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Conformational Analysis

NMR Spectra of Acetals Derived From Diastereomeric 3-Methyl-2,4-Pentanediols

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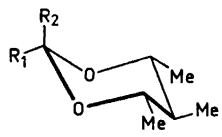
The NMR spectra of three isomeric 4,5,6-trimethyl-1,3-dioxanes, three isomeric 2,2,4,5,6-pentamethyl-1,3-dioxanes and four isomeric 2,4,5,6-tetramethyl-1,3-dioxanes were recorded. The structures of these compounds are discussed in the light of their NMR parameters. The solvent shifts $\Delta\delta(CCl_4-C_6H_6)$ show that the 4-, 5- and 6-positions are shielded, and especially the equatorial 5-position; the axial 2- and 5-positions are little affected, while the equatorial 2-position is deshielded. The spectrum of 2,2,*cis*-4,5,*trans*-6-pentamethyl-1,3-dioxane (X) and the effect of benzene on it are consistent with a skew-boat conformation.

The NMR spectra of alkyl-substituted 1,3-dioxanes have been investigated by several authors.[1–8] However, little attention has been paid to the solvent effects which may give valuable information from the structural details. Moreover, the NMR spectra of 4,5,6-trimethyl-substituted 1,3-dioxanes, except the spectrum of *cis*-4,5,*trans*-6-trimethyl-1,3-dioxane (VII),[1] have not been considered earlier. The NMR parameters and the chemical shifts caused by benzene were measured for ten 1,3-dioxanes derived from diastereomeric 3-methyl-2,4-pentanediols to determine the influence of varying methyl-substitution.

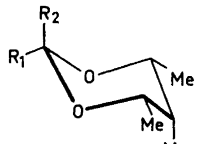
EXPERIMENTAL

All of the studied compounds were prepared earlier.[9] *meso*-4,5,6-Trimethyl-1,3-dioxane was a 67:33 mixture of *cis*-4,5,6-trimethyl- (IV) and *cis*-4,*trans*-5,*cis*-6-trimethyl-1,3-dioxanes (I; Fig. 1).[9] The studied mixture of *meso*-2,2,4,5,6-pentamethyl-1,3-dioxanes consisted of 37 % of III and 63 % of VI (Fig. 1).[9] In contrast, *meso*-2,4,5,6-tetramethyl-1,3-dioxane was assumed to consist mainly of the *cis* form (V) on the basis of kinetic experiments (Fig. 1).[9]

cis-2,4,5,*trans*-6-Tetramethyl-1,3-dioxane (VIII; Fig. 2) was isolated in pure state on a Perkin-Elmer F 21 preparative gas chromatograph equipped with a column containing Carbowax 20 M (5 %) on Chromosorb G (60/80 mesh). Also the sample of *meso*-2,4,5,6-tetramethyl-1,3-dioxane was run through the preparative gas chromatograph before recording the NMR spectrum.

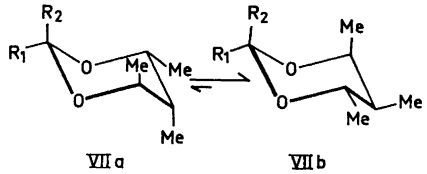


I $R_1 = R_2 = H$
II $R_1 = Me$, $R_2 = H$
III $R_1 = R_2 = Me$



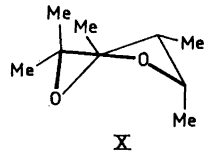
IV $R_1 = R_2 = H$
V $R_1 = Me$, $R_2 = H$
VI $R_1 = R_2 = Me$

Fig. 1. 1,3-Dioxanes derived from *meso*-3-methyl-2,4-pentanediols.



VII a VII b

VII $R_1 = R_2 = H$
VIII (VII a) $R_1 = Me$, $R_2 = H$
IX (VII b) $R_1 = Me$, $R_2 = H$



X

Fig. 2. 1,3-Dioxanes derived from DL-3-methyl-2,4-pentanediol.

