

The Conformational Analysis of Saturated Heterocycles. Part XXVIII.¹ 5-Alkoxy-1,3-dioxans

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cis-trans-Equilibrium constants have been determined for a series of 5-alkoxy-2-aryl-1,3-dioxans. The rotamer populations of the *cis*-derivatives have been investigated by dipole moments. The relative stabilities of the individual rotamers of the various conformers are discussed in terms of specific intramolecular interactions. The range of applicability of the semiquantitative method of conformational analysis by assignment of constant energies to specific intramolecular interactions is surveyed by reference to literature data.

A SEMI-EMPIRICAL method for calculating conformational equilibria has recently been developed in this laboratory.^{2,3} The repulsions (and attractions) experienced in each stable rotamer of alternative conformers are broken down into certain standard interactions to which we can assign energy values. Rotamer, and hence conformer, populations are then calculated by the Boltzmann relation. The object of the present work was to extend the treatment, which had previously encompassed interactions involving C, H, and N, to molecules containing oxygen. We have therefore studied 5-alkoxy-1,3-dioxans by equilibration and by dipole moments. 1,3-Dioxan-5-spiro-2'-tetrahydropyran has been prepared and its dipole moment studied to test some of the conclusions reached.

EXPERIMENTAL

Dipole moments were calculated by the method of Halverstadt and Kumler⁴ from measurements of dielectric constant (ϵ) and specific volume (v) on the solvent (benzene) and four solutions. The specific volume was measured with a 5 cm.³ pycnometer. Dielectric constants at 25° were derived from measurements with a Wayne-Kerr B641 capacitance bridge by use of a glass cell.⁵ A value for the electronic polarisation was obtained by the summation of bond electronic polarisabilities.⁶ No allowance was made for atomic polarisation. As before,⁷ the dielectric constant and specific volume for benzene were taken as 2.2741 and 1.1446 respectively at 25°. The results are recorded in Tables 1 and 2.

Preparation of Compounds.—2-*p*-Chlorophenyl-1,3-dioxan (I) and *cis*-2-*p*-chlorophenyl-5-hydroxy-1,3-dioxan were prepared by the literature methods^{8,9} previously used for the preparation of the 2-phenyl analogues. 2-*p*-Chlorophenyl-5-methoxy- (II) and 5-alkoxy-2-phenyl-1,3-dioxans (IV, V, and VI) were prepared by treating the corresponding

5-hydroxy-1,3-dioxan with the appropriate alkyl iodide and silver oxide (*cf.* ref. 10); the reaction failed with *t*-butyl iodide. All the 5-alkoxy-dioxans used in the dipole moment study were shown to be >98% *cis* isomers by v.p.c

Equilibration of the *cis*- and *trans*-5-alkoxy-compound at 35° (IV, V, and VI) was achieved in 3—4 hr. by treating

TABLE 1
Dielectric constants and specific volumes in benzene
at 25°^a

	10 ⁴ <i>w</i>	(10 ⁴ (<i>v</i> ₁ - <i>v</i> ₁₂))	10 ⁴ (ϵ_{12} - ϵ_1)
<i>cis</i> -5-Methoxy-2-phenyl-1,3-dioxan			
	1060	317	3990
	1380	335	5840
	1530	421	6340
	2550	729	11,220
<i>cis</i> -5-Ethoxy-2-phenyl-1,3-dioxan			
	788	141	3620
	1050	—	4515
	1113	385	4615
	1925	596	8166
<i>cis</i> -5-Isopropoxy-2-phenyl-1,3-dioxan			
	777	306	3121
	920	370	3737
	1290	473	5270
	1815	537	7704
2-Phenyl-1,3-dioxan			
	1479	413	3375
	1920	571	4681
	1950	—	5613
	3560	947	9171
2- <i>p</i> -Chlorophenyl-1,3-dioxan			
	805	400	5372
	1158	568	7683
	1550	631	10,277
	3904	1450	26,805
1,3-Dioxan-5-spiro-2'-tetrahydropyran			
	3730	—	14,100
	3890	974	14,000
	5850	1170	22,100
	6300	2000	24,100
<i>cis</i> -2- <i>p</i> -Chlorophenyl-5-methoxy-1,3-dioxan			
	417	136	3206
	608	261	4803
	982	—	8415
	1177	381	10,016
1,3-Dioxan			
	1796	213	8546
	4430	332	—
	4860	369	25,800
	5250	404	29,890

^a *w* = Weight fraction. ϵ_1 and ϵ_{12} are the dielectric constants for solvent and solution respectively and *v*₁ and *v*₁₂ are the corresponding specific volumes.

¹ Part XXVII, R. A. Y. Jones, A. R. Katritzky, and P. G. Mente, *J. Chem. Soc. (B)*, 1970, 1210.

² A. R. Katritzky, *Bull. Soc. chim. France*, 1967, 3585.

³ P. J. Brignell, K. Brown, and A. R. Katritzky, *J. Chem. Soc. (B)*, 1968, 1462.

⁴ I. F. Halverstadt and W. D. Kumler, *J. Amer. Chem. Soc.*, 1942, **64**, 2988.

⁵ R. A. Y. Jones, A. R. Katritzky, K. A. F. Record, M. Snarey, and R. J. Wyatt, to be submitted to *J. Chem. Soc. (B)*; M. Snarey, Ph.D Thesis, University of East Anglia, 1968.

⁶ R. J. W. Le Fèvre and K. D. Steel, *Chem. and Ind.*, 1961, 670.

⁷ R. J. Bishop, L. E. Sutton, D. Dineen, R. A. Y. Jones, A. R. Katritzky, and R. J. Wyatt, *J. Chem. Soc. (B)*, 1967, 493.

⁸ E. Fischer, *Chem. Ber.*, 1894, **27**, 1524.

⁹ N. Baggett, J. S. Brimacombe, A. B. Foster, M. Stacey, and D. H. Whiffen, *J. Chem. Soc.*, 1960, 2574.

¹⁰ T. Purdie and J. C. Irvine, *J. Chem. Soc.*, 1903, 1021.

