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STRUCTURE AND CONFORMATION OF HETEROCYCLES. 13[1]. CONFORMATIONAL ANALYSIS OF 2,3-DI(R)OXY-1,4-DIOXANES: ANOMERIC AND GAUCHE EFFECTS

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Abstract - A series of trans- and cis-2,3-di(R)oxy-1,4-dioxanes (R = Me,Ph, Ac) and some 2,5-disubstituted analogs were prepared and analysed by various NMR techniques. The trans isomers occur in more than 96% as diaxial conformers. Molecular mechanics calculations largely confirm these findings, which are interpreted in terms of combined anomeric and gauche effects.

INTRODUCTION

Within a comprehensive study of systems exhibiting anomeric and related effects[3-6], we are investigating 1,4-dioxanes and related heterocycles bearing polar substituents[2,7-10]. Such systems possess both 1,3- and 1,4-dihetero interactions, which should be manifest as typical anomeric[3-5] and gauche[6] effects. This report deals with the conformation of 2,3- and 2,5-di(R)oxy substituted 1,4-dioxanes. It follows on from our earlier fruitless efforts to prepare and study the unknown trans-1,4,5,8-tetraoxadecalin (6) as we had succeeded to do with the cis isomer (7) and some of its derivatives[8,9]. This elusiveness of 6 was interpreted as being due mainly to a destabilizing double chair form with all C-O bonds equatorially disposed, as opposed to the pairwise axial-equatorial arrangement in 7.

Hence, we decided to study the analogous but open system (1-3) along with the position isomeric one (4 & 5), in order to pinpoint the factors which operate in such systems and dictate their behaviour. We prepared the compounds (1-5) by known or some new synthetic methods and undertook a detailed ^{1}H-NMR spectroscopic study along with a theoretical probe using molecular mechanics calculations.

PREPARATIVE WORK

The dimethyl ethers (1 t,c)[11] were prepared by reacting trans-2,3-dichloro-1,4-dioxane with sodium methoxide in methanol, and resolved by glpc. The two isomeric 2,3-diacetoxy-1,4-dioxanes (3 t,c) were prepared following an earlier procedure[13] from commercial 2,3-dihydroxy-1,4-dioxane and acetic anhydride/Pyridine; they have been examined in the meantime[14] (but see discussion below). These diesters led us, in fact, to the isomeric diphenoxy ethers(2 t,c) after reacting with phenol in the presence of $ZnCl_2$, followed by chromatographic resolution and isolation.

Turning to the 2,5-disubstituted 1,4-dioxanes(4 t,c) and (5 t,c), they were prepared by published procedures[15,16] but resolution (by glpc) of the geometric isomers was made for the first time.

NMR SPECTROSCOPY

The isomeric 2,3-di(R)oxy-1,4-dioxanes were subjected to a detailed NMR investigation. Since

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† Deceased. This article is dedicated to the memory of Dr. Ulrich Burkert, after his untimely death in February, 1982.

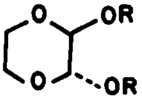
we are aware of the pitfalls which may occur in such studies, we decided to seek corroboration from a number of techniques and criteria in order to insure maximum reliability of our conformational analysis. The data are presented in Table 1.

The first step was configurational assignment, which had not been done previously for most of the components in our hands. This was done by using the magnitude of the vicinal coupling constants both in the AA'BB' pattern of the C^5H_2-C^6H_2 moiety and of the methinic C^2HOR-C^3HOR protons. Thus, of the two isomeric systems, the one exhibiting averaged coupling constants must be assigned the cis configuration with rapid interconversion of the two equienergetic forms (see Figure 1 for an elaboration of the numbering and definition of the spectral patterns).

Turning to conformational analysis, the first step was to make sure that we deal with chair forms of the 1,4-dioxane rings. This was done by calculation of the R values[18] and the corresponding torsion angles[19]. The magnitude of the parameters ($2.0<R<2.28$ and $57.2<\psi<58.7$ - see Table 1) leave no doubt about the chair geometry of all the compounds under consideration. In fact, this feature is eventually confirmed by all the other data as considered below.

The next step was to assess the mobility of the ring system. It was found that the NMR spectra of the trans compounds showed practically no temperature dependence while the cis isomers showed, as required, line broadening at low temperatures, ending up with well defined split patterns at -100°C[20].

Following that, the crucial step was to evaluate the detailed NMR parameters with special



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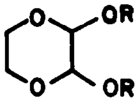

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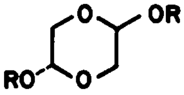

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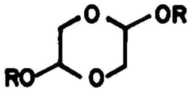

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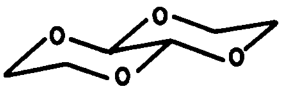
R = Me Ac

4 5



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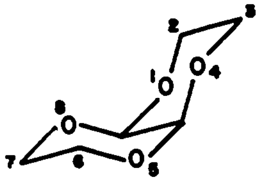

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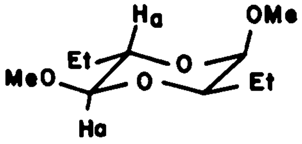

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attention to the vicinal coupling constants. These were secured for all the AA'BB' patterns of the C^5H_2-C^6H_2 systems in 1-3 t & c(see Table 1 and Figure 1a)by simulation technique using the LAOCN 3 program[17]. To ensure high reliability, the spectra were analyzed at two (or more) field strenghts[20] and corroboration was sought from additional quarters, the most informative being the analysis of the methinic protons. Since the latter are isochronous pairs (equvalent in the trans compounds and enantiotopic in the rapidly inverting cis compounds) (Figure 1) they were analyzed using both the bandwidth of their singlet and the ^{13}C-satellites.