The NMR spectra were recorded on a 60 Mcps Perkin-Elmer R 10 NMR spectroscope. The "inactive" solvent was carbon tetrachloride and the "active" solvent benzene. The substrate concentration varied from 15 to 20 vol.%. First-order or "1½-order" [10] analysis was usually applied in the evaluation of the coupling constants. The chemical shifts are shown in Table 1 and the values of the coupling constants in Table 2. The benzene solvent shifts are presented in Table 3.

RESULTS AND DISCUSSION

Integration of the NMR spectrum of the mixture of *meso*-4,5,6-trimethyl-1,3-dioxanes (I and IV; Fig. 1) gave the composition 34 % of I and 66 % of IV, which is in good agreement with the previous estimate based on gas chromatographic analysis.[9] The conformer ratio in *cis*-4,5,*trans*-6-trimethyl-1,3-dioxane (VII; Fig. 2) has been calculated earlier.[1]

Booth and Thornburrow [2] have stated that equatorial methyl groups in positions 4 and 6 lower the value of J_{4a5a} by about 1 cps. The values of this coupling constant in IV and in the other compounds (V and VI) derived from the same diol are about 2 cps lower than the normal value of about 11.3 cps.[3] Thus it seems reasonable to assume that an equatorial methyl group at 5-position decreases the magnitude of the diaxial coupling further.

Eliel and Knoeber [4] have presented values of J_{4a5e} for several alkyl-substituted 1,3-dioxanes. Our values (2.1—2.4 cps) are in satisfactory agreement with their values. Also the value of J_{4e5e} in VIII and that of J_{4e5a} in IX (Fig. 2) are in agreement with the values reported in previous papers.[1-8,11]

Kinetic data led one of us earlier to the conclusion that 2,4,5,6-tetramethyl-1,3-dioxane prepared from a mixture of *meso*-3-methyl-2,4-pentanediols consisted mainly of the all-*cis* configuration (V; Fig. 1).[9] However, on the

Table 1. Chemical shifts in the NMR spectra of the studied compounds. All values in cps. The solvents are carbon tetrachloride and benzene, respectively.

	Compound. Locations of methyl groups	ν_{2e}	ν_{2a}	ν_{4e}	ν_{4a}	ν_{6e}	ν_{6a}	ν_{5e}	ν_{5a}
IV	*cis*-4,*trans*-5,*cis*-6	292.5	275.5	71.0	190.6	71.0	190.6	46.3	[a]
I	*cis*-4,5,6	292.5	275.5	67.3	221.2	67.3	221.2	[a]	51.9
V	*cis*-2,4,*trans*-5,*cis*-6	72.2	275.8	69.7	192.9	69.7	192.9	44.7	[a]
II	*cis*-2,4,5,6	72.2	275.8	66.5	223.7	66.5	223.7	[a]	50.6
VI	2,2,*cis*-4,*trans*-5, *cis*-6	76.5	81.5	66.5	208.2	66.5	208.2	45.8	[a]
III	2,2,*cis*-4,5,6	76.5	81.5	63.5	238.8	63.5	238.8	[a]	48.9
VII	*cis*-4,5,*trans*-6 [d]	280.2	288.0	69.7	215.3	237.8	71.3	50.4	96.2
VIII	*cis*-2,4,5,*trans*-6	69.3	295.7	63.8	241.7	230.8	79.2	[b]	[b]
IX	*cis*-2,4,*trans*-5,6	68.3	293.6	67.0	211.4	237.2	70.7	43.0	107.3
X	2,2,*cis*-4,5,*trans*-6 [c]	74.0	74.0	67.8	198.5	238.5	59.9	47.0	[b]
IV		304.5	273.6	68.5	180.9	68.5	180.9	27.2	[a]
I		302.4	273.6	63.9	208.5	63.9	208.5	[a]	54.1
V		82.6	277.6	68.7	186.9	68.7	186.9	27.9	[a]
II		80.8	275.5	64.2	212.2	64.2	212.2	[a]	52.3
VI		87.5	79.7	67.0	204.2	67.0	204.2	31.0	[a]
III		89.5	79.7	62.7	230.2	62.7	230.2	[a]	52.1
VII [d]		289.3	289.3	65.3	206.1	234.0	59.7	35.2	93.0
VIII		78.6	296.7	61.8	232.8	229.3	68.6	[b]	[b]
IX		78.8	299.0	64.0	205.1	238.3	59.1	21.5	109.1
X [c]		81.4	81.4	68.0	201.3	238.5	59.1	41.0	[a]

