separated from a 25-μl sample of the crude product using preparative gas chromatography (Table III).

Coupling of Ib. Preparation of the Linear Dimer, Trimer, and Tetramer of Ib.—A glass ampoule was charged with 25.2 g of Ib and 330 g of Hg and sealed with exclusion of air. After being heated for 16 hr at 155° the reaction mixture was extracted with hexafluoroxylene and filtered, and the filtrate was examined by glpc; the presence of coupled products was indicated. Pure samples of the three lower boiling coupled products were separated by preparative glpc and identified as IIb dimer, IIb trimer and IIb tetramer (Table III). The infrared spectrum of each compound showed an absorption at 6.48 μ for C═N.

Coupling of Ib. Preparation of Prepolymer.—A well-stirred mixture of 3590 g of Hg and 549 g of Ib was heated to 175° momentarily and then cooled to 160° where the reaction was allowed to continue for 20 hr under a N_2 atmosphere. The cooled, solid reaction mixture was extracted with CH_2Cl_2 and the extract was separated by filtration. The solvent was removed with a rotary evaporator leaving 373 g of a light tan, waxy solid (Table III). Glpc analysis indicated the presence of approximately 65% dimer and 30% trimer with traces of monomer and higher molecular weight species varying from tetramer to octamer. Bromine analysis indicated an average degree of polymerization of 3–4. An infrared spectrum of a film cast from ether showed 6.45 (s) μ, C═N.

Coupling of Ib. Preparation of Low Polymer.—A well-stirred mixture of 734 g of Ib and 724 g of Hg was heated at 160° for 6 hr under a N_2 atmosphere. An additional 1448 g of Hg was added in 362-g increments after 6, 23, 32.5 and 54.5 hr. After 60 hr the syrupy reaction mixture was cooled, chipped out of the flask, and ground in a ball mill for several hours. The low polymer was isolated from the mercury and mercury salts in several batches using a variety of extracting solvents: acetone, isopropyl acetate, and ethyl acetate. The total low polymer obtained (410 g) represents an 89.6% yield assuming an average degree of polymerization of 35–40, as indicated by bromine analysis (Table III).

Coupling of Ib. Preparation of High Polymer.—A mixture of 272 g of Hg and 20.7 g of Ib was sealed in a Pyrex ampoule with the exclusion of air and heated at 200° for 16 hr while being rocked. The reaction mass was extracted with boiling hexafluoroxylene for 4 hr and then filtered. The filtrate was freed of solvent to yield 9.1 g of a light tan powder, mp 120–155°. The insoluble portion was digested in cold aqua regia to remove the mercury and mercury salts, leaving 3.1 g of a light tan solid which did not melt below 350° and whose bromine analysis indicated an average (*n*) of approximately 350 (Table III).

Coupling of IIb (Dimer). Preparation of High Polymer.—A gently stirred mixture of 3.16 g of IIb (dimer) and 1 ml of mercury was gradually heated to 330° for 4 hr under a N_2 atmosphere. After cooling, the clear, amber polymer was peeled off the stirring blade. This polymer did not melt or change appearance at 310° in air for 6 hr.

Coupling of IIb (Low Polymer).—A mixture of 52.6 g of IIb (low polymer) and 50 g of mercury was heated at 300° for 1 hr under a nitrogen atmosphere. The clear, amber polymer (34 g) did not melt below 320° in air.

Attempted Coupling of Ic.—A mixture of 10 g of Hg and 9.1 g of Ic was sealed in a glass ampoule with the exclusion of air and heated at 250° for 16 hr, with rocking. The brown liquid product was examined with glpc and found to contain approximately 96% Ic and 4% IIc.

Attempted Coupling of Id.—A mixture of 0.6 g of Id and 7.35 g of Hg was sealed in a glass ampoule with the exclusion of air and heated at 250° for 19 hr. The colorless liquid product was examined by glpc and found to be pure Id.

Registry No.—Ia, 7601-94-7; Ib, 7601-95-8; Ie, 7648-29-5; CF_2ICO_2Et, 7648-30-8; CF_2ICONH_2, 7601-96-9; CF_2ICN, 7601-97-0; $(CF_2BrCO)_2O$, 7601-98-1; CF_2BrCN, 7601-99-2; Ic, 7602-00-8; Id, 368-66-1; If, 7650-61-5; IIa (Y = F; *n* = 2), 7594-83-4; IIb (Y = Br; *n* = 2), 7594-80-1; IIb (Y = Br; *n* = 3), 7594-81-2; IIb (Y = Br; *n* = 4), 7594-82-3.

