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Conformational Analysis

VI. 6,6-Dialkyl- and 2,6,6-Trialkyl-4-oxo-1,3-dioxans

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Several 6,6-dialkyl- and 2,6,6-trialkyl-substituted 4-oxo-1,3-dioxans were prepared and their PMR spectra recorded. The PMR data together with the results given by chemical equilibration reveal that the ring conformation depends greatly on the substitution pattern. For instance, *trans*-2,6-dimethyl-6-*tert*-butyl-4-oxo-1,3-dioxan exists mainly in a 2,5-boat form whereas the *cis* epimer adopts a distorted half-chair conformation. Obviously, the 6,6-dialkyl derivatives are conformational mixtures of half-chair and 2,5-boat forms.

The effect of the lactone grouping on the ring conformation of some five- and six-membered rings has been the subject of several recent investigations.[1–4] It has also been reported that certain 6-alkyl substituted 4-oxo-1,3-dioxans exist predominantly in half-chair or (twist) boat conformations.[4] To further clarify the energetics and structural properties of these interesting oxalactones, a number of 6,6-dialkyl and 2,6,6-trialkyl derivatives were prepared from suitable 3-hydroxy acids [5] and aldehydes (Table 1) by the method described previously.[6]

Table 1. Physical properties of the 4-oxo-1,3-dioxans synthesised.

R(2)	^{1}R(6)	^{2}R(6)	B.p. °C/torr	n_D^{25} or m.p.°C	d_4^{20}	Yield from hydroxy acid, %	Notes
H	Me	Me	102–4/12	1.4397	1.1063	54	[a]
H	Me	i-Pr	109–114/9	1.4508		65	[a]
H	Me	*t*-Bu	88–90/3	53–55		42	[a]
Me	Me	Me	102–4/12	1.4348	1.0519	33	[a]
Me	Me	i-Pr	107–9/8	1.4450		60	[a,b]
Me	Me	*t*-Bu	107–9/8	1.4493		65	[a,c]
i-Pr	Me	*t*-Bu	127–8/8	1.4507		60	[a,d]

[a] Catalyst *p*-TOS. [b,c,d] Two isomers; isomer ratio 47:53, 38:62 and 36:64, respectively.

Chemical equilibrations of epimeric *cis* and *trans* 2,6-dimethyl-6-isopropyl-, 2,6-dimethyl-6-*tert*-butyl- and 2-isopropyl-6-methyl-6-*tert*-butyl-4-oxo-1,3-dioxans were carried out using the normal procedure.[4] The results are shown in Table 2. The diastereoisomeric 2,6-dimethyl-6-isopropyl-4-oxo-1,3-dioxans

Table 2. Equilibration of the 2,6,6-substituted 4-oxo-1,3-dioxans. Catalyst *p*-TOS. (For experimental details, see Ref. 4.)

R(2)	^{1}R(6)	^{2}R(6)	°C	K[a]	$-\Delta G°$ kJ mol^{-1}	$-\Delta H°$ kJ mol^{-1}	$\Delta S°$ J mol^{-1}K^{-1}
Me	Me	i-Pr	33.5	1.2[b]	0.4		
Me	Me	*t*-Bu	23	1.611	1.18		
			−1.5	1.709	1.21		
			−11	1.744	1.21	1.55 ± 0.08[c]	−1.21 ± 0.29[c]
i-Pr	Me	*t*-Bu	51	1.908	1.74		
			23	1.965	1.665		
			12	1.980	1.62	0.71 ± 0.04[c]	3.26 ± 0.17[c]
			−10	2.025	1.54		

[a] *cis*-R(2), ^{2}R(6)/*trans*-R(2), ^{2}R(6). [b] from NMR-spectrum. [c] Standard deviation.

could not be separated by preparative gas chromatography. The equilibrium ratio had to be determined from the NMR spectrum of the isomer mixture by integrating the signals of the 2 protons which have slightly different chemical shifts in CCl_4.

On the basis of IR spectra Saint-Martino [7] suggested that 6,6-disubstituted 4-oxo-1,3-dioxans exist in a 2,5-boat structure with a planar lactone group, one of the 6-substituents occupying a pseudo-equatorial orientation and the other a pseudo-axial orientation. From our compounds, the *cis*-2,6-dimethyl-6-*tert*-butyl derivative might adopt a 2,5-boat form, whereas the *trans* epimer could hardly exist in a 2,5-boat conformation where either both methyl groups or a *tert*-butyl group would have to be in pseudo-axial positions.

Table 3. The chemical shifts (Hz from internal TMS) of the 6,6- and 2,6,6-substituted 4-oxo-1,3-dioxans.