[a] Lost under alkyl peaks. [b] AB_3 type coupling between 5-proton and 5-methyl. [c] Skew-boat. [d] 28 % of VIIa and 72 % of VIIb (Fig. 2).

Table 2. The values of the coupling constants for the studied compounds in cps. No significant difference between their values in CCl_4 and C_6H_6 was detected.

Compound	$^2J_{gem}$	$^2J_{Mc}$	$^4J_{Me}$	J_{4a5e}	J_{4a5a}	J_{4e5e}	J_{4e5a}
IV	6.2	—	6.2	—	9.3	—	—
I	6.2	—	6.4	2.3	—	—	—
V	—	5.1	6.2	—	9.2	—	—
II	—	5.1	6.4	2.1	—	—	—
VI	—	—	6.2	—	9.3	—	—
III	—	—	6.4	2.1	—	—	—
VII	[a]	—	6.4	—	[a]	[a]	—
VIII	—	5.1	7.1 [b] 6.4	2.4	—	1.3	—
IX	—	5.2	7.0 [b] 6.1	—	10.0	—	5.6
X [c]	—	—	6.3		7.70 ± 0.04 (ten values)		
			6.7		5.29 ± 0.03 (»)		

[a] This compound is a mixture of rapidly interconverting conformers VIIa and VIIb (3:7).[2] [b] The coupling constant of the 6-proton, $^6J_{Me}$. [c] The conformation of the ring is skew-boat.

Table 3. Benzene solvent shifts of the studied compounds. CCl_4 was the "inactive" solvent (Table 1).

Compound	2e		2a		4,6e		4,6a		5e [a]	5a	
	H	Me	H	Me	H	Me	H	Me	Me	H	Me
I	+9.9	–	−1.9	–	–	−3.4	−12.7	–	–	–	+2.2
II	–	+ 8.6	−0.3	–	–	−2.3	−11.5	–	–	–	+1.7
III	–	+11.0	–	−1.8	–	−0.8	−8.6	–	–	–	+3.3
IV	+12.0	–	−1.9	–	–	−2.5	−9.7	–	−19.1	[a]	–
V	–	+10.4	+1.8	–	–	−1.0	−6.0	–	−16.8	[a]	–
VI	–	+13.0	–	−1.8	–	+0.5	−4.0	–	−14.8	[a]	–
VII [d]	+13.2 [e]	–	−3.3 [e]	–	−1.0 [e]	−4.4 [f]	−12.7 [e]	−11.6 [f]	−15.2 [f]	−3.2 [f]	–
VIII	–	+ 9.3	+1.0	–	−1.5	−2.0	−8.9	−10.6	–	–	[b]
IX	–	+10.5	+5.4	–	+1.1	−3.0	−6.3	−11.6	−21.5	+1.8	–
X [c]	–	± 0	–	±0	±0	+0.2	+2.8	−0.8	−6.0	[a]	–
Mean [g]	+11.7	+12.1	±0	−1.8	−0.5	−2.1	−8.9	−11.3	−17.5	−0.7	+2.4

[a] The shifts of 5e-H and some other signals could not be determined because of overlap with methyl signals. [b] AB_3 type spectrum. [c] Skew-boat; not taken to the mean. [d] 28 % of VIIa and 72 % of VIIb.[2] [e] Corrected in respect to the conformer ratio.[d] [f] For the averaged spectrum. [g] Positive values mean downfield shifts.

