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CONFORMATIONAL ANALYSIS—V
2,6-DIALKYL- AND 2,2,6-TRIALKYL-4-OXO-1,3-DIOXANS

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Abstract—Chemical equilibration and ^{1}H NMR spectra were used to determine the ring conformations of 2,6-dialkyl- and 2,2,6-trialkyl-4-oxo-1,3-dioxans. These compounds have no greatly favoured ring conformation but they may exist in half-chair or (twist-) boat forms the distribution between them depending mainly on the steric requirements of the alkyl substituents.

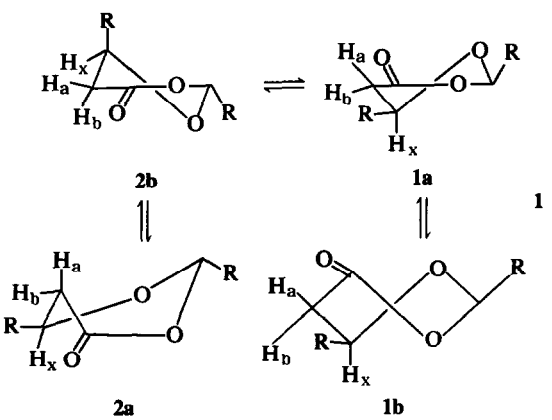
Relatively little but increasing attention has been paid to the ring conformations of 5 and 6-membered lactones.[1-8] The preference for co-planarity of the 5 atoms of the lactone group, C—CO—O—C, implies that in a γ-lactone only the fifth ring atom—β to the CO function—may be either above or below the lactone plane. Correspondingly, a δ-lactone may attain the co-planarity of the lactone grouping in the half-chair or boat conformation.[1,3]

Sheppard and Turner[4] reported slightly flattened half-chair conformations for a number of unstrained steroidal lactones and kept their boat-type conformations inadmissible on the basis of vicinal coupling constants. Carroll and Blackwell[5] studied the conformations of *cis*- and *trans*-3,5-dimethylvalerolactones with the aid of ^{1}H NMR spectra and came to the conclusion that both isomers exist predominantly in half-chair conformations. Later Carroll *et al.*[6] reached the same result from CD properties of the same isomeric lactones.

However, in certain cases the (O—CO—C)-part of the lactone molecules is planar but the third C atom of the lactone grouping deviates somewhat from this plane. For instance, Hackert and Jacobson[7] found by X-ray analysis that the ring conformation of a crystalline gluconolactone is somewhere between a half-chair and a normal chair conformation. Similarly, Jeffrey and Kim[8] pointed out that in some γ-lactones the lactone grouping is not fully planar. Consequently, steric requirements of certain substituents seem to be enough to overwhelm the conjugation effect which favors the planarity of the whole lactone grouping.

To get further information about the effect of the lactone system on the ring conformation of 6-membered rings we started a study of a new family of compounds—4-oxo-1,3-dioxans.[9] These compounds are very suitable objects for a structural and conformational investigation since their acetal counterparts—1,3-dioxans—are extensively investigated during the last few years[10-12] and moreover, the preparation and equilibration of stereoisomeric 4-oxo-1,3-dioxans is not too difficult. In the following we report some results dealing with the conformational effects met in the 2,6-dialkyl- or 2,2,6-trialkyl-substituted derivatives.

Chemical equilibrations



trans		*cis*	
2-R	6-R	2-R	6-R
2: Me	Me	1: Me	Me
4: Me	i-Pr	3: Me	i-Pr
6: Me	t-Bu	5: Me	t-Bu
8: t-Bu	t-Bu	7: t-Bu	t-Bu

At first sight the free energy differences between the stereoisomers (eq. 1, Table 1) are surprising and even confusing because of the relatively little change in the $\Delta G°$ changing the 6 substituent from Me to t-Bu. On the basis of the values of conformational energies for a set of similarly substituted 1,3-dioxans[10-12] and of the preferred conformations of δ-lactones it is concluded that the *trans* 4-oxo-1,3-dioxans (eq. 1) exist either in the half-chair conformation with axial 6 alkyl (**2b**) or in the slightly twisted boat form (**2a**). This is even confirmed by