TABLE 2
Dipole moments of 1,3-dioxans in benzene at 25°^a

Substituents	$d\epsilon/dw$	$-dv/dw$	$P_{T\infty}$	P_E	μ (D)
<i>cis</i> -5-Methoxy-2-phenyl	4.4 ± 0.1	0.28 ± 0.02	210.5 ± 1.2	46.99	2.83 ± 0.01
<i>cis</i> -5-Ethoxy-2-phenyl	4.2 ± 0.1	0.32 ± 0.03	215.4 ± 1.3	51.62	2.83 ± 0.01
<i>cis</i> -5-Isopropoxy-2-phenyl	4.23 ± 0.05	0.30 ± 0.03	232.2 ± 0.5	54.21	2.95 ± 0.006
2-Phenyl	2.8 ± 0.1	0.28 ± 0.02	129.5 ± 0.9	44.48	2.04 ± 0.01
2- <i>p</i> -Chlorophenyl	6.88 ± 0.06	0.35 ± 0.02	304.9 ± 0.9	49.21	3.54 ± 0.006
5-Spiro-2'-tetrahydropyran	3.79 ± 0.07	0.33 ± 0.03	151.1 ± 1.2	39.28	2.34 ± 0.01
<i>cis</i> -2- <i>p</i> -Chlorophenyl-5-methoxy	8.5 ± 0.2	0.33 ± 0.04	424.4 ± 9.6	60.41	4.21 ± 0.03
	4.8 ± 0.1	0.12 ± 0.02	106.0 ± 0.9	20.97	2.04 ± 0.01

^a Errors in $d\epsilon/dw$ and dv/dw are quoted as ± 1 standard deviation based on the least-squares plot. These errors are combined to give the quoted error in μ .

benzene or carbon tetrachloride solutions of the *cis*-forms with anhydrous hydrogen chloride; acetals are known to equilibrate in acidic conditions.^{11,12} The ethoxy-compound (V) was on one occasion equilibrated with a mere trace of

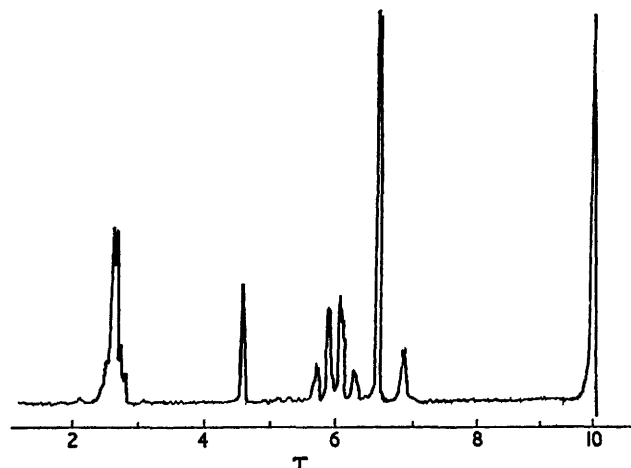


FIGURE 1 60 MHz ¹H n.m.r. spectrum of *cis*-5-methoxy-2-phenyl-1,3-dioxan, 10% solution in carbon tetrachloride

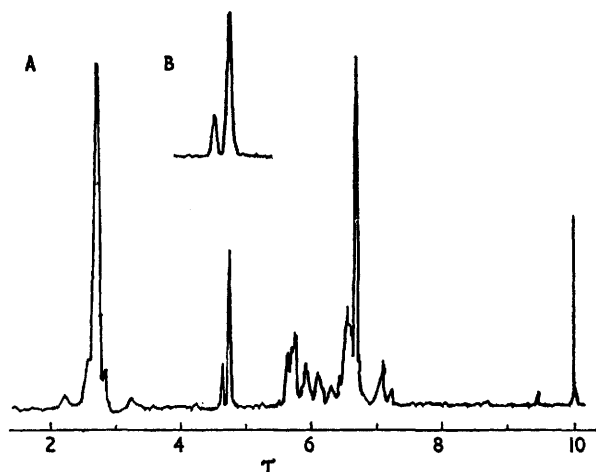


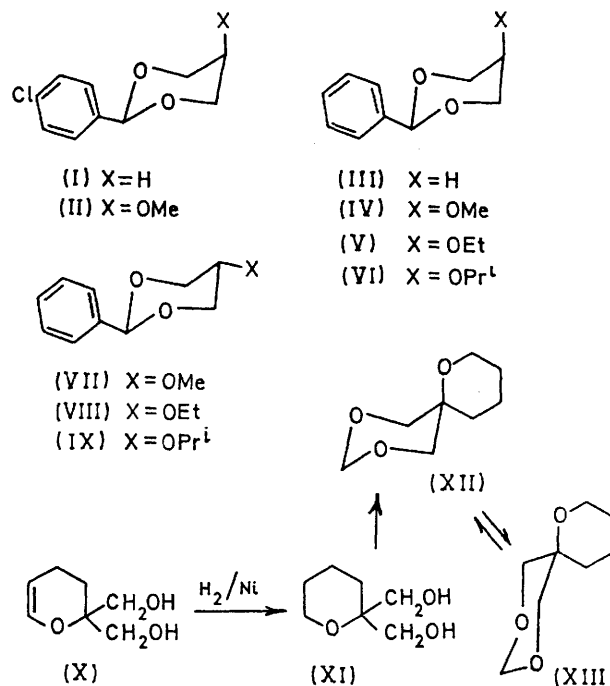
FIGURE 2 A, 60 MHz ¹H n.m.r. spectrum of *cis*-5-methoxy-2-phenyl-1,3-dioxan, 10% solution in carbon tetrachloride, treated with hydrogen chloride; B, expanded spectrum of the 2H-proton

hydrogen chloride; equilibration then needed 3 days, but the final composition of the equilibrium mixture was the same as when larger amounts of catalyst were used. The 2-posi-

¹¹ E. L. Eliel and Sr. C. Knoeber, *J. Amer. Chem. Soc.*, 1968, **90**, 3444.

tion protons for each pair of isomers showed different chemical shifts and the equilibrium constant was determined by integration: Figure 1 shows, as an example, the spectrum of *cis*-5-methoxy-2-phenyl-1,3-dioxan (IV), and Figure 2 shows the equilibrium mixture of it and the *trans*-isomer (VII).