Acknowledgment.—The authors are indebted to Mr. Bruce Blanck, Mr. Anthony J. Butler, and Dr. Louis H. Toporcer for their technical assistance during a portion of this investigation.

Conformation and the Anomeric Effect in 2-Halotetrahydropyrans

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Conformational equilibria of 2-chlorotetrahydropyran, 2-chloro-4-methyltetrahydropyran, 2-bromotetrahydrahydropyran, 2-bromo-4-methyltetrahydropyran, 2-iodotetrahydropyran, and 2-iodo-4-methyltetrahydropyran were examined by nmr methods. The anomeric effects for the chloro and bromo substituents, respectively, were found to be 2.7 and 3.2 kcal/mole or greater. The anomeric effect is rationalized semiquantitatively in terms of the electrostatic interaction of bond dipoles emphasizing the importance of microscopic dielectric constants.

The conformational preference of most substituent groups larger than hydrogen on the cyclohexane ring is for the equatorial position rather than the axial position. However, there are situations where electronegative groups prefer the axial conformation. Such a case exists in the pyranosides where a C-1 methoxyl, acetoxyl, or chloro substituent is more stable in the axial conformation.[1,2] This effect in pyranosides has been called the "anomeric effect."[3] Edward first attributed the anomeric effect to the interaction of the electronegative substituent at the anomeric position with the unshared pairs of electrons of the ring oxygen.[4] Since then the anomeric effect has been more simply attributed to the dipolar interaction of the bond from the pyranoside C-5 to ring oxygen with the bond from the anomeric carbon to the oxysubstituent. The anomeric effect has been explicitly defined as equal to the observed free-energy difference between anomers plus the conformational preference (or *A* value) for the anomeric substituent, since these effects are opposed at the anomeric position.[5] Other cases of electronegative groups favoring the axial orientation are found in *trans*-2,5-dichloro-1,4-dioxane,[6] *trans*-2,3-dichlorotetra-

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[1] L. J. Haynes and F. H. Newth, *Advan. Carbohydrate Chem.*, **10**, 207 (1955); W. A. Bonner, *J. Am. Chem. Soc.*, **81**, 1450 (1959); D. Horton and W. N. Turner, *J. Org. Chem.*, **30**, 3387 (1965).

[2] E. L. Eliel, N. J. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," John Wiley and Sons, Inc., New York, N. Y., 1965, p 375.

[3] R. U. Lemieux, Abstracts, 135th National Meeting of the American Chemical Society, Boston, Mass., April 1959, p 5E; Abstracts, 133rd National Meeting of the American Chemical Society, San Francisco, Calif., 1958, p 31 N.

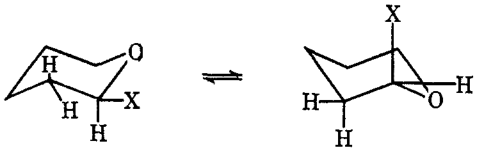
[4] J. T. Edward, *Chem. Ind.* (London), 1102 (1955).

[5] C. T. Bishop and F. P. Cooper, *Can. J. Chem.*, **41**, 2742 (1963).

[6] C. Altona and C. Romers, *Rec. Trav. Chem.*, **82**, 1080 (1963); C. Altona, C. Romers, and E. Havinga, *Tetrahedron Letters*, 16 (1959).

hydropyran,[7] and 1,2-dihalocyclohexanes[8] as well as 2-bromo- and 2-chlorocyclohexanones.[9,11]

