volve some type of averaging effects associated with cis and trans protons, it seems likely that the apparent lack of sensitivity of the homoallylic H–H coupling to replacement of carbon by nitrogen is due to a cancellation of two effects of opposite sign.

Acknowledgment. This work was supported in part by a grant from the National Science Foundation. Services of the University of Arizona Computer Center are gratefully acknowledged. Some valuable comments were provided by Professor F. H. A. Rummens.

Conformational Analysis. XXV. Conformational Equilibria in 5-Heterosubstituted 1,3-Dioxanes. Comparison of Calculated and Experimental Solvent Effects

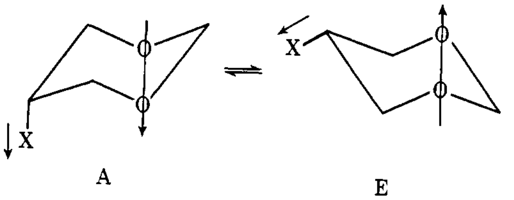
R. J. Abraham,[1] H. D. Banks,[2] E. L. Eliel,*[2] O. Hofer,[2] and M. K. Kaloustian[2,3]

Contributions from the Department of Organic Chemistry of The University of Liverpool, Liverpool, L69 3BX, United Kingdom, and the Department of Chemistry, University of Notre Dame, Notre Dame, Indiana 46556. *Received July 19, 1971*

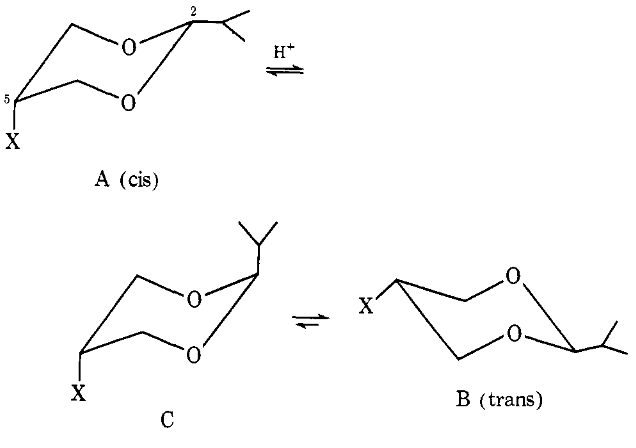
Abstract: *cis*- and *trans*-5-fluoro-, 5-chloro-, 5-bromo-, 5-cyano-, and 5-methoxy-2-isopropyl-1,3-dioxane have been equilibrated, in solvents CCl_4, diethyl ether, benzene, chloroform, and acetonitrile, by means of acid. The $\Delta G°$ values found are summarized in Table I. The preference of fluorine for the axial position in all solvents and of cyano (and, to a minor extent, methoxy) for this position in solvent acetonitrile is of note. The effect of variation of solvent dielectric in the set CCl_4, ether, chloroform, and acetonitrile is compared with predictions based on calculations by a previously published method; the agreement is good. Benzene behaves as an "anomalous" solvent in this regard.

The 1,3-dioxane system has been a fruitful framework for studying a number of conformational equilibria.[4,5] Several advantages of the system have been previously pointed out: 1,3-dioxanes with a variety of substituents in all possible positions can be easily synthesized and equilibrated; their nmr spectra are often susceptible to first-order analysis and yield information regarding configuration and conformation; interactions involving lone pairs on oxygen can be studied. To these advantages should now be added another one: the study of 5-heterosubstituted 1,3-dioxanes affords an accurate means of evaluating dipolar interactions. As seen in Scheme I the ring dipole and the substituent dipole are involved in electrostatic repulsion in the 5-axially substituted compound whereas a slightly attractive electrostatic interaction might be expected in the 5-equatorially substituted isomer. Whereas study of the equilibrium shown in Scheme I, *e.g.*, by spectral means or by measurement of dipole moment, offers no particular advantage over similar studies accomplished in the past in related systems, such as 1,2-dihaloethanes[6] or 2-halocyclohexanones,[7] the conformational equilibrium shown in Scheme I can be readily substituted by a configurational one, as shown in Scheme II; this equilibrium, in turn, can be measured very accurately by gas chromatography.[8] The diaxial intermediate C may be safely disregarded, since the $\Delta G°$ value of a 2-isopropyl group in a 1,3-dioxane is very large, 4.2 kcal/mol;[9] twist-boat forms, also, may be neglected because

Scheme I. Conformational Equilibrium in 5-Heterosubstituted 1,3-Dioxanes



Scheme II. Cis–Trans Equilibria in 5-Heterosubstituted 1,3-Dioxanes



---

[1] The Robert Robinson Laboratories, The University of Liverpool.

[2] University of Notre Dame.

[3] From the Ph.D. Dissertation of M. K. Kaloustian, University of Notre Dame, 1970.

[4] *Cf.* E. L. Eliel, *Accounts Chem. Res.*, 3, 1 (1970).

[5] See also paper XXIV in this series: E. L. Eliel and H. D. Banks, *J. Amer. Chem. Soc.*, 94, 171 (1972).

[6] For calculations concerning such systems, see R. J. Abraham and G. Gatti, *J. Chem. Soc. B*, 961 (1969).

[7] E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Wiley-Interscience, New York, N. Y., 1965, pp 460–469.

[8] For a preliminary report, see E. L. Eliel and M. K. Kaloustian, *Chem. Commun.*, 290 (1970).