2,2-Dihydroxymethyl-Δ⁵-dihydropyran (X) was converted into the spiro-compound (XII \rightleftharpoons XIII) by the route indicated.



2-Phenyl-1,3-dioxan.—This was prepared by Fischer's method;⁸ it was a low-melting solid, b.p. 134–136°/16 mm. (lit.,⁸ b.p. 125°/14 mm.) (Found: C, 73.1; H, 7.6. Calc. for C₁₀H₁₂O₂: C, 73.2; H, 7.4%). *cis*-2-Phenyl-5-hydroxy-1,3-dioxan⁹ had m.p. 80° (lit.,⁹ m.p. 79.5–80.5°).

2-(*p*-Chlorophenyl)-1,3-dioxan (I).—*p*-Chlorobenzaldehyde (21.05 g.), propane-1,3-diol (10.4 g.), and toluene-*p*-sulphonic acid (0.3 g.) were refluxed in benzene (100 ml.) with continuous removal of water from the azeotrope until no more was given off. The benzene was evaporated and the residue distilled at 81–83°/0.05 mm. to give the *dioxan* (5 g., 10%), m.p. 69.5–70.5° (Found: C, 60.2; H, 5.35. C₁₀H₁₁ClO₂ requires C, 60.45; H, 5.5%).

¹² F. G. Riddell and M. J. T. Robinson, *Tetrahedron*, 1967, **23**, 3417.

cis-2-(*p*-Chlorophenyl)-5-hydroxy-1,3-dioxan.—*p*-Chlorobenzaldehyde and glycerol were condensed in benzene as above with toluene-*p*-sulphonic acid as catalyst. After the mixture had been standing for 3 days at 5°, the crystals were filtered off and taken up in fresh benzene. The solution was washed with ammonium hydroxide, dried (MgSO₄), and the solvent removed. The dioxan (6 g., 10%) formed needles, m.p. 115.5–117° (from benzene) (Found: C, 56.0; H, 5.1. C₁₀H₁₁ClO₃ requires C, 55.95; H, 4.6%).

cis-5-Methoxy-2-phenyl-1,3-dioxan (IV).—The *cis*-alcohol (10 g.), chloroform (25 ml.), methyl iodide (40 ml.), and silver oxide (25 g.) were stirred at 20° for 2 days. The

was fractionated to yield the *spiro*-compound (2.5 g., 55%) as an oil, b.p. 74°/1 mm. (Found: C, 61.2; H, 9.2. C₈H₁₄O₃ requires C, 60.8; H, 8.9%). The n.m.r. spectrum (60 MHz) showed AB patterns centred at *ca.* τ 5.3 [2H: C(2)], 6.3 [4H: C(4) and C(6)], and 5.35 [2H: C(8)] and a broad singlet at τ 8.35 [6H: C(9), C(10), and C(11)].

2-Phenyl-1,3-dioxan-5-*spiro*-2'-tetrahydropyran.—This was prepared from benzaldehyde (0.75 g.), 2,2-dihydroxymethyl-tetrahydropyran (1 g.), and toluene-*p*-sulphonic acid (0.1 g.) as above. The product (0.5 g., 35%) recrystallised from ether-light petroleum (b.p. 40–60°) had m.p. 55–56° (Found: C, 71.5; H, 7.6. C₁₄H₁₈O₃ requires C, 71.8; H,

TABLE 3

Solvent effects on proton chemical shifts ^a of *cis*-5-alkoxy-2-phenyl-1,3-dioxans

Proton	Benzene ^b			Carbon tetrachloride ^c			Difference (p.p.m.)		
	OMe	OEt	OPr ⁱ	OMe	OEt	OPr ⁱ	OMe	OEt	OPr ⁱ
H(2) <i>ax</i>	4.50	4.50	4.52	4.60	4.58	4.59	–0.10	–0.08	–0.07
H(4,6) <i>eq</i>	5.79	5.81	5.91	5.84	5.82	6.00	–0.05	–0.01	–0.09
H(4,6) <i>ax</i>	6.39	6.39	6.37	6.16	6.12	6.10	+0.23	+0.27	+0.27
H(5) <i>eq</i>	7.40	7.25	7.20	7.05	6.92	6.85	+0.35	+0.32	+0.35
OMe	6.81	—	—	6.68	—	—	+0.13	—	—

^a P.p.m. on τ scale, measured at 60 MHz. ^b Benzene signal used as internal standard, τ taken as 2.7. ^c Tetramethylsilane used as internal standard.

TABLE 4

Equilibration of *cis*-5-alkoxy-2-phenyl-1,3-dioxans at 35°

Compound	Benzene-HCl			ΔG° (kcal./mole)	Carbon tetrachloride			ΔG° (kcal./mole)	ΔG predict ^a
	Relative area <i>cis</i>	Relative area <i>trans</i>	<i>K</i>		Relative area <i>cis</i>	Relative area <i>trans</i>	<i>K</i>		
OMe	0.8	1.7	2.12 \pm 0.08	0.46 \pm 0.02	0.63 \pm 0.014	2.07 \pm 0.014	3.34 \pm 0.08	0.71 \pm 0.01	1.05
OEt	1.63	4.73	2.90 \pm 0.03	0.65 \pm 0.01	0.65 \pm 0.02	3.30 \pm 0.03	5.07 \pm 0.21	0.99 \pm 0.02	1.06
OPr ⁱ	0.408	2.24	5.48 \pm 0.2	1.04 \pm 0.02	0.44 \pm 0.03	3.92 \pm 0.03	8.9 \pm 0.65	1.34 \pm 0.02	1.14

^a See text.

methyl ether was separated from the unchanged alcohol by column chromatography on alumina using benzene 20% in hexane as eluant. The *methoxy*-compound crystallised from benzene-hexane as prisms (2.5 g., 24%), m.p. 50–50.5° (Found: C, 67.8; H, 7.1. C₁₁H₁₄O₃ requires C, 68.05; H, 7.2%).