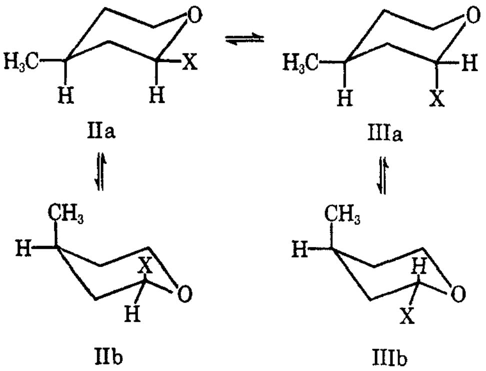
In order to measure the magnitude of the anomeric effect without the complications of multiple substitution, the simple 2-halotetrahydropyrans are of interest. For such a conformationally mobile system as the 2-halotetrahydropyrans where the axial and equatorial conformers are in rapid equilibrium (Ia $\rightleftharpoons$ Ib) and cannot be separated, nmr spectroscopy is a convenient analytical tool for measuring the conformational equilibrium. The nmr spectrum shows a broad signal for the anomeric proton which is a time average of the couplings and the chemical shifts of the anomeric proton in the two conformations, Ia and Ib. The position of the conformational equilibrium may be determined from the nmr spectral measurements (1) using the equation[10] $\delta = N_1\delta_1 + N_2\delta_2$ (where N_1 and N_2 are mole fractions of the two conformers) if, in addition to the time averaged chemical shift of the anomeric proton in the mobile compound (δ), the shifts for the anomeric protons in the two conformations (δ_1 and δ_2) are known from model compounds; or (2) using the relationship[11] $J_0 = N_1J_1 + N_2J_2$ if the width of the anomeric signal in the conformationally mobile compound (J_0) and the widths of the analogous multiplets in the pure conformers (J_1 and J_2) can be measured, the latter from model compounds. Both the chemical shift and the width of the signal for the anomeric proton in the two conformers could in theory be obtained without model compounds by cooling the mobile compound to a temperature low enough so that equilibration of the conformers is slow on the nmr time scale.[12] However this equilibrium lies very far in favor of the axial conformer at room temperature and is likely to be even more extreme at low temperatures making the less stable conformer unobservable. Furthermore one might expect that "freezing" the tetrahydropyran ring should require a lower temperature than cyclohexane because of the ring oxygen.



Ia Ib

Very recently an estimate of the magnitude of the anomeric effect in 2-chloro- and 2-bromotetrahydropyran has been reported.[13] It was observed that the width of the nmr signal for the anomeric proton was the same as the width of the analogous signal for the model compound which had the halo substituent axial. (The model compounds chosen were 2-chloro- and 2-bromocyclohexanones because the 2-halotetrahydropyrans of fixed conformation like 2-halo-4-*t*-butyltetrahydropyran were not readily available.) Consequently the anomeric effect was too large to be measurable by this method. Further it was found that the signal width did not change in a range of solvents of differing polarity (pentane, benzene, and dioxane), whereas 2-bromocyclohexanone shows a change in conformational preference of "0.5 kcal/mole" in free energy for such a solvent range. It was concluded that the free-energy difference between axial and equatorial chloro- or bromotetrahydropyran must be at least 1.8 kcal/mole for the supposed solvent effect to be so small as to be unobservable. Assuming this, if the conformational preference of the bromo or chloro group on cyclohexane is about 0.5 kcal/mole[14] in favor of the equatorial conformation, the anomeric effect must be 1.8 + 0.5 = 2.3 kcal/mole.

We have been interested in effects of dipole–dipole interactions in conformational systems and particularly the anomeric effect,[15] and would now like to report the measurement of the conformational equilibria in 2-halotetrahydropyrans and the calculation of the magnitude of the anomeric effect. Suitable model compounds are the *cis*- and *trans*-2-halo-4-methyltetrahydropyrans (II and III) which are each conformationally homogeneous, existing as the diequatorial *cis* conformer (IIa) and the 2-axial-4-equatorial *trans* conformer (IIIa). An *a priori* conformational analysis of conformer IIa *vs.* conformer IIb indicates that IIb is less stable by the *A* value of the methyl group (1.7 kcal/mole[14]), the *A* value of the substituent X (*ca.* 0.7 for OCH_3 and OAc and *ca.* 0.5 for Cl or Br[14]), and the 1,3 diaxial interaction (*ca.* 2.4 kcal/mole).[16] The conformer IIIa would be estimated to be less stable than IIIb by the *A* value of X but more stable by the anomeric effect (*ca.* 1.4 kcal/mole for oxy substituents[15,5]) while the conformer IIIb would be expected to be less stable by the amount of the *A* value for methyl (1.7 kcal/mole). Consequently the *trans* conformers IIIa and IIIb differ in energy by *ca.* 2.6 kcal/mole which is an estimated preference for conformation IIIa of 98.8%.