[9] F. W. Nader and E. L. Eliel, *J. Amer. Chem. Soc.*, 92, 3050 (1970).

of their high energy.[10] The equilibrium depicted in Scheme II must be very nearly the same as that in Scheme I since it has recently been shown,[11] by proton nmr spectroscopy, that substituents at C-2 in 1,3-dioxanes do not alter the coupling constants of H-4, H-5, and H-6, and since comparison of ^{13}C nmr spectra of 2-*tert*-butyl-substituted 1,3-dioxanes[12] suggests little if any effect of the 2-*tert*-butyl substituent on the signals of C-4, C-5, and C-6 or groups attached to these positions. The synthesis of the compounds depicted in Scheme II is discussed below. Equilibration was effected readily by treating appropriate solutions (0.3–0.7 *M*) with beaded polystyrenesulfonic acid (Amberlyst-15) in a thermostat until equilibrium (approached from both sides) was reached, removing catalyst traces with solid potassium carbonate prior to gas chromatographic analysis. The results of the equilibrations are shown in Table I.

Table I. $\Delta G°$ Values[a] for Cis–Trans Equilibria (Scheme II) in 5-Heterosubstituted 2-Isopropyl-1,3-dioxanes

Solvent (ϵ)[b]	Heterosubstituent				
	F	Cl	Br	CN	OCH_3
Carbon tetrachloride (2.24)	0.36	−1.40	−1.71	Nd[c]	−0.90
Diethyl ether (4.33)	0.62	−1.26	−1.45	−0.21	−0.83
Benzene (2.20)	0.83	−0.89	−1.17	Nd[c]	−0.59
Chloroform (4.81)	0.87	−0.94	−1.35	Nd[c]	−0.16
Acetonitrile (37.5)	1.22	−0.25	−0.68	0.55	0.01

[a] In kcal/mol, at 25° [b] Dielectric constant. [c] Not determined.

Discussion

In a solvent of low dielectric constant, such as CCl_4, one might have expected the equilibria shown in Scheme II to be controlled mainly by dipole repulsion, implying a negative $\Delta G°$. As seen in Table I, this expectation is not fulfilled for fluorine, though it is for the other four groups. Nevertheless, dipole repulsion is clearly important, as evidenced by the strong solvent dependence of $\Delta G°$ for all five groups studied. Therefore the anomalous $\Delta G°$ for fluorine must be due to a strong countervailing contribution to the energy which favors the axial isomer. Let us consider the equilibria in solvent acetonitrile which, by its high dielectric constant, minimizes dipolar interactions. In this solvent, not only does fluorine strongly prefer the axial conformation, but the cyano group prefers it mildly and for the methoxy group $\Delta G° = 0$ within limits of experimental error. The equatorial conformation remains the preferred one for chlorine and bromine.

It may be instructive to compare the acetonitrile values with corresponding $\Delta G°$ values for cyclohexyl-X (which are not notoriously solvent dependent).[13] This comparison is made in Table II. It is clear that the fluorine equilibrium is sharply shifted toward the axial side as the CH_2 groups in cyclohexane are exchanged for oxygen atoms in the dioxane. A lesser shift in the same direction is encountered for OMe and for CN and a still lesser one for chlorine. The shift for bromine is, if anything, in the opposite direction.

Table II. Comparison of $\Delta G°$ Values[a] in Substituted Cyclohexanes and in 5-Substituted Dioxanes[b]

Substituent	F	Cl	Br	CN	OCH_3
$C_4H_7O_2X$	1.22	−0.25	−0.68	0.55	0.01
$C_6H_{11}X$[c]	−0.15	−0.43	−0.38	−0.17	−0.60
$\Delta\Delta G°$[d]	1.37	0.18	−0.30	0.72	0.61

[a] In kcal/mol at 25°. [b] Solvent acetonitrile for the dioxanes. Various solvents have been used for the cyclohexanes. [c] Values taken from J. Hirsch, *Top. Stereochem.*, **1**, 199 (1967). [d] Dioxane value minus cyclohexane value.

If one focuses on the X/ring-oxygen *vs.* X/CH_2 interactions, assuming other interactions to be similar,[14] it would appear that the F/O interaction in the axially substituted dioxane is considerably more attractive (or less repulsive) than the sum of the F/H-3 (syn-axial) and F/C-3 interactions in the axially substituted cyclohexane. The latter interactions, assuming van der Waals radii of 1.35 Å for fluorine, 1.70 Å for carbon, and 1.20 Å for hydrogen, are, according to the approximate distances measured in a Dreiding model, not strongly repulsive; therefore an attractive F/O interaction is suggested.[15] It is of interest that no corresponding overwhelming attractive potential is found for Cl/O nor, *a fortiori*, for Br/O, even though chlorine and bromine are more polarizable and therefore might have been expected to give rise to a stronger attractive nonbonded interaction term in the conventional treatment.[16] Clearly the well-recognized London ($1/r^6$) term is not responsible for the apparent strong F/O attraction and it remains for quantum mechanical calculation to try to pinpoint its origin.[17]

The situation for O/O, CN/O, and Cl/O is not as clear-cut as for F/O, for $\Delta\Delta G°$ is small and it becomes more difficult to sort out its various attractive and repulsive contributors. However, a crude calculation[18]

---

(10) K. Pihlaja, *Acta Chem. Scand.*, 22, 716 (1968); K. Pihlaja and S. Luoma, *ibid.*, 22, 2401 (1968); K. Pihlaja and J. Jalonen, *Org. Mass Spectrom.*, 5, 1363 (1971).

(11) H. R. Buys and E. L. Eliel, *Tetrahedron Lett.*, 2779 (1970).

(12) A. J. Jones, E. L. Eliel, D. M. Grant, M. C. Knoeber, and W. F. Bailey, *J. Amer. Chem. Soc.*, 93, 4772 (1971).

(13) *Cf.* J. Reisse, J. C. Celotti, and G. Chiurdoglu, *Tetrahedron Lett.*, 397 (1965); E. L. Eliel and R. J. L. Martin, *J. Amer. Chem. Soc.*, **90**, 689 (1968).

(14) This is only very roughly true, since the geometry of 1,3-dioxane is appreciably different from that of cyclohexane: A. J. de Kok and C. Romers, *Recl. Trav. Chim. Pays-Bas*, **89**, 313 (1970). However, the interatomic distances in the dioxane are, if anything, shorter than in cyclohexane for the axial substituent, so this feature can account for the observed $\Delta\Delta G°$ values (Table II) only for the case of bromine, if any.

