Tetrahedron. Vol. 29, pp. 3369 to 3373. Pergamon Press 1973. Printed in Great Britain

CONFORMATIONAL ANALYSIS—VIII

^{1}H NMR CONFORMATIONAL STUDY OF 5-METHYL-, 2,5-DIMETHYL- AND 2,2,5-TRIMETHYL-4-OXO-1,3-DIOXANS

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(*Received in the UK* 13 *March* 1973; *Accepted for publication* 4 *June* 1973)

Abstract—Substituent effects on ^{1}H chemical shifts of a large number of methyl-substituted 4-oxo-1,3-dioxans have been estimated and shown to be additive for compounds with a uniform half-chair conformation. The additivity rule fails, however, if the substitution pattern forces the ring into a non half-chair conformation. The ring conformations of 5-methyl-, *cis*- and *trans*-2,5-dimethyl- and 2,2,5-trimethyl-4-oxo-1,3-dioxans have been clarified by NMR and through acid-catalyzed equilibration of the epimeric 2,5-dimethyl derivatives.

Our earlier reports[1-5] showed the 4-oxo-1,3-dioxan ring to exist either in half-chair or in 2,5-boat conformations in which the lactone grouping C—C(=O)—O—C is coplanar. A proper substitution may, however, force the ring into a twist-boat conformation. This paper will consider the additivity of substituent effects on ^{1}H chemical shifts and their application to predict the ring conformations of methyl-substituted 4-oxo-1,3-dioxans.

The inductive and/or anisotropic effects of a given substituent may change the chemical shifts of the ring and exocyclic protons. Starting from simple model compounds with known conformations it is easy to derive the values for different substituent effects since[6,7] $\Delta H(x) = \Delta H(x)_p + \Sigma SE$, (equation 1) where $\Delta H(x)$ is the chemical shifts of the xth proton in a given 4-oxo-1,3-dioxan, $\Delta H(x)_p$ the chemical shift of the same proton in the parent compound and ΣSE the sum of the different substituent effects.

The NMR shift method has been shown to be applicable to many structural problems.[8-10] Recently, Kellie and Riddell[7] used ^{13}C chemical shifts to clarify the ring conformations of alkyl-substituted 1,3-dioxans and ^{1}H chemical shifts were found to be useful in the configurational assignments of polyhydroxy norbornanes.[11]

Of course, the ^{1}H chemical shifts are small in comparison to those observed in, e.g., ^{13}C measurements. Consequently, to get as high accuracy as possible, the proton chemical shift measurements must be carried out uniformly using a standard sample concentration. In the present case the signals of the protons or methyl groups in 2 position are only little affected by substitution, although a distinct dependence on the substitution pattern can still be observed. The chemical shifts of the 5 and 6 protons or methyl groups of 4-oxo-1,3-dioxans are more dependent on substitution. Thus the 5 protons resonate between 130 and 170 Hz and the 5 methyl protons between 66 and 81 Hz downfield from internal TMS. Correspondingly, the 6 proton signals are found between 216 and 265 Hz and those of the 6 methyl protons between 67 and 81 Hz. In the following only the chemical shifts of the 5 and 6 protons or methyl groups will be discussed in detail.

RESULTS AND DISCUSSION

The chemical shifts and coupling constants of 5-methyl-, 2,5-dimethyl- and 2,2,5-trimethyl-4-oxo-oxo-1,3-dioxans are presented in Tables 1 and 2.

Chemical equilibration of the epimeric 2,5-dimethyl-4-oxo-1,3-dioxans at 298 K revealed that the *trans* form is thermodynamically *ca* 0·88 kJ/mol more stable. The magnitude of the vicinal coupling constants (Table 2) shows that the *trans* isomer exists in a half-chair conformation where both methyl groups are pseudoequatorially orientated. The *cis* isomer also assumes a half-chair conformation, the 5 methyl group being now pseudoaxial. In this case the substitution pattern does not exclude the possibility of a 2,5-boat conformation. However, the vicinal coupling constants are of the same order of magnitude and close to the $^3J_{5a6e}$ value of the 2e5e epimer.* In a 2,5-boat form (Fig 1) $^3J_{56}$'s should be about 12 and 6 Hz and hence *cis*-2,5-dimethyl-4-oxo-1,3-dioxan does not exist in this conformation. A similar conclusion can be drawn from the substituent effects (Table 3).