IIa IIIa IIb IIIb

We therefore prepared the 2-chloro- and 2-bromo-4-methyltetrahydropyrans by addition of the hydrogen halide to the 4-methyldihydropyran. The methyldihydropyran was readily obtained by acid-catalyzed elimination of butanol from 2-butoxy-4-methyltetrahydropyran which can be prepared by the Diels–Alder reaction of crotonaldehyde and butyl vinyl ether followed by hydrogenation.[17] The chloro and bromo ethers could be distilled. Nmr spectral data in various solvents are listed in Table I.

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[8] P. Bender, D. L. Flowers, and H. L. Goering, *J. Am. Chem. Soc.*, **77**, 3463 (1955); R. U. Lemieux and J. W. Lown, *Can. J. Chem.*, **42**, 893 (1964).

[9] J. Allinger and N. L. Allinger, *Tetrahedron*, **2**, 64 (1958); N. L. Allinger, J. Allinger, and N. A. LeBel, *J. Am. Chem. Soc.*, **82**, 2926 (1960).

[10] E. L. Eliel and M. H. Gianni, *Tetrahedron Letters*, 97 (1962).

[11] E. W. Garbisch, Jr., *J. Am. Chem. Soc.*, **86**, 1780 (1964).

[12] A. J. Berlin and F. R. Jensen, *Chem. Ind.* (London), 998 (1960).

[13] G. E. Booth and R. J. Ouellette, *J. Org. Chem.*, **31**, 544 (1966).

[14] Reference 2, pp 44, 436.

[15] C. B. Anderson and D. T. Sepp, *Chem. Ind.* (London), 2054 (1964).

[16] Reference 2, p 52.

[17] W. E. Parham and H. E. Holmquist, *J. Am. Chem. Soc.*, **73**, 913 (1951).

TABLE I

NMR SPECTRAL MEASUREMENTS FOR THE ANOMERIC PROTON OF 2-SUBSTITUTED TETRAHYDROPYRANS AT 40° WITH A VARIAN A-60 NMR SPECTROMETER

Tetrahydropyran derivative	Solvent	Chemical shift, τ values[a] ± 0.01	Half-width,[b] cps ± 0.2	J_{1a2e}, J_{1a2a}, cps ± 0.2
2-Chloro-	Neat	3.77 b[c]	6.4	
	CCl_4 10 mole %[d]	3.79 b	4.2	
	Acetone 10 mole %	3.63 b	5.0	
	DMF 10 mole %	3.55 b	4.9	
	Dioxane 10 mole %	3.68 b	4.8	
	CH_3CN 10 mole %	3.64 b	5.0	
2-Chloro-4-methyl-	Neat	3.74 m 4.49 q	6.4 ...	2.5, 7.0
	CCl_4 10 mole %	3.76 m	6.2	
	CCl_4 50 vol. %[e]	3.80 m	6.5	
	Acetone 50 vol. %	3.67 m 4.44 q	6.1 ...	2.5, 7.0
	Acetone 10 mole %	3.58 m	6.2	
	DMF 10 mole %	3.50 m	5.9	
	Dioxane 10 mole %	3.63 m	6.3	
	CH_3CN 50 vol. %	3.66 m 4.4	6.2 ...	
	CH_3CN 10 mole %	3.61 m	6.0	
2-Bromo-	Neat	3.26 b	4.5	
2-Bromo-4-methyl-	Neat	3.26 m	5.6	
2-Iodo-	CCl_4[f]	2.80 b	6.9	
2-Iodo-4-methyl-	CCl_4	2.80 m	6.8	
2-Methoxy-	CCl_4	5.55 b	4.5	
cis-2-Methoxy-4-methyl-	CCl_4	5.85 q	...	2.2, 8.3
trans-2-Methoxy-4-methyl-	CCl_4	5.43 m	6.0	

[a] Relative to tetramethylsilane as an internal reference. Signals for the *cis* isomer (IIa) were weak and in solution were not detected in many cases. A time-averaging computer was used to improve the signal. [b] Some signals were not symmetrical so that the half-width was much less than 6 cps, while below the half-height the width was 6 cps or more. The center of the signal could be determined by eye or by integration to give the weighted center. [c] q, quartet; m, unresolved multiplet; b, broad. [d] 10 mole %. [e] 50 vol. %. [f] Prepared in acetone, solvent removed under vacuum, and CCl_4 added.