Thus, the coupling constant values of 11-12 Hz are characteristic of $^3J_{aa}$ as those of ca.1.4 Hz and ca. 3 Hz are for $^3J_{ee}$ and $^3J_{ae}$, respectively, in a 1,4-dioxane ring[4c,20-22] of defined conformation. Similarly, averaged values of J_{trans}∿6.5 Hz and J_{cis}∿3Hz are well compatible with mobile 1,4-dioxane systems[4c,23]. As expected[24], introduction of an additional (electronegative) R-oxy group in the moiety under scrutiny, as in the 2,5-disubstituted derivatives (4 & 5) causes a decrease of all coupling constants in the (ABX) spectrum (Figure 1b), but the trend remains the same [4c,24].

As to the coupling constants between the methinic protons, we adopted an approach put forward by Chastrette *et al*[14] who have used model compounds to formulate a generalization, namely that J_{anti} and J_{gauche} in tetra(R)oxy-ethanes should be of the order of 7.1 and 1.2 Hz, respectively; we have however, reservations (*vide infra*) on some of these and other numeric values in their work.

The results of all our measurements are, hence, unequivocal. The *trans*-2,3-substituted compounds exhibit vicinal coupling constants which are consistent only with a system bearing *trans diaxial R-oxy groups* either in a non-inverting chair form I (Fig. 1) or, more likely (*vide infra*), in a fast equilibrium between I and II with the former in overwhelming excess. The *cis* isomers, however, exhibit vicinal coupling constants which are clearly averaged out over the time scale of the NMR measurement due to rapid ring inversion(III ⇌ IV) with corresponding axial-equatorial interconversion of the R-oxy group. This, in fact, supports the rapid ring inversion in the trans compounds since the inversion barriers should be, if anything, lower than in III ⇌ IV. Similar reasoning applies to the 2,5-di-substituted compounds 4 and 5. They exhibited ABX spectra which could be analyzed manually (Table 1 and Figure 1b) and interpreted accordingly.

At this point, it should be noted that one of our conformational assignments, namely of the diaxial *trans*-2,3-diacetoxy derivative (3t) is in contradiction of a previously published contention[14] that 3t exists as an almost equimolar equilibrium mixture of 1,2-diaxial and -diequatorial forms. This was based on an alleged value of 5.7 Hz for $J_{2,3}$ which, as seen (Table 1), we could not duplicate. Still, in this context, it is noteworthy that in an earlier short note, Hall[25] had analyzed by NMR *trans*-2,5-diacetoxy-1,4-dioxane and assessed its diaxial conformation. Hence, the acetoxy group forms no exception in its tendency to assume axial conformation in anomeric positions[44].

Additional, albeit qualitative support for our assignments is provided by the chemical shift data (Table 1). Thus, for the AB protons the difference σ_B-σ_A is about half as large for the *cis* as for the *trans* isomers. This is readily explained by the dynamic equilbirium mixture of the two equienergetic forms in the *cis* forms which also implies an axial-equatorial interconversion of the A and B protons (Fig. 1) with consequent reduced chemical shift between them, in contrast to the non-averaged situation in the *trans* isomer with the diaxial form in overwhelming excess. At the same time, the ^{13}C chemical shifts of the $C^{5,6}$ nuclei in the 2,3-disubstituted dioxanes and of the $C^{3,6}$ nuclei in the 2,5-disubstituted ones, are in the *cis* compounds larger by 2-3 ppm as compared with the *trans* isomers. This is clearly a γ effect following established trends[26,27] and would eventually become of diagnostic value if and when a larger body of data would be available. The same applies to the ^{13}C-H coupling constants ($^1J_{H-COR}$)[28].

Finally, we examined the solvent effect on the coupling constants of *trans*-2,3-dimethoxy-1,4-dioxane (1t) using in all cases simulation techniques. The data for four solvents are given in Table 2, but they are too few to warrant attempts for correlation analysis*. It appears that,

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*An attempt to correlate between experimental results and a calculated series of values for the various ^3J's in 1.4-dioxanes using the approach outlined in Ref.24 was considered, but is deferred to a later date, when a larger data base will be available.

