Pred.
(26)	2,2,4,4,6-PentaMe	95.3	101.7	122.7 131.1	$129.6 \\ 132.0$	149-2	$149 \cdot 2$
(27)	2,2-trans-4,5-cis-6- PentaMe	93.6	103·4 b 102·8 c	122.6 h 122.6 h 128.6 h 128.6 h 128.6 h	$ \begin{array}{r} 128 \cdot 1^{f} \\ 125 \cdot 7^{f} \\ 128 \cdot 8 & g \\ 128 \cdot 9 & g \end{array} $	150.4	153·8 b 152·5 ¢
(28)	2,2,4,4,6,6-HexaMe	94.6	109.2	123.0	133.4	147.8	$146 \cdot 2$
(29)	2,2-trans-4,6-TetraMe	93.4	103.3	130.7	$133 \cdot 4$	150.8	$155 \cdot 6$
(30)	4,4,6,6-TetraMe	110.1	110.9	123.0	$126 \cdot 2$	146.2	145.5
(31)	2,4,4,6,6-PentaMe	106.1	105.6	$122 \cdot 6$	$126 \cdot 1$	146.6	146.3
(32)	2,4,4,6-trans-TetraMe	104.6	108·3 d 107·0 с	$122.0 \\ 128.5$	127·5 d 132·1 d	151.2	$152 \cdot 8$
				$122.0 \\ 128.5$	129·8 = 137·2 =	151.2	148·4 e

^a Where two values are presented the upper value refers to C-4 and the lower to C-6. ^b 5-Me equatorial. ^c 5-Me axial ^d 2-Me equatorial. ^e 2-Me axial. ^f 4-Me-equatorial-5-Me-equatorial. ^g 4-Me-axial-5-Me-axial. ^h Two resonances are observed but are not readily ascribed to either C-4 or C-6.

TABLE 4

Observed and predicted chemical shifts in p.p.m. from CS₂ for compounds with a C-5 axial-equatorial equilibrium

Compound	Substituent		C-2			C-4,6 *			C-5		
		Obs.	Pred.(eq)	Pred.(ax)	Obs.	Pred.(eq)	Pred.(ax)	Obs.	Pred.(eq)	Pred.(ax)	
(33)	5-Me	99 ·8	99.9	99.3	120.7	120.8	$122 \cdot 1$	163.6	162.8	162.8	
(34)	2,2,5-TriMe	96.2	96.3	95.7	126.8	128.0	129.3	164.0	163.5	163.5	
(35)	4,4,5-TriMe	105.0	105.9	105.3	$118.5 \\ 120.4$	$118.4 \\ 121.5$	$117.8 \\ 126.0$	153.4	153.9	$152 \cdot 6$	
(36)	4,5-trans-6-cis-TriMe	106.6	$107 \cdot 1$	106.5	$122 \cdot 2 \ \dagger \ 120 \cdot 4 \ \dagger$	$\begin{array}{c} 120 \cdot 9 \\ 118 \cdot 5 \end{array}$	$121.6 \\ 121.7$	153.4	$153 \cdot 1$	151.8	

* In cases where two values occur C-4 is given above C-6. † This assignment of resonances fits our predictions best.

Conformational Equilibria at C-5.—The most widely studied conformational equilibrium in 1,3-dioxans involves substituents on C-5. In many cases these equilibria have over 15% of the axial conformation present, and it was hoped that we would be able to observe some of the equilibria by ¹³C n.m.r. However, the fact that in all cases the predicted differences in chemical shift for the two conformations are small, ruled out this possibility. The results confirm that our substituent effects are reasonable because in all cases the observed chemical shifts fall acceptably close to the values predicted for the equatorial conformation (Table 4).

Chemical Shifts of Alkyl Substituents.-In Part I we

we were able to identify, it has proved impossible, for the present, to derive a consistent pattern for the effect of alkyl substituents on each other. The latter difficulty was also noted by Dalling and Grant for methylated cyclohexanes.⁸ In view of these difficulties we shall defer discussion of the alkyl signals until later.

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