(15) It is desirable to look at the equatorial conformer and the X/H gauche interactions as well. However, the four F/H gauche interactions of the equatorial fluorine and the two F/H gauche interactions of axial fluorine are very nearly the same in cyclohexyl fluoride and 5-fluorodioxane, so their contribution would seem to cancel out. The possibility must be considered, however, that both the F/H gauche interaction and the F/H syn–axial interaction are unexpectedly strongly repulsive. The resulting effects would nearly cancel in cyclohexyl fluoride (equatorial isomer, four F/H gauche interactions; axial isomer, two F/H gauche and two F/H syn–axial interactions) but not in the 5-fluorodioxane in which the two extra F/H gauche interactions of the equatorial isomer are not counterbalanced by corresponding syn–axial interactions in the axial. This point is under experimental investigation; but the recent finding of an attractive-dominant barrier to methyl rotation in *cis*-1-fluoropropene [E. Scarzafava and L. C. Allen, *J. Amer. Chem. Soc.*, 93, 311 (1971)] suggesting a net attractive H/F interaction makes this explanation unlikely. *Ab initio* calculations [S. Wolfe, A. Rauk, L. M. Tel, and I. G. Csizmadia, *J. Chem. Soc. B*, 136 (1971)] also suggest that F/H interactions are smaller than H/H interactions.

(16) *Cf.* E. L. Eliel, *Angew. Chem., Int. Ed. Engl.*, 4, 761 (1965).

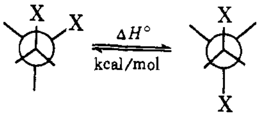
(17) Professor Saul Wolfe, Queens University, Kingston, Ontario, Canada, has suggested to one of us (E. L. E.) that electron–nuclear attraction might dominate the F/O nonbonded potential at the distance in question, as contrasted to nuclear–nuclear and electron–electron repulsions. The latter terms may be more important for elements further down the periodic table, such as bromine; *cf.* N. S. Zefirov, V. S. Blagoveshchensky, I. V. Kazimirchik, and N. S. Surova, *Tetrahedron*, 27, 3111 (1971).

(18) Reference 7, pp 455–456.

indicates that the net potential for an axial chlorine in cyclohexyl chloride is attractive, so it would seem that the corresponding interaction in the dioxane must be *more* attractive and it is likely that a similar argument would apply to O/O and CN/O, the latter interaction being further complicated by possible interactions involving the π electrons as well as the N in addition to the C atom.

Apparent attractive interactions between first-row elements have been previously recorded.[19] Thus it is known that the gauche form is of nearly the same stability as the anti in gaseous 1,2-difluoroethane, but not in the dichloro and dibromo analogs (Table III[20–23]).

Table III



	ΔH°, kcal/mol, for X =		
	F	Cl	Br
Gas phase	0.0 ± 0.2	−1.2 ± 0.1	−1.77 ± 0.15
Liquid phase[a]	*Ca.* +0.9[b]	0.0 ± 0.1	−0.74 ± 0.12
Ref	20	19, 21, 22	19, 21, 22

[a] Because of the higher dielectric constant of the liquid compared to the vapor the dipolar gauche form is favored. [b] This is a calculated value and is undoubtedly too small; using the method described in ref 6 one of us has recently obtained a value of 2.3 kcal/mol: R. J. Abraham and R. H. Kemp, *J. Chem. Soc. B*, 1240 (1971).

Succinonitrile in the liquid phase is more stable in the gauche conformation than in the anti.[23] Both 1,2-dimethoxyethane[24] and poly(ethylene glycol)[25] are predominantly in the gauche conformation about the C–C bond.

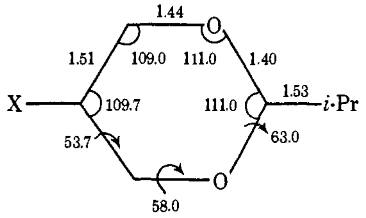
The Solvent Dependence of the Equilibrium. A quantitative theory of the effect of the medium on the rotamer energy differences in substituted ethanes has been given and applied to a variety of such molecules.[6] Thus we now present only the necessary minimum outline of the theory, plus its extension to the systems considered here.

The energy difference[26] $\Delta E^s = E^s_A - E^s_B$ between two rotamers or conformers A and B in any solvent s of dielectric constant ϵ is given in terms of the energy difference in the vapor ΔE^v by[27]

$$\Delta E^s = \Delta E^v - kx/(1 - lx) - 3hx/(5 - x) \qquad (1)$$

where $x = (\epsilon - 1)/(2\epsilon + 1)$ and $l = 2(n_D^2 - 1)/(n_D^2 + 2)$, n_D being the solute refractive index and ϵ bring the dielectric constant of the medium. The parameters k and h are the dipole $(\mu_A^2 - \mu_B^2)/a^3$ and quadrupole $(q_A^2 - q_B^2)/a^5$ molecular fields, where μ and q are the dipole and quadrupole moments of the isomers. a is the molecular radius, given by $4\pi a^3/3$ = molar volume/Avogadro's number. The dipole and quadrupole moments are calculated by placing point dipoles along and at the center of the C–X bonds; thus the only parameters required are the molecular geometries and bond dipole moments.

The 1,3-dioxane ring geometry is taken from the work of de Kok and Romers[14] and is shown below. The substituents are defined in accordance with the standard, but not tetrahedral geometry given previously.[28] Thus all C–C–X angles (X = O, F, Cl, Br, C) are taken as 111.0°.