Table 1. Equilibria between isomeric 2,6-dialkyl-4-oxo-1,3-dioxans and thermodynamic quantities for them

2-R	6-R	°C	K[c]	$-\Delta G°$, kJ/mol	$-\Delta H°$, kJ/mol	$\Delta S°$, J mol^{-1} K^{-1}
Me	Me	23	7·08	4·82		
Me	Me	−11	7·46	4·38	1·0 ± 0·6[a]	13 ± 2[a]
Me	i-Pr	51	5·09	4·39		
Me	i-Pr	23	5·38	4·14		
Me	i-Pr	−1·5	5·64	3·91	1·43 ± 0·05[b]	9·1 ± 0·2[b]
Me	i-Pr	−11	5·78	3·90		
Me	t-Bu	51	7·15	5·30		
Me	t-Bu	23	8·15	5·17	2·5 ± 0·6[b]	8·9 ± 2·1[b]
Me	t-Bu	−10	8·83	4·77		
t-Bu	t-Bu	25	8·8	5·4 ± 0·4[a]	ab. 4[a]	ab. 4[a]

[a]Estimates.
[b]Standard deviations.
[c]GLPC area ratios; response ratios assumed to be unity. K = [*cis*]/[*trans*]

the similar free energy differences between compounds **5** and **6** and **7** and **8**.

As to the conformational energy of an axial t-Bu group it should be much greater (by a factor of 2-3) than that of an axial Me group on position 6 of the 4-oxo-1,3-dioxan ring.[12–14] Comparison of the equilibria (1) for isomer pairs **1** and **2** and **7** and **8** led us inevitably to the conclusion that at least the *trans* isomers cannot exist merely in half-chair forms but the boat forms must have more or less contribution.

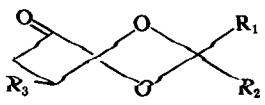
Unfortunately, accurate equilibrations of the epimeric 2,6-dialkyl-4-oxo-1,3-dioxans were very difficult to carry out because of some decomposition products which concealed the less stable *trans* isomer. However, it was possible to find out that the free energy difference between a given pair of epimers do not depend very much on the temperature and moreover, decrease in temperature generally favours the more stable *cis* isomer (Table 1). These conclusions are in close agreement with the results obtained in the equilibration of cis- and trans-2-methyl-6-isopropyl-4-oxo-1,3-dioxans which was successfully completed at four different temperatures (Table 1). The small enthalpy difference, 1·4 kJ/mol, for this isomer pair points out that the different ring conformations of 4-oxo-1,3-dioxan do not differ very much in energy from each other but their relative amounts are greatly dependent on the ring substitution. The entropy difference 9·1 J mol^{-1} K^{-1} in favour of the *cis* isomer may partly be due to a conformational equilibrium between the conformers (Ia and Ib). Pseudorotation of the half-chair form Ia, however, is thought to be responsible for the major part of the rather great entropy difference. Similarly, the predominant conformation of the *trans* forms should be a boat form IIa whereas the proportion of the half-chair IIb is much smaller and decreases further when the size of the 6 substituent increases.

The enthalpy difference (*ca* 1·0 kJ/mol) between isomeric 2,6-dimethyl-4-oxo-1,3-dioxans (eq 1; $R_1 = R_2 = Me$) does not differ significantly from that between the 6-isopropyl compounds (1·4 kJ/mol, Table 1) whereas t-Bu substitution in position 6 decreases the flexibility of the half-chair conformation (Ia) and further the proportion of the *trans* half-chair form (IIb) appreciably. The total effect is illustrated by increased enthalpy difference (2·5–4·2 kJ/mol) and decreased entropy difference (< 8 e.u.) in favour of the more stable *cis* isomers.