R(2)	^{1}R(6)	^{2}R(6)	δ_{2a}	δ_{2e}	δ_{5a}	δ_{5e}	$\delta_{6\text{-CH}_3}$	$\delta_{2\text{-CH}_3}$	$\delta_{6\text{-}t\text{-Bu}}$
H	Me	Me[a]	318.0		155.0		80.5		
H	Me	i-Pr	313.5	313.5	157.0	145.0	73.6		
H	Me	*t*-Bu	315.5	313.0	168.5	139.0	75.8		58.0
Me	Me	Me	332.0		156.0	147.5	77.0 80.5	84.3	
Me	Me	*t*-Bu[b]	326.5		158.5	134.0	75.9	87.0	57.2
Me	Me	*t*-Bu[c]	324.0		174.0	135.5	71.6	83.9	59.2
i-Pr	Me	*t*-Bu[b]	299.5		160.5	132.0	75.3		57.0
i-Pr	Me	*t*-Bu[c]	317.5		173.0	137.0	71.3		59.1

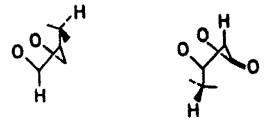
[a] An average spectrum. [b] *cis*-R(2), ^{2}R(6). [c] *trans*-R(2), ^{2}R(6).

Table 4. The coupling constants (Hz) of the 6,6- and 2,6,6-substituted 4-oxo-1,3-dioxans. The notations "a" and "e" mean (pseudo)-axial and (pseudo)-equatorial, respectively.

R(2)	^{1}R(6)	^{2}R(6)	$^2J_{2a2e}$	$^2J_{5a5e}$	$^3J_{2aCH_3}$	$^3J_{2aCH(CH_3)_2}$	$^4J_{5aCH_3}$	$^3J_{CH(CH_3)_2}$
H	Me	i-Pr	c	−16.08			>0	6.5
H	Me	*t*-Bu	−6.26	−16.23			>0	
Me	Me	Me		−16.10	5.20		>0	
Me	Me	*t*-Bu[a]		−16.64	4.95		~0	
Me	Me	*t*-Bu[b]		−15.15	4.98		1.0	
i-Pr	Me	*t*-Bu[a]		−16.60		4.1	~0	6.4
i-Pr	Me	*t*-Bu[b]		−15.00		4.7	1.0	6.2

[a] *cis*-R(2), ^{2}R(6). [b] *trans*-R(2), ^{2}R(6). [c] $\Delta\nu = 0$ in both CCl_4 and C_6H_6.

The ^{1}H NMR spectra were recorded in 10 % CCl_4 solutions (40 mg solute in 400 μl solvent). Chemical shifts and coupling constants are shown in Tables 3 and 4. In the *cis*-2,6-dimethyl-6-*tert*-butyl and the corresponding 2-isopropyl derivatives, the 5a proton signal is a poorly resolved quartet while the signal of the 6 methyl protons is a clearly resolved doublet. This indicates a long range coupling $^4J_{5aCH_3}$ of 1.0 Hz between these protons. A ^4J of this type was not found in the corresponding *trans* epimers. 1,3-Dioxans exhibit the same type of ^4J between a 5 axial methyl group and the 6 axial proton.[8] The protons are necessarily in a W-arrangement for a long range coupling of this order of magnitude.[9,10]



(1)

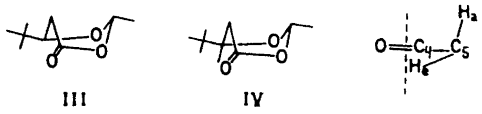
The NMR spectra of the previously [4] described *cis* and *trans* forms of 2-methyl-6-*tert*-butyl-4-oxo-1,3-dioxan will be compared with those of the corresponding isomers of 2,6-dimethyl-6-*tert*-butyl-4-oxo-1,3-dioxan (Table 5).

Table 5. The solvent induced shifts ($\delta_{CCl_4} - \delta_{C_6H_6}$, Hz) and coupling constants for the "*cis*" and "*trans*" epimers of 2-methyl-6-*tert*-butyl and 2,6-dimethyl-6-*tert*-butyl-4-oxo-1,3-dioxan.

	^{1}R (6)		$\Delta\delta_{2a}$	$\Delta\delta_{2-CH_3}$	$\Delta\delta_{5a}$	$\Delta\delta_{5e}$	$\Delta\delta_{6-t-Bu}$	$\Delta\delta_{6-CH_3}$	$^2J_{5a5e}$	$^3J_{2aCH_3}$
I	H	*cis*[a]	27.0	14.7	9.0	13.5	14.6	—	−17.9	4.98
II	Me	*cis*[a]	29.5	14.2	5.5	23.5	9.2	25.6	−16.6	4.95
III	H	*trans*[b]	27.5	12.9	26.0	11.0	18.0	—	−15.5	5.00
IV	Me	*trans*[b]	30.0	12.2	30.0	10.0	19.2	10.6	−15.2	4.98

[a] *cis*-2-methyl-6-*tert*-butyl. [b] *trans*-2-methyl-6-*tert*-butyl.