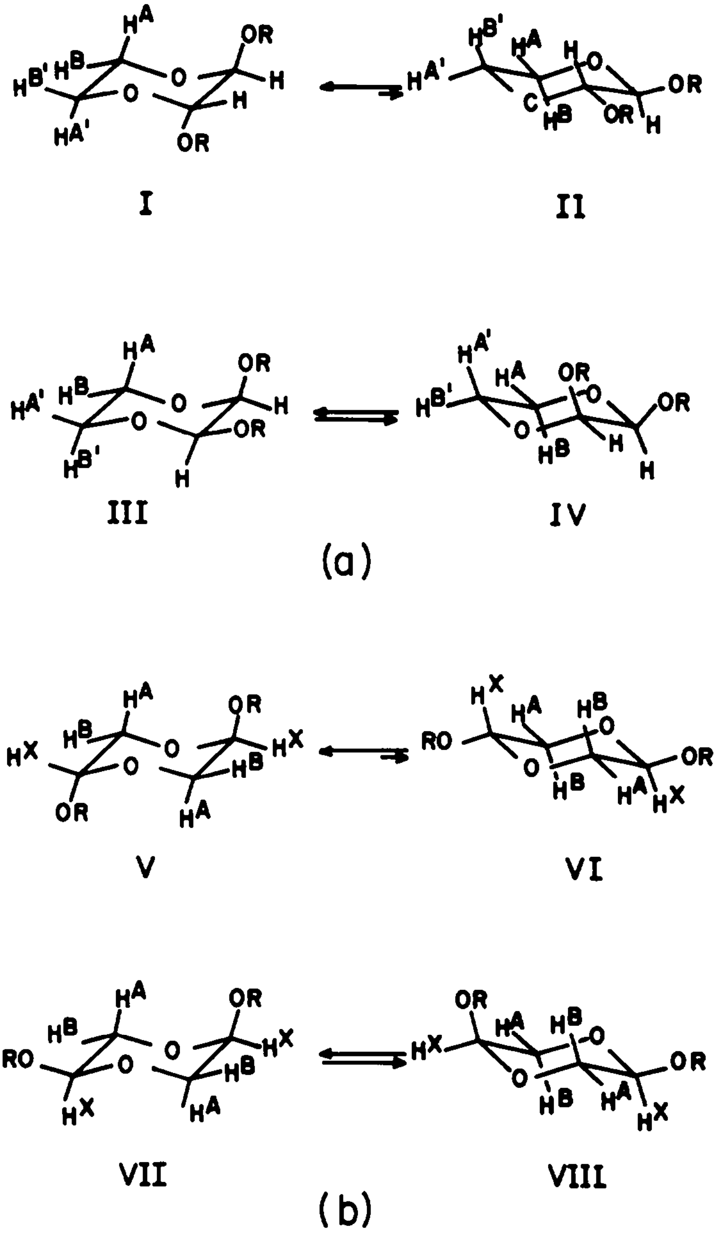

Fig. 1. Definitions and details of conformational equilibria in 2,3-di(R)oxy-1,4-dioxanes (a) and 2,5-di(R)oxy-1,4-dioxanes (b): I & V = trans-diaxial; II & VI = trans-diequatorial; III & VII = cis-axial equatorial; IV & VIII = cis-equatorial axial.

Table 1. NMR Spectroscopic data for the 2,3(and 2,5)-di(R)oxy-1,4-dioxanes (R = Me,Ph,Ac).[a]

Pattern	parameters	(i) *trans*[b] 1t	2t	3t	4t	5t	(ii) *cis*[b] 1c	2c	3c	4c
C^5H_2 – C^6H_2 (AA'BB')[c] or (ABX) C^2HOR – C^3H_2	$^2J_{gem}$	-11.52	-11.47	-12.47	-11.5	-12.60	-11.70	-11.86	-11.88	-11.80
	$^3J_{aa}$	11.30	11.79	12.02			6.35[h]	6.32[h]	6.30[h]	6.05[h]
	$^3J_{ee}$	1.47	1.45	1.15	1.45	0.8	"	"		
	$^3J_{ae(ea)}$	2.99	3.22	3.13	1.85	1.65	2.98	3.05	3.15	2.65
	$\delta_{A(A')}$	3.41	3.51	3.60	3.46	3.64	3.58	3.37	3.72	3.52
	$\delta_{B(B')}$[d]	4.06	4.24	4.18	4.02	4.21	3.94	3.69	3.95	3.78
	δ_X	—	—	—	4.51	5.95	—	—	—	4.48
C^2HOR – C^3HOR	$^3J_{2,3}$[e]	∿2	∿2	2			1.2			
	$W_{½}$[e]	1.3	1.3	1.4			0.4	0.5	0.4	
	$\delta_H^{2,3}$	4.34	5.37	5.76			4.46	5.34	5.97	
	$\delta_{OC\underline{H}_3}$	3.43			3.43		3.48			3.41
^{13}C	$\delta_{O\underline{C}H_3}$	54.78			53.50		55.82			53.69
	$\delta_{\underline{C}}^{2,3}$	96.55	93.46	88.10			97.52	94.81	88.03	
	$\delta_{\underline{C}}^{5,6}$	58.60	58.88	59.74			61.62	61.80	62.33	
	$\delta_{\underline{C}}^{2,5}$				93.98	88.23				94.89
	$\delta_{\underline{C}}^{3,6}$				59.68	61.36				61.43
	$^1J_{H-COR}$	171.4	167.0	170.0			165.5			
	R[f]	2.13	2.06	2.10			2.13	3.07	2.00	2.28
	ψ_{deg}[g]	57.7	57.2	57.5			57.7	57.3	56.7	58.70

