Tetrahedron Vol 39, No 23, pp 3959 to 3963, 1983
Printed in Great Britain

0040-4020/83 $3.00 + .00
Pergamon Press Ltd

CONFORMATIONAL ANALYSIS OF 2,3-DIALKOXY-1, 4-DIOXANES

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(*Received in UK 25 January 1983*)

Abstract—The conformation of several 2,3 - dialkoxy - 1,4 - dioxanes with bulky alkoxy groups has been studied using ^{1}H NMR techniques. For all the *cis*-isomers a degenerated equilibrium between the two axial-equatorial chair conformers is observed. For the *trans*-dineopentiloxy-, and *trans* - 2,3 - diisopropoxy - 1,4 - dioxane a clear preference for the diaxial conformer is observed. For the *trans* - 2,3 - di - t - butoxy derivative a *ca* 1 : 1 equilibrium between the diaxial and diequatorial forms is found. These results can be interpreted on the basis of the relative degree of fulfilment for the *exo*-anomeric requirements in each of the compounds.

The structure and conformational analysis of 1,4-dioxanes bearing polar substituents have been the subject of a large number of studies related to the presence of anomeric effects in such systems.[1,2] On the other hand, 2,3-dialkoxy-1, 4-dioxanes have been used in our laboratory as starting materials for the synthesis of acetylene diethers.[3]

In almost all of the studied examples[1] the results of the conformational analysis have revealed the *trans*-isomers to be found more than 95% in a diaxial conformation. There is, however, an exception to such behaviour: *trans* - bis(trimethylsiloxy) - 1,4 - dioxane exists in solution as a 1 : 1 mixture of diaxial and diequatorial conformers and this fact has been interpreted as a manifestation of a peculiar reverse anomeric effect.[1h] However, since trimethylsiloxy is a very bulky substitutent, steric effects cannot be discarded as a contributing factor influencing the position of the conformational equilibrium in this compound.

Compounds I, II and III (Fig. 1), which we had previously prepared as synthetic intermediates, cover a full series ranging from a primary to a tertiary alkoxy substituent and offer, therefore, a convenient model for the study of the influence of purely steric effects on the position of conformational equilibria. Moreover, our results could, in principle, afford a new light on the steric requirements for the manifestation of the anomeric effect.

EXPERIMENTAL

2,3 - Dialkoxy - 1, 4 - dioxanes were obtained from *trans* - 2,3 - dichloro - 1,4 - dioxane by reaction with the corresponding alcohols in the presence of solid K_2CO_3 according to procedures described.[3] Diastereomeric separation was achieved by flash-chromatography[4] on neutral alumina. In a typical run *ca* 1 g of the diastereomeric mixture was applied to 1 cm ϕ column loaded with *ca* 60 g of 100–125 mesh, Actv. 1 neutral alumina. Elution was performed initially with petroleum ether, until the *trans* isomer had been separated, followed by increasing polarity of petroleum ether/diethyl ether mixtures for the elution of the *cis* - diastereoisomer. The stereochemical purity of each fraction was checked by ^{1}H NMR.

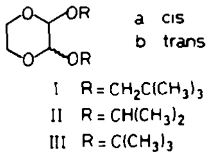


Fig. 1.

NMR spectra were recorded on a Varian XL-200 instrument operating in F. T. mode. Sample concentrations ranged from 2 to 5 mg/ml.

RESULTS

All of the 2,3 - dialkoxy - 1,4 - dioxanes being the subject of this study exhibited in their NMR spectra ($CDCl_3$, 20°) a sharp signal at $\delta = 4.4$–4.8 ppm, due to the acetalic protons, and a complex absorption at $\delta = 3.0$–4.1 ppm due to the $-O-CH_2-CH_2-O-$ moiety of the molecules. Whereas all spectra from *cis* isomers are practically identical, two types of patterns were observed for the corresponding *trans* isomers, the results for IIIb being substantially different from those of Ib and IIb, as it can be seen in Figs. 2 and 3. The forementioned complex signal was first analyzed as a AA'BB' system by means of the LAOCOON 3 program. After full optimization, the simulated spectra were superimposable with the experimental ones (RMS error were in all cases less than 0.5 Hz). Results are summarised in Table 1.