In the nmr spectrum of the pure 2-chloro-4-methyltetrahydropyran, signals are observed at τ 3.74 which is a quartet. The quartet is just barely strong enough to be detected. These signals closely resemble those observed for the *trans* and *cis* isomers of 2-oxy-4-methyltetrahydropyrans[15] where the axial proton resonance occurs at higher field than the equatorial proton resonance as would be expected.[18] The nmr spectral data for the *trans*- and *cis*-2-methoxy-4-methyltetrahydropyrans are included in the table for comparison, although the preparation and nmr spectra were described earlier.[15] The small signal which is a quartet is not likely to be due to an unrelated impurity because the elemental analysis is good. The spectrum of the 2-chloro-4-methyltetrahydropyran integrates correctly for that structure. On the basis of chemical shift and the observed spin–spin multiplicity, the signal at τ 3.74 is identified as the anomeric proton for the *trans* isomer (IIIa), and the signal at 4.49 is the anomeric proton for the *cis* isomer (IIa). The signals for the anomeric proton in the *trans* and *cis* isomers could be integrated, and the composition of 97:3 (*trans*:*cis*, that is IIIa:IIa) could be obtained. The same result was obtained when the compound was saturated with hydrogen chloride. The same value (97:3) within 0.4% (probably error) was obtained in acetone or acetonitrile (50% by volume). Methanol, methanol–hydrogen chloride, and water solvolyzed the halo compound immediately although acetic acid did not.

The 2-chloro-4-methyltetrahydropyran was always a 97:3 mixture of *trans* and *cis* isomers (at 40°) which could only be judged from the nmr spectrum. At higher temperatures the proportion changes slightly but measurably. At 105° in the nmr variable-temperature probe, the integration shows 5.2 ± 0.4% of the *cis* (IIa) isomer, at 78° 4.3 ± 0.4%, and at 55° 3.7 ± 0.4%, while at 40° 3.0 ± 0.4% was found. The temperature can be raised to 105° and returned to 40° obtaining the same values again. At still higher temperatures, the compound turns to a brown tar, and the measured effect is not reversible. The compound is a secondary α-halo ether, and is too reactive for physical separation of the isomers (vpc or distillation). The question of whether or not the system is at equilibrium could not be determined then by equilibrating pure *cis* and pure *trans* isomers separately to the same equilibrium composition. Saturating the compound with hydrogen chloride did not affect the proportion of isomers although acid should catalyze equilibration. A rather roundabout argument supporting the idea that the compound when prepared is an equilibrium mixture of isomers is that the 2-methoxy-4-methyltetrahydropyran, either pure *cis* or pure *trans*, is equilibrated in less than 5 min if 1 drop of the 2-chloro-4-methyltetrahydropyran is added to an nmr tube containing *ca.* 0.5 ml of the methoxy compound. A 2-chlorotetrahydropyran would be expected to isomerize under more mild conditions than a 2-methoxytetrahydropyran, and, therefore, since the methoxy compound was equilibrated, the 2-chloro-4-methyltetrahydropyran must have been at equilibrium also. For all these reasons, the proportion of *trans* to *cis* isomers of 97:3 is judged to be the equilibrium composition at 40°.

The equilibrium composition may also be obtained from the chemical shifts of the anomeric proton by the method of Eliel[10] although for such an extreme equilibrium this method is particularly inexact. As can be seen from the Table I the difference in chemical shift between the axial and the equatorial anomeric proton is 0.75 ppm in the pure compound, and similar in acetone and acetonitrile. The difference between the chemical shift of the conformationally mobile 2-chlorotetrahydropyran and that of the axial-2-chloro-4-methyltetrahydropyran is 0.03 ppm. Consequently the ratio of axial to equatorial conformers (Ib and Ia, respectively) is 72:3 which is 4% equatorial (Ia). This value agrees as well as one could expect with the value obtained by integration of the nmr signals (3%). It is interesting to note (see Table I) that the differences between the chemical shifts of the anomeric protons in the axial 2-chloro-4-methyltetrahydropyran and the 2-chlorotetrahydropyran are about 0.05 ppm

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(18) R. U. Lemieux, R. K. Kullnig, M. J. Bernstein, and W. G. Schneider, *J. Am. Chem. Soc.*, **80**, 6098 (1958).

in dioxane, acetone, and dimethylformamide, probably indicating that there is a larger percentage (7%) of equatorial conformer (Ia) in these solvents. From these data the anomeric effect may be calculated as the sum of the free energy for the observed equilibrium (2.15 kcal/mole) and the *A* value for the chloro substituent (0.5 kcal/mole), or 2.65 kcal/mole in the neat compound which is somewhat larger than previously estimated.[13] In more polar solvents it appears that the anomeric effect may be as low as 1.5 + 0.5 = 2.0 kcal/mole. Values for the equilibrium composition at higher temperatures permit a crude determination of ΔH which is −2.0 kcal/mole and ΔS which is easily within experimental error of 0.