basis of the integrated NMR spectrum, this compound is a 37:63 mixture of V and II (Fig. 1). This discrepancy is easily understood since II and V are not resolved by gas chromatography although several column packings suitable for the resolution of other isomer mixtures are employed. Moreover, II is exceptionally resistant to hydrolysis and this is why only the hydrolysis of V, which led to the erroneous composition, was observed.[9]

Chemical shifts. The values presented in Table 1 show that the position of the axial acetal proton in compounds IV, I, V, and II (Fig. 1) is about 276 cps in CCl_4 and about the same in benzene. Thus the shift of this proton is nearly constant for the different compounds in both solvents. Compounds VII, VIII, and IX (Fig. 2) have a *syn*-axial methyl group and the signals of their axial acetal protons are centered at 292.6,* 295.7, and 293.6 cps, respectively, in CCl_4 solution. Eliel and Knoeber [4] have reported similar values for the shift of the 2-axial proton in several 1,3-dioxanes having *syn*-axial methyl groups.

The equatorial acetal protons of compounds IV and I lie at 292.5 cps, whereas the proton of VII (a methyl group syn-axial with the axial acetal proton) is centered at 276.1 * cps. Also these results are in good agreement with those of Eliel and Knoeber.[4] Generally, benzene has only a slight effect on the chemical shift of the axial acetal proton, whereas it shifts the signal of the equatorial acetal proton downfield about 10—12 cps. Thus the virtual singlet of the 2-protons of VII in benzene is understandable since the signal

* Calculated taking into account that this compound contains about 28 % of VIIa and 72 % of VIIb at 33.5°C.[1]

of the equatorial acetal proton shifts appreciably downfield and this proton becomes magnetically equivalent to the axial proton.

The equatorial 2-methyl groups in compounds II, V, VIII and IX (Figs. 1 and 2) are in the "normal" positions [4,5] (67—72 cps). When benzene was the solvent, these signals were displaced about 10 cps downfield (78—83 cps). The equatorial 2-methyl groups in compounds III and VI are displaced from the "normal" position towards the axial position (76.5 *versus* 81.5 cps in CCl_4 and 87—89 *versus* 79.7 cps in C_6H_6). In these cases the chemical shift difference for the compounds in benzene and carbon tetrachloride is about 12 cps compared with about 10 cps for the other compounds. Both these observations lead to the conclusion that the ring in 2,2-dimethyl-substituted compounds is somewhat distorted from the "regular" chair.

The equatorial 4-methyl groups of the 5-equatorial isomers IV, V, VI, and IX are centered at 71.0, 69.7, 66.5, and 67.0 cps in CCl_4 and at 68.5, 68.7, 67.0, and 64.0 cps in C_6H_6, respectively. The signals of the 5-axial isomers I, II, III, and VIII are placed at 67.3, 66.5, 63.5, and 63.8 cps in CCl_4 and at 63.9, 64.2, 62.7, and 61.8 cps in C_6H_6, respectively. Obviously, the equatorial 4-methyl group is displaced 3—4 cps upfield when an equatorial 5-methyl group is replaced by an axial one. The benzene solvent shift is about 2—3 cps upfield in both series of isomers.

The axial 4-protons of the 5-equatorial isomers (IV, V, VI, and IX) are placed at 190.6, 192.9, 208.2, and 211.4 cps in CCl_4 and at 180.9, 186.9, 204.2, and 205.1 cps in C_6H_6, respectively. These values show that *syn*-axial methyl groups in compounds VI and IX displace the signal of the axial 4-proton appreciably downfield similarly as they displace the signals of the axial acetal protons in these compounds. The benzene solvent shift decreases with increasing substitution. Similarly, the signals of the axial 4-protons of the 5-axial isomers (I, II, III, and VIII) are centered at 221.2, 223.7, 238.8, and 241.7 cps in CCl_4 and at 208.5, 212.2, 230.2, and 232.8 cps in C_6H_6, respectively. These results lead to the conclusion that in every case and in both solvents the 5-axial substitution shifts the signal of the axial 4-proton about 30 cps downfield from the positions of the signals of the protons in the 5-equatorial compounds. Also the benzene solvent shift is almost double in the 5-axial series.