a) Chemical shifts are in ppm from TMS as internal standard in $CDCl_3$ solution (ca. 5%); coupling constants are in Hz; cf. formulae in Figure 1 for numbering and definition of spectral patterns.
b) The data of 5tshow good agreement with those reported by Hall[25].
c) The AA'BB' patterns in compounds 1-3 t & c were analyzed by theoretical simulation using the LAOCN 3 program[17]; long range (1,3-diequatorial) interactions were not included after having made sure that they do not significantly alter the results other than some observed line broadening. The ABX patterns in 4 and 5 lent themselves to direct analysis, using double irradiation techniques.
d) Note the diagnostic value δ_B-δ_A: 0.56-0.73 ppm for *trans*, and 0.23-0.36 ppm for *cis* derivatives.
e) The magnitude of the couplings between the methinic protons ($^3J_{2,3}$) were evaluated from ^{13}C satellite spectra. The half-width ($W_{½}$) of the singlet was taken from the regular spectrum after optimising the natural bandwidth ($W_{½}$ of $CHCl_3$-0.35 Hz). In the cases where the satellites were poorly resolved we chose to quote upper limits for $^3J_{2,3}$.
f) $R = J_t/J_c = ½(J_{aa} + J_{ee})/½(J_{ae} + J\ )$[18].
g) $\psi_{deg} = \arccos\,[3/(2+ 4R)]^{½}$ [18,19].
h) These are average values of $½(J_{AB'} + J_{A'B})$ due to rapid ring inversion.

Table 2. Coupling constants within the C^5H_2 - C^6H_2 moiety of *trans*-2,3-dimethoxy-1,4-dioxane in various solvents (cf. footnote a in Table 1)

Solvent	J_{gem}	J_{aa}	J_{ee}	$J_{ae(ea)}$
CS_2	-11.23	11.10	1.45	2.98
$CDCl_3$	-11.52	11.30	1.47	2.99
CD_3CN	-11.95	11.00	2.00	3.51
CD_3OD	-11.95	10.95	1.84	3.32

within experimental error, similar vicinal coupling constants were obtained in the two less polar solvents CS_2 and $CDCl_3$, suggesting that in both, the system is virtually all diaxial. Moreover, even in polar solvents one can use the well known relation $J_{obs}=XJ_{aa}+(1-X)\ J_{ee}$ to calculate $11.00 = 11.3X + 1.47(1-X)$ and $X \approx 0.97$, i.e., the diaxial conformer prevails by more than 96% (for the sake of accuracy, we invoke this lowest limit: a lower ratio would have been observable in the variable low temperature spectra).

A similar approach for the evaluation of the conformational composition of the *trans*-2,5-disubstituted derivatives was made possible by using as model compound *trans*-2,5-diethyl-*cis*-3,6-dimethoxy-1,4-dioxane(8) which has a fixed conformation to keep both ethyl groups equatorial and exhibits $J_{aa} = 7.7$ Hz. Hence, for *trans*-2,5-dimethoxy-1,4-dioxane (4t) in which $J_{trans} = 1.45$ Hz (Table 1), and taking $J_{ee} = 1.2$ Hz as a lowest value[14], one calculated $J_{obs} = 1.45 = 7.7\ X + 1.2\ (1-X)$ and $X = 0.04$, i.e., the diaxial conformer constitutes 96% of the conformational mixture, in excellent analogy with the 2,3-derivative. Energetically, this means for the above discussed trans sytems, a diaxial vs. diequatorial free energy difference $\Delta G \geqslant 2$ Kcal/mol at 310°C (the temperature of the NMR probe).

MOLECULAR MECHANICS CALCULATIONS

In our quest for establishing reliable criteria for the evaluation of 1,4-dioxanes bearing polar substituents and hence of the anomeric and gauche effects, we sought theoretical complements to our experimental results. Since *ab initio* quantum mechanical methods are, for the time being, prohibitive for molecules of this size and semiempirical methods have proven themselves thoroughly inadequate*, the obvious choice was molecular mechamics (MM)[33].

To start with, we deemed it worthwhile to probe the system using Katritzky's quasi-quantitative (QQ) approach[31] to heterocyclic systems. This is actually a useful extension and elaboration of the classic gauche-butane interaction approach which has met with so much success since the early days of conformational analysis[5b]. It consists essentially in defining basic fragments which make up the system under scrutiny, and quantifying their conformational energies by direct or indirect methods. The conformational preference is subsequently evaluated by invoking a Boltzmann distribution of the conformer mixture. Although the Katritzky method has not been used frequently since its formulation[31], it has been applied successfully in nitrogen[31a,b] and oxygen heterocycles[32], and hence appeared to be attractive enough in spite of its approximate nature and mainly due to its handiness and versatility. We applied it (details available on request) to our system, specifically to *trans*-2,3-dimethoxy-1,4-dioxane (1t) and to the monosubstituted derivative (for comparison). Surprisingly good results were obtained (experimental results in parentheses): 2-methoxy-1,4-dioxane 71.7 (70[4f])% axial conformer; *trans*-2,3-dimethoxy-1,4-dioxane (1t) 94.4 (>96)% diaxial conformer.

While these (QQ) results were gratifying, we aimed for a more precise (MM) calculation of the entire family of *trans*-2,3-dimethoxy-1,4-dioxanes (1t), both in symmetric form as depicted in Fig. 2 as well as in unsymmetric conformations. For comparison we also decided to calculate *trans*-(6) and *cis*-1,4,5,8-tetraoxadecalin (7) whose structure we had studied in detail previously[8].