The 2-bromo-4-methyltetrahydropyran was prepared in the same way as the chloro analog. The nmr spectrum of the compound integrated correctly. However, it was less stable than the chloro compound. The chemical shifts of the anomeric protons for both the conformationally mobile 2-bromotetrahydropyran and the 2-bromo-4-methyltetrahydropyran were the same (see Table I), indicating that the conformational equilibrium is more extreme toward axial bromo than in the case of the chloro analog which was 96–97%. In the nmr spectrum of the pure 2-bromo-4-methyltetrahydropyran, only the anomeric proton for the axial bromo compound was observed with no detectable quartet for the anomeric proton of the equatorial bromo compound. The anomeric effect in 2-bromotetrahydropyrans must then be larger than 2.7 kcal/mole, the value for the chloro compound. If a 0.01-ppm difference in chemical shift could have been detected and if the difference between the chemical shifts of the signals for the axial and equatorial bromo isomers is the same as for the chloro isomers (0.75 ppm), then the equilibrium composition for 2-bromo-4-methyltetrahydropyran is greater than 74 to 1 for *trans vs. cis*. The conformational energy difference between isomers is than greater than 2.7 kcal/mole at 40°, and the anomeric effect for bromo is greater than 3.2 kcal/mole if the *A* value for bromo is 0.5 kcal/mole.[14]

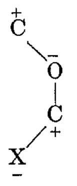
The 2-iodo analogs were prepared in solution from the chloro compounds by treatment with sodium iodide in acetone. The iodo compounds could not be distilled without complete decomposition. When the sodium iodide reactions were complete, the acetone was removed under reduced pressure, carbon tetrachloride was added, and the nmr spectra were taken. As with the nmr spectra of the bromo compounds, the chemical shifts of the anomeric proton of the 2-iodotetrahydropyran and of the 2-iodo-4-methyltetrahydropyran were the same, indicating a larger extent of axial halo conformation than in the chloro compound. Just as for the bromo compounds, the anomeric effect for the iodo group must be greater than 3.1 kcal/mole if the *A* value is 0.4 kcal/mole.[14]

The preparation of the 2-fluoro compounds was attempted by addition of gaseous hydrogen fluoride to the dihydropyran in carbon tetrachloride. Unfortunately elimination occurred on attempted distillation. The nmr spectrum of the reaction solution showed what must have been mostly a dimeric fluoro compound. The 4-methyldihydropyran and hydrogen fluoride also resulted in dimeric and polymeric fluorotetrahydropyran.

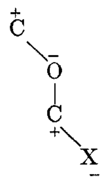
The anomeric effect for the chloro group was expected to be larger than that for oxy substituents because the C–Cl bond moment is larger than the C–O bond moment. The difference in dipole–dipole interaction energy between axial and equatorial conformers (Ib and Ia) may be calculated assuming permanent dipoles from Coulomb's law, $U = e_1e_2/\epsilon r$, and the definition of dipole moment, $\mu = ed$, where U is potential energy in ergs, e is charge, r is the distance between charges, ϵ is the dielectric constant, and d is the bond length. Because the only difference between the axial and equatorial conformations is the distance (r_{ax} and r_{eq}) between the ends of the dipoles, that is from the 6 position of the tetrahydropyran to the substituent atom attached to the anomeric carbon (2 position), the calculation is simply

$$\Delta U = \left(\frac{\mu}{d}\right)_{\mathrm{CO}}\left(\frac{\mu}{d}\right)_{\mathrm{CX}}\left(\frac{1}{\epsilon_{ax}r_{ax}} - \frac{1}{\epsilon_{eq}r_{eq}}\right)$$

