Determination of the Conformation of Substituted 4,6-Dioxo-1,3-dioxanes. Part III.* 13C NMR Chemical Shifts, 13C,H Coupling Constants and Spin-lattice Relaxation Times of 2-, 2,2-, 2,5-, and 2,2,5-Substituted Derivatives

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13C NMR chemical shifts, methyl substituent effects, 13C,H coupling constants and spin-lattice relaxation times (T_1) have been measured for a number of substituted 4,6-dioxo-1,3-dioxanes. The parameters are discussed on the basis of the known conformational behaviour of the compounds.

In recent time increasing attention has been paid to 13C NMR spectra of various ring systems, including those of cyclohexane,[1] cyclohexanone,[2] 1,3-dioxane,[3] and glutaric anhydride.[4] It has been shown that in general the parameters derived from 13C NMR spectra are highly dependent on the configuration of the substituents and on the conformation of the ring. In this paper some 13C NMR parameters for 2-, 2,5-, 2,2-, and 2,2,5-substituted 4,6-dioxo-1,3-dioxanes are reported. These compounds have been shown to exist predominantly in a boat conformation[5,6] and the 13C NMR spectra were expected to give supporting evidence. Furthermore, no previous 13C NMR studies have been reported on the compounds under consideration.

EXPERIMENTAL

The synthesis of the compounds studied is reported elsewhere.[5,6] The 13C NMR spectra were recorded on a JEOL FX-60 NMR spectrometer equipped with the dual probe for 1H
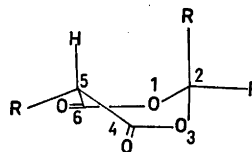
Fig. 1. The preferred ring conformation of 2-, 2,5-, 2,2-, and 2,2,5-substituted 4,6-dioxo-1,3-dioxanes.

and 13C resonance observation. The compounds were examined as ca. 20 % w/v solutions in acetone-d_6 and/or in deuteriochloroform. Chemical shifts are given relative to internal TMS. Their accuracy is believed to be within 0.1 ppm. A spectral width of 4 kHz and a data memory size of 8K were used. The routine spectra were taken under conditions of proton-noise decoupling. Selective proton decoupling, off-resonance decoupling and T_1 measurements were performed in certain cases for signal identification purposes. Inversion-recovery method was used in the T_1 measurements with a pulse repetition time of 150 s. Some of the spectra were also recorded without noise-decoupling to find out the various types of 13C, H couplings. The accuracy of the reported coupling constants is believed to be within 1 Hz (spectral resolution due to limited data capacity was ca. 1 Hz).

RESULTS AND DISCUSSION

1. Spectral assignments. The 13C NMR chemical shift data of the ring carbon atoms together with the shifts of the methyl and aryl side

Table 1. The ^{13}C NMR chemical shifts (δ). Solvent: acetone-d_6.
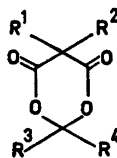
Compound	R^1	R^2	R^3	R^4	C-2	C=O	C-5	2-Me	5-Me
1	H	H	H	Ph	98.4	164.9	39.8	—	—
2	H	Me	H	Ph	97.2	167.8	44.2	—	9.6
3	H	H	Me	Me	106.4	164.0	36.8	27.5	—
4	H	H	Me	i-Bu	108.1	164.0	36.9	26.0	—
5	H	H	Me	t-Bu	111.2	164.3	36.7	21.6(eq)	—
6	H	Me	Me	Me	105.2	166.8	41.9	26.1(ax)	10.7
								28.7(eq)	
7	H	Me	Me	Et	106.6	167.0	42.1	24.3(ax)	10.7
7B	H	Me	Et	Me	107.6	167.0	41.9	25.4(eq)	11.0
8	H	Me	Me	i-Pr	108.1	167.0	42.2	22.2(ax)	10.7
8B	H	Me	i-Pr	Me	108.1	167.0	41.8	21.1(eq)	11.4
9	H	Me	Me	t-Bu	109.5	166.8	41.9	20.4(eq)	10.7
10	H	Me	Ph	Me	105.1	166.8	44.2	30.8(ax)	10.1