The larger $^3J_{56}$ of 5-methyl-4-oxo-1,3-dioxan has a value between the corresponding coupling constants of the *cis* and *trans* isomers of 2,5-dimethyl-4-oxo-1,3-dioxan. This observation is in agreement with the fact that the 5 methyl derivative exists as a mixture of the 5e and 5a half-chair con-

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*The notations e and a will be used to mean equatorial and axial orientations, respectively.

Table 1. Chemical shifts of 5-methyl-, 2,5-dimethyl- and 2,2,5-trimethyl-4-oxo-1,3-dioxans in CCl_4. All values in Hz from TMS.

^{1}R(2)	^{2}R(2)	R(5)	$^{\delta}$2eH	$^{\delta}$2aH	$^{\delta}$6aH	$^{\delta}$6eH	$^{\delta}$5H	$^{\delta}$2-CH_3	$^{\delta}$5-CH_3
H	H	Me	320·5	325·0	218·0	252·0	169·5		72·3
Me	H	Me^a		327·0	216·5	251·5	163·5	86·8	69·1
Me	H	Me^b		332·5	250·5	223·0	167·5	85·8	74·5
Me	Me	Me			226·5	250·5	157·5	92·3^c	71·7

^{a}Trans-2,5-dimethyl. ^{b}Cis-2,5-dimethyl. ^{c}Both 2 methyl signals.

Table 2. Coupling constants (Hz) of 5-methyl-, 2,5-dimethyl- and 2,2,5-trimethyl derivatives in CCl_4

^{1}R(2)	^{2}R(2)	R(5)	$^3J_{2H,CH_3}$	$^2J_{2a2e}$	$^2J_{6a6e}$	$^3J_{6a5}$	$^3J_{6e5}$	$^3J_{5H,CH_3}$	$^4J_{2e6e}$	$^4J_{CH_3,CH_3}$
H	H	Me		−5·70	−10·92	9·53	7·29	7·08	0·8	
Me	H	Me^a	5·16		−11·54	11·86	7·44	7·16		
Me	H	Me^b			−10·81	7·32	6·19	7·10		
Me	Me	Me			−11·84	8·45	6·69	7·22		0·7^c

^{a,b}See Table 1. ^{c}Solvent C_6H_6.

Table 3. The parent chemical shifts and the respective substituent effects in Hz. Positive values mean downfield shifts in CCl_4

Proton or proton grouping	$\Delta H(x)_p$	SE(2e)	SE(2,2)^a	SE(5e)	SE(5a)	SE(6e)	SE(6a)
5a-H	169·0 ± 1^b	−8·0	−12·5	+2·5		−27·0	+11·5
5e-H	162·0 ± 1^b	−4·5	−9·0		+10·0	−3·5	—
5a-CH_3	75·2 ± 0·2^b	−1·1	−4·0	+1·8		−4·2	+5·3
5e-CH_3	70·7 ± 0·2^b	−1·4	−2·9		−1·6	+1·2	−2·6
6a-H	241·0 ± 1^b	−2·0	+14·0	−24·0	+9·0	+6·0	
6e-CH_3	79·5 ± 0·2^b	−1·7	−4·0	+0·7	−7·6		+0·4

^{a}SE(2a) = SE(2,2) − SE(2e). ^{b}Estimated derivations.