To this end we used a force field based on Allinger's MM[36] but modified for oxygen containing compounds[37], which has been satisfactorily tested in carbohydrate calculations[38]. The calculated relative energies in the 2,3-dimethoxy-1,4-dioxane system are given in Fig.3, where only the most stable species in the series were included. As to the 1,4,5,8-tetraoxadecalin system, the *cis* isomer (7) was calculated to be more stable than the *trans* isomer (6) by 3.78 kcal/mol while with MM2[39] we calculated 3.39 kcal.mol . Since, following our findings in the *trans*-1,4,5,8-tetraazadecalin system[1,10] we wondered about the possible occurence of a double-twist-boat conformation in

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*For example, simple CNDO or INDO calculations of 6 and 7 results in $E_7 > E_6$, in flagrant contrast to reality. Similar failures were registered with MINDO/3 calculations of carbohydrates[29]. It appears, though, that a recently reported PCILO calculation of 2-methoxytetrahydropyran[30] succeeded in matching the experimental data (conformational composition) and in providing reasonable relative energies for the anomeric and *exo*-anomeric effects.

the tetraoxa analog, we calculated it to be 4.47 kcal/mol higher than the double-chair form (6); hence the cis isomer (7) is, in accord with experiment[7,8], by far the most stable isomer. It should be noted that even with this improved force field the C-O bond lengths and C-O-C bond angles, which are sensitive probes for the anomeric effect[41], did not reproduce well enough the experimental values[8*].

DISCUSSION

In contrast to the extensive conformational studies of 1,3-dioxanes[4d,40], the 1,4-dioxane system has been surprisingly little studied[2,4c,f,10,22,41] in particular derivatives bearing (R)oxy substituents[2,4f,41] with special reference to the anomeric[3,4,5] and gauche[6] effects.

2-Methoxy-1,4-dioxane has been briefly reported (without a subsequent full account)[4f] to exist in ∿ 70% axial conformation in non-polar solvents and now we found for the di(R)oxy derivatives a preference for the diaxial conformation by more than 96%. Calculations (vide supra) corroborate these values.

To interpret and give some physical meanings to these experimental and computational results, we should like to pinpoint the relevant fragments in the molecules under scrutiny, with relation to their various geometries and energetics. While one can do this in a number of ways, the most concise and conclusive one appears to be the breakdown into dimethoxyethane (COCCOC) and dimethoxymethane (COCOC) moieties. The latter is, evidently, the basic grouping subject to "anomeric" effects[3,4] which means, conformationally, that the C-O-C-O-C unit prefers the $g^{\pm}g^{\pm}$form, as concluded both experimentally[42] and computationally[26,43,47], by as much as 2.4 kcal/mol over the next best $ag^{\pm}$ form; note that the preferred dimethoxymethan $g^{\pm}g^{\pm}$ conformation has two degenerate anomeric effects built in by virtue of its C_2 symmetry. When this basic unit is incorporated in the well known 2-methoxytetrahydropyran system, the stereoelectronic, "anomeric" effect is accompanied by steric interactions which have to be accounted for[4e], making the $g^{\pm}g^{\pm}$ conformation preferred (over the next best $ag^{\pm}$ form) by only ca. 0.7 kcal/mol[30,44]. Here, due to the lack of symmetry one has to differentiate between the 2-axial vs. equatorial "anomeric" effect and the even more pronounced "exo-anomeric" effect[30,34]. The latter operates, though, in both the axial and equatorial forms (see Figure 2 for visualization of all these interactions).

As to dimethoxyethane, the "gauche" effect[6] is by now well accepted to explain its behaviour in that the aaa and aga conformations are roughly equienergetic and make up about 80% of the population, followed by aag and agg with about 9 and 6% respectively, all the others trailing behind to make up the rest[45]. It remains now to analyze our system according to Figures 2 and 3 and the available data from this and earlier investigations.

Of the symmetric conformers displayed in Fig. 2 the diax: g^+g^+ and dieq: g^-g^- are clearly the preferred ones, each in its series; between then, the diax: g^+g^+ is favored by two anomeric effects while the COCCOC interactions make no appreciable difference. To quantify the anomeric effect in the 1,4-dioxane system, one could use the known conformational free energies for 2- and 3-acetoxytetrahydropyran which were evaluated[46] to -0.6 and +0.17 kcal/mol, respectively. The contribution of the steric effect should, in fact, be larger in our case since the four short C-O bonds in the 1,4-dioxane ring are bound to increase the 2,6-diaxial interaction therein. We come up then with an anomeric effect of about 1 kcal/mol or more (as compared to ca. 1.3 kcal/mol in the tetrahydropyran system[44]) and with an energy difference of ca. 2 kcal/mol. This is in good agreement with the experimental results, while the calculated (MM) value (3 kcal/mol) appears to be overestimated.