The other ethers were similarly prepared: *cis*-2-(*p*-chlorophenyl)-5-methoxy-1,3-dioxan (II), needles (from benzene-hexane) (31%), m.p. 107.5–108.5° (Found: C, 57.6; H, 5.9. C₁₁H₁₃ClO₃ requires C, 57.8; H, 5.7%); *cis*-5-ethoxy-2-phenyl-1,3-dioxan (V), needles [from light petroleum (b.p. 40–60°)] (15%), m.p. 53–54° (Found: C, 69.1; H, 7.67. C₁₃H₁₆O₃ requires C, 69.2; H, 7.7%); *cis*-5-isopropoxy-2-phenyl-1,3-dioxan (IX), needles (16%) [from light petroleum (b.p. 40–60°)], m.p. 45.5–46.5° (Found: C, 70.3; H, 8.1. C₁₃H₁₈O₃ requires C, 70.3; H, 8.1%).

1,3-Dioxan-5-*spiro*-2'-tetrahydropyran (XII \rightleftharpoons XIII).—2,2-Dihydroxymethyl- Δ^5 -dihydropyran in ethanol (70 ml.) over Raney nickel (W7, 3 g.) was shaken under hydrogen at 60 lb. in.^{–2} for 18 hr. at 20°. The product was fractionated to give 2,2-dihydroxymethyltetrahydropyran (4.2 g., 95%), b.p. 92–94°/0.12 mm., m.p. 38° (lit.¹³ b.p. 97–100°/0.25 mm., m.p. 44–45°).

2,2-Dihydroxymethyltetrahydropyran (4 g.), paraformaldehyde (1.3 g.), and toluene-*p*-sulphonic acid (0.1 g.) in benzene (50 ml.) were refluxed for $\frac{1}{2}$ hr. with continuous removal of water by a Dean-Stark apparatus. The product

7.7%). The n.m.r. spectrum (60 MHz) showed an AB pattern centred at τ 6.15 [4H: C(4) and C(6)], a singlet at τ 4.65 [1H: C(2)], and a broad multiplet at 8.5 [6H: C(9), C(10), and C(11)].

RESULTS

The n.m.r. spectra (Table 3) were assigned by analogy with literature results. The H(2) and H(5) protons are unique and the 4,6-equatorial protons are at lower field than the axial ones. The *ee* and *ae* vicinal coupling constants are all *ca.* 3 Hz, and J_{gem} was 12 Hz. Changing the solvent from carbon tetrachloride to benzene shifts H(2) downfield by *ca.* 0.1 p.p.m., has little effect on H[4(6)]-equatorial, and shifts H[4(6)]-axial and H(5) upfield by *ca.* 0.2 and 0.3 p.p.m. respectively (Table 3). Anderson¹⁴ found that benzene induced chemical shifts downfield for H(2) and upfield for the other protons of alkyl-1,3-dioxans. Although the postulation of benzene-substrate complexes can rationalise many solvent-induced shifts,¹⁴ no definite complex can be suggested in the present instance.¹⁵

The *cis-trans* equilibration ΔG° values are *ca.* 0.3 kcal./mole lower for benzene than for carbon tetrachloride (Table 4). Benzene has been shown to stabilise diequatorial *trans*-1,2-dibromocyclohexane,¹⁶ *i.e.*, the conformer with the higher dipole, relative to carbon tetrachloride. Perhaps the presently found effect has a similar cause, and benzene is

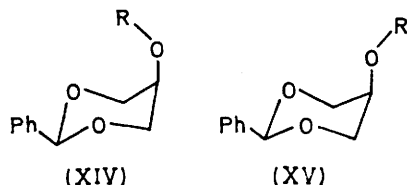
¹⁵ B. J. Hutchinson, Ph.D. Thesis, University of East Anglia, 1968.

¹⁶ P. Klæboe, J. J. Lothe, and K. Lunde, *Acta Chem. Scand.*, 1957, **11**, 1677.

¹³ D. S. P. Eftax and A. P. Dunlop, *J. Org. Chem.*, 1961, **26**, 2106.

¹⁴ J. E. Anderson, *Tetrahedron Letters*, 1965, 4713.

the more polar solvent on the micro-scale. Although hydrogen chloride is more soluble in benzene than carbon tetrachloride, an experiment using a small amount of catalyst indicated that the hydrogen chloride concentration did not affect the results.



cis-5-Alkoxy-2-phenyl-1,3-dioxans can exist as three rotamers, one with the alkyl group 'inside' (XIV) and two equivalent forms with the alkyl group 'outside' (XV). The observed dipole moment is thus given by equation (1).

$$\mu_{\text{obs}}^2 = N\mu_{\text{XIV}}^2 + (1 - N)\mu_{\text{XV}}^2 \quad (1)$$

where N is the mole fraction of the 'alkyl-inside' rotamer. The dipole moments of each of the individual rotamers can be considered to be compounded from two dipole vectors; one, μ_{ϕ} , from the 2-phenyl-1,3-dioxan moiety, has a magnitude of 2.04 D (Table 2); and the other μ_{OR} , from the 5-alkoxy-group, to which we assign a value of 1.23 D by comparison with the other aliphatic ethers.¹⁷ Equation (2)

$$\mu_{\text{XIV}}^2 = \mu_{\phi}^2 + \mu_{\text{OR}}^2 + 2\mu_{\phi}\mu_{\text{OR}} \cos \theta_{\text{XIV}} \quad (2)$$