The C–O bond moment was taken directly from the observed moment (1.30 D)[29] and C–O–C angle (111.5°)[30] of dimethyl ether, to give μ(C–O) = 1.16 D. Using this and the defined geometries gives calculated dipole moments for 2-phenyl-1,3-dioxane and 2-*p*-chlorophenyl-1,3-dioxane of 1.93 and 3.46 D (using the observed value of the Ph–Cl dipole of 1.75 D)[29] which compare well with the observed values (2.04 and 3.54 D).[31] A further check can be obtained from the substituted 2-methoxy-1,3-dioxanes though here there is the additional complication of rotational isomerism about the C–O bond of the methoxyl. For the equatorial 2-methoxyl we obtain dipole moments of 2.22 and 3.00 D for the symmetrical "Me-up" (H–C–O–Me torsional angle 180°) and the enantiomeric 60° rotamer, respectively. The observed values of a number of substituted dioxanes are all between 2.88–2.93 D,[32] corresponding to a preponderance of the enantiomeric forms. For the axial 2-methoxyl compound the calculated values are 2.25 D for the "Me-outside" rotamer (ω = 180°) and 1.38 D for the 60° rotamers. The observed values of substituted dioxanes fall in the range 1.79–1.97 D[32] corresponding to a preponderance of the "Me-outside" form.[33] These results are in complete agreement with previous conclusions regarding the rotational isomerism of the C-2 methoxyl,[32] and further support our model.

For the 5-methoxy-2-isopropyl-1,3-dioxanes studied here, the calculated dipole moments for the two rotamers of the cis and trans compounds are given in

---

(19) For an excellent review, see J. P. Lowe, *Progr. Phys. Org. Chem.*, **6**, 1 (1969).

(20) P. Klaboe and J. R. Nielsen, *J. Chem. Phys.* **33**, 1764 (1960).

(21) S. Mizushima, Y. Morino, I, Watanabe, T. Simanout, and S. Yamaguchi, *ibid.*, **17**, 591 (1949).

(22) Y. A. Pentin and V. M. Tatetevskii, *Dokl. Akad. Nauk. SSSR*, **108**, 290 (1956).

(23) W. E. Fitzgerald and G. J. Janz, *J. Mol. Spectrosc.*, **1**, 49 (1957).

(24) R. G. Snyder and G. Zerbi, *Spectrochim. Acta, Part A*, **23**, 391 (1967).

(25) J. E. Mark and P. J. Flory, *J. Amer. Chem. Soc.*, **88**, 3702 (1966).

(26) The calculations are in terms of potential energy whereas the experimental data are in terms of enthalpy. Since we are interested only in *differences* between solvents, the zero-point energy, contribution of higher vibrational states, and pdV terms are expected to cancel out. For a recent discussion, see J. Reisse in "Conformational Analysis," G. Chiurdoglu, Ed., Academic Press, New York, N. Y., 1971, p 219.

(27) There is an extra term in this equation for polar solutes in polar media. For the present compounds it is negligible and ignored henceforth. Also note that we define h as $q_A - q_B$, rather than $q_B - q_A$ as previously.[6] This merely alters the sign of the quadrupole term in eq 1.

(28) R. J. Abraham and K. Parry, *J. Chem. Soc. B*, 539 (1970).

(29) A. L. McClellan, "Tables of Experimental Dipole Moments," W. H. Freeman, San Francisco, Calif., 1963.

(30) P. H. Kasai and R. J. Myers, *J. Chem. Phys.*, **30**, 1096 (1959).

(31) B. J. Hutchinson, R. A. Y. Jones, A. R. Katritzky, K. A. F. Record, and P. J. Brignell, *J. Chem. Soc. B*, 1224 (1970).

(32) E. L. Eliel and F. W. Nader, *J. Amer. Chem. Soc.*, **92**, 584 (1970).

(33) For a discussion of this problem in the 2-alkoxytetrahydropyrans, see A. J. de Hoog, H. R. Buys, C. Altona, and E. Havinga, *Tetrahedron*, **25**, 3365 (1969).

Table IV. Calculated and Observed Energy Differences (kcal/mol) for 5-Substituted 2-Isopropyl-1,3-dioxanes

	μ, D,[a] for X =				
	F	Cl	Br	OMe (60°)	OMe (180°)
Cis	3.09	3.18 (3.04)	3.18	2.99 (2.85)	2.13
Trans	1.07	1.05 (0.87)	1.05	1.38 (1.30)	2.30
k (Cis–trans)	2.13	2.18	2.14	1.70	
h (Cis–trans)	2.16	1.70	1.47	0.32	

	ΔE^s [b]							
	X = F		X = Cl		X = Br		X = OMe	
Solvent	Calcd	Obsd	Calcd	Obsd	Calcd	Obsd	Calcd	Obsd
Vapor	0.6		2.2		2.5		1.25	
CCl_4	−0.37	−0.36	1.41	1.40	1.75	1.71	0.80	0.90
Et_2O	−0.78	−0.62	0.90	1.26	1.26	1.45	0.47	0.83
$CHCl_3$	−0.84	−0.87	0.85	0.94	1.21	1.35	0.43	0.16
CH_3CN	−1.43	−1.22	0.29	0.25	0.68	0.68	0.08	−0.01

[a] Calculated values; observed values where availabile are shown in parentheses. [b] E^s(cis) − E^s(trans).

Table IV. The observed dipole moments of 2.85 and 1.30 D for the cis and trans isomers again show that the preponderant isomer in both cases is the enantiomeric form (ω = 60°). Thus we shall consider only this form in the solvation energy calculations.

For the halo-substituted dioxanes the values of the C–X moments given by Smith[34] are used (C–F, 1.4 D; C–Cl, C–Br, 1.5 D). For the 5-chloro-2-isopropyl-1,3-dioxanes this gives calculated dipole moments of 3.18 (cis) and 1.05 D (trans) which compare reasonably with the observed values (3.04 and 0.87 D).

The molar volumes and refractive indices of the compounds investigated were, in the absence of experimental data, estimated from those of similar compounds. The molar volumes of 2-isopropyl-1,3-dioxane and its 5-fluoro, chloro, bromo, and methoxy derivatives were taken as 136.2, 143.9, 150.4, 152.9, and 150.0 ml, respectively, and all the refractive indices taken as 1.420.