On the basis of the equilibration results it was, however, very difficult to make any definite conclusions. That is why another method was needed to test the above consideration about the ring conformations of the studied 4-oxo-1,3-dioxans.

^1H NMR results

Chemical shifts. The spectra can be easily analyzed since the various protons or proton groupings are differently shielded by the ring O atoms and the CO function. The 5- and 6-protons form an "ABX" system from which the chemical shifts and coupling constants between these protons are simply resolved and the final parameters computed with the aid of an iterative ABC program.[20] The chemical shift values for the more stable isomers which were designated "*cis*" forms are listed in Table 2 together with those for the 2,2,6-trialkyl-substituted derivatives which most probably also exist in a half-chair conformation (Ia). However, in certain cases the half-chair structure might be distorted towards the twist-boat conformation to reduce the interaction of the 2 axial substituent (structure III).



III

Table 2. Chemical shifts for the *cis*-2,6-dialkyl- and 2,2,6-trialkyl-4-oxo-1,3-dioxans in Hz from internal TMS

2-R_1	2-R_2	6-R	2-H	2-Me	5-H_A	5-H_B	6-H_X	6-Me
Me	H	Me	324·5	87	136·1	155·4	245·5	78
Me	H	i-Pr	320	88	137·1	148·5	214·5	—
Me	H	t-Bu	320·5	88	140	144·5	211·5	—
t-Bu	H	t-Bu	284·5	—	140	144·5	208	—
Me	Me	Me	—	93[a]	130·2	149·1	257·0	76
Me	Me	i-Pr	—	92[a]	131·6	145·4	224	—
t-Bu	Me	Me[b]	—	89	127·7	148·4	254	76

[a]Both 2 methyl groups.
[b]*trans*-2,6-diMe-2-t-Bu-4-oxo-1,3-dioxan.

Table 3. Chemical shifts for the *trans*-2,6-dialkyl-4-oxo-1,3-dioxans in Hz from internal TMS

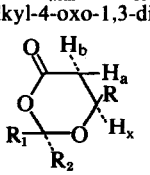
2-R	6-R	2-H	2-Me	5-H_A	5-H_B	6-H_X
Me	Me	335·5	85	148·2	159·2	259·0
Me	i-Pr	325·5	86	152	152	223·5
Me	t-Bu	327·5	86	157·9	145·0	222·5
t-Bu	t-Bu	292	—	158·4	145·5	222·5

Vicinal coupling constants. The most informative PMR parameters are, however, the values of the vicinal and geminal coupling constants. If we inspect the experimental values presented in Tables 4 and 5 we observe that the values of J_{56} are very similar in both isomer series and that a large *trans* coupling prevails in both cases. For *cis* series this supports the existence of ring conformations Ia and/or Ib in agreement with the results obtained from the equilibration data.

The spectrum of *trans*-2,6-dimethyl-4-oxo-1,3-dioxan was recorded also at various temperatures to check whether or not the values of the vicinal coupling constants change continuously. The results are shown in Table 6. The different coupling constants remained practically constant which may be explained by assuming that the molecule is (1) relatively biased or (2) a mixture of two or more conformations the relative amounts of which do not change appreciably with temperature. The change in the vicinal coupling constants from 6-Me to 6-t-Bu compound is, however, so pronounced that it could hardly occur in a biased system and hence the actual situation is best demonstrated by a conformational equilibrium between conformations IIa and IIb in which the amount of the latter decreases with increasing size of the 6-substituent.

If we inspect in more detail the values of the

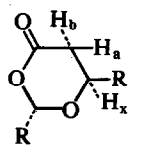
Table 4. The values of J_{gem} and J_{56} for *cis*-2,6-dialkyl- and 2,2,6-trialkyl-4-oxo-1,3-dioxans in Hz.



