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CONFORMATIONAL ANALYSIS OF TRANS-2,3-DIARYLOXY-1,4-DIOXANES. A TOOL FOR DISCRIMINATING BETWEEN STERIC AND ELECTRONIC EFFECTS IN THE POSITION OF THE CONFORMATIONAL EQUILIBRIA OF SUBSTITUTED DIOXANES

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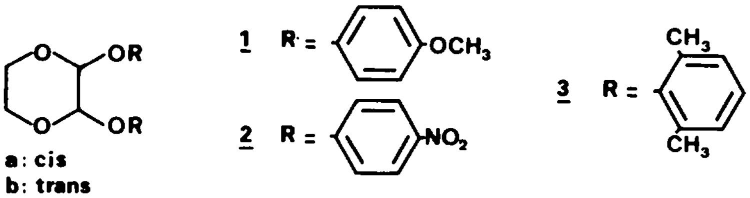
Abstract- The conformation of several trans-2,3-diaryloxy-1,4-dioxanes has been studied using ^{1}H NMR techniques. Trans-2,3-bis(4-nitrophenoxy)-1,4-dioxane and trans-2,3-bis(4-methoxyphenoxy)-1,4-dioxane have been found to be predominantly ($\simeq$98%) in diaxial conformation in $CDCl_3$. On the other hand, trans-2,3-bis(2,6-dimethylphenoxy)-1,4-dioxane exists in the same conditions as a 66:33 mixture of diaxial and diequatorial conformers. An explanation based on the fulfilment of the exo-anomeric effect is provided.

The continuous interest in the anomeric and related stereoelectronic effects has led in recent years to a considerable amount of studies devoted to the conformational analysis of symmetrical trans-2,3-disubstituted-1,4-dioxanes[1,3]. These substances are quite suitable for the study of the forementioned phenomena since, because of their symmetry, they lead to easily analyzed NMR spectra. In the series of 1,4-dioxanes trans-2,3-di(R)oxy substituted, the anomeric effect causes the diaxial conformers to strongly predominate with only two known exceptions[2]: i)B.Fuchs et al. reported in 1979 a ca. 1:1 equilibrium of diaxial and diequatorial forms in the trans-2,3-bis(trimethylsiloxy)-1,4-dioxane[3]. ii) We have recently found a similar behaviour of the trans-2,3-di-t-butoxy-1,4-dioxane[4]. Whereas in the first case either the electropositive character of Si or the existence of some $(p\rightarrow d)\pi$ O-Si bonding were invoked in order to explain the conformational behaviour in terms of a reverse anomeric effect, no obvious inductive effect could be found in our example, so that an alternative explanation ought to be provided.

The tentative explanation given in our first account on this subject for the conformational anomalies observed in 1,4-dioxanes bearing bulky substituents in the 2,3-positions introduced the idea that the lack of predominance of the diaxial conformer was caused by the steric bulk of the axial substituents through the destabilization of the exo-anomeric conformation[4]. In the meantime, some more reports have appeared on the experimentally determined conformations of 2,3-di(R)-oxy-1,4-dioxanes[5] and related aza-analogues[6]. In order to test the validity of our hypothesis and to evaluate the relative weight of electronic and steric factors on the manifestation of the anomeric effect, the study of the conformational equilibria in trans-2,3-diaryloxy-1,4-dioxanes appeared as quite promising: whereas electronic effects can be modulated by means of a proper choice of electron withdrawing or electron donating substituents in the p-position, steric effects can be enhanced by the introduction of bulky groups on the o,o'-positions of the aromatic rings. The only trans-2,3-diaryloxy-1,4-dioxane described so far in the literature is the diphenoxy derivative, and it has been reported that in $CDCl_3$ solution the conformational equilibrium for this compound is shifted ($\simeq$95%) to the diaxial conformer[3]. In this context we report the synthesis and conformational analysis of trans-2,3-bis(4-methoxyphenoxy)-1,4-dioxane 1 , trans-2,3-bis(4-nitrophenoxy)-1,4-dioxane 2 and trans-2,3-bis(2,6-dimethylphenoxy)-1,4-dioxane 3. The conformational analysis of the cis isomers is irrelevant because in all cases there is a fast degenerated equilibrium between two equivalent axial-equatorial chairs.



RESULTS.