				Aryl C-1'	C-2',6'	C-3',5'	C-4'
1				133.4	127.2	129.4	131.2
2				134.0	127.6	129.6	131.4
10				140.6	125.3	130.1	130.4

chain carbons are collected in Table 1. The assignment of the ring carbon signals is straightforward: the carbonyl carbon is found on the lowest field around 165 ppm and is easily recognized. Next to the higher field, at about 100 ppm, is the signal of the C-2 atoms. The C-5 signal is found at around 40 ppm. The aliphatic side chains produce signals in the high field region of the spectrum sometimes obscuring the signal of C-5. They could, however, be identified unequivocally by means of off-resonance, selective decoupling and T_1-measurements. The signals of the aromatic substituent appear at 120 – 140 ppm and are thus clearly separated from the rest of the signals. The signal of C-1' of the aromatic ring is easily recognized due to its weak intensity in the routine spectrum. The signal of C-4' is identified as the second weakest signal in this part of the spectrum while the carbons 2',6' and 3',5' give about twice as strong signals. The order of these two last-mentioned signals given in Table 1 could be reversed but the given order is the same as in Ref. 7 for aryl-substituted glutaric anhydrides.

2. Chemical shifts; substituent effects on the ^{13}C chemical shifts of the ring carbons. It is well known that the substituent effects are indicative of the geometry of the compound under examination though there seem not to be any simple rules. Additivity and similarity of substituent effects in a series of substituted derivatives can be used as a criterion of conformational homogeneity and the absolute values of substituent effects give information about the configuration of the substituent and other geometrical relationships. In the case of 4,6-dioxo-1,3-dioxanes, which are considered in this context, the only useful substituent effect is that of 5-methyl substituent which can be elucidated from the compound pairs (1 – 2), (3 – 6) and (5 – 9) and these are given in Table 2. The corresponding effects in cyclohexane,[1] cyclohexanone,[2] 1,3-dioxane,[3] and glutaric anhydride[4] are given in the same table for comparison.

The similarity of the calculated substituent effects show that these six 4,6-dioxo-1,3-dioxane derivatives have a similar ring conformation, i.e. a boat, as reported earlier,[5,6] The

Table 2. The calculated 5-methyl substituent effects (ppm). Positive values mean shifts to higher fields. Solvent is acetone-d_6. Values found in some other cyclic systems are listed for comparison.

Compound	α(C-5)	β(C=O)	δ(C-2)
1−2	−4.4	−2.9	1.2
3−6	−5.1	−2.8	1.2
5−9	−5.2	−2.5	1.7
Cyclohexane [1]	−6.0		0.3
Cyclohexanone (Me at C-2) [2]	−3.6	−1.5	0.5
1,3-Dioxane (Me at C-5) [3]	−3.1		0.2
Glutaric anhydride (Me at C-2) [4]	−5.7	−1.8	

α-effect of the 5-Me is quite "normal" if compared to cyclohexane but is clearly more negative than in 1,3-dioxane and in cyclohexanone but more positive than in glutaric anhydride. The β-effect of the 5-Me on the carbonyl carbon shielding (on average −2.7 ppm) is significantly more negative than in cyclohexanone (−1.5 ppm) or in glutaric anhydride (−1.8 ppm). This may be a reflection of the more flattened region (O−CO−C(5)−CO−) in 4,6-dioxo-1,3-dioxane than the corresponding regions in cyclohexanone (−C−CO−C−C) or in glutaric anhydride (−O−CO−C−C). The observed δ-effect is anomalously large if compared to the effects of equatorial methyl groups found in other cyclic systems (Table 2). Interestingly, a δ-effect of about the same size (1.1 to 1.4 ppm) can be observed in a series of 1-methyl-substituted norbornanes,[5] where the six-membered ring is forced to a boat conformation. Obviously this large δ-effect is an indication of the boat conformation.

3. Chemical shifts of the methyl and aryl substituents. The chemical shifts of the methyl groups are in the expected range [9,10] and are collected in Table 1. It is easily seen that the shifts of the 5-methyl groups in stereoisomer pairs *(7,7B)* and *(8,8B)* are not markedly different. The same is true for the 2-methyl groups; the 5-Me group is equatorial in all compounds but the 2-Me substituent can be axial (as in *7* and *8*) or equatorial (as in *7B* and *8B*). When there are two methyl substituents at C-2 (as in *6*), the signal of the axial methyl is at a slightly higher field but if the other of the substituents is changed to another alkyl group the order may be reversed, depend-

ing on the kind of the alkyl group: in the epimer pair *(7,7B)* the axial 2-methyl is at higher field but in the isopropyl derivatives *(8,8B)* the axial methyl signal is at a lower field.

