

INSIGHTS GAINED FROM CONFORMATIONAL ANALYSIS IN HETEROCYCLIC SYSTEMS

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ABSTRACT

A review of recent work in the conformational analysis of 1,3-dioxanes carried out at the University of Notre Dame is given. Work on 2-alkyl- and 2-alkoxy-substituted 1,3-dioxanes, 5-hetero-substituted 1,3-dioxanes and 5,5-geminally disubstituted 1,3-dioxanes is summarized. A novel four-component equilibrium approach to the evaluation of conformational energies is presented.

THE conformational features of the 1,3-dioxane and, to a lesser extent, the 1,3-dithiane six-membered heterocyclic rings have been investigated quite intensively during the last three or four years. Since our earlier work in this area has been published in detail^{1,2} and since several reviews of conformational analysis in heterocyclic systems are now available³⁻⁶, this summary will be concerned largely with recent and as yet largely unpublished work from the Notre Dame laboratories.

The 1,3-dioxane and 1,3-dithiane systems are convenient objects of study because, as shown in *Figure 1*, they are easy to synthesize with a wide variety of substituents in the 2-, 4- and 5-positions. Moreover, they show relatively simple n.m.r. spectra, the protons at C-2 ($X-CH_2-X$) usually resonating at appreciably lower field than those at C-4 and C-6 ($X-CH_2-C$) which in turn, are at lower field than those at C-5 ($C-CH_2-C$). Equilibration by means of Lewis acid is also facile (*Figure 2*) and nearly independent of the type and degree of substitution. In our earlier work we had usually effected equilibration by means of boron trifluoride ($\frac{1}{10}$ mole equivalent) in ether for the dioxanes¹; in the case of dithianes, which are less basic, ether competed too effectively for the Lewis acid catalyst and it was necessary to employ chloroform as the solvent and to raise the temperature to effect equilibration in reasonable periods. We have since found that Amberlyst-15 (Rohm and Haas; a beaded polystyrenesulphonic acid resin) is a more convenient catalyst for dioxane equilibration (besides being insoluble and easily removed after reaction, it appears to be less destructive, in some cases, than boron trifluoride) and that the soft acid⁷, antimony trifluoride, is more effective in the equilibration of 1,3-dithianes (soft base⁷!) than is the hard acid boron trifluoride⁸.

The insights gained from the conformational study of 1,3-dioxanes and 1,3-dithianes are concerned mainly with detailed experimental information regarding non-bonded interactions, including interactions of atoms containing unshared *p*-electrons (the ring oxygen or sulphur atoms) with 'fully

saturated' atoms, such as carbon and hydrogen, with other atoms containing unshared *p*-electrons and with groups containing pi-electrons such as $C\equiv N$.

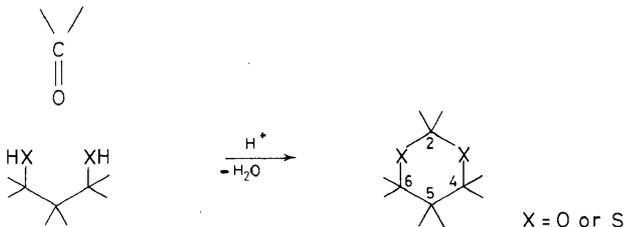


Figure 1

Also obtained is information on dipolar interactions in solvents of varying dielectric constant. Pertinent data will be presented; a complete understanding of the source of all the interactions will probably have to await comparison of experimentally observed with theoretically calculated values,

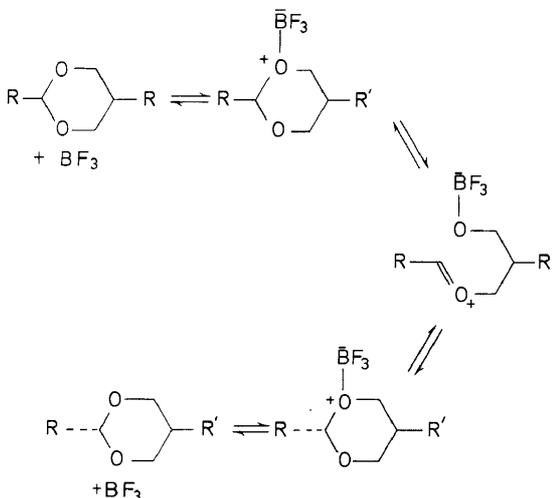


Figure 2

where the calculated values will probably be initially obtained by semi-empirical procedures^{9a}, but eventually, hopefully, by a more fundamental quantum-mechanical treatment^{9b}.

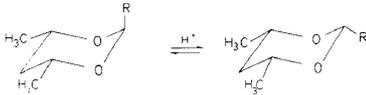
2-SUBSTITUTED 1,3-DIOXANES

The positions of equilibrium in a series of 2-substituted dioxanes (*cis* and *trans* isomers) are summarized in *Table 1*¹⁰. Within 0.1 to 0.2 kcal/mol (see below), the values given in *Table 1* probably correspond to the true conformational equilibria of alkyl groups in 2-alkyl-1,3-dioxanes. It is noteworthy that the $-\Delta G^0$ -values for 2-substituted 1,3-dioxanes are invariably higher than $-\Delta G^0$ values in cyclohexane (shown in *Table 1* for

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comparison); the reason lies in the shorter distance between the axial 2-substituent and the *syn*-axial hydrogens at C-4 and C-6 caused both by the shortness of the C—O bond (1.43 Å) compared to C—C (1.53 Å) and by the puckering of the 1,3-dioxane ring in the O—C—O region which was originally predicted¹ on the basis of model considerations and has now been confirmed¹¹ by x-ray measurements which show a torsional CO—CO angle of 63° in 2-*p*-chlorophenyl-1,3-dioxane.