follows, where θ_{XIV} is the angle between the vectors in rotamer (XIV), and similarly for rotamer (XV). The values of θ are calculated as follows. The direction of μ_{ϕ} relative to the C-phenyl axis is shown to be 28.5° by vector triangulation (XXIII) by use of the dipole moments of 2-phenyl- and 2-*p*-chlorophenyl-1,3-dioxan and of chlorobenzene⁷ (1.61 D). The direction of μ_{OR} is taken as the bisector of the C(5)-O-R angle. The following bond lengths¹⁸ and bond angles¹⁹ were assumed: C-O, 1.417 Å; C-C, 1.537 Å; O-C-O, 111.5°; C-O-C, 111.5°; C-C-O, 111.5°. We also assume that the arrangement about the C(5)-O bond is perfectly staggered although the calculations are not sensitive to small changes in this torsional angle. Trigonometrical calculations then give: $\theta_{\text{XIV}} = 124^\circ$ (XXIV), and $\theta_{\text{XV}} = 54^\circ$ (XXV) and thus $\mu_{\text{XIV}} = 1.69$ D and $\mu_{\text{XV}} = 2.94$ D. Insertion of these values into equation (1) leads to the following values of N : for R = Me, Et, 0.11 ± 0.01 ; for R = Prⁱ, 0.0. The corresponding 'outside'-'inside' equilibrium constants are: for R = Me, Et, 8.1; for R = Prⁱ, ∞ . For the methoxyl-group we have also carried out the analogous calculations with *cis*-2-*p*-chlorophenyl-5-methoxy-1,3-dioxan which gives a value for N of 0.12 ± 0.01 ; the agreement with the value from the 2-phenyl compound is good and gives us confidence in our geometrical assumptions. Values of ΔG° corresponding to these equilibrium constants, and corrected for the 2-fold degeneracy of the alkyl-outside conformer, are listed in Table 5. For the remainder of this paper we use the average value of $\Delta G^\circ = 0.80$ kcal/mole for the methoxy-compounds.

The dipole moments of the two conformations (XII and XIII) of the dioxanspirotetrahydropyran were calculated

¹⁷ A. L. McClellan, 'Tables of Experimental Dipole Moments,' W. H. Freeman and Co., San Francisco, 1963.

¹⁸ L. E. Sutton, Interatomic Distances Supplement, The Chemical Society, Special Publication No. 18, London, 1965.

by vector addition of the moments of tetrahydropyran²⁰ (1.55 D) and 1,3-dioxan. The direction of the tetrahydropyran moment was taken as the bisector of the COC angle, on the assumption that the groups about the C(5)-O bond were perfectly staggered. Two alternative assumptions were made about the direction of the dioxan moment: (1) that, because the moments of 1,3-dioxan and 2-phenyl-1,3-dioxan are identical, the magnitude of the aryl-C(2) bond moment must be zero and that therefore the direction of the 1,3-dioxan moment must be the same as that determined above for 2-phenyl-1,3-dioxan; this corresponds to a direction of 21° from the plane defined by the two oxygen atoms and carbon atoms 4 and 6; (2) that the dioxan moment is compounded of two moments bisecting the COC bonds; this corresponds²¹ to a direction of 35° from the OOC(4)C(6) plane. The results are, in fact, barely sensitive to the difference between these assumptions which are illustrated in (XXVI).

TABLE 5

Rotamer populations at 25° of *cis*-5-alkoxy-2-aryl-1,3-dioxans from dipole moment results in benzene at 25°

Compound	Inside rotamer (XIV)	Outside rotamer (XV)	K	ΔG° (kcal./mole)	$\Delta G^\circ - RT \ln 2$ (kcal./mole)
II-OMe	12 ± 1	88	7.3 ± 2	1.18 ± 0.12	0.77 ± 0.12^a
IV-OMe	11 ± 1	89	8.1 ± 2	1.23 ± 0.15	0.82 ± 0.15^a
V-OEt	11 ± 1	89	8.1 ± 2	1.23 ± 0.15	0.82 ± 0.15
VI-OPr ⁱ	<1	>99	Large	Large	Large

^a Subsequent discussion in this paper uses an average value of 0.80.

The moment of conformer (XII) with the oxygen atom of the tetrahydropyran axial with respect to the dioxan ring is calculated to be 3.21 D whichever assumption about the direction of the dioxan moment is taken; the moment of conformer (XIII) is calculated by assumption (1) to be 1.58 and by assumption (2) to be 1.48 D. The corresponding conformer populations are 38% and 41% respectively of conformer (XII); *i.e.*, the oxygen atom prefers to be axial with ΔG° *ca.* 0.24 kcal./mole.

Equilibration of 2-phenyl-1,3-dioxanspiro-2'-tetrahydropyran in benzene is reasonably consistent with the dipole moment calculations showing about 35% of the oxygen-axial conformer, *i.e.*, $\Delta G^\circ = 0.37$ kcal./mole.

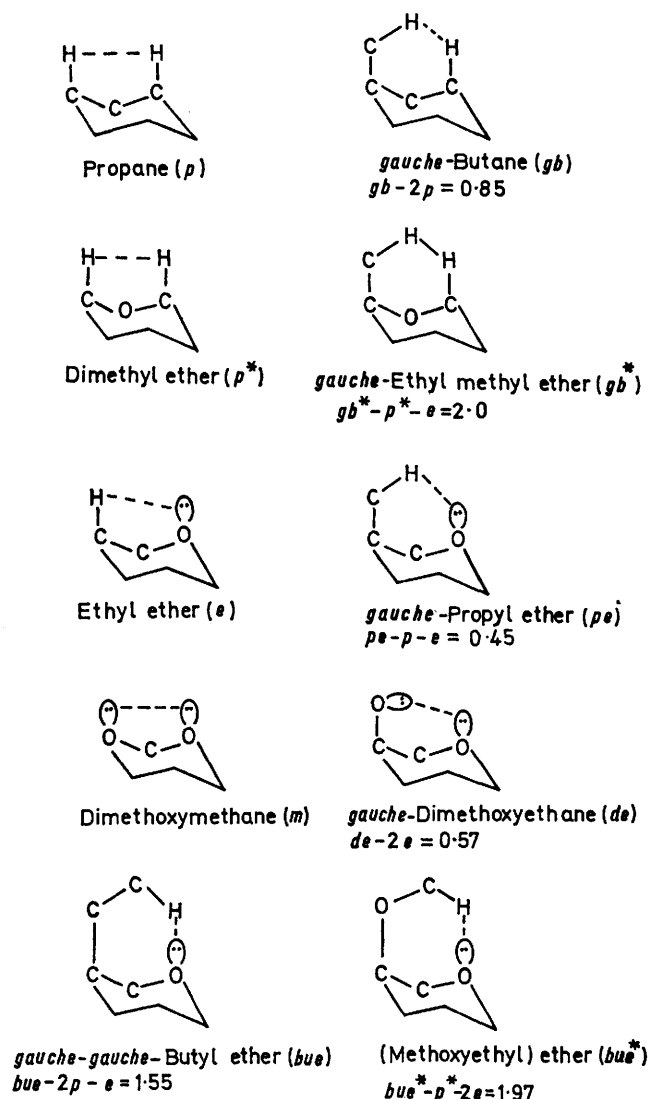
DISCUSSION

Standard Interactions Involving Oxygen.—In the well-known propane and *gauche*-butane interactions (Scheme), a central atom, or alternatively either one or both of the terminal atoms, may be replaced by oxygen to give another six derived interactions as shown. In addition we have to consider the '*gauche-gauche*-butyl ether' and the corresponding '(methoxyethyl) ether' interactions, for it transpires that these are not of such high energy that conformations containing them can be neglected, as is the case for the *gauche-gauche*-pentane. It should be emphasised that in this Scheme, interactions from all