In the aryl-substituted derivatives *1* and *2* the corresponding chemical shifts of the aryl carbons (Table 1) are very similar but the shifts of the third aryl-derivative *(10)* are distinctly different. This is in agreement with the earlier observation [6] that in *1* and *2* the aromatic side chain is equatorial but is axial in *10*.

4. ¹³C,H coupling constants. The ¹³C,H couplings of some representative compounds were measured from non-decoupled spectra and are collected in Table 3. The one-bond couplings are of the expected order of magnitude.[9,10]

An interesting phenomenon occurs in the case of 2-methyl-2-*tert*-butyl derivative *(5)*: the C-5 signal appears in the coupled spectrum as a quartet indicating two different $^1J_{5C_5H}$ coupling constants. To analyze this X-part of an ABX-system the ¹³C-H satellite signals of the C-5 protons in the ¹H spectrum were located. The ABX-analysis yielded the following values: $^2J_{AB} = 21.0$ Hz (main quartet from the ¹²C-H spectrum: 21.4 Hz), $\delta_{AB} = 36.4$ Hz (main quartet: 36.6 Hz), $J_{AX} = 129.0$ Hz and $J_{BX} = 138.3$ Hz (A = axial proton at C-5, B = equatorial proton at C-5). As δ_{AB} is relatively large, this is a nearly first order spectrum: the difference of the inner peaks of the C-5 quartet is 8.5 Hz in acetone-d_6, close to the value $J_{BX} − J_{AX} = 9.3$ Hz. In deuteriochloroform, however, the corresponding difference is only 3.9 Hz as δ_{AB} in this solvent is much smaller (*ca.* 11 Hz) than in acetone-d_6 (36.4 Hz). This is a demonstration of a case where first

Table 3. The J_{CH} coupling constants of the compounds studied. Solvent $CDCl_3$ if not otherwise indicated. Mutually coupled nuclei in italics.

Compound	2^a	5	6	7	7B	9	10
$^1J_{2C2H}$	173.4	—	—	—	—	—	—
$^1J_{5C5Heq}$	—	138.3a	—	—	—	—	—
$^1J_{5C5Hax}$	124.5	129.0a	124.5	124.5	124.5	120.1	123.0
$^1J_{2CH_3eq}$	—	—	129.2	—	—	129.9	130.5
$^1J_{2CH_3ax}$	—	128.6	128.6	128.9	—	128.4	—
$^1J_{5CH_3}$	130.5	—	131.6	131.8	131.8	131.8	131.8
$^1J_{5CH_35H}$	5.4	—	5.9	6.0	6.0	6.1	5.3
$^2J_{CCH_3eq}$	—	—	5	—	b	—	b
$^3J_{CCH_3ax}$	—	5	5	b	—	5	—
$^3J_{CO5Heq}$	—	6.8c	—	—	—	—	—
$^3J_{CO5Hax}$	b	6.8c	9.3	9.5	b	9.3	9.3
$^2J_{5CCH_3}$	b	—	4.2	4.4	4.4	4.9	4.9
$^3J_{CO5CH_3}$	b	—	4.6	4.5	b	4.6	4.6
$^3J_{2CH_32CH_3}$	—	—	3.3	2.4^d	2.9^d	—	—

[a] Solvent $(CD_3)_2CO$. [b] Not resolved. [c] The X-part of the ABX_2-system of $5H_a5H_e(CO)_2$ is a triplet with spacings 6.8 Hz. See text. [d] Actually a coupling $^3J_{2CH_32CH_3CH_3}$.

order treatment of the ^{13}C spectrum would lead to an erroneous result.[11] It is also noted that in all 5-methyl derivatives the $^1J_{C,H}$ at C-5 is in the range $120-130$ Hz indicating an axial 5-proton, in agreement with the previous result.[5,6]

