importance of path a. It is interesting that k_{obsd} values (eq 6) for the reactions of mesitylene,[6] pentamethylbenzene, and hexamethylbenzene in acetic acid are in the approximate ratio 1:1:0.2. Because of favorable electronic effects of polyalkylation of the aromatic nucleus, pentamethylbenzene is usually substantially more reactive than mesitylene in electrophilic substitution processes. The relatively low reactivity of pentamethylbenzene, as well as that of hexamethylbenzene with ICl, is ascribed to a screening of the π electrons of the ring from attack by the bulky halogen when the ring is highly substituted.[12] The enormity of the steric effect is indicated by the differences in the energies of activation for the reactions of penta- ($E_a = 12.5 \pm 0.6$ kcal/mole) and hexamethylbenzene ($E_a = 20.2$ kcal/mole); the corresponding entropies of activation are -20.1 ± 2 and -0.7 eu, respectively. These values have been calculated, respectively, from rate constants for runs at 25.0 and 44.8° (Table II) in which initial concentrations of penta- and hexamethylbenzene were, respectively, 0.2 and 0.05 *M*. It should be noted that the k_{obsd} value for the hexamethylbenzene reaction appears to increase somewhat with decreasing aromatic reactant concentration, and this is attributed to complex formation between the reactants.

In its early phases the iodine-producing reaction of hexamethylbenzene with ICl in nitromethane conforms to the same rate law (eq 6) which applies to the reaction (eq 1) in acetic acid. An explanation of the deviations from this rate law in later phases of reaction is given in the Experimental Section. The k_{obsd} values based on initial slopes of plots of 1/[ICl] *vs.* time for several runs with nitromethane as solvent are listed in Table III. At the outset, at least, hexamethylbenzene is considerably more reactive in nitromethane than in acetic acid (*cf.* Table II). It has been observed previously that aromatic chlorination occurs more rapidly in nitromethane than in acetic acid.[4]

TABLE III

INITIAL RATE CONSTANTS FOR THE REACTION OF HEXAMETHYLBENZENE AND ICl IN NITROMETHANE (25.0°)

$[ArH]_i$, *M*	$[ICl]_i$, *M*	k_{obsd}, mole^{-2} sec^{-1} l^2	Extent of reaction,[a] %
0.0340	0.01295	4.24[b]	20
0.0340	0.00647	4.35[b]	15
0.0342	0.00647	3.94[c]	12
0.0171	0.00323	3.75[c]	9

[a] The per cent of ICl consumed before deviations from the assumed rate law (eq 6) were observed. [b,c] The reactions were followed by spectrophotometric analysis for iodine at wavelengths of 580 and 550 mμ, respectively. These reactions slowed almost to a halt when 70–80% of the ICl was consumed.

Because of difficulties in establishing ICl concentrations in the presence of HCl in nitromethane by spectrophotometric methods, a satisfactory quantitative interpretation of the results of kinetic studies for the ICl–pentamethylbenzene reaction in this solvent has not been achieved (see Experimental Section for details). By analysis of final products of mixtures initially 0.1 *M* in pentamethylbenzene and 0.01 *M* (or less) in ICl in nitromethane, it has been established that at 25° about 6% of the reacting halogen is converted to iodine. As is the case for reaction in acetic acid, this figure is substantially less than that for reaction in carbon tetrachloride.

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(12) A reversal in the normal reactivities of mesitylene and pentamethylbenzene in their zinc chloride catalyzed reactions with ICl in acetic acid has been similarly explained.[6]

Conformational Analysis. V.[1,2] 2-Chloro- and 2-Bromotetrahydropyran

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The sole detectable conformation of both 2-chloro- and 2-bromotetrahydropyran has been found to be that containing the halogen in the axial position. Solvent polarity has no measurable effect on decreasing the fraction of the axial conformer. An estimate of the magnitude of the "anomeric effect" is made and compared with that of the α-halo ketone effect.

The determination of the conformational equilibrium of mobile systems by nmr spectroscopy has been extremely fruitful.[3] The experimental approaches depend on conformationally homogeneous models from which either the chemical shifts or nuclear spin couplings can be obtained. If model substrates are not available, semiquantitative methods can still be applied. By examining a mobile system at reduced temperatures, the conformational isomers may be frozen out, and an estimate of the equilibrium constant can be obtained if the chemical shifts of the reference proton in the two conformers are sufficiently different. However, the percentage of the unstable conformer may be so low at reduced temperatures that the equilibrium constant cannot be determined accurately by this method.[4] At ambient temperatures the equilibrium constant will normally tend to reflect an increase in the percentage of the unstable conformer, and conformational analysis of a mobile system can then be ap-

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(1) Paper IV: R. J. Ouellette, G. E. Booth, and K. Liptak, *J. Am. Chem. Soc.*, **87**, 3436 (1965).

(2) The authors acknowledge a grant-in-aid from The Ohio State University in partial support of this research. A Petroleum Research Fund Grant is also acknowledged. We wish to thank the NSF for grants used for the purchase of the nmr spectrometer.