Dioxanes 1, 2 and 3 were prepared from 2,3-dichloro-1,4-dioxane and the corresponding phenols. Separation of the trans-isomers of 1 and 3 was readily achieved by flash-chromatography on neutral alumina, eluting with hexane/ether mixtures. On the other hand, since separation of cis and trans isomers of 2 could not be achieved and there was no overlapping between their signals in the NMR spectrum, subsequent studies on 2 were performed with a cis/trans mixture. The ^{1}H NMR spectra of trans-1, trans-3 and cis/trans-2 were recorded in $CDCl_3$ solution and the complex signal corresponding to the $O-CH_2-CH_2-O$ moiety was analyzed as an AA'BB' system by means of the spectrometer built in LAOCOON 3 program (Figure 1). In every case, the spectrum synthetized from the calculated parameters was superimposable with the experimental one (RMS error less than 0.5 Hz). Moreover, the coupling constants between the homotopic acetalic protons were measured by means of the ^{13}C satellites. All spectroscopical data are summarized in table 1.

Table 1.- NMR data (in Hz) of trans-2,3-diaryloxy-1,4-dioxanes 1, 2 and 3 (* from AA'BB' analysis, ¶ from ^{13}C satellite, # directly measured).

	ν_A*	ν_C*	ν_E#	J_{AB}*	J_{CD}*	J_{AD}*	J_{AC}*	J_{EF}¶
1	860.7	718.8	1062.6	11.5	1.2	3.3	-12.1	<1
2	846.7	733.5	1102.1	11.5	1.0	3.3	-12.1	<1
3	853.3	739.8	1009.4	8.1	4.9	2.9	-11.9	2.6

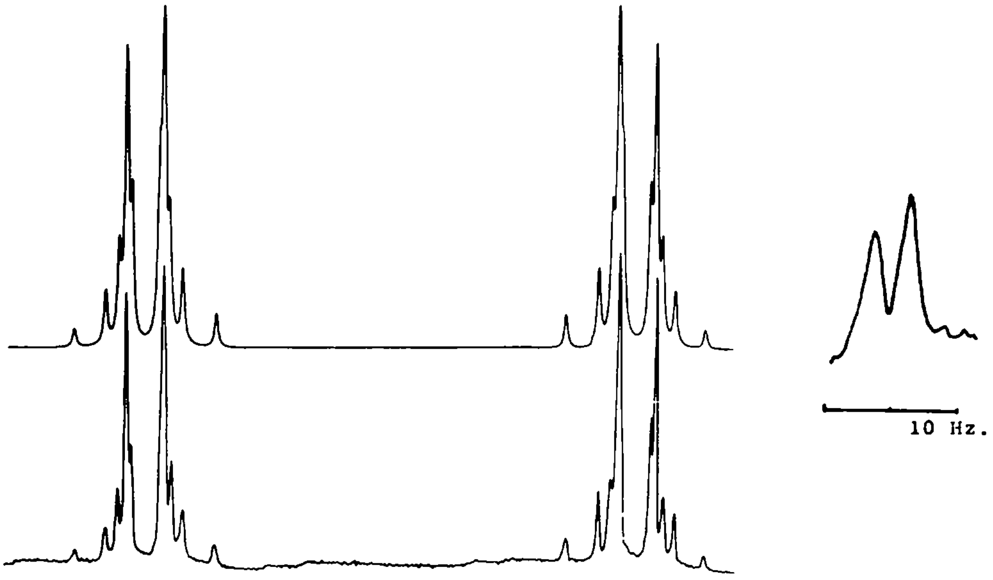


Figure 1. Calculated and observed spectrum of the AA'BB' system in trans-2,3-bis(2,6-dimethylphenoxy)-1,4-dioxane. ^{13}C satellite signal of the acetalic protons shown in the insert.

According to previous results, the conformational equilibrium shown in Figure 2 can be postulated for trans-2,3-diaryloxy-1,4-dioxanes.

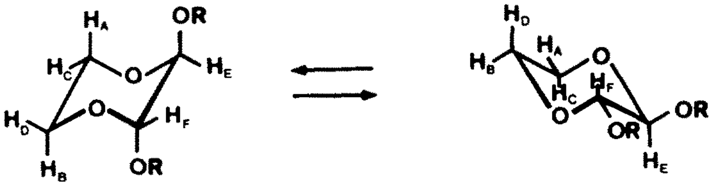


Fig. 2

The absence of geometrical distortions in the chair conformations of the studied compounds was ensured by calculation of the Ψ dihedral angle of the ring according to Lambert[7] (table 2).The deviations relative to the described 57° value for 1,4-dioxane were in all cases less than 2°.

Table 2.- Coupling constants, R values and ring dihedral angles of trans-2,3-diaryloxy-1,4-dioxanes 1, 2 and 3.