2-R_1	2-R_2	6-R	J_{gem}	J_{AX}	J_{BX}	$\Sigma J_{AX}+J_{BX}$
Me	H	Me	−17·83	10·88	4·44	15·32
Me	H	i-Pr	−17·35	10·53	4·73	15·26
Me	H	t-Bu	−17·87	9·81[b]	5·56	15·37
t-Bu	H	t-Bu	−17·65	9·90[b]	5·65	15·55
Me	Me	Me	−17·47	10·98	4·09	15·07
Me	Me	i-Pr	−17·14	10·90	3·94	14·84
t-Bu	Me	Me[a]	−17·42	11·00	3·47	14·47

[a]*trans*-2,6-diMe-2-t-Bu-4-oxo-1,3-dioxan.
[b]solvent $(CD_3)_2NCDO$

Table 5. The values of J_{gem} and J_{56} for *trans*-2,6-dialkyl-4-oxo-1,3-dioxans in Hz



2-R	6-R	J_{gem}	J_{AX}	J_{BX}	$\Sigma J_{AX}+J_{BX}$
Me	Me	−16·72	9·66	6·17	15·83
Me	i-Pr	−15·96[a]	11·08[a]	5·38[a]	16·46
Me	t-Bu	−15·52	12·37	4·95	17·32
t-Bu	t-Bu	−15·33	12·53	5·15	17·67

[a]For benzene solution since $\Delta_{AB}(CCl_4)$ *ca* 0.

Table 6. The dependence of J_{gem} and J_{56} of *trans*-2,6-dimethyl-4-oxo-1,3-dioxan on temperature in benzene

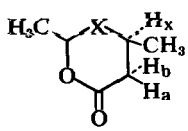
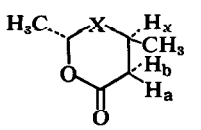
°C	J_{gem}	J_{AX}	J_{BX}	Δ_{AB}
33	−16·72	9·59	6·18	21·3
55	−16·62	9·34	6·18	21·4
70	−16·72	9·62	6·00	21·3
85	−16·82	9·75	5·87	21·3
100	−16·72	9·50	6·27	21·2
115	−16·72	9·84	5·98	21·2

vicinal coupling constants both in the *cis* and in the *trans* series (Tables 4 and 5) it is easily seen, that the sum of $J_{AX}+J_{BX}$ remains nearly constant in the *cis*-2,6-disubstituted compounds whereas in the corresponding *trans* forms the value of this sum increases appreciably with the size of the 6-alkyl group. This is in agreement with the above conclusion that the ring conformation of the *trans* compounds depends greatly on the size of the 6-substituent and resembles more and more IIa when the size of this substituent increases.[16,18]

Moreover, e.g. the value of J_{AX} decreases from 11·0 (Me) to 9·9. (t-Bu) in the *cis*-series but the value of J_{gem} remains practically constant. The change in the values of J_{AX} and J_{BX} is probably mainly due to the nature of 6-substituent but not to an appreciable change of conformation. In the *trans* series the value of J_{AX} increases from 9·7 (Me) to 12·4 Hz (t-Bu) and that of J_{gem} increases from −16·7 (Me) to −15·5 Hz(t-Bu). Thus the values of the vicinal coupling constants of the *cis* and *trans* series change in the opposite directions. Taking into account that the data for the *trans* compounds inevitably demonstrate the increasing contribution of IIa we cannot avoid the conclusion that the conformational change in the *cis* series must occur to the opposite direction (towards Ia) and/or the effect of 6-substituents is otherwise reflected on the values of J_{AX} and J_{BX}.[21]