 Table 1. 2-Substituted dioxanes¹⁰.



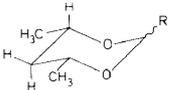
R	ΔG_{25}^0	ΔG_{cyc}^0
CH ₃	-3.97 ^a	-1.70
C ₂ H ₅	-4.0	-1.75
<i>i</i> -C ₃ H ₇	-4.15	-2.15
C ₆ H ₅	-3.1	-3.0
X—C ₆ H ₄	-3.1 to -3.2	?

X = *p*-F, *p*-Br, *p*-CF₃

^a The value for methyl represents a refinement over the one earlier reported¹ (-3.55 kcal/mol) and is now in better agreement with that determined calorimetrically (-4.07 kcal/mole; ref. 36).

The value for phenyl in *Table 1* is surprising, being considerably smaller than that for methyl, contrary to what is observed in the cyclohexane system. However, the fact is confirmed by the finding that in 2-phenyl-2,4,6-trimethyl-1,3-dioxane (ketal from *meso*-2,4-pentanediol and acetophenone) the stereoisomer with axial phenyl and equatorial methyl is much more stable than that with axial methyl and equatorial phenyl¹². A further surprise, shown in *Table 2*, lies in the fact that, whereas the coupling constants in the C-4/

 Table 2. Coupling constants (in Hz)¹⁰.



Conf.	R	J_{aa}	J_{ea}
<i>trans</i> .	Me	10.6	3.8
<i>trans</i>	Et	10.2	4.2
<i>trans</i>	<i>i</i> -Pr	10.4	4.2
<i>cis</i>	Et	10.0	3.8
<i>cis</i>	<i>i</i> -Pr	10.8	2.8
<i>cis</i>	Ar	{ 9.6 to 10.2	{ 3.7 to 4.2
<i>trans</i>	Ar	{ 7.6 to 8.2	{ 5.7 to 6.5
<i>cis</i>	} Me, Ph ^a	{ 10.4 9.0	3.8 4.2
<i>trans</i>			

^a Ketals derived from acetophenone.

C-5/C-6 region in the axially 2-substituted dioxanes with alkyl substituents are nearly the same as those of the isomers with equatorial alkyls, the same is not true for 2-phenyl-1,3-dioxane which shows a diminished J_{aa} and an enhanced J_{ea} when the 2-phenyl substituent is axial. It would appear that the more strained 2-axially substituted alkyldioxanes have the 'normal' 1,3-dioxane chair conformation whereas in the axial 2-aryl derivatives the chair is distorted by flattening. The phenomenon seems to be independent of the nature of the substituent on the phenyl ring (Tables 1, 2) and is thus not sensitive to polar influences:

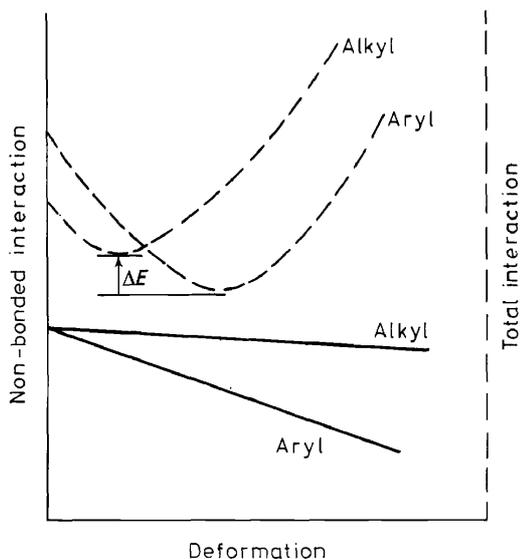


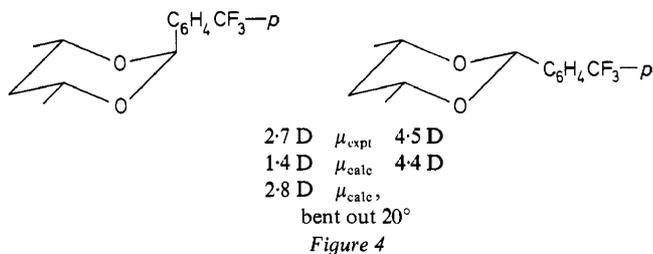
Figure 3

That the more distorted compound (axial 2-aryldioxane) is less strained than the less distorted one (axial 2-alkyldioxane) is quite unusual. It is possible that the van der Waals potential for an axially substituted 2-aryldioxane is unusually steep for relatively small deformations (Figure 3) and that this type of compound therefore improves its energy greatly by deformation, to the point that it becomes more stable than the corresponding 2-alkyl compound which has a normal potential and cannot gain as much by deforming itself. This explanation is not entirely unreasonable, in as much as the interaction of the phenyl group may be mainly an interaction of the pi-electrons which may be very sensitive to distance[†]. However, it must be admitted that the entire anomaly of the 2-aryl groups may be alternatively explained by some unusually strong steric strain in the equatorial phenyl isomer. This problem might perhaps best be resolved by heat-of-combustion measurements which should show whether the axial isomer is unusually

[†] This involves the assumption that the phenyl group confronts the *syn*-axial hydrogens 'broadside on'. The chemical shift of H-4 and H-6 (axial) in the axial 2-phenyl-4,6-dimethyl-1,3-dioxane (3.80 p.p.m.) is nearly the same as the corresponding shift in the equatorial phenyl epimer (3.75 p.p.m.), presumably because the phenyl group is bent out sufficiently so that H-4 and H-6 are no longer in the region of paramagnetic shielding.

