Configurational Preferences of 5-Hetero-substituents in 2-Isopropyl-1,3-dioxans

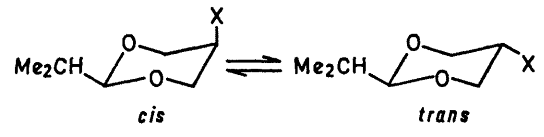
By ERNEST L. ELIEL* and MOSES K. KALOUSTIAN

(*Department of Chemistry, University of Notre Dame, Notre Dame, Indiana* 46556)

Summary Configurational equilibria in 5-hetero-substituted 2-isopropyl-1,3-dioxans are strongly solvent dependent and, in several instances, the axial isomer predominates at equilibrium.

WE have determined (see Table) the positions of equilibrium for eleven pairs of diastereoisomeric 2-isopropyl-1,3-dioxans bearing hetero-substituents at C-5. The compounds are all biased (anancomeric[1]); the choice of the isopropyl group as the "holding group" was based on the finding that $\Delta G^0_{2\text{-Pr}^i} = -\ 4{\cdot}15$ kcal/mole.[2]

Configurational equilibria in 5-*hetero-substituted* 2-*isopropyl*-1,3-*dioxans*[a]



5-Hetero-substituent	Solvent, temperature	ΔG^0 (kcal/mole)
OH	Cyclohexane, 80°	+0·915[b]
	Isopropyl alcohol, 80°	+0·51[c]
	t-Butyl alcohol, 80°	+0·50[c]
	Dimethoxyethane, 80°	+0·27[c]
OMe	Carbon tetrachloride, 28°	−0·89
	Diethyl ether, 50°	−0·83
	Chloroform, 28°	−0·18
	Methanol, 28°	−0·03
	Acetonitrile, 25°	+0·01
OAc	Diethyl ether, 25°	0
F	Diethyl ether, 25°	+0·62
	Methanol, 25°	+0·605
	Benzene, 25°	+0·83
	Acetonitrile, 25°	+1·225
Cl	Diethyl ether, 25°	−1·20
Br	Diethyl ether, 25°	−1·44
NO_2	Carbon tetrachloride, 30°	+0·38
	Chloroform, 30°	+0·63
	Methylene chloride 30°	+0·81
	Deuteriochloroform, 30°	+0·89
CN	Diethyl ether, 30°	−0·21
	Acetonitrile, 30°	+0·55
CO_2Me	Diethyl ether, 30°	−0·82
	Acetonitrile, 27°	−0·22
CH_2OH	Carbon tetrachloride, 27°	+0·27[d]
	Dimethoxyethane, 30°	−0·01[d]
CH_2OMe	Diethyl ether, 30°	−0·05
Me	Diethyl ether, room temp.	−0·80[e]

[a] The catalyst for equilibration was Amberlyst-15 (Rohm and Haas beaded polystyrenesulphonic acid) except for X = OH where Raney nickel was used (ref. 3). [b] Extrapolated to infinite dilution. [c] For 0·1 M-solutions. [d] For 0·2 M-solutions. [e] Ref. 4

The configurational assignments in the Table are based on i.r. (hydrogen bonding) studies (X=OH and, by correlation, OMe, OAc), n.m.r. studies (principally H–H or H–F coupling constants at C-4,-5,-6) (F, Cl, Br, CN, CO_2Me, and, by correlation, CH_2OH and CH_2OMe) and dipole moment measurement (NO_2). Equilibrium composition was determined by g.l.c., with pure *cis*- and *trans*-isomers being isolated and used as calibration standards (for area response ratios) in all cases but NO_2 where only the *cis*-isomer was obtained pure and the analysis was by n.m.r. [ratio of $(CH_3)_2CH$ signals].

The hydroxy-group, in all cases, prefers the axial position, due to the formation of an intramolecular, possibly bifurcated, hydrogen bond.[5] This preference, greatest in the aprotic solvent cyclohexane, diminishes in hydrogen-donor and -acceptor solvents (*cf.* the situation in cyclohexanol[3]).

For the methoxy-group the results show a correlation between ΔG^0 and solvent dielectric constant. In the high-dielectric solvent acetonitrile, ΔG^0 is *ca.* 0; since some unfavourable dipolar interaction must remain, this finding suggests an attractive van der Waals' interaction between the axial methoxy-group and the ring oxygens (*cf.* the predominance of gauche conformation in 1,2-dimethoxyethane and polyoxyethylene[6]).

Surprisingly, in the case of the 5-fluoro-1,3-dioxans, under all conditions studied, the *cis*-isomer is favoured at equilibrium, unlike in the 5-chloro- and 5-bromo-1,3-dioxans. It appears that a strongly attractive F/O gauche interaction of unknown origin stabilizes the *cis*-isomer; in the other halides, the positions of equilibrium are governed by the usual polar and steric interactions. An analogous situation is found in 1,2-dihalogeno-ethanes.[7]

In the case of $X=NO_2$, CN, and CO_2Me the equilibria are strongly solvent dependent; NO_2 in all solvents studied and CN in MeCN show preference for the axial position. Although equatorial CO_2Me is preferred even in MeCN, the increase in ΔG^0 in comparison to $C_6H_{11}X$ (from $-1{\cdot}27$[8] to $-0{\cdot}22$ kcal/mole) is somewhat greater for CO_2Me than for Me (from $-1{\cdot}7$ to $-0{\cdot}8$ kcal/mole). These results will be discussed in the full publication.

The groups CH_2OH and CH_2OMe, unlike Me, show little preference for the equatorial position, even though i.r. measurements surprisingly disclose no hydrogen bonding for axial CH_2OH ($\nu_{OH} = 3643\ cm^{-1}$, single band, for both axial and equatorial CH_2OH in 0·001M-CCl_4 solution). The dipolar interactions for these groups, similar to those of OAc, are complex.

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