¹⁹ P. H. Kasai and R. J. Myers, *J. Chem. Phys.*, 1959, **30**, 1096; U. Blukis, P. H. Kasai, and R. J. Myers, *ibid.*, 1963, **38**, 2753.

²⁰ C. W. N. Cumpner and A. I. Vogel, *J. Chem. Soc.*, 1959, 3521.

²¹ R. J. Bishop, L. E. Sutton, M. J. T. Robinson, and N. W. J. Pumphrey, *Tetrahedron*, 1969, **25**, 1417.



SCHEME The energy relations are in kcal./mole and except for gb are deduced in the text

sources are considered simultaneously, *i.e.*, dipole-dipole as well as non-bonded repulsions and attractions. [Strictly speaking, *gauche-gauche* interactions we are dealing with should be defined as (g^+) (g^-)].

Values for these interactions, or rather for differences between them, may be deduced from the conformational equilibria of both acyclic and cyclic compounds. Thus the well-known relation (3) can be derived from either the

$$gb - 2p = 0.85 \text{ kcal./mole} \quad (3)$$

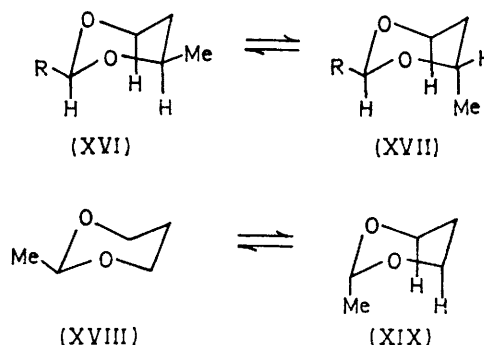
axial-equatorial equilibrium of methylcyclohexane or the *gauche-trans* equilibrium of butane, which give values in good agreement.

A value for gb^* , the interaction corresponding to *gauche*-butane where one of the internal carbon atoms has been replaced by oxygen, can be obtained in three independent ways from literature measurements. (a) The *cis-trans* equilibrium of 2-substituted 4-methyl-1,3-dioxans,¹¹ the ΔG value for which was determined by Eliel and Knoeber as 2.85 ± 0.10 kcal./mole for all four compounds with $R = \text{Me}$ to Bu^t (XVI and XVII) (*cf.* Table 6) yields equation (4), from which (5) follows by use of equation (3). (b) The *cis-trans* equilibrium of

$$(gb - 2p) + (gb^* - p^* - e) = 2.85 \text{ kcal./mole} \quad (4)$$

$$gb^* - p^* - e = 2.00 \text{ kcal./mole} \quad (5)$$

2-methyl-1,3-dioxans¹¹ (XVIII and XIX) (*cf.* Table 6) yields $gb^* - p^* - e \geq 1.75$ kcal./mole, which is in satisfactory agreement.



In less satisfactory agreement is the ΔH° value of 1.5 ± 0.1 kcal./mole for ($gb^* - e - p^*$) derived for the *gauche-trans* rotameric equilibrium of the acyclic com-

TABLE 6
Interactions for simple conformational equilibria

Series	Conformer	Interactions	Relative energy	Reported ΔG° (kcal./mole)
4-Methyl-1,3-dioxan	Me <i>eq</i> (XVI)	$3p + p^* + 2e$	0	2.85 ± 0.1
	Me <i>ax</i> (XVII)	$gb + gb^* + p + e$	$(gb - 2p) + (gb^* - p^* - e)$	
2-Methyl-1,3-dioxan	Me <i>eq</i> (XVIII)	$2p^* + 4e$	0	≥ 3.5
	Me <i>ax</i> (XIX)	$2gb^* + 2e$	$2(gb^* - p^* - e)$	
5-Methyl-1,3-dioxan	Me <i>eq</i>	$4p + 2e$	0	0.90 ± 0.1
	Me <i>ax</i>	$2pe + 2p$	$2(pe - p - e)$	
5-Methyltetrahydropyran	Me <i>eq</i>	$5p + e$	0	1.27
	Me <i>ax</i>	$gb + pe + 2p$	$(gb - 2p) + (pe - p - e)$	
Dioxanspirotetrahydropyran	O <i>eq</i> (XIII)	$2pe + 2e$	0	0.24
	O <i>ax</i> (XII)	$2de + 2p$	$2(de - 2e) - 2(pe - p - e)$	
5-t-Butyl-1,3-dioxan	Bu <i>eq</i>	$4gb + 2p + 2e$	0	1.40
	Bu <i>ax</i>	$2bue + 2gb + 2p$	$2(bue - 2p - e) - 2(gb - 2p)$	

pound ethyl methyl ether²² by i.r. intensity measurements over a temperature range. As ΔS° is expected to be small, this ΔH° value should be close to the ΔG° value expressed in equation (5), but we consider it preferable, at least for solution work, to use the value obtained from the cyclic compounds.