The other $^1J_{C,H}$ in this ring system is that for C-2. A value of 173.4 Hz was measured from the coupled spectrum of 2-phenyl-5-methyl-4,6-dioxo-1,3-dioxane (*2*). This value is large if compared to ^1J at C-5 and is a result of the neighbourhood of the two electronegative oxygen atoms.[9,10]

Several ^2J's and ^3J's could be detected. For example, the carbonyl carbon signal of *5* is a triplet indicating a ^2J of 6.8 Hz to the methylene protons at C-5. This value was determined in $CDCl_3$ and actually the couplings can differ slightly due to the close chemical shifts of the 5-protons; however, the sum of these couplings is 13.6 Hz. In the 5-methyl derivatives the $C=O$ signal appears as a doublet of quartets with couplings of *ca.* 9 and 4.5 Hz. The first coupling is the above-mentioned ^2J of the carbonyl carbon with the axial proton at C-5 and the second is the ^3J between the carbonyl carbon and the protons of the equatorial methyl group at C-5. This is a typical, large long range coupling of properly substituted esters and other carbonyl compounds.[12]

Other long range couplings include the typical ^3J's of the 5-methyl carbon with the methine proton at C-5 and the ^2J coupling of the C-2 with the methyl or methylene protons of the C-2 substituents. A ^3J of *ca.* 3 Hz could be resolved in the spectrum of *6* in both 2-methyl carbon signals: these carbons are coupled to the protons of the second methyl substituent attached at C-2. Couplings of same type were detected also in the case of compounds *7* and *7B*.

Slight variations are noted in values of the ^1J coupling of the C-2 methyl carbon and the methyl protons: in equatorial configuration the coupling is about 1 to 2 Hz larger than in axial configuration of this substituent (compounds *6*, *7* and *7B* in Table 3).

5. T_1 measurements. To get more information about the structural parameters in these compounds, T_1 measurements of some representative compounds were performed. The Auto-T_1 program of the JEOL FX-60 computer system with the pulse sequence $(180-\tau-90t_r)_n$ was used. A value of 150 s was used for t_r (*ca.* 4 times the longest T_1) and τ was varied from 0.1 to 150 s. Concentrated samples in $CDCl_3$ were used and the cycle for each τ was repeated $25-50$ (*n*) times to achieve a proper S/N ratio. Degassing of the samples was found to be necessary due to the slow relaxation of the

Table 4. The measured T_1 values (s) of the compounds studied (mean values of two independent measurements). Solvent CDCl$_3$. For experimental details, see text.

Compound	C=O	C-2	C-5	2-CH$_3$eq	2-CH$_3$ax	5-CH$_3$	Substituents CH$_2$—CH$_3$		C≡(CH$_3$)$_3$	
3	49.7	40.1	2.7	1.7						
5	37.0	41.1	2.7		3.0				23.6	2.3
6	40.4	28.1	2.7	1.2	2.2	1.7				
7ᵃ	46.5	25.9	2.2		2.1	1.5	1.8	1.8		
7Bᵃ	46.5	29.3	1.9	1.0		1.3	2.0	2.6		
9	41.3	38.1	2.5		3.4	1.8			21.3	1.4
10	43.2	32.7	2.7	0.8		1.9				
Mean	43.0	33.6	2.5	1.0	2.7	1.6				

ᵃ These values were determined from a mixture of *7* and *7B*. The chemical shifts of the C=O carbons are the same for both compounds.

Table 5. The measured NOE's for compounds *3* and *9*. Solvent CDCl$_3$. For experimental details, see text.

Compound	C=O	C-2	C-5	2-CH$_3$	5-CH$_3$	2-*t*-Bu
3	1.1	2.2	2.1	2.1		
9	1.9	1.7	2.0	2.2	1.9	1.8ᵃ

ᵃ Both *C*(CH$_3$)$_3$ and C(*C*H$_3$)$_3$.

nonprotonated carbons, C=O and C-2. The results are collected in Table 4.

The computer program did not yield standard deviations of the least squares fits but results from parallel independent measurements indicate a probable error of *ca.* 20 %.