Geminal coupling constants. Let us at first consider the coupling constant values of the isomeric 2,6-dimethyl-4-oxo-1,3-dioxans in comparison with the corresponding quantities of *cis*- and *trans*-3,5-dimethylvalerolactones (Table 7). There is a striking similarity between the coupling constants of the *cis* and *trans* isomer pairs. Carroll and Blackwell[5] presented half-chair conformation for the both valerolactones and later Carroll *et al.*[5,6] came to the same result on the basis of the circular dichroism of the lactones in question. However, the *trans* isomer has a geminal coupling constant of only 16·1 Hz in comparison with the value 17·3 Hz for the *cis* isomer. Similar situation prevails in the 2,6-dimethyl-4-oxo-1,3-dioxans 16·7 Hz *vs* 17·8 Hz. The value of the geminal coupling constant between protons α to a sp^2-bond depends on the dihedral angle between the H—C bond and the C=O bond and this effect is at maximum when the CO group bisects the H—C—H angle.[15] This outcome may vary from 0 to 6 Hz as function of the magnitude of the dihedral angle.

Table 7. Comparison between the corresponding coupling constants of *cis*- and *trans*-3-methylvalerolactones and *cis*- and *trans*-2,6-dimethyl-4-oxo-1,3-dioxans

Structure	X	J_{AB}	J_{AX}	J_{BX}
	CH_2	−17·3	10·3	5·8
	O	−17·83	10·88	4·44
	CH_2	−16·1	9·0	5·6
	O	−16·72	9·66	6·17
trans[a]				

[a]Coupling constants are practically independent of temp.

The normal J_{gem} value for the 5-protons of 1,3-dioxans is around 13 Hz[16] and thus one could expect a −(9–12) Hz minimum for 4-oxo-1,3-dioxans. However, it is well known[17] that the X—CH_2—Y angle also effects on the magnitude of the geminal coupling constant: the smaller the angle, the greater the s character of the CH bonds and the more positive the coupling constant. The C_4—C_5—C_6 angle of 4-oxo-1,3-dioxans is obviously smaller than that in 1,3-dioxans and thus −(17–18) Hz might well represent the maximum value for J_{gem} of the former compounds. For cyclohexanones the corresponding maximum is around −16 Hz whereas the values of the geminal coupling constants for cyclohexanes vary between −(11 to 12) Hz the maximum change −(4–5) Hz being in good agreement with the supposed change between 4-oxo-1,3-dioxans and 1,3-dioxans.

Consequently, all *cis*-2,6-disubstituted as well as the 2,2,6-trialkyl-substituted 4-oxo-1,3-dioxans have ring conformations where (1) the C=O bond bisects the angle formed by the 5 protons and (2) the 6-proton is at *anti* position in respect of the other 5 proton in agreement with the values of the *vicinal coupling constants ca 11 and 4 Hz which* are typical for dihedral angles near 180 and 60°.

Inspection of molecular models indicates that the only ring conformations which meet these requirements for the *cis* isomers are the half-chair form (Ia) which has the planar C—CO—O—C grouping and both alkyl substituents equatorially orientated, and the twist-boat form (IIb; a 2,5-twist-boat[18]) where only the C—CO—O part of the molecule is planar and the both alkyl groups pseudoequatorially located. These conclusions are in close agreement with the proceeding conclusions. The *cis*-2,6-disubstituted compounds undoubtedly exist mainly in a half-chair conformation (Ia) while the conformation of the 2,2,6-trisubstituted compounds might in some cases be distorted towards the 2,5-twist-boat (Ib or III).

In the case of the *trans*-2,6-dialkyl-4-oxo-1,3-dioxans inspection of models reveals that the 2,6-di-t-Bu compound has only one favoured conformation namely the 2,5-boat where the C—CO—O—C grouping is nearly planar. This conformation

Table 8. Physical constants of the prepared 4-oxo-1,3-dioxans

Compound	B.P. °C/torr	n_D^{25} or M.P.	Yield, %	Isomer Ratio
2,6-diMe	60–61/2		55	95:5[a]
2-Me-6-i-Pr	111–3/10	1·4465	55	85:15[a]
2-Me-6-t-Bu	117–9/10	1·4422	55	88:12[a]
2,2,6-triMe	97–8/12	1·4370	10	—
2,2-diMe-6-i-Pr	—	42–43°C	—[b]	—
2,6-di-t-Bu	139–141/11	38–40°C	70	89:11[a]
2,6-diMe-2-t-Bu	102–4/8	41–43°C	25	> 1000:1[c]