A relation (6) involving pe is given by the axial-equatorial equilibrium of 5-methyl-1,3-dioxan¹¹ (cf. Table 6) which gives equation (7). This result can be tested by results reported for the conformational equilibrium of 5-methyltetrahydropyran²³ which imply relation (8) (cf. Table 6) and, through (3), hence lead to $(pe - e - p) = 0.42$ kcal./mole, in satisfactory agreement with relation (7).

$$2pe = 2e + 2p + (0.8 \text{ to } 0.97 \text{ kcal./mole}) \quad (6)$$

$$pe - e - p = 0.45 \text{ kcal./mole} \quad (7)$$

$$(gb - 2p) + (pe - p - e) = 1.27 \text{ kcal./mole} \quad (8)$$

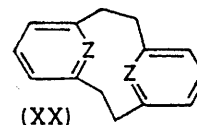
Of the *gauche*-butane type interactions involving oxygen, we have now deduced relations for gb^* and pe . A value for the remaining interaction of this type, de , can be obtained from the results reported above for the dioxanspirotetrahydropyran equilibrium. Counting interactions (cf. Table 6) yields equation (9) and, using (7), we get (10).

$$(de - 2e) - (pe - e - p) = 0.12 \text{ kcal./mole} \quad (9)$$

$$(de - 2e) = 0.57 \text{ kcal./mole} \quad (10)$$

Comparison of relations (3), (5), (7), and (10) allows conclusions to be drawn regarding the effect on the energy of a *gauche*-butane interaction by replacing one or more of the four carbon atoms by oxygen. Unfortunately, we cannot make absolute comparisons as the relative values of the 'three heavy atom' interactions p , p^* , and e are unknown; however, related work^{2,3} in the nitrogen series indicates that these are probably small, and that their differences will probably not exceed 0.2 kcal./mole. Within the range of uncertainty of the quantity $(2p - e - p^*)$, relations (2) and (5) show that a *gauche*-butane interaction is more than doubled by replacing an internal carbon by oxygen, whilst relations (2) and (7) indicate that it is nearly halved by replacing a terminal carbon by oxygen. Replacement of *both* terminal carbon atoms by oxygen is shown to give greater repulsion than replacement of one only. Relations (3), (7), and (10) give, without any assumptions about the value of p or e , that $gb + de = 2pe + 0.52$ kcal./mole which reflects the lower repulsion when just one of the terminal carbon atoms is replaced by oxygen. However, relations (3) and (10) indicate that de is probably itself smaller than gb . This finding is in agreement with the work of Gault, Price, and Sutherland²⁴ who showed that

the inversion of (XX) was much easier for $Z = N$ than for $Z = CH$.



Before proceeding to the alkoxy-dioxan equilibria, we must finally consider interactions of the *gauche-gauche*-butyl ether type. From the axial-equatorial 5-t-butyl-1,3-dioxan equilibrium¹¹ relation (11) is derived (cf. Table 6) and hence (12).

$$(bue - 2p - e) - (gb - 2p) = 0.70 \text{ kcal./mole} \quad (11)$$

$$bue - 2p - e = 1.55 \text{ kcal./mole} \quad (12)$$

Rotamer Populations of cis-5-Methoxy-2-phenyl-1,3-dioxan.—We have described above the determination of the equilibrium constant between rotamers (XIV) and (XV) of 5-axial-methoxy-1,3-dioxan. This result can be used to obtain a relationship involving the (methoxy-ethyl) ether interaction bue^* , and the *gauche*-dimethoxy-ethane interaction, de . As 'outside' rotamer (XV) exists in two equivalent forms, $RT \ln 2$ must be deducted from $RT \ln K$ to obtain the ΔG° value between the 'inside' and 'outside' rotamers (XIV) and (XV) (cf. Table 6). Interactions in the methoxy-compound are recorded in Table 7. Relation (13) follows, and hence (14).

$$2(bue^* - p^* - 2e) - 3.14 = 0.80 \text{ kcal./mole} \quad (13)$$

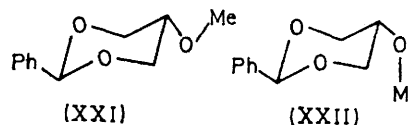
$$bue^* - p^* - 2e = 1.97 \text{ kcal./mole} \quad (14)$$

If we again neglect the difference $(2p - p^* - e)$, we can deduce from relations (12) and (14) that the interaction bue^* is greater than bue , as would be expected for the substitution of an internal carbon atom by oxygen, cf. the greater values of gb^* than gb . If anything, the value of bue^* is surprisingly small when compared with gb^* .

Equilibration of cis and trans-5-Methoxy-2-phenyl-1,3-dioxan (XIV \rightleftharpoons XV) and (XXI \rightleftharpoons XXII).—We must consider the individual rotamers of the equatorial and of the axial forms (XIV, XV; R = Me). The relevant interactions are given in Table 7. Applying the Boltzmann law now gives (15), which is equivalent to

$$K = \frac{[trans]}{[cis]} = \frac{2 + \exp(-3.33)}{2 \exp(-1.90) + \exp(-3.23)} = 5.99 \quad (15)$$

$\Delta G^\circ = 1.05$ kcal./mole, significantly higher than the observed value of 0.71 kcal./mole.



²² T. Kitagawa and T. Mihazawa, *Bull. Chem. Soc. Japan*, 1968, **41**, 1976.

²³ C. B. Anderson and D. T. Sepp, *J. Org. Chem.*, 1968, **33**, 3272.

²⁴ I. Gault, B. J. Price, and I. O. Sutherland, *Chem. Comm.*, 1967, 540.

TABLE 7
Interactions for rotamers of *cis*- and *trans*-5-methoxy-2-phenyl-1,3-dioxan

Isomer	Rotamer	Interactions relative to 2-phenyl-1,3-dioxan	Energy (kcal./mole) relative to (XV) from equations (5) and (10)	Energy (kcal./mole) relative to (XXI) from equations (5), (10), and (14)
<i>cis</i>	(XIV)	$2bue^* + 2e$	$2(bue^* - p^* - 2e) - 3.14$	1.94
	(XV) (2 equivalent forms)	$2de + gb^* + p^* + e$	0	1.14
<i>trans</i>	(XXI) (2 equivalent forms)	$gb^* + p^* + 5e$	(Not applicable)	0
	(XXII)	$2gb^* + 4e$	(Not applicable)	2.0

TABLE 8
Interactions in 5-ethoxy-2-phenyl-1,3-dioxan

Isomer	Rotation around C(5)-O bond	Rotation around O-CH ₂ bond	Interactions relative to 2-phenyl-1,3-dioxan	Energy (kcal./mole) relative to (iv) ^a	Energy (kcal./mole) relative to (x) ^a
<i>cis</i> (<i>ax</i> -OEt)	'Ethoxy in'	i	$2bue^* + 4e$	0.80	1.94
		ii = iii	(High)	—	—
		iv	$2de + gb^* + p^* + 3e$	0	1.14
	'Ethoxy out' (Two equivalent)	v	$2de + 2gb^* + 2e$	2.0	3.14
		vi	(High)	—	—
<i>trans</i> (<i>eq</i> -OEt)	'Ethoxy down'	vii	$2gb^* + 6e$	—	2.0
		viii = ix	(High)	—	—
		x	$gb^* + 7e + p^*$	—	0
	'Ethoxy out' (Two equivalent)	xi	$2gb^* + 6e$	—	2.0
		xii	(High)	—	—

^a These designations refer to those in the third column.