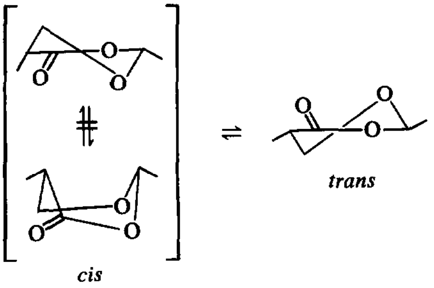

Fig 1.

formation. Taking into account that the expression

$$K = \frac{J_{obs.} - J_{ee}}{J_{aa} - J_{obs.}} = \frac{9{\cdot}53 - 6{\cdot}19}{11{\cdot}86 - 9{\cdot}53}$$

$$= \frac{3{\cdot}34 \pm 0{\cdot}2}{2{\cdot}33 \pm 0{\cdot}2} = 1{\cdot}4 \pm 0{\cdot}2 \qquad (2)$$

can be used to estimate the conformational equilibrium constants the value 0·9 ± 0·4 kJ mol^{-1} is obtained at 306 K for the conformational free energy of a pseudoaxial 5 methyl group in excellent agreement with the value based on chemical equilibration. The other coupling constants, $^3J_{5a6e}$ and $^3J_{5e6a}$, are too close to each other to allow any energy calculations.

Also the chemical shifts of the 5e and 5a methyl groups can be used in a similar manner (Table 3):

$$K = \frac{\nu(5a) - \nu(\text{obs.})}{\nu(\text{obs.}) - \nu(5e)} = \frac{75{\cdot}2 - 72{\cdot}3}{72{\cdot}3 - 70{\cdot}7}$$

$$= \frac{2{\cdot}9 \pm 0{\cdot}4}{1{\cdot}6 \pm 0{\cdot}4} = 1{\cdot}8 \pm 0{\cdot}7$$

The value 1·5 ± 1·0 kJ mol^{-1} is then obtained for the conformational energy of a pseudoaxial 5 methyl group. This estimate is not too far from those derived from chemical equilibration and vicinal coupling constants taking into account the more crude nature of chemical shift calculations.[13]

The values of the vicinal coupling constants of 2,2,5-trimethyl-4-oxo-1,3-dioxan are indicative for a conformation mixture including also other than half-chair forms. Also chemical shift calculations support this view (Table 3), although the half-chair form with a 5e methyl group is likely the most favoured conformation. This conclusion is in agreement with our previous observation that 2,2,6e-

Table 4. Observed and predicted chemical shifts in Hz from TMS for a set of compounds with half-chair conformations

	$^{\delta}$5eH		$^{\delta}$5aH		$^{\delta}$6aH		$^{\delta}$5eMe		$^{\delta}$5aMe		$^{\delta}$6eMe	
	Obs.	Calcd.	Obs.	Calcd.	Obs.	Calcd.	Obs	Calcd.	Obs.	Calcd.	Obs.	Calcd.
6e	158·5	158·5	142·0	142·0	247·0	247·0	—				79·3	79·5
2e6e	155·0	154·0	135·5	134·0	245·5	245·0					77·7	77·8
2e5e			163·5	163·5	216·5	215·0	69·1	69·3				
226e[a]	149·5	149·5	131·0	129·5	257·0	261·0					75·8	75·5
5e6e			145·5	144·5	225·0	223·0	71·6	71·9			80·2	80·2
5a6e	169·5	168·5			257·0	256·0			70·7	71·0	72·1	71·9
2e5e6e			136·5	136·5	222·5	221·0	70·6	70·5			78·4	78·5
2e5a6e	164·0	164·0			254·5	254·0			70·3	69·9	70·6	70·2
225e6e			131·5	132·0	238·5	237·0	69·5	69·0			76·5	76·2
2e55[b]					222·0	224·0	68·1	67·7	80·2[b]	75·9		
556e					229·0	232·0	70·6	70·3	73·2	72·8	72·7	72·6
2e5e66			148·0	148·0			67·9	67·9			78·8	78·9
2e556e					229·5	230·0	68·9	68·9	71·4	71·7	71·0	70·9
2e5566							66·3	66·3	76·7	77·0	71·4	71·3
22556e					247·0	246·0	66·9	67·4	69·2	68·8	67·8	68·6
2e5a	167·5	167·5			250·5	248·0			74·5	74·1		

[a] Probably somewhat distorted.

[b] The 5aMe chemical shift similarly exceptional as in methyl-substituted 1,3-dioxans, cf K. Pihlaja and P. Äyräs, *Acta Chem. Scand.* **24**, 531 (1970).