The equation often used,[19] which was derived for dipolar particles,[20] is inappropriate here because the distance between dipoles is not large compared with the length of the dipoles. For the purposes of this calculation, the distances (r) can be measured sufficiently accurately from models although the values used here were calculated assuming tetrahedral angles in the ring. In the equation, μ is the bond moment (C–O, 1.2 D.; C–Cl, 1.8 D.; C–Br, 1.9 D.)[21] and d, the bond length (C–O, 1.43 A, C–Cl, 1.77 A; C–Br, 1.91 A).[21] The dielectric constant (ϵ) cannot be evaluated directly because the dielectric constant here is not the bulk dielectric constant of the solvent but the microscopic dielectric constant between the charges. In the 2-axial conformation, the distance (r_{ax}) passes through relatively empty space between the ends of the dipoles (structure IV), whereas in the 2-equatorial conformation the line (r_{eq}) passes through the ring C–O bond (see structure V). Therefore ϵ_{ax} must be smaller than ϵ_{eq}. If gross approximations are made allowing $\epsilon_{ax} = 1$ as under vacuum and $\epsilon_{eq} = 2$ as in hydrocarbons, dioxane, etc., dipole–dipole interaction energies are estimated as 1.5, 2.7, and 2.4 kcal/mole for the 2-oxy-, 2-chloro-, and 2-bromotetrahydropyrans which agree with the experimentally determined anomeric effects of 1.3 and 2.7 kcal/mole for the oxy[15] and chloro substituents. This agreement may be somewhat fortuitous because the bond moments in these molecules may not be the same as those of alkyl halides and ethers which were used and, of course, also because of the arbitrary choice of dielectric constants. If the dielectric constants are ignored ($\epsilon_{ax} = \epsilon_{eq} = 1$), the respective dipole–dipole interaction values calculated for O, Cl, and Br



IV



V

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[19] Reference 2, p 461.

[20] J. Jeans, "Mathematical Theory of Electricity and Magnetism," 5th ed, Cambridge University Press, London, 1943, pp 377–379; *cf.* ref 22, pp 99–100.

[21] E. S. Gould, Mechanism and Structure in Organic Chemistry, Henry Holt and Co., Inc., New York, N. Y., 1959, pp 44, 62.

are 0.88, 1.08, and 0.95 kcal/mole which are substantially smaller than those measured. This difference shows the large dependence on the dielectric constant in this calculation.

The value calculated for bromo is smaller than that calculated for chloro because the C–Br and C–Cl bond moments are about the same but the C–Br bond is longer. However, here as in the case of the 2-halocyclohexanones, the bromo substituent experimentally is found to prefer the axial conformation to a larger degree than chloro. With a view to solving this anomaly in the 2-halocyclohexanones, Allinger[9] considered quantitatively the effect of dipole–dipole interaction, induced dipolar interaction, and van der Waals interactions, but without success. A similar relationship between the *trans*-1,2-dibromo- and *trans*-1,2-dichlorocyclohexanes was quantitatively accounted for by the repulsive van der Waals interactions between 1,2-diequatorial bromo substituents,[9] but this van der Waals effect is negligible in 2-halocyclohexanones and 2-halotetrahydropyrans.

A more sophisticated consideration of the electrostatic interaction does however suggest at least a qualitative explanation. The two ends of the dipoles in each conformation (see IV or V) may be imagined at the ends of an ellipsoidal volume which includes portions of the molecule (and solvent possibly) and through which the electrostatic lines of force pass. For the equatorial conformation, the other atoms of the molecule including the C–X bond lie near the center of the ellipsoid, but for the axial conformation, these atoms are more peripheral to the ellipsoid. The polarization of the atoms within this ellipsoid by the electrostatic field screens the charges from each other and constitutes an increased dielectric constant. Furthermore, because the C–Br bond is more polarizable than the C–Cl bond, the effective dielectric constant, ϵ_{eq}, should be larger in the case of the bromotetrahydropyran than it is in the case of the chloro compound. The dielectric constant, ϵ_{ax}, will be affected less because the C–X bond is far from the center of the ellipsoid in the axial conformation. If then ϵ_{eq} is larger for bromo than chloro and ϵ_{ax} is about the same, the dipole–dipole interaction would be larger for bromo with respect to chloro than expected on the basis of bond moments. As expected from the order of polarizability of C–O, C–Cl, C–Br bonds (*e.g.*, 1.34, 2.59, and 3.73×10^{-24} cm^3),[22] the deviations of the calculated dipole–dipole interactions from the experimental anomeric effects suggest that the dielectric constant (ϵ_{eq}) for the oxy substituents is too large and for the bromo is too small relative to chloro. The above considerations can also be applied with good agreement to the 2-halocyclohexanones using dielectric constants of the order of 2. In the 2-halocyclohexanones the difference between conformations is smaller than in the case of the halotetrahydropyrans presented here.