If we assume that the introduction of our bulky substituents do not cause any geometrical distortion, the conformational equilibria shown in Fig. 4 should exist. The absence of geometrical distortion in the chair conformations could be confirmed by calculation of the dihedral angle ψ according to Lambert[5] (Fig. 5). Results are summarized in Table 2. In all cases, the deviation was less than 2° from the reported (57°)[6] value for 1,4 - dioxane.

The analysis of the *cis* isomers Ia, IIa, and IIIa, together with the calculated ψ values confirmed the presence of a fast degenerated equilibrium between two equivalent axial-equatorial chairs.

Population analyses for the *trans* isomers were subsequently performed using the values of J_{aa} and J_{ee} found for deuterated dioxanes as a model[7] (Table 3).

$$J_{AB} = x\,J_{aa} + (1 - x)J_{ee}$$

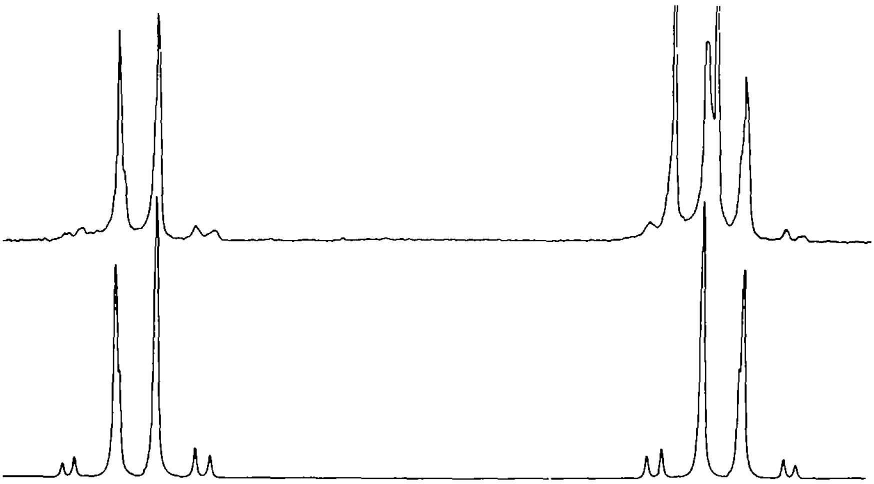


Fig. 2. Observed and calculated spectrum of the AA'BB' system in *trans* - 2,3 - dineopentiloxy - 1,4 - dioxane Ib. (Methylene signals from neopentiloxy group are superposed to the observed AA'BB' system.)

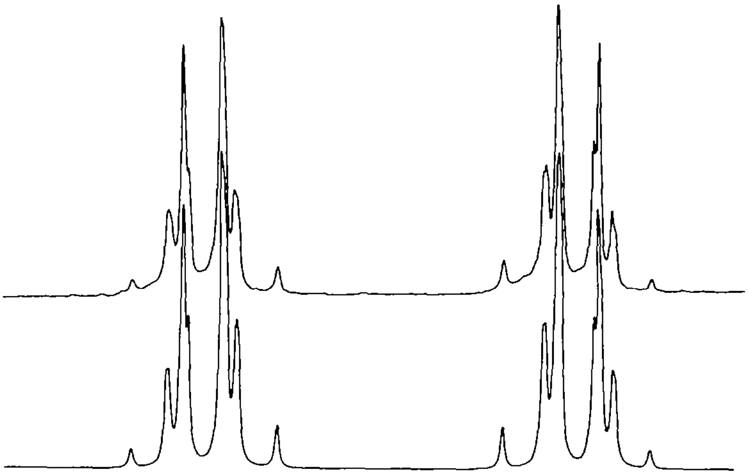


Fig. 3. Observed and calculated spectrum of the AA'BB' system in *trans* - 2,3 - di - t - butoxy - 1,4 - dioxane IIIb.

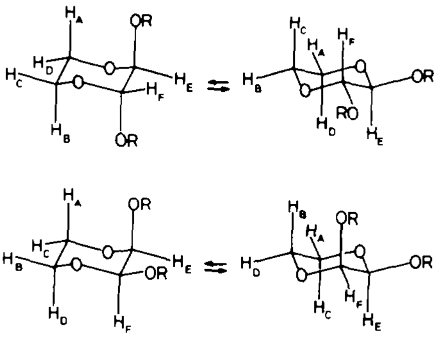


Fig. 4.