The solvation energies of the isomers can now be calculated from eq 1. They are given for the substituted compounds in Table IV, together with the observed values. The values of *k* and *h* given in the table can be used directly with eq 1 to give the solvation energies for any solvent of given dielectric. A slight correction was made in the solution dielectric by taking into account the appropriate dielectric constant of the solute (*e.g.*, ϵ = 6 for X = F) at 10% v/v (*ca.* 0.5 *M*) concentration. In Table IV, we merely list those solvents for which experimental data are available.

The theory only calculates $\Delta E^v - \Delta E^s$, and hence $\Delta E^{s_1} - \Delta E^{s_2}$, the difference in ΔE between different solvents; it does not calculate ΔE for a single given solvent. The significance of the results in Table IV lies in the agreement between the different solutions. It can be seen that there is generally good agreement between the observed and calculated values. [The agreement for the methoxy compound is less than that for the halides, perhaps because of the conformational (rotameric) inhomogeneity of the OCH_3 substituent.] Thus the large solvent effects found in these systems can be completely explained on the basis of this theory. This good general agreement leads to two further useful conclusions. Significant deviations from the predicted values may be very reasonably explained as due to specific solvent–solute interaction. Such deviations occur for the methoxy compound in solvent chloroform and for all four compounds studied in solvent benzene, for which the calculated values are nearly the same as in carbon tetrachloride, whereas the experimental data (Table I) show a substantially greater preference for the axial conformation. These abnormal situations will be discussed in a future paper.

Also the agreement allows the prediction of ΔE^v from solution data as shown in Table IV. Of particular interest here is the positive value of ΔE^v for the fluoro compound; *i.e.*, in the vapor state it is predicted that the C-5 fluorine prefers the trans (equatorial) conformation. This does not affect the discussion given earlier concerning the F···O interactions, as in the vapor charge–charge repulsions of *ca.* 2 kcal/mol between the fluorine and oxygen atoms are present (*cf.* the calculations on 1,2-difluoroethane, with a polar repulsive contribution of *ca.* 1 kcal/mol in favor of the anti-periplanar rotamer).[28] Thus the fluorine is still considerably more stable in the axial configuration than expected.

Synthesis and Assignment of Configuration. The 5-cyano- and 5-halodioxanes (Scheme II, X = F, Cl, Br, CN) were synthesized from isobutyraldehyde and the corresponding 2-substituted 1,3-propanediols, $HOCH_2CHXCH_2OH$. 2-Fluoro-1,3-propanediol was obtained by lithium aluminum hydride reduction of diethyl 2-fluoromalonate.[35] Attempted similar synthesis of 2-chloro-1,3-propanediol led to considerable loss of chlorine in the reduction step; therefore aluminum hydride was used as the reducing agent. Reduction of diethyl 2-bromomalonate led to loss of bromine under all reducing conditions tried; the 5-bromo-2-isopropyl-1,3-dioxanes were therefore synthesized from *cis*-5-hydroxy-2-isopropyl-1,3-dioxane (see below), tri-*n*-octylphosphine, and carbon tetrabromide.[36] Alternatively, both 2-chloro-[37] and 2-bromo-1,3-propanediol[38] were obtained by addition of the appropriate hypohalous acid to allyl alcohol. This procedure gave approximately equal amounts of the desired $HOCH_2CHXCH_2OH$ and $XCH_2CHOHCH_2OH$. Subsequent partial removal of the dioxolane by condensation with acetone followed by treatment with isobutyraldehyde and acid gave the two diastereoisomeric 5-halo-1,3-dioxanes along with two 4-halomethyl-1,3-dioxolanes. The desired dioxanes were separated by preparative gas chromatography. 2-Carbethoxy-2-cyano-1,3-propanediol was synthesized from ethyl cyanoacetate and formaldehyde. Condensation with isobutyraldehyde followed by mild hydrolysis and decarboxylation gave the 5-cyano-2-isopropyl-1,3-dioxanes. *cis*-5-Hydroxy-2-isopropyl-1,3-dioxane was synthesized by the procedure of Trister and Hibbert[39] and was methylated with methyl iodide and silver oxide[39] or, more conveniently, with methyl iodide and sodium hydride.[40] It was found that the mixture of 5-hydroxy-1,3-dioxanes and 4-hy-

---

[34] J. W. Smith, "Electric Dipole Moments," Butterworths, London, 1955, p 92.

[35] Obtained as described by E. D. Bergmann, S. Cohen, and I. Shahak, *J. Chem. Soc.*, 3286 (1959), or more conveniently, by the method of H. Gershon, J. A. A. Renwick, W. K. Wynn, and R. D'Ascoli, *J. Org. Chem.*, 31, 916 (1966).

[36] J. Hooz and S. Giliani, *Can. J. Chem.*, 46, 86 (1968).

[37] *Cf.* L. Smith and J. Lindberg, *Ber.*, 64B, 505 (1931).

[38] L. Smith and J. Laudon, *ibid.*, 66B, 899 (1933).

[39] S. M. Trister and H. Hibbert, *Can. J. Res.*, 14B, 415 (1936).

[40] U. E. Diner, F. Sweet, and R. K. Brown, *Can. J. Chem.*, 44, 1591 (1966).

droxymethyl-1,3-dioxolanes obtained by condensation of glycerol with isobutyraldehyde[39] could be enriched in the dioxane components by leaving it to equilibrate for 2 days in the refrigerator (*ca.* 5°) before work-up. Low temperatures favor the dioxanes over the dioxolanes at equilibrium, since the six-membered ring system is favored enthalpically but (being more rigid) disfavored entropically.[41] *trans*-5-Hydroxy-2-isopropyl-1,3-dioxane was prepared from the cis isomer by inversion *via* the mesylate as previously described[42] and was converted to the methyl ether in the same way as the cis isomer.