Applying the same reasoning to 2-methoxy-1,4-dioxane, we have the ax:ag^-g^- vs. the eq:aag^- conformations (cf. Fig. 2 for visualization), hence the axial form is favored by one anomeric effect while there is a slight difference in COCCOC interactions in favor of the second (equatorial) form. The axial form should then prevail by less than 1 kcal/mol which fits again the tentative experimental result[4f]. As to the 1,4,5,8-tetraoxadecalins, both isomers (6 and 7) have similar

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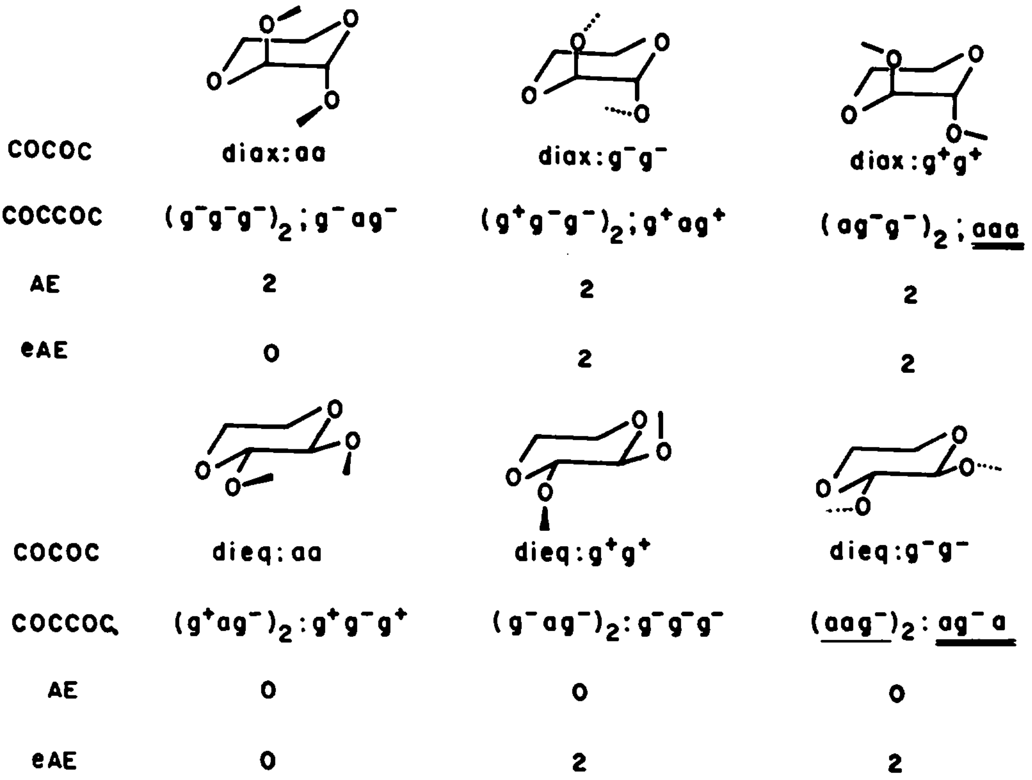
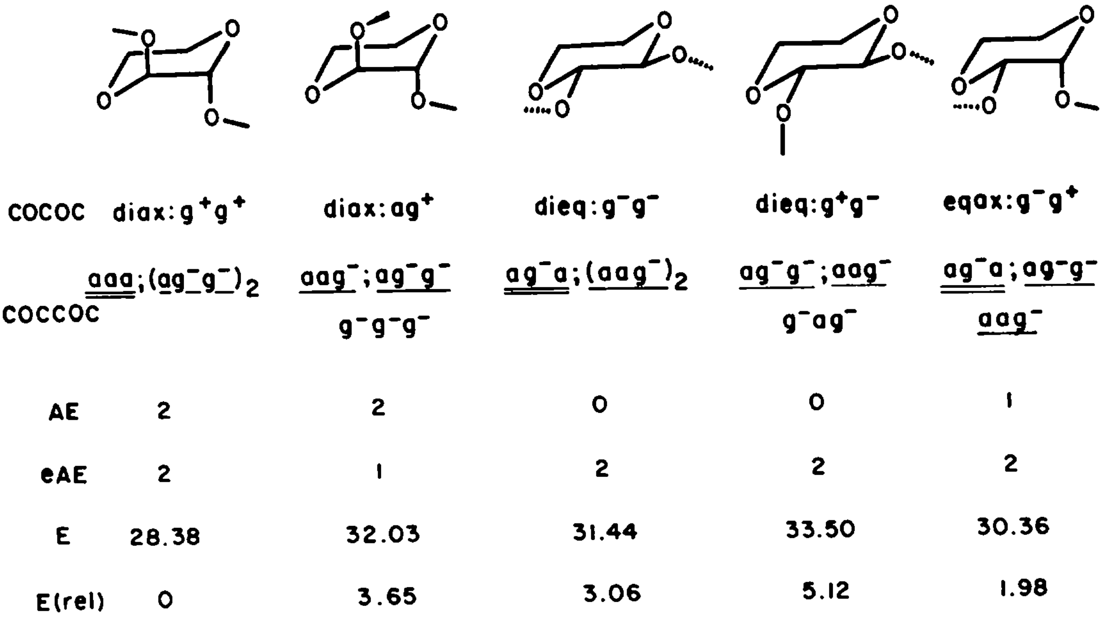
[*] After this work has been completed an article appeared[35] in which the tetraoxadecalins (6 & 7) were calculated by MM1; an energy difference between 6 & 7 of 3.95 kcal/mol was obtained but bond lengths and angles did not match well the experimental data.