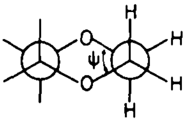


Fig. 5.

Table 1. NMR data (in Hz) of 2,3 - dialkoxy - 1,4 - dioxanes I, II and III. (* from AA'BB' analysis, † from ^{13}C satellite, § directly measured)

	ν_A*	ν_C*	ν_E§	J_{AB} = J_{CD}*	J_{AC}*	J_{AD}*	J_{EF}†
Ia	793.28	717.82	902.00	3.18	-11.76	6.36	1.8
IIa	802.03	721.55	910.77	3.17	-11.63	6.36	1.8
IIIa	784.12	695.09	918.24	3.17	-11.47	6.36	1.6

	ν_A*	ν_C*	ν_E§	J_{AB}*	J_{CD}*	J_{AC}*	J_{AD}*	J_{EF}†
Ib	813.85	689.13	884.00	10.40	1.86	3.28	-12.16	1.2
IIb	816.76	681.94	896.26	10.40	2.08	3.28	-12.11	1.2
IIIb	791.15	711.65	893.95	6.50	5.89	2.86	-12.16	3.8

Table 2. Coupling constants, R-values and ring dihedral angles of 2,3 - dialkoxy - 1,4 - dioxanes I, II and III

	J_{trans}(Hz)	J_{cis}(Hz)	R	ψ(°)
Ia	6.36	3.18	2.00	56.8
IIa	6.36	3.17	2.01	56.8
IIIa	6.36	3.17	2.01	56.8
Ib	6.13	3.28	1.87	55.8
IIb	6.24	3.28	1.90	56.0
IIIb	6.19	2.86	2.16	57.9

Table 3. Diaxial-diequatorial equilibria and free energy differences for *trans* - 2,3 - dialkoxy - 1,4 - dioxanes

	% diaxial from J_{EF} (^{13}C satellite)	% diaxial from J_{AB} and J_{CD} (AA'BB' analysis)		ΔG°_{ea} (kJ/mol)
Ib	96	88	92	5.4
IIb	96	88	90	5.0
IIIb	46	51	54	0.2

$$J_{CD} = y\,J_{aa} + (1 - y)\,J_{ee}$$

$$J_{aa} = 11.7\ \text{Hz} \quad J_{ee} = 1\ \text{Hz}$$

It was *a priori* somewhat surprising that, whereas in the compounds Ib and IIb the equilibria were shifted towards the diaxial form, according with previous results in the 2,3 - dialkoxy - 1,4 - dioxane series, in the case of IIIb, were the bulk of the substituents reaches a maximum, practically none of the conformers was predominant.

These results could be confirmed by the measurements of J_{EF} between the acetalic protons (Fig. 6). Since these protons are chemically equivalent, the measure must be performed on the basis of the ^{1}H–^{13}C satellites corresponding to their signals (Table 1). A second population analysis was performed with these data using the coupling constants of 5 - t - butyl - 2,3 - dimethoxy - 1,4 - dioxans as a model.[1h]

$$J_{EF} = x\,J_{aa} + (1 - x)\,J_{ee}; \quad J_{aa} = 6.2\ \text{Hz} \quad J_{ee} = 1\ \text{Hz}$$

Results of this analysis (Table 3) completely confirmed those obtained by the analysis of the AA'BB' system.

DISCUSSION

The preference of *trans* - 1,4 - dioxanes with electronegative substituents in positions 2 and 3 to adopt a diaxial conformation has been traditionally interpreted in terms of the anomeric effect, i.e. the preference of electronegative substituents in position 2 of tetrahydropyrane rings for the axial orientation.[8] Several controversial theoretical models for the explanation of the anomeric effect have been proposed.[9]