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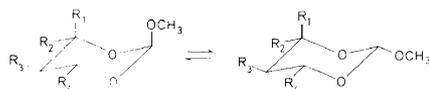
stable or the equatorial one unusually strained. Regardless of the source of the small strain difference, there is no question that the distortion of the axially 2-aryl-substituted dioxanes is real. In addition to coupling constants, comparison of experimental and calculated dipole moments in the case of the 2-*p*-trifluoromethylphenyl-4,6-dimethyl-1,3-dioxanes (Figure 4) confirms that the axially substituted isomer must have the phenyl group bent outward by a considerable angle.

 Dipole moments¹⁰


Equilibria in 2-alkoxy substituted 1,3-dioxanes^{10, 13-15} are summarized in Table 3. In 4-methyl- and *cis*-4,6-dimethyl-2-methoxy-1,3-dioxanes, the axial methoxyl group is preferred over equatorial, despite the unquestionable steric repulsion which must exist in the axial isomer. Here, as in the glycosides¹⁶ and in the simpler 2-alkoxytetrahydropyrans¹⁴, dipolar factors (less favourable interaction of the dipoles in the equatorial as compared to the axial alkoxy compound) more than overcome the steric factor. A detailed discussion of these dipolar factors in terms of the 'anomeric effect'¹⁶ or, in a more general sense, the 'rabbit ear' effect¹⁷ has been given elsewhere⁵. Here we shall discuss only two aspects of the data summarized in Table 3: the difference between the *cis*-4,6-dimethyl- and 4,4,6-trimethyl-2-methoxy-1,3-dioxanes and the difference between the 4,6-dimethyl- and 5-*t*-butyl-substituted compounds.

That the axial isomer in 2-methoxy-4,4,6-trimethyl-1,3-dioxane is less stable than that in 2-methoxy-*cis*-4,6-dimethyl-1,3-dioxane is clearly due to the additional *syn*-axial methyl-methoxyl interaction in the former.

Table 3. Equilibria in 2-methoxy-1,3-dioxanes.



2-Methoxydioxane	R ₁	R ₂	R ₃	R ₄	ΔG_{25}^0 kcal/mol	Ref.
4-methyl	H	H	H	Me	+0.36	14
<i>cis</i> -4,6-dimethyl	H	Me	H	Me	+0.41	10
4,4,6-trimethyl	Me	Me	H	Me	-0.05	10
5- <i>t</i> -butyl	H	H	<i>t</i> -Bu	H	+0.50 ^a	10
unsubstituted	H	H	H	H	+0.62 ^b	15

^a Value corrected for conformational inhomogeneity: 0.60 kcal/mol.

^b From dipole moment. All other values are by direct equilibration.

If we call this interaction X, it is clear (see top of Table 3) that for the trimethyl compound: $X + \text{Me}/\text{H}_4 + \text{MeO}/\text{H} = \text{Me}/\text{H}_4 + \text{Me}/\text{H}_2 + A + 0.05$ where A is the anomeric effect and $\text{Me}/\text{H}_2 = 1/2 \times 4$ (see above) = 2, whence

$$X + \text{MeO}/\text{H} = A + 2.05 \quad (\text{i})$$

$$\text{For the dimethyl compound: } 2 \text{ MeO}/\text{H} + 0.41 = A \quad (\text{ii})$$

$$\text{Subtracting (ii) from (i): } X - \text{MeO}/\text{H} = 2.46 \text{ kcal/mol}$$

i.e. the MeO/Me *syn*-axial interaction exceeds MeO/H by 2.46 kcal/mol. (It is not possible to calculate the interactions individually, since the magnitude of the anomeric effect A in 1,3-dioxane is not known.) A comparable value in cyclohexane is that for the difference of *syn*-axial OH/Me and OH/H interactions, which may be calculated to be 1.7 kcal/mol¹⁸. That the difference should be greater in the more compressed (*vide supra*) dioxane molecule is, of course, reasonable.

Whereas ΔG^0 for the 2-methoxy-4-methyl- and 2-methoxy-*cis*-4,6-dimethyl-1,3-dioxanes is 0.36–0.41 kcal/mol (Table 3), the corresponding value for the 5-*t*-butyl-2-methoxydioxanes, after correction for the conformational inhomogeneity of the *trans* isomer†, is 0.60 kcal/mole. Also, comparison of the dipole moment of the conformationally mobile 2-methoxy-1,3-dioxane (Figure 5), 2.24 D, with the average value (1.95 D) for axial (e.g. 1)

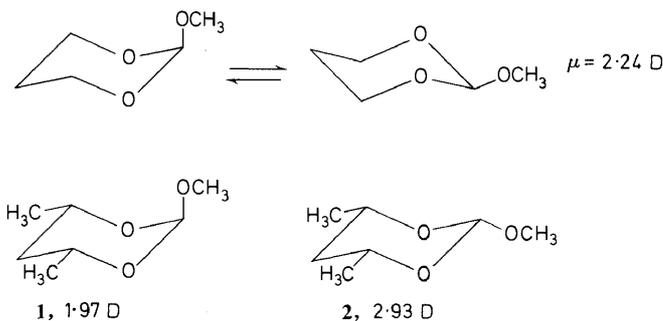


Figure 5

and that (2.91 D) for equatorial (e.g. 2) prototypes suggests a ΔG^0 -value (Figure 4) of 0.62 kcal/mol, using the relationship¹⁹ $\mu^2 = N_e \mu_e^2 + N_a \mu_a^2$. It is interesting that the ΔG^0 -values for the unsubstituted and the 5-*t*-butyl-substituted 2-methoxy-dioxanes are similar whereas those of the 4- and 4,6-substituted compounds are somewhat biased toward the equatorial