Table 5. Observed and predicted chemical shifts for compounds (in Hz from TMS) suggested earlier[1-5] to exist in non-half-chair conformations

		δ5eH		δ5aH		δ6aH		δ5eMe		δ5aMe		δ6eMe	
Compound	Conformation*	Obs.	Calcd.	Obs.	Calcd.	Obs.	Calcd.	Obs.	Calcd.	Obs.	Calcd.	Obs.	Calcd.
2e6a	em	148·0	—	159·0	172·5								
2a6e	em	159·0	154·0	148·0	137·5	258·5	253·0					79·5	77·2
2e5e6a	em			144·0	175·0			71·5	66·7				
2a5a6e	em	144·0	164·0			223·0	260·5			71·5	70·7	77·9	77·6
2a5e6e	em	150·5	—							69·3	79·4		
2a5e6e	em			150·5	140·0	228·5	229·0	69·3	70·4			80·3	77·9
225a6e	tb	146·0	159·5			264·0	268·5			71·3	67·0	70·9	67·9
225e6a	tb			146·0	168·0			71·3	65·2				
2e66	em	156·0	—	147·5	145·5							80·5	78·2
2a66	em	147·5	—	156·0	149·0							77·0	77·6
5a66	b	164·5	—							67·8	76·3	69·5	72·3
5e66	b			164·5	156·0			67·8	69·3			81·3	80·6
2e5a66	b	164·5	—							66·9	75·2	65·9	70·6
2a5e66	b			164·5	149·0			66·9	66·2			80·8	78·3
2e556a	tb							67·8	65·1	79·6	81·2		
2a556e	tb					239·5	236·5	67·8	68·8	79·6	69·9	77·8	70·3
225e	em			157·5	159·0	226·5	231·0	71·7	67·8				
225a	em	157·5	163·0			250·5	264·0			71·7	71·2		

*em means a conformation mixture, b a 2,5-boat conformation and tb a twist-boat conformation. The shifts have been calculated for hypothetical half-chair conformations. Hence in this context the symbols a and e show only the relative orientations of different substituents.

trimethyl- and 2,2,5e6e-tetramethyl derivatives exist mainly in half-chair forms whereas 2,2,5a6e-tetramethyl derivative assumes a twist-boat conformation.[1-5]

Thus a 2,2,5a-trimethyl substitution seems to be enough to force the 4-oxo-1,3-dioxan ring at least partly in a twist-boat conformation.

Estimation of the substituent effects on the ^{1}H chemical shifts. Table 3 lists the parent chemical shifts for the 5 protons and methyl groups and for the 6 axial proton and 6 equatorial methyl group and the values of different substituent effects on them. These values were estimated from equation 1 to find out the best fit between the observed and calculated chemical shifts of those derivatives existing in half-chair conformations (Table 4).[1-5] The values based on differently substituted compounds were relatively close to each other although slight variation occurred from compound to compound. However, any general trend could not be observed and hence only the "best" values for the substituent effects are shown in Table 3.

Despite the nice fit between the observed and calculated chemical shifts of those methyl-substituted 4-oxo-1,3-dioxans (Table 4) with greatly preferred half-chair conformations, substantial discrepancies between observed and predicted chemical shifts were found for compounds that would have non-half-chair conformations (Table 5).[1-5] The observed discrepancies confirm and correlate accurately the conformational conclusions in our previous reports.[1-5]

EXPERIMENTAL

Syntheses, separation of the isomers, the method of chemical equilibration and configurational and conformational assignments of most of the derivatives have been described earlier.[1-5, 14] The NMR spectra were recorded on a 60 MHz Perkin-Elmer R 10 spectrometer using 10% solutions (w/v) and TMS as internal standard. The chemical shifts of the methyl protons are mean values of 6 to 10 scans (scale factor 1 Hz, accuracy ±0·2 Hz) and those of the ring protons mean values of 2 to 3 scans (scale factor 3 Hz, accuracy ±2 Hz). The ABC subspectra were analyzed with an IBM 1130 computer with the aid of an iterative program.[1]

Acknowledgements—One of the authors (PÄ) is greatly indebted to the *Foundations of Neste Oy and Emil Aaltonen* for financial support. Both authors wish to express their gratitude to the *Finnish National Science Foundation* for fellowships.

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