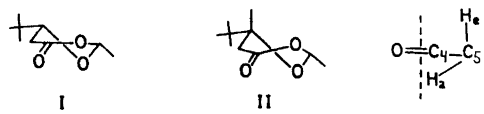
The benzene-induced solvent shifts were measured to get further information.[11] The values for the "*trans*" compounds (III and IV) show that the ring conformations are similar. All the respective parameters are nearly equal. A slightly twisted boat form (2,5-boat) has been suggested [4] for III. If the 6 proton is replaced by a methyl group, the orientation of the methyl protons with respect to the 5a proton allows the fragment $H_a-C_5-C_6-C_{Me}-H$ to attain an exactly planar W-arrangement. This structure (IV) is further sup-



(2)

ported by the value of J_{gem} of the 5 protons since the angle $H_e-C=O$ should be about 15° and the angle $H_a-C=O$ close to 105.°[4,12] The solvent shifts also confirm this: the 5e proton lies near the reference plane [13] used to predict the magnitude of ASIS for carbonyl compounds, and the 5a proton lies well above this plane in accordance with its *ca.* three times greater solvent shift.

Comparison of the NMR spectra of the "*cis*" compounds (I and II) shows that their ring conformations are different. We found a half-chair structure for *cis*-2-methyl-6-*tert*-butyl-4-oxo-1,3-dioxan (I).[4] In II, the axial methyl substituent obviously distorts the ring conformation towards a twist-boat (2,5-twist [14]).



(3)

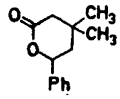
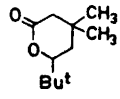
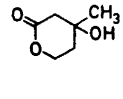
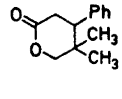
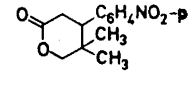
The slightly increased value of J_{gem} and the special solvent shifts for the 5 protons can also be explained by this kind of distortion. It can be seen from Tables 3–4 that an isopropyl substituent in position 2 does not alter the NMR parameters appreciably and so has little or no effect on the epimer conformations suggested above for the 2 methyl derivatives.

The other compounds studied are very likely equilibrium mixtures of different ring conformations in agreement with the above structural considerations and demonstrated by the value of J_{gem} for the 5 protons: the values around −16.2 Hz are intermediates between the limiting values of −15.3 and −17.9 Hz.[4] The J_{gem} value, −6.26 Hz, of the 2 protons in 6-methyl-6-*tert*-butyl-4-oxo-1,3-dioxan is very similar to those of the 1,3-dioxans (chair conformation) [15] and about 0.5–1.0 Hz lower than those of 6-alkyl substituted 4-oxo-1,3-dioxans having a half-chair conformation.[16] In a chair (as in 1,3-dioxan) or a boat (2,5-boat), the C(2)–H bonds are staggered against the lone-pair orbitals of the ring oxygen atoms, but in a half-chair conformation the C(2)–H bonds are eclipsed with one of the two pairs of lone-pair orbitals in accordance with the more positive value of J_{gem} for the latter.[17]

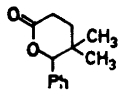
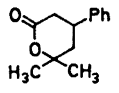
Consequently, the energy parameters shown in Table 2 seem to reflect mainly enthalpy and entropy differences between different ring conformations.

An isopropyl substituent in position 2 does not appreciably alter the enthalpy value, but the entropy difference is considerably greater than the value for the corresponding 2 methyl epimers (Table 2) and, moreover, is of different sign. This is certainly due to a slightly hindered rotation of the isopropyl group in the *trans* form (boat conformation),[18] and is also demonstrated by the coupling constants $^3J_{2H,CH(CH_3)_2}$ being slightly increased in the *trans* epimer (4.7 *vs.* 4.1 Hz).[19]

Johnson and Riggs have prepared several *gem*-dimethylphenylvalerolactones which are structurally related to the 4-oxo-1,3-dioxans.[3] They observed that the compounds could be divided into two classes on the basis of the J_{gem} values of the protons in an α position to the carbonyl group (the 5 protons in 4-oxo-1,3-dioxans). Some examples are given below:

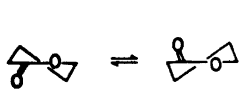






	I	II	III	IV	V
J_{gem} at C(2)	−16.1	−16.0	−17.0	−18.1	−17.9

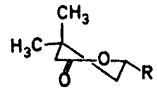



	VI	VII
J_{gem} at C(2)	−18.3	−17.9

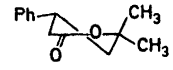
(4



III-VI



I, II



VII

(5)

The first three compounds have a J_{gem} which is clearly larger than the others and carry a geminal substitution in a β-position to the carbonyl group. Compounds IV–VI form a freely inter-converting system of two half-chair structures, compound VII exists predominantly in a half-chair conformation with a pseudoequatorial phenyl group, whereas compound III is an equilibrium mixture of two half-chair conformations ($\Delta G = 2.9$ kJ/mol = free energy difference between a pseudo-axial methyl and a hydroxyl group).[3] Johnson and Riggs suggested half-chair conformations with a pseudo-equatorial phenyl or *tert*-butyl group for compounds I and II. However, in the light of our investigations, it seems more probable that compounds I–III as well exist to a considerable extent in boat forms.

We conclude once again that the ring conformation of 4-oxo-1,3-dioxan depends very greatly on the ring substitution. In general the ring adopts a conformation in which the steric interactions are minimized – usually a half-chair, a slightly twisted boat (2,5-boat), a twist-boat (2,5-twist[14]), or a dynamic equilibrium state between all of these.

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