The conformational analysis of compounds Ib and IIb

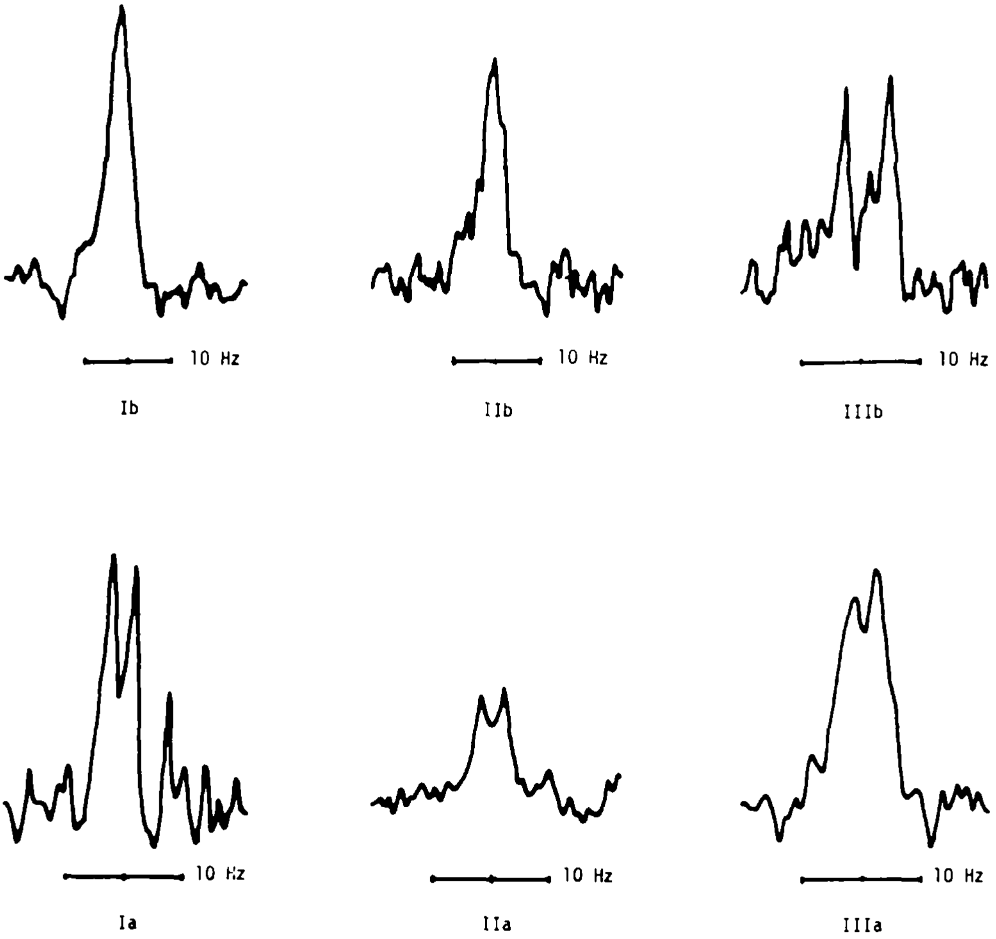


Fig. 6. ^{13}C satellite signals from acetalic protons in 2,3 - dialkoxy - 1,4 - dioxanes I, II and III.

gives to results in good agreement with those previously described for *trans* - 2,3 - dichloro, -difluoro, -dibromo, -dimethoxy, -diphenoxy and -diacetoxy - 1,4 - dioxanes.[1] A statistical weight major than 95% of the diaxial conformer was found in all of these cases. On the contrary, the diaxial and diequatorial conformers of compound IIIb have approximately the same population. A similar situation has been previously described for the *trans* - 2,3 - bis(trimethylsiloxy) - 1,4 - dioxane. Fuchs *et al.* reported a *ca* 1 : 1 diaxial/diequatorial equilibrium for this compound from ^1H and ^{13}C NMR evidence.[1h] These authors interpreted their results on the basis of a peculiar "reverse anomeric effect"[8c] which could arise either from the inductive effect of Si or from a $(p\rightarrow d)\pi$ O–Si bonding interaction. Since none of these factors can be present in the case of *trans* - 2,3-di - t - butoxy - 1,4 - dioxane (IIIb) it is clear that, at least for this compound, other effects must be invoked. As is shown in Table 4, it does not exist a clear correlation between the position of the conformational equilibrium in compound IIIb and the solvent polarity, and, therefore, an explanation based exclusively in electrostatic interactions must be excluded.[8d,10]

The dramatic change of the relative conformer stability in compound IIIb in comparison to compounds Ib and IIb, strongly suggests that the substitution degree in the α-C of the substituent plays an important role. This can be connected with the ν Charton steric parameters[11] based on the effective van der Walls radii (Bu^{t}O: 1.22, Pr^{i}O: 0.75, Bu^{t}CH$_2$O: 0.70, EtO: 0.48 and MeO: 0.36).