† The *cis* isomer will exist nearly entirely (*ca.* 95 per cent) in the conformation in which the 5-*t*-butyl substituent occupies the more stable equatorial conformation and the 2-methoxy group the more stable axial conformation. However, the *trans* isomer will not be entirely in the diequatorial conformation: it costs¹ only 1.4 kcal/mol to shift the 5-*t*-butyl group into the axial position and 0.4 kcal/mol is gained back by shifting the 2-methoxy group into the axial position (*vide supra*), thus $\Delta G_{ee \rightarrow aa}^0$ is 1.4 – 0.4 or 1.0 kcal/mol and only about 85 per cent of the molecules will exist in the *ee*-conformation. The concentration of the *ee*-conformational isomer is therefore 0.85 times the stoichiometric concentration of the *trans* isomer at equilibrium. In arriving at the 0.60 kcal/mol figure, the appropriate correction has been iterated for both epimers, even though for the *cis* compound it is very minor. For the methodology, see E. L. Eliel and R. S. Ro. *J. Amer. Chem. Soc.* **79**, 5992 (1957).

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methoxyl. The situation here is similar to that in cyclohexane²⁰; an explanation has been given²¹ in terms of a buttressing effect: equatorial substituents at C-4 and C-6 prevent the axial hydrogens at these positions from splaying outward and thus increase their *syn*-axial interaction with axial substituents at C-2.

The orthoformates shown in *Table 3* and *Figure 5* are easily prepared from trimethyl orthoformate and the appropriate diols by an ester interchange¹³⁻¹⁵; moreover, diastereoisomers are easily separated because of their large differences in dipole moments which give rise to a correspondingly large difference (about 15°C at 20 mm) in boiling point²². We have studied¹⁵ the stereochemistry of the reaction of orthoformates with Grignard reagents with the results shown in *Figure 6*. Axial 2-alkoxy-1,3-dioxanes react very

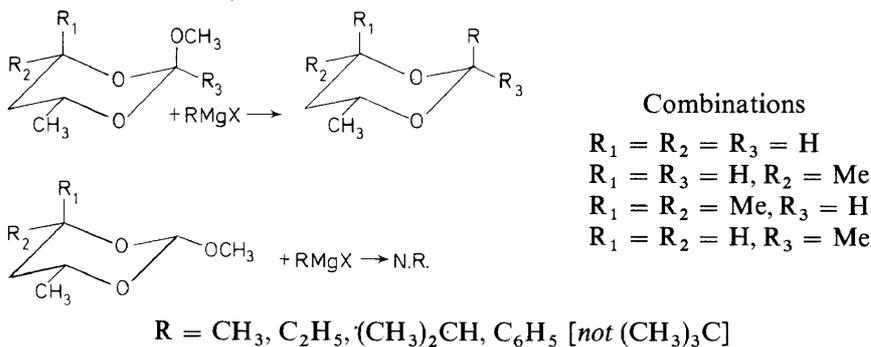


Figure 6

readily with Grignard reagents in ether at room temperature to give almost entirely axially substituted 2-alkyl-1,3-dioxanes. Under the same conditions, equatorially substituted 2-alkoxy-1,3-dioxanes are totally inert. The result has been interpreted¹⁵ in terms of maximum participation of the stereo-electronically favourably disposed axial electron pairs on the ring oxygens in the transition states for formation of the dialkoxy-carbonium ion (*Figure 7*) and for its reaction with the alkyl anion part of the Grignard reagent.

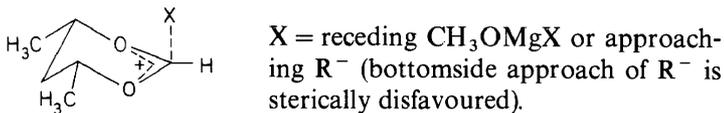


Figure 7

The reaction of 2-alkoxy-1,3-dioxanes (either axial isomers, or *cis-trans* mixtures, the equatorial isomer being inert with Grignard reagents) constitutes the synthesis of choice for 1,3-dioxanes with axial substituents in the 2-position which otherwise, because of the instability of the axial 2-substituent toward acid (cf. *Table 1*), are quite inaccessible. Unfortunately, only reduction takes place with *t*-butylmagnesium chloride and we have not yet been able to synthesize a 1,3-dioxane with an axial *t*-butyl substituent at position 2.

The reactions of the 2-alkoxy-1,3-dioxanes with lithium aluminium deuteride, aluminium deuteride and dichloroaluminium deuteride have also

been studied²³. The rather sluggish reaction with LiAlD_4 and the much faster reaction with AlD_3 differ substantially in mechanism from the Grignard reactions in that they proceed with predominant retention of configuration (Figure 8), probably through a four-centre mechanism. However, the reaction with AlCl_2D leads predominantly to the dioxane with axial deuterium.