It is known that several mechanisms may be responsible for the observable spin-lattice relaxation process. In general, the dipole-dipole mechanism is the most effective for protonated carbons in medium-sized compounds and is prevailing also for nonprotonated carbons.[9,10,13] A measure for the preference of the dipole-dipole mechanism can be derived by measuring the Nuclear Overhauser Effects (NOE) by integration of the fully relaxed spectrum and assuming complete NOE for protonated carbons or by internally comparing the intensities in normal and gated (proton decoupling off under FID sampling) spectra. The latter method was used (pulse interval 200 s) to find out the NOE's of compounds *3* and *9* (these represent the "smallest" and "largest" of the compounds under examination) and the results are collected in Table 5. The probable error is *ca.* 10 %. As the theoretical maximum of NOE in proton noise-decoupled spectra is

1.998, the results indicate that dipole-dipole relaxation is prevailing for all carbon atoms in compound *9*. In compound *3* the same is true for all but the C=O carbons, for which the observed NOE is only 1.1 indicating two or more competing relaxation mechanisms. This compound (*3*), moreover, is a conformational mixture of two interconverting identical boat conformations, and also hereby differing from the rest of the compounds in Table 4.

The differentiation between the protonated and nonprotonated carbon atoms is an easy task as the nonprotonated carbons relax distinctlty slower. However, there are slight variations from compound to compound indicating that also other factors are involved. It is known that in case of a uniform relaxation mechanism (here dipole-dipole mechanism) the molecular motion is reflected in T_1 values.[9,10,13] Thus in medium-sized compounds methyl carbons usually relax slower than secondary or tertiary carbons of a rigid skeleton, this being related to the short correlation time, *i.e.* fast rotation of the substituent (in small symmetrical molecules spin-rotation mechanism will also contribute). Similarly, in substituted benzenes and biphenyls, the *para* carbons

relax faster (long correlation time) than *ortho* and *meta* carbons (short correlation time) due to preferred rotation of the molecule around the C_1-C_{para} axic.[14],[15]

Some conclusions from the T_1 values in Table 4 can be drawn. The longer relaxation of the C-2 in compounds 5 and 9 if compared to this relaxation time in the rest of the compounds, obviously reflects the lack of nearby hydrogens. The relaxation of C-2 of 3 is also slow but here it can be explained by the conformational mobility of this compound. The relaxation of the carbonyl carbon is also very slow and the fastest relaxation is observed in the case of 5 where there are two hydrogens at position 5. As mentioned above, other relaxation mechanisms may contribute to some extent for these carbons. The relaxation of the C-5 atom does not vary much from compound to compound. The fastest relaxation would be expected in the case of 5. Actually the relaxation time is about the same as in the methyl derivative 9.

The T_1 values of the methyl carbons show a significant dependence on the location and configuration of the substituent. Slowest relaxation is found in the case of axial 2-methyl (mean 2.5 s) while the equatorial 2-methyl (mean 1.0) and equatorial 5-methyl (mean 1.6) relax distinctly faster. An explanation to this phenomenon may be given in terms of anisotropic tumbling of the molecule around a certain preferred axis. The equatorial methyl groups lie close to the average plane of the ring the axial methyl group being more displaced from this plane. Rotation of the molecule about an axis in the symmetry plane of the molecule and close to the average plane of the ring would lead to a situation where the axial 2-methyl group has a shorter correlation time
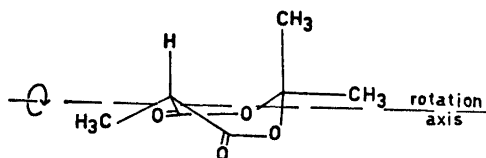

Fig. 2. An explanation to the observed differences in the T_1 values of the methyl groups. The molecules have a preferred axis of rotation and the carbons more displaced from this axis have a shorter relative correlation time and hence a longer relative relaxation time than the carbons close to the axis.

and, consequently, a slower relaxation (Fig. 2). A similar trend can be noted in the T_1 values of the carbons of the ethyl chain at C-2 (compounds 7 and 7B: in axial configuration these carbons relax slower (compound 7) than in equatorial configuration (compound 7B).

Summarizing, the current ^{13}C NMR data are found to be consistent with conclusions obtained from the earlier ^{1}H NMR data of 4,6-dioxo-1,3-dioxans.[5],[6]

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