The term *exo*-anomeric effect was introduced in the series of 2-alkoxytetrahydropiranes to account for the preference of the aglyconic carbon to be in near synclinal orientation to both the ring oxygen and the anomeric hydrogen.[8b,d] The *exo*-anomeric effect has received recently very extensive experimental and theoretical attention and most probably the same kind of interactions that results in the anomeric affect[8,12] must be invoke to account for it.

If this effect operates in the case of 2,3 - dialkoxy - 1,4 - dioxanes, the conformation of the alkoxy substituents should be antiperiplanar to the C_2–C_3 bond of the ring. In order to test this expectation from a theoretical point of view, MNDO calculations were performed on the rotation of the OMe substituent in the axial conformer of 2 - methoxy-1,4 - dioxane, which was taken as a model

Table 4. Solvent effect on the conformational equlibrium for *trans* - 2,3 - di - t - butoxy - 1,4 - dioxane

solvent	J_{EF}	% diaxial
CCl_4	2.7	67
$DCCl_3$	3.8	46
CD_3CN	2.8	65

compound for the 2,3 - dialkoxy - 1,4 - dioxanes. Geometries were optimized in respect to all geometrical parameters except for those defining the bending of the ring, which were fixed at 57° in order to preclude the known tendency of MNDO calculations to flatten saturated six-membered rings. Results are summarized in Table 5.

Allowance of the free rotation of the OMe group led to the absolute minimum of the selected energy hypersurface. This corresponds to a 87° value of the ω angle, a conformation in which, according to the IUPAC criteria, the methoxy substituent adopts an antiperiplanar arrangement relative to the C_2–C_3 bond of the ring. It can be concluded that MNDO calculations[13] predicts the existence of *exo*-anomeric effect in alkoxy substituted dioxanes. It seems reasonable that the same effect operates in the case of *trans* - 2,3 - dialkoxy - 1,4 - dioxanes and thus the dimethoxy, diisopropoxy and dineopentiloxy compounds would be in a conformation that satisfies the requirements for the *exo*-anomeric effect. However, in the case of *trans* - 2,3 - di - t - butoxy - 1,4 - dioxane, simple examination of space filling molecular models of the diaxial conformation with both alkoxy groups antiperiplanar relative to the C_2–C_3 bond reveals the presence of unavoidable non-bonded repulsion with the axial hidrogen atoms on C_5 and C_6.

These repulsions can be easily released through opening of both (ω and ω') torsion angles (Fig. 7), but the resulting conformation does not satisfy any more the *exo*-anomeric requirements, being consequently destabilized relative to the diequatorial conformation, in which the interactions with annular H atoms are absent. The position of the equilibrium is then shifted to the diequatorial form. Perhaps these same arguments apply to the conformer relative stability in the *trans* - 2,3 - bis(trimethylsiloxy) - 1,4 - dioxane, previously studied by Fuchs *et al.*[1h] If our reasoning is correct, the *exo*-anomeric effect is of a primordial importance in the case of alkoxy substituents, so that the reason why bulky substituents minimize the anomeric effect would be the steric hindrance to reach the *exo*-anomeric conformation.

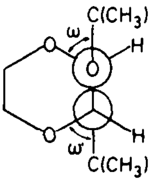


Fig. 7

REFERENCES

[1a] C. Altona, C. Romers and E. Havinga, *Tetrahedron Letters* 16 (1959); [b] C. Altona and C. Romers, *Acta Cryst.* **16**, 1225 (1963); [c] C. Altona and C. Romers, *Recl. Trav. Chim. Pays Bas* **82**, 1080 (1963); [d] R. R. Fraser and C. Reyes-Zamora, *Canad. J. Chem* **43**, 3445 (1965); [e] D. Jung, *Chem. Ber.* **99**, 566 (1966); [f] C. Altona and E. Havinga, *Tetrahedron* **22**, 2275 (1966); [g] B. Fuchs and A. Ellencweig, *J. Org. Chem.* **44**, 2274 (1979); [h] B. Fuchs and A. Ellencweig, *Nouv. J. Chem.* **3**, 145 (1979).