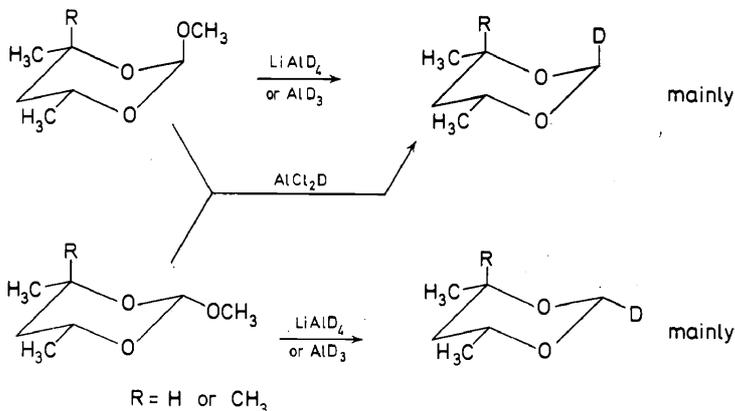


Figure 8

Presumably this reaction, like the reaction with Grignard reagents, proceeds via the dioxocarbenium ion. However, it differs from the Grignard alkylation in that *both equatorial and axial* 2-alkoxy-1,3-dioxanes react. This may be ascribed either to a lower overall activation energy for the dichloroalane reaction (so that participation of the *p*-electrons on oxygen becomes less crucial) or less probably to a rapid isomerization by AlDCl_2 of the equatorial 2-alkoxydioxane prior to reaction[†].

5-SUBSTITUTED 1,3-DIOXANES

Whereas the 2-substituted 1,3-dioxanes illustrate the interplay of polar factors with strongly repulsive non-bonded interactions, the 5-substituted systems present an interplay of polar factors with van der Waals interactions which are either only weakly repulsive or are actually attractive. A summary of the equilibria studied in 5-substituted 1,3-dioxanes is given in Table 4²⁴. It should be noted that, whereas in 2-substituted 1,3-dioxanes polar factors favour the axial conformation for an electron-withdrawing substituent, the contrary is true at C-5: because of the direction of the ring dipole, an electron-withdrawing substituent is more favourably disposed, on polar grounds, when equatorial.

A more detailed survey of 5-substituted 1,3-dioxanes is given in the following tables. Table 5 shows the equilibrium for 2-isopropyl-5-hydroxy-1,3-dioxane in various solvents[‡]. Because of intramolecular hydrogen bonding²⁵,

[†] In the absence of excess hydride, the 2-alkoxydioxane is rapidly destroyed in the reaction medium.

[‡] It should be noted that since the $-\Delta G^0$ -value for isopropyl is 4.2 kcal/mole (Table 1) and that for most of the 5-substituents studied is 1 kcal/mol or less, the compounds shown in Table 4 and the following tables are all essentially conformationally biased ('anacomeric'²⁶) toward the conformation with equatorial isopropyl, i.e. isopropyl at C-2 is a good 'holding group'.

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 Table 4. Equilibria in 5-substituted 1,3-dioxanes²⁴.

X	ΔG_{25}^0 (kcal/mole)	ΔG_{cyc}^0 ^a
CH ₃	-0.80	-1.70
OH	+0.89 (C ₆ H ₁₂)	-0.52
OMe	-0.83	-0.60
OAc	0.0	-0.60
F	+0.62	-0.15
Cl	-1.20	-0.43
Br	-1.44	-0.38
NO ₂	+0.38 (CCl ₄)	-1.10
CN	-0.21	-0.17
COOMe	-0.82	-1.27
CH ₂ OH	+0.27 (CCl ₄)	-1.65
CH ₂ OMe	-0.05	?

^a Corresponding values in cyclohexyl-X: J. A. Hirsch in *Topics in Stereochemistry*, Vol. 1, chap. 4. N. L. Allinger and E. L. Eliel, (eds). Interscience/Wiley: New York (1967).

the axial position of the hydroxyl group is preferred. The preference in an aprotic solvent (cyclohexane) is somewhat lessened as the concentration is increased, as the equatorial isomer gains in energy through intermolecular hydrogen bonding; a similar situation is observed in 4-*t*-butylcyclohexanol¹⁸. The equatorial isomer is actually favoured in a hydrogen donor solvent (alcohol), presumably because hydrogen bonding from solvent to hydroxy-dioxane is more effective when the hydroxyl group is equatorial than when it is axial. Again this situation has its parallel in cyclohexanol¹⁸, but the effect is much more marked in the 5-hydroxy-1,3-dioxane, presumably because the *intramolecular* hydrogen bond stabilizing the axial isomer is replaced by *intermolecular* hydrogen bonds stabilizing the equatorial one. A similar situation is found in solvent 1,2-dimethoxyethane and, though to a lesser extent, in solvent acetonitrile. These solvents must of course function as hydrogen acceptors.

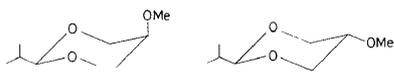
 Table 5. Conformational energy of hydroxyl²⁴.

Solvent	Conc. <i>M</i>	ΔG_{25}^0 kcal/mol	ΔG_{cyc}^0 ^a
C ₆ H ₁₂	0.05	+0.89	-0.60
	0.10	+0.86	-0.61
	0.20	+0.81	-0.61
CH ₃ CN	0.10	+0.04	—
	(MeOCH ₂) ₂	0.10	-0.51
<i>i</i> -PrOH	0.10	-0.71	-0.95

^a Corresponding value in C₆H₁₁OH, ref. 18.

The equilibria of the 2-isopropyl-5-methoxy-1,3-dioxanes in various solvents are tabulated in *Table 6*. The results show a (not very smooth) dependence of ΔG^0 on solvent dielectric constant \dagger . It appears that the strong preference of methoxyl for the equatorial position in solvent carbon tetrachloride is largely due to a dipole interaction, for in the high-dielectric solvent acetonitrile there is almost no difference in free energy between

Table 6. Conformational energy of methoxyl²⁵.