Configurational assignments of the 5-fluoro compounds were based on H-5/H-4 and F-5/H-4 coupling constants. The isomer assigned the equatorial fluorine conformation (trans) had proton coupling constants J_{aa} = 10.0 Hz, J_{ae} = 5.5 Hz and fluorine coupling constants J_{gem} = 49 Hz, $J_{ee} + J_{ea} < 6.5$ Hz. The isomer assigned axial fluorine (cis) had $J_{ee} = J_{ea}$ = 1.6 Hz for the proton couplings and J_{gem} = 47.9 Hz, J_{ae} = 18.0 Hz, J_{aa} = 36.9 Hz for the fluorine proton couplings. The assignment of the 5-chloro compounds rested on the dipole moments (cis isomer, 3.04 D; trans isomer, 0.87 D) as well as on the coupling constants of the 5 proton (cis isomer, $J_{ea} = J_{ee}$ = 1.6 Hz; trans isomer, J_{aa} = 12.4 Hz, J_{ae} = 5.6 Hz).[43] The nmr spectra of the 5-bromo compounds were too tightly coupled for analysis of the H-4,5 region but configurational assignments could be based on overall similarities of the spectra with those of the configurationally analogous chloro compounds. The configurations of the methoxy compounds are correlated, by preparation, with those of their hydroxy precursors whose stereochemistry had been previously assigned[31] on the basis of the fact that only the cis isomer shows complete intramolecular hydrogen bonding in dilute solution. The assignments are corroborated by dipole measurements (cis, 2.85 D; trans, 1.30 D). The configurational assignment of the cyano compounds rests on proton coupling constants (first-order analysis) (cis isomer, $J_{ee} = J_{ea}$ = 1.4 Hz; trans isomer, J_{aa} = 10.5 Hz, J_{ae} = 4.8 Hz). All assignments are compatible with the predicted solvent effect on equilibrium (Table I: polar solvent favors the more dipolar axial isomer) and also with the observation, made in the case of the halo and cyano compounds, that the more dipolar cis isomers had glpc retention times which were four to six times as long as those of their trans epimers.

Experimental Section

Nmr spectra were recorded on a Varian A-60A instrument, except for the fluorine spectra which were recorded on a Varian Model V4311 HR-60 spectrometer. Infrared spectra were recorded on a Perkin-Elmer Model 457 grating spectrometer. Analytical gas chromatography was effected on an F & M Scientific Corp. Model 810-29 or 810-19 dual column instrument equipped with thermal conductivity detector and integrator; all chromatograms were calibrated for area response with known mixtures of pure components. Preparative gas chromatography was carried out on a Nester-Faust Model 850 Prepkromatik instrument equipped with 3-ft "biwall" 0.75-in. annular columns or (for smaller samples) with a Varian Aerograph Model 1520 instrument. Dipole moments were recorded on a WTW Dipolmeter DM 01 equipped with a DFL 2/D cell.

cis- **and** *trans-***5-Fluoro-2-isopropyl-1,3-dioxane.** In a 250-ml flask equipped with reflux condenser, mechanical stirrer, and dropping funnel were placed 0.90 g (24 mmol) of lithium aluminum hydride and 25 ml of anhydrous ether. The mixture was stirred under dry nitrogen (1 hr), diethyl fluoromalonate[35] (3.0 g, 16.6 mmol) in 25 ml ether was added over 30 min, and the mixture was refluxed for 3 hr. Work-up involved treatment with 0.9 ml of water, 0.9 ml of 15% sodium hydroxide, and 2.7 ml of water, stirring for 1 hr, and filtration. The precipitate was extracted with four 25-ml portions of hot tetrahydrofuran. After drying over magnesium sulfate and filtration, concentration yielded 1.39 g of crude diol.

The diol was condensed with an equivalent amount of isobutyraldehyde in the presence of *ca.* 50 mg of *p*-toluenesulfonic acid in 5 ml of Skellysolve F (petroleum ether, bp 30–60°) with a Dean–Stark trap at reflux, condensation period 20 hr. The acid was buffered with *ca.* 50 mg of sodium acetate; the mixture was stirred for 0.5 hr, diluted with *ca.* 50 ml of ether, and washed twice with 25 ml of water. After drying over magnesium sulfate, filtering, and concentration the material was chromatographed on a 12-ft column (9-ft Carbowax and 3-ft FFAP, 20% on Chromosorb W, 45–60 mesh) at 105°, He flow 600 ml/min. The retention time for the cis isomer was 74 min (16% yield based on diol); n^{25}D 1.4210; ir (neat) 800, 840, 867, 924, 942, 965, 975 cm^{-1}. The retention time for the trans isomer was 14 min (10.1% yield); n^{25}D 1.4068; ir (neat) 907, 952, 989, 1050, 1102, 1150 cm^{-1}.

Anal. Calcd for $C_7H_{13}O_2F$: C, 56.74; H, 8.84. Found (cis isomer): C, 57.44; H, 9.05. Found (trans isomer): C, 56.72; H, 9.02.

cis- **and** *trans-***5-Chloro-2-isopropyl-1,3-dioxane.** (a)[44] In a 1-l. three-necked flask flushed with dry nitrogen, equipped as above, were placed 500 ml of dry tetrahydrofuran (THF) and 16 g (0.4 mol) of lithium aluminum hydride. After the mixture was stirred for 1 hr, the flask was placed in an ice bath and 20.6 g (11.2 ml) of 100% sulfuric acid was added dropwise with vigorous stirring. Addition took 15 min and stirring was continued for 1 hr after which a solution of 29.2 g (0.15 mol) of diethyl chloromalonate in 150 ml of THF was added over a period of 30 min. After 15 min of additional stirring, there were added 16 ml of water (caution!), 16 ml of 15% sodium hydroxide, and 48 ml of water, stirring being continued for 1 hr. The precipitate was filtered and extracted three times with 200-ml portions of boiling THF. The combined THF solutions were dried over magnesium sulfate, filtered and concentrated to give 16.4 g of crude diol.