[2a] R. K. Summerbell and H. E. Lunk, *J. Am. Chem. Soc.* **79**, 4802 (1957); [b] E. Caspi, Th. A. Wittstruck and D. M. Piatak, *J. Org. Chem.* **27**, 3183 (1962); [c] C. Y. Chen and R. J. W. Le Febre, *J. Chem. Soc.* 558 (1965).

[3a] A. Bou, M. A. Pericàs and F. Serratosa, *Tetrahedron* **37**, 1441 (1981); [b] M. A. Pericàs, A. Riera and F. Serratosa, *Ibid.* **38**, 1505 (1982).

[4] W. Clark Still, M. Kahn and A. Mitra, *J. Org. Chem.* **43**, 2923 (1978).

[5a] J. B. Lambert, *J. Am. Chem. Soc.* **89**, 1836 (1967); [b] J. B. Lambert, *Acc. Chem. Res.* **4**, 87 (1971); [c] J. B. Lambert and H. Sun, *Org. Mag. Res.* **9**, 621 (1977).

[6a] H. R. Buys and H. J. Geise, *Tetrahedron Letters* 2991 (1970); [b] M. Davis and O. Hassel, *Acta Chem. Scand.* **17**, 1181 (1963)

[7] F. R. Jensen and R. A. Neese, *J. Am. Chem. Soc.* **97**, 4345 (1975).

[8a] R. U. Lemieux *et al. Ibid.* **80**, 6098 (1958); [b] R. U. Lemieux, Abstracts of Papers, *Ibid.* **134**, 5*E* (1959). [c] R. U. Lemieux, *Pure. Appl. Chem.* **25**, 527 (1971); [d] A. J. Hoog, H. R. Buys, C. Altona and E. Havinga, *Tetrahedron* **25**, 3365 (1969); [e] W. A. Szarek and D. Horton (Eds.) *Anomeric Effect, Origin and Consequences* A. C. S. Washington 1979 (A. C. S. Symposium Series No. 87).

[9a] L. Radom, W. J. Hehre and J. A. Pople, *J. Am. Chem. Soc.* **93**, 289 (1971); [b] S. Wolfe, A. Rauk, L. M. Tel and I. G. Csizmadia, *J. Chem. Soc.* B, 136 (1971); [c] S. Wolfe, *Acc. Chem. Res.* **5**, 102 (1972); [d] S. David, O. Eisenstein, W. J. Hehre, L. Salem and R. Hoffman, *J. Am. Chem. Soc.* **95**, 3806 (1973); [e] M. H. Whangbo and S. Wolfe, *Can. J. Chem.* **54**, 963 (1976); [f] I. Tavaroska and T. Bleha, *Ibid.* **57**, 424 (1979).

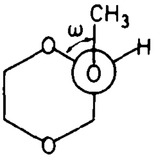
[10] J. T. Edward, *Chem & Ind.* 1102 (1955)

[11a] M. Charton, *Progr. Phys. Org. Chem* **10**, 81 (1973), [b] M. Charton, *J. Org. Chem.* **43**, 3995 (1978).

[12] H. Booth, T. B. Grindley and K. A. Khedhair, *J. Chem. Soc.* Chem. Commun., 1047 (1982).

[13] M. J. S. Dewar and W. Thiel, *J. Am. Chem. Soc.* **99**, 4899, 4907 (1977).

Table 5. MNDO calculated heats of formation of the conformations of axial 2 - methoxy - 1,4 - dioxane as a function of the torsional angle ω. (* values are referred to the calculated minimum energy conformation $\omega = 87°$, $\Delta H_f^\circ = -526.3$ kJ/mol)



	0°	60°	120°	180°	240°	300°
ΔH_f° (kJ/mol)	-498.6	-523.3	-522.8	-513.3	-503.5	-496.6
E_{rel} *	27.7	3.0	3.5	13.0	22.8	29.7