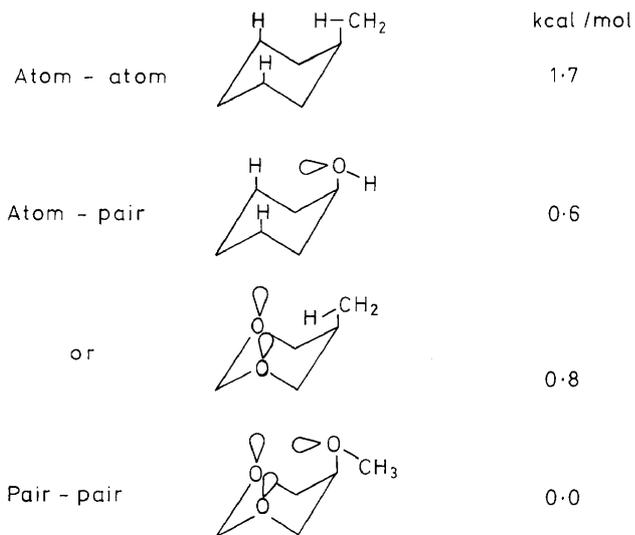
Solvent	ϵ_{25}	ΔG_{25}^0 (kcal/mol)
CCl_4	2.2	-0.89
Et_2O	4.3	-0.83
CHCl_3	4.8	-0.18
CH_3OH	32.6	-0.03
CH_3CN	37.5	+0.01

equatorial and axial methoxyl; in other words, the non-bonded (as distinct from dipolar) forces, if anything, slightly favour the axial isomer, in contrast to the situation in methoxycyclohexane where the equatorial conformation is preferred¹⁸ (see *Table 4*). The result is of particular interest because of the question of the relative magnitude of lone pair/lone pair interaction in comparison with, say, atom/atom and atom/lone pair interactions. The situation is summarized in *Figure 9*. The axial conformation of methylcyclohexane displays two *syn*-axial methyl/hydrogen interactions (atom/atom) of 0.85 kcal/mol each. The corresponding hydroxyl/hydrogen interaction in cyclohexanol or 5-methyldioxane (atom/pair) is 0.3 to 0.4 kcal/mol. The related pair/pair (oxygen/oxygen) interaction in 5-methoxy-1,3-dioxane (axial conformation) is very nearly zero, or at least the interaction for axial OMe is no greater than that for equatorial OMe.

ΔG^0 -values of other 5-substituents as a function of solvent are shown in *Table 7*²⁴. A complete interpretation of these data is not yet possible; for example, it is rather puzzling why fluorine with its relatively low polarizability prefers the axial conformation even in a solvent of such low polarity as ether whereas the more polarizable chlorine and bromine, which engender similar dipoles and are effectively only slightly larger in cyclohexyl halides, prefer the equatorial position, the difference being of the order of 2 kcal/mol. Strong solvent effects are found with almost all the substituents, the equatorial preference being least (or the axial preference greatest) in solvents of

\dagger The quantitatively predicted effect of solvent dielectric on ΔG^0 is complex. For a recent discussion, see ref. 27.

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Atom/atom > atom/pair > pair/pair

Figure 9

high dielectric constant, as already explained in the case of CH_3O . The substantial preference of NO_2 and CN for the axial position (in the case of CN only in the case of a high-dielectric solvent) is particularly interesting

Table 7. Dependence of conformational energies on solvent²⁵.

X	Solvent	ϵ_{25}	ΔG_{25}^0	ΔG_{cyc}^0 ^a
F	CH_3CN	37.5	+1.22	
	CH_3OH	32.6	+0.60	(-0.15)
	C_6H_6	2.3	+0.83	
	Et_2O	4.3	+0.62	
Cl	Et_2O	4.3	-1.20	(-0.43)
Br	Et_2O	4.3	-1.44	(-0.38)
NO_2	CCl_4	2.2	+0.38	
	CHCl_3	4.8	+0.63	(-1.10)
	CH_2Cl_2	9.1	+0.81	
CN	Et_2O	4.3	-0.21	(-0.17)
	CH_3CN	37.5	+0.55	
COOMe	Et_2O	4.3	-0.82	(-1.27)
	CH_3CN	37.5	-0.22	
CH_2OH	CCl_4	2.2	+0.27	(-1.65)
	$(\text{MeOCH}_2)_2$	6.8	-0.01	(-2.06)
CH_2OMe	Et_2O	4.3	-0.05	

^a Corresponding value in $\text{C}_6\text{H}_{11}\text{X}$.

and tends to suggest that there may be an attractive interaction between the pi-electron clouds in these functional groups and the *p*-electrons of oxygen†.

The fact that CH₂OH is more biased toward the axial position in the non-hydrogen-bonding solvent carbon tetrachloride than in the hydrogen acceptor dimethoxyethane might, at first sight, suggest that intramolecular hydrogen bonding is responsible for the axial preference, as had, in fact, been postulated^{28a} for the axial preference of CH₂OH over CH₃ in 5-hydroxymethyl-5-methyl-1,3-dioxane. However, it should be noted (*Table 7*) that there is a similarity in ΔG^0 between CH₂OH and CH₂OMe; in addition the solvent dependence of the CH₂OH group is not very different from that in cyclohexylmethanol²⁹: $-\Delta G^0 = 1.65$ kcal/mol in cyclohexane, 2.06 kcal/mol in isopropyl alcohol. Moreover, attempts to put into evidence an intramolecular hydrogen bond in *cis*-5-hydroxymethyl-2-isopropyl-1,3-dioxane surprisingly proved to be quite fruitless²⁴: the compound, in dilute carbon tetrachloride solution, shows a single OH-stretching band in the infra-red at 3 643 cm⁻¹ which is exactly the same frequency where the OH-stretching frequency of the corresponding *trans* isomer is found^{28b}. It would appear that steric or dipolar factors prevent the axial CH₂OH group from pointing into the ring in a position suitable for bonding to one of the ring oxygens^{28b}.