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proached by examination of the time-averaged coupling constants.[5] Ideally, the coupling constants from the appropriate conformationally homogeneous models should be determined. However, there are certain cases for which sufficient data are currently available in the literature to estimate the necessary coupling constants for those cases where the exact model compounds are not readily available.

Examples of interest for which the appropriate models are not readily available are 2-chloro- and 2-bromotetrahydropyran. The instability of these compounds usually precludes their isolation and they are customarily produced and allowed to react *in situ*.[6] Therefore, the chances of preparing and isolating the *cis*- and *trans*-4-*t*-butyl-substituted compounds were regarded as unlikely. Indeed, these compounds were found to be unnecessary after examination of the data on the unsubstituted compounds.

The 1-substituted derivatives of α-D-glucose and other sugars are more stable than the β derivatives,[7] although the latter contain the substituent in the equatorial position. The term "anomeric effect" has been used by Lemieux and Chu[8] for this phenomenon which has been interpreted in terms of a dipole–dipole interaction between the bond from the anomeric substituent and the carbon–oxygen bonds of the ring.[9] Therefore, the "anomeric effect" can be viewed as similar in nature to the α-halo ketone effect examined in detail by Allinger.[10] Several reference texts contain extensive discussions, with references of the "anomeric effect."[11]

While the majority of the work on the evaluation of the "anomeric effect" has been in the field of carbohydrates, it has been shown that *trans*-2,5-dichloro-1,4-dioxane, *trans*-2,3-dibromo-1,2-dioxane, and *trans*-2,3-dichlorotetrahydropyran exist in conformations in which the halogen atoms occupy the axial position.[12] However, the disubstituted pyrans and dioxanes do not allow the assignment of a quantitative value of the "anomeric effect" owing to the presence of several dipole–dipole and steric interactions. That *trans*-2,3-dichlorotetrahydropyran exists solely in the diaxial conformation is not surprising, considering that *trans*-1,2-dichlorocyclohexane exists to the extent of 48% in the diaxial conformation in carbon tetrachloride.[13] The determination of the "anomeric effect" is difficult in systems which already tend to exist in the conformation which will become more favored as additional structural features are introduced. Accordingly, it was decided to examine the simplest models, 2-chloro- and 2-bromotetrahydropyran, in order to place a quantitative value or at least a lower limit on the "anomeric effect."

Results and Discussion

The observed coupling constants for a rapidly equilibrating system are time averages of the components of the system. The equilibrium constant between the two conformational isomers of the 2-halotetrahydropyrans, I and II, can be estimated if the proton spin couplings between H-2 and H-3_a and H-3_e are known. The necessary coupling constants can be estimated from the 2-halocyclohexanones.[14] The systems under consideration are of the ABX type[15] where X is the C-2 proton. C-2 protons in the halotetrahydropyrans are well removed from the other hydrogen resonances. In the chloro compound the resonance is centered at τ 3.8 and in the bromo compound at τ 3.4. If weak combination transitions are neglected, the separation between the terminal peaks of the X resonance is equal to $J_{2,3a} + J_{2,3e}$. These coupling constant sums will be called $J_{\rm I}$ and $J_{\rm II}$ for I and II, respectively. The observed separation, $J°$, for the mobile system will be $J° = J_{\rm I}N_{\rm I} + J_{\rm II}N_{\rm II}$, where $N_{\rm I}$ and $N_{\rm II}$ refer to the mole fractions of I and II. Approximate values of $J_{\rm I}$ and $J_{\rm II}$ chosen for this study in the absence of the *cis*- and *trans*-4-*t*-butyl-substituted compounds are 6.0 and 18.0 cps, respectively.

Ia, R = Br
b, R = Cl

IIa, R = Br
b, R = Cl

In order to eliminate concentration dependence of the coupling constants due to changes in solvent polarity, the concentration of substrate was kept at approximately 3 mole %. The observed $J°$ values for 2-chloro- and 2-bromotetrahydropyran are given in Table I as a function of solvent.

TABLE I

ANOMERIC PROTON OF 2-HALOTETRAHYDROPYRAN

2-Halotetrahydropyran	Solvent	$J°$, cps	Chemical shift, τ
Bromo-	Pentane	6.3 ± 0.2	3.41 ± 0.02
Bromo-	Carbon tetrachloride	6.3 ± 0.2	3.38 ± 0.02
Bromo-	Benzene	6.5 ± 0.3	3.47 ± 0.02
Bromo-	Dioxane	6.6 ± 0.2	3.22 ± 0.02
Chloro-	Pentane	6.4 ± 0.2	3.92 ± 0.02
Chloro-	Carbon tetrachloride	6.5 ± 0.2	3.83 ± 0.02
Chloro-	Benzene	6.2 ± 0.3	3.92 ± 0.02
Chloro-	Dioxane	6.4 ± 0.2	3.70 ± 0.02

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The mole percentages of I and II cannot be determined accurately by the present experimental method, for the magnitude of the "anomeric effect" in 2-chloro- and 2-bromotetrahydropyran is still so large that the percentage of the equatorial conformer is too small to be detected by nmr analysis. The fact that the X resonance remains as a broad partially resolved multiplet similar to that observed for *trans*-2-bromo-4-*t*-butylcyclohexanone[14] and does not broaden to any significant extent in solvents of increasing dielectric constant is strong evidence for the exclusive existance of the axial conformer. This conclusion is independent of any assumptions regarding the magnitude of J°.