Condensation of the diol with isobutyraldehyde was effected as described for the fluoro compound above; the condensation period was 48 hr. The crude chlorodioxanes were distilled (bp 57–65° (1 mm)) and chromatographed on a 12-ft 20% Carbowax 20M plus 12-ft 20% FFAP (in series) column (on Chromosorb W, 45–60 mesh) at 140°, He flow 300 ml/min. Cis isomer: retention time, 128 min; 11.5% yield based on crude diol; mp 41–41.5°; ir 622, 815, 865, 924, 945 cm^{-1}. Trans isomer: retention time, 34 min; n^{25}D 1.4410; 20% yield; ir 824, 908, 951, 1038, 1092 cm^{-1}.

Anal. Calcd for $C_7H_{13}O_2Cl$: C, 51.10; H, 7.91. Found (cis isomer): C, 50.80; H, 8.03. Found (trans isomer): C, 51.39; H, 8.04.

(b) The compounds were prepared as described below for the bromo compounds, except that chlorine was bubbled into the allyl alcohol solution until the theoretical amount had been absorbed. Yields and composition (dioxanes:dioxolanes) were similar to those of the bromine analogs.

cis- **and** *trans-***5-Methoxy-2-isopropyl-1,3-dioxane.** The described procedure was modified as follows. A mixture of freshly distilled glycerol (422 g, 4.60 mol), isobutyraldehyde (167.5 g, 2.30 mol), and 2.5 ml of 40% sulfuric acid in a 2-l. flask fitted with a reflux condenser with Dean–Stark trap was boiled for several hours until no more water was collected. The solution was cooled and stored in the refrigerator at 5° for 2 days, then neutralized with 10% aqueous KOH, and extracted with ether; the ether layer was dried over K_2CO_3, filtered and concentrated. Distillation yielded 297 g (88%) of mixed acetals, bp 78–93° (5–6 mm) (lit.[39] 102–108° (12–15 mm)]. The mixture of acetals was benzoylated as described

---

[41] *Cf.* J. D. van Roon, *Recl. Trav. Chim. Pays-Bas*, **48**, 173 (1929); G. Aksnes, P. Albriktsen and P. Juvvik, *Acta Chem. Scand.*, **19**, 920 (1965).

[42] N. Baggett, M. A. Bukhari, A. B. Foster, J. Lehmann, and J. M. Webber, *J. Chem. Soc.*, 4157 (1963).

[43] The spectrum was recorded at 250 MHz by Dr. R. J. Wiersema and Professor F. A. L. Anet, University of California, Los Angeles, Calif.

[44] Patterned after the procedure of N. M. Yoon and H. C. Brown, *J. Amer. Chem. Soc.*, **90**, 2927 (1968).

previously[39] to give 45.3 g (19.0%) of the crude cis benzoate. Recrystallization from Skellysolve B (bp 60–70°) gave material of mp 70.5–72° [lit.[39] 73.5°]. This material (30 g, 0.12 mol) was saponified with 15 g of KOH dissolved in 15 ml of H_2O and 90 ml of diethylene glycol by heating at 80° with swirling for 3 min, followed by vigorous shaking in a stoppered flask and heating for an additional 2 min. After cooling the mixture was extracted continuously for 48 hr with Skellysolve F. The extracts were dried over magnesium sulfate, filtered and concentrated to give, upon crystallization from Skellysolve F, 13.3 g (75.8%) of *cis*-5-hydroxy-2-isopropyl-1,3-dioxane, mp 40.5–41° (lit.[39] 38–39°].

Alternatively, the *cis*-hydroxydioxane was obtained by chromatographing the crude mixture of hydroxyacetals (bp 78–93° (5–6 mm)) on a 3-ft column packed with 16.6% THEED on Chromosorb P (45–60 mesh) at 115°, He flow rate 600 ml/min. The retention time of the *cis*-2-isopropyl-5-hydroxy-1,3-dioxane was 6 min and the material melted at 40.5–41° (recovery about 30% of the crude acetal mixture).

To a solution of 3.25 g (22.2 mmol) of the dioxane and 3.68 g (26.0 mmol) of methyl iodide in 13.5 ml of dry 1,2-dimethoxyethane was cautiously added 0.58 g (24.2 mmol) of sodium hydride over a period of 45 min. After the mixture was stirred for 30 min, an additional 3.68 g methyl iodide was added and the solution stirred at room temperature for 3 hr. Excess methyl iodide and solvent were removed by distillation, and the residue was filtered and chromatographed on a 12-ft column of 20% Carbowax 20M on Chromosorb W, 45–60 mesh, at 148° with a He flow rate of 400 ml/min, retention time 9 min: yield 2.14 g (60.0%); $n^{25}\text{D}$ 1.4364 [lit.[39] 1.4393]; ir (neat) 777, 847, 869 cm^{-1}.

The *trans*-5-hydroxy compound was prepared from the cis compound *via* the methanesulfonate, mp 98–99° [lit.[42] 99–100°], and inverted benzoate, mp 59.5–60° [lit.[42] 49–50°], as previously described[42] and melted at 45–45.5°.

Anal. Calcd for $C_7H_{14}O_3$: C, 57.51; H, 9.65. Found: C, 57.51; H, 9.46.

The same material was isolated in the gas chromatographic separation of the crude acetal mixture (see above) in *ca.* 20% yield, retention time 36 min.

The methyl ether was prepared as described for the cis isomer: yield 79.0%; bp 27–29° (8 mm); $n^{25}\text{D}$ 1.4251; ir (neat) 855, 899 cm^{-1}.

Anal. Calcd for $C_8H_{16}O_3$: C, 59.98; H, 10.07. Found: C, 60.18; H, 10.07.