	J_{trans}(Hz)	J_{cis}(Hz)	R	Ψ(°)
1	6.35	3.28	1.936	56.3
2	6.25	3.28	1.905	56.0
3	6.51	2.86	2.276	58.6

Population analyses were subsequently performed by two independent ways: i) starting from the calculated coupling constants of the AA'BB' systems and ii) by using the ^{13}C satellite directly measured coupling constants between the acetalic protons.In the first case, the observed J_{aa} and J_{ee} values for deuterated dioxanes[8] (J_{aa}= 11.7 Hz ; J_{ee}= 1 Hz) were taken as standard values in the equations (where x and y are respectively the molar fraction of diaxial and diequatorial conformers):

$$J_{AB} = x\ J_{aa} + (1-x)\ J_{ee};\ J_{CD} = y\ J_{aa} + (1-y)\ J_{ee}$$

For the second population analysis, the observed J_{aa} and J_{ee} values for the 5-tert-butyl-2,3-dimethoxy-1,4-dioxanes[3] (J_{aa}= 6.2 Hz ; J_{ee}= 1 Hz) were taken as standard values in the equation:

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

Our results, summarized in table 3, clearly indicate that the presence in the para position of the phenyl ring of either an electron-withdrawing or an electron-donating substituent does not modify the position of the conformational equilibrium at all. On the other hand, the presence of two methyl groups in the o,o'-positions of the phenyl ring greatly modifies the position of the conformational equilibrium, leading to an important population of the diequatorial conformer.

Table 3.- Diaxial-diequatorial equilibria and free energy differences for trans-2,3-diaryloxy-1,4-dioxanes (# from ^{13}C satellite, * from AA'BB' analysis, ¶ calculated from the % diaxial averaged values)

	% diaxial from J_{EF}#	% diaxial from J_{AB}* and J_{CD}*		$\Delta G°_{ea}$(kJ/mol)¶
1	100	98	98	9.6
2	100	98	100	9.6
3	69	66	63	1.6

The possible influence of the polarity of the solvent on the position of the conformational equilibria was also investigated. No change was observed in the AA'BB' portion of the spectrum of trans-2, when more polar solvents were used (CD_3CN and CD_3SOCD_3) thus indicating that no modification of the equilibrium position had ocurred and, consequently, that no reverse anomeric effect was operating on this substance. On the other hand, the conformational equilibrium of trans-2,3-bis(2,6-dimethylphenoxy)-1,4-dioxane, which is already reasonably well balanced in $CDCl_3$ solution, should be more sensitive to solvent effects. When the NMR spectrum of trans-3 was recorded in more polar solvents (CD_3COCD_3 and CD_3SOCD_3), the conformational equilibrium was slightly shifted to the diequatorial conformer (table 4). The observed shift corresponds to a change of less than 0.9 kJ/mol in the ΔG°_{ae} value.

Table 4.- NMR data and population analysis of trans-2,3-bis(2,6-dimethylphenoxy)-1,4-dioxane 3 in different solvents. The values in $CDCl_3$ are also included here for comparison purposes. (* from AA'BB' analysis, # from ^{13}C satellite)

	J_{AB}*	J_{CD}*	J_{EF}#	% diaxial from J_{EF}#	% diaxial from J_{AB}* and J_{CD}*		ΔG°_{ea}(kJ/mol)
3 ($CDCl_3$)	8.1	4.9	2.6	69	66	63	1.6
3 (CD_3COCD_3)	7.0	5.7	3.2	58	56	56	0.7
3 (CD_3SOCD_3)	7.0	5.7	3.0	62	56	56	0.8

It can be thus concluded from our results that the presence of electron-donating or electron-withdrawing substituents in the para position of the aryl groups of trans-2,3-diaryloxy-1,4-dioxanes is irrelevant to the manifestation of the anomeric effect, whereas the presence of two methyl substituents in the ortho, ortho' positions of the aryl groups considerably reduces the manifestation of the effect.

It should be mentioned that in most of previous work on the anomeric effects in the 1,4-dioxane series the possible influence of the orientation of the ring substituents has been ignored, probably due to the lack of simple methods allowing to measure it. However, it can be of considerable importance in the case of R(oxy) substituents. In fact, the conformations of an acetalic system must be treated as a whole, and either simple qualitative stereoelectronic considerations, or molecular mechanics calculations[5] suggest that among the possible "diaxial" conformations, only the one fulfiling the requirements of the so-called "exo-anomeric" effect is clearly more stable than any of the possible "diequatorial" conformations. Thus, if the steric bulk of the axial substituents is increased up to a level in which a repulsive interaction appears between the considered substituent and the nearest axial hydrogen atom of the OCH_2CH_2O moiety of the ring, the "diaxial exo-anomeric" conformation can no longer be adopted and the set of diaxial conformers is destabilized relative to the set of the more extended, repulsion free, diequatorial conformers (Figure 2).