The effect of solvent polarity on the conformational equilibrium in 2-bromocyclohexanone is well known.[10] The solvent stabilization of the equatorial conformer of 2-bromocyclohexanone in going from heptane to dioxane is approximately 0.5 kcal/mole. In order for such a factor to be undetected in the 2-bromotetrahydropyrans, in which an even greater dipole–dipole term is operative, the equilibrium constant for the equatorial–axial conversion would have to be of the order of 20 or greater. The free-energy change for such an equilibrium constant is of the order of 1.8 kcal/mole. Since the conformational preferences of bromine and chlorine in cyclohexane are approximately 0.5 kcal/mole,[16] the magnitude of the "anomeric effect" is approximately 2.3 kcal/mole. That the observed J° for 2-bromotetrahydropyran is similar to that of the *trans*-2-bromo-4-*t*-butylcyclohexanone is reasonable, but the conclusions are independent of this fact.

The J° of 2-chlorotetrahydropyran is identical with that of 2-bromotetrahydropyran. This was anticipated, as substituted α-D-glucopyranosyl chlorides and bromides exhibit the same coupling constants.[17] Apparently the "anomeric effect" is still so significant in 2-chlorotetrahydropyran to preclude any significant amount of the equatorial conformer even in dioxane. In dioxane, 2-chlorocyclohexanone exists to the extent of 63% of the equatorial conformer.[10] The solvent stabilization in 2-chlorotetrahydropyran would be expected to be similar to that of 2-chlorocyclohexanone. However, the conformational equilibrium constant of the former compound favors the axial isomer to such an extent as to make such solvent free-energy changes of diminished importance in detecting a change in equilibrium constant by the nmr method.

The chemical shifts of the X hydrogen vary as a function of solvent. The largest change is for that of dioxane. While the shifts are in the order of magnitude that would be expected if a major change in conformer population occurred, such a change is not possible without simultaneously noting an increase in J°. The shift as a function of solvent must be due to either bulk diamagnetic susceptibility of the solvent or a specific intermolecular interaction with solvent. An intermolecular interaction would not be unreasonable in the case of dioxane as the oxygen atom and the X hydrogen might be expected to associate. Even the less acidic iodomethane is affected by dioxane in a similar manner.[18]

The qualitative observation that the conformer with an axial halogen is the more stable in both 2-chloro- and 2-bromotetrahydropyran was anticipated. Unfortunately, even in the simplest system in which the "anomeric effect" can be examined, only a limit of the dipole–dipole interaction can be set. By analogy with the 2-halocyclohexanones, 2-fluorotetrahydropyran might be expected to exist to a larger extent as the equatorial conformer. However, the level of the "anomeric effect" is so high that probably even 2-fluorotetrahydropyran, which has not been synthesized to date, would exist predominately in the axial conformation and the nmr method could not provide a quantitative value for the conformational equilibrium constant.

Experimental Section

The 2-chloro- and 2-bromotetrahydropyran were prepared fresh by bubbling the appropriate gaseous hydrogen halide into dihydropyran in anhydrous ethyl ether at 0°. Distillation under reduced pressure yielded 2-chlorotetrahydropyran, bp 35–36° (12 mm), and 2-bromotetrahydropyran, bp 61–63° (16 mm), as colorless liquids. The samples were immediately dissolved in solvents, and their nmr spectra were determined, utilizing a Varian A-60 instrument operated at 38°. Chemical shift coupling constants are reproducible to ±0.02 ppm and ±0.2 cps, respectively.

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Conformational Analysis. VI.[1,2] 1-Vinylcyclohexanol

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Dilution studies have been carried out to determine the chemical shift of the hydroxyl proton at infinite dilution of 1-vinylcyclohexanol, 1-vinyl-*cis*-4-*t*-butylcyclohexanol, and 1-vinyl-*trans*-4-*t*-butylcyclohexanol. Utilizing 0.75 kcal/mole for the conformational preference of the hydroxyl group and assuming that the free-energy terms are additive, the conformational preference of the vinyl group is calculated to be 1.35 kcal/mole.

In two early papers in this series[4] a method was developed for determination of the conformational preference of substituents in the cyclohexane series. The method depends on the difference in magnetic environment of the axial and equatorial hydroxyl protons in cyclohexanols. The principal advantage

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(1) Paper V: G. E. Booth and R. J. Ouellette, *J. Org. Chem.*, **31**, 544 (1966).

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(3) National Science Foundation Undergraduate Summer Research Participant.

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