GEMINALLY DISUBSTITUTED 1,3-DIOXANES

The study of conformational preferences in geminally disubstituted cyclohexanes has been experimentally difficult³⁰. In contrast, the facile equilibration of epimers in the 1,3-dioxane series may be easily extended to geminally disubstituted species. 2,2-Disubstituted 1,3-dioxanes are readily available from 1,3-diols and ketones (cf. *Figure 1*), appropriate diols for synthesis of 4,4-disubstituted 1,3-dioxanes are available by the Prins reaction³¹, and the diols required for preparation of 5,5-disubstituted dioxanes are easily prepared either by the Tollens condensation of an alpha-branched aldehyde with formaldehyde or by reduction of dialkylmalonic esters. We have studied³² a series of 5,5-disubstituted compounds, using an isopropyl group at C-2 as the holding group; the results of equilibration are shown in *Table 8*. As had been found previously^{30a}, the ΔG^0 -values for rotamerically non-symmetrical substituents (e.g. ethyl, isopropyl, phenyl) are not additive (ΔG^0 values computed by subtracting ΔG_R^0 are shown, for comparison, in the last column of *Table 8*). The reason for non-additivity is that certain rotational conformations which are favoured in the monosubstituted rings become unfavourable in the geminally disubstituted compounds because of geminal interactions; as a result, the substituents are forced into less favourable rotational arrangements and become effectively 'larger'³³. An example for an equatorial ethyl group is shown in *Figure 10* (for any—unspecified—

† We had at one time thought that the preference of NO₂ (which has a very large group dipole of 3.3 D) for the axial position indicated a Coulombic attraction between the positive end of the NO₂ dipole and the electron clouds around the ring oxygen. However, the finding that the axial conformation is preferred more, rather than less, in a solvent of high dielectric constant speaks against a Coulombic interpretation.

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 Table 8. Dioxanes with geminal substituents in the 5-position³².

R	R'	ΔG^0 exp.	ΔG^0 calc.	ΔG^0 add.
CH ₃	C ₂ H ₅	+0.06	0.14	+0.13
CH ₃	(CH ₃) ₂ CH	-0.30	0.33	-0.18
CH ₃	(CH ₃) ₃ C	-0.81	-0.60	-0.60
CH ₃	C ₆ H ₅	-0.54	?	-0.23
C ₂ H ₅	(CH ₃) ₂ CH	-0.32	-0.33	-0.18
C ₂ H ₅	C ₆ H ₅	-0.51	?	-0.36
OH	CH ₃	-0.41	?	-0.49
CH ₃ O	CH ₃	+0.34	?	-0.07
CH ₂ OH	CH ₃	-0.68	?	-0.87
CH ₂ OCH ₃	CH ₃	-0.63	?	-0.85
NO ₂	CH ₃	-0.43 ^a	?	-1.24

^a in CCl₄. Other values are in ether.

six-membered ring): when R = H (monosubstituted ring), the favoured conformation of the ethyl group is **A** or its mirror image (where there is a single *gauche* interaction of the terminal methyl with the ring) rather than **B** (where there are two unfavourable *gauche* interactions), but when R = Me (geminally disubstituted ring) and extra *gauche* interaction is introduced in **A** but not in **B**, the energy advantage of **A** is destroyed, the rotational populations of the three rotamers are equalized and the overall energy of the equatorial ethyl group is increased.



Figure 10

The fourth column in Table 8 gives the calculated ΔG^0 taking into account all pertinent rotameric restrictions with the assumption that apart from these restrictions, ΔG^0 is the same as in a monosubstituted dioxane and setting the value of a *gauche* interaction as one-half the value of a *syn*-axial interaction. Unfortunately the difference between the additive values (column 5) and the calculated values (column 4) is not very large and it cannot really be claimed that the agreement with the latter is, overall, materially better than that with the former (it is slightly better in two cases and slightly less good in one). What is perhaps more striking is that even in the cases of rotamerically symmetrical groups, such as methyl and *t*-butyl, where ΔG^0 -values should be additive, appreciable deviations are found. It would appear, then, that buttressing or other interaction effects interfere with additivity of ΔG^0 -values even in these circumstances³⁴. Further work in the area of geminally disubstituted dioxanes is clearly called for and is under way.

FOUR-COMPONENT EQUILIBRIA³⁵

It occurred to us that the 1,3-dioxane system lends itself to the study of four-component equilibria of the type shown in *Figure 11*. The mechanism of establishment of such equilibria is evidently slightly more complex than that for the simple equilibria shown in *Figure 2*; somewhere along the line, following oxocarbenium formation, a bimolecular reaction followed by an interchange of diol (or carbonyl) components must occur, and, in fact, the equilibria are reached more slowly than the simple ones discussed so far and require higher concentrations of substrates. Whereas the cases shown in *Figure 11* merely serve to test the feasibility of the method (the predicted