Rotamers of the *cis*-5-Ethoxy- and *cis*-5-Isopropoxy-compounds (V and VI).—Two types of rotation must be considered, around the ring-O and O-CH₂ bonds. Table 8 records the interactions for the ethoxy-isomers and

from these we can predict the *cis*-rotameric equilibrium constant by equation (16). From equation (16) $\Delta G^\circ_{\text{calc}} = 1.24$ in good agreement with $\Delta G^\circ_{\text{obs}} = 1.23$ kcal./mole.

$$K_{\text{calc}} = \frac{\exp(-1.33)}{2 + 2 \exp(-3.33)} - 0.13 \quad (16)$$

The corresponding isopropoxy-compound cannot exist with the 'propoxy-in' rotamer in an all-staggered conformation (*cf.* Table 9) and this accords with the dipole moment observations that no detectable proportion exists in this form.

cis-trans Equilibration of Ethoxy- and Isopropoxy-compounds.—We can now predict the *cis-trans* equilibrium constant for the ethoxy-compound as equation (17), from the interactions listed in Table 8. This

$$K_{\text{calc}} = \frac{2 + 3 \exp(-3.33)}{\exp(-3.33) + 2 \exp(-1.90) + 2 \exp(-5.23)} = 6.02 \quad (17)$$

corresponds to ΔG° of 1.06 kcal./mole which is in good agreement with the measured value of 0.99 kcal./mole. For the isopropoxy-derivatives, only one rotamer is expected to be populated for both the *cis*- and *trans*-forms. The ΔG° difference predicted here is 1.14 kcal./mole, in good agreement with the observed ΔG° of 1.04. It is disturbing that whereas the theory predicts a very small increase in ΔG° from the methoxy- to the isopropoxy-series, a much larger change is observed experimentally. However, the relative values of these interactions are evidently considerably influenced by solvent, as shown by the different values for equilibrium constants determined in benzene and carbon tetrachloride solution (Table 4). We have used the values for benzene in the comparisons in this paper, because the present dipole moments were also determined in benzene, but some of

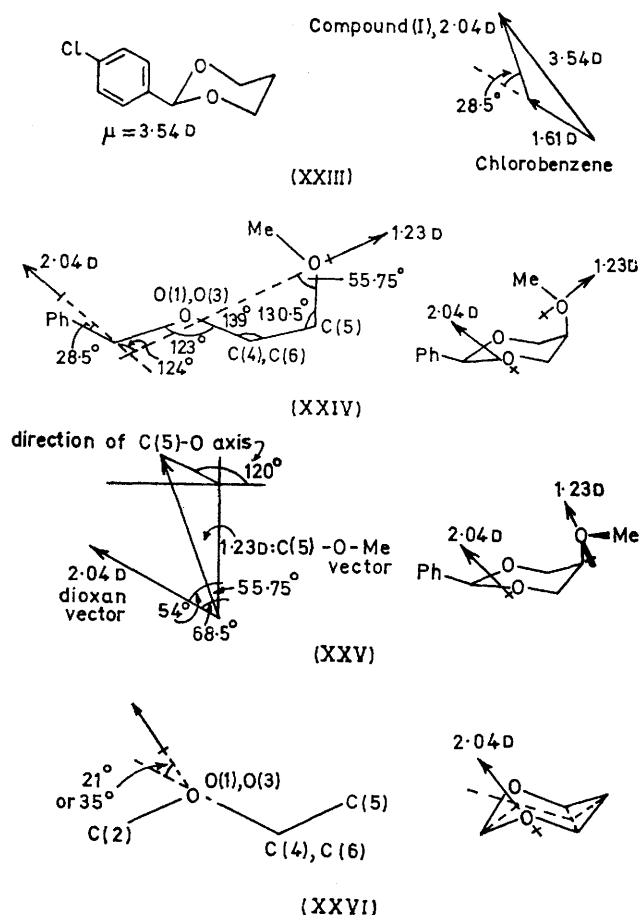


TABLE 9
Interactions in 5-isopropoxy-2-phenyl-1,3-dioxan

Isomer	Rotation around C(5)-O	Rotation around O-CHMe ₂	Interactions relative to 2-phenyl-1,3-dioxan	Energy (kcal./mole) relative to (x) ^a
<i>cis</i> (<i>ax</i> -OPr ^t)	' Isopropoxy in '	(i), (ii), (iii)	(All high)	—
	' Isopropoxy out '	(iv)	$2de + 2gb^* + 4e$	1.14
	(Two equivalent)	(v), (vi)	(Both high)	—
<i>trans</i> (<i>eq</i> -OPr ^t)	' Isopropoxy down '	(vii), (viii), (ix)	(All high)	—
	' Isopropoxy out '	(x)	$2gb^* + 8e$	0
	(Two equivalent)	(xi), (xii)	(Both high)	—

^a This refers to the rotamer assigned in the third column.

the other data used were for other solvents. Clearly, for a consistent treatment, data from a common solvent should be used.

General Conclusions.—It has been shown that the method of standard interactions, previously outlined for nitrogen-containing compounds,^{2,3} can be extended to the oxygen series. We again emphasise that this

approximate method neglects the effects of distortions, but that it can be applied easily and rapidly to estimate the order of magnitude of conformational and other equilibria.

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