Experimental Section

2-Chloro-4-methyltetrahydropyran.—The Diels–Alder reaction of crotonaldehyde and isobutyl vinyl ether yielded 2-isobutoxy-4-methyl-2,3-dihydropyran, which after hydrogenation in ethanol with palladium–carbon catalyst, was converted to 4-methyldihydropyran by distillation from toluenesulfonic acid.[17] The 2-chloro compound was prepared by bubbling anhydrous hydrogen chloride through a 50-ml ether solution containing 12 g of the dihydropyran for 10 min at 0°. The solvent was removed with a rotary evaporator and the resulting colored solution was distilled. Fraction 1 (1 g) had bp 35–41° (5 mm). Fraction 2 (5.5 g) had bp 41–42° (5 mm). Fraction 3 (3 g) had bp 42° (5 mm) (yield 57%). The middle fraction was analyzed. *Anal.* Calcd for $C_6H_{11}ClO$: C, 53.54; H, 8.24. Found: C, 53.81; H, 8.26.

2-Bromo-4-methyltetrahydropyran.—The compound was prepared as was the chloro compound and distilled, and the middle fraction was used for measurements, bp 52–53° (6 mm). *Anal.* Calcd for $C_6H_{11}BrO$: C, 40.24; H, 6.19. Found: C, 40.84; H, 6.62.

2-Chloro- and 2-Bromotetrahydropyrans.—These 2-chloro and 2-bromo compounds were prepared as above, bp 35–36° (12 mm) and bp 61–63° (16 mm),[23] respectively.

2-Iodotetrahydropyran and 2-Iodo-4-methyltetrahydropyran.—A solution of 5 g of 2-chlorotetrahydropyran or 2-chloro-4-methyltetrahydropyran and 50 ml of 1 *M* sodium iodide in acetone was prepared by adding the chloro compound dropwise to a freshly prepared sodium iodide–acetone solution. Sodium chloride precipitated immediately. An equal volume of carbon tetrachloride was added, and the mixture was filtered. The clear yellow filtrate was evaporated under reduced pressure at room temperature using a rotary evaporator to half the original volume. Another 50 ml of carbon tetrachloride was added, and the volume of solution was evaporated to 50 ml. This solution was used for nmr spectral analysis. Attempts at further concentration and isolation of the pure iodotetrahydropyrans resulted in dark brown, viscous materials.

Registry No.—2-Chlorotetrahydropyran, 3136-02-5; 2-chloro-4-methyltetrahydropyran, 7429-23-4; 2-bromotetrahydropyran, 6667-26-1; 2-bromo-4-methyltetrahydropyran, 7444-97-5; 2-iodotetrahydropyran, 7429-25-6; 2-iodo-4-methyltetrahydropyran, 7429-26-7; 2-methoxytetrahydropyran, 931-60-2; *cis*-2-methoxy-4-methyltetrahydropyran, 7429-27-8; *trans* isomer of **8**, 7429-28-9; tetramethylsilane, 75-76-3; crotonaldehyde, 123-73-9; isobutyl vinyl ether, 109-53-5; 2-isobutoxy-4-methyl-2,3-dihydropyran, 7429-29-0; 4-methyldihydropyran, 2270-61-3; *trans*-2,5-dichloro-1,4-dioxane, 7429-31-4; *trans*-2,3-dichlorotetrahydropyran, 7429-32-5; 2-bromocyclohexanone, 822-85-5; 2-chlorocyclohexanone, 822-87-7; butanol, 71-36-3; 2-butoxy-4-methyltetrahydropyran, 7429-33-6; 2-oxy-4-methyltetrahydropyran, 7429-34-7; *cis* isomer of **22**, 7429-35-8; *cis* isomer of **2**, 7429-36-9; *trans*-1,2-dibromocyclohexane, 7429-37-0; *trans*-1,2-dichlorocyclohexane, 822-86-6; 2-bromo-4-methylcyclohexane, 7428-97-9; 2-iodo-4-methylcyclohexane, 7428-98-0.

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