***trans*-2-Isopropyl-5-bromo-1,3-dioxane.** (a) To a magnetically stirred solution of 10.0 g of *cis*-2-isopropyl-5-hydroxy-1,3-dioxane (68.5 mmol) and 44.2 g of carbon tetrabromide (133.2 mmol) in 140 ml of anhydrous ether, cooled in an ice–water bath, was added 50.8 g of tri-*n*-octylphosphine (137.5 mmol). An exothermic reaction ensued and the solution turned orange. The mixture was stirred for 10 min at room temperature, the ether distilled, and the residue distilled at 0.5 mm until the oil bath temperature reached 170°. The distillate was chromatographed from pentane on a column (25 × 220 mm) containing 105 g of Fisher basic alumina (Brockman Activity I). Elution was with 17 30-ml fractions of pentane followed by six 30-ml fractions of ether. Concentration of fractions 6–23 followed by gas chromatography on a 9-ft 20% Carbowax 20M on 45–60 mesh Chromosorb W at 125°, He flow rate 425 ml/min, gave 3.7 g (25.8%) of product: retention time 24 min; $n^{25}\text{D}$ 1.4657; ir (neat) 788, 905, 950, 1025, 1084, 1111, 1140 cm^{-1}.

Anal. Calcd for $C_7H_{13}O_2Br$: C, 40.21; H, 6.26. Found: C, 40.49; H, 6.21.

(b) To a mechanically stirred solution of 116 g (2.0 mol) of allyl alcohol in 750 ml of ice water, 260 g of bromine was added dropwise, over a period of 6 hr, keeping the temperature below 10°.[38] The mixture was allowed to stand overnight and then extracted with two 200-ml portions of ether which were discarded. The aqueous phase was concentrated on a rotary evaporator at reduced pressure. The residue was dissolved in 100 ml of acetone and 500 ml of pentane. After addition of 2.0 g of *p*-toluenesulfonic acid, water was distilled azeotropically, using a Dean–Stark trap. After 20 hr the solution was cooled, stirred for 0.5 hr with 2.0 g of anhydrous K_2CO_3, and filtered. The upper (pentane) layer was discarded and the lower (diol) layer extracted twice with 100 ml of pentane (discarded). The residue was treated with 50 ml of isobutyraldehyde and 500 ml of pentane as described above for the acetone condensation. After 20 hr the mixture was cooled, twice extracted with 100-ml portions of water (discarded), and dried over magnesium sulfate. Filtration, concentration, and distillation gave 83.7 g of crude product, bp 67–85° (2–3 mm), consisting, according to glpc analysis, about equally of dioxanes and dioxolanes. The material was dissolved in 200 ml of acetonitrile and equilibrated over Amberlyst-15 at room temperature for 48 hr. After neutralization with anhydrous K_2CO_3 and filtration, concentration yielded a mixture from which the pure dioxanes were isolated by preparative gas chromatography (see above).

***cis*-2-Isopropyl-5-bromo-1,3-dioxane.** (a) A solution of 3.7 g of the trans isomer in 50 ml of anhydrous ether was equilibrated over Amberlyst-15 at room temperature for 14 days. The solution was decanted, shaken with anhydrous potassium carbonate, filtered, concentrated, and gas chromatographed as described for the trans isomer: retention time, 2 hr; $n^{28}\text{D}$ 1.4742, mp 27–28°; ir (CS_2) 801, 860, 920, 941, 1011, 1055, 1089, 1114, 1140 cm^{-1}.

Anal. Calcd for $C_7H_{13}O_2Br$: C, 40.21; H, 6.26. Found: C, 40.00; H, 6.28.

(b) Method b described for the trans isomer above also yielded the cis compound.

***cis*- and *trans*-5-Cyano-1,3-dioxane.** 2-Cyano-2-carbethoxy-1,3-propanediol was obtained from ethyl cyanoacetate and formaldehyde exactly as described for the reaction of diethyl malonate and formaldehyde.[45] The condensation with isobutyraldehyde was effected as described above for the chloro compound, reaction time 9 hr, yield of 5-cyano-5-carbethoxy-1,3-dioxane 72.5% (based on ethyl cyanoacetate), bp 165–170° (2–3 mm). The material was saponified at room temperature for 12 hr using 1 equiv of 30% potassium hydroxide following the procedure of Adams and Rogers.[46] Decarboxylation was best carried out by heating with 2,6-lutidine.[47] The mixed 5-cyano-2-isopropyl-1,3-dioxanes (cis:trans ratio 4.2:1 by glpc) were obtained in 24% overall yield based on ethyl cyanoacetate.

The nitriles were separated by chromatography on a 9-ft 20% FFAP on Chromosorb W (45–60 mesh) column at 155°, He flow 425 ml/min. Cis isomer: retention time 108 min; mp 81–82°; ir ($CHCl_3$) 862, 946, 969, 1012, 1085, 1117, 1148, 2248 cm^{-1}. Trans isomer: retention time, 17 min; mp 39.5–41°; ir ($CHCl_3$) 910, 955, 989, 1018, 1045, 2245, 2260 cm^{-1}.

Anal. Calcd for $C_8H_{13}O_2N$: C, 61.91; H, 8.44. Found (cis isomer): C, 61.75; H, 859. Found (trans isomer): C, 61.91; H, 9.48.

Acknowledgment. We are grateful to the donors of the Petroleum Research Fund administered by the American Chemical Society (Grant 2272-C) and to the Air Force Office of Scientific Research (Grant AF-AFOSR-772) for partial support of this work. H. D. B. and O. H. were supported by postdoctoral fellowships under an NSF Science Development grant.

---

(45) P. Block, *Org. Syn.*, **40**, 27 (1960).

(46) R. Adams and E. F. Rogers, *J. Amer. Chem. Soc.*, **63**, 228 (1941).

(47) E. L. Eliel, P. H. Wilken, and F. T. Fang, *J. Org. Chem.*, **22**, 231 (1957).