COCOC	diax:aa	diax:g^-g^-	diax:g^+g^+
COCCOC	$(g^-g^-g^-)_2;g^-ag^-$	$(g^+g^-g^-)_2;g^+ag^+$	$(ag^-g^-)_2;\underline{\underline{aaa}}$
AE	2	2	2
eAE	0	2	2
COCOC	dieq:aa	dieq:g^+g^+	dieq:g^-g^-
COCCOC	$(g^+ag^-)_2:g^+g^-g^+$	$(g^-ag^-)_2:g^-g^-g^-$	$(\underline{aag^-})_2:\underline{\underline{ag^-a}}$
AE	0	0	0
eAE	0	2	2

Fig. 2. All the (symmetric) chair forms and substituent conformations and interactions for trans-2,3-dimethoxy-1,4-dioxane: a=anti, g=gauche, diax=diaxial, dieq=diequatorial. The notation for the (dimethoxymethane) COCOC moieties defines the two O-C-O dihedral angles and that in the (dimethoxyethane) COCCOC moieties defines the three O-C-C-O dehydral angles; AE=anomeric effect and eAE=exo-Anomeric Effect.



COCOC	diax:g^+g^+	diax:ag^+	dieq:g^-g^-	dieq:g^+g^-	eqax:g^-g^+
COCCOC	$\underline{\underline{aaa}};(\underline{ag^-g^-})_2$	$\underline{aag^-};\underline{ag^-g^-}$ $g^-g^-g^-$	$\underline{\underline{ag^-a}};(\underline{aag^-})_2$	$\underline{ag^-g^-};\underline{aag^-}$ g^-ag^-	$\underline{\underline{ag^-a}};\underline{ag^-g^-}$ $\underline{aag^-}$
AE	2	2	0	0	1
eAE	2	1	2	2	2
E	28.38	32.03	31.44	33.50	30.36
E(rel)	0	3.65	3.06	5.12	1.98

Fig. 3. Interactions and calculated energies (E in kcal/mol) for the most stable 2,3-dimethoxy-1,4-dioxanes: two in the trans-diaxial series, two in the trans-diequatorial series and one in the cis series (see also caption of Fig. 2 for notation and definitions).

COCCOC interactions: $(g^+ag^-)_2$ vs. g^+ag^+; $g^+g^+g^+$ but they differ in the anomeric geometry from two aa moieties in the trans isomer (6) to two $ag^{\pm}$ moieties in cis (7). This amounts to much more than two regular anomeric interactions ($g^{\pm}g^{\pm}$ vs. $ag^{\pm}$) and has been evaluated in dimethoxymethane by quantum-chemical calculations (ca. 5 kcal/mol!)[43] and by MM calculations (2.5 kcal/mol)[47]. As much as these results differ in magnitude, they show the same trend as our own calculated value of E_{7-6} = 3.79 kcal/mol and the complete elusiveness of (6) in reaction conditions under thermodynamic control.

In conclusion, we feel that we achieved good agreement from all the described approaches for obtaining a consistent picture of the 1,4-dioxanes bearing (R)oxy substituents as an interplay of anomeric and gauche effects. We shall report shortly on another probe of these effects in related systems.

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EXPERIMENTAL

NMR spectra were measured on Bruker WH-90, Jeol C-60-HL and Varian 300 MHz instruments. Theoretical spectra were calculated using the LAOCN 3 simulation program[17]. Mass spectra were taken on a Dupont 21-491 B mass spectrometer. Gas chromatography was performed on Varian Aerograph 1800 and HP-3850 instruments using a Carbowax 15% Chromosorb W column. Elemental analyses were performed at Scandinavian Microanalytical Laboratory, Denmark.

The NMR data are given in Table 1. All other physical data are given in Table 3.

trans-2,3-Dichloro-1,4-dioxane was prepared following the known literature procedure[12].

trans-and cis-2,3-Dimethoxy-1,4-dioxane (1t & 1c). To a methanolic sodium methoxide solution (made by dissolution of 1g. sodium in 50 ml. absolute methanol) 3.2 g trans-2,3-dichloro-1,4-dioxane were added in small portions, with stirring. Precipitation of sodium chloride occured immediately. The mixture was stirred 30 minutes at reflux and overnight at room temperature. After filtering and evaporation of the solvent, the residue was taken up in ether and washed with a 5% sodium bicarbonate solution and water, dried on $MgSO_4$ and evaporated to dryness. The residue was distilled in vacuo, b.p. 85-95°/17 Torr. to give 1.9 g (64%) of the stereoisomeric mixture, which showed (glpc) a composition of 1t:1c = 56:44. The latter was resolved by preparative glpc (140°C). The trans isomer (1t) emerged after 15 minutes followed by the cis isomer with r.t. 24 minutes.

The stereoisomeric mixture was also prepared following an old published procedure[11] but was subsequently resolved as above, to give the same pure isomers.

trans-2,3-Diisopropoxy-1,4-dioxane was obtained by an analogous procedure using sodium isoproxide in iso-propanol. The yield was 61%, b.p. 102-103°C/15 Torr. (no cis isomer was isolated).

trans- and cis-2,3-Diacetoxy-1,4-dioxane (3t & 3c)[9b].

Acetic anhydride (9.5 g) was added dropwise and with stirring to a solution of a commercial (Eastman-Kodak) diastereoisomeric mixture of 2,3-dihydroxy-1,4-dioxane (7 g) in dry pyridine (10 ml.). After stirring overnight, the reaction mixture was poured on ice and extracted with chloroform. The organic solution was washed well with dilute aqueous HCl and water and dried on $MgSO_4$. Evaporation of the solvent left 6.4 g of crude residue which on repeated crystallization from ether gave altogether 2.8 g (22%) trans-2,3-diacetoxy-1,4-dioxane (2t), identical with the substance described in an old procedure[48].