According to these ideas, our results constitute a solid evidence on the predominance of steric over electronic effects of the substituents in the inhibition of the anomeric effect in the series of trans-2,3-disubstituted-1,4-dioxanes.

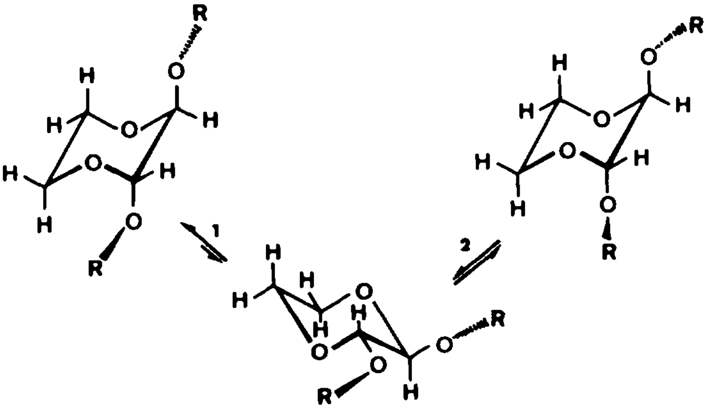


Fig 2.- Conformational equilibria stablished when R is small (1) and when R is large (2).

EXPERIMENTAL.

NMR spectra were recorded on a Varian XL 200 instrument operating in FT mode. IR spectra were recorded on a Perkin-Elmer 681 instrument. Melting points were determined on a Kofler microscope and are uncorrected.

2,3-Diaryloxy-1,4-dioxanes: Typical experimental procedure.

Trans-2,3-dichloro-1,4-dioxane (5 mmol) dissolved in 1,2-dicloroethane (80 ml) was mixed with the corresponding phenol (50 mmol) and K_2CO_3 (28g). With vigorous stirring, the mixture was heated under reflux overnight. Methylene dichloride (150 ml) was added at room temperature and the mixture was washed with 5% NaOH. After drying with $MgSO_4$ and solvent evaporation under vacuum, the crude mixture of *cis* and *trans*-2,3-diaryloxy-1,4-dioxanes was obtained. The *cis*/*trans* ratio found was 1a/1b: 30/70, 2a/2b: 70/30 and 3a/3b: 0/100. Chromatographic separation and/or purification was achieved by flash chromatography on neutral alumina (100-125 mesh, Actv. 1) eluting by hexane:ether mixtures.

***trans*-2,3-bis(4-methoxyphenoxy)-1,4-dioxane** (1b).(yield 50%); m.p. 114-5º; Found C,64.83%; H,6.08%. Calc. for $C_{18}H_{20}O_6$ C,65.05%; H,6.07%. NMR ($DCCl_3$): 7.0-6.8 (m, 8H), 5.31 (s, 2H), 3.5-4.3 (AA'BB', 4H) ppm. IR (KBr): 3070, 3050, 3000, 2960, 2940, 2840, 1510, 1465, 1445, 1235, 1210, 1185, 1150, 1145, 1030, 1010, 915, 875, 840 cm^{-1}

***cis* and *trans*-2,3-bis(4-nitrophenoxy)-1,4-dioxane** (2). (yield 50%); Found C,53.32%; H,3.86%; N,7.77%. Calc. for $C_{16}H_{14}O_8N_2$ C,53.04%; H,3.90%; N,7.73%. NMR ($DCCl_3$): 8.3-7.2 (m, 8H *cis*; 8H *trans*), 5.56 (s, 2H *trans*), 5.51 (s, 2H *cis*), 4.2-3.8 (AA'BB', 4H *cis*; AA'BB', 4H *trans*) ppm. IR (KBr): 3120, 3080, 3000, 2930, 2840, 1615, 1595, 1505, 1490, 1340, 1240, 1150, 1110, 1000, 920, 875, 850 cm^{-1}

***trans*-2,3-bis(2,6-dimethylphenoxy)-1,4-dioxane** (3b). (yield 60%); m.p. 110º; Found C,72.94%; H,7.36% Cal. for $C_{20}H_{24}O_4$ C,73.14%; H,7.37%. NMR ($DCCl_3$): 7.0-6.9 (m, 6H) 5.05 (s, 2H) 4.3-3.6 (AA'BB', 4H) 2.30 (s, 12H) ppm. IR (KBr): 3060, 3030, 2990, 2930, 2870, 1475, 1280, 1270, 1190, 1120, 1095, 1070, 1010, 980, 840, 780, 770, 635 cm^{-1}.

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