The equatorial 6-protons of compounds VII and IX (Fig. 2) are found at 237.8 and 237.2 cps in CCl_4 and are only slightly shifted in benzene (at 234.0 and 238.3 cps, respectively). Thus, together with the coupling patterns of the 4-axial and 6-equatorial protons of VIII (Fig. 2) the above data support the fact that the signal of the axial 4-proton in this compound is exceptionally centered about 11 cps downfield from the signal of the equatorial 6-proton.*

If the chemical shifts of 5-methyl groups are considered, a very clear-cut difference is found between the equatorial and axial methyl groups. In CCl_4 the equatorial 5-methyl group is placed approximately at 45 cps, whereas in C_6H_6 it is displaced upfield 15—25 cps. The position of the axial 5-methyl group is around 50 cps in both solvents.

* The 4-axial proton is at 241.7 cps in CCl_4 and at 232.8 cps in benzene and the 4-equatorial proton at 230.8 cps in CCl_4 and 229.3 cps in C_6H_6. These were erroneously assigned in Ref. 1.

Compound X was not included in the above discussion. This is due to the fact that in our opinion this compound has the skew-boat conformation. One of us has previously suggested that *trans*-2,2,4,6-tetramethyl-1,3-dioxane exists in the skew-boat form owing to the large interaction between *syn*-axial methyl groups at 2 and 4 positions.[12,13] Already the structural similarity of the above compounds suggests the same ring conformation for both. Moreover, the NMR spectrum of X is consistent with the skew-boat form. The signals of 2-methyl groups are placed at 74.0 cps in CCl_4 and 81.4 cps in C_6H_6. The signal of the 4-methyl group is placed at the "equatorial" position (67.8 cps) in CCl_4 but is not displaced in benzene (68.0 cps), which is in contrast to the 3—4 cps upfield shifts in the other instances. The 6-methyl group of X is at an "abnormal" high position (59.9 cps) in CCl_4 but is at the same location in benzene (59.1 cps) as compared with the appreciable shifts (10—20 cps) of the group in the other compounds. Similarly, the signals of both 4- and 6-protons are located at nearly the same positions in both solvents, at 198.5 and 238.5 cps in CCl_4 and 201.3 and 238.5 cps in benzene. Highly unexpected is the position of the signal of the 5-methyl group, which is displaced only 5 cps upfield in benzene as compared with the 15—25 cps shifts of the groups in IV—VII and IX.

Probably X has a "biased" skew-boat conformation in which the 5-methyl group projects outward from the ring since otherwise it would be crowded by one of the 2-methyl groups. The values of the coupling constants of the 4- (or 6-) and 5-protons, 7.70 and 5.29 cps, are also consistent with the skew-boat conformation since the dihedral angles are about 35° for *cis*-4,5-protons (J_{HH},(35°)=5.2 cps [14]) and about 160° for *trans*-6,5-protons (J_{HH},(160°)=7.9 cps [14]).[5]

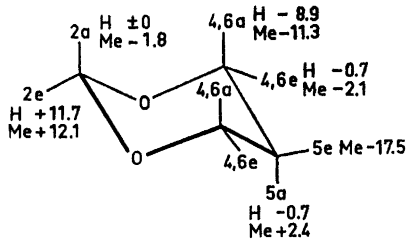


Fig. 3. The mean benzene solvent shifts of the studied compounds in cps. Positive values mean downfield shifts.

Anderson [15] has suggested that complex formation occurs between benzene and a methyl-substituted 1,3-dioxane which is also compatible with the benzene solvent shifts observed in this work (Table 3 and Fig. 3). The mean benzene solvent shifts (Fig. 3) show that 4-, 5-, and 6-positions are shielded except the 5-axial methyl group which is slightly deshielded. The axial 2-position is little affected whereas the equatorial hydrogen atoms and methyl groups in this position are deshielded.

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