The mother liquor from above was thus enriched in the hitherto unknown cis isomer (2c), which was eventually isolated by preparative glpc (160°C) as a colorless oil. Anal. $C_8H_{12}O_6$ requires: C 39.50, H 6.03; found: C 39.10. H 6.00.

trans- and cis-2,3-Diphenoxy-1,4-dioxane(2t & 2c). A mixture of 3t & 3c (6.7 g), zinc chloride (0.33 g) and phenol (6.15 g) was heated in a 100 ml. flask at 95° for 30 minutes. After cooling, 150 ml. benzene were added and the organic solution was washed with water, 1N NaOH and water again. After drying on calcium chloride, filtering and removal of the solvent, a crude product (6 g) was obtained and chromatographed on neutral alumina (activity 3). The first compound to emerge (petrol ether/chloroform 19:1) was trans-2,3-diphenoxy-1,4-dioxane (2t)(2.2 g. 24%), m.p. 118-120°C (from ethanol). Next (petrol ether/chloroform 9:1) came a small amount (105 mg)of cis-2-chloro-3-phenoxy-1,4-dioxane: ν_{max} (CS_2) 1170, 950, 748 cm^{-1}; ms m/z 179 (10%, M-Cl), 178 (41), 121 (100), 94 (5), 77 (5); δ ($CDCl_3$/TMS) 4.2-4.36 (m, 4H, OCH_2-CH_2O), 4.67 (d, 1H, CHOPh, J = 3.0 Hz), 5.51 (d, 1H, CHCl, J = 3.0 Hz), 7.4-6.9 (m, 5H, C_6H_5). Finally, the same solvent mixture eluted cis-2,3-diphenoxy-1,4-dioxane (2c) (2.4 g,26%), m.p. 95-96°C (from ethanol).

An old literature procedure[49] gave only the trans-isomer.

trans- and cis-2,5-Dimethoxy-1,4-dioxane (4t & 4c).

The stereoisomeric mixture was obtained following literature procedures[15,16]. The pure stereoisomers, however, were isolated for the first time by preparative glpc resolution of the above mixture. At 105°C, cis-2,5-dimethoxy-1,4-dioxane (4c)(31% yield) emerged after 28.5 minutes followed by the trans isomer (4t) at r.t. 32.5 minutes (48% yield). A number of by-products (21%) were not further investigated.

trans-2,5-Diacetoxy-1,4-dioxane (5t) was prepared following an old literature procedure[15].

trans-2,5-Diethyl-cis-3,6-dimethoxy-1,4-dioxane (8) was obtained following a published procedure[50], by acid (H_2SO_4) treatment of α-hydroxybutyraldehyde dimethyl acetal and dimerization. Three main products were obtained and resolved by preparative glpc, with the following retention times at 120°: 15.5, 17.5 and 25 minutes. The first compound was isolated and assigned structure

8 on the strength of its spectral data.

Table 3. Spectroscopic (IR and MS) data of all compounds (1-8)

Compound	IR $\nu_{max}^{CCl_4}$, cm^{-1}	MS M/z (rel. abound. %)
1t	1188, 1158, 1114, 1078, 1062	148(0.1), 117(10), 88(60), 61(100), 60(28), 59(27), 45(52)
1c	1215, 1200, 1160, 1122, 1085, 1055	148(0.5), 117(5), 88(57), 61(100), 60(4), 59(15), 57(4), 45(42)
2t	1600, 1495, 1220, 1089, 1031	272(8), 199(19), 179(92), 178(100), 135(10), 121(38), 107(45),94(27), 86(37), 79(8), 77(27), 73(22), 69(19), 65(9), 57(11), 55(10)
2c	1600, 1485, 1233, 1225, 1120	272(13), 199(42), 179(98), 178(100), 149(11), 136(12), 129(12), 121 (43), 107(54), 94(42), 86(28), 77(40), 73(42), 69(24), 57(39), 55(41)
3t	1762, 1365, 1210, 1170, 1000	204(0.1), 161(2), 145(13), 103(8), 87(2), 73(17), 45(10), 44(8), 43 (100)
3c	1760, 1370, 1210, 1160, 1010	204(0.1), 161(1), 145(1), 103(1), 87(0.5), 73(2), 45(1), 44(5), 43 (100)
4t	1268, 1158, 1080, 1050	148(6), 117(22), 89(7), 73(9), 59(30), 58(100), 45(28)
4c	1272, 1200, 1140, 1065, 1050	148(0.2), 117(14), 85(7), 83(11), 73(12), 59(20), 58(100), 45(14)
5t	1760, 1330, 1215, 1155, 1070, 940	204(0.1), 159(2), 145(92), 131(12), 116(7), 103(8), 102(22), 86(12), 85(59), 74(3), 73(3), 57(5), 44(47), 43(100)
8	1180, 1155, 1100, 1080	204(3), 172(3), 115(2), 87(7), 86(100), 85(6), 73(12), 71(90), 58 (14), 55(10), 45(10), 43(67)

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