[a][*cis*]/[*trans*].
[b]Purified by preparative GLPC.
[c]Predominantly *trans*-2,6-diMe-2-t-Bu-4-oxo-1,3-dioxan.

includes also correct spatial arrangements for a small J_{gem} (−15·3 Hz) and for the values 12·5 and 5·2 of the vicinal coupling constants which are typical for this type of boat form.[18] When the size of the 6-substituent decreases the contribution of the half-chair conformation (IIb), where this substituent is axially orientated, increases. Simultaneously, the value of J_{gem} decreases from −15·3 to −16·7 Hz and the value of J_{56}(anti) from 12·5 to 9·7 Hz.

If we select the values −17·8 and −15·3 Hz to present the limiting values of J_{gem} in Ia and IIa, respectively we can estimate that *trans*-2,6-dimethyl-4-oxo-1,3-dioxan consists of 56% of the half-chair form and of 44% of the boat form. respectively, we can estimate that *trans*-2,6- Consequently, the energy difference between the half-chair and boat conformations is of the same order of magnitude as the conformational energy of an axial 6-Me group in the half-chair form in this case. Generally, the 4-oxo-1,3-dioxan ring seems to be a very mobile system for which it is difficult to define any certain conformation. Substitution of the ring affects greatly on the availability of different conformations and the results obtained in the present study confirm the view that the normal chair form has very little or no contribution whereas the amounts of half-chair and boat conformations depend greatly on the orientation of the different substituents.

EXPERIMENTAL

The studied compounds were prepared from suitable 3-alkyl-3-hydroxypropanoic acids[19] and aldehydes or ketones.[9a] 2,2-Dimethoxypropane was used instead of acetone in preparation 2,2-dimethyl-6-alkyl-4-oxo-1,3-dioxans.[18] Physical constants of the synthesized samples are shown in Table 8.

Chemical equilibrations were carried out in CCl_4 solns (*ca* 10% v/v of the substrate). Several catalysts were tested and Dowex 50 ionexchange resin proved to be the best. Equilibrium states were reached very rapidly even within a few hr. This is demonstrated by the fact that in the case of the epimeric 2-Me-6-isoPr-4-oxo-1,3-dioxans repeatable equilibrium ratios were obtained at each temp after few hr and the same equilibration mixture could generally be used at least at two temps. The equilibrium ratio for the isomeric 2-Me-6-t-Bu-4-oxo-1,3-dioxans at −11° was determined using *p*-toluene-sulphonic acid as catalyst but at the higher temps Dowex 50 was preferred since the formation of a disturbing decomposition product was much more rapid when using *p*-TOS at temps above 0°. Samples including *p*-TOS were of course neutralized by 2–3 drops of diethylamine before GLPC analysis. Accurate equilibrations were made very difficult by some decomposition products which tended to conceal the peak of the less stable *trans* isomer. This phenomenon was most disturbing in the case of 2,6-diMe-4-oxo-1,3-dioxans whereas equilibration of 2-Me-6-iso-Pr-4-oxo-1,3-dioxans was easily carried out at various temps.

NMR spectra were recorded usually in CCl_4 solns (10% w/v) but sometimes also other solvents might be used. The spectra were recorded with Perkin-Elmer R 10 spectrometer working at 60 MHz and the equilibration samples were analyzed by Perkin-Elmer F 11 gas chromatograph equipped with a 2 m × 1/8 in column containing 10% Carbowax 20 M on Chromosorb G (60/80 mesh). The stereoisomers were separated and the single products purified by Perkin-Elmer F 21 preparative gas chromatograph using 4·5 m × 3/8 in 5% Carbowax 20 M column. The equilibrations were started from both sides either from pure isomers or from initially *cis*-rich and *trans*-rich samples. NMR and equilibration results are collected in Tables 1-7.

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