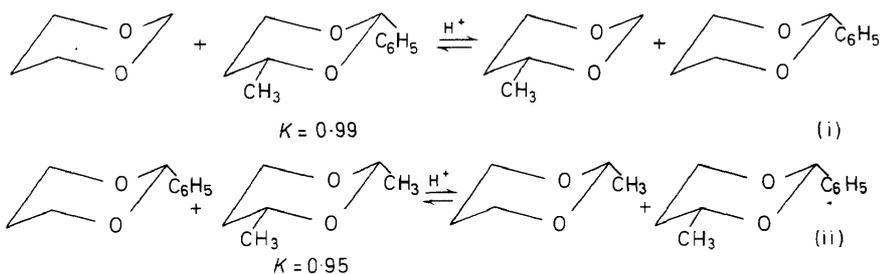


Figure 11

K is unity), some more interesting combinations are shown in *Figure 12*. The four-component equilibria result in a switch of the diol and the carbonyl parts of two different 1,3-dioxanes. In this way, one may study situations not accessible by simple equilibration. In particular, we are able to study buttressing effects, as in (iii) directly and we can assess quantitatively interactions which are too large to lend themselves to study by simple equilibration, as in (iv). In the latter situation, the very large *syn*-axial (or twist-boat) interaction on the left-hand side is partially compensated by the Me-2/H/H and Me-4/H/H interactions on the right; the sum of these latter interactions amounts^{1, 10} to 6.9 kcal/mol and the interaction in **3** on the left becomes accessible to experimental study even though it is as large as 7.2 kcal/mol.

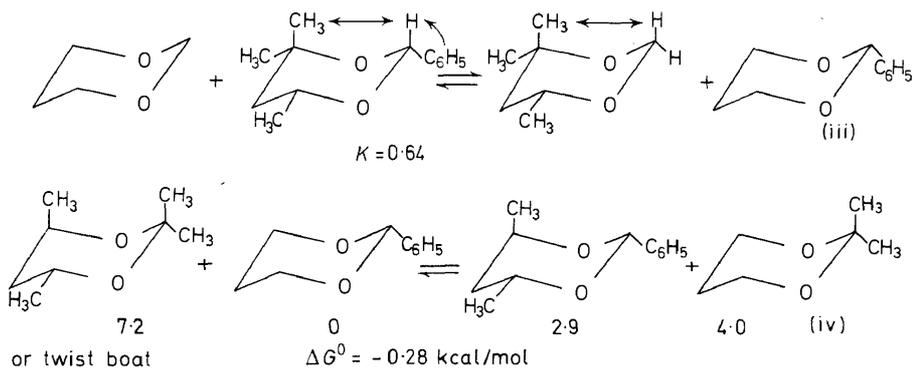


Figure 12

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The conformational ΔG -value of 7.2 kcal/mol for the tetramethyldioxane **3** (Figure 12) superficially appears to agree with the heat-of-combustion value of 7.1 kcal/mol recently determined by Pihlaja and co-workers³⁶. However, Pihlaja's value represents ΔH and should agree with ΔG only if the conformational entropy $\Delta S = 0$. It is hard to see how this can be true if **3** exists in the flexible form; the conformational entropy of this form should be at least 3.5 e.u.³⁶ so that a ΔG_{25} -value of 7.2 kcal/mol would require $\Delta H = 8.3$ kcal/mol. One is forced to conclude that either Pihlaja's experimental ΔH -value for **3** is too small, or **3** exists as a deformed chair rather than a twist-boat and does not have a large conformational entropy.

There is another finding¹⁰ suggesting that the $\Delta H = 7.1$ kcal/mol value³⁶ for the twist form in 1,3-dioxane is too low. Equilibration of the 2,4,4,6-tetramethyl-1,3-dioxanes (**4**, Figure 13) produces no palpable amount of the

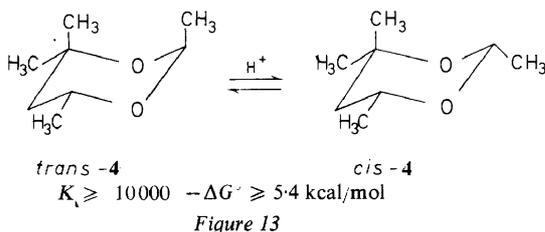


Figure 13

trans isomer at equilibrium (reached from either side) from which one may conclude that $-\Delta G^0$ for the process shown in Figure 13 exceeds 5.4 kcal/mol¹⁰. Adding 2.9 kcal/mol for the residual interaction on the right (Figure 13), the interaction on the left (in *trans*-**4**) must exceed 8.3 kcal/mol. Even if the boat form of *trans*-**4** has a residual conformational energy of 0.9 kcal/mol (*syn*-axial Me-4/H-6), if *trans*-**4** exists as a boat†, the conformational energy of the boat must amount to no less than 7.4 kcal/mol and its conformational enthalpy must therefore be probably well in excess of 8 kcal/mol, even allowing for the fact that equatorial methyl groups at C-4 and C-6 tend to make the boat form rather stiff and thus reduce its conformational entropy².

The combined thrust of the arguments is to suggest that ΔH_{boat} in 1,3-dioxane is well in excess of 8 kcal/mol; if **3** and *trans*-**4** are, in fact, in the twist or boat form, this follows directly from the above arguments; if either **3** or *trans*-**4** or both are in deformed chair forms rather than in boat forms, this fact by itself puts a minimum value of 8 kcal/mol on the instability of the boat form. The reason for the greater instability of the 1,3-dioxane boat or skew-boat form compared to that in cyclohexane (5.9 kcal/mol³⁷) may be sought in the greater compactness of the dioxane molecule which enhances the contribution which transannular interactions make to the high energy of the boat form.

† The coupling constants $J_{4,5}$ for *trans*-**4**, 6.8 and 7.9 Hz at 39°C (ref. 10), suggest the compound exists as a twist form at room temperature. The coupling constants are highly temperature dependent (values at -83°C 9.5 and 5.1 Hz, at +147°C 7.3 and 7.3 Hz) suggesting a transition from chair to flexible boat or from stiff boat to flexible boat as the temperature rises¹⁰.

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